University of Alberta

Greener Chemistry Using Boronic Acids as Organocatalysts and Stoichiometric Reaction Promoters

by

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A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry

Fall 2012
Edmonton, Alberta

Abstract

Catalysis is crucial for society in view of producing pharmaceutical agents and commodity chemicals. Industry and academia alike are constantly searching for organic transformations which can not only efficiently produce important pharmaceuticals and commodity chemicals, but can also do so in a manner that is environmentally sound. During the past five years, arylboronic acids have been emerging as a promising new class of organocatalysts for the direct activation of carboxylic acids, alcohols and diols through reversible formation of boronate adducts. Such unique activation modes have resulted in the application of boronic acid catalysis toward the development of more efficient and milder protocols for existing transformations. Boronic Acid Catalysis (BAC) provides such a platform for the pursuit of "green chemistry" by providing a mild means to achieve reactions that would otherwise require harsh or wasteful conditions. To this end, several new methods employing diversely substituted arylboronic acids as organocatalysts and stoichiometric reaction promoters were developed.

ortho-Substituted arylboronic acids activate unsaturated carboxylic acids presumably through the formation of an active monoacyl boronate species, which can provide electrophilic activation of the carboxylate group through H-bonding. Chapter 2 describes the application of this activation concept to a variety of cycloadditions and nucleophilic conjugate additions involving unsaturated carboxylic acids.

Due to their Lewis acidic character, electron-deficient arylboronic acids exhibit excellent catalytic activity for the activation of hydroxyl groups by facilitating the complete and partial ionization of the C–O bond. This strategy allows the direct activation of hydroxyl groups without recourse to prior activation operations, thus permitting direct functionalizations in a step- and atom-economical manner. The successful application of these catalytic systems to a broad range of classical chemical transformations is also discussed in Chapter 3.

Owing to their remarkable binding ability to 1,2- or 1,3-diol frameworks, benzoboroxoles have the potential to serve as transient masks or organocatalysts to control regioselectivity in the glycosylation of fully unprotected sugars. Chapter 4 describes initial attempts in this important area.

In search of a milder preparation of 2-aryl-1,3,2-aryldioxaborins, which are stable *o*-quinomethane precursors, an efficient $ZrCl_4$ catalyzed *ortho*-hydroxyalkylation of phenols with aldehydes promoted by 3,5-bis(trifluoromethyl)phenylboronic acid was investigated and optimized. This methodology is presented in Chapter 5.

Acknowledgements

Although this thesis bears only my name, the work presented here is certainly a collective effort. I am deeply indebted to a vast group of people without whom this thesis would not have been possible.

First and foremost, I am very thankful to my supervisor, Professor Dennis Hall, for his invaluable guidance, expert advice, unrelenting support and constant inspiration throughout my entire graduate studies. I consider myself very fortunate to work with such a wonderful professor like him. Under his excellent supervision, my research and communication skills have significantly improved. Additionally, I am very appreciative for his willingness to send me to conferences that allowed me broaden my horizons. He has tremendously helped me not only at the scientific level but also on a personal level. He gave me a lot of precious help and advice regarding my future career.

My appreciation and thanks are also offered to the rest of my Supervisory Committee and my PhD Examination Committee members: Professor Todd Lowary, Professor Alex Brown, Professor John Vederas, Professor Cairo Christopher, Professor Gabriel Hanna, Professor Carlos Velázquez and Professor Mark Taylor for their guidance and help throughout the thesis research. I benefited greatly from their diverse opinions and comments in the PhD candidacy examination and each of the annual progress report meetings.

I would like to thank all of the Hall group members, past and present, for their support. I feel so lucky to have worked with so many talented and dedicated people who helped to make my graduate studies an enjoyable journey. I owe special acknowledgements to Ho-Yan Sun and Dr. Jin-Yong Lu for their generous help in proofreading my thesis, scholarship applications and manuscripts. I am also particularly thankful to Jack Chang Hung Lee and Jinyue Ding for their friendship, help, and the stimulating discussions. I would also like to thank all the

collaborators, Dr. Michal Lejkowski, Sina Ghanbari, Shinji Nakamura and Michal Nicpon, for their fruitful cooperation.

Also, my research greatly benefited from the first-class research services at the University of Alberta. I am grateful to the NMR staff (particularly Mark Miskolzie) and all the people in the Spectral Services labs, the Mass Spectrometry Lab, the X-Ray Crystallography Lab, the machine shop, the storeroom and the glass shop. All of them have contributed to my research and made my stay enjoyable in the Department of Chemistry.

I am also thankful for all the help of our secretary, Diane Dowhaniuk, who processed various applications and forms for me over the years. Moreover, my experience as a graduate student would have been incomplete without imparting my knowledge to other students. In this regard, I would like to thank Dr. Norman Gee and Dr. Hayley Wan for their efforts in organizing undergraduate labs. Also, I want to thank Dr. Hayley Wan for nominating me for a graduate teaching award. This recognition definitely will make me feel confident in improving my communication skills.

The research presented in this thesis would not have been possible without the help of various funding agencies. I would like to acknowledge the support of Alberta Ingenuity, the University of Alberta, and Novartis Canada for providing me with graduate scholarships. I am also thankful to the Natural Research and Engineering Research Council (NSERC) Canada, the province of Alberta and the University of Alberta for supporting my research. I am also thankful for the travel award administered by the Faculty of Graduate Studies and Research (FGSR) that allowed me attend the American Chemical Society's 240th national meeting held at Boston.

Last but not least, I would like extend my deepest gratitude to my parents for giving birth to me in the first place and supporting me spiritually throughout my life.

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List of Abbreviations

Ac	Acetyl
ACS	American Chemical Society
Ar	Aryl group
BA	Boronic Acid
BAC	Boronic Acid Catalysis
t-Boc	*tert*-Butyloxycarbonyl
Bn	Benzyl
br	Broad
BSA	Bis(trimethylsilyl)acetamide
n-Bu	Butyl
t-Bu	*tert*-Butyl
calcd	Calculated
CAN	Cerium Ammonium Nitrate
Cbz	Carbobenzyloxy
cm^{-1}	Wavenumbers
COSY	Correlation spectroscopy
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane

DCM	Dichloromethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMM	Dimethoxymethane
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dq	Doublet of quartets
dt	Doublet of triplets
ee	Enantiomeric excess
EI	Electron impact
eq	Equation
equiv	Equivalents
ESI	Electrospray Ionization
Et	Ethyl
Et_2O	Diethyl Ether
EtOAc	Ethyl Acetate

EtOH	Ethanol
Fmoc	9-Fluorenylmethoxycarbonyl
c-Hex	Cyclohexyl
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear single-quantum correlation spectroscopy
IR	Infrared Spectroscopy
LA	Lewis Acid
LDA	Lithium Diisopropylamide
LUMO	Lowest Unoccupied Molecular Orbital
m	Multiplet
Me	Methyl
MeOH	Methanol
MS	Molecular Sieves
NHC	*N*-Heterocyclic Carbene
NIS	*N*-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser effect spectroscopy

Nu	Nucleophile
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PCC	Pyridinium chlorochromate
Ph	Phenyl
pin	Pinacolato
i-Pr	Isopropyl
n-Pr	Propyl
q	Quartet
qd	Quartet of doublets
qq	Quartet of quartets
qt	Quartet of triplets
quint	Quintet
rt	Room Temperature
SOMO	Singly Occupied Molecular Orbital
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
td	Triplet of doublets
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl

THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TMSA	Trimethylsilylacetylene
Ts	*para*-Toluenesulfonyl
TS	Transition State
tt	Triplet of triplets
tq	Triplet of quartets

Note

The same compound is assigned different compound numbers if it is described in different chapters. To avoid any confusion which could arise from the numbering system used in this thesis, the related information is provided as following:

1 **1-20k**, **3-1a**, and **4-1a** correspond to the same compound (phenylboronic acid).

2 **1-2a**, **3-1i**, and **4-1f** correspond to the same compound (3,4,5-trifluorophenylboronic acid).

3 **1-20e, 2-8**, and **3-1c** correspond to the same compound (2-bromophenylboronic acid).

4 **1-20f** and **3-9** correspond to the same compound (2-iodophenylboronic acid).

5 **2-15** and **3-1d** correspond to the same compound (2-nitrophenylboronic acid).

6 **1-20j** and **3-1j** correspond to the same compound (2,3,4,5,6-pentafluorophenylboronic acid).

7 **3-1k** and **4-1g** correspond to the same compound (2,3,4,5-tetrafluorophenylboronic acid).

8 **1-20g** and **2-6** correspond to the same compound (5-methoxy-2-iodophenylboronic acid).

9 **3-1h** and **5-9** correspond to the same compound (3,5-bis(trifluoromethyl)phenylboronic acid).

10 **1-20i** and **4-1d** correspond to the same compound (3,3-dimethylbenzo[*c*][1,2]oxaborol-1(3*H*)-ol)

Chapter 1

Introduction: Catalysis, Organocatalysis, and Boronic Acid

Catalysis

1.1 Overview and importance of catalysis

Catalysis is ubiquitous to life as well as modern society. Catalysts facilitate chemical reactions by lowering the activation energy (**Figure 1-1**) and as such are crucial in the multi-billion dollar production of pharmaceutical drugs and commodity chemicals.[1] Currently, sustainability has received increasing attention in chemistry. The consideration of energy, atom, and step economy and the use of more environmentally friendly reactions is becoming a key focus in industry and research laboratories.[2] Since catalysis lies at the heart of the chemical industry, the discovery and development of sustainable chemistry will rely heavily on advances in the field of catalysis. Therefore, it is logical for scientists to continually seek for new types of catalysts to improve reaction efficiency and to reduce damage of chemical processes to the environment.

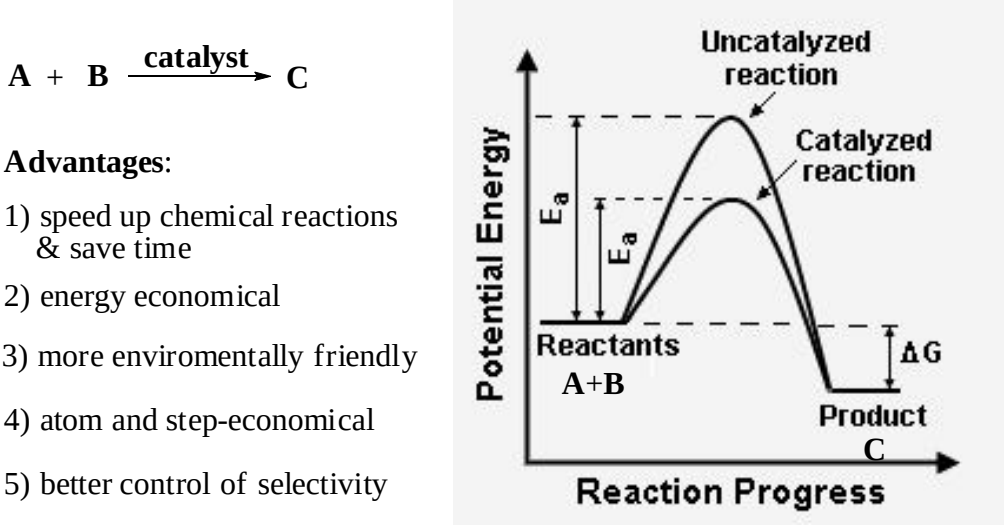


Figure 1-1: Potential energy diagram with/without catalysis

1.2 Overview of organocatalysis

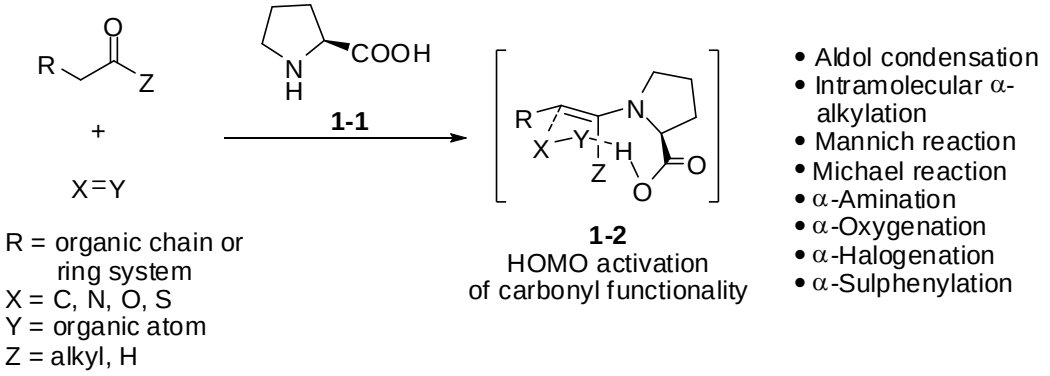
Over the past decade, catalysis of reactions by simple metal-free organic molecules (organocatalysis) has become an important area of research. Although organocatalysis often requires a high catalyst loading and long reaction times, compared with catalysts made of metal complexes, organocatalysts show many special advantages including their lack of sensitivity to moisture and oxygen, their ease of preparation, low toxicity and low cost.[3] All of these advantages are attractive towards the production of pharmaceutical intermediates. Essentially, organocatalysts can be divided into four types based on their modes of activation: Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids.

1.2.1 Lewis base organocatalysts

Lewis base type organocatalysts such as amines, pyridines and carbenes occupy a dominant position in the rapidly developing field of organocatalysis. These catalysts initiate their catalytic cycle by providing electrons to a substrate or a transition state. Usually, organocatalytic processes of this type proceed *via* covalent formation of the catalyst-substrate adduct to form an activated complex.

1.2.1.1 Enamine catalysis

Enamine catalysis allows electrophilic substitution to occur at the α-position of carbonyl compounds. Primary and secondary amines, like proline **1-1**, are

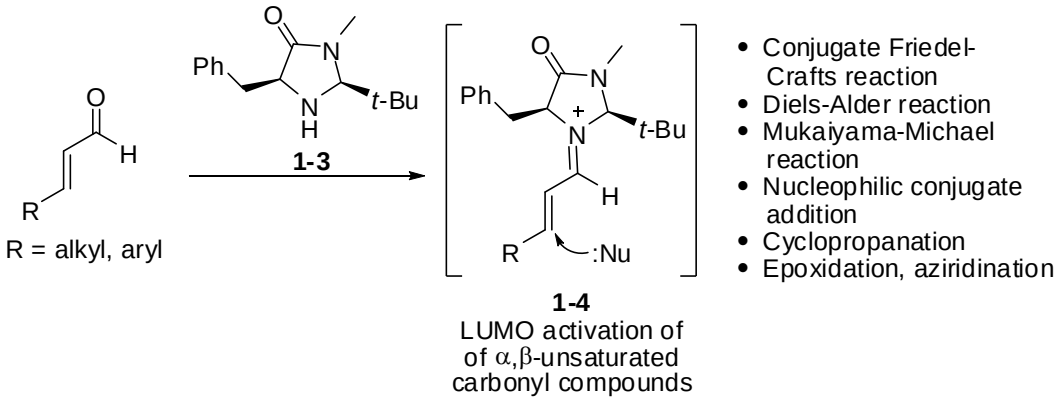


Scheme 1-1: Activation mode for enamine catalysis

typically used as the catalysts and these reactions are said to proceed *via* enamine intermediate **1-2** (**Scheme 1-1**).[4] The key to enamine catalysis is to increase the nucleophilicity of the α-carbon, which is accomplished by transforming the carbonyl moiety to the corresponding enamine. This transformation results in the raising of the HOMO of the nucleophile, thus increasing its nucleophilic character. Mechanistically, enamine catalysis can be regarded as a type of bifunctional catalysis due to the simultaneous engagement of amine-containing catalyst **1-1** with an electrophile through either hydrogen bonding or electrostatic attraction besides the reversible formation of the enamine intermediate (**Scheme 1-1**).[3] Until now, this organocatalytic activation concept has been employed tremendously in a broad range of α-functionalization reactions of carbonyl compounds (**Scheme 1-1**).[4]

1.2.1.2 Iminium catalysis

The catalysis by primary and secondary amines (for example **1-3**, **Scheme 1-2**) of a variety of chemical transformations involving the unsaturated bonds of α,β-unsaturated carbonyl compounds *via* an iminium ion intermediate **1-4** is called iminium catalysis (**Scheme 1-2**).[5] The reversible formation of the iminium ion intermediate **1-4** results in the generation of sufficiently activated species due

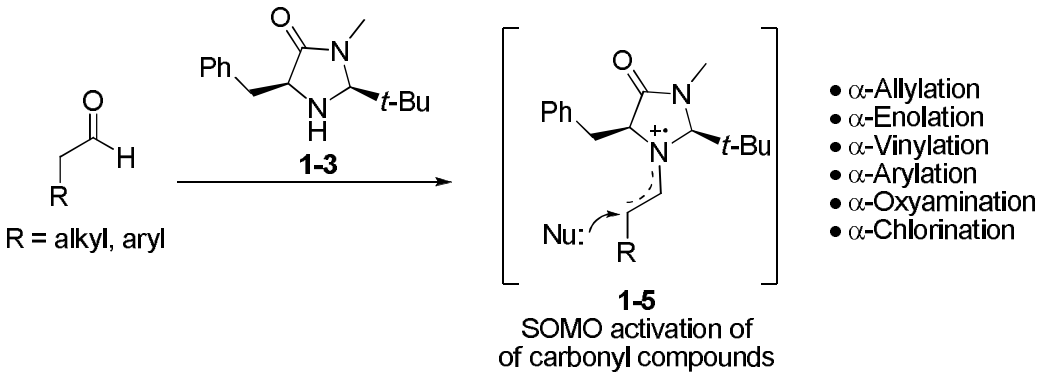


Scheme 1-2: Activation mode for iminium catalysis

to a LUMO-lowering effect, which resembles Lewis acid catalysis *via* carbonyl complexation (**Scheme 1-2**).[5] Currently, this type of catalysis has been a workhorse in the field of carbonyl activation of α,β-unsaturated carbonyl compounds. Examples in which iminium catalysis is widely employed include Diels-Alder reactions and nucleophilic conjugate additions (**Scheme 1-2**).[5]

1.2.1.3 SOMO catalysis

The electron-richness of an enamine allows the formation of a more reactive 3π-enamine intermediate **1-5** under selective one-electron oxidation conditions (**Scheme 1-3**). Taking advantage of this concept, secondary amines (such as **1-3**) together with a suitable one-electron oxidant (such as CAN or TEMPO) or a photoredox catalyst (such as $[Ru(bpy)_3]Cl_2$) can effectively activate the carbonyl functionality to generate a species **1-5**, which is reactive with a wide spectrum of weak nucleophiles (**Scheme 1-3**).[3] This concept has been successfully applied in several α-functionalizations of carbonyl compounds.[3] The SOMO catalysis extends the substrate scope of electrophilic substitution at the α-position of carbonyl compounds and is complementary to enamine catalysis.[3]

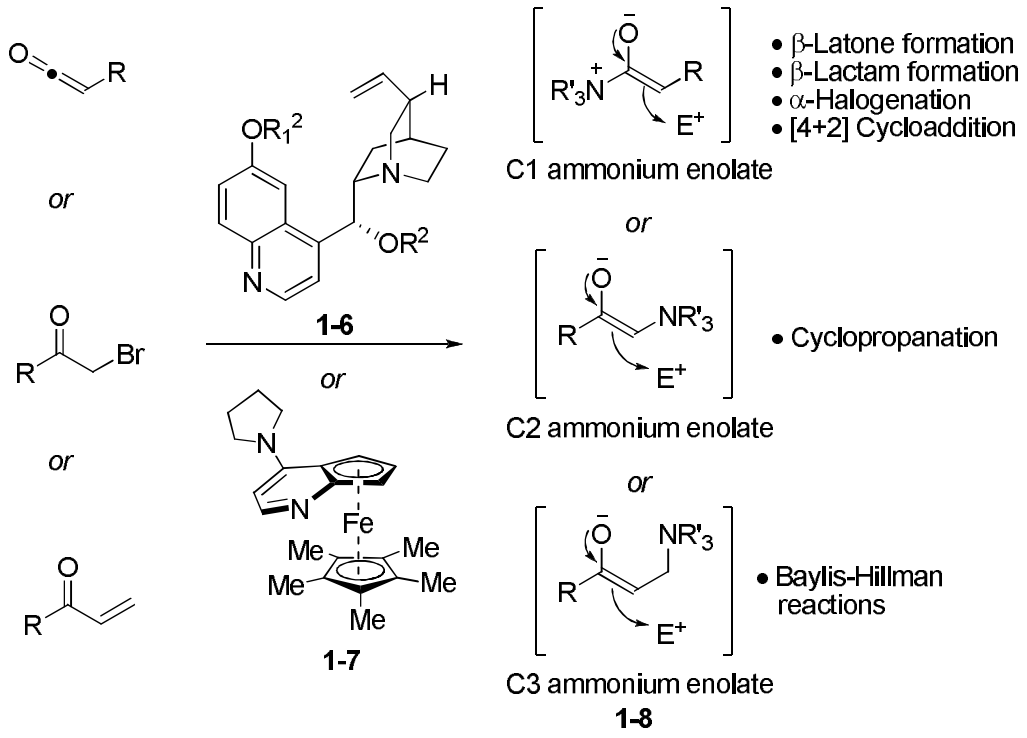


Scheme 1-3: Activation mode for SOMO catalysis

1.2.1.4 Ammonium enolate catalysis

Unlike the enamine catalysis where a primary or secondary amine is used to

activate the carbonyl compounds by increasing the nucleophilicity of the α-carbon *via* an enamine intermediate, ammonium enolate catalysis employs a tertiary amine such as the cinchona alkaloid **1-6** or planar chiral DMAP derivative **1-7** to activate the carbonyl compounds by directly generating enolate equivalents **1-8** (**Scheme 1-4**).[6] Such a catalytic concept makes it possible to perform α-functionalizations of relatively inert carbonyl compounds such as esters, amides and nitriles, which are not attainable with enamine catalysis. Ammonium enolate catalysis has succeeded in yielding a series of enantioselective transformations and exhibits a high potential for organic synthesis.

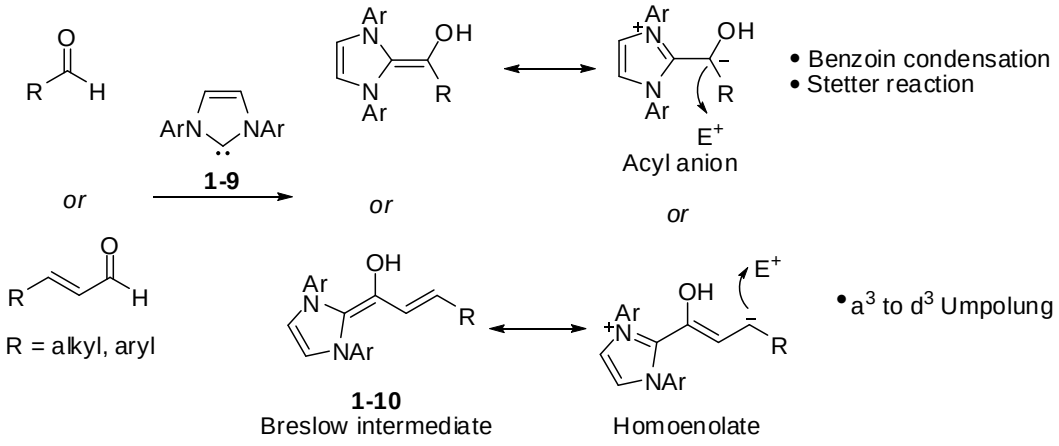


Scheme 1-4: Activation mode for ammonium enolate catalysis

1.2.1.5 *N*-Heterocyclic carbene catalysis

N-Heterocyclic carbene (NHC) catalysis has received considerable attention due to its ability to invert the classical reactivity of aldehydes (**Scheme 1-5**).[7] In NHC

catalysis, an NHC such as **1-9** is employed as a catalyst to achieve the umpolung reactivity of aldehydes by generating the corresponding acyl anions or homoenolate equivalents *via* Breslow intermediates **1-10** (**Scheme 1-5**).[7] This unique activation mode has enabled a great variety of organic reactions, allowing new bond formation in an unpolung manner that is extremely difficult to access *via* the normal reactivity of aldehydes.[7] Therefore, NHC catalysis opens up new synthetic pathways for the construction of complex molecules.



Scheme 1-5: Activation mode for NHC catalysis

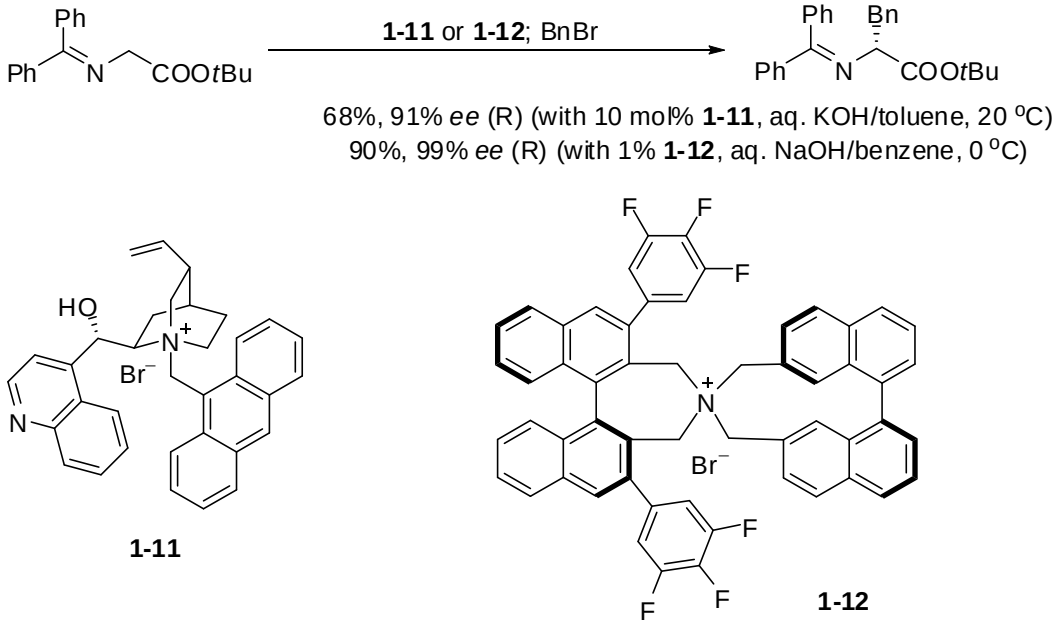
1.2.2 Lewis acid organocatalysts

Compared with heavily employed Lewis base organocatalysts, Lewis acid organocatalysts are rarely used. Based on List's definition,[8] phase transfer catalysts and ketone catalysts for the epoxidation of olefins belong to this category, as they both activate the nucleophilic substrate by removing electrons from the substrate.

1.2.2.1 Phase transfer catalysis

Phase transfer catalysis refers to the acceleration of a reaction by facilitating the transfer of a reactant from one phase into another phase where reaction occurs

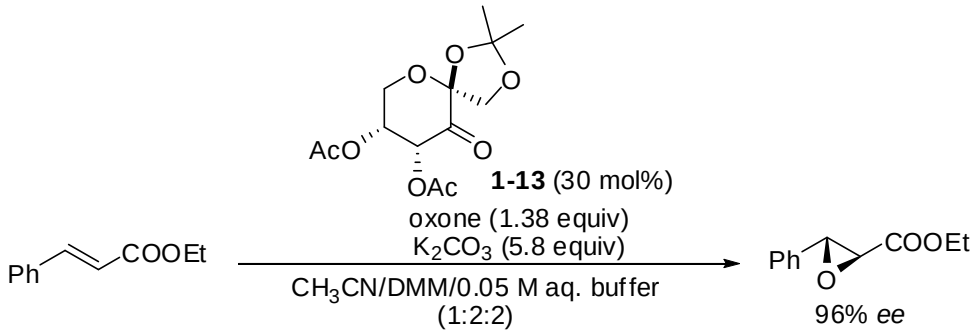
upon the addition of the phase transfer catalyst. A widely used example of this catalytic system is the enantioselective preparation of α-amino acids through *N*-anthracenyl cinchonidium salts (for example **1-11**) catalyzed asymmetric α-alkylation of protected glycine derivatives (**Scheme 1-6**).[9] Subsequently, a highly efficient and enantioselective C_2-symmetric chiral spiro ammonium salt such as **1-12** was developed. This type of catalyst was successfully applied to promoting the enantioselective α-alkylation of protected glycine derivatives as well as other synthetically useful reactions.[9]



Scheme 1-6: Phase transfer catalysis

1.2.2.2 Ketone catalyzed epoxidation of olefins

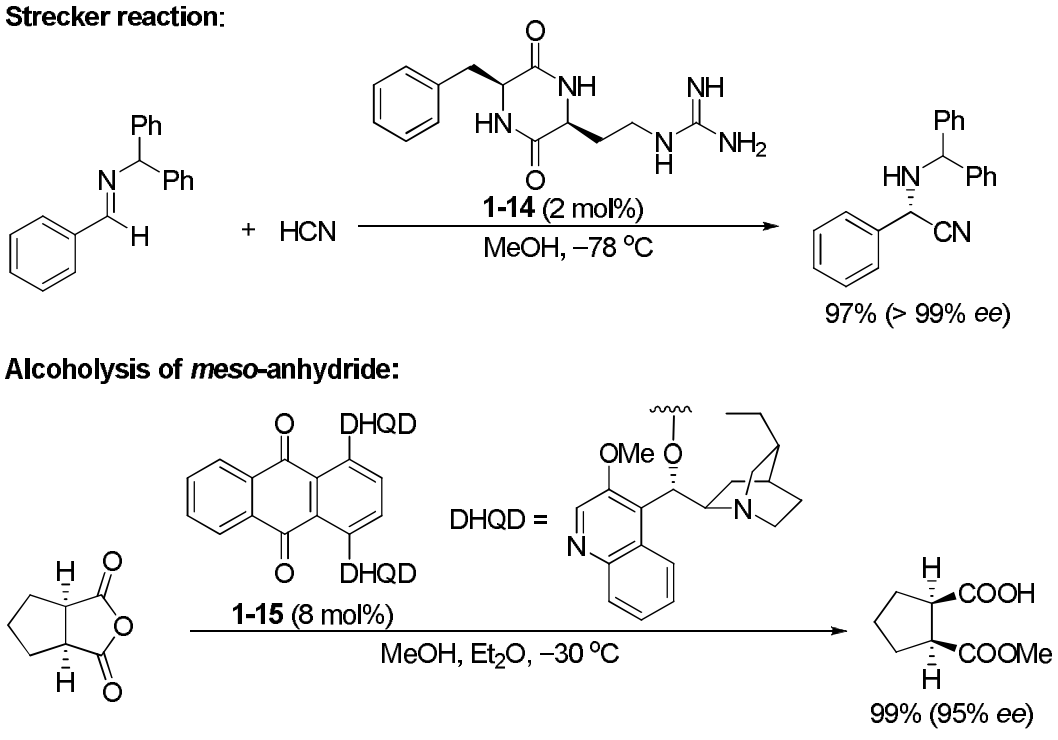
Ketone catalyzed epoxidation of olefins represents another important class of Lewis acid organocatalysis.[10] A well known example is the Shi epoxidation where a D-fructose derived ketone catalyst **1-13** was elegantly developed to react *in situ* with oxone to generate chiral dioxiranes that promote the enantioselective epoxidation of stilbenes, α,β-unsaturated esters, and terminal olefins (**Scheme 1-7**).[10]



Scheme 1-7: Ketone catalyzed epoxidation of olefins

1.2.3 Brønsted base organocatalysts

In this field of organocatalysis, a Brønsted base such as an amine is employed to activate nucleophilic substrates *via* hydrogen bonding. A typical example is the asymmetric Strecker reaction of various *N*-benzhydryl imines catalyzed by cyclopeptide **1-14** for the preparation of α-aminonitriles (**Scheme 1-8**).[8] In this case, catalyst **1-14** acts as a base to abstract a proton from hydrogen cyanide to



Scheme 1-8: Brønsted base organocatalysts

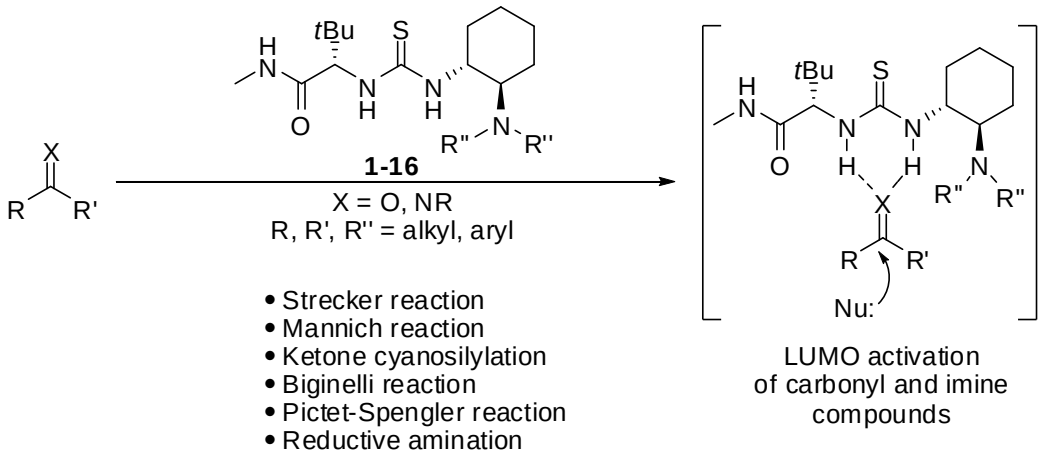
generate a cyanide ion, which is nucleophilic enough to add to the imine coordinated with the catalyst **1-14** through hydrogen bonding.[8] In a similar manner, a modified cinchona alkaloid **1-15** can serve as an efficient catalyst to activate the alcohol *via* hydrogen bonding for nucleophilic attack on the anhydride in a process that achieves the desymmetrization of cyclic *meso*-anhydrides (Scheme 1-8).[11]

1.2.4 Brønsted acid organocatalysts

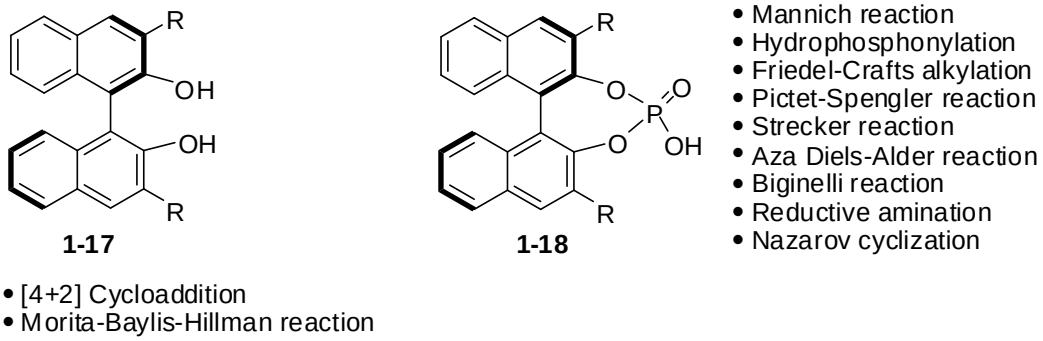
Since the late 1990s, Brønsted acid organocatalysis has grown significantly. H-bonding catalysis and counterion catalysis constitute two major areas within this research field.

1.2.4.1 H-bonding catalysis

Although H-bonding catalysts have been known for a long time, until recently the application of chiral Brønsted acids has received little attention.[12] In this type of catalytic system, a Brønsted acid such as thiourea **1-16**, chiral diol **1-17** or binol-derived phosphoric acid **1-18** is used as a hydrogen donor to activate carbonyl and imine compounds *via* hydrogen bonding in a similar manner to Lewis acid activation (**Scheme 1-9**).[12] This activation mode has been successfully applied in many synthetically important organic reactions and has become the foundation of a large and dynamic area of research.[12]



Other popular H-bonding organocatalysts:

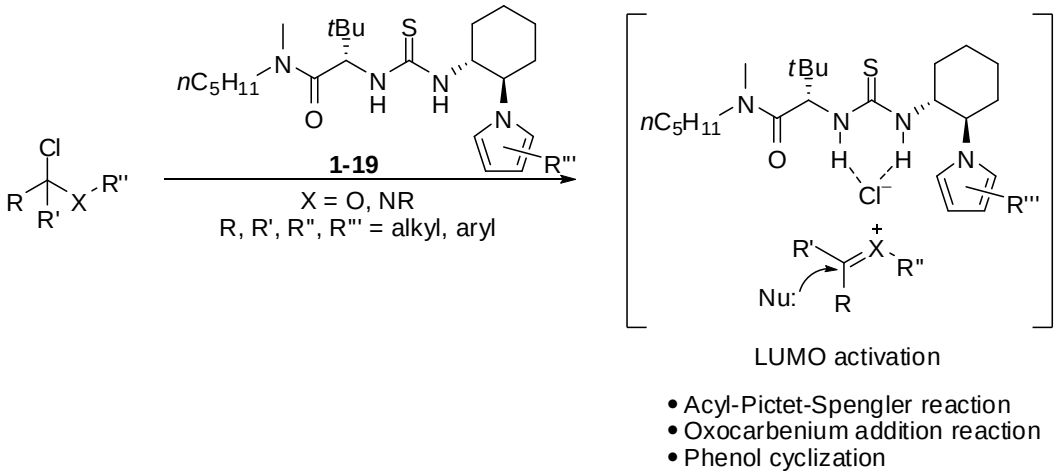


Scheme 1-9: Activation mode for hydrogen bonding catalysis

1.2.4.2 Counterion catalysis

Counterion catalysis is a new and emerging area in organocatalysis. In this conceptually novel catalytic system, a Brønsted acid such as thiourea **1-19** or binol-derived phosphoric acid **1-18** was employed to completely ionize the C–Cl or C–O bond in electrophiles, triggering nucleophilic attack in an S_N1 or S_N1' fashion *via* iminium ion, oxocarbenium, or carbocation intermediates (**Scheme 1-10**).[3,13] As opposed to classical asymmetric organocatalysis where the stereochemical information is transferred from the catalyst to the substrate through covalent bonds, counterion catalysis can achieve stereochemical fidelity

through space.[13] Such an activation mode offers a possible way of controlling stereochemistry in organic reactions involving iminium ion, oxocarbenium, or carbocation intermediate. Therefore, counterion catalysis has the potential to solve many longstanding problems in asymmetric catalysis.



Scheme 1-10: Activation mode for counterion catalysis

1.3 Overview of boronic acid catalysis (BAC)

As shown in Section 1.2, current strategies in organocatalysis mainly focus on developing Lewis base and Brønsted acid catalysts for activating ketone, aldehyde, and imine functionalities. Very few strategies, however, have been exploited for the activation of carboxylic acids and alcohols. In this regard, diversely substituted arylboronic acids **1-20** are emerging as a promising new class of organocatalysts due to their Lewis acidity, which can be easily modulated by their substitution pattern (R) (**Figure 1-2**). Furthermore, *ortho*-substituted arylboronic acids can be regarded as bifunctional catalysts. The boronic acid functionality can form temporary covalent bonds with alcohols, carboxylic acids, or amines that are readily cleaved in subsequent steps. These covalent intermediates can activate the alcohol or carboxylic acid for a reaction. In this context, the *ortho*-substituent (X)

can further activate the substrate, or serve as a handle or template for directing reagents *via* cooperative effects. Recent progress toward boronic acid catalyzed chemical transformations involving the activation of carboxylic acids, alcohols, diols, or carbonyl groups will be reviewed in this section.[14]

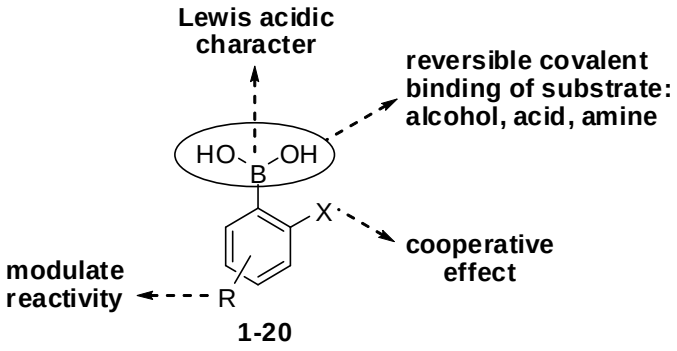
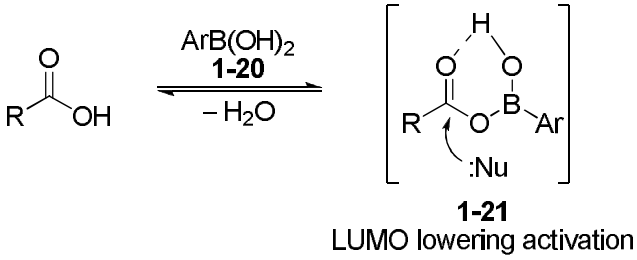


Figure 1-2: Arylboronic acids as organocatalysts

1.3.1 Activation of carboxylic acids

Arylboronic acids **1-20** have the ability to form reversible covalent bonds with carboxylic acid to generate an active monoacyl boronate species **1-21**, which could provide electrophilic activation of the carboxylate group through internal H-bonding (**Scheme 1-11**). Recently, such a novel activation mode has been successfully applied in several important organic reactions.

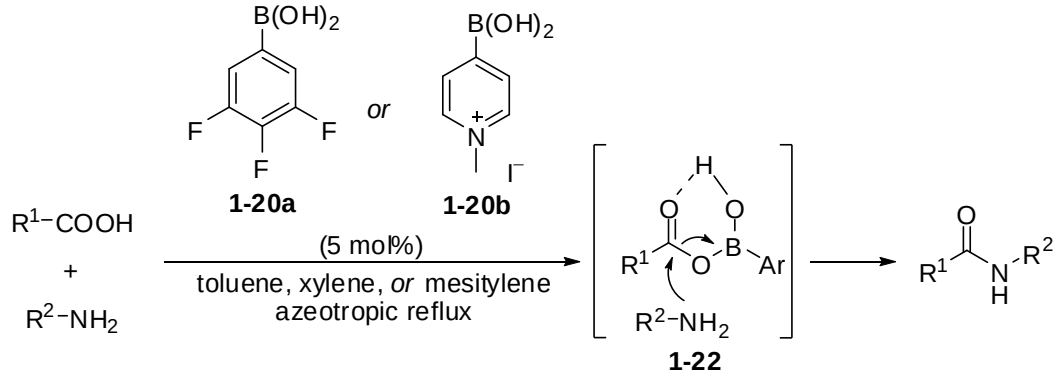


Scheme 1-11: Activation of carboxylic acids with boronic acid catalysis

1.3.1.1 Direct amidation between carboxylic acids and amines

The first and most popular example using carboxylic acid activation is the

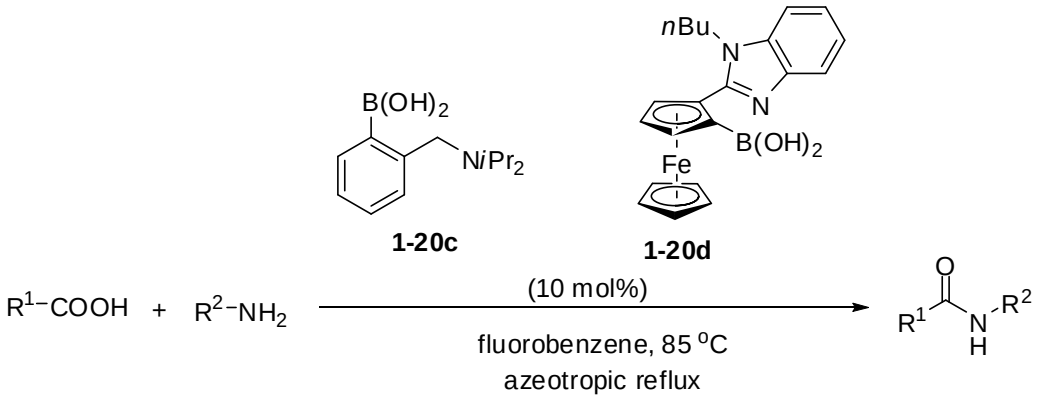
arylboronic acid catalyzed direct amide formation between carboxylic acids and amines.[15] In 1996, Yamamoto and co-workers described that electron-deficient polyfluorinated phenylboronic acids, such as 3,4,5-trifluorophenylboronic acid **1-20a** exhibited catalytic activity for the amidation between carboxylic acids and amines (**Scheme 1-12**) in non-polar solvents.[15c] Later, they discovered that electron-deficient pyridiniumboronic acid **1-20b** demonstrated better efficiency than **1-20a** for catalyzing direct amide formation.[15d] In both cases, the reaction needs to be executed under azeotropic reflux conditions (110–165 ^{o}C). The superior catalytic activity of electron-deficient arylboronic acids is most likely due to the enhanced Lewis acidity of the boron atom, which could facilitate the formation of the proposed monoacyl boronate intermediate **1-22** or nucleophilic attack in **1-22**.



Scheme 1-12: Direct amidation catalyzed by Yamamoto's electron-poor arylboronic acid catalysts

More recently, Whiting and co-workers demonstrated that a bifunctional *ortho*-amine substituted arylboronic acid, 2-diisopropylaminomethyl-phenyl boronic acid **1-20c**, showed higher catalytic activity, permitting the same amidation reaction to proceed at a lower reaction temperature (around 85 ^{o}C) (**Scheme 1-13**).[15e] They claimed that this catalyst **1-20c** operates as a bifunctional catalyst where the *ortho*-amine substituent might help deprotonate the ammonium

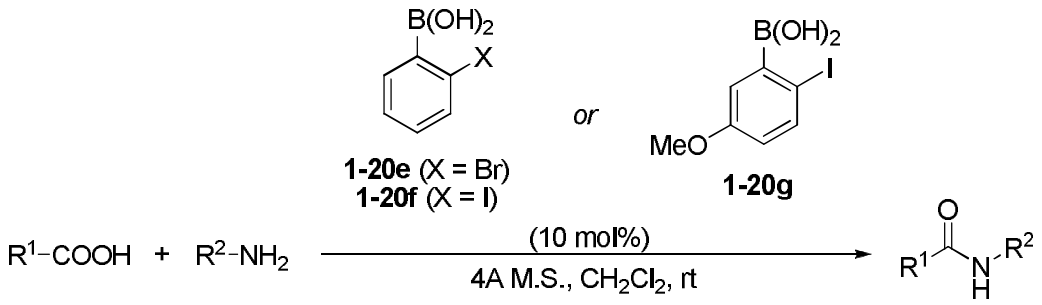
to regenerate the amine. In addition, this catalyst could potentially form H-bonding with both the amine and carboxylic acid, consequently increasing the proximity of the starting materials with the boronic acid catalyst.[15e] Soon afterwards, the same group designed a chiral ferrocene-based bifunctional *ortho*-amine substituted arylboronic acid **1-20d** for the asymmetric direct amidation *via* kinetic amine resolution of racemic α-substituted benzylamines with achiral carboxylic acids (**Scheme 1-13**).[15f] Although low yields and enantioselectivity (up to 41% ee) were obtained because of the competing *ipso*-protodeboronation reaction of the catalyst **1-20d**, it represents the first example of asymmetric direct amidation reactions and opens up a new direction for kinetic amine resolution.



Scheme 1-13: Whiting's bifunctional arylboronic acid catalysts for direct amidation

Lately, our group discovered that *ortho*-halo phenylboronic acids **1-20e** and **1-20f** possess superior catalytic activity for direct amidation of carboxylic acids and amines at room temperature in the presence of molecular sieves (**Scheme 1-14**).[15g] Catalyst **1-20f** with an iodo substituent at the *ortho* position showed better catalytic efficiency than catalyst **1-20e** with a bromo group under the same reaction conditions. After carefully optimizing the arene core of the

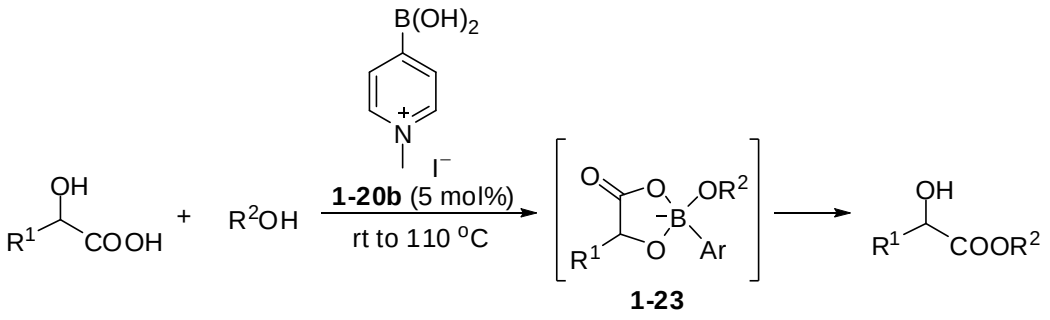
ortho-haloarylboronic acid catalyst with regards to the steric and electronic effects of ring substitution, 5-methoxy-2-iodophenylboronic acid **1-20g** (**Scheme 1-14**) was identified as the best catalyst.[15h] Although the detailed mechanism is uncertain at present, DFT calculations and preliminary experiments suggest that the catalytic activity of *ortho*-haloarylboronic acids results from the Lewis basic character of the halogen atom, which would be implicated as a H-bonding acceptor facilitating the elimination of water from the ortho-aminal intermediate that was proposed as the rate-determining step.[15h, 15i] This method provided a mild means of preparing amides.



Scheme 1-14: Our group's *ortho*-haloarylboronic acid catalysts for direct amidation

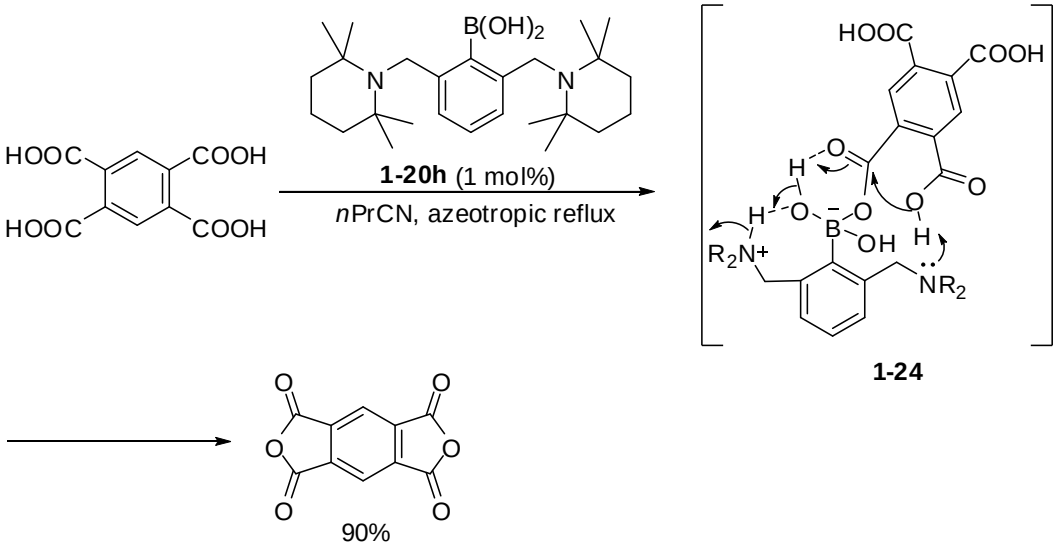
1.3.1.2 Other chemical transformations

The electron-deficient pyridiniumboronic acid **1-20b** was also found to possess the ability to activate the carboxylic acid in polar solvents and as such it was employed to catalyze the esterification of hydroxycarboxylic acids with excess alcohols as the solvent (**Scheme 1-15**).[15d] An alcohol functionality at the α- or β-position of the carboxylic acid is essential for this unexpected reactivity of α-hydroxycarboxylic acids with alcohols because it can participate in the formation of thermally stable 2-alkoxy-2-(*N*-methylpyridinium-4-yl)-4-oxo-1,3,2-dioxaborolan-2-uides **1-23** as a proposed active anionic intermediate.[15d,16] Alternatively, boric acid can catalyze the same reaction with stoichiometric amounts of alcohols.[15d]



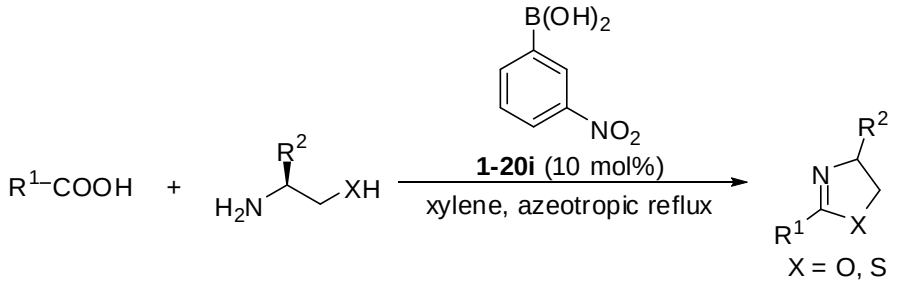
Scheme 1-15: Esterification of hydroxycarboxylic acids catalyzed by 1-20b

In light of the ability of Whiting's bifunctional *ortho*-aminomethyl substituted arylboronic acid **1-20c** in activating carboxylic acids, Ishihara and co-workers developed a similar *ortho*-aminomethyl substituted arylboronic acid **1-20h** which could effectively catalyze the dehydrative intramolecular condensation of dicarboxylic acids at significantly milder temperatures compared to the thermal variant (**Scheme 1-16**).[17] The authors claimed that this catalyst works as a bifunctional catalyst, with the amine substituent serving as a Brønsted base to deprotonate the carboxylic acid, thus increasing the nucleophilicity of the



Scheme 1-16: Dehydrative intramolecular condensation of dicarboxylic acids catalyzed by 1-20h

carboxylate functionality in the proposed monoacyl boronate intermediate **1-24** (**Scheme 1-16**).[17] Moreover, the second protonated amine substituent could act as a Brønsted acid to further activate the carbonyl group through two consecutive hydrogen bonding interactions.[17]

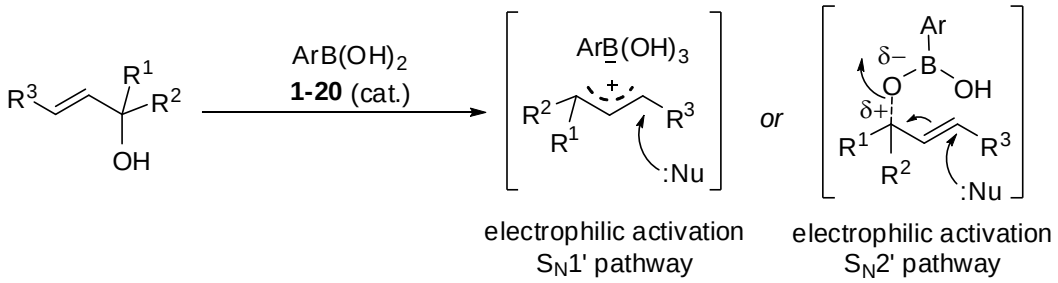


Scheme 1-17: Tandem condensation-cyclodehydration of carboxylic acids with amino alcohols or amino thiols catalyzed by 1-20i

Taking advantage of Yamamoto's direct amidation protocol, Wipf and co-workers developed a method for the preparation of a combinatorial library of biologically active oxazolines and thiazolines (**Scheme 1-17**).[18] In this methodology, electron-deficient 3-nitrophenylboronic acid **1-20i** was employed as a catalyst to promote a tandem condensation-cyclodehydration of carboxylic acids with amino alcohols or amino thiols.[18]

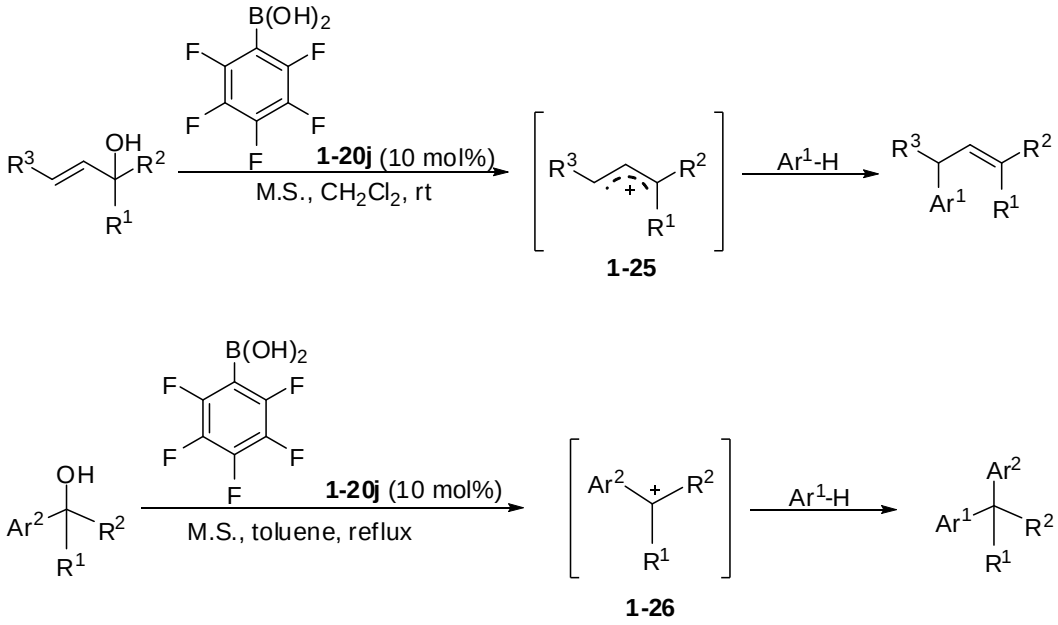
1.3.2 Activation of alcohols

Due to their Lewis acidity, arylboronic acids **1-20** could provide electrophilic activation of the hydroxyl group of alcohols by facilitating the complete or partial ionization of the C–O bond (**Scheme 1-18**). Such a concept for alcohol activation could be highly beneficial for chemical transformations involving carbocations as the intermediates.



Scheme 1-18: Activation of allylic alcohols with boronic acid catalysis

Recently, McCubbin and co-workers reported that a highly Lewis acidic boronic acid, pentafluorophenylboronic acid **1-20j**, showed excellent catalytic activity for regioselective Friedel-Crafts reactions of allylic alcohols with electron-rich arenes or heteroarenes at room temperature in the presence of molecular sieves (**Scheme 1-19**).[19a] A diverse set of highly substituted arenes and heteroarenes can be prepared in this manner, and the reaction was presumed to proceed through an S_N1' pathway *via* the allylic carbocation **1-25** with the regioselectivity being



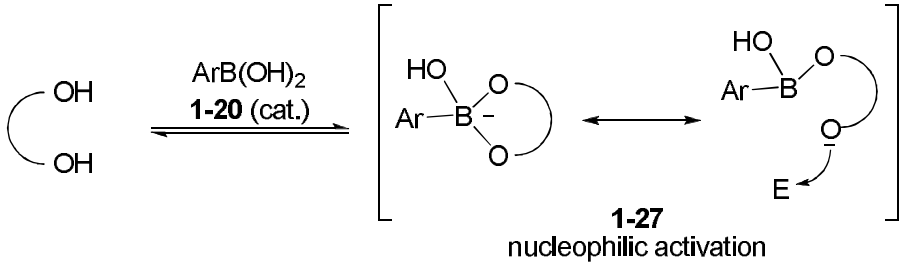
Ar^1 = electron-rich arenes; M.S. = molecular sieves

Scheme 1-19: Friedel-Crafts reactions of allylic or benzylic alcohols with electron-rich aromatics catalyzed by 1-20j

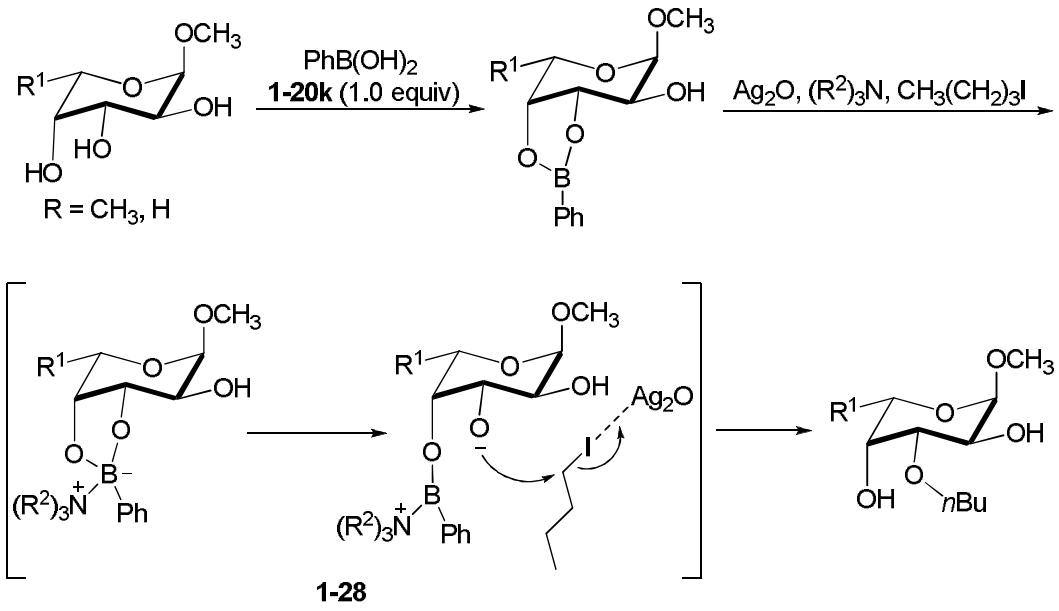
controlled by steric effects. Benzylic alcohols were also suitable substrates for this methodology, however, higher reaction temperatures were needed (**Scheme 1-19**).[19b] Similar benzylic carbocation intermediates **1-26** were proposed. Later, the same group extended this catalytic system to propargylic alcohol substrates, developing a highly effective and selective methodology for propargylation and allenylation of electron-rich aromatics.[19c] An S_N1 or S_N1' pathway involving an *in situ* generated carbocation intermediate was suggested by the authors.[19c] Although the substrate scope is only limited to extremely electron-rich aromatic compounds in these methodologies, this work represents a milder and more environmentally friendly means for alcohol activation compared to existing strategies using Lewis acids, Brønsted acids and transition-metal catalysts.

1.3.3 Activation of diols

Boronic acids can form tetra-coordinated cyclic boronates **1-27** with diols or sugars and the resulting boronates are susceptible to hydrolysis. The formation of tetra-coordinated cyclic boronates **1-27** might alter the nucleophilicity of two hydroxyl groups in 1,2- or 1,3-diol frameworks, biasing their potential toward the electrophilic attack (**Scheme 1-20**). Such an activation concept could become an efficient tool for controlling the regioselectivity in substrates bearing multiple hydroxyl groups.



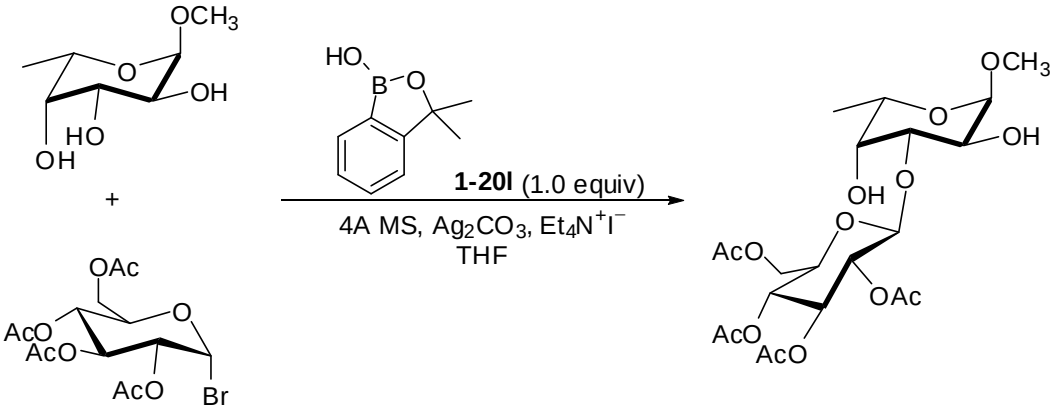
Scheme 1-20: Nucleophilic activation of diol systems with boronic acid catalysis



Scheme 1-21: Regioselective alkylation of methyl fucopyranoside mediated by 1-20k

In 1997, Aoyama and co-workers, for the first time, discovered that phenylboronic acid **1-20k** could serve as a stoichiometric mediator to promote the regioselective alkylation of methyl fucopyranoside *via* a proposed tetra-coordinated boronate intermediate **1-28** (**Scheme 1-21**).[20a] The amine was an essential additive to facilitate the formation of tetra-coordinated boronate **1-28** which could selectively lead to the 3-O^- nucleophile. This regioselectivity was believed to result from the difference in steric environment between the 3-O^- nucleophile and the 4-O^- nucleophile. Furthermore, the 2-OH might provide additional stabilization of the 3-O^- nucleophilic anion through hydrogen bonding to further enhance the regioselectivity.[20a] Soon afterwards, this effective system was put to use in the regiospecific glycosylation of unprotected sugars (**Scheme 1-22**).[20b] The boroxole **1-20l** was identified as an efficient stoichiometric promoter which allows selective and direct glycosylation at the 3- or 6-positions of a variety of carbohydrates. Although this protocol could be a powerful tool for the preparation of biologically important oligosaccharides, the necessity for a stoichiometric amount of boronic

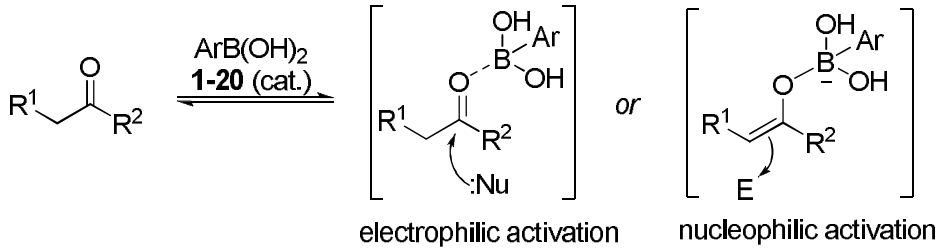
acid catalyst is a significant disadvantage. Recently, this shortcoming was elegantly addressed by Taylor and co-workers with the use of borinic acids, which promote the same regioselective glycosylation and other related reactions in a catalytic manner.[21] DFT calculations and mechanistic studies hinted that the borinic acid activates the diols by enhancing the nucleophilicity of 3-O *via* a tetra-coordinated 2,3- or 3,4-borinate intermediate, thus exhibiting remarkable regioselectivity at the 3-O position in the corresponding chemical transformations.[21]



Scheme 1-22: Regiospecific glycosylation of unprotected sugars mediated by 1-20l

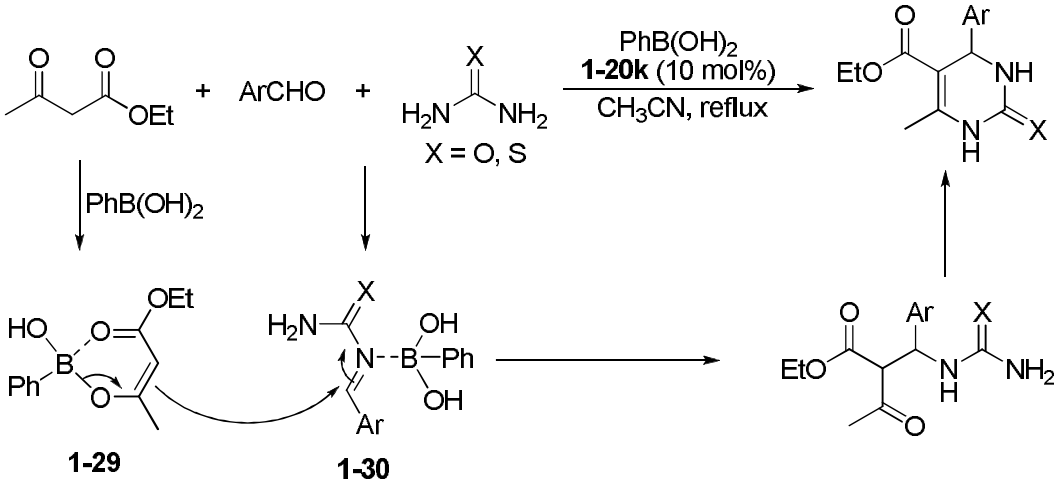
1.3.4 Activation of carbonyl groups

Due to their Lewis acidity, arylboronic acids can activate carbonyl compounds by increasing the electrophilicity of the carbonyl carbon or the nucleophilicity of the α-carbon in a similar manner to other Lewis acids (**Scheme 1-23**). Lately, several interesting methodologies using this carbonyl activation concept were developed.



Scheme 1-23: Activation of carbonyl groups with boronic acid catalysis

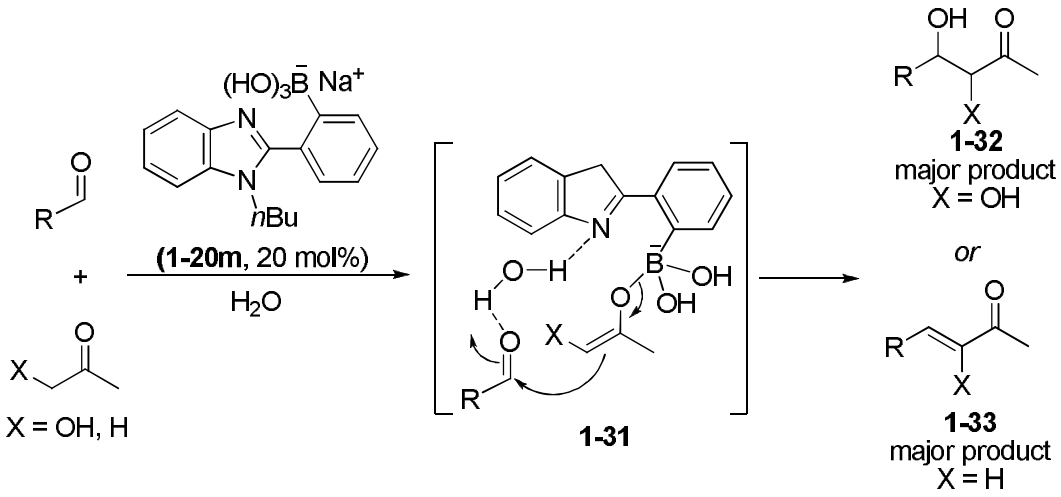
In 2006, Carboni and co-workers found that phenylboronic acid **1-20k** could act as a catalyst to accelerate a one-pot three component Biginelli synthesis of 3,4-hydropyrimidinone (**Scheme 1-24**).[22a] The boronic acid was proposed to serve a dual function in this process as it could not only increase the nucleophilicity of ethyl acetoacetate through the formation of the boron enolate **1-29**, but it could also enhance the electrophilicity of the acylimine intermediate **1-30** through a boron-nitrogen coordination (**Scheme 1-24**).[22a] This concept of carbonyl activation was also applied by the same group for other three-component reactions for the preparation of 1,4-dihydropyridines and tetrahydrobenzo[*b*]pyrans.[22b,22c]



Scheme 1-24: Biginelli reaction catalyzed by 1-20k

In 2008, Whiting and co-workers reported that *N*-butyl-1-benzimidazole-2-phenyl

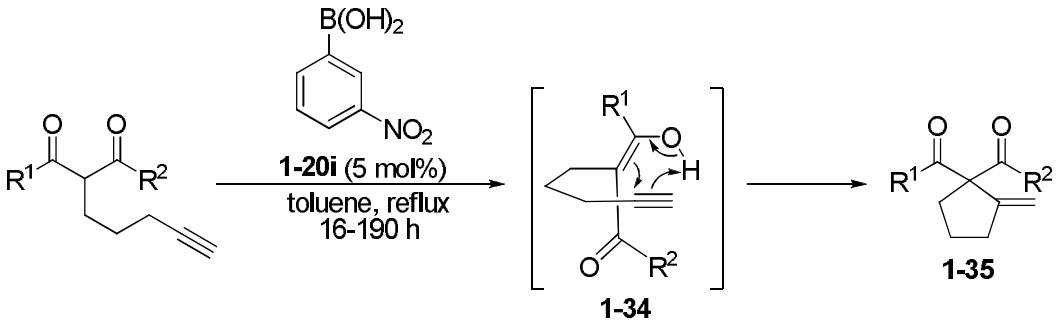
boronic acid hydroxide complex **1-20m** exhibits excellent catalytic activity for promoting the aldol condensation and aldol addition between hydroxyacetone or acetone, and different aldehydes in water (**Scheme 1-25**).[23] The superior catalytic activity of **1-20m** is believed to result from cooperative interactions between the boronate complex and the imidazole function in the proposed transition state **1-31**. Boronic acid hydroxide complex could induce the formation of a more nucleophilic boron enolate and the imidazole functionality could activate the aldehyde through three consecutive hydrogen bonding interactions (**Scheme 1-25**).[23] Aldol addition products **1-32** predominated with hydroxyacetone, whereas aldol condensation products **1-33** were obtained as the major product with acetone (**Scheme 1-25**).[23]



Scheme 1-25: Aldol reaction and condensation catalyzed by 1-20m

More recently, Dixon and co-workers found that 3-nitrophenylboronic acid **1-20i** can efficiently promote the enolization of 1,3-dicarbonyl compounds. In refluxing toluene, the generated enol **1-34** subsequently underwent a concerted ene carbocyclization with an alkyne substituent to afford carbocyclic products **1-35** in good yields (**Scheme 1-26**).[24] In addition, boronic acids are known to activate the epoxide functionality in a similar fashion to other Lewis acids, triggering a

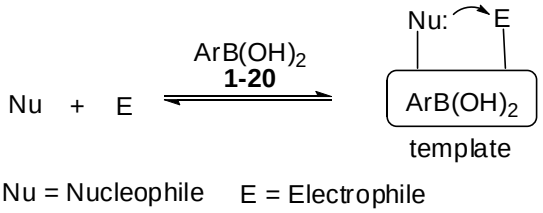
tandem semi-pinacol rearrangement-alkylation of α-epoxy alcohols.[25]



Scheme 1-26: Ene carbocyclization of alkyne-substituted dicarbonyl compounds catalyzed by 1-20i

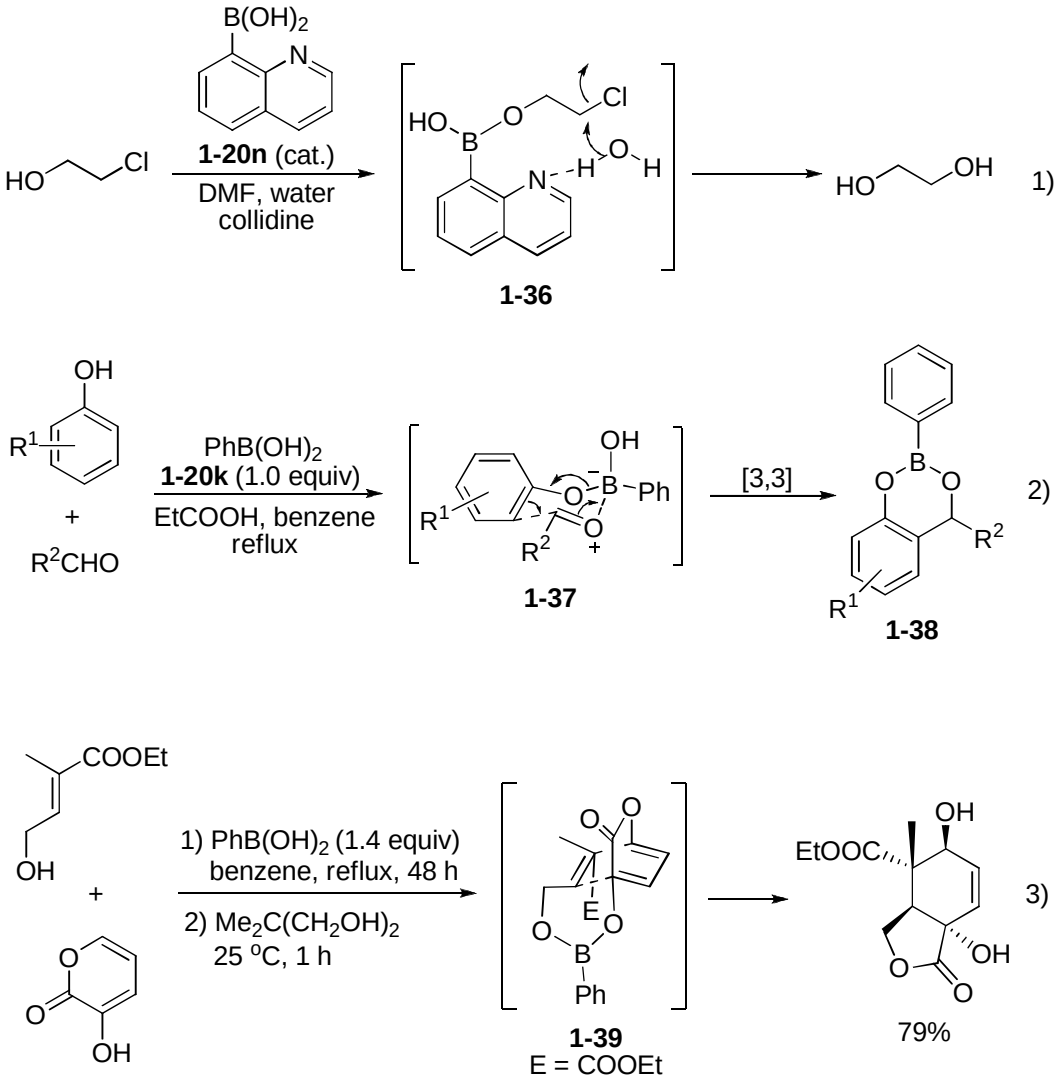
1.3.5 Use of arylboronic acids as reaction templates

Arylboronic acids **1-20** can form covalent bonds with alcohols in a reversible manner and thus could provide a template upon which the reactants are brought together and properly oriented in order to accelerate the reactions (**Scheme 1-27**). Faster reactions and unique selectivity are the main benefits provided by template-accelerated synthetic strategies.[26-30]



Scheme 1-27: Boronic acid as reaction template

The use of arylboronic acids as templates to facilitate chemical transformations was demonstrated several decades ago. In 1963, Letsinger and co-workers found that quinolin-8-ylboronic acid **1-20n** could promote the hydrolysis and alcoholysis of chloro-substituted alcohols in the presence of collidine to afford diols as the products (eq 1, **Scheme 1-28**).[26] The boronic acid functionality serves as a template to bind the alcohol substrate through covalent hemiester **1-36**

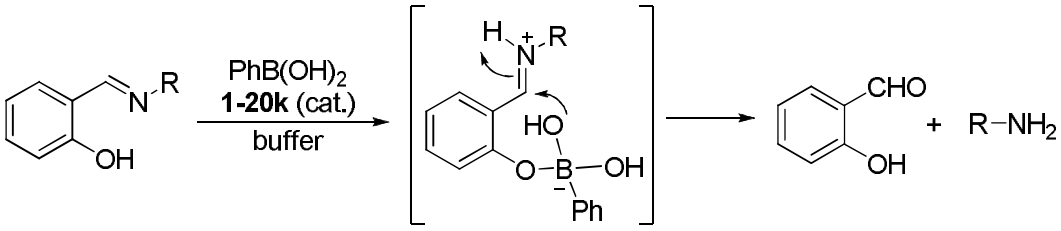


Scheme 1-28: Examples of applications of boronic acids as template

formation and the nitrogen atom of quinolin-8-ylboronic acid assists chloride displacement presumably through a cooperative general base effect.[26] Although this work has no practical value since the product is much easier to prepare than the starting material, it is the first example of boronic acid catalysis and represents a milestone in this class of organocatalysis. Later, Nagata and co-workers claimed that phenylboronic acid **1-20k** can be employed as a stoichiometric reaction promoter to accelerate the *ortho*-hydroxyalkylation of phenols and aldehydes by holding the two reactants in place, leading to the formation of

2-aryl-4*H*-1,3,2-benzodioxaborins **1-38**, which are a useful class of stable *ortho*-quinone methide precursors (eq 2, **Scheme 1-28**).[27] This process is presumed to involve the formation of intermediate **1-37**, which then undergoes a [3,3]-sigmatropic rearrangement to furnish the desired product **1-38**.[27] A similar templating strategy was also used by Narasaka and co-workers to achieve Diels-Alder cycloadditions with inverted regioselectivity (eq 3, **Scheme 1-28**).[28a] This unusual regioselectivity was believed to arise from transition state **1-39** where phenylboronic acid **1-20k** serves as a template to hold a diene and a dienophile in the desired orientation (eq 3, **Scheme 1-28**).[28a] Soon afterwards, this method was successfully applied in the synthesis of a key intermediate in the total synthesis of taxol by Nicolaou and co-workers.[28b]

In 1991, Philipp and co-workers discovered that phenylboronic acid **1-20k** could accelerate the hydrolysis of salicylaldehyde imines (**Scheme 1-29**).[29] In this case, phenylboronic acid **1-20k** not only functions as a template to bind the starting material but also serves as a hydroxide source for the nucleophilic attack of the imine group.[29] Phenylboronic acid **1-20k** was also reported to act in such a dual role for 1,3-transpositions of allylic alcohols,[30a] Meyer-Schuster rearrangement of propargylic alcohols,[30b,30c] and asymmetric oxo-Michael additions.[30d]



Scheme 1-29: Hydrolysis of salicylaldehyde imines catalyzed by 1-20k

1.4 Thesis objectives

Arylboronic acids can activate carboxylic acids, alcohols and diols through reversible formation of boronate intermediates without recourse to prior activation and protection operations, thus allowing direct functionalizations in a step- and atom-economical fashion. Such discoveries have resulted in applications of boronic acid catalysis that have advanced the development of more efficient and milder protocols for existing transformations. The goal of this thesis is to develop new and more powerful boronic acid-based catalytic systems for the activation of carboxylic acids, alcohols and diols ultimately leading to more effective and environmentally friendly ways of promoting synthetically useful organic reactions.

In light of the success of *ortho*-substituted boronic acids for catalytic activation of carboxylic acids, my project started by extending this concept to the activation of unsaturated carboxylic acids. In particular, Chapter 2 discusses our findings towards applying this activation concept to a variety of cycloadditions and nucleophilic conjugate additions involving unsaturated carboxylic acids. The preliminary mechanism of this activation mode was investigated and these results are presented in Chapter 2.

Inspired by a recent discovery that electron-deficient arylboronic acids can activate allylic alcohols by the ionization of the C–O bond in an S_N1' manner *via* a carbocation intermediate, several more Lewis acidic arylboronic acid catalysts were designed and found to exhibit superior reactivity over previously reported catalysts. The applications of these catalytic systems to a broad range of classical chemical transformations are discussed in Chapter 3.

Boroxoles can form tetra-coordinated cyclic boronates with diols or sugars and the resulting boronates are susceptible to hydrolysis. Therefore, boroxoles have

the potential to serve as transient masks, used stoichiometrically or even catalytically, to control the regioselectivity in the glycosylation of fully unprotected sugars. Chapter 4 describes our initial attempts in this area.

In the pursuit of greener chemistry using arylboronic acids as reaction templates, an efficient $ZrCl_4$ catalyzed *ortho*-hydroxyalkylation of phenols with aldehydes promoted by 3,5-bis(trifluoromethyl)phenylboronic acid was investigated and optimized. This methodology represents a milder protocol for the preparation of 2-aryl-1,3,2-aryldioxaborins, a useful class of stable *o*-quinomethane precursors, and is presented in Chapter 5.

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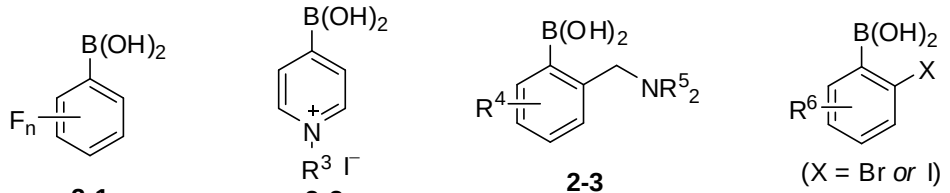
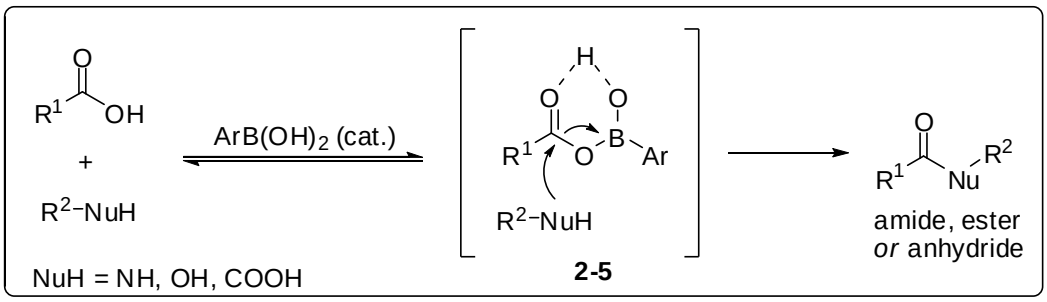
Chapter 2

Boronic Acid Catalyzed Chemical Transformations *via* Carboxylic Acid Activation

2.1 Introduction

As mentioned in Chapter One, several types of arylboronic acids such as polyfluorinated arylboronic acids **2-1**, pyridiniumboronic acid **2-2**, *ortho*-aminomethyl-substituted arylboronic acids **2-3**, and *ortho*-halo-substituted arylboronic acids **2-4** exhibit superior catalytic activity to electrophilically activate the carboxylic acid group in a mild fashion (**Scheme 2-1**).[1] Taking advantage of the concept of carboxylic acid activation, "boronic acid catalysis" has been applied to a series of synthetically useful reactions, such as amidations between carboxylic acids and amines,[2] the esterification of α- or β-hydroxycarboxylic acids with excess alcohols,[3] the dehydrative intramolecular condensation of dicarboxylic acids,[4] and the tandem condensation-

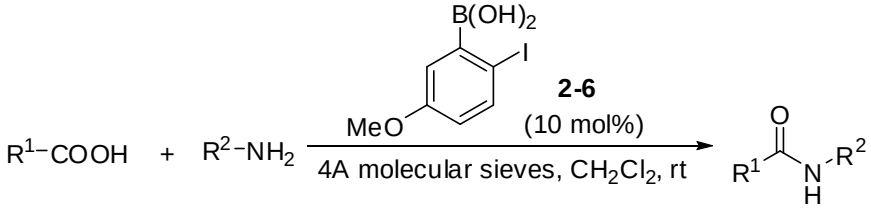




Scheme 2-1: The concept of boronic acid catalysis for the activation of the carboxylic acid group

cyclodehydration of carboxylic acids with amino alcohols or aminothiols.[5] It was proposed that the catalytic activity of boronic acids may arise from the formation of an active monoacyl boronate species **2-5**, which can provide electrophilic activation of the carboxylate group through internal H-bonding (**Scheme 2-1**).[2a,2d]

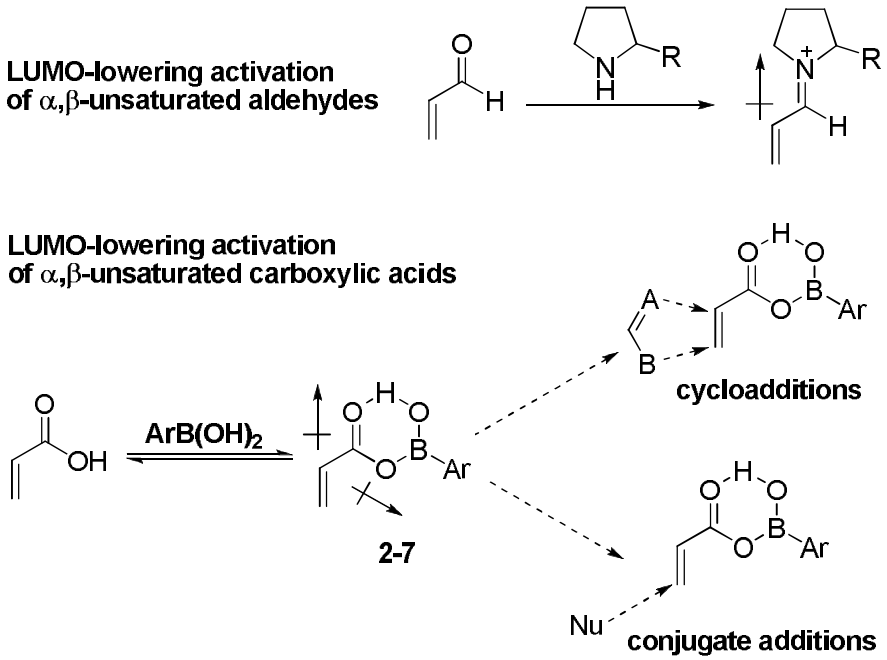
Our group has made great efforts to develop a method for the organocatalytic activation of carboxylic acids using *ortho*-substituted arylboronic acids as bifunctional catalysts toward a direct and waste-free strategy for the formation of amides at room temperature.[2d,2g] With the assistance of 4A molecular sieves, *ortho*-halo-substituted arylboronic acids **2-4** (**Scheme 2-1**) can promote the direct amidation between carboxylic acids and amines at room temperature.[2d] After carefully optimizing the arene core of the *ortho*-haloarylboronic acid catalyst with regards to the steric and electronic effects of ring substitution, 5-methoxy-2-iodophenylboronic acid **2-6** (**Scheme 2-2**) was identified as the best catalyst.[2g] This method provided a mild and atom-economical approach for the preparation of amides.



Scheme 2-2: Direct amidation of carboxylic acids with amines catalyzed by *ortho*-haloarylboronic acids

Encouraged by the success of the amidation reaction, we planned to explore the use of *ortho*-substituted arylboronic acids **2-4** (**Scheme 2-1**) as bifunctional catalysts for other important synthetic transformations such as cycloadditions and conjugate additions using the concept of electrophilic carboxylic acid activation. Indeed, catalytic activation of carboxylic acids is difficult to achieve because of

the inherent chemical properties of this functional group. The acidic character of carboxylic acids can create chemical compatibility issues. As a result, the carboxylic acid functionality is usually handled in a masked form such as a suitable carboxylic ester, which requires additional synthetic steps. A direct method for electrophilic (or LUMO-lowering) activation of unsaturated carboxylic acids towards cycloadditions and conjugate additions would be very advantageous in terms of atom- and step-economy. It can be envisioned that boronic acids could catalyze the direct cycloaddition or conjugate addition to α,β-unsaturated carboxylic acids *via* intermediate **2-7** by lowering the LUMO energy of the unsaturated carboxylic acid (**Scheme 2-3**). Such a concept of electrophilic activation would be complementary to the pyrrolidine-catalyzed iminium ion activation of α,β-unsaturated ketones and aldehydes (**Scheme 2-3**).[6] In this chapter, interesting results toward a variety of cycloadditions of α,β-unsaturated carboxylic acids together with preliminary results for conjugate additions of α,β-unsaturated carboxylic acids will be described.

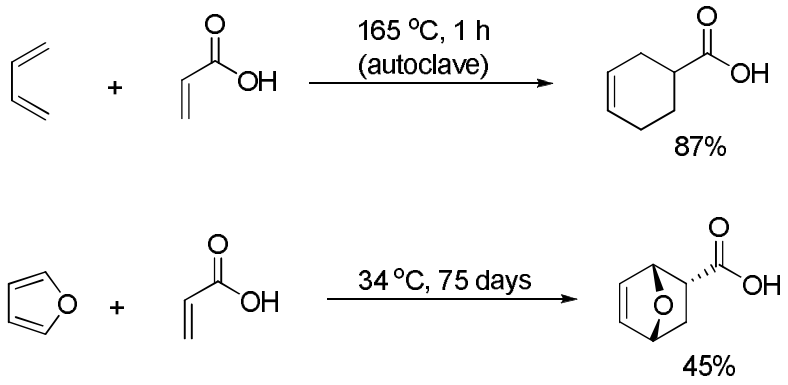


Scheme 2-3: Proposal for organocatalytic activation of α,β-unsaturated carboxylic acids

2.2 Boronic acid catalyzed Diels-Alder reactions of α,β-unsaturated carboxylic acids

2.2.1 Boronic acid catalyzed Diels-Alder reactions of acrylic acids[1d]

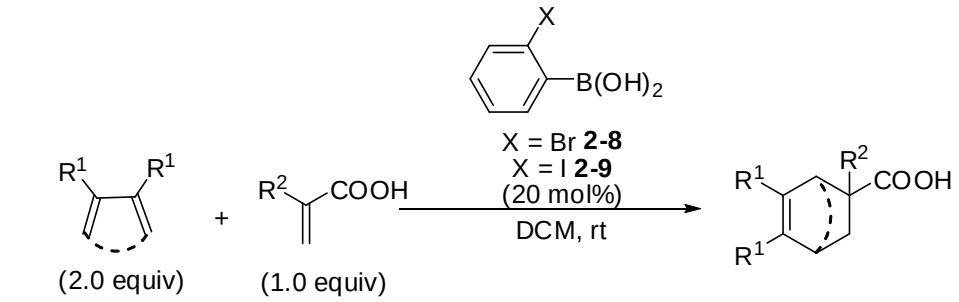
As a starting point, acrylic acid was chosen as the model substrate due to the notorious challenges associated with its participation in thermal Diels-Alder cycloadditions. Acrylic acid was reported to induce decomposition of functionalized dienes at high temperatures and it is quite unreactive at low temperatures. For examples, very harsh reaction conditions (165 ^{o}C) or extremely long reaction times (75 days) were required for the thermal Diels-Alder cycloadditions between acrylic acid and 1,3-butadiene and furan, respectively, to achieve synthetically useful yields of the desired cycloadducts (**Scheme 2-4**).[7]



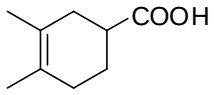
Scheme 2-4: Thermal Diels-Alder cycloadditions of acrylic acid

Using the same boronic acid catalysts **2-8** and **2-9** from the previous amidation studies,[2d] a model cycloaddition between 2,3-dimethyl-1,3-diene and acrylic acid was studied (eq 1, **Scheme 2-5**). It was found that *ortho*-bromophenylboronic acid **2-8** could effectively catalyze this reaction, giving the desired product in 90% yield, whereas the same cycloaddition gave only 5% yield in the absence of the boronic acid catalyst (eq 1, **Scheme 2-5**). Contrary to the boronic acid catalyzed amidation protocol where a dehydrating agent such as molecular sieves was

crucial for the reaction, a low yield was obtained in the presence of molecular sieves (eq 1, **Scheme 2-5**). Indeed, a small amount of water formed by the condensation between the boronic acid and the carboxylic acid is necessary to allow catalyst turnover. Excess water, however, reduced the product yield substantially (eq 1, **Scheme 2-5**). Compared to the linear dienes, cyclopentadiene reacted even more efficiently (eq 2, **Scheme 2-5**). For more challenging substrates such as furan, the more active boronic acid **2-9** was necessary (eq 3, **Scheme 2-5**). Other than acrylic acid, α-bromoacrylic acid was also found to be a suitable dienophile for this boronic acid catalyzed Diels-Alder reaction method (eq 4, **Scheme 2-5**). Since all the work depicted in **Scheme 2-5** was completed by our previous group member, Dr. Olivier Marion,[2d] it will not be discussed here in detail.

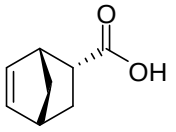


1)



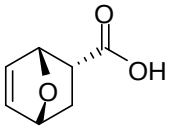
5% (no catalyst, 48 h)
25% (with **2-8**, 1.0 equiv H_2O,48 h)
76% (with **2-8**, 0.1 equiv H_2O, 48 h)
90% (with **2-8**, 48 h)
20% (with **2-8**, 4A molecular sieves, 48 h)

2)



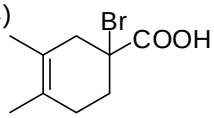
99% (with **2-8**, 24 h)

3)



35% (with **2-9**, 48 h)

4)



71% (with **2-8**, 48 h)

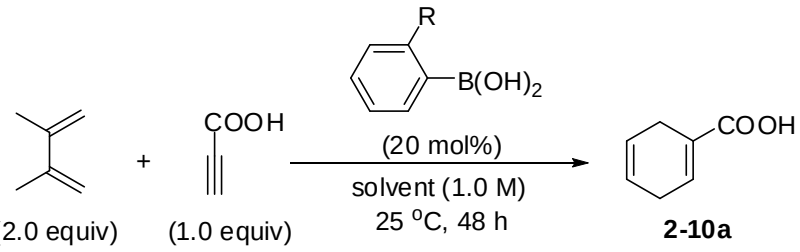
Scheme 2-5: Diels-Alder cycloadditions of acrylic acid catalyzed by boronic acids 2-8 and 2-9

2.2.2 Boronic acid catalyzed Diels-Alder reactions of 2-alkynoic acids[8]

As shown in **Section 2.2.1**, the concept of electrophilic activation of unsaturated carboxylic acids had been demonstrated in [4+2] cycloadditions of acrylic acid. Herein, we extend this concept to the use of 2-alkynoic acids in [4+2] cycloadditions to access polysubstituted cyclohexadienes and arenes functionalized with a carboxylic acid. Faster reactions, milder conditions, and increased regioselectivity are the main benefits provided by boronic acid catalysis (BAC).

2.2.2.1 Optimization of reaction conditions

Ortho-halo substituted arylboronic acids were previously found to be potent catalysts in [4+2] cycloadditions of acrylic acid (see **Section 2.2.1**),[2d] therefore our initial screening of potential catalysts focused on the same class of boronic acids along with a few more electron-poor arylboronic acids (entries 1–9, **Table 2-1**). All the catalysts were subjected to the model reaction by stopping the reactions prior to completion. This procedure ensured that the most active catalysts could be compared more accurately and rapidly. A limitation of this approach, however, is that small differences in yields (ca. 5%) should not be considered significant. It was found that *ortho*-iodophenylboronic acid (entry 1, **Table 2-1**), *ortho*-nitrophenylboronic acid (entry 5, **Table 2-1**), and *ortho*-bromophenylboronic acid (entry 6, **Table 2-1**) were the most efficient amongst the boronic acids tested. Moreover, the fact that *meta*-nitrophenylboronic acid and *meta*-bromophenylboronic acid are significantly less effective confirms the crucial importance of the ortho position (entries 7–8, **Table 2-1**). A comparison with electron-deficient 2,3,4,5-tetrafluorophenyl boronic acid confirmed that *ortho*-bromophenylboronic acid or *ortho*-nitrophenylboronic acid are superior catalysts (entries 5–6 *vs* entry 9, **Table 2-1**). This observation suggested that the acidity of the boronic acid catalysts alone could not account for



(2.0 equiv) (1.0 equiv) **2-10a**

Entry	R =	Additive	Solvent	Yield[a] (%)
1	I	no additive	CH_2Cl_2	80
2	F	no additive	CH_2Cl_2	52
3	Cl	no additive	CH_2Cl_2	71
4	CN	no additive	CH_2Cl_2	39
5	NO_2	no additive	CH_2Cl_2	82
6	**Br**	no additive	**CH_2Cl_2**	**86**
7[b]	–	no additive	CH_2Cl_2	31
8[c]	–	no additive	CH_2Cl_2	37
9[d]	–	no additive	CH_2Cl_2	42
10	Br	no additive	toluene	80
11	Br	no additive	MeOH	6
12	Br	no additive	THF	59
13	Br	no additive	CH_3CN	24
14	Br	4A molecular sieves	CH_2Cl_2	20
15	Br	H_2O (1.0 equiv)	CH_2Cl_2	71
16	no catalyst	no additive	CH_2Cl_2	3

[a]Isolated yields of product after purification by flash column chromatography; [b]3-Bromophenyl boronic acid was employed as the catalyst; [c]3-Nitrophenyl boronic acid was employed as the catalyst; [d]2,3,4,5-tetrafluorophenyl boronic acid was employed as the catalyst.

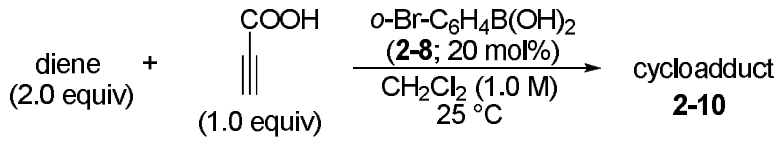
Table 2-1: Optimization of reaction conditions for the BAC of a model Diels-Alder cycloaddition with propiolic acid

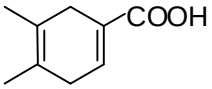
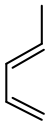
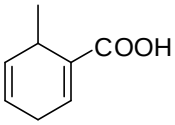
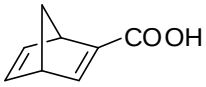
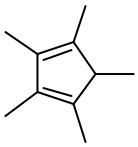
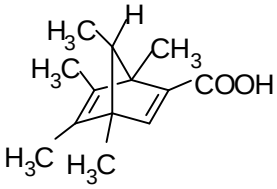
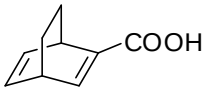
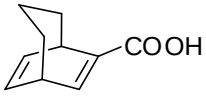
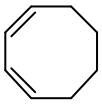
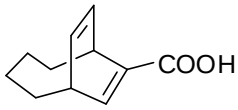
the superiority of *ortho*-bromophenylboronic acid or *ortho*-nitrophenylboronic acid. It is known that boronic acids can readily dehydrate and form oligomeric anhydrides (boroxines)[9] and therefore boronic acids contain a certain amount of boroxines when under relatively dry conditions. The different ratio of free boronic

acid to boroxine in these boronic acid catalysts might be responsible for the inferior efficacy of 2,3,4,5-tetrafluorophenyl boronic acid versus *ortho*-bromophenylboronic acid or *ortho*-nitrophenylboronic acid. Since *ortho*-bromophenylboronic acid is readily commercially available and inexpensive, it was selected as the catalyst to evaluate this protocol. Solvent dependency was examined next and chlorinated solvent CH_2Cl_2 was found to be superior for this reaction (entries 10–13, **Table 2-1**). A control experiment was run, and it was found that the same cycloaddition gave only 3% yield in the absence of the boronic acid catalyst (entry 16, **Table 2-1**). It is noteworthy that a low yield was obtained in the presence of molecular sieves (entry 14, **Table 2-1**), which is in line with our previous reports on [4+2] cycloadditions of acrylic acid (**Section 2.2.1**).[2d] Indeed, a small amount of water formed by the condensation between the boronic acid and the carboxylic acid is necessary to allow the catalyst turnover. In contrast, excess water reduced the product yield substantially (entry 15, **Table 2-1**).

2.2.2.2 Substrate scope

Using the optimal conditions, the scope of diene was explored using propiolic acid as the dienophile (**Table 2-2**). In the event, a wide selection of substituted butadienes was tolerated. In all cases, the boronic acid catalyzed variant gave greatly improved yields over the uncatalyzed reaction. Acyclic dienes proceeded smoothly under optimized conditions (entries 1–2, **Table 2-2**). Interestingly, for the asymmetric diene, penta-1,3-diene, complete regioselectivity was realized under BAC (entry 2, **Table 2-2**). The preferred orientation in product **2-10b** can be well described in terms of partial positive and negative charges that exist in the diene and dienophile (**Figure 2-1**). Carbon with a partial negative charge interacts readily with carbon bearing a partial positive charge, resulting in high regioselectivity in the formation of **2-10b**. Moreover, the formation of boronate,



Entry	Diene	t (h)	Cycloadduct	Number	Yield[a] (%)
1		48		**2-10a**	86 (3)
2		48		**2-10b**	83[b] (6)
3		8		**2-10c**	91 (6)
4		6		**2-10d**	92[c] (3)
5		48		**2-10e**	82 (trace)
6		72		**2-10f**	62 (trace)
7		720		**2-10g**	trace (0)

[a]Isolated yields of product after purification by flash column chromatography. Yields in brackets represent the control reactions performed without boronic acid as the catalyst; [b]Only one regioisomer was obtained; [c]Diastereomeric ratio: 3:1.

Table 2-2: Substrate scope for the BAC of Diels-Alder cycloadditions with propiolic acid

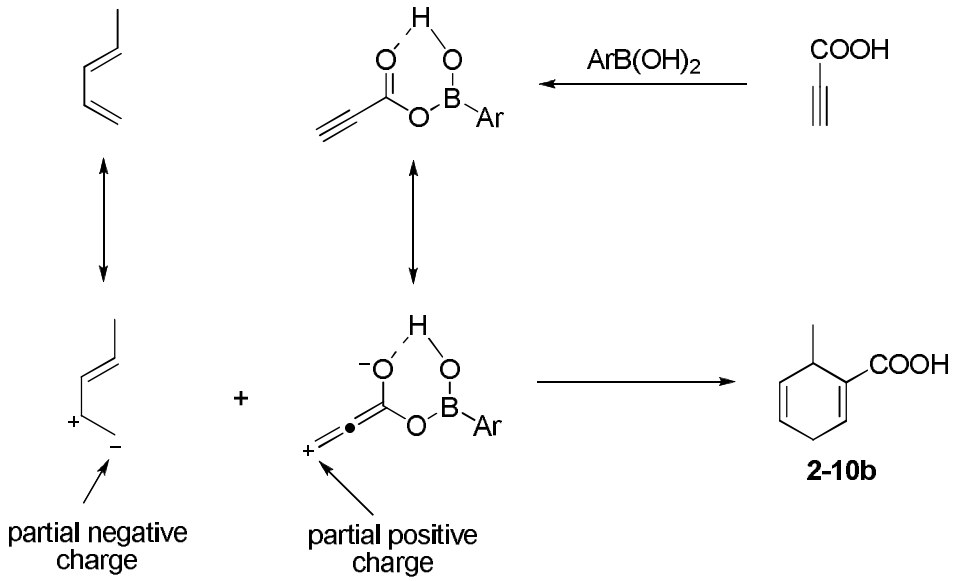


Figure 2-1: Regioselectivity in the formation of 2-10b

which could increase the electrophilicity of the remote carbon through internal H-bonding, further enhances the regioselectivity (**Figure 2-1**). The structure of **2-10b** was confirmed by a 2D COSY experiment (see **Section 2.6.2.3**). Compared to the linear dienes, cyclopentadiene reacted even more efficiently (entry 3, **Table 2-2**). In the case of a substituted cyclopentadiene, a mixture of diastereoisomers

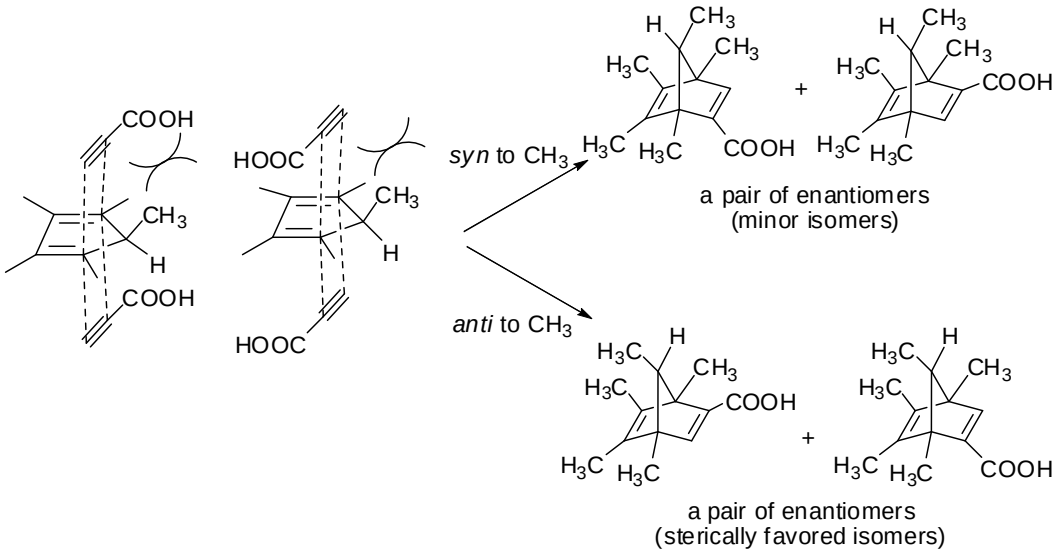
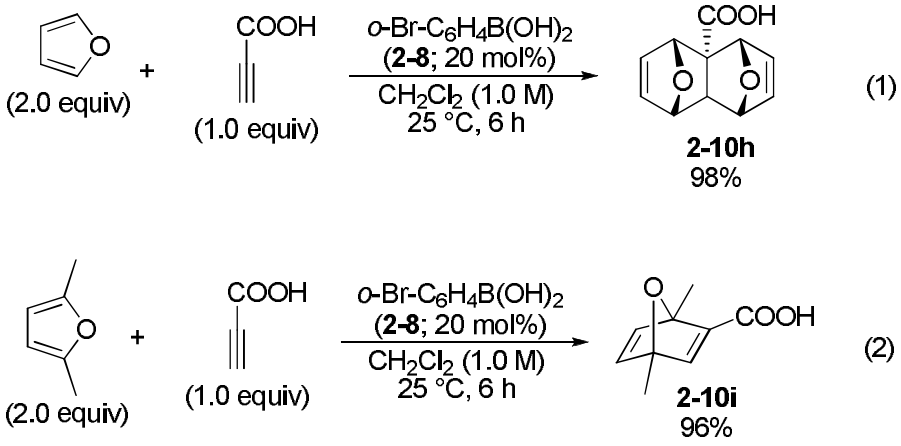


Figure 2-2: Diastereoselectivity in the formation of 2-10d

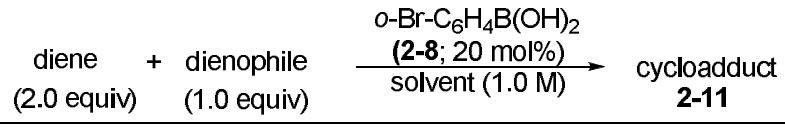
(3:1) was obtained (entry 4, **Table 2-2**). This π-facial selectivity most likely results from the steric repulsion between the allylic methyl group on the diene and the dienophile (**Figure 2-2**). The stereochemistry of **2-10d** was confimed by ^{1}H NMR experiments (see **Section 2.6.2.5**). The ring size of cyclic dienes played an important role in the reaction, the larger the ring size, the lower the reaction yield (entries 3–7, **Table 2-2**). Only trace amounts of product in the crude reaction mixture was detected with cycloocta-1,3-diene after 30 days (entry 9, **Table 2-2**). To our satisfaction, furans are also suitable substrates for this cycloaddition, the double Diels-Alder cycloadduct **2-10h** (eq 1, **Scheme 2-6**) and the dienecarboxylic acid **2-10i** (eq 2, **Scheme 2-6**) (not stable at room temperature after isolation) were obtained in excellent yields.

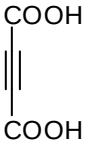
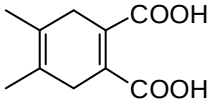
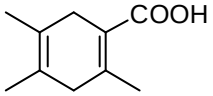
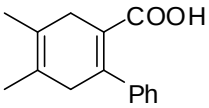
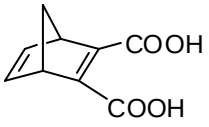
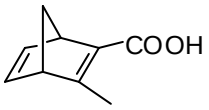
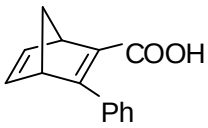


Scheme 2-6: Diels-Alder cycloadditions of propiolic acid and furan catalyzed by boronic acid 2-8

To further expand this methodology, substituted 2-butynoic acids were employed as the dienophiles (**Table 2-3**). With 2,3-dimethyl-1,3-butadiene, the desired dienecarboxylic acids **2-11a**–**2-11c** were obtained in acceptable yields using a slightly elevated temperature and longer reaction times (entries 1–3, **Table 2-3**). Compared to 2,3-dimethyl-1,3-butadiene, cyclopentadiene showed increased reactivity, and could react with substituted 2-butynoic acids to provide the desired

cycloadducts **2-11d**–**2-11f** in excellent yields under relatively mild conditions (entries 4–6, **Table 2-3**).



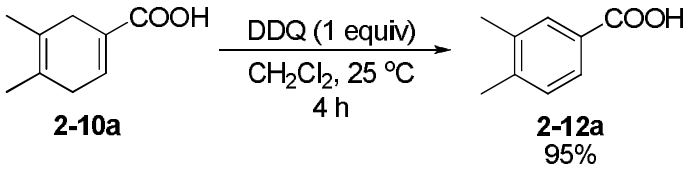
Entry	Diene	Dienophile	Reaction conditions	Product	Yield[a] (%)
1			DCM, 25 °C, 8 h	 **2-11a**	89 (18)
2			DCE, 50 °C, 96 h	 **2-11b**	44 (trace)
3			THF 50 °C, 48 h	 **2-11c**	41 (trace)
4			DCM 25 °C, 48 h	 **2-11d**	84 (12)
5			DCM 25 °C, 48 h	 **2-11e**	81 (7)
6			THF 25 °C, 48 h	 **2-11f**	85 (12)

[a]Isolated yields of product after purification by flash column chromatography. Yields in brackets represent the control reactions performed without boronic acid as the catalyst.

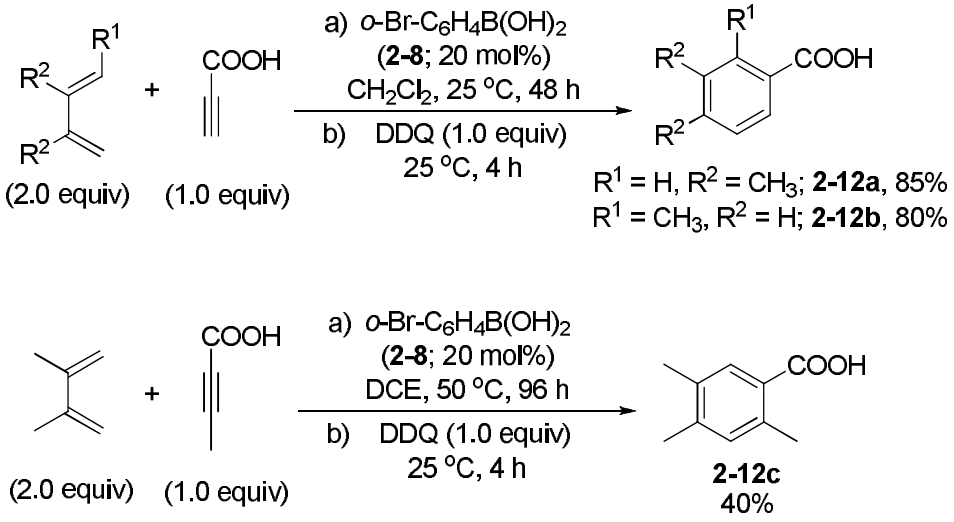
Table 2-3: Substrate scope for the BAC of Diels-Alder cycloadditions with substituted 2-butynoic acids

2.2.2.3 Application to a one-pot sequential boronic acid catalyzed Diels-Alder cycloaddition/aromatization

The 1,4-cyclohexadienyl carboxylic acids **2-10** and **2-11** synthesized by this method could be conveniently converted to synthetically and biologically useful polysubstituted arylcarboxylic acids (**Scheme 2-7**).[10] This was accomplished by using a DDQ mediated aromatization of dienecarboxylic acid **2-10a**, which afforded the polysubstituted arene **2-12a** in a nearly quantitative yield. Based on this promising result, a one-pot sequential boronic acid-catalyzed Diels-Alder cycloaddition/aromatization was envisioned in terms of maximizing step-economy and synthetic efficiency (**Scheme 2-8**). Following the one-pot



Scheme 2-7: DDQ promoted aromatization of 2-10a into 2-12a

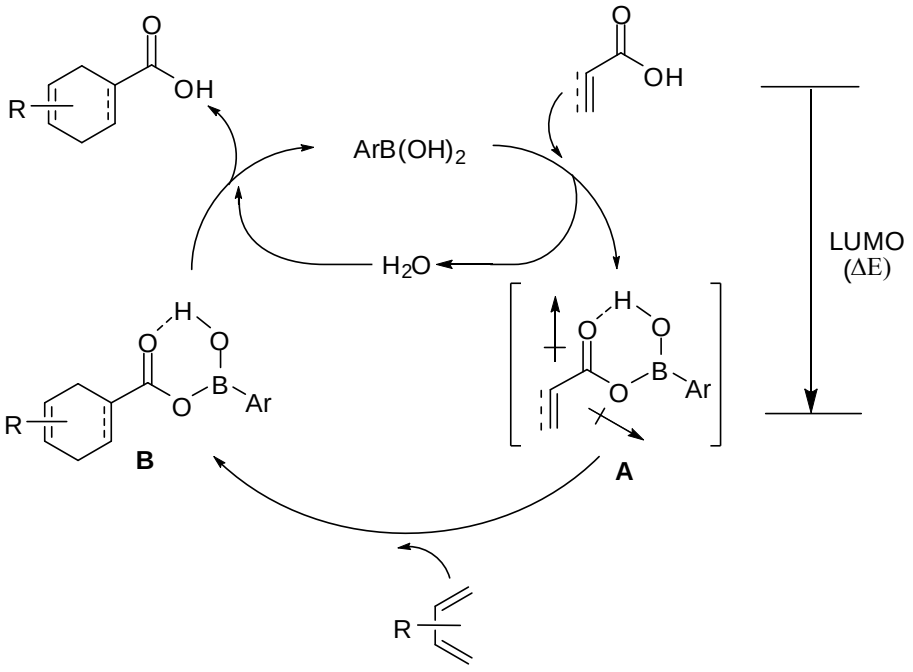


Scheme 2-8: One-pot sequential boronic acid-catalyzed Diels-Alder cycloaddition/aromatization

procedure, the polysubstituted arenes **2-12a**–**2-12c** were obtained in good to excellent yields.

2.2.2.4 Mechanistic investigation

Nearly in all cases, the *o*-$BrC_6H_4B(OH)_2$-catalyzed variant give greatly improved yields over the uncatalyzed reaction (**Tables 2-2** and **2-3**). Similar to Lewis acid activation of α,β-unsaturated carbonyl compounds,[11] boronic acids could activate α,β-unsaturated carboxylic acids *via* intermediate **A** by lowering the LUMO energy of the unsaturated carboxylic acid (**Scheme 2-9**). This effect contributes to reducing the energy gap between the HOMO of diene and the LUMO of the dienophile and hence an increase in the rate of Diels-Alder cycloadditions. A detailed mechanistic discussion of this LUMO activation assumption will be presented in **Section 2.3.5**. As mentioned in **Section 2.2.2.1**, water plays an essential role in this boronic acid-catalyzed Diels-Alder cycloadditions of

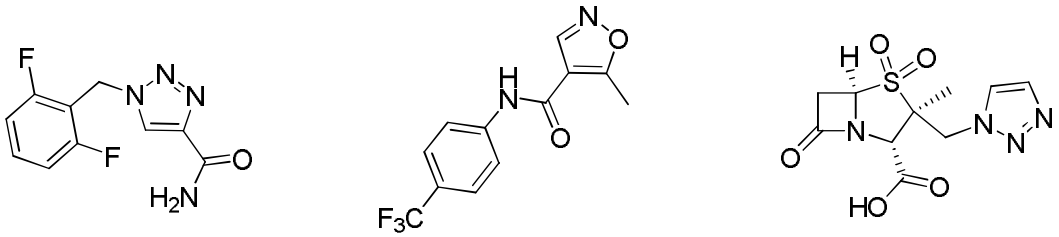


Scheme 2-9: The proposed catalytic cycle for the boronic acid-catalyzed Diels-Alder cycloadditions of unsaturated carboxylic acids

unsaturated carboxylic acids. A small amount of water formed by the condensation between the boronic acid and the carboxylic acid is necessary to allow the catalyst turnover. However, excess water substantially deactivates the boronic acid catalysts likely by hydrolyzing the activated intermediate **A** back to the starting materials (**Scheme 2-9**). These assumptions about the requirement for a small amount of water are depicted in the proposed catalytic cycle of **Scheme 2-9**. In this cycle, the water released in the formation of activated boronate **A** eventually serves in the hydrolytic release of the catalyst from the cycloadduct intermediate **B** (**Scheme 2-9**). Recently, it was discovered that the reproducibility of this methodology was highly dependent on the stoichiometry of water in the reaction system. It is known that boronic acids can readily dehydrate and form oligomeric anhydrides (boroxines)[9] and therefore boronic acids usually contain a certain amount of boroxines when under relatively dry conditions. The different ratio of free boronic acid to boroxine in commercial *ortho*-bromophenylboronic acid might be responsible for this reproducibility problem. This issue could be effectively addressed by employing 2-nitrophenylboronic acid as the catalyst, as reactions proved more reproducible than those with 2-bromophenylboronic acid.

2.3 Boronic acid catalyzed 1,3-dipolar cycloadditions of α,β-unsaturated carboxylic acids[12]

1,3-Dipolar cycloaddition is a powerful tool for the construction of various five-membered O- and N-containing heterocycles, which are important components of numerous pharmaceutical agents (some examples are shown in **Figure 2-3**). Thermal 1,3-dipolar cycloadditions, however, require harsh reaction conditions (e.g. high reaction temperature) and often produce the desired heterocycles with poor regioselectivity.[13] In **Section 2.2**, boronic acid catalysis (BAC) was demonstrated to be an effective way to activate unsaturated carboxylic acids in Diels-Alder cycloadditions.[2d,8] In this section, a significant expansion of



rufinamide (anticonvulsant) **leflunomide** (immunomodulator) **tazobactam** (antibiotic)

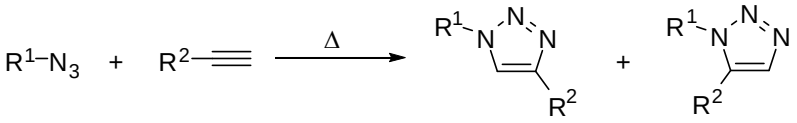
Figure 2-3: Examples of heterocyclic pharmaceutical agents

the BAC concept into several classical dipolar [3+2] cycloadditions of unsaturated carboxylic acid will be presented. These protocols represent mild and selective ways of generating biologically important small heterocyclic products containing a free carboxylic acid functionality. Faster reaction time, milder reaction conditions, and increased regioselectivity are the main benefits provided by BAC.

2.3.1 Optimization of catalyst and solvent for azide-alkyne cycloaddition

1,2,3-Triazole compounds are important motifs in both synthetic and medicinal chemistry.[14] A traditional approach to the synthesis of 1,2,3-triazoles is the thermal 1,3-dipolar cycloaddition between azides and alkynes (Hüisgen cycloaddition), which requires harsh reaction conditions (e.g. high reaction temperature) and often produces the desired 1,2,3-triazoles with poor regioselectivity (eq 1, **Scheme 2-10**).[13] Recently, Cu(I) and Ru(II) complexes were found to catalyze this reaction in a milder and regioselective manner, affording 1,4-regioisomers or 1,5-regioisomers respectively (eqs 2–3, **Scheme 2-10**).[15] Numerous examples have proven that Cu-catalyzed Hüisgen azide-alkyne cycloaddition can serve as a powerful tool for bioconjugation, materials science, organic synthesis and drug discovery,[14] however, the presence of transition-metal catalysts can create compatibility issues with biological systems.[16] In this context, the development of metal-free azide-alkyne cycloaddition is particularly relevant. Since the concept of electrophilic activation of unsaturated carboxylic acids using

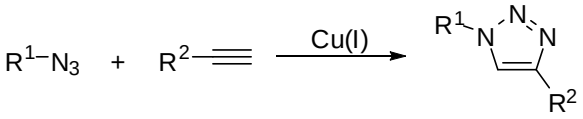
Thermal azide-alkyne cycloaddition:



1)

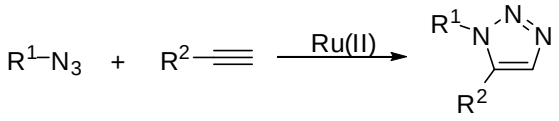
poor regioselectivity

Cu-catalyzed azide-alkyne cycloaddition:



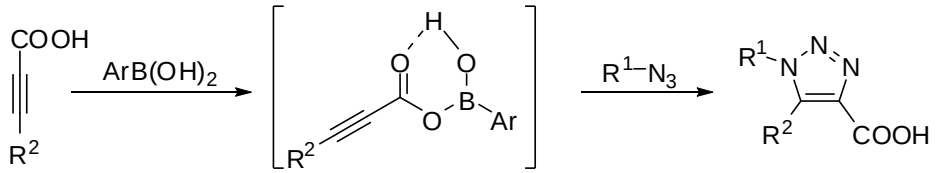
2)

Ru-catalyzed azide-alkyne cycloaddition:



3)

Our proposal:



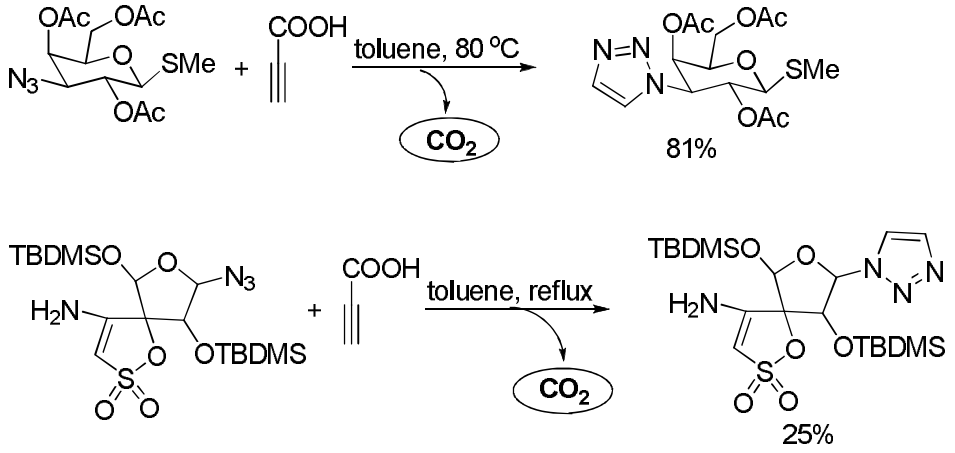
4)

electrophilic LUMO-lowering activation

Scheme 2-10: Azide-alkyne cycloadditions

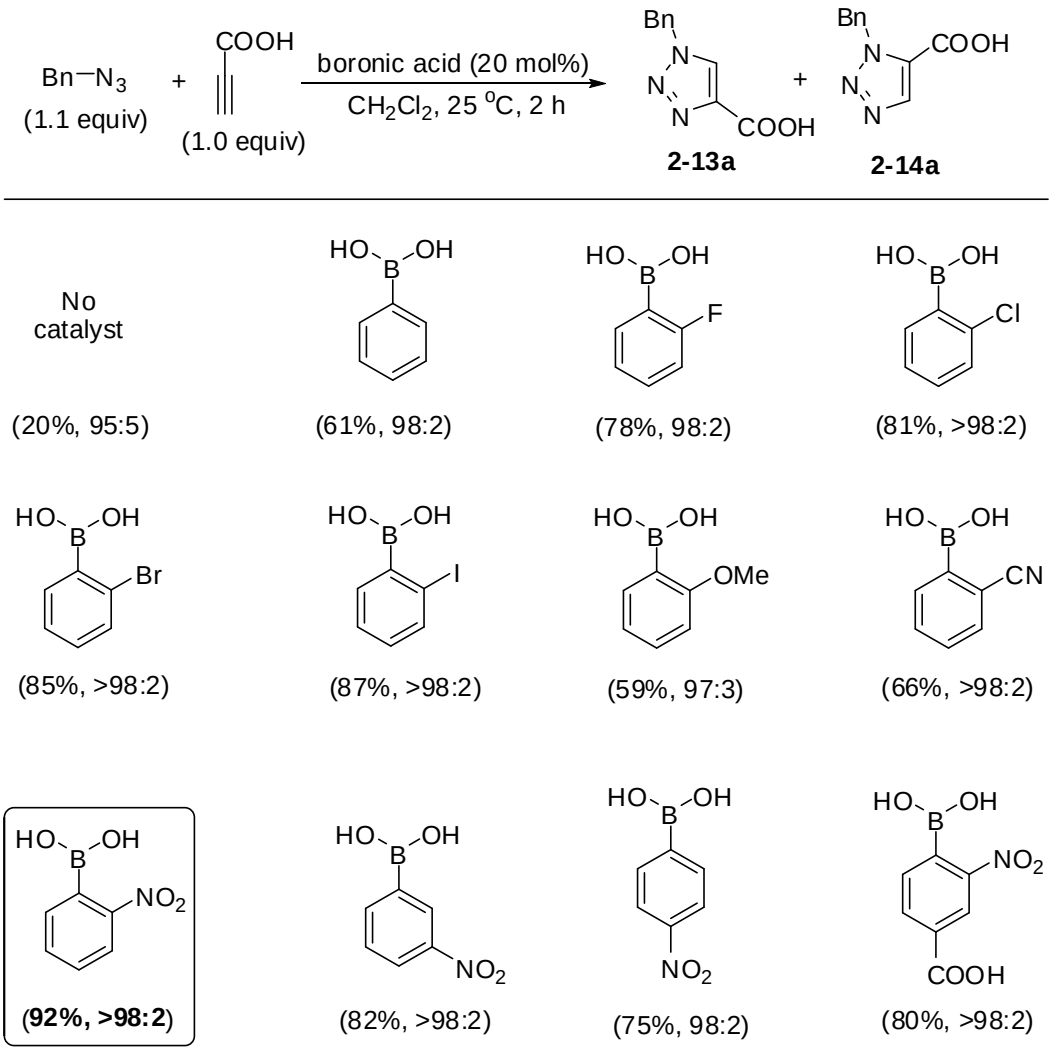
BAC had been successfully demonstrated in [4+2] cycloadditions of unsaturated carboxylic acids (see **Section 2.2**), it was deemed reasonable that such a concept could be extendable to azide-alkyne cycloadditions of unsaturated carboxylic acids (eq 4, **Scheme 2-10**). Unsaturated carboxylic acids are rarely employed as dipolarophiles in 1,3-dipolar [3+2] azide-alkyne cycloaddition due to chemical compatibility issues which can be created by the acidic character of carboxylic acids.[13-16] Therefore, the carboxylic acid functionality is usually handled in a masked form such as a suitable carboxylic ester, which requires additional

synthetic steps.[13-16] Moreover, the thermal Hüisgen azide-alkyne [3+2] cycloadditions of propiolic acid is known to require elevated temperatures that lead to substantial decarboxylation of the 1,2,3-triazene cycloadduct formed (**Scheme 2-11**).[17] It was hoped that milder conditions employing BAC at room temperature could help to address these issues.



Scheme 2-11: Decarboxylation issues in the thermal azide-alkyne cycloadditions of propiolic acid

Because *ortho*-halosubstituted arylboronic acids were previously found to be potent catalysts in [4+2] cycloadditions of unsaturated carboxylic acids (see **Section 2.2**),[2d,8] our initial screening of potential catalysts focused on this class of compounds. Thus, a large number of *ortho*-substituted arylboronic acids were evaluated for their ability to accelerate the Hüisgen azide–alkyne [3+2] cycloaddition. All the catalysts were subjected to the model reaction by stopping the reactions prior to completion. This procedure ensured that the most active catalysts could be compared more accurately and rapidly. A limitation of this approach, however, is that small differences in yields (ca. 5%) should not be considered significant. In the event, all the arylboronic acids tested provided a significant increase in yield for a reaction between benzyl azide and propiolic acid when used at 20 mol% loading, after two hours of stirring at room temperature in

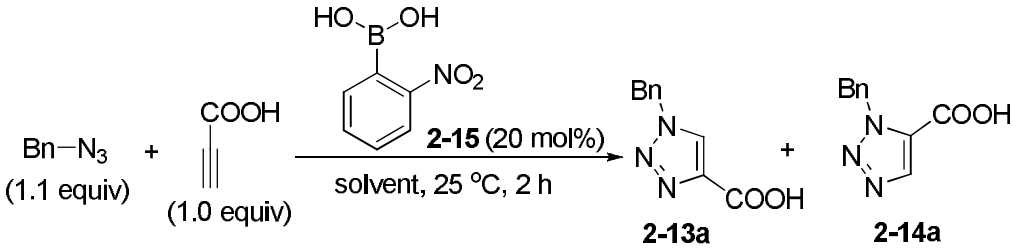


The ratios in brackets represent the regioselectivity **2-13a**:**2-14a**

Figure 2-4: Survey of arylboronic acids for catalytic activity in a model azide-alkyne cycloaddition

dry dichloromethane (**Figure 2-4**). Whereas the uncatalyzed process gave only 20% yield, the best catalyst identified, *ortho*-nitrophenylboronic acid, led to a yield of 92% of triazene product **2-13a** as a single regioisomer observed.[9] When *meta*-nitrophenylboronic acid and *para*-nitrophenylboronic acid were employed as the catalysts, the same reaction gave lower yields (**Figure 2-4**). This result suggested that a nitro group in the ortho position to the boronyl group is important. In addition, the fact that the boronic acid catalyst containing a carboxyl group

exhibits slightly decreased catalytic efficiency hinted that the rate of azide-alkyne cycloaddition could not be accelerated in the presence of Brønsted acid (**Figure 2-4**).



Entry	Solvent	Catalyst (mol%)	Additive	Yield[a] (%)	Regioselectivity[b] (**2-13a**:**2-14a**)
1	Et_2O	20	no additive	18	95:5
2	THF	20	no additive	40	95:5
3	CH_3CN	20	no additive	33	96:4
4	acetone	20	no additive	58	96:4
5	EtOH	20	no additive	38	95:5
6	DMF	20	no additive	70	97:3
7	toluene	20	no additive	81	>98:2
8	CH_2Cl_2	20	no additive	90	>98:2
9	DCE	20	no additive	95	>98:2
10	DCE	20	4A molecular sieves	18	95:5
11	DCE	20	H_2O (1.0 equiv)	75	>98:2
12	DCE	20	H_2O (10.0 equiv)	26	95:5
13	DCE	10	no additive	95	>98:2
14	**DCE**	**5**	**no additive**	**94**	**>98:2**
15	DCE	2	no additive	61	98:2

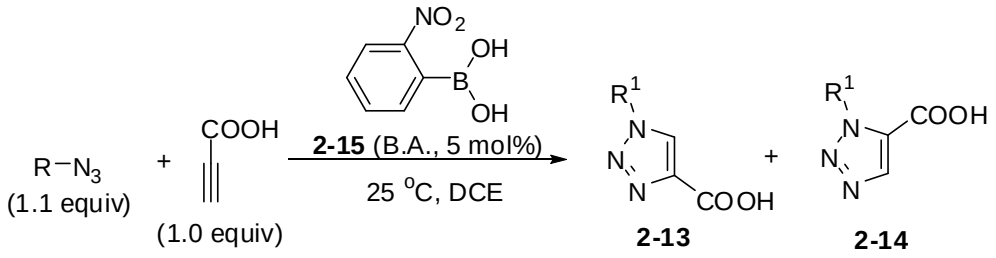
[a]Isolated yields of the product after purification by simple filtration. [b]Measured by ^{1}H-NMR spectroscopy of the crude reaction product.

Table 2-4: Optimization of solvent and catalyst loading for the BAC of a model azide-alkyne cycloaddition

By using *ortho*-nitrophenylboronic acid **2-15** at 20 mol% loading, a solvent optimization study was completed (**Table 2-4**) and showed that halogenated solvents are preferable for this reaction. Thus, 1,2-dichloroethane provided a near-quantitative yield and only a single observable regioisomer (entry 9, **Table 2-4**). As in our previous report on [4+2] cycloadditions (see **Section 2.2**),[2d,8] a substoichiometric amount of water (formed *in situ* from the condensation between the boronic acid and the carboxylic acid) is necessary to ensure catalyst turnover, which is confirmed by the low product yield in the presence of molecular sieves (entry 10, **Table 2-4**). On the other hand, stoichiometric quantities of water lead to reduced yields (entries 11 and 12, **Table 2-4**). Further optimization of catalyst loading revealed that catalysis was still effective at only 5 mol% stoichiometry (entry 14, **Table 2-4**); however, a further decrease to 2 mol% led to a significant reduction in the yield (entry 15, **Table 2-4**).

2.3.2 Substrate scope for alkyne-azide cycloadditions

With the optimal conditions in hand (entry 14, **Table 2-4**: 5 mol% *o*-$NO_2C_6H_4B(OH)_2$ **2-15** in $ClCH_2CH_2Cl$ at 25 ^oC), we then examined the azide and alkyne substrate scope of this [3+2] cycloaddition. For the azide component, it is clear that a very wide variety of aliphatic substrates (entries 1–6, **Table 2-5**) can be employed. The reactivity of azides is highly dependent on the steric effect of aliphatic substituents. The scope revealed the order of reactivity of azides being primary > secondary > tertiary (entries 1–6, **Table 2-5**). All reactions with aliphatic azides proceeded smoothly at room temperature under BAC. It took only 4 hours for primary azides to achieve excellent yields (entries 1–3, **Table 2-5**). More sterically hindered secondary (entries 4–5, **Table 2-5**) and tertiary (entry 6, **Table 2-5**) azides required much longer reaction times, 24 and 96 hours respectively, to obtain synthetically useful yields of desired products.



2-13 **2-14**

Entry	R	t (h)	Number	Yield[a,b] (%)	Regioselectivity[a,c] (**2-13**:**2-14**)
1	$PhCH_2$	4	**2-13a**	96 (23)	>98:2 (95:5)
2	EtO_2CCH_2	4	**2-13b**	92 (21)	>98:2 (>98:2)
3	$NCCH_2$	4	**2-13c**	96 (15)	>98:2 (>98:2)
4	PhCH(Me)	24	**2-13d**	84 (22)	>98:2 (95:5)
5	$MeO_2CCH(Me)$	24	**2-13e**	89 (25)	>98:2 (9:1)
6	EtO_2CCMe_2	96	**2-13f**	71 (4)	>98:2 (>98:2)
7	Ph	24	**2-13g**	82 (18)	>98:2 (16:1)
8	2-naphthalene	72	**2-13h**	80 (15)	>98:2 (95:5)
9	4-$MeOC_6H_4$	24	**2-13i**	93 (17)	5:1 (1.5:1)
10	4-tolyl	48	**2-13j**	85 (19)	16:1 (5:1)
11	4-ClC_6H_4	72	**2-13k**	73 (12)	>98:2 (3:1)
12	2-$MeOC_6H_4$	24	**2-13l**	87 (13)	>98:2 (15:1)
13	2-tolyl	72	**2-13m**	78 (9)	>98:2 (9:1)
14	2-ClC_6H_4	72	**2-13n**	72 (8)	>98:2 (7:1)

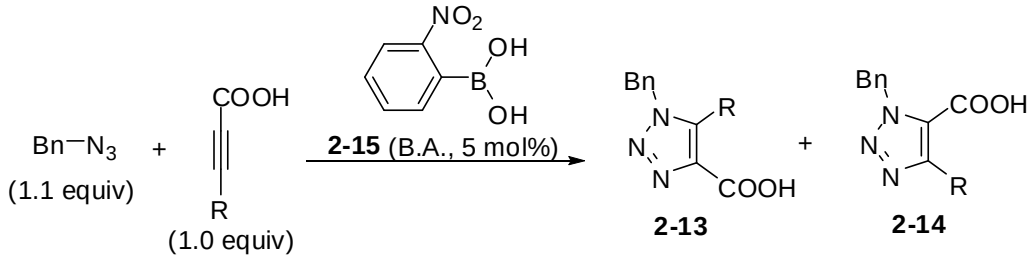
[a]Values in parentheses refer to the uncatalyzed process. [b]Isolated yields of the product after purification by simple filtration. [c]Measured by ^1H NMR spectroscopy of the crude reaction product.

Table 2-5: Substrate scope for the boronic acid catalyzed cycloaddition between azides and propiolic acid

The substrate scope of boronic acid catalyzed azide-alkyne cycloadditions is not limited to aliphatic azides. A set of aromatic azides (entries 7–14, **Table 2-5**) are also suitable substrates. Both electronic and steric effects from the aromatic ring substituents have a large impact on reactivity and regioselectivity of boronic acid catalyzed azide-alkyne cycloadditions. Electron-rich aryl azides tended to react

faster and gave the desired 1,2,3-triazole compounds in poorer selectivity compared with neutral and electron-deficient aryl azides (entries 9–10 *vs* entries 7, 8, and 11, **Table 2-5**). More sterically hindered *ortho*-substituted aryl azides tended to react slower and gave the desired heterocycles in higher selectivity than *para*-substituted counterparts (entries 12–14 *vs* entries 9–11, **Table 2-5**).

Satisfactorily, it was found that 3-substituted 2-alkynoic acids can also be successfully utilized provided a slightly elevated temperature or longer time period is used (**Table 2-6**). These azide-internal alkyne cycloadditions are not readily accessible by using well-established Cu(I)-catalyzed variants, which are only applicable for terminal alkynes.[15a,15b] Interestingly, in one case of boronic acid catalyzed azide-internal alkyne cycloaddition, increasing the catalyst loading from 5 mol% to 20 mol% further increased the regioselectivity (entry 4, **Table 2-6**). The single azide unsuccessful in undergoing the reaction was

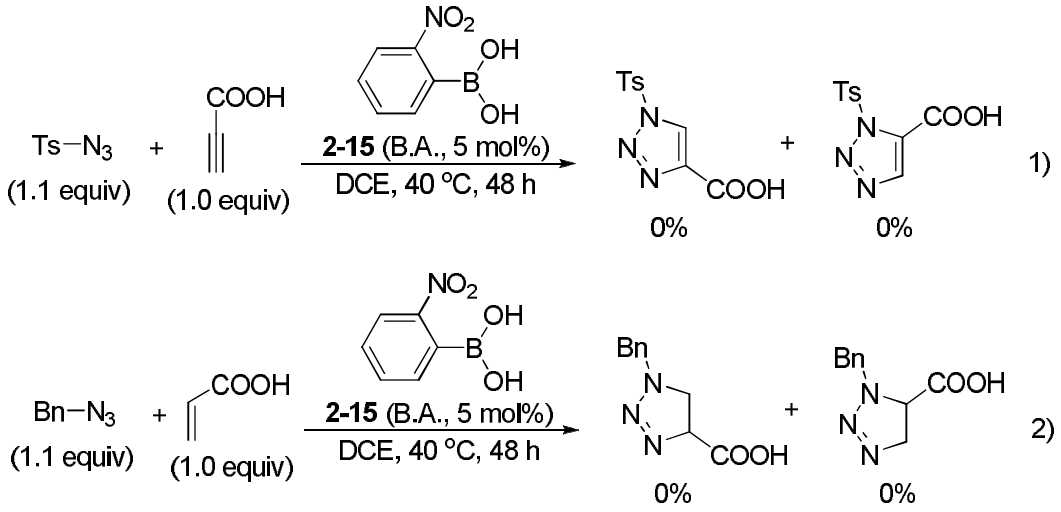


Entry[a]	R	T (^{o}C)	t (h)	Number	Yield[b] (%)	Regioselectivity[c] (**2-13**:**2-14**)
1[d]	COOH	25	24	**2-13o**	92 (25)	–
2	CH_3	40	48	**2-13p**	70 (12)	>98:2 (6:1)
3	Ph	40	96	**2-13q**	68 (15)	5:1 (1.4:1)
4[e]	COOMe	25	24	**2-13r**	73 (16)	4.5:1 (1.1:1)

[a]Values in parentheses refer to the uncatalyzed process. [b]Isolated yields of the product after purification by simple filtration. [c]Measured by ^{1}H NMR spectroscopy of the crude reaction product. [d]The solvent is THF. [e]When 20 mol% stoichiometry **2-15** was employed, the desired product **2-13r** was obtained in 73% yield (**2-13r**:**2-14r** >98:2).

Table 2-6: Substrate scope for the boronic acid catalyzed cycloaddition of internal alkynes

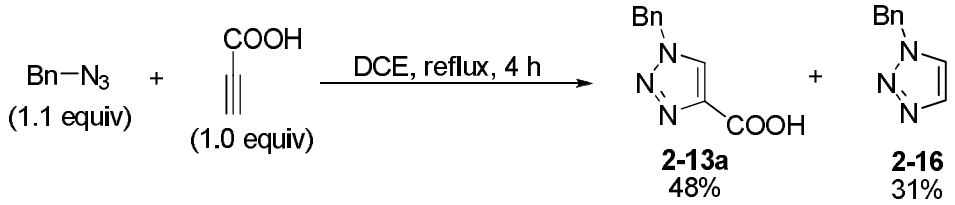
p-toluenesulfonyl azide (eq 1, **Scheme 2-12**). The low reactivity of *p*-toluenesulfonyl azide is most likely due to the deactivation of the 1,3-dipolar system by the electron-withdrawing tosyl group. Likewise, alkenoic acids are unsuitable substrates, as indicated by the failure of acrylic acid to react with benzyl azide, which is presumably due to the instability of the triazoline product (eq 2, **Scheme 2-12**).[18]



Scheme 2-12: Unsuccessful substrates for the boronic acid catalyzed azide-alkyne/alkene cycloaddition

Nearly in all cases, not only did the *o*-$NO_2C_6H_4B(OH)_2$-catalyzed variant give greatly improved yields over the uncatalyzed reaction, but the regioselectivity was also significantly improved, to the point of avoiding isomer separation in most cases (**Tables 2-5** and **2-6**). As mentioned in **Section 2.2.2.4**, boronic acids could activate α,β-unsaturated carboxylic acids *via* intermediate **2-7** by lowering the LUMO energy of the unsaturated carboxylic acid (**Scheme 2-3**). This effect contributes to reducing the energy gap between the HOMO of dipole and the LUMO of the diolarophile and hence an increase in the rate and regioselectivity of azide-alkyne cycloadditions. A detailed mechanistic discussion of this LUMO activation assumption and a detailed description of the experimental method

(2D-NMR: COSY, HSQC and HMBC) used for the identification of regioisomers will be presented in **Section 2.3.5** and **Section 2.6.6** respectively. As a result, 1,2,3-triazenes **2-13a**–**2-13r** were obtained in yields as high as 96%, whereas, in the absence of the catalyst, the same cycloadditions typically occurred with yields of less than 20%. The boronic acid catalyzed Hüisgen cycloaddition of unsaturated carboxylic acids does not just display an interesting substrate scope, it also circumvents the decarboxylation problem that plagues the thermal, uncatalyzed variant. For example, when run in typical conditions of refluxing 1,2-dichloroethane for just a few hours, the initial product in the reaction of benzyl azide and propiolic acid, **2-13a**, was accompanied by as much as 31% of the decarboxylated adduct **2-16** (**Scheme 2-13**). In contrast, when using the **2-15**-catalyzed variant at room temperature, the desired product **2-13a** was obtained in 96% yield exclusively after 4 hours (entry 1, **Table 2-5**).

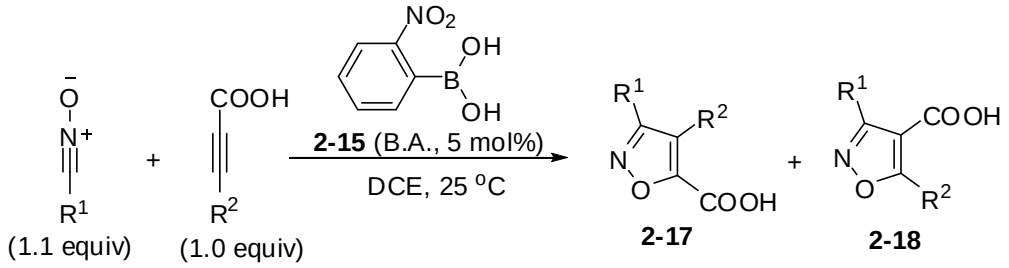


Scheme 2-13: Hüisgen cycloaddition of propiolic acid under thermal uncatalyzed conditions

2.3.3 Substrate scope for nitrile oxide cycloadditions

Isoxazole and isoxazolines, two of the key O- and N-containing five-membered ring heterocycles, possess significant synthetic and biological applications.[19] The 1,3-dipolar [3+2] cycloaddition of nitrile oxides to alkynes or alkenes offers a convenient one-step route to the construction of this class of heterocycles, however, this process often suffers from poor regioselectivity.[19a–19c] Unsaturated carboxylic acids are rarely employed as dipolarophiles in 1,3-dipolar [3+2] cycloaddition of nitrile oxides due to chemical compatibility issues which can be

created by the acidic character of carboxylic acids.[20] Therefore, the carboxylic acid functionality is usually handled in a masked form such as a suitable carboxylic ester, which requires additional synthetic steps.[20] To address these issues, the generality of the BAC concept for activation of unsaturated carboxylic acids was then assessed for 1,3-dipolar [3+2] cycloaddition of nitrile oxides to the unsaturated carboxylic acids. Remarkably, nitrile oxides were found to add to alkynoic acids under catalysis with *o*-$NO_2C_6H_4B(OH)_2$ **2-15** in much improved yields and regioselectivities compared with the corresponding thermal, uncatalyzed reactions (**Table 2-7**). The sterically favored carboxyisoxazole isomers **2-17** were isolated from aromatic (entry 1, **Table 2-7**), unsaturated (entry 2, **Table 2-7**), and aliphatic (entry 3, **Table 2-7**) nitrile oxides as single products

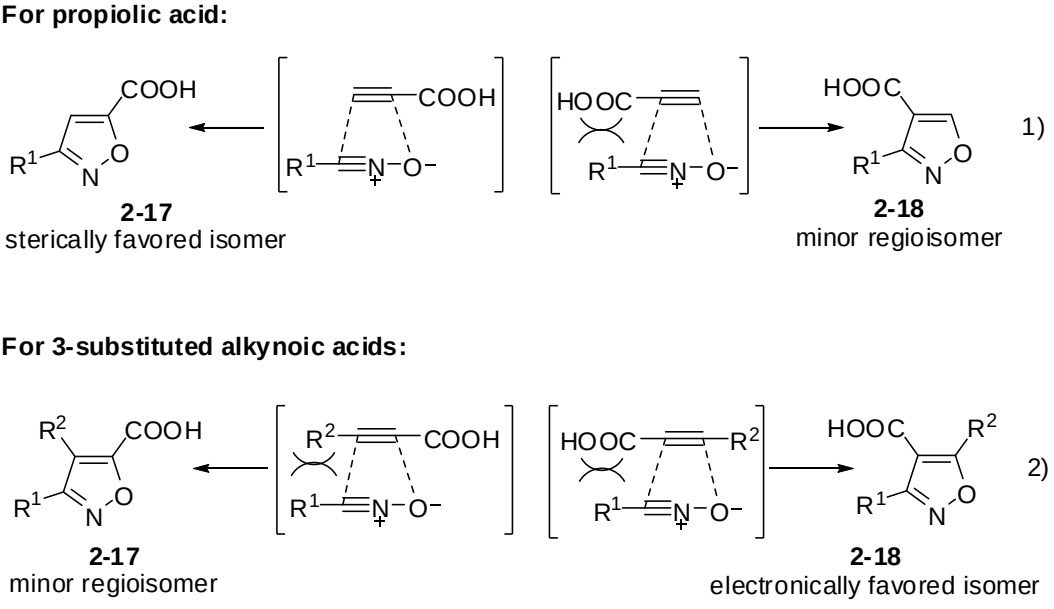


Entry[a]	R^1	R^2	t (h)	Number	Yield[b] (%)	Regioselectivity[c] (**2-17**:**2-18**)
1	Ph	H	2	**2-17a**	87 (15)	>98:2 (9:1)
2	PhCH=CH	H	24	**2-17b**	71 (4)	>98:2 (6:1)
3	$PhCH_2CH_2$	H	24	**2-17c**	73 (5)	>98:2 (3:1)
4[d]	Ph	Ph	24	**2-18d**	69 (5)	1:6 (1:1.2)
5[e]	Ph	Me	24	**2-18e**	78 (10)	1:16 (1:5)

[a]Values in parentheses refer to the uncatalyzed process. [b]Isolated yields of the product purified by acid-base extraction. [c]Measured by ^{1}H NMR spectroscopy of the crude reaction product. [d]When 20 mol% stoichiometry **2-15** was employed, the desired product **2-18d** was obtained in 75% yield (**2-17d**:**2-18d** <2:98). [e]When 20 mol% stoichiometry **2-15** was employed, the desired product **2-18e** was obtained in 80% yield (**2-17e**:**2-18e** <2:98).

Table 2-7: Substrate scope for the boronic acid catalyzed cycloaddition between nitrile oxides and 2-alkynoic acids

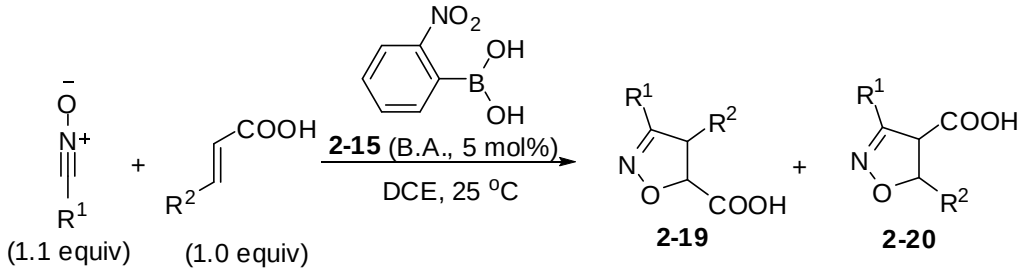
in good to high yields. 3-Substituted alkynoic acids can also be employed with success, but give the opposite regioisomers **2-18** (entries 4 and 5, **Table 2-7**) as the major isomer, apparently under electronic control.[19a–19c] In the cases using propiolic acid as dipolarophiles (entries 1–3, **Table 2-7**), the steric repulsion between R^1 and the carboxyl group plays a major role for controlling the regioselectivity and thus **2-17** were obtained as the predominant isomer (eq 1, **Scheme 2-14**). However, in the cases using 3-substituted alkynoic acids as dipolarophiles (entries 4–5, **Table 2-7**), the steric repulsion between R^1 and the carboxyl group is close to the one between R^1 and R^2 and therefore electronic effects become a major factor governing the regioselectivity (eq 2, **Scheme 2-14**). Since the oxygen atom of nitrile oxides and the β-carbon atom of 2-alkynoic acids bear a partial negative and positive charge respectively, those two atoms interact with each other ($HOMO_{1,3\text{-dipole}}$-$LUMO_{dipolarophile}$ interaction) to direct the orientation of two reacting partners, leading to the major regioisomer **2-18** (eq 2, **Scheme 2-14**). Satisfactorily, by increasing catalyst loading from 5 mol% to 20



Scheme 2-14: Regioselectivity in the boronic acid catalyzed cycloaddition between nitrile oxides and 2-alkynoic acids

mol%, the regioselectivity could be enhanced significantly and only one single regioisomer was obtained in both cases (entries 4 and 5, **Table 2-7**) to avoid the separation issue caused by a mixture of regioisomers.

Acrylic acid and its 3-substituted derivatives were also found to be suitable substrates in reactions with nitrile oxides, giving dihydroisoxazole products **2-19** or **2-20** in greatly improved yields and regioselectivities compared with the uncatalyzed cycloadditions (**Table 2-8**). Similar to alkynoic acids (**Scheme 2-14**), acrylic acid tended to provide sterically favored isomers **2-19** (entries 1–3, **Table 2-8)** and 3-substituted alkenoic acids generated electronically controlled isomer **2-20** (entries 4–5, **Table 2-8**). Surprisingly, mixtures of diastereomers were formed for 3-substituted alkenoic acids (entries 4–5, **Table 2-8**) which seemed to contradict the widely accepted concerted reaction pathway for 1,3-dipolar

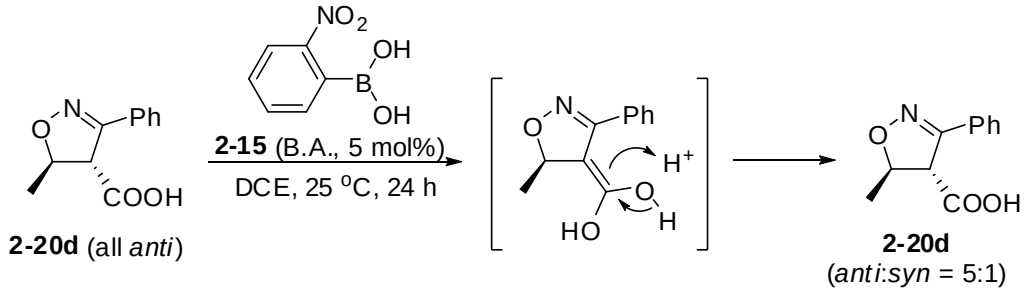


Entry[a]	R^1	R^2	t (h)	Number	Yield[b] (%)	Regioselectivity[c] (**2-19**:**2-20**)
1	Ph	H	24	**2-19a**	67 (7)	>98:2 (95:5)
2	PhCH=CH	H	48	**2-19b**	67 (6)	>98:2 (10:1)
3	$PhCH_2CH_2$	H	48	**2-19c**	65 (3)	>98:2 (5:1)
4[d]	Ph	Me	24	**2-20d**	77 (10)	<2:98 (<2:98)
5[e]	Ph	Ph	24	**2-20e**	65 (10)	<2:98 (<2:98)

[a]Values in parentheses refer to the uncatalyzed process. [b]Isolated yields of the product purified by acid-base extraction. [c]Measured by ^{1}H NMR spectroscopy of the crude reaction product. [d]Diastereomeric ratio: 5:1 *syn*:*anti*. [e] Diastereomeric ratio: 40:1 *syn*:*anti*.

Table 2-8: Substrate scope for the boronic acid catalyzed cycloaddition between nitrile oxides and 2-alkenoic acids

cycloadditions. Luckily, after recrystalization twice from Et_2O, heterocycle **2-20d** could be obtained as a single *anti* diastereomer. This single diastereomer was then subjected to the same reaction conditions and converted into a mixture of diastereomers 5:1 (*anti*:*syn*) after 24 hours (**Scheme 2-15**). Those experiments suggest that boronic acid catalyzed 1,3-dipolar cycloadditions proceeded through a concerted mechanism and the mixture of diastereomers were resulting from acid-induced epimerization (**Scheme 2-15**).

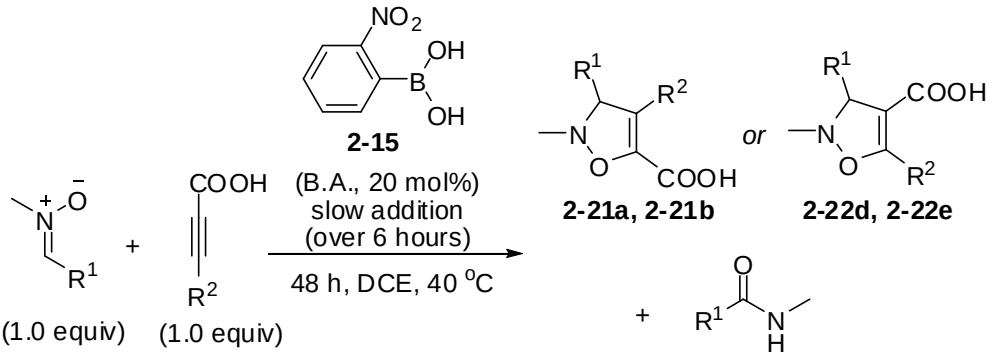


Scheme 2-15: Acid-induced epimerization of 2-20d

Nearly in all cases, not only did the *o*-$NO_2C_6H_4B(OH)_2$-catalyzed variant give greatly improved yields over the uncatalyzed reaction, but the regioselectivity was also significantly improved, to the point of avoiding isomer separation in most cases (**Tables 2-7** and **2-8**).In this regard, boronic acid catalysis may provide both LUMO-lowering activation of α,β-unsaturated carboxylic acids (**Section 2.2.2.4**), along with a templating effect (similar to Carreira's strategy[19d–19e]) whereby the nitrile oxide could bind to the catalyst too. Those two factors combine to contribute to an increase in the rate and regioselectivity of nitrile oxide-alkyne/alkene cycloadditions. A detailed mechanistic discussion of this LUMO activation assumption and a detailed description of the experimental method used for the identification of regioisomers will be presented in **Section 2.3.5** and **Section 2.6.6** respectively.

2.3.4 Substrate scope for nitrone cycloadditions

Isoxazolines and isoxazolidines are versatile synthetic precursors of biologically important compounds such as 1,3-amino alcohols or β-lactams.[21] The 1,3-dipolar [3+2] cycloaddition of nitrones to alkynes or alkenes represents an effective one-step route to the construction of this class of heterocycles, however, this process often suffers from poor regioselectivity.[21] Moreover, unsaturated carboxylic acids are unsuitable dipolarophiles for 1,3-dipolar [3+2] cycloaddition of nitrones because the acidic character of carboxylic acids can induce the Beckmann rearrangement of the nitrone into an amide product.[22] As a result, isoxazolines and isoxazolidines bearing a carboxyl group were usually prepared



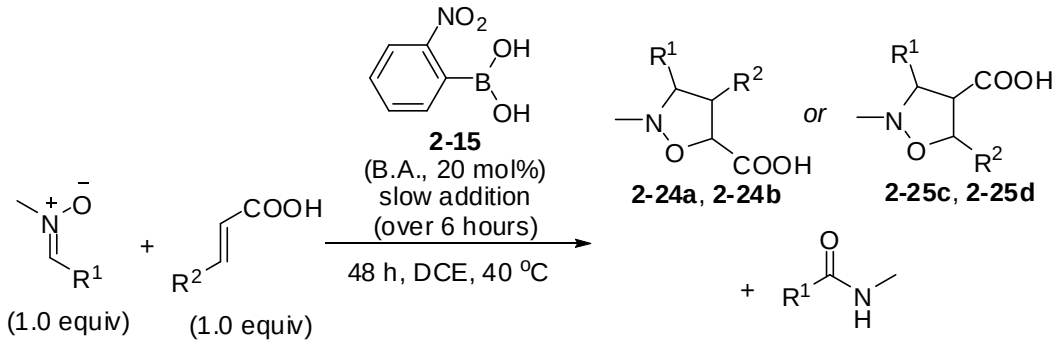
Entry[a]	R^1	R^2	Number	Yield (**2-21**/**2-22**)[b] (%)	Yield (**2-23**)[b] (%)
1	Ph	H	**2-21a**	71 (0)	<2 (41)
2	$PhCH_2CH_2$	H	**2-21b**	62 (<2)	<5 (60)
3	PhCH=CH	H	**2-21c**	–[c] (0)	–[c] (43)
4	Ph	Ph	**2-22d**	50 (<2)	0 (54)
5	Ph	Me	**2-22e**	52 (<5)	<2 (54)

[a]Values in parentheses refer to the uncatalyzed process. [b]Isolated yields of the product purified by flash column chromatography on a short column; entries 1 and 2: product **2-21a** and **2-21b** were obtained as a single regioisomer; entries 4 and 5: product **2-22d** and **2-22e** were obtained as a single regioisomer. [c]A complex mixture was obtained.

Table 2-9: Substrate scope for the boronic acid catalyzed cycloaddition between nitrones and 2-alkynoic acids

using a multi-step sequence involving 1,3-dipolar [3+2] cycloaddition between nitrones and the corresponding carboxylic esters of unsaturated carboxylic acids followed by hydrolysis (deprotection).[21,22] Therefore, a regioselective 1,3-dipolar [3+2] cycloaddition using unsaturated carboxylic acids as dipolarophiles is highly demanded in terms of providing better atom- and step-economy. For this purpose, the feasibility of these dipolar cycloadditions in reactions with nitrones was examined next.[22] In the event, the dipolar cycloaddition of nitrones to 2-alkynoic acids presented an extra challenge caused by the acid-catalyzed Beckmann rearrangement, which leads to decomposition of the nitrone into an amide product.[17] While this reaction is unavoidable under thermal uncatalyzed conditions, we found that it could be suppressed by slow addition of the carboxylic acid, so as to keep it in its neutral, catalyst-activated form necessary for the dipolar cycloaddition. In the event, under conditions of syringe pump addition (over 6 hours), isoxazolecarboxylic acids **2-21a** and **2-21b** and **2-22d** and **2-22e** were isolated in moderate yields and pure regioisomeric forms with only traces of amides **2-23** synthesized (**Table 2-9**).

As with nitrile oxides, acrylic acid and its 3-substituted derivatives were found to be suitable substrates in the cycloadditions of nitrones, giving isoxazolidine products **2-24** or **2-25** in greatly improved yields and regioselectivities compared with the uncatalyzed cycloadditions (**Table 2-10**). The same slow addition procedure employed for the alkynoic acids also prevented amides **2-23** from forming during these reactions. The major regioisomeric cycloadducts were similar to those observed with alkynoic acids: acrylic acid gives sterically controlled formation of **2-24a** and **2-24b** (entries 1–2, **Table 2-10**), whereas 2-butenoic acid affords **2-25c** and **2-25d** through electronic control (entries 3–4, **Table 2-10**). Since a similar rationale behind the experimentally observed regioselectivity was already discussed in **Section 2.3.3** (**Scheme 2-14**), it will not



Entry[a]	R^1	R^2	Number	Yield (**2-24**/**2-25**)[b] (%)	Yield (**2-23**)[b] (%)
1	Ph	H	**2-24a**[c]	75 (<2)	<2 (36)
2	$PhCH_2CH_2$	H	**2-24b**[d]	73 (<2)	<2 (40)
3	Ph	Me	**2-25c**[e]	66 (<2)	<2 (50)
4	$PhCH_2CH_2$	Me	**2-25d**[f]	69 (<2)	0 (53)
5	Ph	Ph	**2-24e/2-25e**	<10, nd[g]	0 (53)
6	$PhCH_2CH_2$	Ph	**2-24f/2-25f**	<10, nd[g]	0 (45)

[a]Values in parentheses refer to the uncatalyzed process. [b]Isolated yields of the product purified by flash column chromatography on a short column; entries 1 and 2: product **2-24a** and **2-24b** were obtained as a single regioisomer; entries 3 and 4: product **2-25c** and **2-25d** were obtained as a single regioisomer. [c]Diastereomeric ratio: 23:1 *anti*:*syn*. [d]Diastereomeric ratio: 2:1 *anti*:*syn*. [e]Diastereomeric ratio: 3:2.5:1:0. [f]Diastereomeric ratio: 3.5:1:0:0. [g] Diastereomeric ratio: not determined.

Table 2-10: Substrate scope for the BAC of nitrone cycloadditions to 2-alkenoic acids

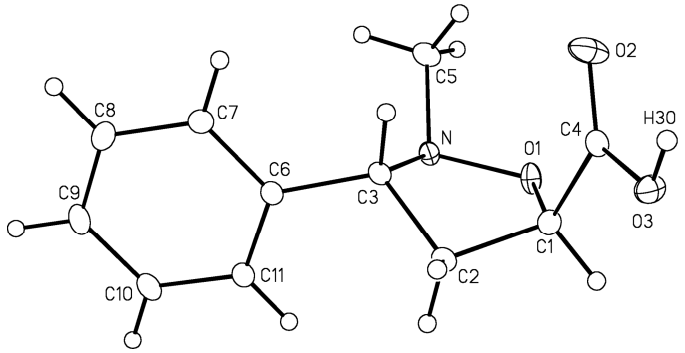
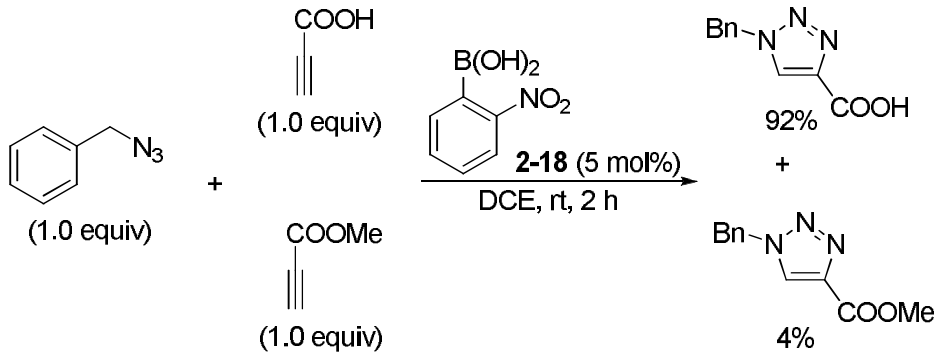


Figure 2-5: ORTEP view of 2-methyl-3-phenylisoxazolidine-5-carboxylic acid (2-24a). Thermal Gaussian ellipsoids at the 20% probability level.

be repeated here. The structure of the predominant *anti*:*syn* diastereomer of **2-24a** was ascertained by X-ray crystallography, which helped support the stereochemical assignments of the other cycloadducts (**Figure 2-5**).[23] A detailed description of the experimental method (a combination of NMR experiments and X-Ray crystallography) used for the identification of stereoisomers will be presented in **Section 2.6.6**.

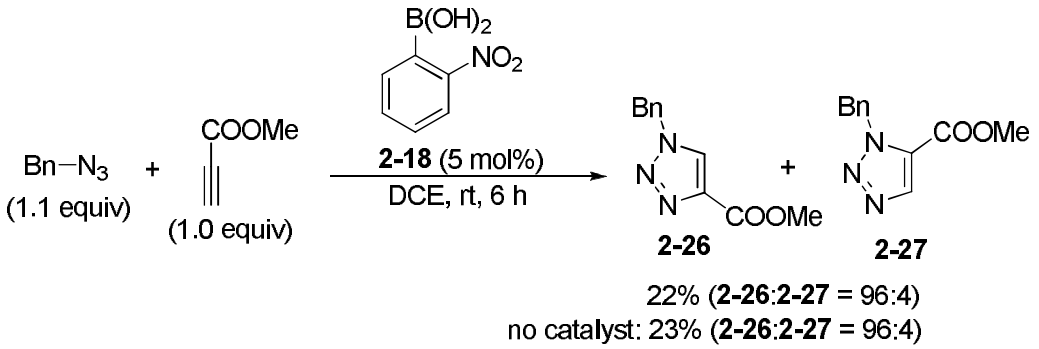
2.3.5 Mechanistic investigations

Although there are a few reported cases of Lewis acid catalyzed cycloadditions of unsaturated carboxylic acids,[18] the current system permits a remarkable selectivity over the corresponding esters that would be difficult to achieve with noncovalent catalysis. The observation depicted in **Scheme 2-16** strongly suggests that the carboxylic acids instead of carboxylic esters are the target functionalities activated by boronic acids.



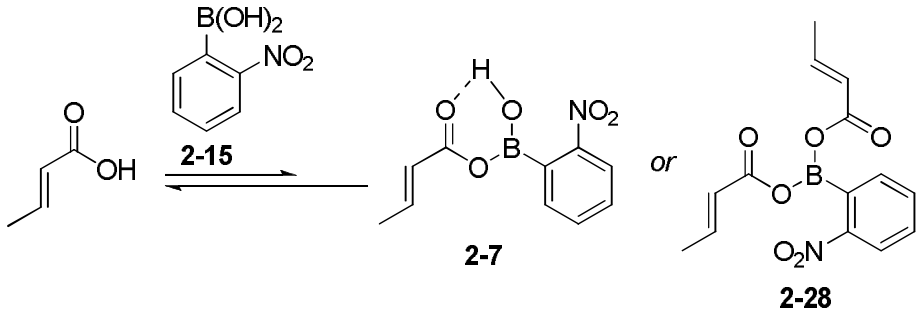
Scheme 2-16: Evidence for selective activation of unsaturated carboxylic acids by BAC

Preliminary experiments were conducted in order to understand the mechanism of the activation provided by the boronic acid catalyst. Because no rate acceleration for methyl propiolate was observed in the presence of *o*-$NO_2C_6H_4B(OH)_2$ **2-18** (**Scheme 2-17**), dehydrative borylation of the carboxylic acid must be an essential step.

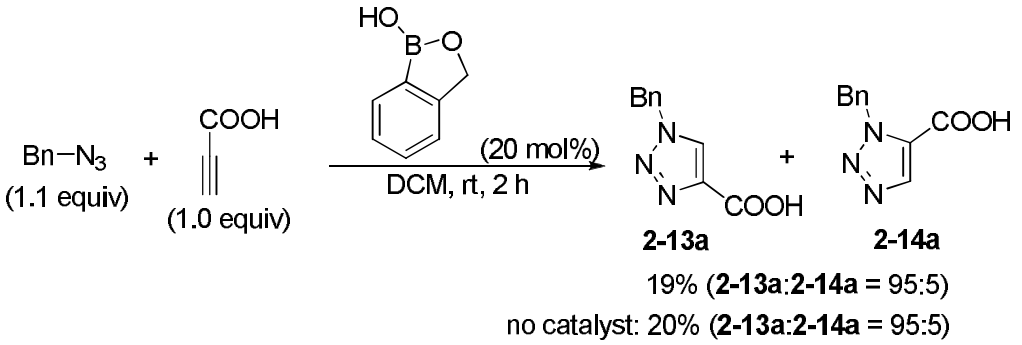


Scheme 2-17: Control experiments for the cycloaddition of methyl propiolate

Therefore, the two most viable activated intermediates that can be formed between the unsaturated carboxylic acid and *o*-nitrophenylboronic acid **2-18** are the hydrogen-bonded, monoacylated, hemiboronic ester **2-7** and the diacylated species **2-28** (**Scheme 2-18**).[2a] Attempts were made to isolate the intermediates by condensing (*E*)-crotonic acid with *o*-$NO_2C_6H_4B(OH)_2$ **2-18** under strictly anhydrous conditions, by using molecular sieves. It is notable that no adduct was formed without a dehydrating agent, implying that the dehydrative borylation is unfavorable and that the activated intermediate must exist in a very small concentration under the reaction conditions. This proposal is supported by the retardation effect of water on the cycloaddition (entries 11 and 12, **Table 2-4**). Stoichiometric condensation experiments were conducted with a varying ratio of (*E*)-crotonic acid to the boronic acid (1:1, 1:2, 2:1) at room temperature in the



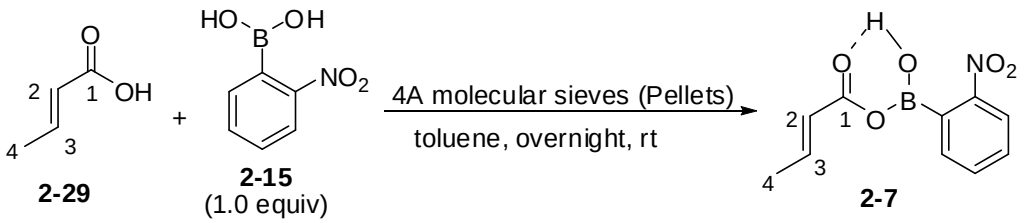
Scheme 2-18: Two possible activated intermediates for boronic acid catalyzed cycloadditions of unsaturated carboxylic acids



Scheme 2-19: Control reaction using cyclic benzoboroxole as catalyst

presence of 4A molecular sieves (for detailed information, see **Section 2.6.7.3**). Regardless of the ratio used, even with excess crotonic acid, only a single species and leftover crotonic acid were observed. No crotonic anhydride was detected by ^{1}H NMR spectroscopy. This result suggests that the activated intermediate is the monoacylated hemiboronic ester **2-7**. This claim is also supported by the poor activity of the cyclic benzoboroxole (**Scheme 2-19**), which is incapable of the same internal hydrogen bonding suspected in intermediate **2-7**.

Using the Childs method,[24] we observed a large increase of 6.9 ppm for the ^{13}C NMR chemical shift of the β carbon (C3) of the mono-acylated intermediate **2-7** (**Figure 2-6**). The extent of this chemical shift increase is similar to that observed in the complexation of methyl crotonate with moderate Lewis acids, such as $SnCl_4$.[24] Under the same conditions the boronic acid had a negligible effect on the ^{13}C NMR chemical shifts of methyl crotonate (**Figure 2-7**). According to these results, *o*-$NO_2C_6H_4B(OH)_2$ **2-15** catalyzes the dipolar cycloadditions through a powerful LUMO-lowering activation of the dipolarophile by the formation of a covalent adduct with the unsaturated carboxylic acid.



^{13}C-NMR shift (ppm, CD_2Cl_2)	C1	C2	**C3**	C4
2-29	172.6	122.4	**148.2**	18.2
2-7	176.4	122.0	**155.1**	19.1

^{13}C-NMR spectra:

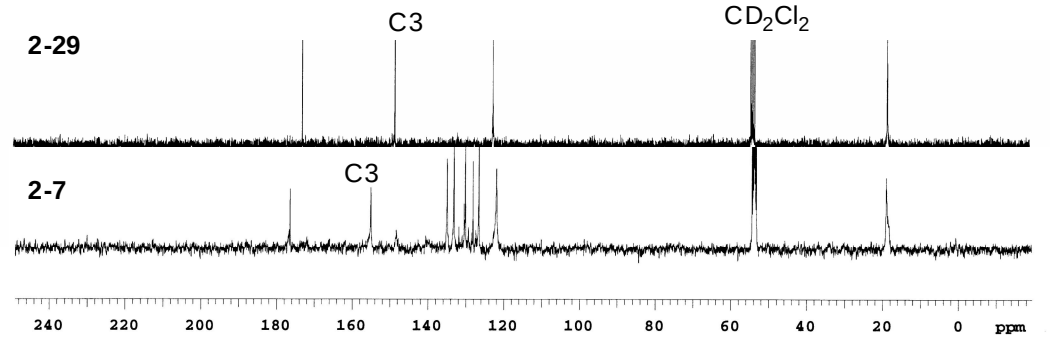
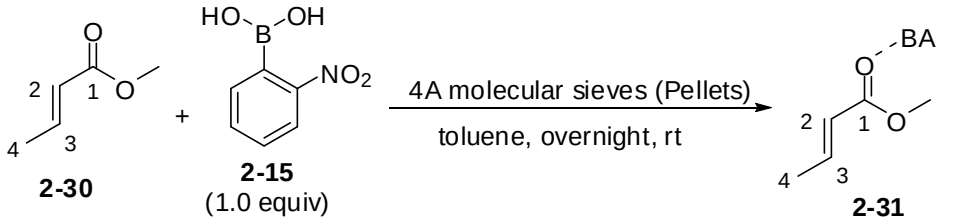


Figure 2-6: Mechanistic NMR experiments to address the origin of the activation in the boronic acid catalyzed cycloadditions

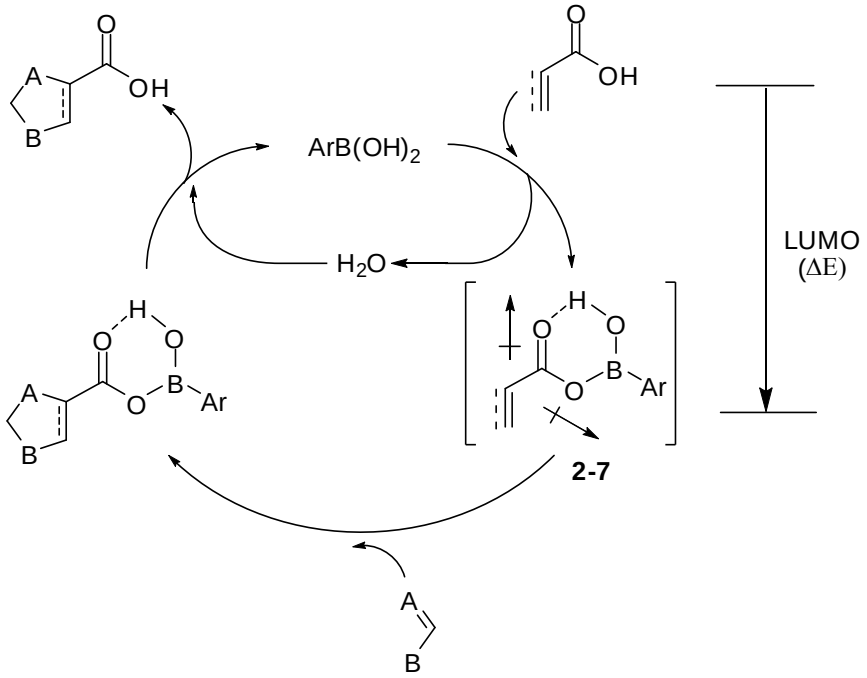


^{13}C-NMR shift (ppm, CD_2Cl_2)	C1	C2	C3	C4
2-30	167.1	122.6	145.0	18.1
2-31	167.4	122.6	145.4	18.1

Figure 2-7: Control preliminary mechanistic experiments to address the origin of the activation in the boronic acid catalyzed cycloadditions

Altogether, this preliminary mechanistic study, combined with the role of water described above, leads to the proposed catalytic cycle depicted in **Scheme 2-20**, in

which both *o*-$NO_2C_6H_4B(OH)_2$ **2-15** and water are recycled in the cycloaddition process. However, excess water substantially deactivates the boronic acid catalysts likely by hydrolyzing the activated intermediate **2-7** back to the starting materials (**Scheme 2-20**). Nearly in all cases, not only did the *o*-$NO_2C_6H_4B(OH)_2$-catalyzed variant give greatly improved yields over the uncatalyzed reaction, but the regioselectivity was also significantly improved, to the point of avoiding isomer separation in most cases. Similar to Lewis acid activation of α,β-unsaturated carbonyl compounds,[18] boronic acids could activate α,β-unsaturated carboxylic acids *via* intermediate **2-7** by lowering the LUMO energy of the unsaturated carboxylic acid (**Scheme 2-20**). This effect contributes to reducing the energy gap between the HOMO of dipole and the LUMO of the diolarophile and hence an increase in the rate and regioselectivity of 1,3-dipolar [3+2] cycloaddition.

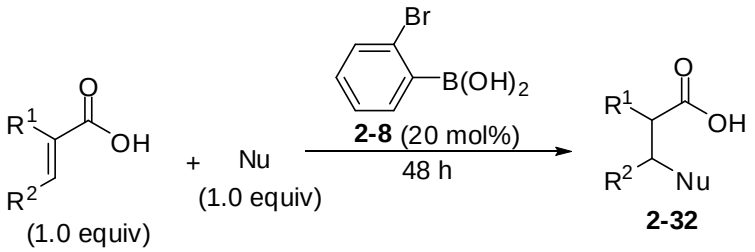


Scheme 2-20: Proposed catalytic cycle for the boronic acid catalyzed cycloadditions of unsaturated carboxylic acids

2.4 Other attempted reactions of carboxylic acid catalyzed by boronic acid

2.4.1 Nucleophilic conjugate addition

Nucleophilic conjugate addition is a classical chemical transformation widely employed in the total syntheses of numerous natural products.[25] Inspired by the successful application of the unsaturated carboxylic acid activation concept using boronic acid catalysis in a variety of cycloaddition reactions, we sought to expand this boronic acid catalysis concept to nucleophilic conjugate addition to further demonstrate its mildness and versatility. Initially, to evaluate this class of reactions, sodium azide and different α,β-unsaturated conjugate carboxylic acids



Entry	R^1, R^2	Nu	Solvent	T (^{o} C)	Product	Yield[a] (%)
1	H, H	NaN_3	DCM	25	**2-32a**	0
2	H, H	NaN_3	DCE	50	**2-32a**	0
3	H, H	NaN_3	DMF	100	**2-32a**	0
4	-$(CH_2)_3$-	NaN_3	DCM	25	**2-32b**	0
5	-$(CH_2)_3$-	NaN_3	DCE	50	**2-32b**	0
6	-$(CH_2)_3$-	NaN_3	DMF	100	**2-32b**	0
7	-$(CH_2)_4$-	NaN_3	DCM	25	**2-32c**	0
8	-$(CH_2)_4$-	NaN_3	DCE	50	**2-32c**	0
9	-$(CH_2)_4$-	NaN_3	DMF	100	**2-32c**	0
10	H, H	PhSH	DCM	25	**2-32d**	65
11[b]	H, H	PhSH	DCM	25	**2-32d**	34

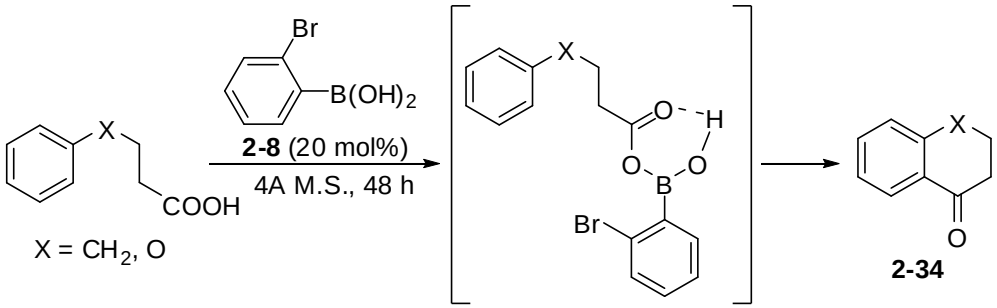
[a]Isolated yields of the product after purification by silica gel column chromatography. [b]Without boronic acid **2-8** as the catalyst.

Table 2-11: Preliminary results for the boronic acid catalyzed nucleophilic conjugate additions of unsaturated carboxylic acids

were chosen as the nucleophile and conjugate addition acceptors respectively (entries 1–9, **Table 2-11**). It was found that they all failed to provide any desired products even under harsh reaction conditions (100 ^{o}C). To our satisfaction, the more nucleophilic thiophenol could facilitate the conjugate addition, providing the desired product **2-32d** in better yield in comparison with the background reaction (entry 10 *vs* 11, **Table 2-11**). These interesting preliminary results suggest *ortho*-bromophenyl boronic acid **2-8** possesses enough catalytic activity to promote the nucleophilic conjugate addition of thiophenol to unsaturated carboxylic acids, which we intend to explore in the near future.

2.4.2 Intramolecular Friedel-Crafts acylation

The carboxylic acid activation concept using boronic acid catalysis was attempted in a variety of other synthetically useful transformations such as the



Entry	X	Solvent	T (^{o} C)	Product	Yield (%)
1	CH_2	DCM	25	**2-34a**	0
2	CH_2	DCE	50	**2-34a**	0
3	CH_2	DMF	100	**2-34a**	0
4	O	DCM	25	**2-34b**	0
5	O	DCE	50	**2-34b**	0
6	O	DMF	100	**2-34b**	0

Table 2-12: Unsuccessful attempts using carboxylic acid activation concept with BAC

sulfonamidation between sulfonic acids and amines and the esterification between carboxylic acids and alcohols. Since no positive results were obtained in these two projects, they will not be discussed here in detail. One example, however, was an attempt to develop a methodology toward intramolecular Friedel-Crafts acylation[26] that would take advantage of the increased electrophilicity of the activated monoacylated hemiboronic ester intermediate **2-33** (**Table 2-12**). In all attempts, no desired cyclic products **2-34** were observed in the presence of 4A molecular sieves (**Table 2-12**).

2.5 Conclusions

In summary, *ortho*-substituted arylboronic acids were found to be a promising class of bifunctional organocatalysts for the activation of carboxylic acids, which is difficult to achieve by traditional means because of the inherent chemical properties of this functional group. The concept of boronic acid catalysis (BAC) for the activation of unsaturated carboxylic acids was applied to several classical cycloadditions such as the Diels-Alder reaction and dipolar [3+2] cycloadditions involving acyclic dienes, cyclic dienes, azides, nitrile oxides, and nitrones as partners. These cycloadditions can directly produce pharmaceutically interesting, small carbocyclic and heterocyclic products that contain a free carboxylic acid functionality. This carboxylate can be employed for further transformations, thereby avoiding prior masking or functionalization of this group. In all cases, BAC provides faster reactions, under milder conditions, with much improved product yields and regioselectivities. Compared to conventional cycloaddition methods, our system does not need to pre-protect unsaturated carboxylic acid substrates and is much more atom-economical, avoiding protection and deprotection steps. Moreover, our procedure requires very mild conditions (room temperature) and has a low environmental impact because no waste and by-products are produced. In some instances, such as triazole formation from

azides and 2-alkynoic acids, catalysis with *ortho*-nitrophenylboronic acid **2-18** circumvents the undesirable product decarboxylation observed when only using thermal activation. By using NMR spectroscopic studies, the boronic acid catalyst was proposed to provide activation by lowering the LUMO of the unsaturated carboxylic acid likely *via* a monoacylated hemiboronic ester intermediate. This electrophilic carboxylic acid activation concept was also attempted in a variety of other classical chemical transformations, including nucleophilic conjugate addition and intramolecular Friedel-Crafts acylation. Among them, *ortho*-bromophenyl boronic acid **2-8** showed slight catalytic activity toward accelerating the nucleophilic conjugate addition of thiophenol to unsaturated carboxylic acids. These new methods allow the direct use of carboxylic acids to streamline organic synthesis, and thus will be attractive technologies in pharmaceutical process chemistry.

2.6 Experimental

2.6.1 General information

Unless otherwise stated, all reactions were performed under an argon atmosphere using flame-dried glassware. Toluene, acetonitrile, 1,2-dichloroethane and dichloromethane were distilled from CaH_2. THF and Et_2O were distilled from sodium with benzophenone as an indicator. Acetone was distilled from 4A molecular sieves. Anhydrous DMF and absolute EtOH were commercially available. All commercially available dienes, aldehydes, acrylic acid and propiolic acid were purified by Kugelrohr distillation prior to use. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and was visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on Varian INOVA-400 or INOVA-500 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. ^1H NMR

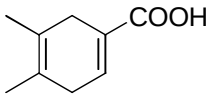
data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; qnt, quintet; dd, doublet of doublets; dt, doublet of triplets; ddd, doublet of double doublets; m, multiplet. High-resolution mass spectra (HRMS) were recorded by the University of Alberta mass spectrometry services laboratory using either electron impact (EI) or electrospray ionization (ESI) techniques. Infrared spectra (IR) were obtained on a Nicolet Magna-IR with frequencies expressed in cm^{-1}. X-ray crystallographic analyses were performed using a Bruker P4/RA/SMART 1000 CCD diffractometer. Powdered 4A molecular sieves (< 5 micron, Aldrich) were dried overnight in a vacuum oven (138 ^{o}C) prior to use. 4A Molecular sieves (1/16 inch pellets) were dried overnight in a vacuum oven (138 ^{o}C) prior to use. 2-Nitrophenylboronic acid **2-15** was made following a literature procedure.[27] 2-Iodophenylboronic acid **2-9** was prepared based on a procedure published by our group.[2d] The other substituted arylboronic acids were obtained from commercial sources.

2.6.2 Boronic acid catalyzed Diels-Alder cycloadditions with 2-alkynoic acids (Section 2.2.2)

2.6.2.1 General procedure (Table 2-2, Scheme 2-6, and Table 2-3)

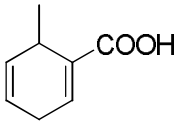
To a solution of 2-alkynoic acid (1.0 mmol) in the indicated solvent (1 mL) was added *ortho*-bromophenylboronic acid **2-8** (40 mg, 0.2 mmol) and the resulting solution was stirred at 25 ^{o}C or 50 ^{o}C for 10 minutes. The diene (2.0 mmol) was then added and the resulting mixture was stirred at 25 ^{o}C or 50 ^{o}C for a given time. The solvent was removed under vacuum and the resulting residue was purified by silica gel column chromatography (Et_2O/*n*-pentane = 1:3) to give the title dienecarboxylic acid in pure form.

2.6.2.2 4,5-Dimethylcyclohexa-1,4-dienecarboxylic acid (2-10a, Table 2-2)

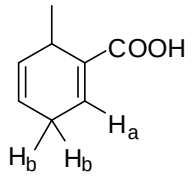


The title compound was prepared using the general procedure for boronic acid catalyzed Diels-Alder cycloadditions with 2-alkynoic acids (propiolic acid and 2,3-dimethylbuta-1,3-diene). The solvent was dichloromethane; the reaction temperature was 25 ^{o}C; the reaction time was 48 hours (86% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$ with one drop DMSO-d_6) δ 11.70 (br s, 1H), 7.12–7.08 (m, 1H), 2.90–2.82 (m, 4H), 1.73–1.66 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$ with one drop DMSO-d_6) δ 169.0, 136.5, 128.2, 123.2, 121.1, 34.0, 31.7, 18.4, 17.9; **IR** (Microscope, cm^{-1}) 3400–2300, 1710, 1649; **HRMS** (EI) for $C_9H_{12}O_2$: calcd. 152.08373; found 152.08355.

2.6.2.3 6-Methylcyclohexa-1,4-dienecarboxylic acid (2-10b, Table 2-2)

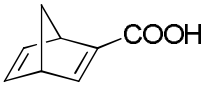


The title compound was prepared using the general procedure for boronic acid catalyzed Diels-Alder cycloadditions with 2-alkynoic acids (propiolic acid and penta-1,3-diene). The solvent was dichloromethane; the reaction temperature was 25 ^{o}C; the reaction time was 48 hours (83% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.18 (br s, 1H), 7.15–7.10 (m, 1H), 5.80–5.74 (m, 1H), 5.68–5.62 (m, 1H), 3.26–3.14 (m, 1H), 2.92–2.86 (m, 2H), 1.20 (d, J = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.4, 139.0, 132.7, 131.2, 120.7, 29.5, 27.4, 21.7; **IR** (Microscope, cm^{-1}) 3400–2300, 1684, 1656; **HRMS** (EI) for $C_8H_{10}O_2$: calcd. 138.06808; found 138.06812.



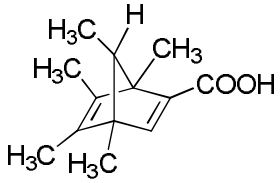
The above regioisomer was determined by 2D-NMR spectroscopy. From ^{1}H-NMR spectrum, H_a and H_b (see the above figure) could be identified as 7.15–7.10 (m, 1H) and 2.92–2.86 (m, 2H) respectively. A strong correlation δ H_a ↔ H_b on the COSY spectrum strongly suggests that the desired product was the above regioisomer.

2.6.2.4 Bicyclo[2.2.1]hepta-2,5-diene-2-carboxylic acid (2-10c, Table 2-2)

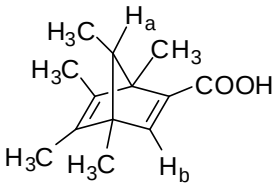


The title compound was prepared using the general procedure for boronic acid catalyzed Diels-Alder cycloadditions with 2-alkynoic acids (propiolic acid and cyclopenta-1,3-diene). The solvent was dichloromethane; the reaction temperature was 25 ^{o}C; the reaction time was 8 hours (91% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (dt, *J* = 3.2, 0.9 Hz, 1H), 6.93 (dd, *J* = 4.8, 3.1 Hz, 1H), 6.73 (dd, *J* = 5.1, 3.2 Hz, 1H), 3.92–3.88 (m, 1H), 3.77–3.72 (m, 1H), 2.21–2.13 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.3, 159.1, 149.1, 143.8, 141.5, 74.5, 51.8, 49.7; **IR** (Microscope, cm^{-1}) 3400–2300, 1658, 1588, 1555; **HRMS** (EI) for $C_8H_8O_2$: calcd. 136.05243; found 136.05216.

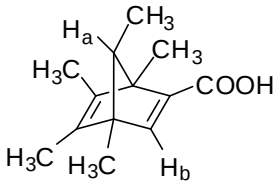
2.6.2.5 1,4,5,6,7-Pentamethylbicyclo[2.2.1]hepta-2,5-diene-2-carboxylic acid (2-10d, Table 2-2)



The title compound was prepared using the general procedure for boronic acid catalyzed Diels-Alder cycloadditions with 2-alkynoic acids (propiolic acid and 1,2,3,4,5-pentamethylcyclopenta-1,3-diene). The solvent was dichloromethane; the reaction temperature was 25 ^{o}C; the reaction time was 6 hours (92% yield and 3:1 diastereomeric ratio, white solid). The two diastereomers were inseparable and the characterization data for the major diastereomer were listed as following: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.17 (br s, 1H), 7.69 (s, 1H), 2.26 (q, *J* = 6.3 Hz, 1H), 1.64 (q, *J* = 1.3 Hz, 3H), 1.58 (q, *J* = 1.4 Hz, 3H), 1.36 (s, 3H), 1.22 (s, 3H), 0.71 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.3, 165.7, 151.0, 142.0, 139.2, 81.8, 61.6, 61.2, 12.5, 12.0, 11.70, 11.68, 9.86; **IR** (Microscope, cm^{-1}) 3400–2300, 1678, 1581; **HRMS** (EI) for $C_{13}H_{18}O_2$: calcd. 206.13068; found 206.13047.



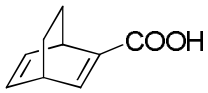
major isomers



minor isomers

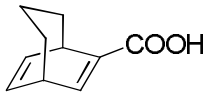
The above regioisomer was determined by ^{1}H-NMR spectroscopy. From ^{1}H-NMR spectrum, H_a and H_b (see the above figure) for the major isomers could be identified as 2.26 (q, *J* = 6.3 Hz, 1H) and 7.69 (s, 1H) respectively. The fact that there is no W coupling between H_a and H_b strongly suggests that the major isomers correspond to the structure shown on the left (see the above figure). On the other hand, the fact that there exists a W coupling (*J* = 1.0 Hz) between H_a and H_b strongly suggests that the minor isomers correspond to the structure shown on the right (see the above figure).

2.6.2.6 Bicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid (2-10e, Table 2-2)



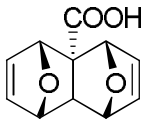
The title compound was prepared using the general procedure for boronic acid catalyzed Diels-Alder cycloadditions with 2-alkynoic acids (propiolic acid and cyclohexa-1,3-diene). The solvent was dichloromethane; the reaction temperature was 25 ^{o}C; the reaction time was 48 hours (82% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.49 (br s, 1H), 7.47 (dd, *J* = 6.4, 2.0 Hz, 1H), 6.41 (ddd, *J* = 7.4, 6.2, 1.5 Hz, 1H), 6.29 (ddd, *J* = 7.4, 5.8, 1.5 Hz, 1H), 4.23–4.19 (m, 1H), 3.85–3.79 (m, 1H), 1.44–1.32 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.9, 148.8, 138.1, 134.7, 132.6, 38.1, 36.2, 24.5, 24.1; **IR** (Microscope, cm^{-1}) 3400–2300, 1674, 1625, 1595, 1588; **HRMS** (EI) for $C_9H_{10}O_2$: calcd. 150.06808; found 150.06808.

2.6.2.7 Bicyclo[3.2.2]nona-6,8-diene-6-carboxylic acid (2-10f, Table 2-2)



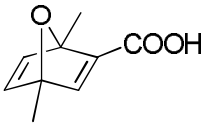
The title compound was prepared using the general procedure for boronic acid catalyzed Diels-Alder cycloadditions with 2-alkynoic acids (propiolic acid and cyclohepta-1,3-diene). The solvent was dichloromethane; the reaction temperature was 25 ^{o}C; the reaction time was 72 hours (62% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.35 (br s, 1H), 7.57 (dd, *J* = 6.8, 1.8 Hz, 1H), 6.34 (ddd, *J* = 8.1, 6.5, 1.4 Hz, 1H), 6.23 (ddd, *J* = 7.7, 6.1, 1.2 Hz, 1H), 3.51–3.45 (m, 1H), 3.14–3.07 (m, 1H), 1.85–1.73 (m, 1H), 1.70–1.59 (m, 1H), 1.48–1.36 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.5, 148.6, 137.3, 133.6, 132.0, 35.8, 34.2, 23.2, 22.1, 21.7; **IR** (Microscope, cm^{-1}) 3500–2300, 1687, 1651, 1613, 1553; **HRMS** (EI) for $C_{10}H_{12}O_2$: calcd. 164.08372; found 164.08347.

2.6.2.8 1,5,8,8a-Tetrahydro-1,4:5,8-diepoxynaphthalene-4a-carboxylic acid (2-10h, Scheme 2-6)



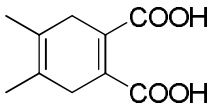
The title compound was prepared using the general procedure for boronic acid catalyzed Diels-Alder cycloadditions with 2-alkynoic acids (propiolic acid and furan). The solvent was dichloromethane; the reaction temperature was 25 ^{o}C; the reaction time was 6 hours (98% yield, white solid). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.31 (br s, 1H), 6.62 (dd, J = 5.7, 1.6 Hz, 2H), 6.31 (dd, J = 5.7, 1.4 Hz, 2H), 4.92 (s, 2H), 4.79 (s, 2H), 2.08 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 172.1, 140.3, 136.8, 80.7, 80.5, 65.5, 51.9; **IR** (Microscope, cm^{-1}) 3500–2700, 1731, 1564; **HRMS** (ESI) for $C_{11}H_9O_4$: calcd. 205.05060; found 205.05020.

2.6.2.9 1,4-Dimethyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2-carboxylic acid (2-10i, Scheme 2-6)



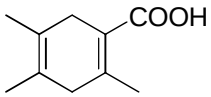
The title compound was prepared using the general procedure for boronic acid catalyzed Diels-Alder cycloadditions with 2-alkynoic acids (propiolic acid and 2,5-dimethylfuran). The solvent was dichloromethane; the reaction temperature was 25 ^{o}C; the reaction time was 2 hours (96% yield). The characterization data for this compound matched those of a previous report.[28]

2.6.2.10 4,5-Dimethylcyclohexa-1,4-diene-1,2-dicarboxylic acid (2-11a, Table 2-3)



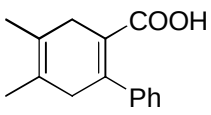
The title compound was prepared using the general procedure for boronic acid catalyzed Diels-Alder cycloadditions with 2-alkynoic acids (but-2-ynedioic acid and 2,3-dimethylbuta-1,3-diene). The solvent was dichloromethane; the reaction temperature was 25 ^{o}C; the reaction time was 8 hours (89% yield, white solid). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.60 (br s, 2H), 2.81 (s, 4H), 1.61 (s, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 168.8, 131.6, 121.4, 33.8, 17.7; **IR** (Microscope, cm^{-1}) 3400–2300, 1692, 1580, 1510; **HRMS** (ESI) for $C_{10}H_{11}O_4$: calcd. 195.06630; found 195.06620.

2.6.2.11 2,4,5-Trimethylcyclohexa-1,4-dienecarboxylic acid (2-11b, Table 2-3)



The title compound was prepared using the general procedure for boronic acid catalyzed Diels-Alder cycloadditions with 2-alkynoic acids (but-2-ynoic acid and 2,3-dimethylbuta-1,3-diene). The solvent was 1,2-dichloroethane; the reaction temperature was 50 ^{o}C; the reaction time was 96 hours (44% yield, white solid). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.14 (br s, 1H), 2.77–2.70 (m, 2H), 2.69–2.61 (m, 2H), 1.94 (s, 3H), 1.59 (s, 3H), 1.56 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 168.8, 142.1, 122.6, 121.8, 121.2, 40.9, 34.4, 20.3, 17.7, 17.4; **IR** (Microscope, cm^{-1}) 3400–2300, 1654, 1631; **HRMS** (ESI) for $C_{10}H_{13}O_2$: calcd. 165.09210; found 165.09190.

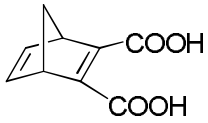
2.6.2.12 4,5-Dimethyl-2-phenylcyclohexa-1,4-dienecarboxylic acid (2-11c, Table 2-3)



The title compound was prepared using the general procedure for boronic acid

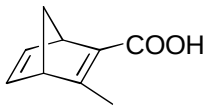
catalyzed Diels-Alder cycloadditions with 2-alkynoic acids (3-phenylpropiolic acid and 2,3-dimethylbuta-1,3-diene). The solvent was THF; the reaction temperature was 50 ^{o}C; the reaction time was 48 hours (41% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.00 (br s, 1H), 7.36–7.26 (m, 3H), 7.17–7.11 (m, 2H), 3.06–2.96 (m, 4H), 1.72 (s, 3H), 1.67 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.2, 147.4, 142.1, 128.1, 127.2, 126.5, 123.5, 122.9, 121.7, 41.9, 34.7, 17.9, 17.8; **IR** (Microscope, cm^{-1}) 3400–2300, 1691, 1665, 1639, 1558; **HRMS** (ESI) for $C_{15}H_{16}NaO_2$: calcd. 250.10480; found 250.10430.

2.6.2.13 Bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylic acid (2-11d, Table 2-3)



The title compound was prepared using the general procedure for boronic acid catalyzed Diels-Alder cycloadditions with 2-alkynoic acids (but-2-ynedioic acid and cyclopenta-1,3-diene). The solvent was dichloromethane; the reaction temperature was 25 ^{o}C; the reaction time was 48 hours (84% yield). The characterization data for this compound matched those of a previous report.[29]

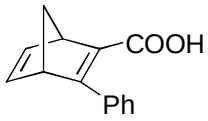
2.6.2.14 3-Methylbicyclo[2.2.1]hepta-2,5-diene-2-carboxylic acid (2-11e, Table 2-3)



The title compound was prepared using the general procedure for boronic acid catalyzed Diels-Alder cycloadditions with 2-alkynoic acids (but-2-ynoic acid and cyclopenta-1,3-diene). The solvent was dichloromethane; the reaction temperature was 25 ^{o}C; the reaction time was 48 hours (81% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.00 (br s, 1H), 6.91 (dd, J = 4.9, 3.0 Hz, 1H), 6.73 (dd, J =

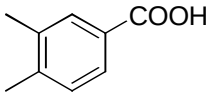
4.3, 3.3 Hz, 1H), 3.92–3.88 (m, 1H), 3.46–3.42 (m, 1H), 2.27 (s, 3H), 2.11–2.06 (m, 1H), 2.01–1.96 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.6, 171.4, 144.2, 140.1, 137.8, 70.9, 58.5, 50.8, 17.5; **IR** (Microscope, cm^{-1}) 3400–2300, 1660, 1614, 1559; **HRMS** (EI) for $C_9H_{10}O_2$: calcd. 150.06808; found 150.06832.

2.6.2.15 3-Phenylbicyclo[2.2.1]hepta-2,5-diene-2-carboxylic acid (2-11f, Table 2-3)



The title compound was prepared using the general procedure for boronic acid catalyzed Diels-Alder cycloadditions with 2-alkynoic acids (3-phenylpropiolic acid and cyclopenta-1,3-diene). The solvent was THF; the reaction temperature was 25 ^{o}C; the reaction time was 48 hours (85% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.00 (br s, 1H), 7.56–7.51 (m, 2H), 7.40–7.31 (m, 3H), 7.01 (dd, *J* = 5.0, 3.1 Hz, 1H), 6.92 (dd, *J* = 4.8, 3.1 Hz, 1H), 4.11–4.07 (m, 1H), 3.91–3.86 (m, 1H), 2.28 (dt, *J* = 6.7, 1.5 Hz, 1H), 2.09 (dt, *J* = 6.7, 1.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.7, 169.9, 143.8, 140.6, 138.3, 135.4, 128.8, 128.0, 127.8, 70.5, 59.1, 52.9; **IR** (Microscope, cm^{-1}) 3400–2300, 1668, 1593, 1560; **HRMS** (EI) for $C_{14}H_{12}O_2$: calcd. 212.08372; found 212.08369.

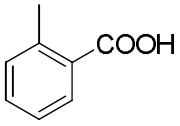
2.6.2.16 Preparation of 3,4-dimethylbenzoic acid 2-12a (Scheme 2-8)



To a solution of propiolic acid (70 mg, 1.0 mmol) in dichloromethane (1 mL) was added *ortho*-bromophenylboronic acid **2-8** (40 mg, 0.2 mmol) and the resulting solution was stirred at room temperature (25 ^{o}C) for 10 minutes. 2,3-Dimethyl-1,3-butadiene (164 mg, 2.0 mmol) was then added and the resulting mixture was stirred at room temperature (25 ^{o}C) for 48 hours.

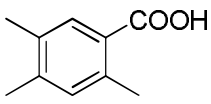
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (227 mg, 1.0 mmol) was added and the resulting mixture was stirred at room temperature (25 ^{o}C) for 4 hours. The solvent was removed under vacuum at room temperature (25 ^{o}C). The residue was purified by silica gel column chromatography (Et_2O/*n*-pentane = 1:3) to give the title polysubstituted arene **2-12a** (128 mg, 85%) as a colorless solid in pure form. The characterization data for this compound matched those of a previous report.[30]

2.6.2.17 Preparation of 3,4-dimethylbenzoic acid 2-12b (Scheme 2-8)



To a solution of propiolic acid (70 mg, 1.0 mmol) in dichloromethane (1 mL) was added *ortho*-bromophenylboronic acid **2-8** (40 mg, 0.2 mmol) and the resulting solution was stirred at room temperature (25 ^{o}C) for 10 minutes. 1,3-Pentadiene (136 mg, 2.0 mmol) was then added and the resulting mixture was stirred at room temperature (25 ^{o}C) for 48 hours. DDQ (227 mg, 1.0 mmol) was added and the resulting mixture was stirred at room temperature (25 ^{o}C) for 4 hours. The solvent was removed under vacuum at room temperature (25 ^{o}C). The residue was purified by silica gel column chromatography (Et_2O/*n*-pentane = 1:3) to give the title polysubstituted arene **2-12b** (109 mg, 80%) as a colorless solid in pure form. The characterization data for this compound matched those of a previous report.[31]

2.6.2.18 Preparation of 3,4-dimethylbenzoic acid 2-12c (Scheme 2-8)



To a solution of 2-butynoic acid (84 mg, 1.0 mmol) in 1,2-dichloroethane (1 mL) was added *ortho*-bromophenylboronic acid **2-8** (40 mg, 0.2 mmol) and the

resulting solution was stirred at 50 °C for 10 minutes. 2,3-Dimethyl-1,3-butadiene (164 mg, 2.0 mmol) was then added and the resulting mixture was stirred at 50 °C for 96 hours. DDQ (227 mg, 1.0 mmol) was added and the resulting mixture was stirred at room temperature (25 °C) for 4 hours. The solvent was removed under vacuum at room temperature (25 °C). The residue was purified by silica gel column chromatography (Et_2O/*n*-pentane = 1:3) to give the title polysubstituted arene **2-12c** (66 mg, 40%) as a colorless solid in pure form. The characterization data for this compound matched those of a previous report.[32]

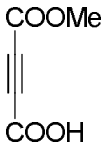
2.6.3 BAC of azide-alkyne cycloadditions (Section 2.3.2)

2.6.3.1 Preparation of azides

All aliphatic azides were prepared following a literature procedure.[33] All aromatic azides were prepared following a literature procedure.[34]

2.6.3.2 Preparation of alkynoic acids and alkenoic acids

2.6.3.2.1 Preparation of 4-methoxy-4-oxobut-2-ynoic acid



To a stirred solution of methyl propiolate (84 mg, 1.0 mmol) in THF (20 mL) at –78 °C was added dropwise *n*-BuLi (2.5 M in hexanes, 0.44 mL, 1.1 mmol) under argon and this solution was stirred at –78 °C for 2 hours. Dry ice (about 3.0 g) was then added and the resulting mixture was allowed to stir at –78 °C for another 1 hour. The reaction mixture was treated with 6 M HCl (10 mL) and extracted with Et_2O (3 × 5 mL). The organic layers were collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (91 mg, 71%) in pure form. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.18 (br s, 1H), 3.87 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.1, 152.0, 76.5, 74.0, 53.6; **IR** (Microscope, cm^{-1})

3600-2100 (broad), 1726; **HRMS** (EI) for $C_5H_4O_4$: calcd. 128.01096; found 128.01089.

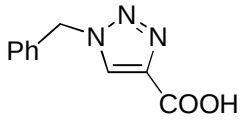
2.6.3.2.2 Other unsaturated carboxylic acids

The other alkynoic acids and alkenoic acids were commercially available.

2.6.3.3 General procedure for BAC of organocatalytic azide-alkynoic acid cycloadditions (Tables 2-5 and 2-6)

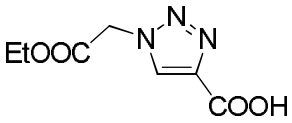
To a solution of alkynoic acid (1.0 mmol) in 1,2-dichloroethane (2 mL) was added the *ortho*-nitrophenylboronic acid **2-15** (8 mg, 0.05 mmol) and this solution was stirred at 25 ^{o}C or 40 ^{o}C (see the detailed information about each of the following examples) for 10 minutes. The azide (1.1 mmol) was then added and the resulting mixture was stirred at 25 ^{o}C or 40 ^{o}C for a given time. The solvent was removed under vacuum at room temperature (25 ^{o}C). The residue was saturated with Et_2O (5 mL) to provide a precipitate, which was filtered and washed with Et_2O (2 × 5 mL) to give the title compound in pure form.

2.6.3.4 1-Benzyl-1*H*-1,2,3-triazole-4-carboxylic acid (2-13a, Table 2-5)



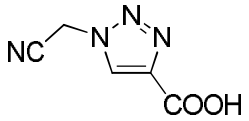
The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 4 hours (96% yield). The characterization data for this compound matched those of previous reports.[35]

2.6.3.5 1-(2-Ethoxy-2-oxoethyl)-1*H*-1,2,3-triazole-4-carboxylic acid (2-13b, Table 2-5)



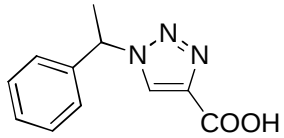
The title compound was prepared using the general procedure for the organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 4 hours (92% yield, white solid). The regioisomer was identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.15 (br s, 1H), 8.65 (s, 1H), 5.44 (s, 2H), 4.18 (q, J = 7.1 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.8, 161.5, 139.7, 130.2, 61.6, 50.5, 13.9; **IR** (Microscope, cm^{-1}) 3200-2200 (broad), 1738, 1680; **HRMS** (ESI) for $C_7H_8N_3O_4$: calcd. 198.05203; found 198.05204.

2.6.3.6 1-(Cyanomethyl)-1*H*-1,2,3-triazole-4-carboxylic acid (2-13c, Table 2-5)



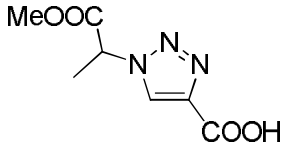
The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 4 hours (96% yield, white solid). The regioisomer was identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (500 MHz, DMSO-d_6) δ 13.31 (br s, 1H), 8.78 (s, 1H), 5.82 (s, 2H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 161.2, 140.1, 129.8, 114.7, 37.6; **IR** (Microscope, cm^{-1}) 3300-2200 (broad), 1686, 1548; **HRMS** (ESI) for $C_5H_3N_4O_2$: calcd. 151.02615; found 151.02614.

2.6.3.7 1-(1-Phenylethyl)-1*H*-1,2,3-triazole-4-carboxylic acid (2-13d, Table 2-5)



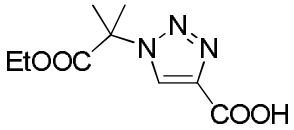
The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 24 hours (84% yield, white solid). The regioisomer was identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.06 (br s, 1H), 8.83 (s, 1H), 7.39-7.28 (m, 5H), 5.99 (q, J = 7.1 Hz, 1H), 1.90 (d, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 161.6, 140.4, 139.7, 128.7, 128.1, 127.6, 126.4, 59.6, 20.7; **IR** (Microscope, cm^{-1}) 3300-2200 (broad), 1694, 1552; **HRMS** (ESI) for $C_{11}H_{10}N_3O_2$: calcd. 216.07785; found 216.07789.

2.6.3.8 1-(1-Methoxy-1-oxopropan-2-yl)-1*H*-1,2,3-triazole-4-carboxylic acid (2-13e, Table 2-5)



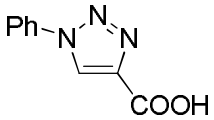
The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 24 hours (92% yield, white solid). The regioisomer was identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.13 (br s, 1H), 8.81 (s, 1H), 5.72 (q, J = 7.3 Hz, 1H), 3.68 (s, 3H), 1.78 (d, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 169.4, 161.5, 139.6, 128.9, 57.7, 52.9, 16.9; **IR** (Microscope, cm^{-1}) 3300-2200 (broad), 1749, 1693; **HRMS** (ESI) for $C_7H_8N_3O_4$: calcd. 198.05203; found 198.05207.

2.6.3.9 1-(1-Ethoxy-2-methyl-1-oxopropan-2-yl)-1*H*-1,2,3-triazole-4-carboxylic acid (2-13f, Table 2-5)



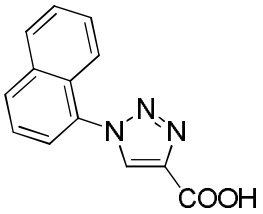
The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 96 hours (71% yield, white solid). The regioisomer was identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.12 (br s, 1H), 8.88 (s, 1H), 4.12 (q, J = 7.1 Hz, 2H), 1.88 (s, 6H), 1.13 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.8, 161.6, 139.5, 128.1, 64.6, 61.9, 25.0, 13.7; **IR** (Microscope, cm^{-1}) 3300-2200 (broad), 1752, 1695, 1556; **HRMS** (ESI) for $C_9H_{13}N_3O_4$: calcd. 228.09788; found 228.09806.

2.6.3.10 1-Phenyl-1*H*-1,2,3-triazole-4-carboxylic acid (2-13g, Table 2-5)



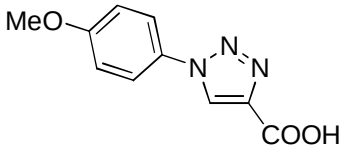
The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 24 hours (82% yield, white solid). The regioisomer was identified by 2D NMR experiment (see **Section 2.6.6.1**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.28 (br s, 1H), 9.38 (s, 1H), 7.96 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.8 Hz, 2H), 7.52 (t, J = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 161.5, 140.7, 136.2, 129.8, 129.1, 126.9, 120.4; **IR** (Microscope, cm^{-1}) 3245, 3061, 2906, 2754, 2551, 1713; **HRMS** (EI) for $C_9H_7N_3O_2$: calcd. 189.05383; found 189.05406.

2.6.3.11 1-(Naphthalen-1-yl)-1*H*-1,2,3-triazole-4-carboxylic acid (2-13h, Table 2-5)



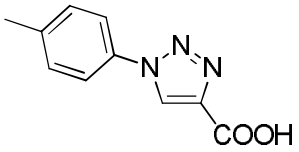
The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 72 hours (80% yield). The characterization data for this compound matched those of a previous report.[36]

2.6.3.12 1-(4-Methoxyphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid (2-13i, Table 2-5)



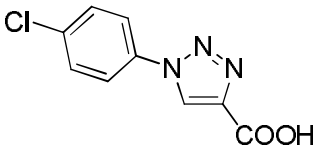
The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 24 hours (93% yield and 5:1 regioisomer ratio, white solid). The regioisomers were identified by 2D NMR experiments (see **Section 2.6.6.1**). The two regioisomers were inseparable and the characterization data for the major regioisomer were listed as following: **^{1}H NMR** (500 MHz, DMSO-d_6) δ 13.25 (br s, 1H), 9.26 (s, 1H), 7.86 (d, J = 9.2 Hz, 2H), 7.13 (d, J = 9.2 Hz, 2H), 3.82 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 161.5, 159.6, 140.4, .129.5, 127.2, 122.2, 114.8, 55.5; **IR** (Microscope, cm^{-1}) 3300-2200 (broad), 1690, 1520; **HRMS** (ESI) for $C_{10}H_8N_3O_3$: calcd. 218.05711; found 218.05704.

2.6.3.13 1-(4-Methoxyphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid (2-13j, Table 2-5)



The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 48 hours (85% yield and 16:1 regioisomer ratio, white solid). The regioisomers were identified by 2D NMR experiments (see **Section 2.6.6.1**). The two regioisomers were inseparable and the characterization data for the major regioisomer were listed as following: **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.30 (br s, 1H), 9.31 (s, 1H), 7.82 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 2.36 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 161.5, 140.5, 138.8, 133.9, 130.2, 126.8, 120.3, 20.5; **IR** (Microscope, cm^{-1}) 3300-2200 (broad), 1707, 1515; **HRMS** (ESI) for $C_{10}H_8N_3O_2$: calcd. 202.06220; found 202.06239.

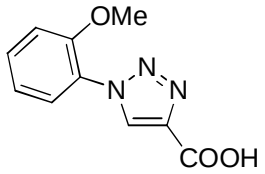
2.6.3.14 1-(4-Chlorophenyl)-1*H*-1,2,3-triazole-4-carboxylic acid (2-13k, Table 2-5)



The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 72 hours (73% yield, white solid). The regioisomers were identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.33 (br s, 1H), 9.40 (s, 1H), 8.00 (d, J = 8.9 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ

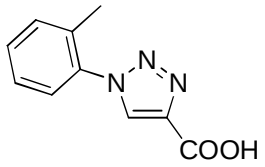
161.4, 140.8, 135.0, 133.5, 129.8, 127.2, 122.2; **IR** (Microscope, cm^{-1}) 3300-2200 (broad), 1707, 1694, 1558, 1503; **HRMS** (ESI) for $C_9H_5ClN_3O_2$: calcd. 222.00758; found 222.00732.

2.6.3.15 1-(2-Methoxyphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid (2-13l, Table 2-5)



The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (25 ^oC) and the reaction time was 24 hours (87% yield, white solid). The regioisomers were identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (500 MHz, DMSO-d_6) δ 13.24 (br s, 1H), 8.95 (s, 1H), 7.65 (dd, J = 7.8, 1.6 Hz, 1H), 7.56 (ddd, J = 8.5, 7.6, 1.7 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.16 (dt, J = 7.6, 1.2 Hz, 1H), 3.85 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 161.6, 151.8, 139.6, 131.2, 130.6, 126.0, 125.1, 120.8, 113.0, 56.2; **IR** (Microscope, cm^{-1}) 3300-2200 (broad), 1716, 1688, 1560, 1534; **HRMS** (ESI) for $C_{10}H_8N_3O_3$: calcd. 218.05711; found 218.05718.

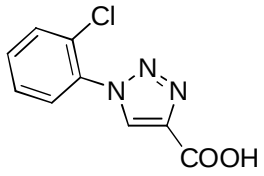
2.6.3.16 1-*O*-tolyl-1*H*-1,2,3-triazole-4-carboxylic acid (2-13m, Table 2-5)



The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (25 ^oC) and the reaction time was 72 hours (78% yield, white solid). The regioisomer was identified by 2D NMR experiments (see **Section**

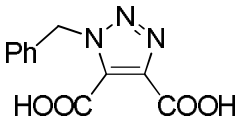
2.6.6.1). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.25 (br s, 1H), 9.05 (s, 1H), 7.53-7.38 (m, 4H), 2.14 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 161.6, 139.9, 135.7, 133.2, 131.3, 130.3, 130.2, 127.0, 126.2, 17.2; **IR** (Microscope, cm^{-1}) 3300-2200 (broad), 1730, 1549; **HRMS** (ESI) for $C_{10}H_8N_3O_2$: calcd. 202.06220; found 202.06220.

2.6.3.17 1-(2-Chlorophenyl)-1*H*-1,2,3-triazole-4-carboxylic acid (2-13n, Table 2-5)



The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 72 hours (63% yield, white solid). The regioisomers were identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.34 (br s, 1H), 9.14 (s, 1H), 7.78 (dd, J = 7.9, 1.3 Hz, 1H), 7.74 (dd, J = 7.7, 1.8 Hz, 1H), 7.66 (dt, J = 7.5, 1.7 Hz, 1H), 7.59 (dt, J = 7.7, 1.5 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 161.4, 139.8, 133.9, 132.1, 131.0, 130.4, 128.8, 128.6, 128.4; **IR** (Microscope, cm^{-1}) 3300-2200 (broad), 1717, 1699, 1564; **HRMS** (ESI) for $C_9H_6ClN_3O_2Na$: calcd. 246.00408; found 246.00426.

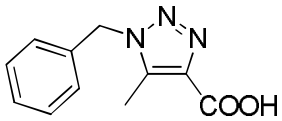
2.6.3.18 1-Benzyl-1*H*-1,2,3-triazole-4,5-dicarboxylic acid (2-13o, Table 2-6)



The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 24 hours. THF was used as

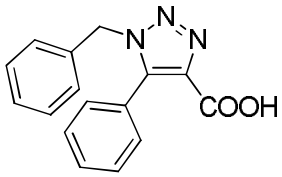
the solvent for this substrate (92% yield, white solid). The structure of this compound was also confirmed by X-ray crystallography.[23] **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.04 (br s, 2H), 7.36-7.26 (m, 3H), 7.22 (m, 2H), 5.84 (s, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 161.6, 159.3, 140.0, 135.4, 131.5, 128.7, 128.1, 127.6, 52.6; **IR** (Microscope, cm^{-1}) 3200-2200 (broad), 1750, 1715; **HRMS** (ESI) for $C_{11}H_8N_3O_4Na_2$: calcd. 292.03047; found 292.03046.

2.6.3.19 1-Benzyl-5-methyl-1*H*-1,2,3-triazole-4-carboxylic acid (2-13p, Table 2-6)



The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was 40 ^oC and the reaction time was 48 hours (70% yield). The characterization data for this compound matched those of a previous report.[37]

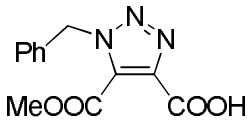
2.6.3.20 1-Benzyl-5-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid (2-13q, Table 2-6)



The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (40 ^oC) and the reaction time was 96 hours (68% yield and 5:1 regioisomer ratio, white solid). The regioisomers were identified by comparing the NMR data of their corresponding ethyl esters with the data in the reported literature (see **Section 2.6.6.2**).[38] The two regioisomers were inseparable and the characterization data for the major regioisomer were listed as following: **^{1}H NMR**

(500 MHz, DMSO-d_6) δ 13.00 (br s, 1H), 7.50-7.40 (m, 3H), 7.36-7.29 (m, 2H), 7.25-7.20 (m, 3H), 6.90 (m, 2H), 5.45 (s, 2H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 161.7, 140.6, 137.0, 135.2, 129.8, 128.6, 128.3, 127.9, 127.6, 127.2, 126.1, 51.3; **IR** (Microscope, cm^{-1}) 3300-2200 (broad), 1696, 1565; **HRMS** (ESI) for $C_{16}H_{12}N_3O_2$: calcd. 278.09350; found 278.09330.

2.6.3.21 1-Benzyl-5-(methoxycarbonyl)-1*H*-1,2,3-triazole-4-carboxylic acid (2-13r, Table 2-6)



The title compound was prepared using the general procedure for the BAC of organocatalytic azide-alkynoic acid cycloadditions. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 24 hours. A higher loading of the catalyst 2-nitrophenylboronic acid (20 mol%) was used (73% yield, white solid). The regioisomer was identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.38-7.30 (m, 3H), 7.24-7.20 (m, 2H), 5.78 (s, 2H), 3.84 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 160.4, 159.2, 138.6, 134.9, 131.7, 128.8, 128.3, 127.6, 52.8, 52.4; **IR** (Microscope, cm^{-1}) 3300-2200 (broad), 1723, 1610, 1539; **HRMS** (ESI) for $C_{12}H_{11}N_3O_4Na$: calcd. 284.06418; found 284.06421.

2.6.3.22 Thermal azide-alkyne cycloaddition (Scheme 2-13)

The mixture of benzyl azide (133 mg, 1.0 mmol) and propiolic acid (70 mg, 1.0 mmol) in 1,2-dichloroethane (2 mL) was heated to reflux for 4 hours. The solvent was removed under vacuum at room temperature (25 ^{o}C). The residue was washed with Et_2O (3 × 5 mL) and filtered to give the triazole acid **2-13a** (98 mg, 48%) in pure form as a white solid. The filtrate was evaporated under reduced pressure and the residue was purified by flash column chromatography (EtOAc/Hexanes = 1:5)

to give the triazole **2-16** (49 mg, 31%) in pure form as an off-white solid. The characterization data for compound **2-16** matched those of a previous report.[39]

2.6.4 Boronic acid catalyzed 1,3-dipolar cycloadditions of nitrile oxides (Section 2.3.3)

2.6.4.1 Preparation of hydroximoyl chloride (nitrile oxide precursor)

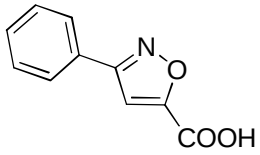
To a stirred solution of oxime (4.0 mmol) in DMF (30 mL) was added a solution of *N*-chlorosuccinimide (534 mg, 4.0 mmol) in DMF (20 mL), dropwise, over 30 minutes, at 50 ^{o}C. After stirring for 1 hour, the water bath was removed and the reaction mixture was allowed to stir at room temperature (25 ^{o}C) overnight. The reaction was quenched by pouring the mixture onto ice-water (30 mL) and extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with ice-water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure to give the title hydroximoyl chloride in pure form.

2.6.4.2 General procedure for the BAC of organocatalytic nitrile oxide-alkynoic acid cycloadditions (Table 2-7)

To an ice-cooled (0 ^{o}C) and stirred solution of hydroximoyl chloride (1.1 mmol) in 1,2-dichloroethane (2 mL) was added triethylamine (111 mg, 1.1 mmol), and after 3 minutes, the mixture was washed with water (2 × 4 mL) and dried over anhydrous Na_2SO_4. The resulting solution was filtered to get the corresponding nitrile oxide solution (around 4 mL). To the thusly-prepared nitrile oxide solution was added the solution of alkynoic acid (1.0 mmol) and *ortho*-nitrophenylboronic acid **2-15** (8 mg, 0.05 mmol) in 1,2-dichloroethane (4 mL). After stirring for a given time at room temperature (25 ^{o}C), the solvent was removed under vacuum at room temperature (25 ^{o}C). Then 1 M NaOH (5 mL) was added to the above residue and this mixture was washed with Et_2O (3 × 5 mL). The aqueous layer

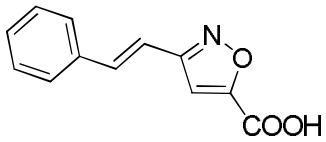
was adjusted to pH 4 by adding 6 M HCl dropwise. The resulting aqueous layer was extracted with EtOAc (3 × 10 mL) and the organic layer was dried over Na_2SO_4. After filtration, the removal of the solvent gave the title isoxazole acid in pure form.

2.6.4.3 3-Phenylisoxazole-5-carboxylic acid (2-17a, Table 2-7)



The title compound was prepared using the general procedure for the BAC of organocatalytic nitrile oxide-alkynoic acid cycloadditions. The reaction time was 2 hours (87% yield, white solid). The regioisomer was identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.30 (br s, 1H), 7.95 (m, 2H), 7.77 (s, 1H), 7.52 (m, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 162.7, 161.7, 157.6, 130.6, 129.1, 127.6, 126.7, 107.5; **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1705, 1595, 1579; **HRMS** (ESI) for $C_{10}H_6NO_3$: calcd. 188.03532; found 188.03545.

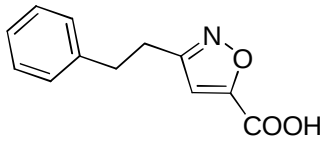
2.6.4.4 (*E*)-3-Styrylisoxazole-5-carboxylic acid (2-17b, Table 2-7)



The title compound was prepared using the general procedure for the BAC of organocatalytic nitrile oxide-alkynoic acid cycloadditions. The reaction time was 24 hours (71% yield, white solid). The regioisomer was identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.30 (br s, 1H), 7.66 (d, J = 7.3 Hz, 2H), 7.63 (s, 1H), 7.58 (d, J = 16.6 Hz, 1H), 7.41 (t, J = 7.7 Hz, 2H), 7.35 (t, J = 7.4 Hz, 1H), 7.27 (d, J = 16.5 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 162.5, 160.9, 157.7, 137.7, 135.4, 129.1, 128.8, 127.2, 114.8,

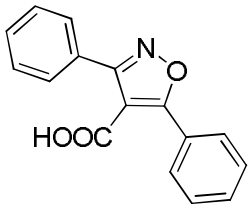
106.7; **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1751, 1644, 1586; **HRMS** (ESI) for $C_{12}H_8NO_3$: calcd. 214.05097; found 214.05051.

2.6.4.5 3-Phenethylisoxazole-5-carboxylic acid (2-17c, Table 2-7)



The title compound was prepared using the general procedure for the BAC of organocatalytic nitrile oxide-alkynoic acid cycloadditions. The reaction time was 24 hours (73% yield, white solid). The regioisomer was identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.00 (br s, 1H), 7.27 (t, J = 7.3 Hz, 2H), 7.23 (d, J = 6.5 Hz, 2H), 7.18 (t, J = 6.9 Hz, 1H), 7.03 (s, 1H), 2.97 (m, 4H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 164.0, 161.0, 157.9, 140.4, 128.3, 128.3, 126.1, 108.9, 33.1, 27.0; **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1693, 1591; **HRMS** (ESI) for $C_{12}H_{10}NO_3$: calcd. 216.06662; found 216.06693.

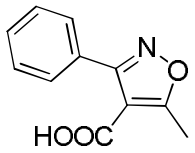
2.6.4.6 3,5-Diphenylisoxazole-4-carboxylic acid (2-18d, Table 2-7)



The title compound was prepared using the general procedure for the BAC of organocatalytic nitrile oxide-alkynoic acid cycloadditions. The reaction time was 24 hours and a higher loading of the catalyst 2-nitrophenylboronic acid (20 mol%) was used for this substrate (80% yield, white solid). The regioisomer was identified by X-ray crystallography.[23] **^{1}H NMR** (500 MHz, DMSO-d_6) δ 13.44 (br s, 1H), 7.89 (m, 2H), 7.66 (m, 2H), 7.59 (m, 3H), 7.52 (m, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 171.4, 163.8, 163.0, 132.0, 130.7, 129.5, 129.3, 129.2, 128.9,

128.9, 127.1, 109.9; **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1727, 1607, 1586, 1566; **HRMS** (ESI) for $C_{16}H_{10}NO_3$: calcd. 264.06662; found 264.06675.

2.6.4.7 5-Methyl-3-phenylisoxazole-4-carboxylic acid (2-18e, Table 2-7)

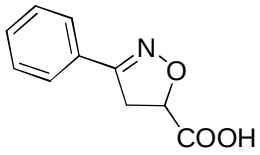


The tile compound was prepared using the general procedure for the BAC of organocatalytic nitrile oxide-alkynoic acid cycloadditions. The reaction time was 24 hours and a higher loading of the catalyst 2-nitrophenylboronic acid (20 mol%) was used for this substrate (75% yield). The characterization data for this compound matched those of a previous report.[40]

2.6.4.8 General procedure for the BAC of organocatalytic nitrile oxide-alkenoic acid cycloadditions (Table 2-8)

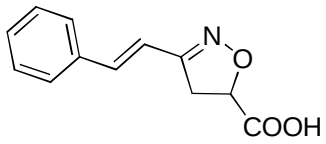
To an ice-cooled (0 ^oC) and stirred solution of hydroximoyl chloride (1.1 mmol) in 1,2-dichloroethane (2 mL) was added triethylamine (111 mg, 1.1 mmol), and after 3 minutes, the mixture was washed with water (2 × 4 mL) and dried over Na_2SO_4. The resulting solution was filtered to give the corresponding nitrile oxide solution (around 4 mL). To thusly-prepared nitrile oxide solution was added the solution of alkenoic acid (1.0 mmol) and *ortho*-nitrophenylboronic acid **2-15** (8 mg, 0.05 mmol) in 1,2-dichloroethane (4 mL). After stirring for a given time at room temperature (25 ^oC), the solvent was removed under vacuum at room temperature (25 ^oC). Then 1 M NaOH (5 mL) was added to the above residue and this mixture was washed with Et_2O (3 × 5 mL). The aqueous layer was adjusted to pH 4 by adding 6 M HCl dropwise. The resulting aqueous layer was extracted with EtOAc (3 × 10 mL) and the organic layer was dried over Na_2SO_4. After filtration, solvent removal gave the title 4,5-dihydroisoxazole acid in pure form.

2.6.4.9 3-Phenyl-4,5-dihydroisoxazole-5-carboxylic acid (2-19a, Table 2-8)



The title compound was prepared using the general procedure for the BAC of organocatalytic nitrile oxide-alkenoic acid cycloadditions. The reaction time was 24 hours (67% yield, white solid). The regioisomer was identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.19 (br s, 1H), 7.68 (m, 2H), 7.45 (m, 3H), 5.14 (dd, *J* = 11.7, 6.9 Hz, 1H), 3.72 (dd, *J* = 17.4, 11.9 Hz, 1H), 3.56 (dd, *J* = 17.3, 6.8 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.5, 156.0, 130.3, 128.8, 128.6, 126.7, 77.7, 38.4; **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1726, 1704, 1600; **HRMS** (ESI) for $C_{10}H_8NO_3$: calcd. 190.05097; found 190.05074.

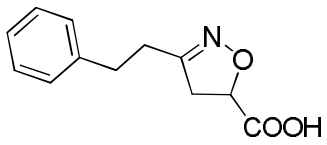
2.6.4.10 (*E*)-3-Styryl-4,5-dihydroisoxazole-5-carboxylic acid (2-19b, Table 2-8)



The title compound was prepared using the general procedure for the BAC of organocatalytic nitrile oxide-alkenoic acid cycloadditions. The reaction time was 48 hours (67% yield, white solid). The regioisomer was identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.15 (br s, 1H), 7.61 (d, *J* = 7.1 Hz, 2H), 7.38 (t, *J* = 6.9 Hz, 2H), 7.32 (t, *J* = 7.1 Hz, 1H), 7.11 (d, *J* = 16.5 Hz, 1H), 7.00 (d, *J* = 16.4 Hz, 1H), 5.10 (dd, *J* = 11.5, 6.6 Hz, 1H), 3.54 (dd, *J* = 17.0, 11.6 Hz, 1H), 3.42 (dd, *J* = 17.0, 6.6 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.5, 157.2, 137.6, 135.6, 129.0, 128.8, 127.1, 116.6, 77.6, 37.2; **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1709; **HRMS** (ESI) for

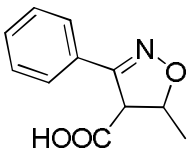
$C_{12}H_{10}NO_3$: calcd. 216.06662; found 216.06639.

2.6.4.11 3-Phenethyl-4,5-dihydroisoxazole-5-carboxylic acid (2-19c, Table 2-8)



The title compound was prepared using the general procedure for the BAC of organocatalytic nitrile oxide-alkenoic acid cycloadditions. The reaction time was 48 hours (65% yield, white solid). The regioisomer was identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.16 (br s, 1H), 7.31 (t, *J* = 6.9 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.20 (d, *J* = 6.8 Hz, 2H), 5.00 (dd, *J* = 11.4, 6.0 Hz, 1H), 3.26 (dd, *J* = 17.5, 11.3 Hz, 1H), 3.17 (dd, *J* = 17.5, 6.0 Hz, 1H), 2.93 (t, *J* = 7.8 Hz, 2H), 2.71 (t, *J* = 7.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.0, 158.6, 139.9, 128.7, 128.2, 126.6, 76.3, 41.7, 32.5, 28.9; **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1740, 1632, 1496; **HRMS** (ESI) for $C_{12}H_{12}NO_3$: calcd. 218.08227; found 218.08215.

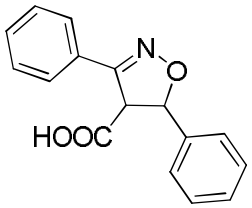
2.6.4.12 5-Methyl-3-phenyl-4,5-dihydroisoxazole-4-carboxylic acid (2-20d, Table 2-8)



The title compound was prepared using the general procedure for the BAC of organocatalytic nitrile oxide-alkenoic acid cycloadditions. The reaction time was 24 hours (77% yield, diastereomeric ratio: 5:1 *anti*:*syn*, white solid). The regioisomers and diastereomers were identified by comparing the NMR data of their corresponding methyl esters with the data in the reported literature (see **Section 2.6.6.2**).[41] The two diastereomers were inseparable and the

characterization data for the major diastereomer were listed as following: **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.12 (br s, 1H), 7.68 (m, 2H), 7.44 (m, 3H), 4.99 (app qnt, J = 6.3 Hz, 1H), 4.35 (d, J = 5.7 Hz, 1H), 1.32 (d, J = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.8, 154.3, 129.9, 129.0, 128.7, 126.7, 81.7, 59.0, 20.5; **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1704; **HRMS** (ESI) for $C_{11}H_{11}NO_3Na$: calcd. 228.06311; found 228.06354.

2.6.4.13 3.5-Diphenyl-4,5-dihydroisoxazole-4-carboxylic acid (2-20e, Table 2-8)



The title compound was prepared using the general procedure for the BAC of organocatalytic nitrile oxide-alkenoic acid cycloadditions. The reaction time was 24 hours (65% yield, diastereomeric ratio: 40:1 *anti*:*syn*, white solid). The regioisomers and diastereomers were identified by comparing the NMR data of their corresponding methyl esters with the data in the reported literature (see **Section 2.6.6.2**).[42] The two diastereomers were inseparable and the characterization data for the major diastereomer were listed as following: **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.76 (m, 2H), 7.48-7.36 (m, 8H), 5.97 (d, J = 6.2 Hz, 1H), 4.75 (d, J = 6.2 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.5, 154.5, 139.6, 130.2, 128.7, 128.7, 128.5, 128.5, 126.9, 125.9, 86.3, 60.5; **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1732, 1619, 1564, 1496; **HRMS** (ESI) for $C_{16}H_{13}NO_3Na$: calcd. 290.07876; found 290.07915.

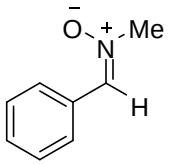
2.6.5 Boronic acid catalyzed 1,3-dipolar cycloadditions of nitrones (Section 2.3.4)

2.6.5.1 Preparation of nitrone substrates

2.6.5.1.1 General procedure for the preparation of nitrones

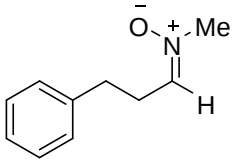
To a stirred mixture of aldehyde (15.0 mmol), triethylamine (2.79 mL, 20.0 mmol) and anhydrous $MgSO_4$ (6.02 g, 50.0 mmol) in DCM (30 mL) was added *N*-methylhydroxylamine hydrochloride (835 mg, 10.0 mmol) at 0 ^oC. After stirring for 2 days at room temperature (25 ^oC), the reaction mixture was partitioned between water (30 mL) and DCM (20 mL). The aqueous phase was extracted with DCM (50 mL) and EtOAc (50 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (100% EtOAc) to give the title nitrones in pure form.

2.6.5.1.2 (*Z*)-*N*-Benzylidenemethanamine oxide



The tile compound was synthesized using the general procedure for the preparation of nitrones (91% yield). The characterization data of this compound matched those of a previous report.[43]

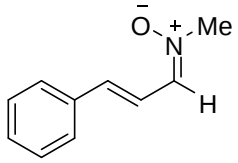
2.6.5.1.3 (*Z*)-*N*-(3-Phenylpropylidene)methanamine oxide



The tile compound was synthesized using the general procedure for the preparation of nitrones (85% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ

7.29 (m, 2H), 7.21 (m, 3H), 6.64 (t, *J* = 5.6 Hz, 1H), 3.64 (s, 3H), 2.84 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.3, 139.1, 128.6, 128.2, 126.3, 52.4, 31.1, 28.0; **IR** (Microscope, cm^{-1}) 3060, 3027, 2928, 1603, 1497; **HRMS** (ESI) for $C_{10}H_{14}NO$: calcd. 164.10699; found 164.10698.

2.6.5.1.4 (*Z*)-*N*-(3-Phenylpropylidene)methanamine oxide

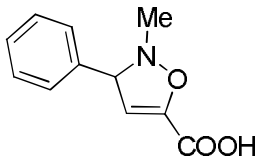


The tile compound was synthesized using the general procedure for the preparation of nitrones (62% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.4 Hz, 2H), 7.43 (dd, *J* = 16.3, 9.6 Hz, 1H), 7.36-7.28 (m, 3H), 7.23 (d, *J* = 9.5 Hz, 1H), 6.95 (d, *J* = 16.3 Hz, 1H), 3.74 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.0, 137.5, 136.0, 129.2, 128.8, 127.3, 118.4, 52.4; **IR** (Microscope, cm^{-1}) 3059, 3003, 2941, 1563; **HRMS** (ESI) for $C_{10}H_{12}NO$: calcd. 162.09134; found 162.09134.

2.6.5.2 General procedure for the BAC of organocatalytic nitrone-alkynoic acid cycloadditions (Table 2-9)

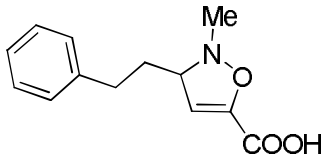
To a warm (40 ^{o}C) and stirred solution of nitrone (1.0 mmol) in 1,2-dichloroethane (4 mL) was slowly added the solution of alkynoic acid (1.0 mmol) and *ortho*-nitrophenylboronic acid **2-15** (33 mg, 0.2 mmol) in 1,2-dichloroethane (4 mL) *via* syringe pump over 6 hours. After stirring at 40 ^{o}C for 48 hours, the solvent was removed under vacuum and the crude product was purified by flash column chromatography (EtOAc/Hexanes = 1:2) to give the title 2,3-dihydroisoxazolecarboxylic acid in pure form. Without 2-nitrophenylboronic acid as the catalyst, this reaction gave the rearrangement amide product **2-23** in pure form.

2.6.5.3 2-Methyl-3-phenyl-2,3-dihydroisoxazole-5-carboxylic acid (2-21a, Table 2-9)



The title compound was prepared using the general procedure for the BAC of organocatalytic nitrone-alkynoic acid cycloadditions (71% yield, white solid). The regioisomer was identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.36 (br s, 1H), 7.38-7.24 (m, 5H), 5.97 (d, J = 3.0 Hz, 1H), 4.97 (d, J = 2.9 Hz, 1H), 2.81 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 160.0, 144.8, 140.7, 128.4, 127.6, 126.7, 109.8, 74.8, 46.6; **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1714, 1642, 1555; **HRMS** (ESI) for $C_{11}H_{10}NO_3$: calcd. 204.06662; found 204.06635. Without 2-nitrophenylboronic acid **2-15** as the catalyst, this reaction gave *N*-methylbenzamide **2-23a** in 41% yield. The characterization data for *N*-methylbenzamide **2-23a** matched those of a previous report.[40]

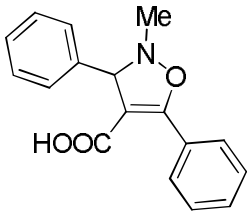
2.6.5.4 2-Methyl-3-phenethyl-2,3-dihydroisoxazole-5-carboxylic acid (2-21b, Table 2-9)



The title compound was prepared using the general procedure for the BAC of organocatalytic nitrone-alkynoic acid cycloadditions (62% yield, white solid). The regioisomer was identified by 2D NMR experiments (see **Section 2.6.6.1**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.23 (br s, 1H), 7.26 (t, J = 7.4 Hz, 2H), 7.20-7.13 (m, 3H), 5.84 (d, J = 2.8 Hz, 1H), 3.75 (dt, J = 6.7, 2.8 Hz, 1H), 2.65 (s, 3H), 2.62 (m, 2H), 1.69 (m, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 160.0, 144.8,

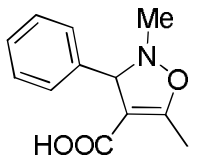
141.5, 128.3, 128.2, 125.7, 109.7, 71.7, 46.6, 36.5, 31.0; **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1725, 1642, 1497; **HRMS** (ESI) for $C_{13}H_{16}NO_3$: calcd. 234.11247; found 234.11278. Without 2-nitrophenylboronic acid **2-15** as the catalyst, this reaction gave *N*-methyl-3-phenylpropanamide **2-23b** in 60% yield. The characterization data for *N*-methyl-3-phenylpropanamide **2-23b** matched those of a previous report.[44]

2.6.5.5 2-Methyl-3,5-diphenyl-2,3-dihydroisoxazole-4-carboxylic acid (2-22d, Table 2-9)



The title compound was prepared using the general procedure for the BAC of organocatalytic nitrone-alkynoic acid cycloadditions (50% yield, white solid). The regioisomer was identified by comparing the NMR data of its corresponding methyl ester with the data in the reported literature (see **Section 2.6.6.2**).[45] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.0 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 4H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.0 Hz, 1H), 5.08 (s, 1H), 3.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.3, 164.0, 141.0, 131.5, 130.1, 128.6, 128.0, 128.0, 127.2, 126.9, 102.7, 76.3, 47.0; **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1670, 1624, 1597, 1575, 1493; **HRMS** (ESI) for $C_{17}H_{14}NO_3$: calcd. 280.09792; found 280.09805. Without 2-nitrophenylboronic acid **2-15** as the catalyst, this reaction gave *N*-methylbenzamide **2-23a** in 54% yield. The characterization data for *N*-methylbenzamide **2-23a** matched those of a previous report.[40]

2.6.5.6 2,5-Dimethyl-3-phenyl-2,3-dihydroisoxazole-4-carboxylic acid (2-22e, Table 2-9)

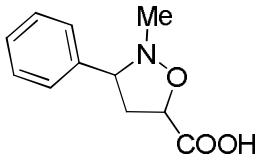


The title compound was prepared using the general procedure for the BAC of organocatalytic nitrone-alkynoic acid cycloadditions (52% yield, white solid). The regioisomer was identified by comparing the NMR data of its corresponding methyl ester with the data in the reported literature (see **Section 2.6.6.2**).[46] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H), 4.87 (s, 1H), 2.92 (s, 3H), 2.32 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.4, 166.5, 141.0, 128.4, 127.9, 127.2, 103.0, 75.2, 47.3, 12.6; **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1673, 1632; **HRMS** (ESI) for $C_{12}H_{12}NO_3$: calcd. 218.08227; found 218.08201. Without 2-nitrophenylboronic acid **2-15** as the catalyst, this reaction gave *N*-methylbenzamide **2-23a** in 54% yield. The characterization data for *N*-methylbenzamide **2-23a** matched those of a previous report.[40]

2.6.5.7 General procedure for the BAC of organocatalytic nitrone-alkenoic acid cycloadditions (Table 2-10)

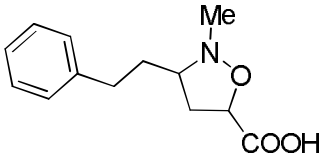
To a warm (40 ^{o}C) and stirred solution of nitrone (1.0 mmol) in 1,2-dichloroethane (4 mL) was slowly added the solution of alkenoic acid (1.0 mmol) and *ortho*-nitrophenylboronic acid **2-15** (33 mg, 0.2 mmol) in 1,2-dichloroethane (4 mL) *via* syringe pump over 6 hours. After stirring at 40 ^{o}C for 48 hours, the solvent was removed under vacuum and the crude product was purified by flash column chromatography (EtOAc/Hexanes = 1:2) to give the title isoxazolidinecarboxylic acid in pure form. Without 2-nitrophenylboronic acid as the catalyst, this reaction gave the rearrangement amide product **2-23** in pure form.

2.6.5.8 2-Methyl-3-phenylisoxazolidine-5-carboxylic acid (2-24a, Table 2-10)



The title compound was prepared using the general procedure for the BAC of organocatalytic nitrone-alkenoic acid cycloadditions (75% yield, regioisomeric ratio: 24:1 **2-24a**:**2-25a**, diastereomeric ratio: 23:1 *anti*:*syn*, white solid). The major isomer was identified by X-ray crystallography.[23] The isomers were inseparable and the characterization data for the major isomer were listed as following: **^{1}H NMR** (400 MHz, acetone-d_6) δ 7.40 (dt, J = 6.9, 1.7 Hz, 2H), 7.34 (tt, J = 7.1, 1.8 Hz, 2H), 7.27 (tt, J = 7.3, 1.5 Hz, 1H), 4.60 (dd, J = 8.9, 5.1 Hz, 1H), 3.73 (m, 1H), 2.79 (ddd, J = 12.6, 7.5, 5.4 Hz, 1H), 2.68-2.52 (m, 1H), 2.57 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 172.3, 138.9, 128.3, 127.5, 127.4, 74.4, 70.6, 43.4, 42.0; **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1734; **HRMS** (ESI) for $C_{11}H_{14}NO_3$: calcd. 208.09682; found 208.09681. Without 2-nitrophenylboronic acid **2-15** as the catalyst, this reaction gave *N*-methylbenzamide **2-23a** in 36% yield. The characterization data for *N*-methylbenzamide **2-23a** matched those of a previous report.[40]

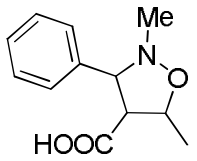
2.6.5.9 2-Methyl-3-phenethylisoxazolidine-5-carboxylic acid (2-24b, Scheme 2-19)



The title compound was prepared using the general procedure for the organocatalytic nitrone-alkenoic acid cycloadditions (73% yield, regioisomeric ratio: 40:1 **2-24b**:**2-25b**, diastereomeric ratio: 2:1 *anti*:*syn*, white solid). The regioisomers and diastereomers were identified by 2D NMR experiments (see

Section 2.6.6.1). The isomers were inseparable and the characterization data for the mixture of isomers were listed as following: **^{1}H NMR** (400 MHz, CD_3OD) δ 7.29-7.12 (m, 5H), 4.60 (dd, *J* = 9.2, 5.9 Hz, 1H)*, 4.56-4.48 (m, 1H), 2.95-2.57 (m, 8H), 2.43-2.32 (m, 1H), 2.22-2.12 (m, 1H)*, 1.95-1.84 (m, 1H), 1.74-1.59 (m, 1H) (*:*syn* isomer); **^{13}C NMR** (125 MHz, CD_3OD) δ 175.6*, 175.2, 142.8*, 142.7, 129.5, 129.4, 127.1, 127.0*, 76.7, 75.2*, 68.9*, 68.3, 45.0, 44.1*, 39.8, 39.7*, 35.4*, 35.3, 33.8 (*:*syn* isomer); **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1723; **HRMS** (ESI) for $C_{13}H_{16}NO_3$: calcd. 234.11357; found 234.11314. Without 2-nitrophenylboronic acid **2-15** as the catalyst, this reaction gave *N*-methylcinnamamide **2-23b** in 40% yield. The characterization data for *N*-methylcinnamamide **2-23b** matched those of a previous report.[44]

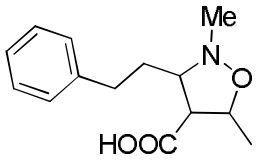
2.6.5.10 2,5-Dimethyl-3-phenylisoxazolidine-4-carboxylic acid (2-25c, Table 2-10)



The title compound was prepared using the general procedure for the BAC of organocatalytic nitrone-alkenoic acid cycloadditions (66% yield, diastereomeric ratio: 3:2.5:1:0, white solid). The regioisomers and diastereomers were identified by 2D NMR experiments (see **Section 2.6.6.1**). The isomers were inseparable and the characterization data for the mixture of isomers were listed as following: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.41 (br s, 1H), 7.42-7.20 (m, 5H), 4.64 (m, 1H), 4.54 (m, 1H)*, 4.05-3.93 (m, 1H), 3.51 (t, *J* = 8.8 Hz, 1H)*, 3.15 (dd, *J* = 8.1, 6.7 Hz, 1H), 2.63 (s, 3H), 2.60 (s, 3H)*, 1.50 (d, *J* = 6.2 Hz, 3H), 1.39 (d, *J* = 6.2 Hz, 3H)*, 1.32 (d, *J* = 6.4 Hz, 3H)* (*:minor isomer); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.5*, 176.0, 175.5*, 137.9*, 137.1, 135.8*, 129.1, 129.0, 128.7*, 128.6*, 128.6*, 128.5*, 128.5*, 128.3, 128.0*, 76.5, 76.4*, 76.0*, 74.5, 64.1*, 61.1, 60.5*,

43.5*, 42.7, 21.0*, 18.9*, 15.7 (*:minor isomer); **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1715; **HRMS** (ESI) for $C_{12}H_{14}NO_3$: calcd. 220.09792; found 220.09750; Without 2-nitrophenylboronic acid **2-15** as the catalyst, this reaction gave *N*-methylbenzamide **2-23a** in 50% yield. The characterization data for *N*-methylbenzamide **2-23a** matched those of a previous report.[40]

2.6.5.11 2,5-Dimethyl-3-phenethylisoxazolidine-4-carboxylic acid (2-25d, Table 2-10)

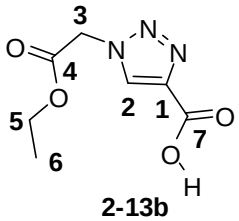


The title compound was prepared using the general procedure for the BAC of organocatalytic nitrone-alkenoic acid cycloadditions (69% yield, diastereomeric ratio: 3.5:1:0:0, white solid). The regioisomers and diastereomers were identified by 2D NMR experiments (see **Section 2.6.6.1**). The isomers were inseparable and the characterization data for the mixture of isomers were listed as following: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.89 (br s, 1H), 7.28-7.12 (m, 5H), 4.45 (m, 1H), 3.26-3.08 (m, 2H), 3.02-2.90 (m, 2H)*, 2.80-2.68 (m, 5H), 1.92 (m, 1H), 1.35 (d, *J* = 6.2 Hz, 3H), 1.27 (d, *J* = 6.4 Hz, 3H)* (*:minor isomer); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.5*, 174.7, 141.2, 141.1*, 128.7, 128.6, 128.4*, 126.4*, 126.4, 76.7*, 74.7, 72.2*, 70.0, 57.8*, 57.6, 44.7, 43.2*, 33.7*, 32.9, 32.8*, 30.6, 20.0, 15.1* (*:minor isomer); **IR** (Microscope, cm^{-1}) 3400-2100 (broad), 1722; **HRMS** (ESI) for $C_{14}H_{18}NO_3$: calcd. 248.12922; found 248.12881. Without 2-nitrophenylboronic acid **2-15** as the catalyst, this reaction gave *N*-methylcinnamamide **2-23b** in 41% yield. The characterization data for *N*-methylcinnamamide **2-23b** matched those of a previous report.[44]

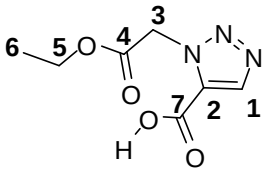
2.6.6 Determination of regioisomers

2.6.6.1 2D-NMR experiments (HSQC and HMBC)

The regioisomers of most new compounds including **2-13b**–**2-13g** (**Table 2-5**), **2-13i**–**2-13n** (**Table 2-5**), **2-13r** (**Table 2-6**), **2-17a**–**2-17c** (**Table 2-7**), **2-19a**–**2-19c** (**Table 2-8**), **2-21a**–**2-21b** (**Table 2-9**), **2-24b** (**Table 2-10**), and **2-25c**–**2-25d** (**Table 2-10**) were determined by this method. Here, one example is showed to determine the regioisomer **2-13b**. The regioisomers of the other new compounds were determined by a similar method.



2-13b



2-14b

	δ_C	δ_H
1	139.7	N/A
2	130.2	8.65 (s, 1H)
3	50.5	5.44 (s, 2H)
4	166.8	N/A
5	61.6	4.18 (q, 2H)
6	13.9	1.21 (t, 3H)
7	161.5	N/A

	δ_C	δ_H
1	130.2	8.65 (s, 1H)
2	139.7	N/A
3	50.5	5.44 (s, 2H)
4	166.8	N/A
5	61.6	4.18 (q, 2H)
6	13.9	1.21 (t, 3H)
7	161.5	N/A

From the HSQC spectrum, all peaks in ^{1}H-NMR and ^{13}C-NMR could be assigned according to the above numbering system. Then a correlation δ 130.0 ↔ 5.44 was observed from ^{13}C–^{1}H HMBC spectrum. If the product was **2-14b**, C1 and H3 should not have a correlation on the HMBC spectrum; if the product was **2-13b**, C2 and H3 should have a correlation on HMBC spectrum. Thus, it can be concluded that the regioisomer is **2-13b** instead of **2-14b**.

2.6.6.2 Esterification of carboxylic acids

Besides the 2-D NMR method, the regioisomers of five new compounds including **2-13q** (**Table 2-6**), **2-20d**–**2-20e** (**Table 2-8**), and **2-22d**–**2-22e** (**Table 2-9**) were identified by comparing the NMR data of their corresponding methyl esters or ethyl esters with the data in the reported literature. The procedures for converting the carboxylic acids to their corresponding esters are as follows:

Method A: The solution of carboxylic acid (0.5 mmol) and concentrated H_2SO_4 (0.5 mL) in MeOH or EtOH (5 mL) was heated to reflux for 21 hours. The solvent was removed under vacuum at room temperature (25 ^oC). The residue was purified by flash column chromatography (EtOAc/Hexanes = 5:1) to give the corresponding ester in pure form.

The ethyl ester of compound **2-13q** was prepared using the above procedure (81% yield) and its characterization data matched those of a previous report.[38]

The methyl ester of compound **2-20d** was prepared using the above procedure (63% yield) and its characterization data matched those of a previous report.[41]

The methyl ester of compound **2-20e** was prepared using the above procedure (72% yield) and its characterization data matched those of a previous report.[42]

Method B: A solution of methyl iodide (71 mg, 0.5 mmol) in toluene (1 mL) was added to a solution of carboxylic acid (0.5 mmol) and DBU (76 mg, 0.5 mmol) in toluene (5 mL) and the mixture was stirred at room temperature (25 ^oC) overnight. The reaction mixture was then washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/Hexanes = 1:5) to give the corresponding ester in pure form.

The methyl ester of compound **2-22d** was prepared using the above procedure (78% yield) and its characterization data matched those of a previous report.[45]

The methyl ester of compound **2-22e** was prepared using the above procedure (65% yield) and its characterization data matched those of a previous report.[46]

2.6.7 Mechanistic investigations (Section 2.3.5)

2.6.7.1 Competition reaction (Scheme 2-16)

To a solution of propiolic acid (70 mg, 1.0 mmol) and methyl propiolate (84 mg, 1.0 mmol) in 1,2-dichloroethane (2 mL) was added the *ortho*-nitrophenylboronic acid **2-15** (8 mg, 0.05 mmol) and this solution was stirred at room temperature (25 ^{o}C) for 10 minutes. Benzyl azide (133 mg, 1.0 mmol) was then added and the resulting mixture was stirred at room temperature (25 ^{o}C) for 2 hours. The solvent was removed under vacuum at room temperature (25 ^{o}C). The residue was washed with Et_2O (3 × 5 mL) and filtered to give the triazole acid **2-13a** (187 mg, 92%) in pure form as a white solid. The filtrate was evaporated under reduced pressure and the residue was purified by flash column chromatography (EtOAc/Hexanes = 1:5) to give methyl 1-benzyl-1*H*-1,2,3-triazole-4-carboxylate (8 mg, 4%) in pure form. The characterization data for methyl 1-benzyl-1*H*-1,2,3-triazole-4-carboxylate matched those of previous reports.[47]

2.6.7.2 Control experiment (Scheme 2-17)

To a solution of methyl propiolate (84 mg, 1.0 mmol) in 1,2-dichloroethane (2 mL) was added the *ortho*-nitrophenylboronic acid (8 mg, 0.05 mmol) and this mixture was stirred at room temperature (25 ^{o}C) for 10 minutes. Benzyl azide (146 mg, 1.1 mmol) was then added and the resulting mixture was stirred at room temperature (25 ^{o}C) for 6 hours. The solvent was removed under vacuum at room temperature (25 ^{o}C) and the residue was purified by flash column chromatography (EtOAc/Hexanes = 1:5) to give methyl 1-benzyl-1*H*-1,2,3-triazole-4-carboxylate **2-26** (48 mg, 22%) as a off-white solid (96:4 for regioselectivity ratio, by ^{1}H-NMR of crude reaction mixture). The characterization data for methyl

1-benzyl-1*H*-1,2,3-triazole-4-carboxylate **2-26** matched those of previous reports.[47] Also, without 2-nitrophenylboronic acid **2-15** as catalyst, this reaction gave methyl 1-benzyl-1*H*-1,2,3-triazole-4-carboxylate in almost the same yield (23%).

2.6.7.3 Childs' NMR shift experiment (Figure 2-6)[24]

A mixture of (*E*)-crotonic acid **2-29** (86 mg, 1.0 mmol), 2-nitrophenylboronic acid **2-15** (167 mg, 1.0 mmol) and 4A molecular sieves (1/16 inch pellets, 2 g) in dry toluene (5 mL) was stirred at room temperature (25 ^{o}C) overnight. The reaction mixture was filtered and evaporated under reduced pressure. The residue was dissolved in CD_2Cl_2 for further NMR analyses.

For ratio 1:2, crotonic acid **2-29** (86 mg, 1.0 mmol) and 2-nitrophenylboronic acid **2-15** (334 mg, 2.0 mmol) were used according to the above procedure.

For ratio 2:1, crotonic acid **2-29** (172 mg, 2.0 mmol) and 2-nitrophenylboronic acid **2-15** (167 mg, 1.0 mmol) were used according to the above procedure.

2.6.7.4 Control experiment for Childs' NMR shift experiment (Figure 2-7)

A mixture of methyl crotonate **2-30** (100 mg, 1.0 mmol), 2-nitrophenylboronic acid **2-15** (167 mg, 1.0 mmol) and 4A molecular sieves (1/16 inch pellets, 2 g) in dry toluene (5 mL) was stirred at room temperature (25 ^{o}C) overnight. The reaction mixture was filtered and evaporated under reduced pressure. The residue was dissolved in CD_2Cl_2 for further NMR analyses.

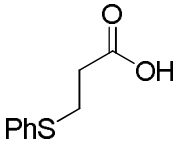
2.6.8 BAC of nucleophilic conjugate addition (Section 2.4.1)

2.6.8.1 General procedure (Table 2-11)

To a solution of unsaturated carboxylic acid (1.0 mmol) in the indicated solvent (2 mL) was added the *ortho*-bromophenylboronic acid **2-8** (40 mg, 0.2 mmol) and this solution was stirred at the indicated temperature for 10 minutes. The

nucleophile (1.0 mmol) was then added and the resulting mixture was stirred at the indicated temperature for 48 hours. The solvent was removed under vacuum and the crude product was purified by flash column chromatography (EtOAc/Hexanes = 1:2) to give the title product **2-32** in pure form.

2.6.8.2 3-(Phenylthio)propanoic acid (2-32d, Table 2-11)



The title compound was prepared using the general procedure for the organocatalytic nucleophilic conjugate addition. The reaction temperature was room temperature (25 ^{o}C), the solvent was CH_2Cl_2 and the nucleophile was thiophenol (65% yield). The characterization data for this compound matched those of a previous report.[48]

2.7 References

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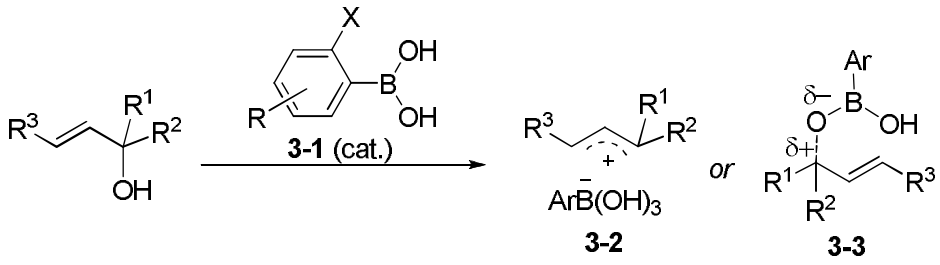
Chapter 3

Boronic Acid Catalyzed Chemical Transformations *via* Hydroxyl Activation

3.1 Introduction

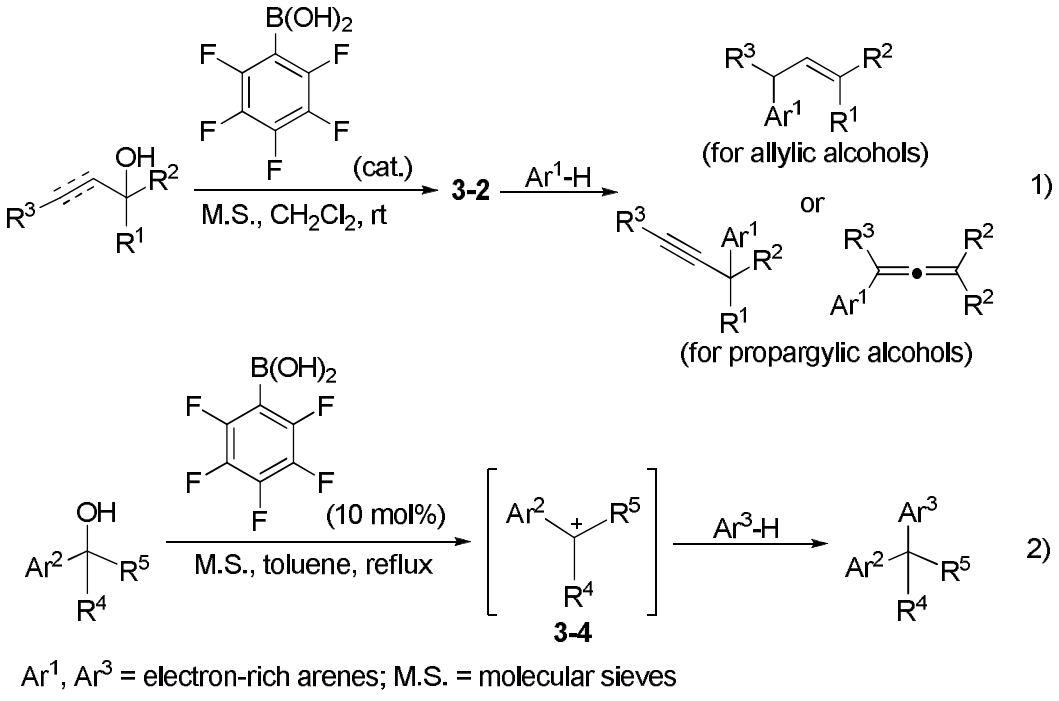
Hydroxyl is a poor leaving group and therefore pre-activation with recourse to intermediary functionalities such as halides and pseudo-halides (e.g.; sulfonates, oxyphosphonium) is usually required for nucleophilic substitution.[1a] Although transition metal catalysis is an effective strategy for the direct activation of alcohols as leaving groups in nucleophilic substitution, it requires toxic transition metal catalysts that can exhibit a negative impact on the environment.[1a] The consideration of atom-, and step-economy and the use of more environmentally benign reactions is becoming a key theme in many research areas. In this regard, the *ACS Green Chemistry Institute Pharmaceutical Roundtable* ranked "alcohol activation for nucleophilic substitution" the second most important priority area for green chemistry research.[2] Recently, a new strategy for the activation of alcohols toward nucleophilic substitution based on the facile formation of cyclopropenium esters was developed to address this unmet need.[3] However, the strong acid (HCl), produced as a byproduct in this catalytic system, can create chemical compatibility issues. Therefore, a milder and environmentally friendlier system for the activation of alcohols toward nucleophilic substitution is highly



Scheme 3-1: The concept of hydroxyl activation with boronic acid catalysis

desirable. Electron-deficient arylboronic acids **3-1** are emerging as a promising new class of organocatalysts for direct alcohol activation due to their Lewis acidity, which can be modulated by substituents (R). It can be envisioned that arylboronic acids **3-1** could promote the complete or partial ionization of alcohols to give the activated intermediates **3-2** or **3-3**, which could further undergo nucleophilic substitution in an S_N1 or an S_N2 manner (**Scheme 3-1**).[4]

Recently, McCubbin and co-workers reported that electron-deficient pentafluorophenyl boronic acid showed excellent catalytic activity for regioselective Friedel-Crafts reactions of allylic or propargylic alcohols with electron-rich arenes or heteroarenes at room temperature in the presence of molecular sieves (eq 1, **Scheme 3-2**).[4a,4c] A diversity of highly substituted arenes or heteroarenes can be prepared in this manner, and the reaction was presumed to proceed through an S_N1' pathway *via* carbocations **3-2** with the regioselectivity being controlled by steric effects. Benzylic alcohols were also suitable substrates



Scheme 3-2: Boronic acid catalyzed Friedel-Crafts reactions

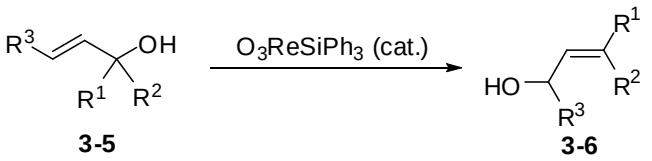
for this methodology; however, higher relative reaction temperatures were needed (eq 2, **Scheme 3-2**). Similar carbocation intermediates **3-4** were proposed.[4b]

Inspired by McCubbin's methodology, we sought to apply this hydroxyl activation concept with boronic acid catalysis (BAC) toward several synthetically important chemical transformations including 1,3-transpositions of allylic and propargylic alcohols,[5] cationic cyclizations of allylic alcohols,[6] and allylic substitutions. The design, development, and application of these methodologies will be presented in this chapter.

3.2 Boronic acid catalyzed 1,3-transpositions of allylic and propargylic alcohols

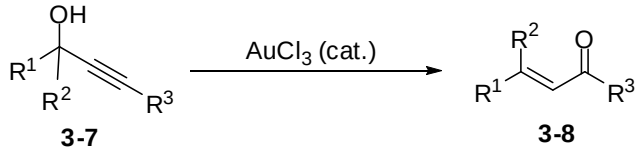
The 1,3-transposition of allylic alcohols[7] and the related Meyer–Schuster rearrangement of propargylic alcohols[8] are synthetically useful processes that can be catalyzed in various manners. Several methods, however, require stoichiometric activation of the hydroxyl group,[9] or the use of transition metals[10] or strong protic acid catalysts[11] often under harsh conditions such as high temperature. Although rhenium(VII) oxo complexes (eq 1, **Scheme 3-3**) and gold (III) complexes (eq 2, **Scheme 3-3**) are generally very effective catalysts for the 1,3-transposition of allylic alcohols and the Meyer–Schuster rearrangement of propargylic alcohols respectively, they usually need to be stored and used under strictly anhydrous conditions.[8,12] Based on recent reports from McCubbin and co-workers describing mild Friedel–Crafts alkylations by activation of allylic/propargylic/benzylic alcohols with air-stable boronic acids (**Scheme 3-2**),[4] we reasoned that allylic alcohols **3-5** could rearrange selectively to provide thermodynamically stable isomers **3-6** in the absence of an external nucleophile *via* either a carbocation intermediate **3-2** or a six-membered transition state **3-3** (eq 3, **Scheme 3-3**).

Re Catalyzed 1,3-transposition of allylic alcohols:



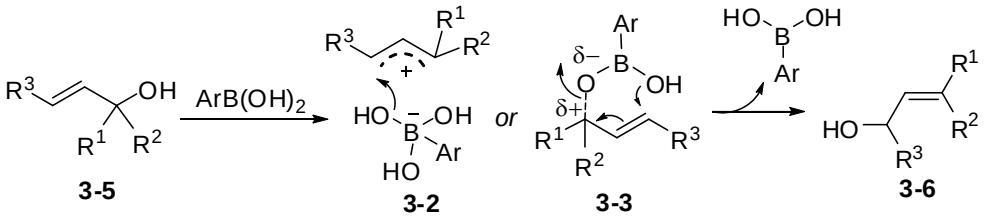
1)

Au Catalyzed Meyer-Schuster rearrangement of propargylic alcohols:



2)

Our proposal:



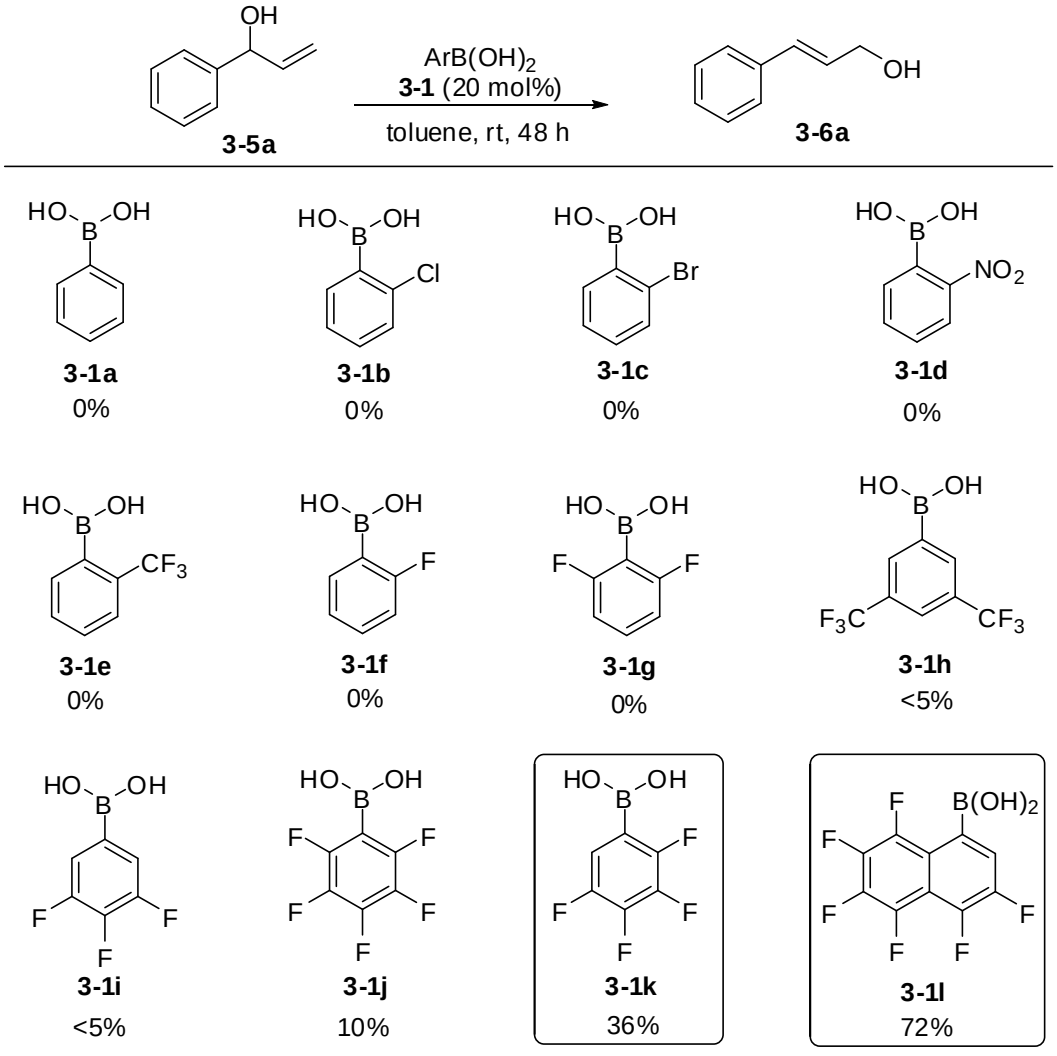
3)

Scheme 3-3: Proposal for boronic acid catalyzed 1,3-transpositions

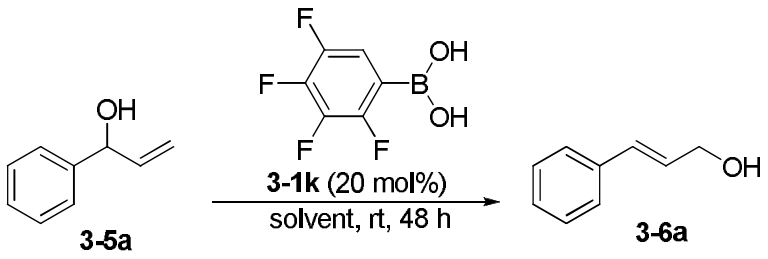
3.2.1 Optimization of reaction conditions

In the first round of optimization, a large number of arylboronic acids were evaluated for their ability to accelerate the allylic rearrangement of 1-phenylprop-2-en-1-ol **3-5a** as a model alcohol (**Scheme 3-4**). All the catalysts were subjected to the model reaction by stopping the reactions prior to completion. This procedure ensured that the most active catalysts could be compared more accurately and rapidly. A limitation of this approach, however, is that small differences in yields (ca. 5%) should not be considered significant. It was found that electron-poor arylboronic acids showed the highest catalytic activity for this 1,3-transposition. Just like the recently reported Friedel–Crafts alkylations of McCubbin and co-workers,[4] highly electron-deficient polyfluorinated arylboronic acids were found to be preferable. Thus, at the onset pentafluorophenylboronic

acid **3-1j** stood out as a promising catalyst. By taking into account our previous observations in the catalysis of direct amidations with *ortho*-halogenated arylboronic acids, we reasoned that the removal of one of the *ortho* fluoride substituents may provide steric relief and accelerate the rearrangement despite the attenuation of electronic effects. In the event, 2,3,4,5-tetrafluorophenylboronic acid **3-1k** was found to be significantly superior to **3-1j**. Based on this result, hexafluoronaphthalene catalyst **3-1l** was designed and showed to be even superior to **3-1k**.



Scheme 3-4: Survey of arylboronic acids for catalytic activity in a model 1,3-transposition of allylic alcohol 3-5a



Entry	Solvent	Catalyst (mol%)	Additive	Yield[a] (%)
1	MeOH	20	no additive	0
2	CH_3CN	20	no additive	trace
3	Et_2O	20	no additive	5
4	THF	20	no additive	7
5	acetone	20	no additive	13
6	EtOAc	20	no additive	12
7	DMF	20	no additive	17
8	CH_2Cl_2	20	no additive	26
9	DCE	20	no additive	25
10	**toluene**	**20**	**no additive**	**36**
11	toluene	10	no additive	14
12	toluene	5	no additive	8
13	toluene	20	$ZrCl_4$ (20 mol%)	complex mixture
14	toluene	20	TsOH (20 mol%)	25
15	toluene	20	4A molecular sieves	18
16	toluene	20	H_2O (1.0 equiv)	5

[a]Isolated yields of the product after purification by silica gel column chromatography.

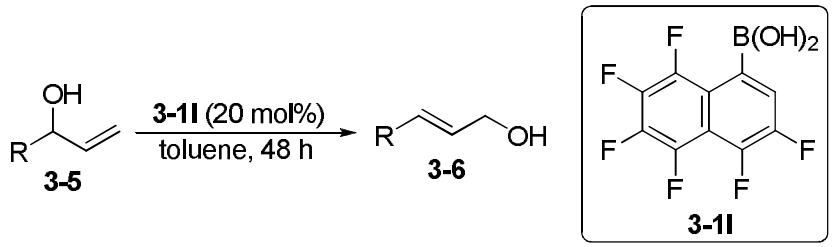
Table 3-1: Optimization of solvent and catalyst loading for the boronic acid catalysis of a model 1,3-transposition of allylic alcohol

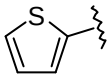
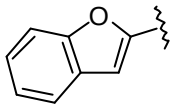
Further optimization of solvent and catalyst loading confirmed that the use of 20 mol% **3-1k** or **3-1l** in toluene provided the best reaction conditions (entries 1–12, **Table 3-1**). Since acids were reported to possess the catalytic activity to promote the 1,3-transposition of allylic alcohols,[11] a number of simple Lewis acid or Brønsted acid additives were screened but provided no rate acceleration (entries

13–14, **Table 3-1**). Furthermore, the use of molecular sieves was detrimental, while excess water suppressed the reaction (entries 15 and 16, **Table 3-1**). These observations suggest that a small quantity of water is required for the catalytic turnover, but that a larger excess interferes with formation of reactive intermediates. The outcome of mechanistic studies will be discussed in greater detail later in **Section 3.2.5**.

3.2.2 Substrate scope for 1,3-transposition of allylic alcohols

The scope of substrates was explored using the optimal reaction conditions (20 mol% catalyst **3-1k** or **3-1l** in toluene). While commercially available catalyst **3-1k** was suitable with many substrates, catalyst **3-1l** was employed with the more difficult ones. Secondary allylic alcohols substituted with an aryl or heteroaryl group provided good to excellent yields of products (entries 1–11, **Table 3-2**). Both electronic and steric effects from the aromatic ring substituents have a large impact on the reactivity of this boronic acid catalyzed 1,3-transposition of allylic alcohols. Allylic alcohols with an electron-donating substituent undergo the 1,3-transposition effectively at room temperature (entries 3–5 and 8, **Table 3-2**), whereas substrates bearing a weakly electron-withdrawing substituent required a higher temperature (entries 6–7 and 9, **Table 3-2**). More sterically hindered allylic alcohols with an *ortho*-substituent tended to react slower and gave the desired product in lower yields compared with their isomers containing a *para*-substituent (entries 4, 7 *vs* entries 8, 9, **Table 3-2**). It is noteworthy that substrate **3-5e** with an acid-sensitive phenolic silyl group tolerated these very mild conditions (entry 5, **Table 3-2**). A model secondary alcohol substrate substituted with an aliphatic side chain was unreactive even at higher reaction temperatures (entry 12, **Table 3-2**).

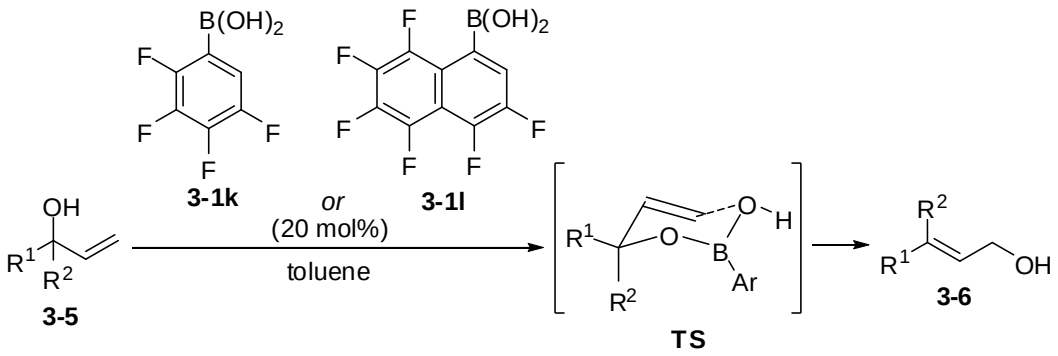


Entry	R	T (^{o}C)	Product	Yield[a] (%)	*E*:*Z*[b]
1	Ph	50	**3-6a**	93 (72)[c]	>20:1
2	2-naphthalene	50	**3-6b**	71	>20:1
3	4-tolyl	rt	**3-6c**	78	>20:1
4	4-$MeOC_6H_4$	rt	**3-6d**	82	>20:1
5	4-$TIPSOC_6H_4$	rt	**3-6e**	75	>20:1
6	4-BrC_6H_4	50	**3-6f**	70	>20:1
7	4-ClC_6H_4	50	**3-6g**	67	>20:1
8	2-$MeOC_6H_4$	rt	**3-6h**	60	>20:1
9	2-ClC_6H_4	50	**3-6i**	8	>20:1
10		rt	**3-6j**	61	>20:1
11		rt	**3-6k**	75	>20:1
12	*c*-hex	80	**3-6l**	0	–

[a]Isolated yields of the product after purification by silica gel column chromatography. [b]The *E*/*Z* ratio was measured by ^{1}H-NMR of the crude reaction product. [c]The yield in bracket is for the reaction performed at room temperature.

Table 3-2: Substrate scope for the boronic acid catalyzed 1,3-transposition of secondary allylic alcohols

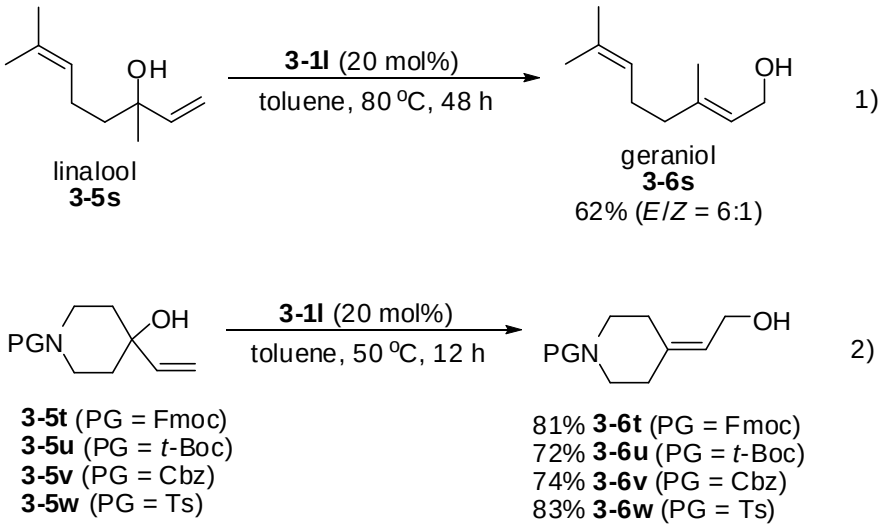
Compared with secondary allylic alcohols, all tertiary alcohols showed higher reactivity and provided the desired allylic alcohol products with a trisubstituted alkene in good to excellent yields (entries 1–6, **Table 3-3**). All examples of entries 2–6 (**Table 3-3**) exhibited high *E/Z* selectivities which were governed by the relative size of the two substituents R^1 and R^2; significantly more so than the corresponding rhenium oxo catalyzed reactions.[12] The *E*/*Z* selectivities can be



Entry	R^1	R^2	Catalyst	T (^oC)	t (h)	Product	Yield[a] (%)	*E*:*Z*[b]
1	Ph	Ph	**3-1k**	rt	24	**3-6m**	80	–
2	Ph	Et	**3-1k**	rt	24	**3-6n**	72	8:1
3	*c*-C_3H_5	Ph	**3-1k**	rt	48	**3-6o**	76	1:20
4	*c*-C_5H_9	Ph	**3-1l**	rt	48	**3-6p**	79	<1:20
5	*c*-C_6H_{11}	Ph	**3-1l**	rt	48	**3-6q**	75	<1:20
6	*c*-C_6H_{11}	Me	**3-1l**	80	48	**3-6r**	77	>20:1

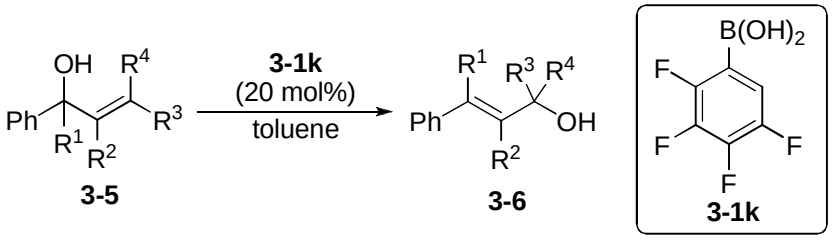
[a]Isolated yields of the product after purification by silica gel column chromatography. [b]The *E*/*Z* ratio was measured by ^{1}H-NMR of the crude reaction product.

Table 3-3: Substrate scope for the boronic acid catalyzed 1,3-transposition of tertiary allylic alcohols



Scheme 3-5: Substrate scope for the BAC of 1,3-transposition of tertiary functionalized allylic alcohols

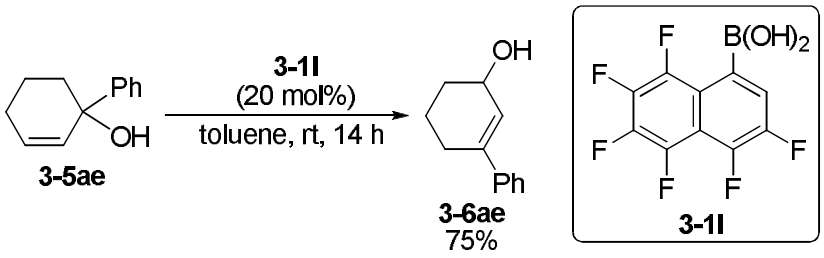
explained *via* cyclic chairlike transition state (**TS**, **Table 3-3**), where the bulkier group R^1 preferentially occupies the equatorial position to minimize 1,3-diaxial interactions. These rearrangements occur readily at room temperature except for the fully aliphatic substrates **3-6r**, which required an elevated temperature (entry 6, **Table 3-3**). Interestingly, the isomerization of linalool into geraniol (eq 1, **Scheme 3-5**), an industrial process, proceeded with a selectivity superior to that of a vanadium or rhenium oxo catalyzed process (see **Section 3.2.4**). Moreover, our methodology displayed remarkable functional group tolerance and several protected amines were recovered intact under the reaction conditions, whereas substrate **3-5u** failed to undergo 1,3-transposition under rhenium oxo catalyzed reaction conditions (eq 2, **Scheme 3-5**).



Entry	R^1	R^2	R^3	R^4	T (^oC)	t (h)	Product	Yield[a] (%)	*E*:*Z*[b]
1	H	H	Me	H	rt	4	**3-6x**	73	>20:1
2	H	H	Me	Me	rt	2	**3-6y**	75	>20:1
3	H	Me	Me	H	50	48	**3-6z**	66	>20:1
4	Ph	H	Me	H	rt	24	**3-6aa**	78	>20:1
5	Ph	H	Me	Me	rt	24	**3-6ab**	72	>20:1
6	Ph	Me	Me	H	rt	48	**3-6ac**	71	>20:1
7	H	COOEt	H	H	80	48	**3-6ad**	20	5:1

[a]Isolated yields of the product after purification by silica gel column chromatography. [b]The *E*/*Z* ratio was measured by ^{1}H-NMR of the crude reaction product.

Table 3-4: Substrate scope for the BAC of 1,3-transposition of other allylic alcohols



Scheme 3-6: Substrate scope for the BAC of 1,3-transposition of cyclic allylic alcohols

Substrates with substitution on the alkene were studied next (**Table 3-4**). Alkyl and aryl substituents (R^1, R^2, R^3, and R^4) can enhance the rate of the transposition since they can further stabilize the cationic intermediates (entries 1–6, **Table 3-4**), whereas electron-withdrawing groups such as a carboxyester retard the rearrangement (entry 7, **Table 3-4**). In addition, a cyclic tertiary alcohol, **3-5ae**, provided the expected product **3-6ae** in a good yield (**Scheme 3-6**).

3.2.3 Substrate scope for Meyer-Schuster rearrangement of propargylic alcohols

The corresponding transposition of propargylic alcohols, known as the Meyer-Schuster rearrangement, is a useful two-step alternative process to phosphorous-based olefination methods that circumvents the need to separate

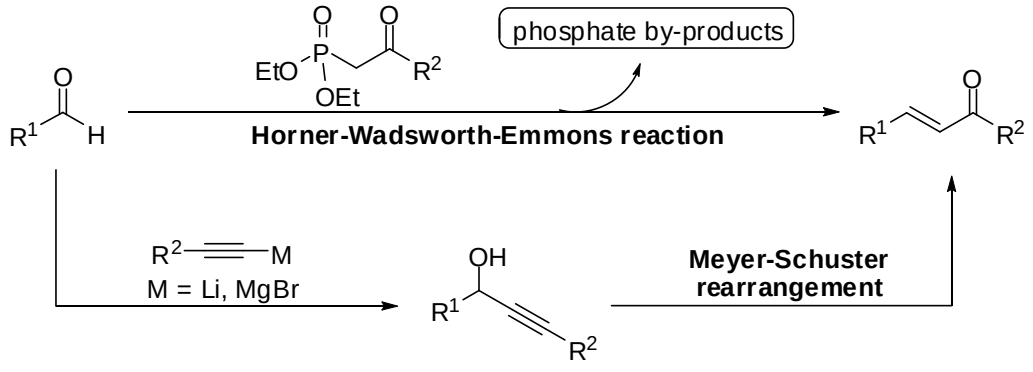
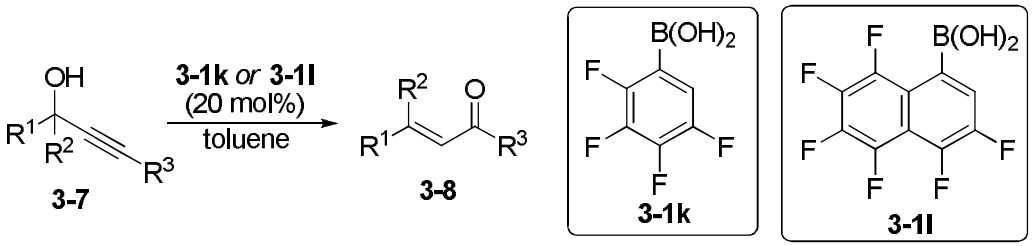


Figure 3-1: Carbonyl olefination strategies



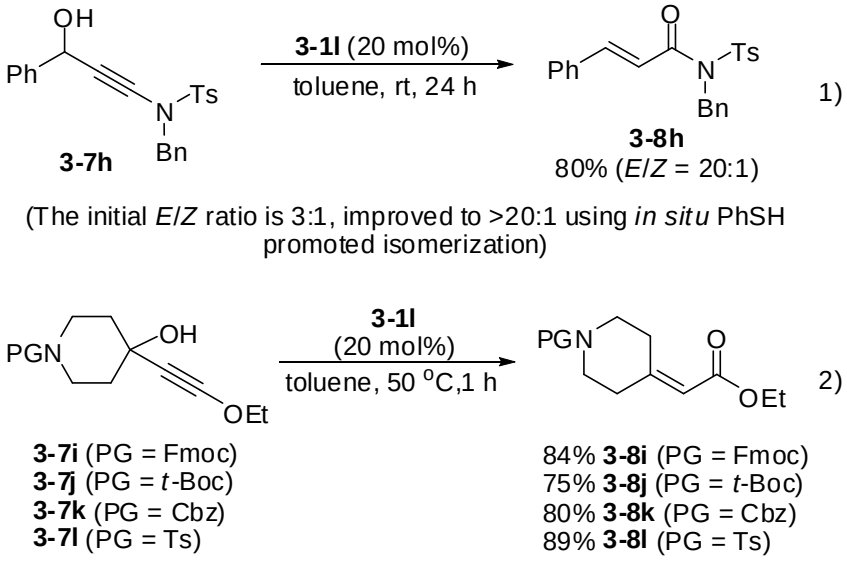
Entry	R^1	R^2	R^3	Catalyst	T (^oC)	t (h)	Product	Yield[a] (%)	*E*:*Z*[b]
1	Ph	H	H	**3-1l**	50	6	**3-8a**	75	>20:1
2	Ph	Ph	H	**3-1k**	rt	0.3	**3-8b**	87	–
3	Ph	Ph	*n*-C_6H_{13}	**3-1k**	rt	0.3	**3-8c**	90	–
4	Ph	Ph	Ph	**3-1k**	rt	1	**3-8d**	89	–
5	Ph	H	OEt	**3-1k**	rt	2	**3-8e**	80	>20:1[c]
6	*t*-Bu	H	OEt	**3-1l**	50	6	**3-8f**	78	>20:1
7	Ph	Ph	SMe	**3-1l**	rt	0.5	**3-8g**	88	–

[a]Isolated yields of the product after purification by silica gel column chromatography. [b]The *E*/*Z* ratio was measured by ^{1}H-NMR of the crude reaction product. [c]The initial *E*/*Z* ratio is 4:3, improved to >20:1 using *in situ* PhSH promoted isomerization.

Table 3-5: Substrate scope for the BAC of Meyer-Schuster rearrangement of propargylic alcohols

phosphate by-products (**Figure 3-1**).[8] The facile addition of acetylide anions onto aldehydes and ketones provides the requisite propargylic alcohols, and boronic acid catalysis was shown to be very effective on those substrates. While a secondary alcohol substrate with a terminal alkyne required catalyst **3-1l** (entry 1, **Table 3-5**), a tertiary alcohol rearranged efficiently within short time with **3-1k** at room temperature to give the enal product in high yield (entry 2, **Table 3-5**). Tertiary propargylic alcohols with a disubstituted alkyne also reacted readily to provide the enone products in high yields (entries 3–4, **Table 3-5**). Finally, 1-ethoxy alkynyl carbinols were found to rearrange very readily, as shown with **3-7e**, which gave the α,β-unsaturated ester **3-8e** in a good yield with high *E*/*Z* selectivity (*E*/*Z* >20:1) when using thiophenol as an additive for *in situ*

isomerization (entry 5, **Table 3-5**), whereas in the absence of thiophenol, the same reaction proceeded with significantly poorer *E*/*Z* selectivity (*E*/*Z* = 4:3). This thiophenol induced *E*/*Z* isomerization of alkene likely occurs by an addition-elimination pathway leading to thermodynamically stable *E* isomers. Contrary to the analogous allylic alcohols, a secondary propargylic alcohol with a hindered aliphatic side chain successfully rearranged to give α,β-unsaturated ester **3-8f** in high yield and high *E/Z* selectivity (entry 6, **Table 3-5**). Remarkably, unsaturated thioesters (entry 7, **Table 3-5**) and amides (eq 1, **Scheme 3-7**) were also prepared under similar conditions. Similar to the 1,3-transposition of allylic alcohols, the boronic acid catalyzed Meyer-Schuster rearrangement of propargylic alcohols also demonstrated exceptional functional group compatibility. Different amine protecting groups are well tolerated under the mild boronic acid catalysis conditions (eq 2, **Scheme 3-7**).



Scheme 3-7: Substrate scope for the BAC of Meyer-Schuster rearrangement of functionalized propargylic alcohols

3.2.4 Comparison of boronic acid and transition metal catalyzed processes

Not only did our BAC system exhibit a remarkable mildness for 1,3-transposition

reactions, which is compatible with both acid and base sensitive groups, but it also showed better yields and selectivities over the well-established Re catalyzed variants in most cases (entries 1–7, **Table 3-6**). As demonstrated with a broad panel of substrates, it is noteworthy that contrary to rhenium oxo[12e] and gold catalysis[8d], which can respectively only promote the 1,3-transposition of allylic

Entry[a]	Reaction	BAC system	Re system[b]	Au system[c]
1	**3-5n** to **3-6n** (**Table 3-3**)	72% (8:1)	74% (5:1)	–
2	**3-5o** to **3-6o** (**Table 3-3**)	76% (1:20)	63% (1:3.5)	–
3	**3-5p** to **3-6p** (**Table 3-3**)	79% (<1:20)	68% (<1:20)	–
4	**3-5q** to **3-6q** (**Table 3-3**)	75% (<1:20)	65% (<1:20)	–
5	**3-5r** to **3-6r** (**Table 3-3**)	77% (>20:1)	85% (5:1)	–
6	**3-5s** to **3-6s** (**Scheme 3-5**)	62% (6:1)	81% (3:1)	–
7	**3-5u** to **3-6u** (**Scheme 3-5**)	72%	trace	–
8	**3-7a** to **3-8a** (**Table 3-5**)	75% (>20:1)	20%	–
9	**3-7c** to **3-8c** (**Table 3-5**)	90%	trace	–
10	**3-5a** to **3-6a** (**Table 3-2**)	93% (>20:1)	–	trace

[a]The numbers outside the brackets represent the isolated yields and the ratios in the brackets represent the *E*/*Z* ratio measured by ^{1}H-NMR of the crude reaction product. [b]Reaction conditions: $O_3ReSiPh_3$ (2.0 mmol%), BAS (1.0 equiv), TMSA (0.2 equiv), Et_2O, 0 ^oC or rt, 30 min or 6 h or 12 h. [c]Reaction conditions: $AuCl_3$ (20 mol%), EtOH (5.0 equiv), CH_2Cl_2, rt, 1 h.

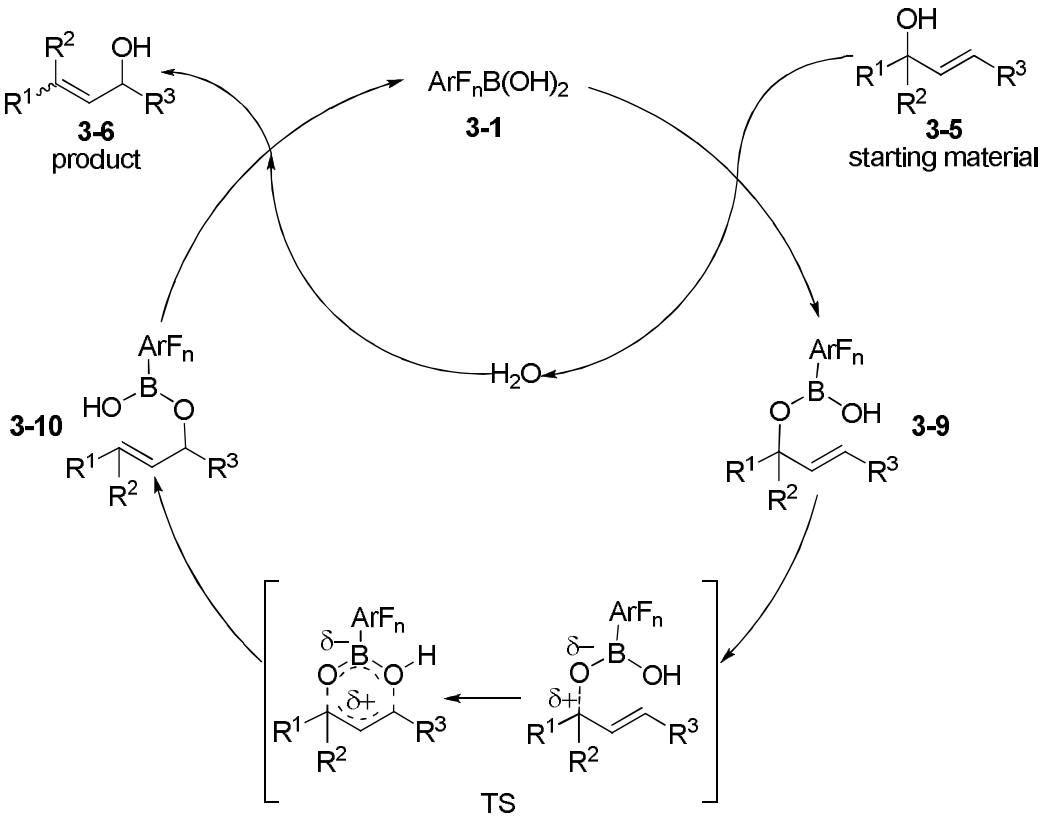
Table 3-6: Comparison of BAC system with Re or Au system

(entries 8–9, **Table 3-6**) or propargylic alcohols (entry 10, **Table 3-6**), BAC is effective with both allylic and propargylic alcohols. Unlike the rhenium oxo catalysts[12e], which usually need to be stored and used under strictly anhydrous conditions, boronic acid catalysts are stable to air and moisture. Moreover, the boronic acid catalyst **3-1k** is robust under the reaction conditions and is still fully effective even after 24 hours in the reaction mixture, which implies the potential recyclability of the boronic acid catalysts. This conclusion was drawn based on a control experiment where, after completion of a reaction with substrate **3-5m** (**Table 3-3**) under the optimized reaction conditions (24 h), an additional, equal amount of starting material **3-5m** was added to the reaction mixture and the reaction gave the desired product **3-6m** in the same yield (80%) upon stirring for another 24 hours.

3.2.5 Mechanistic investigations

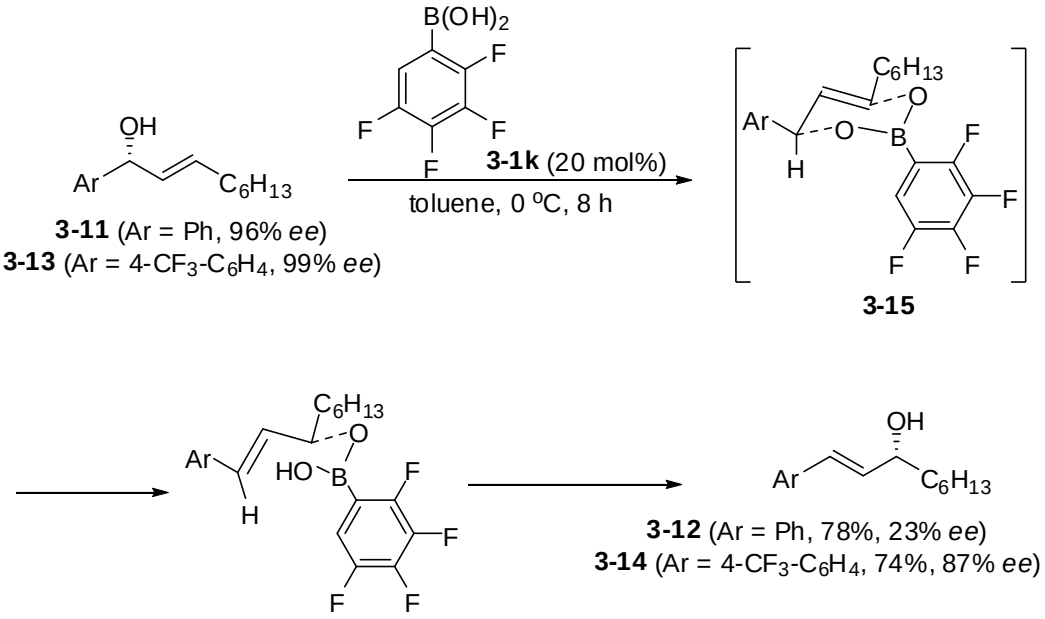
The scope of substrates, reaction times, and product yields of these boronic acid-catalyzed 1,3-transpositions of allylic and propargylic alcohols are consistent with a pseudo S_N1' mechanism involving partial or full ionization of the alcohol into an allylic (or propargylic) carbocation.[13a] Thus, substrates bearing multiple alkyl and aryl substituents on the 3-carbon framework underwent a faster transposition while substrates with fewer substituents such as **3-5a** (**Table 3-2**), or others such as **3-5g** (**Table 3-2**), **3-5i** (**Table 3-2**) or **3-5ad** (**Table 3-4**) with electron-withdrawing groups were less favorable substrates. In this context, a highly electron-poor boronic acid catalyst **3-1k** or **3-1l** is required in order to help ionize the hydroxyl C–O bond. In addition, as mentioned before, a small quantity of water is required for the catalytic turnover, but that a larger excess interferes with formation of reactive intermediates (entries 15–16, **Table 3-1**). These assumptions and our observations about the requirement for a small amount of water are depicted in the proposed catalytic cycle of **Scheme 3-8**. In this cycle, the

water released in the formation of hemiboronic ester **3-9** eventually serves in the hydrolytic release of the catalyst from the transposed intermediate **3-10**.

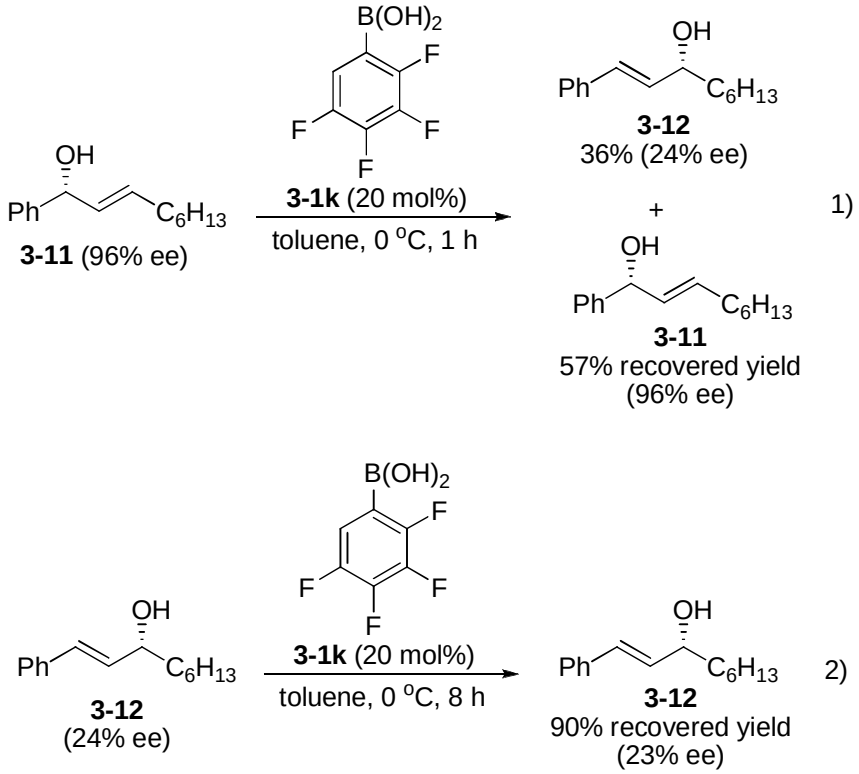


Scheme 3-8: Proposed catalytic cycle for the 1,3-transposition of allylic alcohols catalyzed by electron-poor boronic acids 3-1

To gain more mechanistic insight, stereochemical experiments involving the boronic acid catalyzed transpositions of allylic alcohols were conducted. It was found that under the same reaction conditions, both optically enriched allylic alcohols **3-11** and **3-13** could undergo the isomerization to provide the respective products **3-12** and **3-14** in a stereoselective manner (**Scheme 3-9**). The absolute configuration of products **3-12** and **3-14** is consistent with a six membered cyclic chairlike transition state **3-15** similar to that proposed with the Re-catalyzed variants.[12e] However, the observation of different levels of chirality transfer for **3-11** and **3-13** during the isomerization process hints at a substrate-dependent

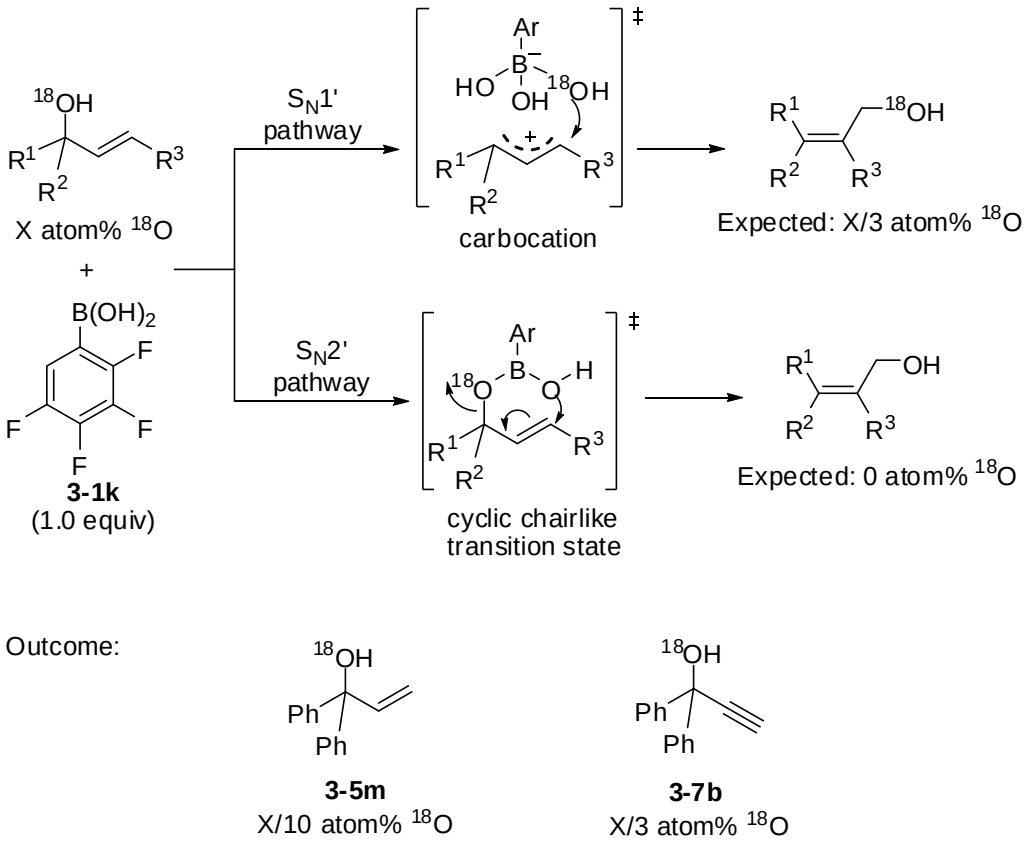


Scheme 3-9: Stereochemical study of 1,3-transposition of allylic alcohols



Scheme 3-10: Control experiments for stereochemical study of 1,3-transposition of allylic alcohols

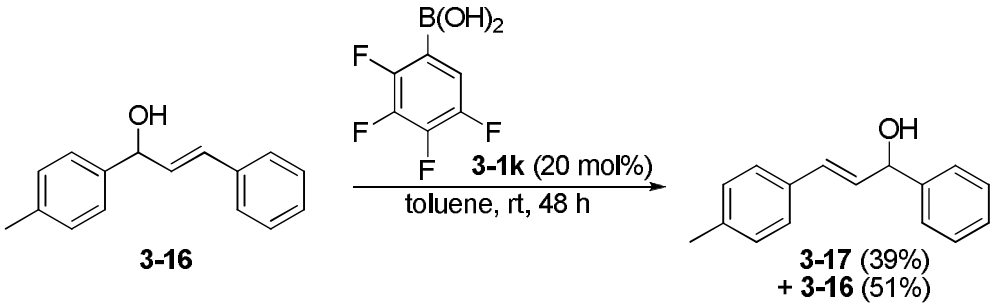
degree of ionization and concertedness for the transposition. Moreover, in the case of **3-11**, both the unreacted starting material **3-11** (eq. 1, **Scheme 3-10**) and the product **3-12** (eq. 2, **Scheme 3-10**) kept their stereochemical integrity upon exposure to the reaction conditions. These results suggest that the formation of hemiboronic acid intermediate **3-9** (**Scheme 3-8**) is likely irreversible (i.e., the 1,3-transposition occurs faster), and that epimerization occurs on the latter intermediate and does so more readily on substrates capable of greater stabilization of an allylic carbocation.



Scheme 3-11: Mechanistic investigation of 1,3-transposition of allylic and propargylic alcohols using ^{18}O labeling experiments

The 1,3-transpositions of ^{18}O labeled substrates **3-5m** and **3-7b** were performed to further investigate the mechanism, in particular, the issue of reaction

concertedness. As shown in **Scheme 3-11**, the isomerization could proceed through two possible pathways; an S_N1' pathway *via* a carbocation (open transition state) or an S_N2' pathway *via* a cyclic chairlike transition state. If the reaction proceeds through the S_N1' pathway, the three OH groups in the tetrahedral boronate counteranion would have an approximately equal chance to attack the intermediate carbocation. Thus, when a stoichiometric amount of **3-1k** is employed, it is expected, statistically, that one third of the labeled oxygen atom would transfer from the starting material to the final product. If the reaction proceeds through a concerted cyclic chairlike transition state, very little or close to none of the labeled oxygen atom would be expected to transfer to the final product. The experimental data for isomerization of **3-5m** showed that 10.1% of the labeled oxygen atom was transferred to the final product, which is consistent with a high degree of concertedness in the transposition of allylic alcohols. The experimental data for the 1,3-transposition of **3-7b** showed that 33.2% ^{18}O atom was transferred to the final product, which clearly supports the involvement of a nonconcerted process with propargylic alcohols presumably due to geometrical constraints. The linear geometry of alkynes makes them extremely difficult to accommodate in a six-membered chairlike transition state and thus restricts the 1,3-transposition of propargylic alcohols to a nonconcerted pathway.

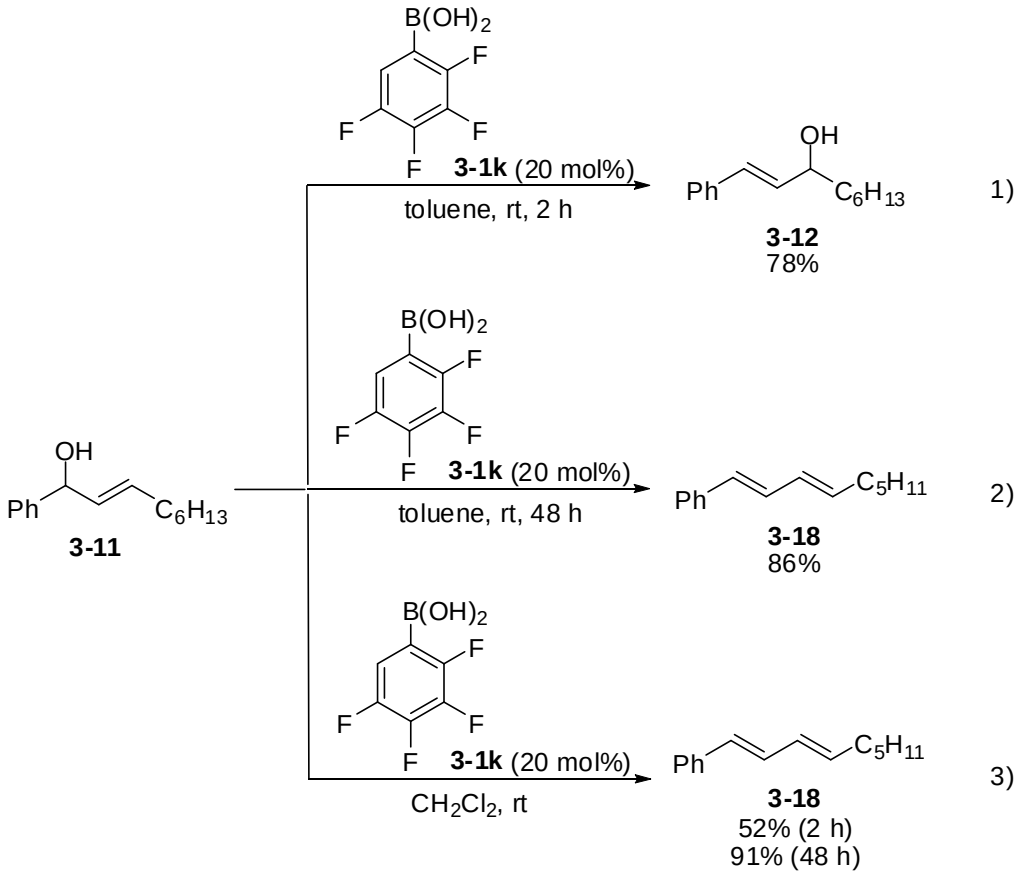


Scheme 3-12: Control experiment for thermodynamics of 1,3-transposition

1,3-Transpositions of allylic alcohols are potentially reversible and tend to generate a more thermodynamically stable isomer with a higher degree of alkene substitution or with extended conjugation at equilibrium. Therefore, in specific cases where the starting material and product have a similar level of stability, a mixture was obtained under boronic acid catalysis conditions (**Scheme 3-12**).

3.2.6 Competitive elimination reactions

The major competitive side-reaction for 1,3-transpositions catalyzed by boronic acid is elimination. In some specific cases, it was found that the rearranged allylic alcohols could further undergo a dehydrative elimination to provide substituted

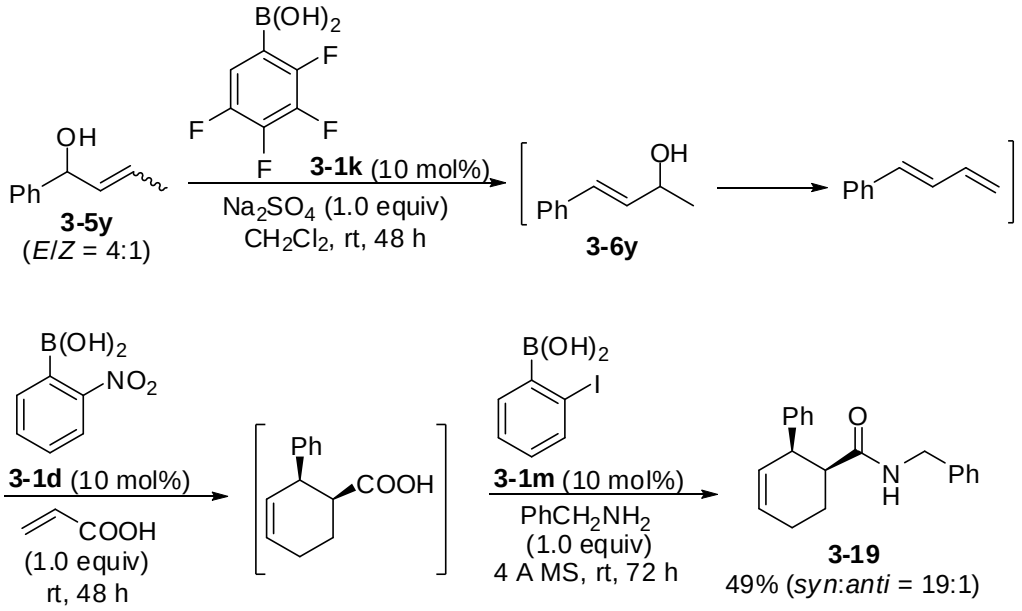


Scheme 3-13: Selective time- or solvent-controlled elimination to form substituted 1,3-butadienes

butadienes such as **3-18** when an extended reaction time was employed (eqs 1–2, **Scheme 3-13**).[13b–13c] Further studies showed that this elimination was highly solvent dependent and halogenated solvents such as CH_2Cl_2 favored this process (eq 3, **Scheme 3-13**).

3.2.7 Application to a multicatalytic tandem reaction process

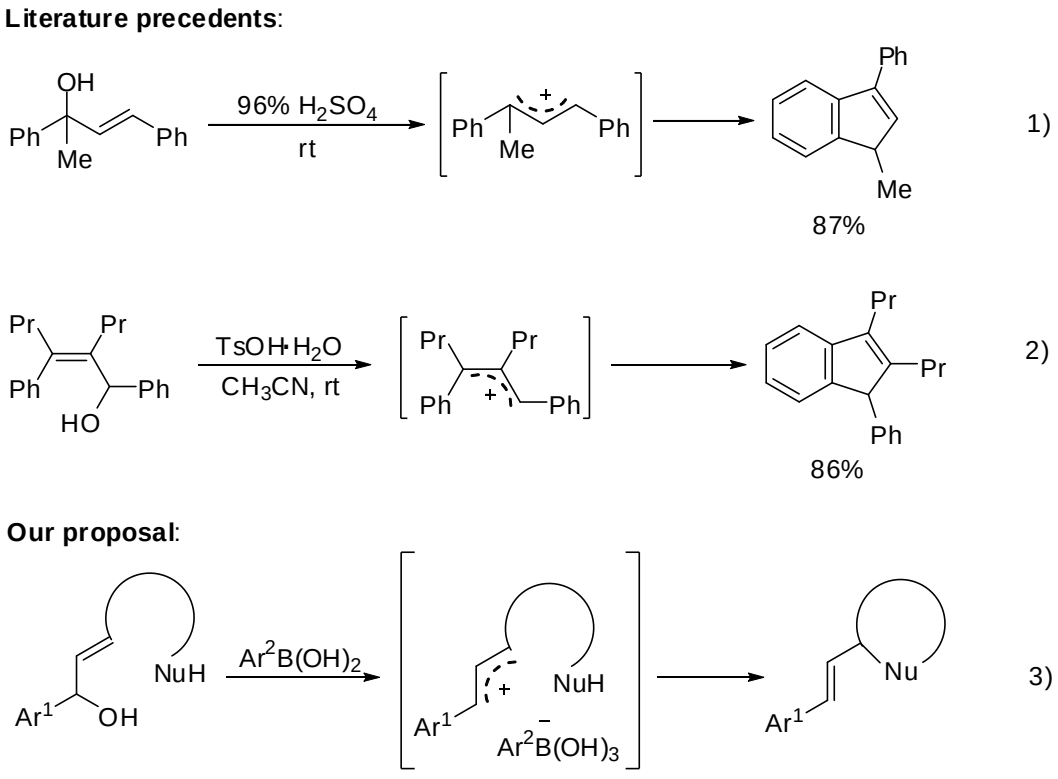
Since substituted butadienes are capable of participating in a wide range of chemical transformations such as Diels-Alder cycloaddition, the interesting finding mentioned in **Section 3.2.6** prompted us to design a multicatalytic tandem reaction process using the boronic acid catalysis concept. In conjunction with previously identified boronic acid catalyzed Diels-Alder cycloadditions and amidations, a simple one-pot sequential 1,3-transposition/elimination/[4 + 2] cycloaddition/amidation process using three different boronic acid catalysts was developed (**Scheme 3-14**).[14] Such a tandem process allows the construction of complex structures in a single synthetic operation and as such represents a powerful tool for the quick assembly of highly functionalized amide libraries.



Scheme 3-14: Multicatalytic tandem reaction process

3.3 Boronic acid catalyzed cationic cyclizations of allylic alcohols

In **Section 3.2**, electron-deficient arylboronic acids were identified to possess an excellent catalytic activity for activating hydroxyl groups in 1,3-transpositions of allylic and propargylic alcohols. By exploiting the same concept, we reasoned that a suitably placed nucleophilic functionality on the allylic alcohol substrate could lead to the formation of cyclic products under boronic acid catalysis (eq 3, **Scheme 3-15**). The pK_a of boronic acids is in the range of 5-9, which is significantly higher than the strong protic acids usually required in cationic cyclizations.[15] For example, under very strongly acidic conditions, protonation of allylic alcohols can give the allyl carbocations, then effecting a subsequent intramolecular Friedel-Crafts reaction to provide highly substituted indenes (eqs 1–2, **Scheme 3-15**).[15b,15c] Therefore, an unusually mild strategy for cationic

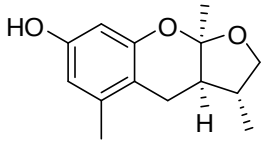


Scheme 3-15: Proposed cationic cyclizations of allylic alcohols catalyzed by boronic acid catalysts

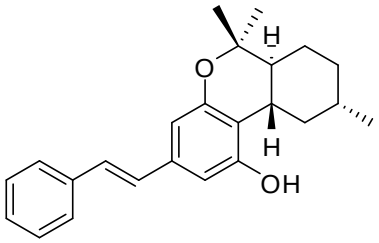
cyclizations using boronic acid catalysis was envisioned. In this section, boronic acid catalysis was applied to a variety of cationic carbo- and hetero-cyclizations of allylic alcohols that demonstrate its versatility and mildness (low temperature, functional group tolerance) in comparison with traditional methods employing strong Lewis and Brønsted acids.[1]

3.3.1 Optimization of reaction conditions

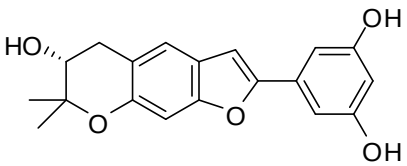
Chroman (dihydrobenzopyran) is found ubiquitously in important biologically active natural products and their derivatives (**Figure 3-2**).[16] One of the most straightforward routes for preparation of the chroman framework is the intramolecular Friedel-Crafts cyclizations of allylic alcohols such as **3-20a** (**Scheme 3-16**).[17] Therefore, this model reaction was chosen to test the concept of hydroxyl activation/cyclization with boronic acid catalysis. It was proposed that electron-deficient arylboronic acids could facilitate ionization of allylic alcohol **3-20a**, and that the generated intermediate allylic carbocation could undergo the intramolecular Friedel-Crafts cyclization to furnish chroman derivative **3-21a** (**Scheme 3-16)**.[6] Since water was generated from the reaction, it need to be



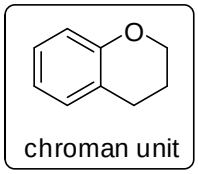
alboatrin



machaeriol B

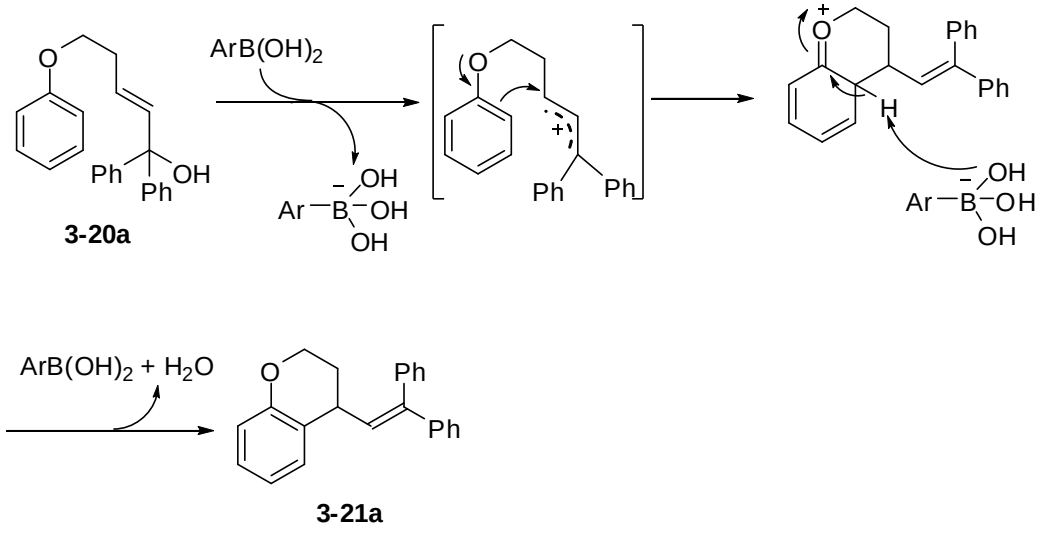


(-)-moracin P



chroman unit

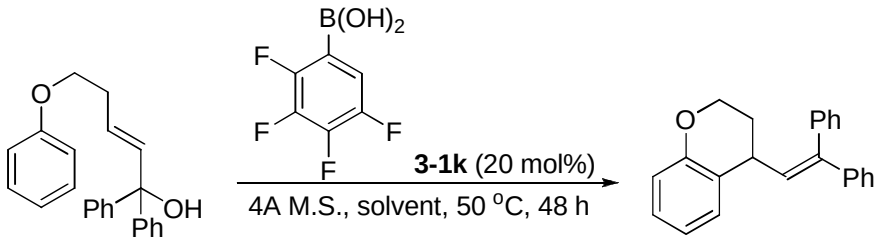
Figure 3-2: Selected examples of natural products containing a chroman unit



Scheme 3-16: Proposal for boronic acid catalyzed Friedel-Crafts cyclizations

determined if a dehydrating agent is necessary for sequestering the water to drive the equilibrium to favor the forward reaction. The experimental results associated with this issue will be discussed in more detail in this section.

In the first round of optimization, several solvents were evaluated in the Friedel-Crafts cyclization of model alcohol **3-20a** catalyzed by **3-1k** (**Table 3-7**). Although some non-polar aprotic solvents like toluene and hexanes were quite effective, they could not completely circumvent side reactions such as the 1,3-transposition and elimination. Gratifyingly, the highly polar solvent nitromethane (with a high dielectric constant $\varepsilon_r = 35.87\ \varepsilon_0$) was found to be much superior in suppressing the formation of side products (entry 8, **Table 3-7**).



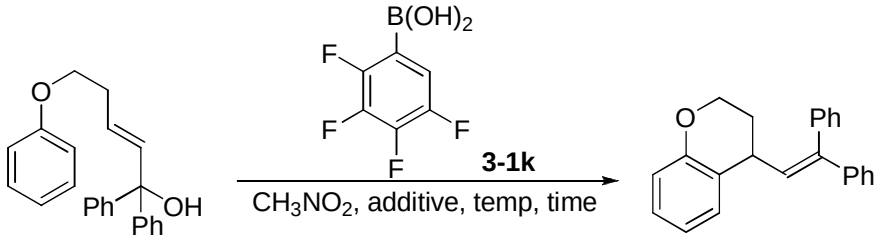
3-20a **3-21a**

Entry	Solvent	Yield[a] (%)
1	DMF	trace
2	EtOAc	trace
3	THF	19
4	1,4-dioxane	23
5	CH_3CN	30
6	toluene	55
7	hexanes	67
8	**CH_3NO_2**	**92**

[a]Isolated yields of the product after purification by silica gel column chromatography.

Table 3-7: Solvent optimization in the boronic acid catalyzed cyclization of model allylic alcohol 3-20a

Since water was generated from the reaction, it can be reasoned that the use of a dehydrating agent could help drive the equilibrium to favor the forward reaction. However, a control run without any dehydrating agents showed that there were no advantages to using them (entries 1–3 and 6–7, **Table 3-8**). These results hinted that water has little or no effect on this type of cyclizations. Furthermore, a number of simple Lewis acid and Brønsted acid additives were screened but provided no rate acceleration (entries 4–5, **Table 3-8**). The catalyst is effective even at room temperature provided a longer reaction time is employed (entry 8, **Table 3-8**). A lower yield, however, was obtained when using a lower catalyst loading (entries 9-10). A comparison with pentafluorophenylboronic acid (entry 11) confirmed that **3-1k** (entry 8) is a superior catalyst. This outcome is similar to that obtained with the 1,3-transposition chemistry (see **Section 3.2**).



3-20a **3-21a**

Entry	Cat. Loading (mol%)	Additive	Temp (^oC)	Time (h)	Yield[a] (%)
1	20	4A molecular sieves	50	48	92
2	20	$MgSO_4$ (5.0 equiv)	50	48	89
3	20	Na_2SO_4 (5.0 equiv)	50	48	82
4	20	$ZrCl_4$ (20 mol%)	50	48	72
5	20	TsOH (20 mol%)	50	48	32
6	20	H_2O (1.0 equiv)	50	48	80
7	**20**	**No additive**	**50**	**48**	**97**
8	**20**	**No additive**	**rt**	**60**	**97**
9	10	No additive	rt	60	67
10	5	No additive	rt	60	8
11[b]	20	No additive	rt	60	68

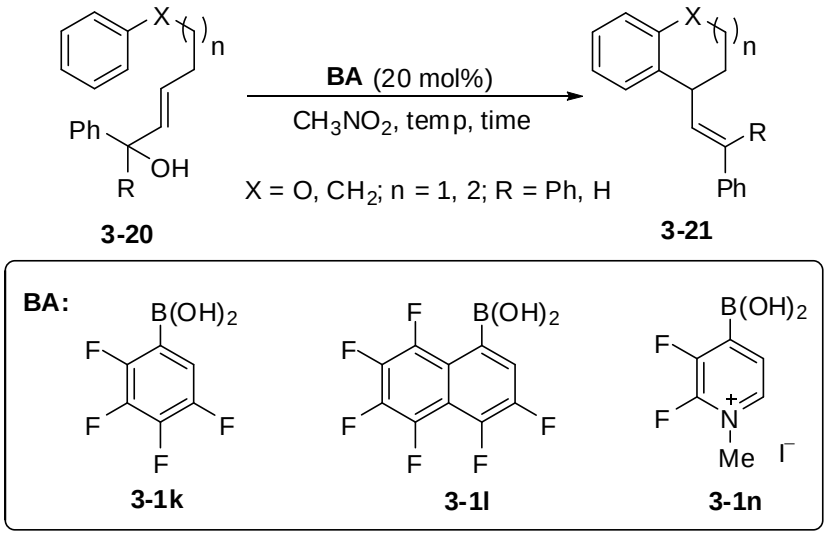
[a]Isolated yields of the product after purification by silica gel column chromatography. [b]Using pentafluorophenylboronic acid (20 mol%) as the catalyst.

Table 3-8: Optimization of reaction conditions in the boronic acid catalyzed cyclization of model allylic alcohol 3-20a

3.3.2 Substrate scope in the boronic acid catalyzed intramolecular Friedel-Crafts cyclizations of allylic alcohols

The scope of substrates was explored using the optimal reaction conditions: 20 mol% catalyst **3-1k** in nitromethane (**Table 3-9**). Most substrates provided cyclic products at room temperature but reaction times can be reduced significantly by performing the reactions at 50 °C. Both benzopyrans **3-21a** and **3-21b** were obtained in high yield, thus demonstrating that a single phenyl group in **3-21b** is sufficient to promote effective activation by the catalyst (entries 1-2, **Table 3-9**).

The unactivated arene substrate **3-20c** was quite a challenging substrate. With boronic acid **3-1k** or **3-1l** as the catalyst, the desired product **3-21c** was only obtained in 50% or 60% yield respectively (entries 3-4, **Table 3-9**). This result drove us to design a more active catalyst for the cationic cyclizations. To our satisfaction, it was found that the even more electronically impoverished boronic acid **3-1n** exhibited a remarkable catalytic activity for the intramolecular Friedel-Crafts cyclization of unactivated arene substrate **3-20c**. It afforded a 72%



Entry	R	n	X	Catalyst	Temp (^oC)	Time (h)	Product[a]	Yield[b] (%)
1	Ph	1	O	**3-1k**	rt	60	**3-21a**	97
2	H	1	O	**3-1k**	rt	48	**3-21b**	79
3	Ph	1	CH_2	**3-1k**	50	48	**3-21c**	50
4	Ph	1	CH_2	**3-1l**	50	48	**3-21c**	60
5	Ph	1	CH_2	**3-1n**	50	48	**3-21c**	72
6	H	2	O	**3-1k**	50	48	**3-21d**	21
7	H	2	O	**3-1n**	50	48	**3-21d**	60

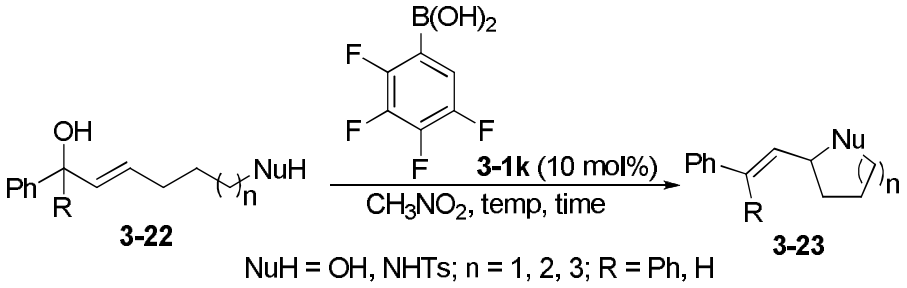
[a]*E*/*Z* isomer ratio > 20:1 for **3-21b** and **3-21d**. [b]Isolated yields of product after purification by silica gel column chromatography.

Table 3-9: Substrate scope in the boronic acid catalyzed intramolecular Friedel-Crafts cyclizations of allylic alcohols

yield of product **3-21c** when using the same reaction time as for catalysts **3-1k** and **3-1l** (entry 5, **Table 3-9**). With the more active boronic acid catalyst 2,3-difluoro-4-methylpyridiniumboronic acid **3-1n** in hand, the substrate scope of these Friedel-Crafts-type alkylations can be greatly extended. For example, the use of the new and more active catalyst **3-1n** was necessary for effecting a medium ring closure affording **3-21d** in a reasonable yield of 60% compared to only 21% with catalyst **3-1k** (entries 6-7, **Table 3-9**).

3.3.3 Substrate scope in the boronic acid catalyzed heterocyclizations of allylic alcohols

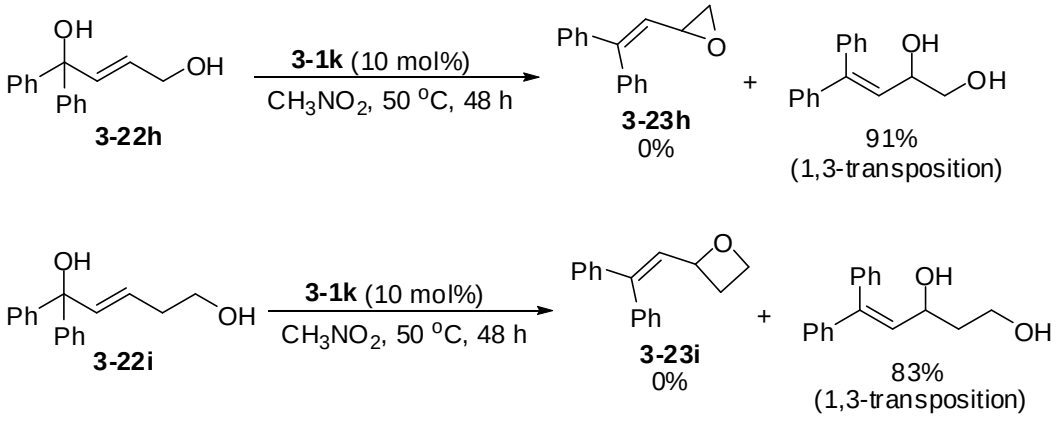
Boronic acid catalyzed cationic cyclizations are not limited to C–C bond formation. Heteroatom cyclizations with diols and aminoalcohols are possible, as shown with the isolation of tetrahydrofurans **3-23a**–**3-23b** (entries 1–3), pyrans **3-23c**–**3-23d** (entries 4–5), oxepan **3-23e** (entry 6), pyrrolidine **2-23f** (entry 7), and piperidine **3-23g** (entry 8) (**Table 3–10**). The rate of cyclizations is greatly influenced by the ring size of the cyclic products. The formation of a 7-membered ring (entry 6) is much slower than the formation of 5- and 6-membered rings (entries 4–5), so much that the competitive side reaction of 1,3-transposition could not be avoided completely with substrate **3-22e**. In the case of pyran ring formation, a small amount of oxocane (8-membered ring) was obtained as a side product indicating a competitive S_N1 or S_N2 reaction pathway (entry 4). Further attempts for the formation of oxirane (3-membered ring) **3-23h** and oxetane (4-membered ring) **3-23i** were not successful and undesired 1,3-isomerization products were generated instead (**Scheme 3-17**).



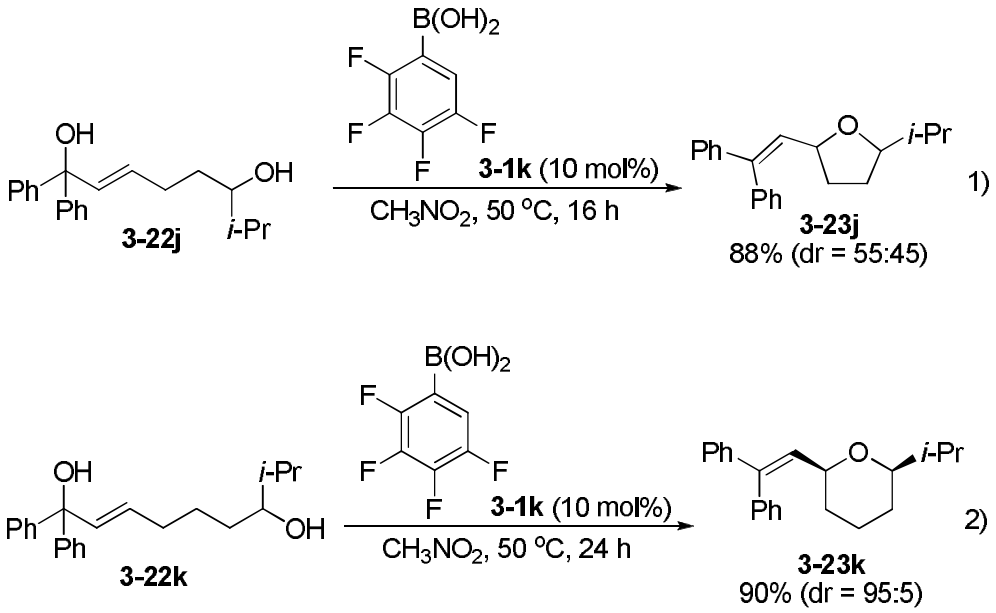
Entry	R	n	NuH	Temp (^oC)	Time (h)	Product[a]	Yield[b] (%)
1	Ph	1	OH	rt	24	**3-23a**	95
2	Ph	1	OH	50	16	**3-23a**	99
3	H	1	OH	50	16	**3-23b**	89
4	Ph	2	OH	50	16	**3-23c**	87[c]
5	H	2	OH	50	48	**3-23d**	94
6	Ph	3	OH	50	16	**3-23e**	62[d]
7	Ph	1	NHTs	50	16	**3-23f**	88
8	Ph	2	NHTs	50	16	**3-23g**	85

[a]*E*/*Z* isomer ratio > 20:1 for **3-23b** and **3-23d**. [b]Isolated yields of the product after purification by silica gel column chromatography. [c]5% S_N1 or S_N2 product (8-membered ring) was isolated. [d]30% of 1,3-hydroxyl transposition product was isolated.

Table 3-10: Substrate scope in the boronic acid catalyzed heterocyclizations of allylic alcohols



Scheme 3-17: Unsuccessful examples for heterocyclizations of allylic alcohols



Scheme 3-18: More examples to show stereoselectivity in the boronic acid catalyzed heterocyclizations of secondary allylic alcohols

Secondary alcohols were also employed successfully, providing furan **3-23j** and pyran **3-23h** in excellent yields (**Scheme 3-18**). Compared with the furan **3-23j** which was obtained in poor diastereoselectivity (eq 1, **Scheme 3-18**), the pyran **3-23h** was furnished in very high diastereoselectivity with two substituents syn to

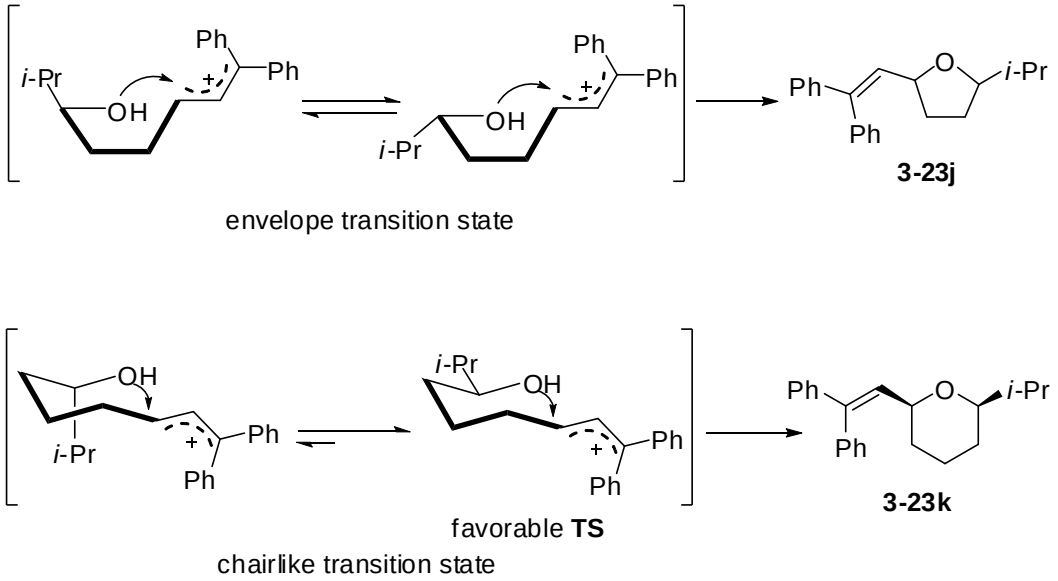
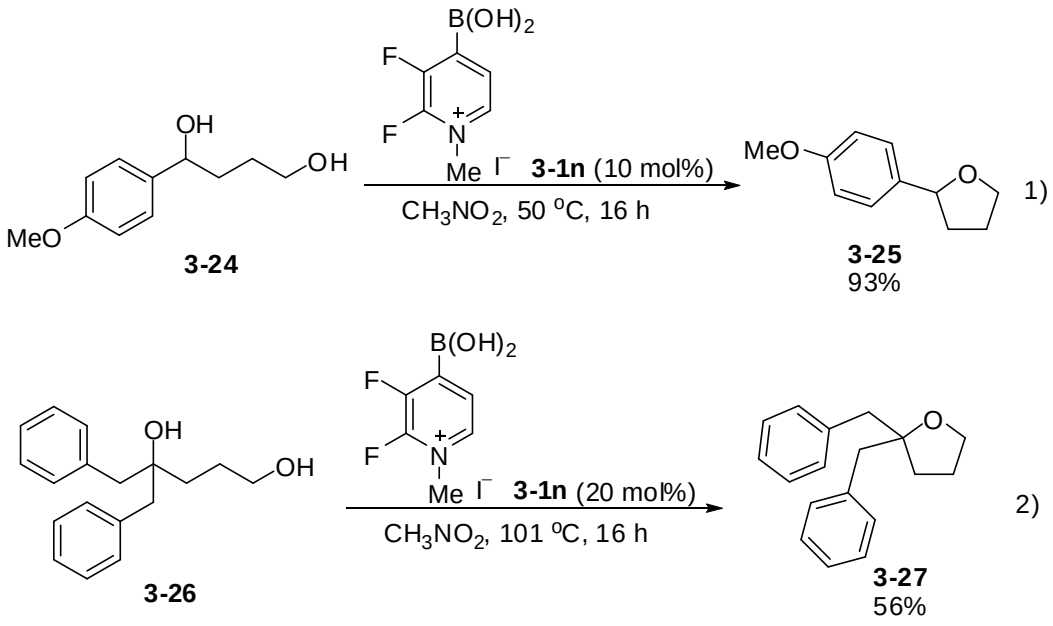


Figure 3-3: Transition states for the formation of 3-23j and 3-23k

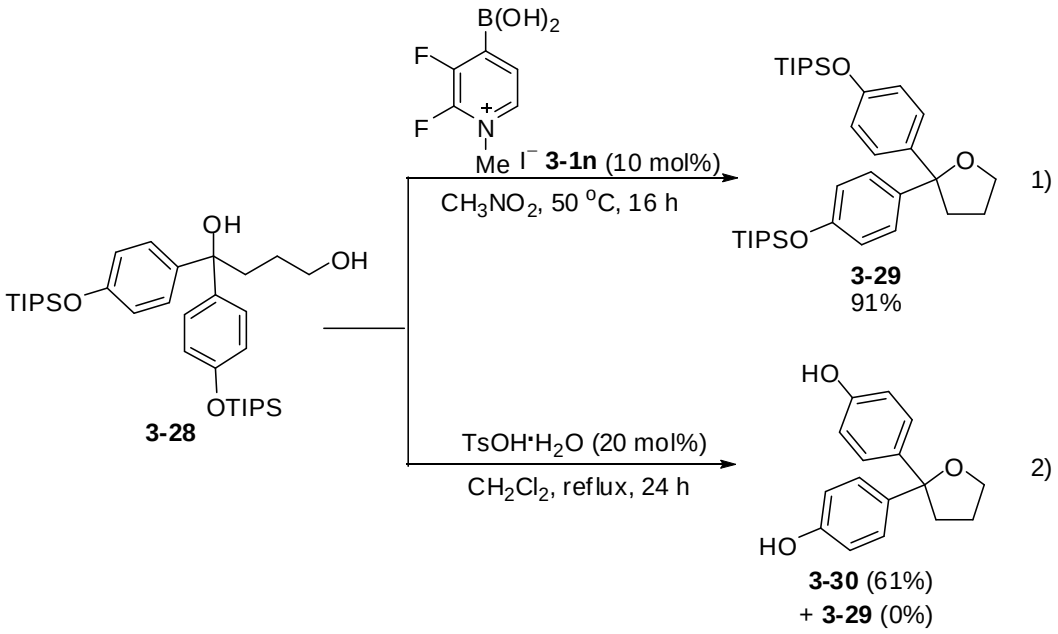
each other to minimize the 1,3-diaxial interaction in the chairlike transition state (eq 2, **Scheme 3-18**). In the case of furan formation, the subtle energy difference between several envelope transition states results in poor diastereoselectivity, whereas, in the case of pyran formation, the chairlike transition state where two substituents occupy equatorial positions is much more favorable leading to the product in high diastereoselectivity (**Figure 3-3**).

3.3.4 Substrate scope in the boronic acid catalyzed heterocyclizations of non-allylic alcohols

Compared with "activated" allylic alcohols which can form carbocations more easily, non-allylic alcohols are more challenging substrates and the more active boronic acid **3-1n** is necessary for their effective cyclization (**Scheme 3-19**). The example of diol **3-24** shows that benzylic alcohols, which are also activated, are suitable substrates (eq 1, **Scheme 3-19**). The tertiary nonstabilized alcohol **3-26** afforded the desired product **3-27**, albeit in moderate yield using a higher catalyst loading and a much higher reaction temperature (eq 2, **Scheme 3-19**).



Scheme 3-19: Boronic acid catalyzed heterocyclizations of non-allylic alcohols

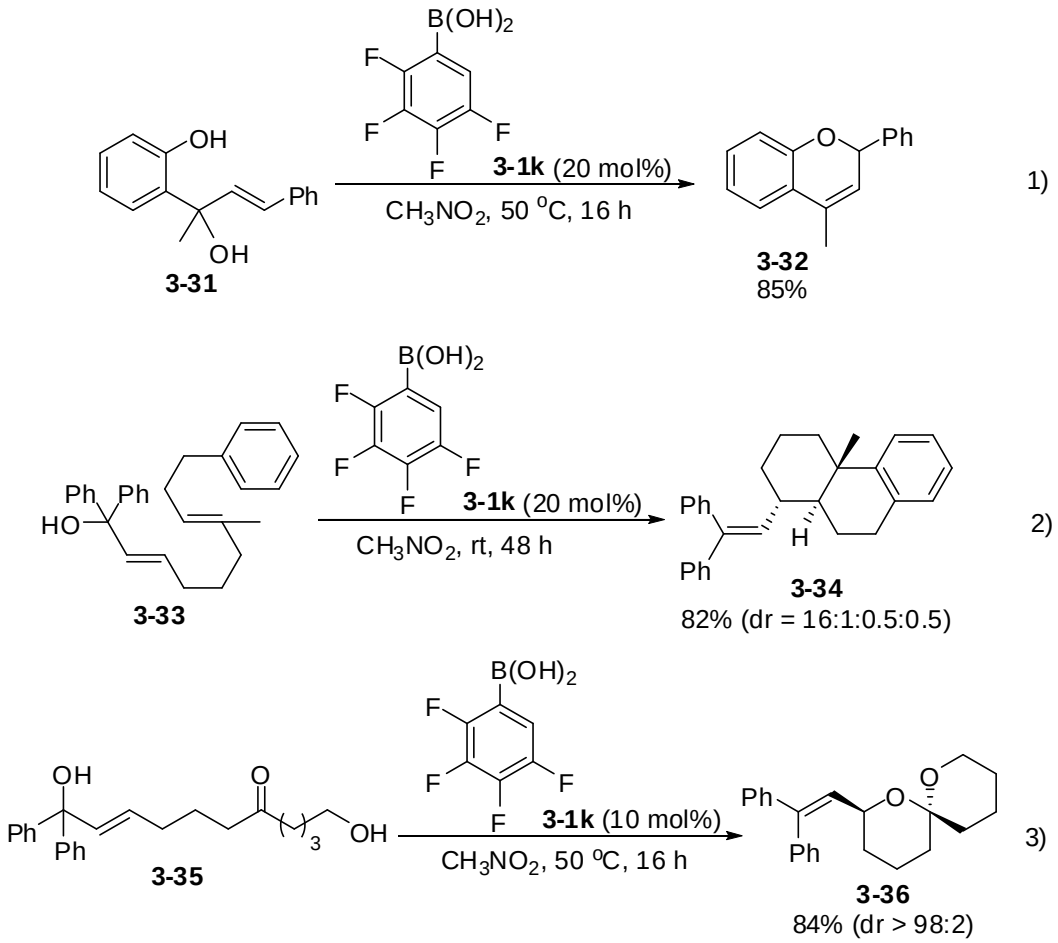


Scheme 3-20: Evidence for the mildness of boronic acid catalysis

Not only did our methodology show a broad substrate scope, but it also demonstrated remarkable functional group compatibility. For example, the *p*-TsOH-catalyzed reaction of diol **3-28** gave product in only 61% yield as the doubly deprotected bisphenol **3-30** (eq 2, **Scheme 3-20**), whereas with boronic acid catalysis, diol **3-28** led to a high yield of cyclized product **3-29** with intact phenolic silyl ethers. This observation is a testimony to the high tolerance of acid-sensitive functional groups afforded by these reaction conditions (eq 1, **Scheme 3-20**).

3.3.5 Substrate scope in the boronic acid catalyzed other cyclizations of allylic alcohols

Several other variants of the above cationic cyclizations demonstrate the versatility of boronic acid catalysis in promoting ring-forming reactions (**Scheme 3-21**). The benzopyran **3-32** was formed in high yield by cyclization of a phenol as the nucleophile (eq 1, **Scheme 3-21**). The remarkable cascade polycyclization



Scheme 3-21: Other examples of boronic acid catalyzed cyclizations of allylic alcohols

Figure 3-4: Transition states for the formation of 3-34 and 3-36

of substrate **3-33** provided the desired tricycle **3-34** in high diastereoselectivity (eq 2, **Scheme 3-21**), while the use of a ketone as a nucleophile led to an efficient

spiroketalization reaction (eq 3, **Scheme 3-21**). In the latter two cases (eqs 2–3, Scheme **3-21**), chairlike transition states were proposed to account for the excellent diastereoselectivities (**Figure 3-4**). The stereochemistry of **3-34** and **3-36** were confirmed by 2D NMR. The detailed information for structure determination of **3-34** and **3-36** will be presented in **Section 3.8.4.4.2.2** and **Section 3.8.4.4.2.3** respectively.

3.3.6 Comparison of boronic acid and *p*-TsOH catalyzed processes

Not only does our BAC system exhibit a remarkable mildness for a variety of cyclization reactions that can tolerate many acid-sensitive functional groups, it

Entry[a]	Reaction	BAC system	*p*-TsOH system[b]
1	**3-20c** to **3-21c** (**Table 3-9**)	72%	21%
2	**3-22a** to **3-23a** (**Table 3-10**)	99%	52%
3	**3-22b** to **3-23b** (**Table 3-10**)	89%	27%
4	**3-22c** to **3-23c** (**Table 3-10**)	87%	32%
5	**3-22e** to **3-23e** (**Table 3-10**)	62%	complex mixture
6	**3-22f** to **3-23f** (**Table 3-10**)	88%	13%
7	**3-22g** to **3-23g** (**Table 3-10**)	85%	18%
8	**3-22j** to **3-23j** (**Scheme 3-18**)	88% (55:45)	38% (55:45)
9	**3-22k** to **3-23k** (**Scheme 3-18**)	90% (95:5)	24% (95:5)
10	**3-35** to **3-36** (**Scheme 3-21**)	84% (>98:2)	39% (>98:2)

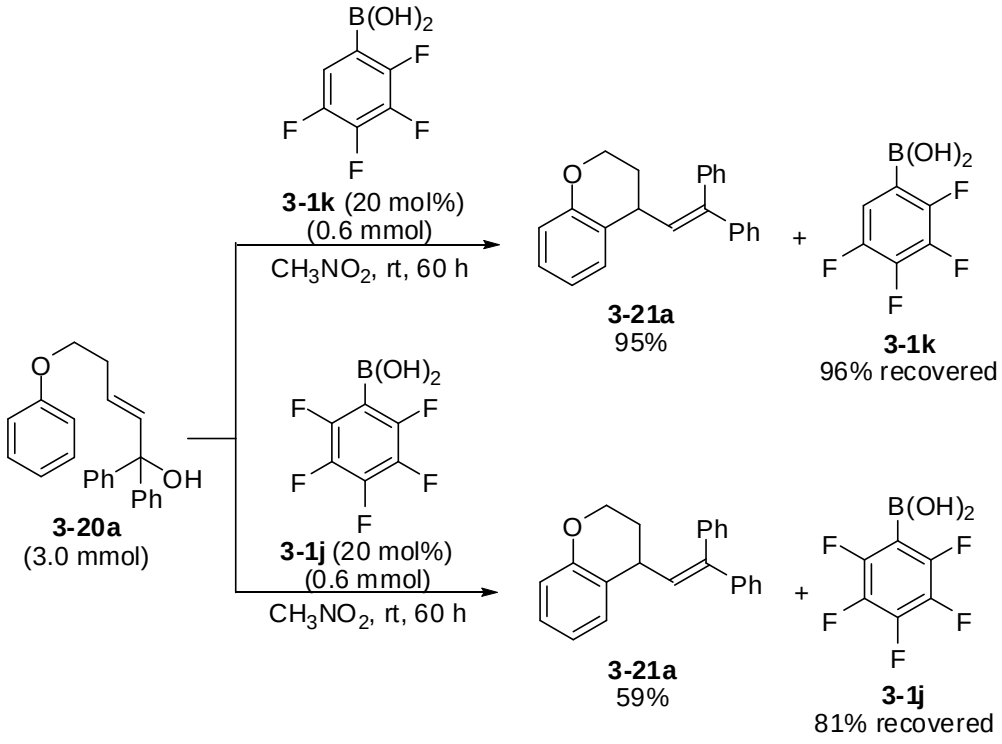
[a]The numbers outside the bracket represent the isolated yields and the ratios in the bracket represent the diastereomeric ratio measured by ^{1}H-NMR of the crude reaction product. [b]Reaction conditions: TsOH·H_2O (20 mol%), CH_2Cl_2, reflux, 24 h.

Table 3-11: Comparison between BAC system and *p*-TsOH system

also provides better yields over the traditional Brønsted acid catalyzed variants in all cases examined (**Table 3-11**). The mildness and effectiveness of these BAC procedures are remarkable. When attempted under optimized protic conditions (20 mol% *p*-TsOH in refluxing CH_2Cl_2 for 24 hours), the same transformations led to products **3-21c**, **3-23b**, **3-23f,** and **3-23g** in very low yields of 21%, 27%, 13%, and 24% respectively (**Table 3-11**).

3.3.7 The stability and recyclability of boronic acid catalysts

To test the stability and recyclability of the boronic acid catalyst **3-1k**, the cyclization of allylic alcohol **3-20a** catalyzed by **3-1k** was repeated on a larger scale (3.0 mmol) to give a 95% yield of **3-21a** with a 96% recovered yield of the catalyst **3-1k** (**Scheme 3-22**). Thus, **3-1k** is stable to protodeboronation under the reaction conditions and is recyclable upon purification with an acid-base



Scheme 3-22: Boronic acid catalyzed cyclization of model allylic alcohol 3-20a in a larger scale reaction

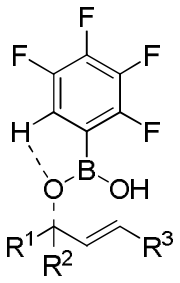


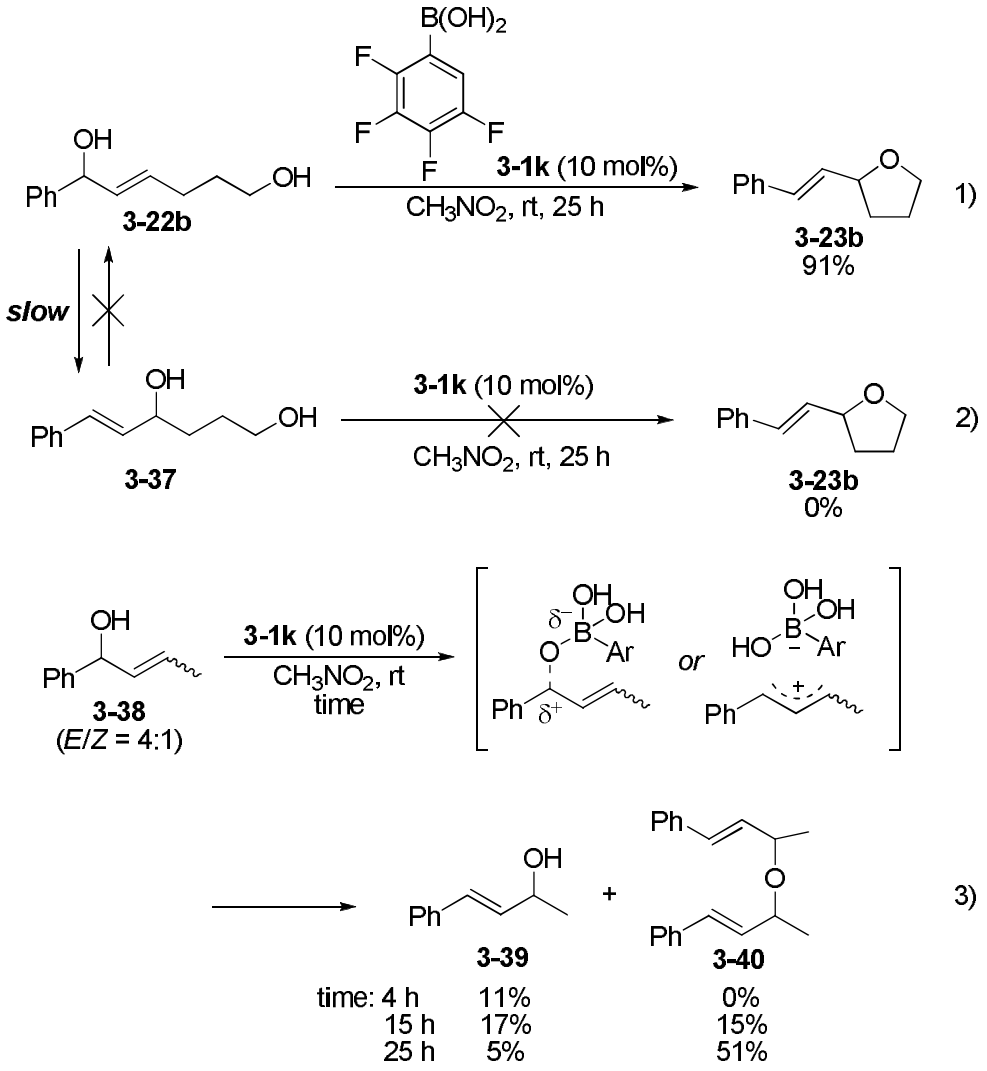
Figure 3-5: Proposed additional H-bonding activation of allylic alcohols by boronic acid catalyst 3-1k

extraction. A similar experiment also proved that pentafluorophenyl boronic acid **3-1j** can be recovered upon purification by recrystallization and is reusable under the same reaction conditions (**Scheme 3-22**). Since both catalysts can be recovered intact after the reaction, the inferior efficacy of pentafluoro- versus tetrafluorophenylboronic acid **3-1k** cannot be due to a difference in stability. One explanation for the superiority of **3-1k** is the possibility for additional substrate activation from the relatively acidic *ortho* C–H bond of **3-1k** (and **3-1l**, **3-1n**) (**Figure 3-5**).

3.3.8 Preliminary mechanistic investigation

The scope of substrates of these cyclizations of nucleophile-tethered allylic alcohols is consistent with a mechanism involving complete or near-complete ionization into an allylic carbocation. For example, while substrate **3-22b** undergoes a smooth and high-yielding reaction to give tetrahydrofuran **3-23b** at room temperature (eq 1, **Scheme 3-23**), the isomeric allylic alcohol **3-37** is inert and reacts slowly only at a temperature of 80 °C (eq 2, **Scheme 3-23**). Because ionization of **3-22b** is greatly facilitated by the benzylic nature of this alcohol, this outcome is consistent with a S_N1' mechanism. Given that **3-37** does not cyclize readily, cyclization of **3-22b** must be significantly faster than the 1,3-allylic hydroxyl transposition giving isomer **3-37** *via* a S_N2'-like mechanism.[4] Likewise, reverse transposition of **3-37** to **3-22b** is obviously not occurring under these

conditions. Allylic alcohol **3-38** was reported to provide transposed alcohol **3-39** in a yield of 73% in less than 4 hours when using toluene as solvent.[5] In nitromethane, **3-39** forms much slower, but over time it acts as a nucleophile to give ether **3-40** (eq 3, **Scheme 3-23**). The latter may be formed either *via* a highly polarized S_N2' mechanism or *via* S_N1' attack of **3-39** at the least hindered terminus of a full allylic carbocation. As shown with the outcome of **3-37**, catalyst **3-1k** would be incapable of ionizing or transposing **3-39** at room temperature, thus **3-39**

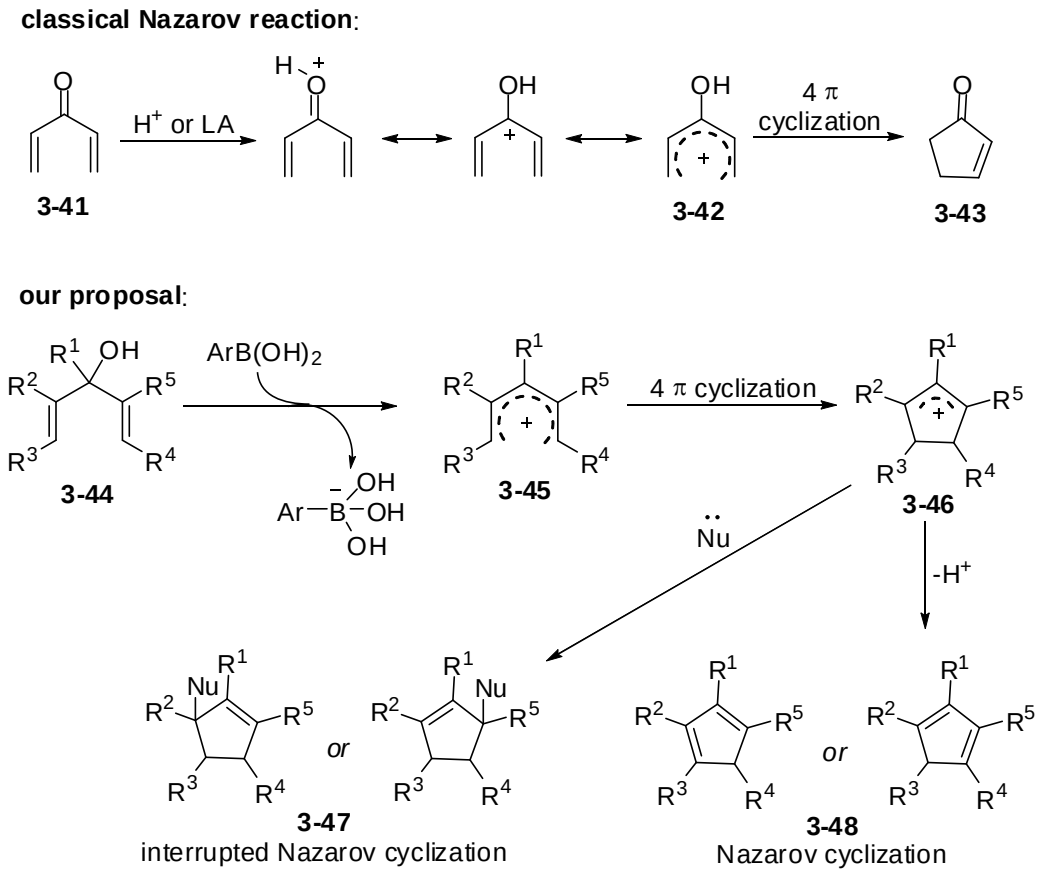


Scheme 3-23: Mechanistic control experiment with alcohols 3-22b, 3-37, and 3-38

can only act as a nucleophile. Altogether these results support the formation of carbocation-like intermediates, which formation is highly favored in the polar aprotic solvent nitromethane. In the future, control experiments with optically enriched alcohol **3-22b** and *Z* isomers may shed more light on the nature of the reaction intermediate.

3.4 Boronic acid catalyzed Nazarov cyclizations

The Nazarov cyclization is a widely employed chemical transformation allowing the synthesis of cyclopentenones such as **3-43** from divinyl ketone **3-41** (**Scheme 3-24**).[18] In the classical Nazarov reaction, upon activation with Lewis or Brønsted acids, the divinyl ketone substrate **3-41** generates a hydroxyl pentadienyl cation **3-42** as a key intermediate, which then undergoes a 4π-electrocyclic ring closure

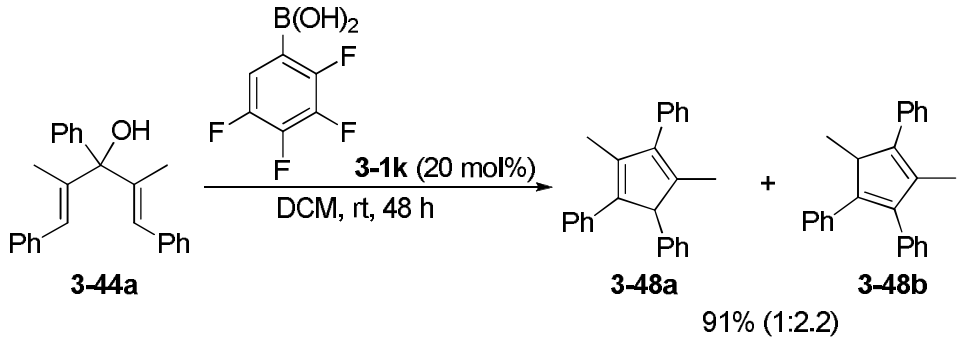


Scheme 3-24: Proposed boronic acid catalyzed Nazarov reaction

to furnish the cyclopentenones **3-43** as the final product (**Scheme 3-24**).[18] It can be envisioned that a pentadienyl cation **3-45** can be generated from a different substrate, divinyl alcohol **3-44**, in a similar manner (**Scheme 3-24**). Subsequently, the formed pentadienyl cation **3-45** can experience the "interrupted" Nazarov cyclization or Nazarov cyclization to provide synthetically useful cyclic products **3-47** or **3-48** respectively *via* a cyclopentyl allylic cation **3-46** (**Scheme 3-24**). Although the Nazarov reactions of divinyl ketone substrates have been intensively studied,[18] there are only sporadic reports of using divinyl alcohols **3-44** as starting materials.[19] Nearly all methods in the literature require either strongly acidic or toxic metal based catalysts. Inspired by the successful applications of the hydroxyl activation concept using boronic acid catalysis in 1,3-transpositions and a variety of cationic cyclizations of allylic alcohols, we sought to expand this boronic acid catalysis concept to Nazarov cyclizations to further demonstrate its mildness and versatility.[20]

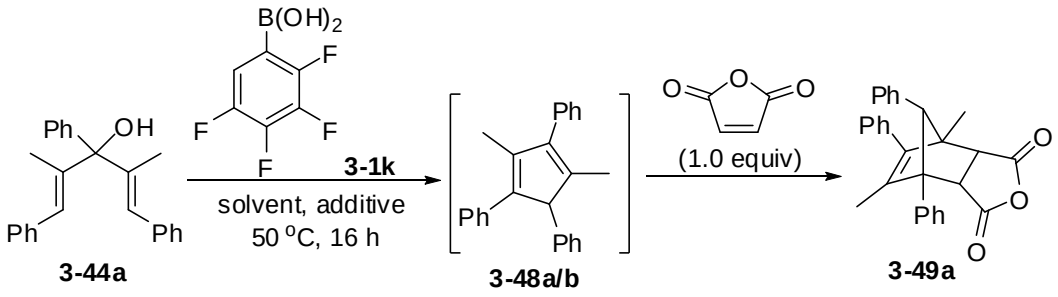
3.4.1 Optimization of reaction conditions

As a preliminary test, the Nazarov reaction of divinyl alcohol **3-44a** was found to proceed smoothly at room temperature using electron deficient arylboronic acid **3-1k** as the catalyst, providing mixtures of polysubstituted cyclopentadienes **3-48a**



Scheme 3-25: A preliminary test for the boronic acid catalyzed Nazarov reaction

and **3-48b** in excellent yield (**Scheme 3-25**). This result showed the feasibility of electron deficient arylboronic acid **3-1k** as a catalyst to promote the Nazarov reaction.



Entry	Solvent	Catalyst (mol%)	Additive	Yield[a] (%)
1	DMF	20	no additive	12
2	EtOAc	20	no additive	16
3	THF	20	no additive	31
4	Acetone	20	no additive	58
5	Hexanes	20	no additive	85
6	DCE	20	no additive	88
7	Toluene	20	no additive	90
8	**CH_3NO_2**	**20**	**no additive**	**95**
9	CH_3NO_2	10	no additive	71
10	CH_3NO_2	5	no additive	41
11	CH_3NO_2	20	4A molecular sieves	32
12	CH_3NO_2	20	H_2O (1.0 equiv)	83
13	CH_3NO_2	20	TsOH (20 mol%)	31[b]
14	CH_3NO_2	20	$ZrCl_4$ (20 mol%)	complex mixture
15[c]	CH_3NO_2	20	no additive	0

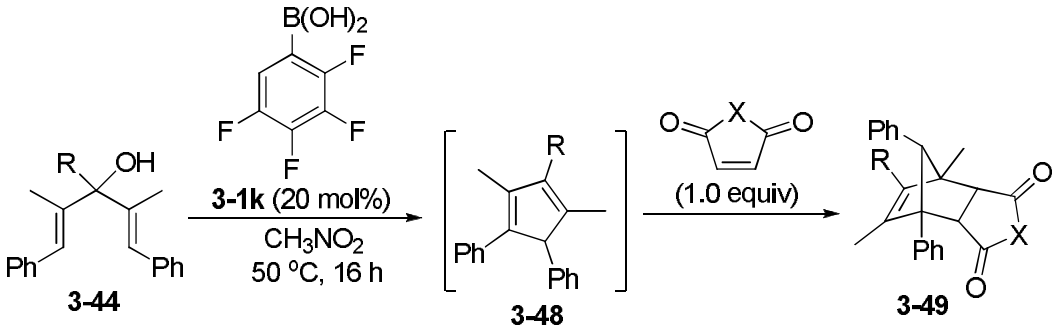
[a]Isolated yields of the product after purification by silica gel column chromatography. [b]60% hydrolysis product (dicarboxylic acid) was isolated. [c]The reaction was performed in the absence of boronic acid catalyst **3-1k**.

Table 3-12: Optimization of reaction conditions in the boronic acid catalyzed Nazarov reaction/Diels-Alder trapping

Maleic anhydride is a remarkably good dienophile and as such it was employed to trap the formed dienes **3-48** (**Table 3-12**). Although the Nazarov reactions of divinyl alcohols could proceed smoothly at room temperature (**Scheme 3-25**), a slightly higher reaction temperature (50 ^{o}C) was necessary to ensure the completion of the subsequent Diels-Alder cycloaddition within a reasonable time (**Table 3-12**). In the first round of optimization, several solvents were evaluated in the sequential Nazarov cyclization/Diels-Alder trapping of model divinyl alcohol **3-44a** catalyzed by **3-1k** (**Table 3-12**). Although some non-polar aprotic or halogenated solvents like toluene, hexanes or 1,2-dichloroethane were quite effective, the highly polar solvent nitromethane was superior (entry 8, **Table 3-12**). A lower yield was obtained when a lower catalyst loading was employed (entries 9–10, **Table 3-12**). Furthermore, the use of dehydrating agents such as molecular sieves was detrimental, while excess water showed a subtle influence on the reaction (entries 11–12, **Table 3-12**). Then, a number of simple additives were screened but none provided any observable rate acceleration (entries 13–14, **Table 3-12**). Interestingly, when a strong Brønsted acid like *p*-TsOH was used as the additive, the formed cycloadduct **3-49a** could further undergo hydrolysis to provide the corresponding dicarboxylic acid as the major product (entry 13, **Table 3-12**). This provided an evidence for the mildness of our methodology. Finally, a control run in the absence of boronic acid catalyst **3-1k** led to no product formation (entry 15, **Table 3-12**).

3.4.2 Substrate scope in the boronic acid catalyzed Nazarov cyclization/Diels-Alder trapping of divinyl alcohols

Using the optimal conditions, the scope of divinyl alcohols was explored using maleic anhydride as the dienophile (entries 1–6, **Table 3-13**). In the event, a wide selection of substituted divinyl alcohols was tolerated. In all cases, the desired cycloadduct **3-49** was obtained in excellent yield as a single isomer (entry 1–5,



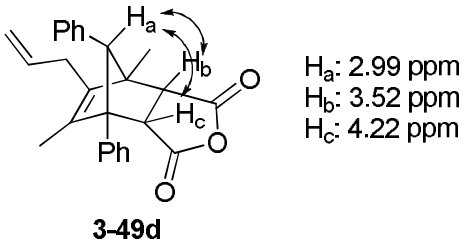
Entry	R	X	Product	Yield[a] (%)
1	Ph	O	**3-49a**	95
2	*n*-Bu	O	**3-49b**	88
3	Me	O	**3-49c**	91
4	$CH_2CH=CH_2$	O	**3-49d**	85
5	C≡CPh	O	**3-49e**	87
6	$CH=CH_2$	O	**3-49f**	30
7	Ph	NPh	**3-49g**	58
8	*n*-Bu	NPh	**3-49h**	62
9	Me	NPh	**3-49i**	60
10	$CH_2CH=CH_2$	NPh	**3-49j**	55

[a]Isolated yields of the product after purification by silica gel column chromatography.

Table 3-13: Substrate scope in the boronic acid catalyzed Nazarov reaction/Diels-Alder trapping of divinyl alcohols

Table 3-13). However, a trivinyl alcohol tended to give a low yield of the desired products due to the competition between two possible Nazarov cyclizations (entry 6, **Table 3-13**). Phenylmaleimide is also suitable as a dienophile for trapping the formed cyclopentadienes **3-48** (entries 7–10, **Table 3-13**). Compared with maleic anhydride, it exhibited lower efficiency for the sequential Nazarov cyclization/Diels-Alder trapping (entries 7–10, **Table 3-13**). NMR experiments were performed on **3-49d** to determine the relative stereochemistry of the cycloadducts. From the ^{1}H-NMR spectrum, H_a, H_b, and H_c could be identified as the signals at 2.99 ppm, 3.52 ppm, and 4.22 ppm respectively. Then the strong

nOe correlations of $H_a \leftrightarrow H_b$ and $H_a \leftrightarrow H_c$ clearly indicated that the produced cycloadducts **3-49** corresponded to the endo isomer (**Figure 3-6**). To address the origin of the stereoselectivity in this sequential process, a control experiment was conducted. When one isomer **3-48b** was re-subjected to the reaction conditions, a mixture of two isomers (**3-48a** and **3-48b**) was obtained. This result confirms that a thermodynamic equilibration between two isomers is occurring under the reaction conditions, likely *via* 1,5-H shift. The subsequent Diels-Alder reaction is most likely under kinetic control and favored with the less sterically hindered isomer **3-48a**, thus providing the cycloadduct **3-49a** as the exclusive diastereomer. In addition, less activated dienophiles such as methyl acrylate and methyl propiolate were investigated for trapping of the formed cyclopentadienes **3-48**, however, no cycloaddition products were observed in the crude reaction mixtures.



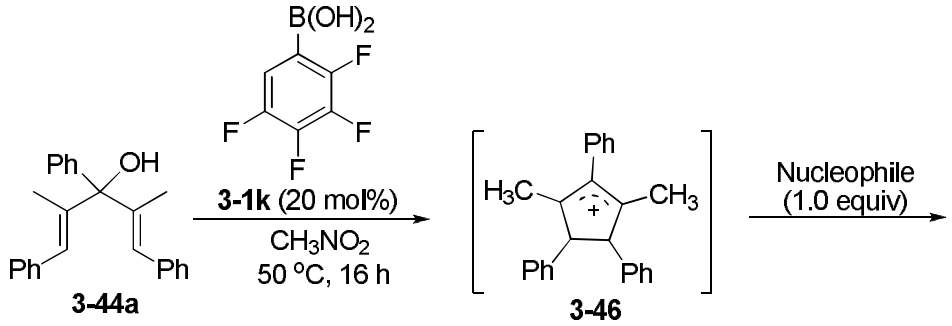
3-49d

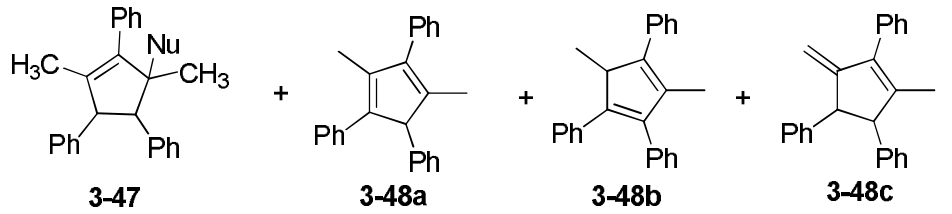
Figure 3-6: Illustration of nOe for 3-49d

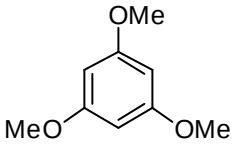
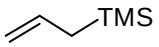
3.4.3 "Interrupted" Nazarov cyclizations of divinyl alcohols

The Nazarov reaction of divinyl alcohols proceeds *via* a cyclopentadienyl cation **3-46**, therefore, in the presence of a suitable nucleophile, the "interrupted" Nazarov reaction is possible.[21] However, several attempts using electron-rich aromatics, allylsilanes, sodium azide, silanes, thiophenol as nucleophiles failed to interrupt the Nazarov reaction. As a result, the mixture of dienes **3-48** was obtained in different ratios (**Table 3-14**). Perhaps, under boronic acid catalysis conditions, the lifetime of the cyclopentadienyl cation **3-46** is extremely short so that it is quite challenging to nucleophilically capture this reactive intermediate.

Performing the reactions at lower temperature may help slow down the unwanted elimination reaction and therefore could be a potential solution to address this issue. Such experiments will be conducted in the near future.





Entry[a]	Nucleophile	**3-47**	**3-48a**	**3-48b**	**3-48c**
1		0%	28%	60%	0%
2	NaN_3	0%	0%	0%	90%
3	Et_3SiH	0%	40%	44%	0%
4		0%	39%	48%	0%
5	PhSH	0%	40%	49%	0%

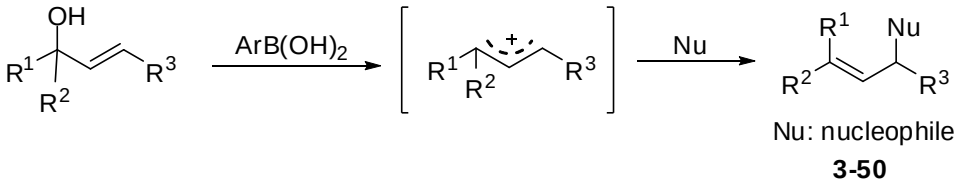
[a]Yields are based on ratios measured in crude NMR spectra of the product mixtures.

Table 3-14: Attempts of boronic acid catalyzed "interrupted" Nazarov cyclizations of the divinyl alcohol 3-44a

3.5 Boronic acid catalyzed allylic substitutions

As previously mentioned, McCubbin and co-workers described the use of a

catalytic amount of pentafluorophenylboronic acid to promote a series of Friedel-Crafts reactions of structurally diverse allylic alcohols with a variety of electron-rich aromatic and heteroaromatic substrates in the presence of molecular sieves at room temperature.[4] However, this protocol is only limited to highly reactive aromatics.[4] Since earlier studies showed our newly developed boronic acid catalysts **3-1k** and **3-1n** were superior to pentafluorophenylboronic acid in 1,3-transpositions[5] and cationic cyclizations of allylic alcohols,[6] it was proposed that the substrate scope of the above-mentioned Friedel-Crafts reaction could be greatly extended with the assistance of our superior boronic acid catalysts (**Scheme 3-26**). Beyond aromatics, several other external nucleophiles were also examined to expand the realm of boronic acid catalyzed allylic substitutions (**Scheme 3-26**).

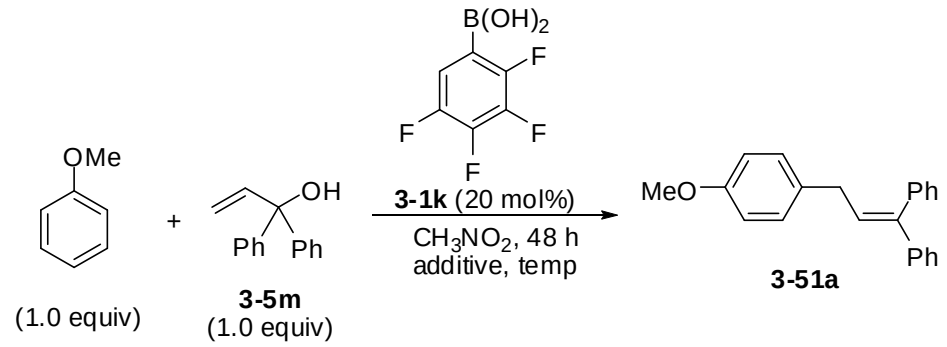


Scheme 3-26: Proposed boronic acid catalyzed allylic substitutions

3.5.1 Boronic acid catalyzed intermolecular Friedel-Crafts reaction

The intermolecular Friedel-Crafts reaction of allylic alcohol **3-5m** with anisole failed in the methodology developed by McCubbin and co-workers,[4] therefore it was selected as a model reaction for the preliminary evaluation of our catalytic system (**Table 3-15**). Employing the same reaction conditions as its intramolecular version (see **Table 3-9**), we were glad to see that the intermolecular Friedel-Crafts reaction of allylic alcohol **3-5m** with anisole proceeded smoothly, providing the desired product **3-51a** in 75% yield as a single regioisomer (entry 1, **Table 3-9**). In McCubbin's previously reported protocol,[4] molecular sieves were employed for the removal of water generated from the

reaction system. However, surprisingly, it was discovered that the use of this dehydrating agent or any other was detrimental in our catalytic system (entries 2–4, **Table 3-15**). Reasons for this observation are currently unknown. Remarkably, our catalytic system is still effective at room temperature with the same substrates (entry 5, **Table 3-15**).

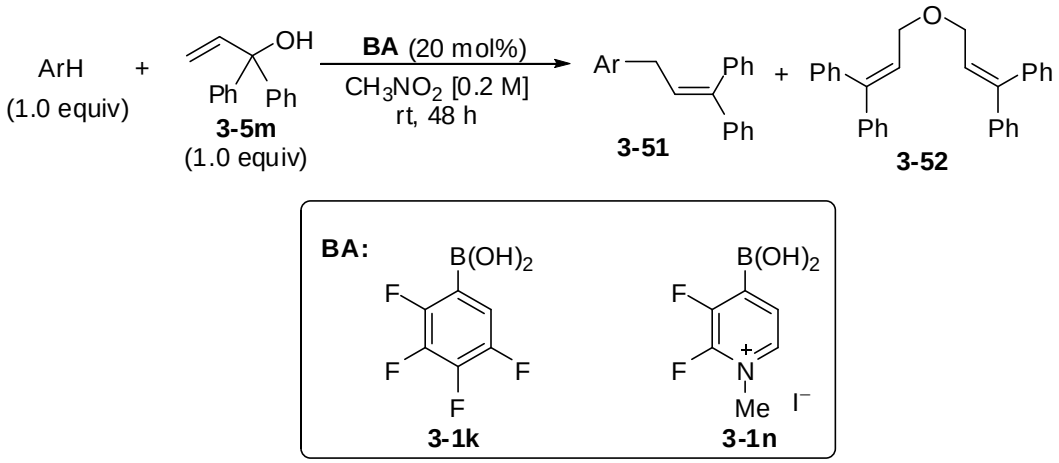


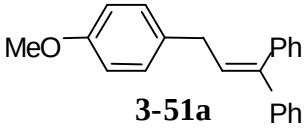
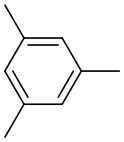
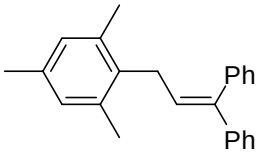
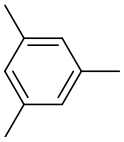
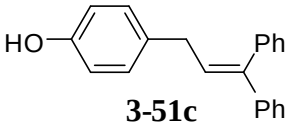
Entry	Temp (^{o}C)	Additive	Yield[a] (%)
1	50	no additive	75
2	50	4A molecular sieves	6
3	50	Na_2SO_4	57
4	50	$MgSO_4$	60
5	rt	no additive	70

[a]Isolated yields of product **3-51a** after purification by silica gel column chromatography.

Table 3-15: Study of additives in the boronic acid catalyzed intermolecular Friedel-Crafts reaction of allylic alcohol 3-5m with anisole

The scope of substrates was explored using the optimal reaction conditions: 20 mol% catalyst **3-1k** or **3-1n** in nitromethane (**Table 3-16**). Several electron-rich aromatics such as anisole, mesitylene, and phenol transformed effectively at room temperature, furnishing the desired products **3-51** in high yields with excellent regioselectivity (entries 1–6, **Table 3-16**). Since the rearranged allylic alcohol of **3-5m** can act as a competitive nucleophile, the ether **3-52** is the main side product for this intermolecular Friedel-Crafts reaction. In all three cases,



Entry	ArH	Catalyst	Product	Yield[a] (%)
1	anisole	**3-1k**	 **3-51a**	70
2	anisole	**3-1n**	**3-51a**	84
3		**3-1k**	 **3-51b**	80
4		**3-1n**	**3-51b**	90
5	phenol	**3-1k**	 **3-51c**	54
6	phenol	**3-1n**	**3-51c**	72

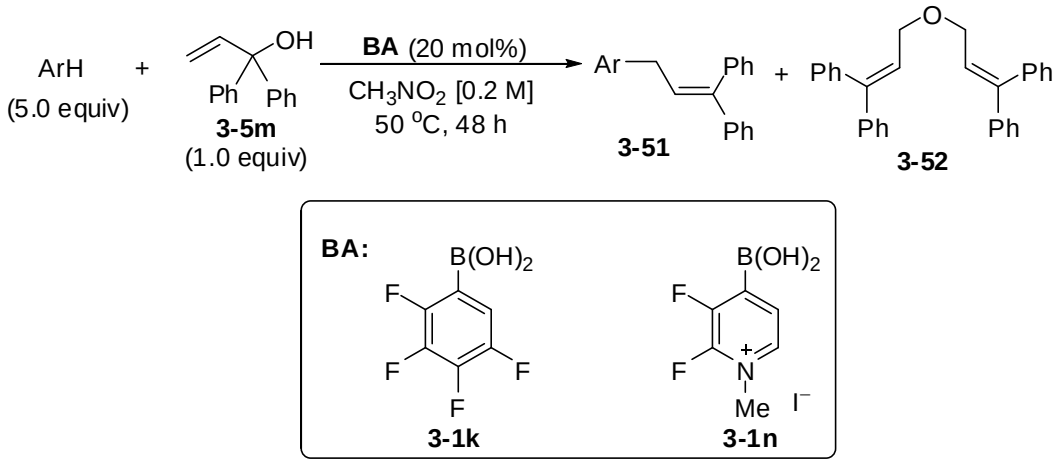
[a]Isolated yields of product **3-51** after purification by silica gel column chromatography.

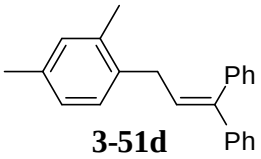
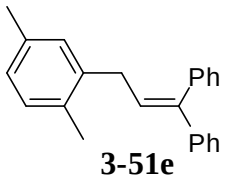
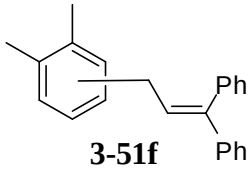
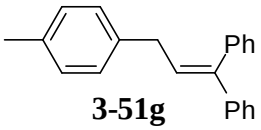
Table 3-16: Substrate scope in the boronic acid catalyzed intermolecular Friedel-Crafts reaction of allylic alcohol 3-5m

pyridiniumboronic acid catalyst **3-1n** exhibited higher efficiency at suppressing the formation of **3-52** compared to **3-1k** (entries 1, 3, 5 *vs* 2, 4 ,6, **Table 3-16**).

Interestingly, in the case of phenol, the corresponding C-alkylation product **3-51c** was obtained exclusively without any trace of O-alkylated product (entries 5–6, **Table 3-16**).

Relatively electron-poor arenes such as xylene isomers are quite difficult substrates because of their lower nucleophilicity, which is similar to that of the competitive rearranged allylic alcohol. Therefore, excess amounts of xylenes, the more active boronic acid catalyst **3-1n**, and an elevated reaction temperature were all necessary in order to ensure reasonable yields (entries 1–6, **Table 3-17**). Both *m*-xylene and *p*-xylene reacted with alcohol **3-5m** to afford the desired products **3-51d** and **3-51e** with excellent regioselectivity with respect to the site of allylic substitution (entries 1–4, **Table 3-17**). In the case of *o*-xylene, a 2.2:1 mixture of C^4 and C^3 allylation products **3-51f** was observed (entries 5–6, **Table 3-17**). In contrast, the even less nucleophilic substrate toluene failed to react with **3-5m** and the undesired product **3-52** was obtained as the major product (entry 7, **Table 3-17**). In light of these results, it is apparent that even more active boronic acid catalysts are needed in order to expand the substrate scope. Research on the design and preparation of more active boronic acid catalysts, along with the evaluation of their catalytic activity for intermolecular Friedel-Crafts reaction is still in progress.



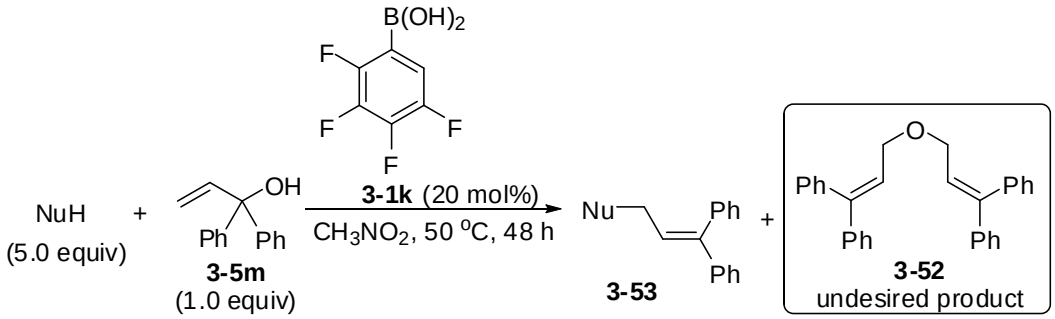
Entry	ArH	Catalyst	Product	Yield[a] (%)
1	*m*-xylene	**3-1k**	 **3-51d**	57
2	*m*-xylene	**3-1n**	**3-51d**	74
3	*p*-xylene	**3-1k**	 **3-51e**	20
4	*p*-xylene	**3-1n**	**3-51e**	48
5	*o*-xylene	**3-1k**	 **3-51f**	18[b]
6	*o*-xylene	**3-1n**	**3-51f**	48[b]
7[c]	toluene	**3-1n**	 **3-51g**	trace

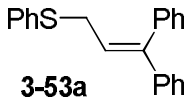
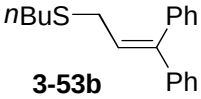
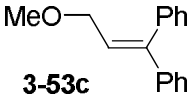
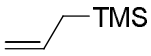
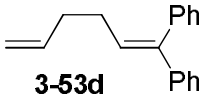
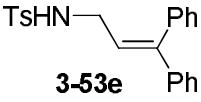
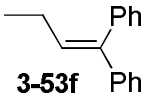
[a]Isolated yields of product **3-51** after purification by silica gel column chromatography. [b]The regioisomeric ratio is 2.2:1 (C^4:C^3). [c]71% **3-52** was separated as the major product.

Table 3-17: Substrate scope in the boronic acid catalyzed intermolecular Friedel-Crafts reaction of allylic alcohol 3-5m with xylenes and toluene

3.5.2 Preliminary examination of other allylic substitutions catalyzed by boronic acids

Besides aromatic compounds, other nucleophiles also demonstrated the potential to capture the intermediate allylic carbocation (**Table 3-18**). Both thiophenol and



Entry	NuH	Product	Yield[a] (%)
1	PhSH	 **3-53a**	81
2	*n*BuSH	 **3-53b**	84
3	MeOH	 **3-53c**	31
4		 **3-53d**	22
5	$TsNH_2$	 **3-53e**	0
6	Et_3SiH	 **3-53f**	0

[a]Isolated yields of product **3-53** after purification by silica gel column chromatography.

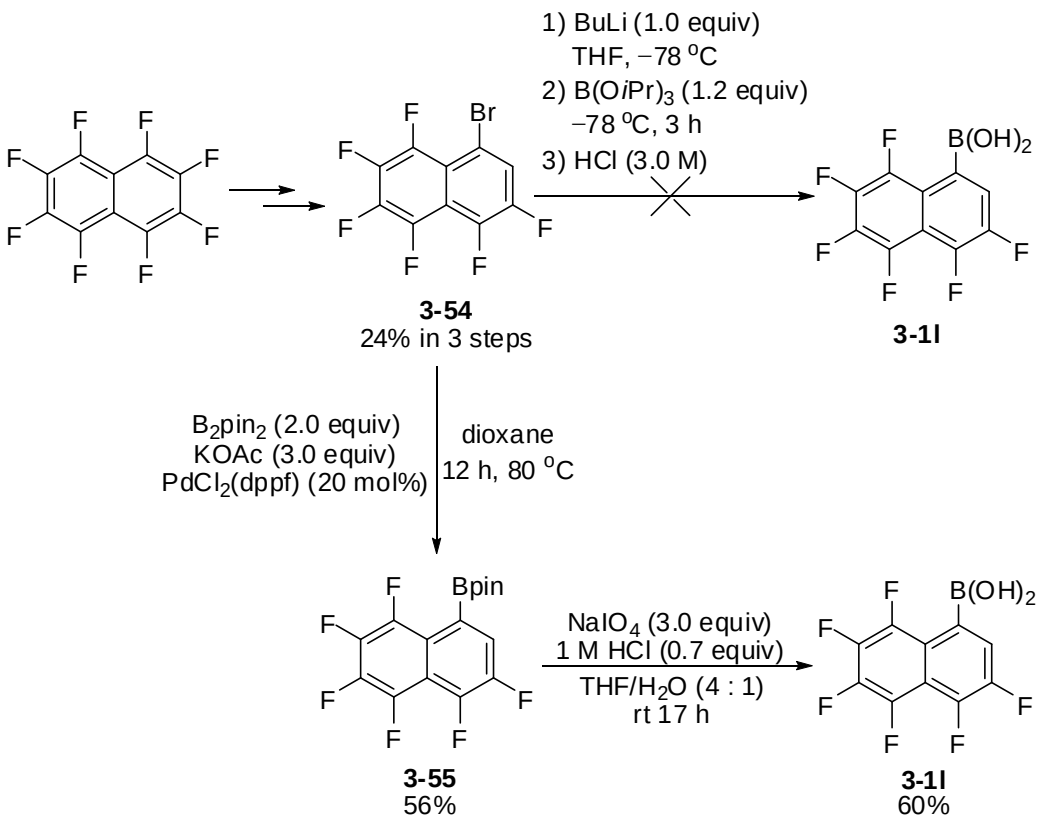
Table 3-18: Substrate scope in the boronic acid catalyzed allylic substitutions

1-butanethiol are suitable reagents, generating the corresponding thioethers **3-53a** and **3-53b** in good yields with excellent regioselectivity (entries 1–2, Table **3-18**). The less nucleophilic methanol and allyltrimethylsilane showed weaker abilities to compete with the rearranged allylic alcohol of **3-5m**, leading to substantial amounts of **3-52** and lower yields of desired products **3-53c** and **3-53d** (entries 3–4, Table **3-18**). Unfortunately, amine and hydride donor were not compatible with the boronic acid catalyst **3-1k** and therefore disabled the catalytic activity of **3-1k** during the reactions. As a result, the starting material **3-5m** was recovered in both cases (entries 5–6, Table **3-18**). It is noteworthy to mention that the yields of these transformations were not optimized and could be potentially improved by employing the more active **3-1n** as the catalyst.

3.6 Preparation of novel boronic acid catalysts

3.6.1 Preparation of boronic acid catalyst 3-1l

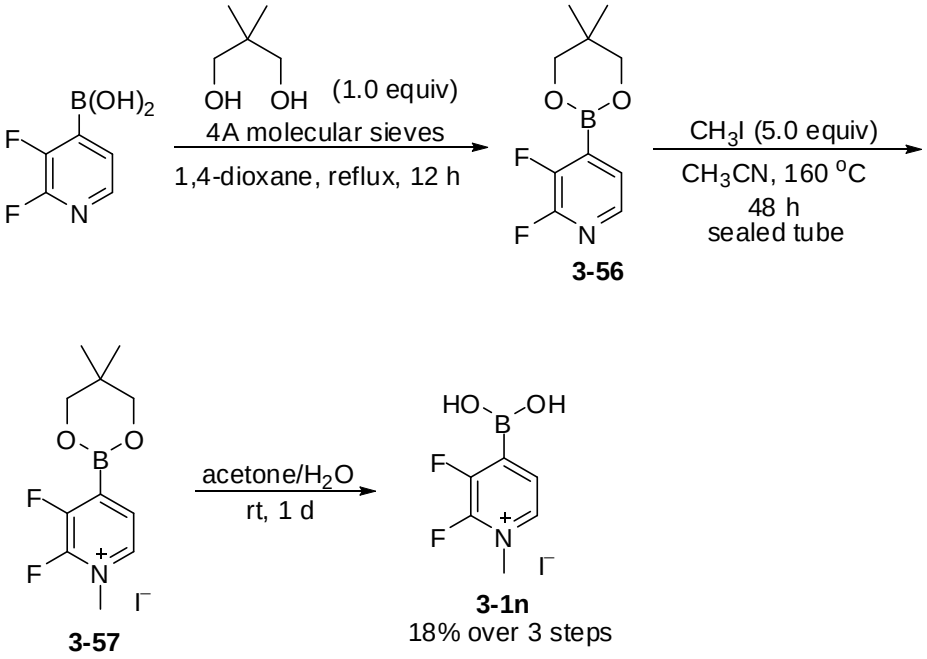
One of the most common methods for synthesizing arylboronic acids involves electrophilic borate trapping of an arylmetal intermediate at low temperature.[15a] As such, it was considered initially as the strategy for the preparation of the new boronic acid catalyst **3-1l**. Fortunately, the synthetic precursor, aryl bromide **3-54**, is a known compound and was prepared smoothly in isomerically pure form following a three-step procedure by Piers and coworkers from commercially available octafluoronaphthalene.[22] Lithium/halogen exchange of **3-54**, however, led to a complex mixture (**Scheme 3-27**). Gratifyingly, the same synthetic precursor **3-54** was subjected to Miyaura borylation followed by deprotection with $NaIO_4$ in an acidic solution to provide the boronic acid catalyst **3-1l** as a white solid successfully (**Scheme 3-27**).



Scheme 3-27: Synthetic route to boronic acid catalyst 3-1l

3.6.2 Preparation of boronic acid catalyst 3-1n

Like most pyridinum boronic acids, 2,3-difluoro-4-methylpyridiniumboronic acid **3-1n** can be prepared through a protection/methylation/deprotection sequence from commercially available 2,3-difluoropyridin-4-ylboronic acid (**Scheme 3-28**).[23] However, the methylation step (from **3-56** to **3-57**) was problematic due to the largely reduced nucleophilicity of the pyridine nitrogen from the effect of two electron-withdrawing fluoro substituents. After preliminary optimization of reaction conditions, the desired boronic acid catalyst **3-1n** can be obtained in a very low yield under harsh reaction conditions (**Scheme 3-28**). This troublesome step needs to be improved in the future by finding a more efficient methylation methodology.



Scheme 3-28: Synthetic route to boronic acid catalyst 3-1n

3.7 Conclusions

In summary, highly electron-deficient arylboronic acids such as **3-1k**, **3-1l**, and **3-1n** were found to be a promising class of organocatalysts for the activation of hydroxyl groups, allowing their direct nucleophilic substitution in an atom- and step-economical fashion. The versatility of this hydroxyl activation concept using boronic acid catalysis was convincingly demonstrated by its successful application to a broad range of classical chemical transformations, including 1,3-transpositions of allylic alcohols, Meyer-Schuster rearrangements of propargylic alcohols, a variety of cationic cyclizations of allylic alcohols, Nazarov cyclizations/Diels-Alder trapping of divinyl alcohols, and allylic substitutions. In addition to avoiding the use of reactive leaving groups like sulfonates or halides, boronic acid catalysis provides operationally simple reactions using air-stable, reusable catalysts under very mild conditions. Moreover, boronic acid catalysis exhibits a remarkable efficiency and outstanding functional group tolerance, providing the desired synthetically useful products in better yields and

selectivities compared to transition metal, traditional Lewis or protic acid catalysis. Preliminary mechanistic investigations suggested that 1,3-transpositions of propargylic alcohols and cationic cyclizations of allylic alcohols proceed through an S_N1' pathway *via* a carbocation (open transition state) and 1,3-transpositions of allylic alcohols were controlled by two parallel, substrate-dependent pathways, an S_N1' pathway and an S_N2' pathway (cyclic chairlike transition state). Since carbocations are likely intermediates, it can be envisaged that for reactions where stereogenic centers are formed, boronate anion exchange with chiral counter-anions may offer a possible way of controlling the stereoselectivity. Such applications, along with the design of superior catalysts, are the next challenges to be tackled in our laboratory.

3.8 Experimental

3.8.1 General information

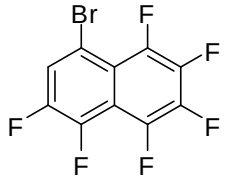
Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. Toluene, THF, DMF, MeOH and dichloromethane were treated using the Fisher Scientific-MBraun MB SPS* double-column solvent purification system prior to use. All commercially available aldehydes and acrylic acid were purified by Kugelrohr distillation prior to use. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and was visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on Varian INOVA-400, MERCURY-400, INOVA-500, and VNMRS-500 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. ^1H NMR data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; qnt,

quintet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; td, triplet of doublets; tt, triplet of triplets; qd, quartet of doublets; qq, quartet of quartets; ddd, doublet of doublet of doublets; m, multiplet. High-resolution mass spectra (HRMS) were recorded by the University of Alberta mass spectrometry services laboratory using either electron impact (EI) or electrospray ionization (ESI) techniques. Infrared spectra (IR) were obtained on a Nicolet Magna-IR with frequencies expressed in cm^{-1}. Powdered 4A molecular sieves (< 5 micron, Aldrich) were dried overnight in a vacuum oven (250 ^{o}C) prior to use. 4A Molecular sieves (1/16 inch pellets) were dried overnight in a vacuum oven (250 ^{o}C) prior to use. All Grignard reagents were purchased from Sigma-Aldrich and used directly without any further purification.

3.8.2 Preparation of arylboronic acid catalysts (Section 3.6)

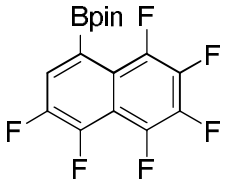
3.8.2.1 Preparation of boronic acid catalyst 3-1l (Scheme 3-27)

3.8.2.1.1 8-Bromo-1,2,3,4,5,6-hexafluoronaphthalene (3-54)



8-Bromo-1,2,3,4,5,6-hexafluoronaphthalene **3-54** was made following a literature procedure (24% over three steps).[22]

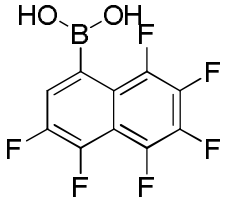
3.8.2.1.2 3,4,5,6,7,8-Hexafluoronaphthalen-1-ylboronic acid pinacol ester (3-55)



To a suspension of 8-bromo-1,2,3,4,5,6-hexafluoronaphthalene (**3-54**, 933 mg, 3.0

mmol), KOAc (880 mg, 3.0 mmol) and B_2pin_2 (1.52 g, 6.0 mmol) in 1,4-dioxane (20 mL) at room temperature was added $PdCl_2dppf$ (490 mg, 0.6 mmol). The reaction mixture was stirred at 80 ^oC for 12 hours. Then the reaction mixture was filtered through Celite and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:20) to give the title boronic acid pinacol ester **3-55** (565 mg, 52% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 9.5, 7.8 Hz, 1H), 1.42 (s, 12 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.5, 144.7, 144.6, 143.0, 141.4, 139.2, 138.2, 124.2, 119.6, 112.1, 85.1, 24.6; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –138.8 (m, 1F), –139.0 (t, *J* = 16.0 Hz, 1F), –142.9 (m, 1F), –146.3 (dddd, *J* = 57.7, 17.5, 15.1, 5.7 Hz, 1F), –155.8 (t, *J* = 18.7 Hz, 1F), –157.5 (tdd, *J* = 19.0, 7.6, 4.2 Hz, 1F); **^{11}B NMR** (128 MHz, $CDCl_3$) 31.1; **IR** (Microscope, cm^{-1}) 2988, 2935, 1667, 1638, 1527, 1500; **HRMS** (EI) for $C_{16}H_{13}{}^{11}BF_6O_2$: calcd. 362.09128; found 362.09160.

3.8.2.1.3 3,4,5,6,7,8-Hexafluoronaphthalen-1-ylboronic acid (3-1l)

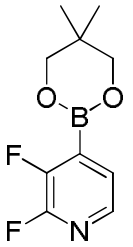


To a solution of boronic acid pinacol ester **3-55** (360 mg, 1.0 mmol) in THF/H_2O (10 mL, 4:1) at room temperature was added $NaIO_4$ (642 mg, 3.0 mmol). The resulting mixture was stirred at room temperature for 30 minutes. Then 1 N HCl (0.7 mL) was added and the resulting reaction mixture was stirred at room temperature for 17 hours. The mixture was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with H_2O (2 × 20 mL), brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was washed with hexanes to give the title boronic acid **3-1l** (168 mg, 60% yield)

as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.55 (br s, 2H), 7.77-7.70 (m, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 147.2, 142.6, 142.3, 140.5, 138.4, 137.1, 130.8, 121.7, 118.6, 111.0; **^{19}F NMR** (376 MHz, DMSO-d_6) δ –139.2 (m, 1F), –139.8 (m, 1F), –147.8 (m, 2F), –156.6 (t, J = 17.2 Hz, 1F), –159.4 (t, J = 17.8 Hz, 1F); **^{11}B NMR** (128 MHz, DMSO-d_6) 29.0; **IR** (Microscope, cm^{-1}) 3299, 1667, 1637, 1525; **HRMS** (EI) for $C_{10}H_3{}^{11}BF_6O_2$: calcd. 280.01303; found 280.01308.

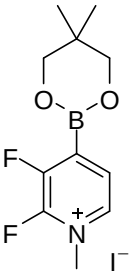
3.8.2.2 Preparation of boronic acid catalyst 3-1n (Scheme 3-28)

3.8.2.2.1 4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2,3-difluoropyridine (3-56)



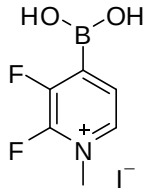
A mixture of 2,3-difluoropyridin-4-ylboronic acid (159 mg, 1.0 mmol), 2,2-dimethylpropane-1,3-diol (104 mg, 1.0 mmol), and 4A molecular sieves (1/16 inch pellets, 200 mg) in 1,4-dioxane (5 mL) was heated under reflux for 12 hours. The reaction mixture was filtered and evaporated under reduced pressure to give the crude **3-56** as a light yellow solid, which was used directly in the next step without any further purification.

3.8.2.2.2 4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2,3-difluoro-1-methylpyridinium iodide (3-57)



To a solution of the crude **3-56** in CH_3CN (10 mL) in a sealed tube at room temperature was added CH_3I (710 mg, 5.0 mmol). The reaction mixture was heated at 160 ^oC for 48 hours. Then the reaction mixture was cooled down to room temperature and evaporated under reduced pressure to give the crude **3-57** as a light yellow solid, which was used directly in the next step without any further purification.

3.8.2.2.3 4-Borono-2,3-difluoro-1-methylpyridinium iodide (3-1n)



A solution of the crude **3-57** in a mixture of acetone/H_2O (5 mL/5 mL) was stirred at room temperature for 1 day. The acetone was removed under reduced vacuum and additional H_2O (5 mL) was added to the mixture. The aqueous layer was washed with Et_2O (10 × 10 mL), and evaporated under reduced pressure. The residue was saturated with MeOH/Et_2O (2 mL/4 mL) to provide a precipitate which was filtered and washed with Et_2O (2 × 10 mL) to give the title boronic acid **1c** (54 mg, 18% over 3 steps) as a light yellow solid. **^{1}H NMR** (500 MHz, DMSO-d_6 with one drop D_2O) δ 7.98-7.91 (m, 1H), 7.41-7.34 (m, 1H), 4.34 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6 with one drop D_2O) δ 151.4 (dd, $J_{C\text{-}F}$ = 236.1, 17.3 Hz), 147.2 (dd, $J_{C\text{-}F}$ = 255.4, 26.5 Hz), 141.4 (dd, $J_{C\text{-}F}$ = 11.9, 5.9 Hz), 136.6 (br s), 127.3 (t, $J_{C\text{-}F}$ = 4.0 Hz), 63.6; **^{19}F NMR** (376 MHz, DMSO-d_6 with one drop D_2O) δ –90.8 (d, J = 29.8 Hz, 1F), –134.4 (d, J = 29.8 Hz, 1F); **^{11}B NMR** (128 MHz, DMSO-d_6 with one drop D_2O) δ 27.5; **IR** (Microscope, cm^{-1}) 3400-2200, 1630, 1473, 1442, 1401; **HRMS** (EI) for $C_6H_7BF_2INO_2$: calcd. 300.9583; found 300.9585.

3.8.2.3 Preparation of other boronic acid catalysts

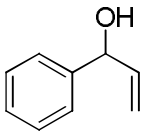
2,3,4,5-Tetrafluorophenyl boronic acid **3-1k** was made following a literature procedure.[24] 2-Nitrophenylboronic acid **3-1d** was made following a literature procedure.[25] The other arylboronic acids were obtained from commercial sources (purchased from either Combi-Blocks Inc. or Sigma-Aldrich).

3.8.3 Boronic acid catalyzed 1,3-transpositions of allylic alcohols and propargylic alcohols (Section 3.2)

3.8.3.1 General procedure for the preparation of allylic alcohols 3-5

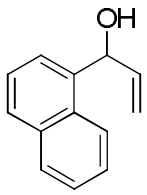
To a solution of aldehyde or ketone (5.0 mmol) in THF (10 mL) at 0 ^{o}C was added Grignard reagent solution (1.0 M in THF, 6.0 mL, 6.0 mmol) dropwise. The reaction mixture was stirred at 0 ^{o}C for 30 minutes. Then the reaction mixture was allowed to warm to room temperature and further stirred at room temperature for 2 hours. A saturated aqueous NH_4Cl solution (20 mL) was added to quench the reaction and the reaction mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:15) to give the title allylic alcohols **3-5** in pure form.

3.8.3.1.1 1-Phenylprop-2-en-1-ol (3-5a, Table 3-2)



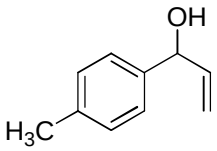
The title compound was prepared using the general procedure for the preparation of allylic alcohols (81% yield). The characterization data for this compound matched those of a previous report.[26]

3.8.3.1.2 1-(Naphthalen-1-yl)prop-2-en-1-ol (3-5b, Table 3-2)



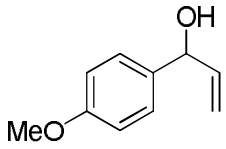
The title compound was prepared using the general procedure for the preparation of allylic alcohols (94% yield). The characterization data for this compound matched those of a previous report.[26]

3.8.3.1.3 1-*p*-Tolylprop-2-en-1-ol (3-5c, Table 3-2)



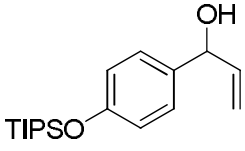
The title compound was prepared using the general procedure for the preparation of allylic alcohols (90% yield). The characterization data for this compound matched those of a previous report.[27]

3.8.3.1.4 1-(4-Methoxyphenyl)prop-2-en-1-ol (3-5d, Table 3-2)



The title compound was prepared using the general procedure for the preparation of allylic alcohols (93% yield). The characterization data for this compound matched those of a previous report.[28]

3.8.3.1.5 1-(4-(Triisopropylsilyloxy)phenyl)prop-2-en-1-ol (3-5e, Table 3-2)



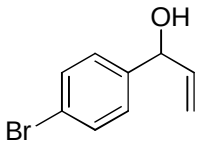
To a solution of *p*-hydroxybenzaldehyde (366 mg, 3.0 mmol) in CH_2Cl_2 (12 mL)

at 0 ^{o}C was slowly added 2,6-lutidine (963 mg, 9.0 mmol). The reaction mixture was stirred at 0 ^{o}C for 15 minutes and triisopropylsilyl trifluoromethanesulfonate (1.10 g, 3.6 mmol) was added dropwise. Then the reaction mixture was stirred at 0 ^{o}C for 3 hours. Et_2O (100 mL) was added to dilute the reaction mixture. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (2 × 50 mL), brine (50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:50) to give 4-(triisopropylsilyloxy)benzaldehyde (802 mg, 96% yield) as a colorless oil.

To a solution of 4-(triisopropylsilyloxy)benzaldehyde (557 mg, 2.0 mmol) in THF (5 mL) at 0 ^{o}C was added Grignard reagent solution (1.0 M in THF, 2.4 mL, 2.4 mmol) dropwise. The reaction mixture was stirred at 0 ^{o}C for 30 minutes. Then the reaction mixture was allowed to warm to room temperature and further stirred at room temperature for 2 hours. NH_4Cl solution (10 mL) was added to quench the reaction and the reaction mixture was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:15) to give the title allylic alcohols **3-5e** (564 mg, 92% yield) as a pale yellow oil.

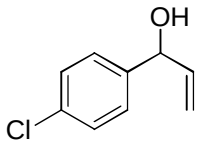
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.22 (m, 2H), 6.90-6.86 (m, 2H), 6.07 (ddd, *J* = 17.4, 10.6, 6.1 Hz, 1H), 5.34 (dt, *J* = 17.1, 1.6 Hz, 1H), 5.20 (dd, *J* = 10.3, 1.5 Hz, 1H), 5.16 (dd, *J* = 5.6, 4.4 Hz, 1H), 1.96 (br s, 1H), 1.27 (dq, *J* = 7.3, 1.9 Hz, 3H), 1.12 (d, *J* = 7.3 Hz, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.0, 140.7, 135.3, 127.8, 120.1, 114.9, 75.2, 18.2, 12.9; **IR** (Microscope, cm^{-1}) 3330, 3080, 2945, 2893, 2868, 1607, 1582, 1510, 1464, 1416; **HRMS** (EI) for $C_{18}H_{30}O_2Si$: calcd. 306.20151; found 306.20195.

3.8.3.1.6 1-(4-Bromophenyl)prop-2-en-1-ol (3-5f, Table 3-2)



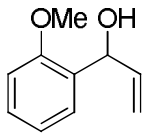
The title compound was prepared using the general procedure for the preparation of allylic alcohols (70% yield). The characterization data for this compound matched those of a previous report.[28]

3.8.3.1.7 1-(4-Chlorophenyl)prop-2-en-1-ol (3-5g, Table 3-2)



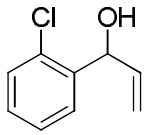
The title compound was prepared using the general procedure for the preparation of allylic alcohols (84% yield). The characterization data for this compound matched those of a previous report.[26]

3.8.3.1.8 1-(2-Methoxyphenyl)prop-2-en-1-ol (3-5h, Table 3-2)



The title compound was prepared using the general procedure for the preparation of allylic alcohols (quantitative yield). The characterization data for this compound matched those of a previous report.[12e]

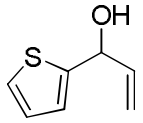
3.8.3.1.9 1-(2-Chlorophenyl)prop-2-en-1-ol (3-5i, Table 3-2)



The title compound was prepared using the general procedure for the preparation of allylic alcohols (89% yield). The characterization data for this compound

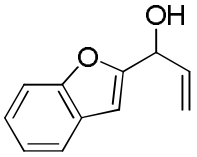
matched those of a previous report.[29]

3.8.3.1.10 1-(Thiophen-2-yl)prop-2-en-1-ol (3-5j, Table 3-2)



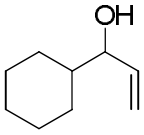
The title compound was prepared using the general procedure for the preparation of allylic alcohols (82% yield). The characterization data for this compound matched those of a previous report.[12h]

3.8.3.1.11 1-(Benzofuran-2-yl)prop-2-en-1-ol (3-5k, Table 3-2)



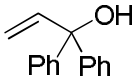
The title compound was prepared using the general procedure for the preparation of allylic alcohols (90% yield). The characterization data for this compound matched those of a previous report.[12h]

3.8.3.1.12 1-Cyclohexylprop-2-en-1-ol (3-5l, Table 3-2)



The title compound was prepared using the general procedure for the preparation of allylic alcohols (97% yield). The characterization data for this compound matched those of a previous report.[30]

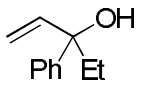
3.8.3.1.13 1,1-Diphenylprop-2-en-1-ol (3-5m, Table 3-3)



The title compound was prepared using the general procedure for the preparation of allylic alcohols (95% yield). The characterization data for this compound

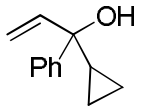
matched those of a previous report.[31]

3.8.3.1.14 3-Phenylpent-1-en-3-ol (3-5n, Table 3-3)



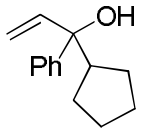
The title compound was prepared using the general procedure for the preparation of allylic alcohols (79% yield). The characterization data for this compound matched those of a previous report.[12h]

3.8.3.1.15 1-Cyclopropyl-1-phenylprop-2-en-1-ol (3-5o, Table 3-3)



The title compound was prepared using the general procedure for the preparation of allylic alcohols (87% yield). The characterization data for this compound matched those of a previous report.[32]

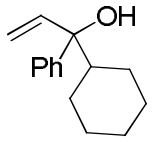
3.8.3.1.16 1-Cyclopentyl-1-phenylprop-2-en-1-ol (3-5p, Table 3-3)



The title compound was prepared using the general procedure for the preparation of allylic alcohols (93% yield, pale yellow oil).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.46 (m, 2H), 7.40-7.32 (m, 2H), 7.29-7.23 (m, 1H), 6.30 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.32 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.17 (dd, *J* = 10.8, 1.2 Hz, 1H), 2.56 (quin, *J* = 8.5 Hz, 1H), 1.86 (br s, 1H), 1.74-1.32 (m, 8H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.4, 144.0, 128.3, 126.8, 125.7, 112.6, 78.6, 49.4, 27.5, 27.2, 26.4, 26.3; **IR** (Microscope, cm^{-1}) 3483, 2954, 2868, 1492, 1447, 1409; **HRMS** (EI) for $C_{14}H_{18}O$: calcd. 202.13577; found 202.13617.

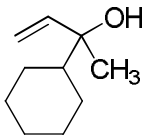
3.8.3.1.17 1-Cyclohexyl-1-phenylprop-2-en-1-ol (3-5q, Table 3-3)



The title compound was prepared using the general procedure for the preparation of allylic alcohols (90% yield, colorless oil).

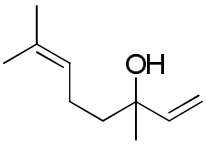
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.42 (m, 2H), 7.38-7.32 (m, 2H), 7.28-7.21 (m, 1H), 6.31 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.32 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.19 (dd, *J* = 10.8, 1.2 Hz, 1H), 1.84-1.62 (m, 6H), 1.52-1.44 (m, 1H), 1.29-0.96 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.6, 143.3, 128.0, 126.5, 125.5, 112.5, 76.7, 47.7, 27.2, 26.8, 26.7, 26.5, 26.4; **IR** (Microscope, cm^{-1}) 3481, 3087, 3059, 3025, 2930, 2852, 1492, 1447; **HRMS** (EI) for $C_{15}H_{20}O$: calcd. 216.15141; found 216.15147.

3.8.3.1.18 2-Cyclohexylbut-3-en-2-ol (3-5r, Table 3-3)



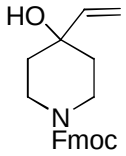
The title compound was prepared using the general procedure for the preparation of allylic alcohols (64% yield). The characterization data for this compound matched those of a previous report.[12e]

3.8.3.1.19 Linalool (3-5s, Scheme 3-5)



Linalool **3-5s** was purchased from Fluka Analytical (Sigma-Aldrich).

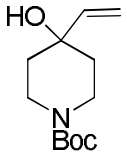
3.8.3.1.20 9*H*-Fluoren-9-yl)methyl 4-hydroxy-4-vinylpiperidine-1-carboxyl ate (3-5t, Scheme 3-5)



The title compound was prepared using the general procedure for the preparation of allylic alcohols (57% yield, colorless oil).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dt, *J* = 7.6, 0.8 Hz, 2H), 7.61 (ddd, *J* = 7.4, 1.9, 0.9 Hz, 2H), 7.43 (ddt, *J* = 7.5, 1.1, 0.7 Hz, 2H), 7.34 (dt, *J* = 7.4, 1.2 Hz, 2H), 5.95 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.29 (dd, *J* = 17.4, 1.0 Hz, 1H), 5.13 (dd, *J* = 10.8, 1.0 Hz, 1H), 4.48 (d, *J* = 6.9 Hz, 2H), 4.27 (t, *J* = 6.7 Hz, 1H), 4.00-3.78 (m, 2H), 3.36-3.27 (m, 2H), 1.73-1.53 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.4, 145.1, 144.4, 141.6, 127.9, 127.3, 125.2, 120.2, 112.8, 70.2, 67.4, 47.7, 40.2, 36.8; **IR** (Microscope, cm^{-1}) 3436, 3066, 3008, 2949, 1912, 1681, 1580, 1477, 1450; **HRMS** (EI) for $C_{22}H_{23}NO_3$: calcd. 349.16779; found 349.16725.

3.8.3.1.21 *tert*-Butyl 4-hydroxy-4-vinylpiperidine-1-carboxylate (3-5u, Scheme 3-5)

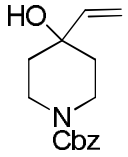


The title compound was prepared using the general procedure for the preparation of allylic alcohols (22% yield, colorless oil).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (dd, *J* = 17.3, 11.3 Hz, 1H), 5.25 (dd, *J* = 17.4, 0.9 Hz, 1H), 5.06 (dd, *J* = 10.7, 0.8 Hz, 1H), 3.88-3.66 (m, 2H), 3.28-3.12 (m, 2H), 2.05 (br s, 1H), 1.70-1.58 (m, 2H), 1.56-1.48 (m, 2H), 1.43 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.4, 144.6, 111.9, 79.0, 69.5, 39.7, 36.2, 28.0; **IR** (Microscope, cm^{-1}) 3434, 3087, 3007, 2977, 2945, 2876, 1695, 1671; **HRMS** (EI)

for $C_{12}H_{21}NO_3$: calcd. 227.15215; found 227.15229.

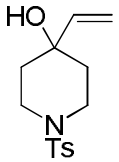
3.8.3.1.22 Benzyl 4-hydroxy-4-vinylpiperidine-1-carboxylate (3-5v, Scheme 3-5)



The title compound was prepared using the general procedure for the preparation of allylic alcohols (61% yield, colorless oil).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.30 (m, 5H), 5.94 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.28 (dd, *J* = 17.4, 1.4 Hz, 1H), 5.14 (s, 2H), 5.11 (dd, *J* = 10.8, 1.0 Hz, 1H), 4.00-3.81 (m, 2H), 3.32 (t, *J* = 12.6 Hz, 2H), 1.91 (s, 1H), 1.75-1.63 (m, 2H), 1.61-1.52 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.5, 145.1, 137.1, 128.8, 128.2, 128.1, 112.7, 70.1, 67.3, 40.2, 36.8; **IR** (Microscope, cm^{-1}) 3438, 3088, 3065, 3033, 3007, 2948, 2876, 1699, 1679, 1587, 1497, 1474, 1435; **HRMS** (EI) for $C_{15}H_{19}NO_3$: calcd. 261.13651; found 261.13649.

3.8.3.1.23 1-Tosyl-4-vinylpiperidin-4-ol (3-5w, Scheme 3-5)

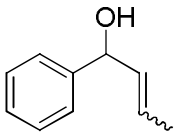


The title compound was prepared using the general procedure for the preparation of allylic alcohols (7% yield, white solid).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 5.90 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.24 (dd, *J* = 17.4, 0.8 Hz, 1H), 5.09 (dd, *J* = 10.7, 0.7 Hz, 1H), 3.61-3.54 (m, 2H), 2.72 (td, *J* = 11.9, 2.8 Hz, 2H), 2.45 (s, 3H), 1.85 (td, *J* = 13.2, 4.5 Hz, 2H), 1.64-1.58 (m, 2H), 1.26 (br s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 144.5, 143.5, 133.3, 129.7, 127.7, 112.8, 69.1, 42.0, 36.3, 21.5; **IR** (Microscope, cm^{-1}) 3506, 3093, 2992, 2954, 2926, 2866, 1598, 1459, 1404;

HRMS (EI) for $C_{14}H_{19}NO_3S$: calcd. 281.1086; found 281.1084.

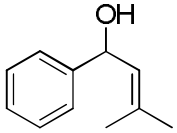
3.8.3.1.24 1-Phenylbut-2-en-1-ol (3-5x, Scheme 3-5)



E : *Z* = 4 : 1

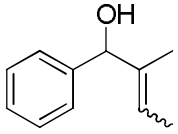
The title compound was prepared using the general procedure for the preparation of allylic alcohols (86% yield, *E* : *Z* = 4 : 1, inseparable, determined by ^{1}H NMR). The characterization data for this compound matched those of a previous report.[33]

3.8.3.1.25 3-Methyl-1-phenylbut-2-en-1-ol (3-5y, Scheme 3-5)



The title compound was prepared using the general procedure for the preparation of allylic alcohols (88% yield). The characterization data for this compound matched those of a previous report.[30]

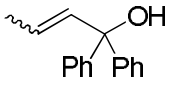
3.8.3.1.26 2-Methyl-1-phenylbut-2-en-1-ol (3-5z, Scheme 3-5)



(*E* : *Z* = 4 : 1)

The title compound was prepared using the general procedure for the preparation of allylic alcohols (81% yield, *E* : *Z* = 4 : 1, inseparable, determined by ^{1}H NMR). The characterization data for this compound matched those of a previous report.[31]

3.8.3.1.27 1,1-Diphenylbut-2-en-1-ol (3-5aa, Scheme 3-5)



E:*Z* = 1 : 2

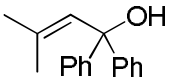
The title compound was prepared using the general procedure for the preparation of allylic alcohols (quantitative yield, *E* : *Z* = 1 : 2, inseparable, determined by ^{1}H NMR, pale yellow oil).

Z isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50-7.45 (m, 2H), 7.36-7.30 (m, 3H), 6.17 (dq, *J* = 11.5, 1.8 Hz, 1H), 5.82 (dq, *J* = 11.6, 7.3 Hz, 1H), 2.39 (br s, 1H), 1.58 (dd, *J* = 7.2, 1.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.6, 136.9, 128.1, 126.88, 126.87, 126.4, 79.0, 14.8.

E isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42-7.38 (m, 2H), 7.29-7.22 (m, 3H), 6.15 (dq, *J* = 15.3, 1.7 Hz, 1H), 5.65 (dq, *J* = 15.3, 6.5 Hz, 1H), 2.30 (br s, 1H), 1.80 (dd, *J* = 6.6, 1.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.4, 136.9, 129.2, 128.0, 127.1, 125.9, 79.0, 17.8.

IR (Microscope, cm^{-1}) 3463, 3059, 3025, 2962, 2936, 2915, 1598, 1491, 1448; **HRMS** (EI) for $C_{16}H_{16}O$: calcd. 224.12012; found 224.12026.

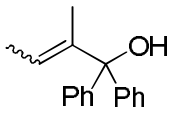
3.8.3.1.28 3-Methyl-1,1-diphenylbut-2-en-1-ol (3-5ab, Scheme 3-5)



The title compound was prepared using the general procedure for the preparation of allylic alcohols (60% yield, colorless oil).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.51 (m, 4H), 7.40-7.33 (m, 4H), 7.30-7.24 (m, 2H), 6.21-6.18 (m, 1H), 2.52 (br s, 1H), 1.91 (d, *J* = 1.4 Hz, 3H), 1.63 (d, *J* = 1.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.7, 139.1, 132.4, 128.4, 126.9, 126.6, 78.6, 27.4, 20..2; **IR** (Microscope, cm^{-1}) 3469, 3059, 3023, 2930, 2911, 1659, 1598, 1490, 1447; **HRMS** (EI) for $C_{17}H_{18}O$: calcd. 238.13577; found 238.13579.

3.8.3.1.29 2-Methyl-1,1-diphenylbut-2-en-1-ol (3-5ac, Scheme 3-5)



E : *Z* = 1 : 2.2

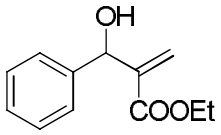
The title compound was prepared using the general procedure for the preparation of allylic alcohols (80% yield, *E* : *Z* = 1 : 2.2, inseparable, determined by ^{1}H NMR, pale yellow oil).

Z isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41-7.26 (m, 10H), 5.67 (qq, *J* = 7.3, 1.4 Hz, 1H), 2.53 (br s, 1H), 1.74 (quin, *J* = 1.5 Hz, 3H), 1.24 (dq, *J* = 7.4, 1.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.5, 140.6, 128.3, 127.8, 127.4, 124.8, 82.3, 24.4, 15.7.

E isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41-7.26 (m, 10H), 5.24 (qq, *J* = 6.6, 1.2 Hz, 1H), 2.50 (br s, 1H), 1.71 (quin, *J* = 1.1 Hz, 3H), 1.24 (dq, *J* = 6.7, 1.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.7, 140.3, 128.1, 128.0, 127.3, 124.5, 84.1, 14.3, 13.9.

IR (Microscope, cm^{-1}) 3476, 3059, 3025, 2969, 2946, 2919, 1599, 1491, 1447; **HRMS** (EI) for $C_{17}H_{18}O$: calcd. 238.13577; found 238.13564.

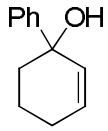
3.8.3.1.30 Ethyl 2-(hydroxy(phenyl)methyl)acrylate (3-5ad, Scheme 3-5)



A mixture of ethyl acrylate (2.00 g, 20.0 mmol), benzaldehyde (1.06 g, 10.0 mmol) and DABCO (112 mg, 1.0 mmol) was stirred at room temperature for 72 hours. Then the reaction mixture was directly purified by silica gel column chromatography (EtOAc/Hexanes = 1:5) to give the title allylic alcohol **3-5ad** (1.75 g, 85% yield) as a yellow oil.

The characterization data for this compound matched those of a previous report.[34]

3.8.3.1.31 1-Phenylcyclohex-2-enol (3-5ae, Scheme 3-6)

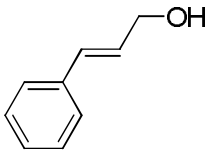


Compound **3-5ae** was made following a literature procedure.[35] The characterization data for this compound matched those of a previous report.[35]

3.8.3.2 General procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (Tables 3-2, 3-3, and 3-4; Schemes 3-5 and 3-6)

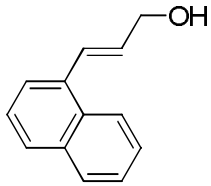
To a solution of allylic alcohol **3-5** (0.4 mmol) in toluene (1 mL) at the indicated temperature was added phenyl boronic acid **3-1k** or **3-1l** (0.08 mmol). The resulting solution was stirred at the indicated temperature for the indicated period of time. Then the resulting reaction mixture was directly purified by silica gel column chromatography (EtOAc/Hexanes = 1:8) to give the alcohols **3-6** in pure form.

3.8.3.2.1 (*E*)-3-Phenylprop-2-en-1-ol (3-6a, Table 3-2)



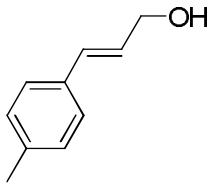
The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 48 hours (72% yield, catalyst is **3-1l**). The reaction temperature was 50 ^{o}C and the reaction time was 48 hours (93% yield, catalyst is **1i**). The characterization data for this compound matched those of a previous report.[36]

3.8.3.2.2 (*E*)-3-(Naphthalen-1-yl)prop-2-en-1-ol (3-6b, Table 3-2)



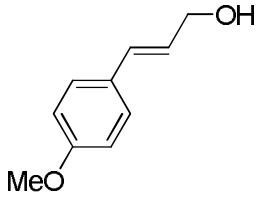
The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction temperature was 50 ^{o}C and the reaction time was 48 hours (71% yield). The characterization data for this compound matched those of a previous report.[26]

3.8.3.2.3 (*E*)-3-*p*-Tolylprop-2-en-1-ol (3-6c, Table 3-2)



The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 48 hours (78% yield). The characterization data for this compound matched those of a previous report.[37]

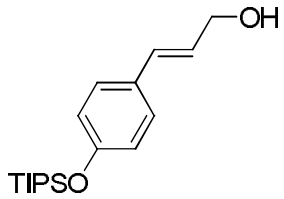
3.8.3.2.4 (*E*)-3-(4-Methoxyphenyl)prop-2-en-1-ol (3-6d, Table 3-2)



The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**).. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 48 hours (82% yield). The characterization data for this compound matched those of a

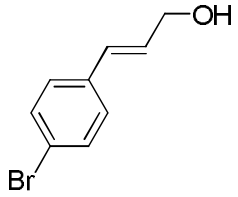
previous report.[26]

3.8.3.2.5 (*E*)-3-(4-(Triisopropylsilyloxy)phenyl)prop-2-en-1-ol (3-6e, Table 3-2)



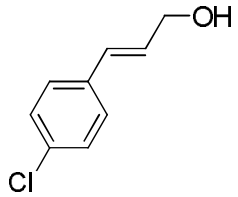
The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 48 hours (75% yield). The characterization data for this compound matched those of a previous report.[38]

3.8.3.2.6 (*E*)-3-(4-Bromophenyl)prop-2-en-1-ol (3-6f, Table 3-2)



The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction temperature was 50 ^{o}C and the reaction time was 48 hours (70% yield). The characterization data for this compound matched those of a previous report.[26]

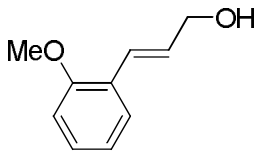
3.8.3.2.7 (*E*)-3-(4-Chlorophenyl)prop-2-en-1-ol (3-6g, Table 3-2)



The title compound was prepared using the general procedure for the boronic acid

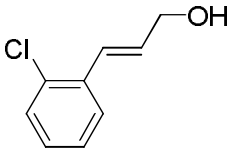
catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction temperature was 50 ^{o}C and the reaction time was 48 hours (67% yield). The characterization data for this compound matched those of a previous report.[26]

3.8.3.2.8 (*E*)-3-(2-Methoxyphenyl)prop-2-en-1-ol (3-6h, Table 3-2)



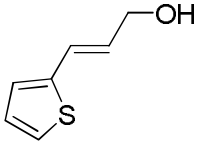
The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 48 hours (60% yield). The characterization data for this compound matched those of a previous report.[12e]

3.8.3.2.9 (*E*)-3-(2-Chlorophenyl)prop-2-en-1-ol (3-6i, Table 3-2)



The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction temperature was 50 ^{o}C and the reaction time was 48 hours (8% yield). The characterization data for this compound matched those of a previous report.[39]

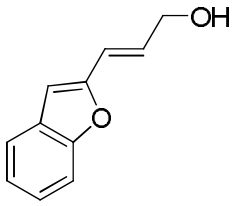
3.8.3.2.10 (*E*)-3-(Thiophen-2-yl)prop-2-en-1-ol (3-6j, Table 3-2)



The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction

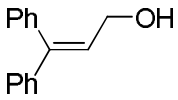
temperature was room temperature (25 ^{o}C) and the reaction time was 48 hours (61% yield). The characterization data for this compound matched those of a previous report.[12h]

3.8.3.2.11 (*E*)-3-(Benzofuran-2-yl)prop-2-en-1-ol (3-6k, Table 3-2)



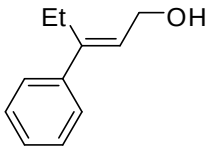
The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 48 hours (75% yield). The characterization data for this compound matched those of a previous report.[12h]

3.8.3.2.12 3,3-Diphenylprop-2-en-1-ol (3-6m, Table 3-3)



The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1k**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 24 hours (80% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.16 (m, 10H), 6.27 (t, *J* = 7.4 Hz, 1H), 4.23 (d, *J* = 6.8 Hz, 2H), 1.95 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.1, 141.8, 139.1, 129.8, 128.23, 128.20, 128.1, 127.64, 127.60, 127.57, 60.7; **IR** (Microscope, cm^{-1}) 3326, 3080, 3056, 3026, 2926, 2867, 1494, 1444; **HRMS** (EI) for $C_{15}H_{14}O$: calcd. 210.10446; found 210.10441.

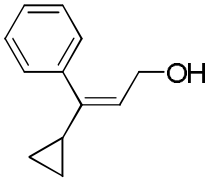
3.8.3.2.13 (*E*)-3-Phenylpent-2-en-1-ol (3-6n, Table 3-3)



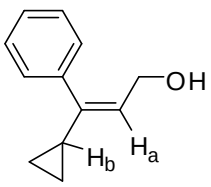
(*E* : *Z* = 8 : 1)

The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1k**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 24 hours (72% yield). The characterization data for this compound matched those of a previous report.[12h]

3.8.3.2.14 (*Z*)-3-Cyclopropyl-3-phenylprop-2-en-1-ol (3-6o, Table 3-3)



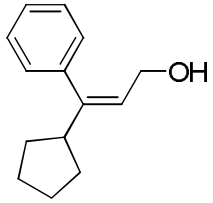
The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1k**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 48 hours (76% yield, pale yellow oil). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.25 (m, 3H), 7.18-7.12 (m, 2H), 5.65 (t, *J* = 7.0 Hz, 1H), 3.98 (d, *J* = 7.0 Hz, 2H), 1.66-1.57 (m, 1H), 1.28 (br s, 1H), 0.74-0.67 (m, 2H), 0.53-0.46 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.8, 139.1, 128.5, 128.0, 127.1, 123.6, 60.2, 18.2, 5.7; **IR** (Microscope, cm^{-1}) 3323, 3081, 3056, 3011, 2927, 2873, 1648, 1493, 1442; **HRMS** (EI) for $C_{12}H_{14}O$: calcd. 174.10446; found 174.10422.



The above stereoisomer was determined by 2D-NMR spectroscopy (TROESY).

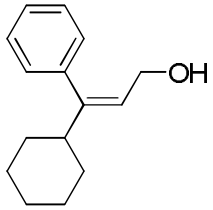
From ^{1}H-NMR spectrum, H_a and H_b (see the above figure) could be identified as 5.65 (t, *J* = 7.0 Hz, 1H) and 1.66-1.57 (m, 1H) respectively. A strong correlation δ $H_a \leftrightarrow H_b$ on the TROESY spectrum strongly suggests that the desired product was *Z*-stereoisomer.

3.8.3.2.15 (*Z*)-3-Cyclopentyl-3-phenylprop-2-en-1-ol (3-6p, Table 3-3)



The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 48 hours (79% yield, yellow oil). The stereochemistry was confirmed by 2D-NMR spectroscopy (TROESY) in a similar manner to that described for **3-6o**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.23 (m, 3H), 7.12-7.06 (m, 2H), 5.70 (dt, *J* = 6.9, 1.4 Hz, 1H), 3.96 (d, *J* = 6.7 Hz, 2H), 2.76-2.66 (m, 1H), 1.80-1.71 (m, 2H), 1.69-1.50 (m, 4H), 1.45-1.34 (m, 2H), 1.24 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.16, 140.6, 128.3, 127.9, 126.8, 123.6, 60.4, 48.0, 31.4, 24.5; **IR** (Microscope, cm^{-1}) 3318, 3102, 3078, 2955, 2869, 1493, 1452, 1441; **HRMS** (EI) for $C_{14}H_{18}O$: calcd. 202.13577; found 202.13593.

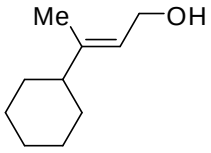
3.8.3.2.16 (*Z*)-3-Cyclohexyl-3-phenylprop-2-en-1-ol (3-6q, Table 3-3)



The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction

temperature was room temperature (25 ^{o}C) and the reaction time was 48 hours (75% yield, pale yellow oil). The stereochemistry was confirmed by 2D-NMR spectroscopy (TROESY) in a similar manner to that described for **3-6o**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.24 (m, 3H), 7.09-7.04 (m, 2H), 5.63 (dt, *J* = 6.9, 1.2 Hz, 1H), 3.96 (d, *J* = 6.9 Hz, 2H), 2.24-2.14 (m, 1H), 1.82-1.71 (m, 4H), 1.66 (br s, 1H), 1.33-1.05 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.4, 140.5, 128.5, 128.0, 126.8, 123.6, 60.5, 45.8, 32.2, 26.7, 26.3; **IR** (Microscope, cm^{-1}) 3309, 3078, 3054, 3020, 2926, 2852, 1493, 1449, 1442; **HRMS** (EI) for $C_{15}H_{20}O$: calcd. 216.15141; found 216.15167.

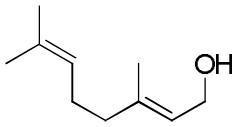
3.8.3.2.17 (*E*)-3-Cyclohexylbut-2-en-1-ol (3-6r, Table 3-3)



E : *Z* = 20 : 1

The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction temperature was 80 ^{o}C and the reaction time was 48 hours (77% yield). The characterization data for this compound matched those of a previous report.[12e]

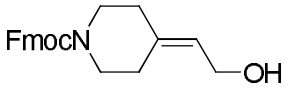
3.8.3.2.18 Geraniol (3-6s, Scheme 3-5)



E/*Z* = 6:1

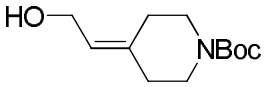
The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction temperature was 80 ^{o}C and the reaction time was 48 hours (62% yield). The characterization data for this compound matched those of a previous report.[40]

3.8.3.2.19 9*H*-Fluoren-9-yl)methyl 4-(2-hydroxyethylidene)piperidine-1-carboxylate (3-6t, Scheme 3-5)



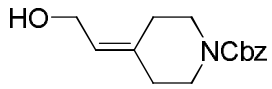
The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction temperature was 50 ^{o}C and the reaction time was 12 hours (81% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.5 Hz, 2H), 7.61 (dd, *J* = 7.5, 0.8 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.34 (td, *J* = 7.5, 1.2 Hz, 2H), 5.53 (t, *J* = 7.0 Hz, 1H), 4.48 (d, *J* = 6.8 Hz, 2H), 4.28 (t, *J* = 6.7 Hz, 1H), 4.19 (d, *J* = 6.5 Hz, 2H), 3.58-3.40 (m, 4H), 2.36-2.12 (m, 4H), 1.56 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.1, 144.1, 144.0, 141.4, 127.7, 127.1, 125.0, 123.3, 120.0, 67.3, 58.3, 47.4, 45.5, 44.8; **IR** (Microscope, cm^{-1}) 3439, 3066, 2950, 2897, 2871, 1699; **HRMS** (EI) for $C_{22}H_{23}NO_3$: calcd. 349.16779; found 349.16639

3.8.3.2.20 *tert*-Butyl 4-(2-hydroxyethylidene)piperidine-1-carboxylate (3-6u, Scheme 3-5)



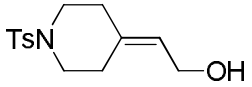
The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction temperature was 50 ^{o}C and the reaction time was 12 hours (72% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.49 (t, *J* = 7.0 Hz, 1H), 4.17 (d, *J* = 6.9 Hz, 2H), 3.46-3.36 (m, 4H), 2.26 (t, *J* = 5.7 Hz, 2H), 2.18 (t, *J* = 5.3 Hz, 2H), 1.65 (br s, 1H), 1.47 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.7, 139.2, 123.0, 79.6, 58.2, 45.1, 35.7, 28.4; **IR** (Microscope, cm^{-1}) 3422, 2974, 2932, 2868, 1696, 1672; **HRMS** (EI) for $C_{12}H_{21}NO_3$: calcd. 227.15215; found 227.15187.

3.8.3.2.21 Benzyl 4-(2-hydroxyethylidene)piperidine-1-carboxylate (3-6v, Scheme 3-5)



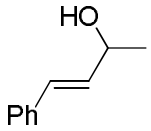
The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction temperature was 50 ^{o}C and the reaction time was 12 hours (74% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 5.52 (t, *J* = 6.9 Hz, 1H), 5.16 (s, 2H), 4.18 (d, *J* = 6.7 Hz, 2H), 3.56-3.48 (m, 4H), 2.35-2.18 (m, 4H), 1.57 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.2, 138.7, 136.8, 128.5, 128.0, 127.9, 123.3, 67.2, 58.3, 45.5, 44.8; **IR** (Microscope, cm^{-1}) 3414, 3064, 2942, 2871, 1698; **HRMS** (EI) for $C_{15}H_{19}NO_3$: calcd. 261.13651; found 261.13641.

3.8.3.2.22 2-(1-Tosylpiperidin-4-ylidene)ethanol (3-6w, Scheme 3-5)



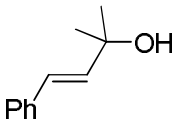
The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction temperature was 50 ^{o}C and the reaction time was 12 hours (83% yield, white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64-7.60 (m, 2H), 7.33-7.28 (m, 2H), 5.42 (t, *J* = 7.0 Hz, 1H), 4.08 (dd, *J* = 6.7, 4.5 Hz, 2H), 3.07-2.99 (m, 4H), 2.42 (s, 3H), 2.37 (t, *J* = 5.3 Hz, 2H), 2.29 (t, *J* = 5.4 Hz, 2H), 1.32 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.2, 137.1, 132.8, 129.2, 123.2, 57.7, 47.3, 46.7, 34.7, 27.4, 21.1; **IR** (Microscope, cm^{-1}) 3526, 3400, 2908, 2847, 1598, 1466; **HRMS** (ESI) for $C_{14}H_{19}NO_3S$: calcd. 281.1086; found 281.1083.

3.8.3.2.23 (*E*)-4-Phenylbut-3-en-2-ol (3-6x, Table 3-4)



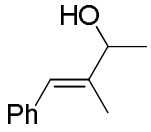
The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1k**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 4 hours (73% yield). The characterization data for this compound matched those of a previous report.[41]

3.8.3.2.24 (*E*)-2-Methyl-4-phenylbut-3-en-2-ol (3-6y, Table 3-4)



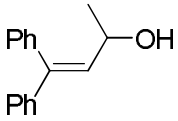
The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1k**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 2 hours (75% yield). The characterization data for this compound matched those of a previous report.[42]

3.8.3.2.25 (*E*)-3-Methyl-4-phenylbut-3-en-2-ol (3-6z, Table 3-4)



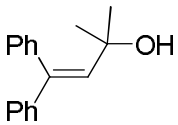
The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1k**). The reaction temperature was 50 ^{o}C and the reaction time was 48 hours (66% yield). The characterization data for this compound matched those of a previous report.[42]

3.8.3.2.26 4,4-Diphenylbut-3-en-2-ol (3-6aa, Table 3-4)



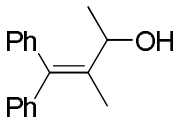
The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1k**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 24 hours (78% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43-7.19 (m, 10H), 6.10 (d, *J* = 9.2 Hz, 1H), 4.41 (dq, *J* = 9.1, 6.3 Hz, 1H), 1.73 (br s, 1H), 1.36 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.5, 141.7, 139.3, 132.4, 129.7, 128.3, 128.2, 127.6, 127.5, 127.5, 65.7, 23.7; **IR** (Microscope, cm^{-1}) 3328, 3102, 3080, 3057, 3023, 2971, 2926, 2868, 1600, 1576, 1493, 1444; **HRMS** (EI) for $C_{16}H_{16}O$: calcd. 224.12012; found 224.12012.

3.8.3.2.27 2-Methyl-4,4-diphenylbut-3-en-2-ol (3-6ab, Table 3-4)



The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1k**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 24 hours (72% yield). The characterization data for this compound matched those of a previous report.[43]

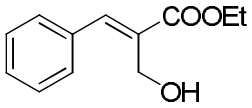
3.8.3.2.28 2-Methyl-4,4-diphenylbut-3-en-2-ol (3-6ac, Table 3-4)



The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1k**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 48 hours

(71% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.14 (m, 10H), 4.64 (q, *J* = 6.4 Hz, 1H), 1.83 (s, 3H), 1.54 (br s, 1H), 1.34 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.5, 142.1, 139.0, 136.8, 129.4, 129.2, 128.2, 128.0, 126.6, 126.5, 68.1, 21.6, 13.2; **IR** (Microscope, cm^{-1}) 3345, 3078, 3054, 3021, 2976, 2929, 2860, 1598, 1576, 1491, 1442; **HRMS** (EI) for $C_{17}H_{18}O$: calcd. 238.13577; found 238.13604.

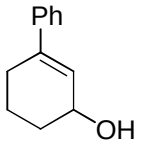
3.8.3.2.29 (*E*)-Ethyl 2-(hydroxymethyl)-3-phenylacrylate (3-6ad, Table 3-4)



E/*Z* = 5:1

The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1k**). The reaction temperature was 80 ^oC and the reaction time was 48 hours (20% yield). The characterization data for this compound matched those of a previous report.[44]

3.8.3.2.30 3-Phenylcyclohex-2-enol (3-6ae, Scheme 3-6)



The title compound was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (catalyst is **3-1l**). The reaction temperature was room temperature (25 ^oC) and the reaction time was 14 hours (75% yield). The characterization data for this compound matched those of a previous report.[45]

3.8.3.3 General procedure for the preparation of propargylic alcohols 3-7

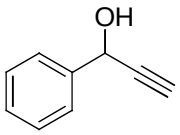
Method A: To a solution of alkyne (18.0 mmol) in THF (15 mL) at –78 ^oC was added *n*BuLi solution (2.5 M in hexanes, 2.8 mL, 6.8 mmol). The solution was

allowed to warm to 0 ^{o}C over 1 hour and stirred at 0 ^{o}C for 30 minutes. Then the solution was cooled to –78 ^{o}C and aldehyde or ketone (4.8 mmol) was added. The reaction mixture was allowed to warm to room temperature over 1 hour and stirred at room temperature for 3 hours. NH_4Cl solution (20 mL) was added to quench the reaction and the reaction mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (20 mL), saturated $NaHCO_3$ solution (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure to give the crude product. The crude propargylic alcohol bearing trimethylsilyl substituent was dissolved in MeOH/THF (1:1, 20 mL). Then K_2CO_3 (6.63 g, 48.0 mmol) was added and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was filtered and evaporated. The residue was dissolved in EtOAc (30 mL) and washed with saturated NH_4Cl solution (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:15) to give the title propargylic alcohols **3-7** in pure form.

Method B: To a solution of alkyne (18.0 mmol) in THF (15 mL) at –78 ^{o}C was added *n*BuLi solution (2.5 M in hexanes, 2.8 mL, 6.8 mmol). The solution was allowed to warm to 0 ^{o}C over 1 hour and stirred at 0 ^{o}C for 30 minutes. Then the solution was cooled to –78 ^{o}C and aldehyde or ketone (4.8 mmol) was added. The reaction mixture was allowed to warm to room temperature over 1 hour and stirred at room temperature for 3 hours. NH_4Cl solution (20 mL) was added to quench the reaction and the reaction mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (20 mL), saturated $NaHCO_3$ solution (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:15) to give the title propargylic alcohols

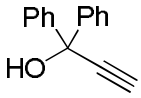
3-7 in pure form.

3.8.3.3.1 1-Phenylprop-2-yn-1-ol (3-7a, Table 3-5)



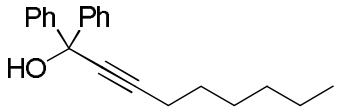
The title compound was prepared using the general procedure (Method A) for the preparation of propargylic alcohols (92% yield). The characterization data for this compound matched those of a previous report.[46]

3.8.3.3.2 1,1-Diphenylprop-2-yn-1-ol (3-7b, Table 3-5)



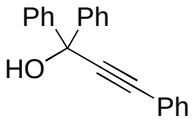
The title compound was prepared using the general procedure (Method A) for the preparation of propargylic alcohols (98% yield). The characterization data for this compound matched those of a previous report.[47]

3.8.3.3.3 1,1-Diphenylnon-2-yn-1-ol (3-7c, Table 3-5)



The title compound was prepared using the general procedure (Method B) for the preparation of propargylic alcohols (97% yield). The characterization data for this compound matched those of a previous report.[48]

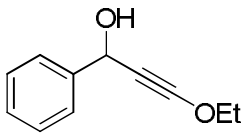
3.8.3.3.4 1,1,3-Triphenylprop-2-yn-1-ol (3-7d, Table 3-5)



The title compound was prepared using the general procedure (Method B) for the preparation of propargylic alcohols (97% yield). The characterization data for this

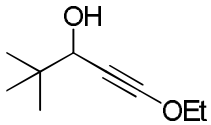
compound matched those of a previous report.[47]

3.8.3.3.5 3-Ethoxy-1-phenylprop-2-yn-1-ol (3-7e, Table 3-5)



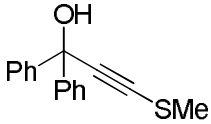
The title compound was prepared using the general procedure (Method B) for the preparation of propargylic alcohols (quantitative yield). The characterization data for this compound matched those of a previous report.[49]

3.8.3.3.6 1-Ethoxy-4,4-dimethylpent-1-yn-3-ol (3-7f, Table 3-5)



The title compound was prepared using the general procedure (Method B) for the preparation of propargylic alcohols (97% yield). The characterization data for this compound matched those of a previous report.[50]

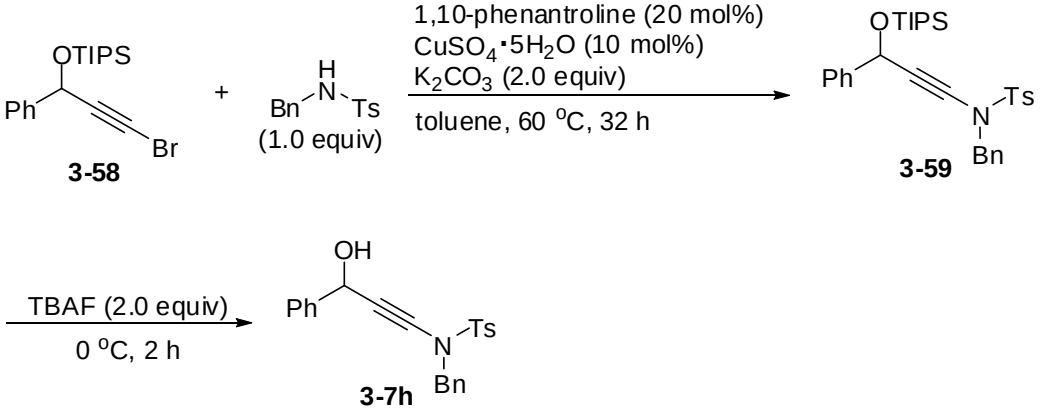
3.8.3.3.7 3-(Methylthio)-1,1-diphenylprop-2-yn-1-ol (3-7g, Table 3-5)



To a solution of 1,1-diphenylprop-2-yn-1-ol **3-7b** (415 mg, 2.0 mmol) in THF (15 mL) at –78 ^{o}C was added *n*BuLi solution (2.5 M in hexanes, 1.68 mL, 4.2 mmol). The solution was stirred at –78 ^{o}C for 1 hour. Then MeSSMe (375 mg, 4.0 mmol) was added. The reaction mixture was allowed to warm to room temperature over 1 hour and stirred at room temperature for 3 hours. NH_4Cl solution (20 mL) was added to quench the reaction and the reaction mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:9)

to give the title propargylic alcohol **3-7g** (356 mg, 72% yield) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65-7.60 (m, 4H), 7.38-7.27 (m, 6H), 2.84 (br s, 1H), 2.46 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.1, 128.5, 127.9, 126.3, 95.2, 79.9, 75.4, 19.3; **IR** (Microscope, cm^{-1}) 3542, 3447, 3059, 3085, 3026, 2927, 2168, 1953, 1890, 1813, 1767, 1597, 1490, 1449; **HRMS** (EI) for $C_{16}H_{14}OS$: calcd. 254.07654; found 254.07647.

3.8.3.3.8 3-(Methylthio)-1,1-diphenylprop-2-yn-1-ol (3-7h, Scheme 3-7)

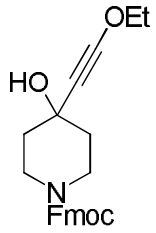


Step 1: To a solution of **3-58** (130 mg, 0.5 mmol) in toluene (1 mL) at room temperature was added 1,10-phenantroline (18 mg, 0.1 mmol), $CuSO_4 \cdot 5H_2O$ (12 mg, 0.05 mmol) and *N*-benzyl-4-methylbenzene-sulfonamide (130 mg, 0.5 mmol). The suspension was stirred at 60 °C for 32 hours. The mixture was diluted with CH_2Cl_2 (10 mL), filtered through Celite and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:9) to give the title ynamine **3-59** (240 mg, 88% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.40-7.20 (m, 12H), 5.60 (s, 1H), 4.55 (d, *J* = 13.9 Hz, 1H), 4.43 (d, *J* = 13.9 Hz, 1H), 2.45 (s, 3H), 1.09 (dq, *J* = 8.4, 6.9 Hz, 3H), 1.02 (dd, *J* = 8.4, 6.9 Hz, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.6, 142.6, 134.9, 134.8, 129.8, 129.0, 128.7, 128.4, 128.3, 128.0, 127.6, 126.2, 79.4, 73.3, 65.2, 55.6, 21.9, 18.3, 12.5; **IR** (Microscope, cm^{-1}) 3089, 3065, 3032, 2943, 2890, 2865, 2725, 2242, 1948, 1884, 1805, 1759, 1598, 1494, 1456; **HRMS**

(ESI) for $C_{32}H_{42}NO_3SSi$: calcd. 548.26490; found 548.26510.

Step2: To a solution of **3-59** (170 mg, 0.3 mmol) in THF (5 mL) at 0 ^oC was slowly added TBAF (0.6 mL, 1.0 M in THF). The resulting solution was stirred at 0 ^oC for 2 hours. The reaction mixture was diluted with Et_2O (10 mL) and washed with NH_4Cl solution (20 mL), brine (20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:5) to give the title amino alcohol **3-7h** (117 mg, 97% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.34-7.27 (m, 12H), 5.50 (s, 1H), 4.53 (q, *J* = 13.9 Hz, 2H), 2.46 (s, 3H), 2.19 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.0, 140.8, 134.8, 134.5, 130.0, 129.1, 128.8, 128.7, 128.6, 128.4, 127.9, 126.8, 80.6, 71.9, 65.0, 55.6, 21.9; **IR** (Microscope, cm^{-1}) 3497, 3064, 3032, 2928, 2869, 2244, 2191, 2055, 1678, 1635, 1597, 1579, 1494; **HRMS** (ESI) for $C_{23}H_{22}NO_3S$: calcd. 392.13150; found 392.13140.

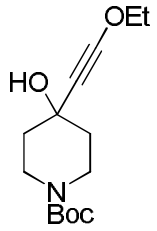
3.8.3.3.9 (9*H*-Fluoren-9-yl)methyl 4-(ethoxyethynyl)-4-hydroxypiperidine-1-carboxylate (3-7i, Scheme 3-7)



The title compound was prepared using the general procedure (Method B) for the preparation of propargylic alcohols (71% yield, pale yellow oil). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.5 Hz, 2H), 7.63-7.59 (m, 2H), 7.42 (tq, *J* = 7.4, 0.6 Hz, 2H), 7.34 (tt, *J* = 7.6, 1.2 Hz, 2H), 4.50-4.40 (m ,2H), 4.27 (t, *J* = 6.8 Hz, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.96-3.74 (m, 2H), 3.32 (ddd, *J* = 13.2, 9.5, 3.3 Hz, 2H), 2.21 (br s, 1H), 1.96-1.60 (m, 4H), 1.40 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.3, 144.3, 141.6, 127.9, 127.3, 125.2, 120.2, 94.4, 75.0, 67.5, 66.9,

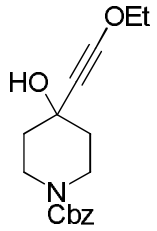
47.6, 41.6, 40.8, 40.0, 14.6; **IR** (Microscope, cm^{-1}) 3410, 3065, 2954, 2927, 2259, 1698, 1681, 1477, 1450; **HRMS** (ESI) for $C_{24}H_{25}NNaO_4$: calcd. 414.1676; found 414.1674.

3.8.3.3.10 *tert*-Butyl 4-(ethoxyethynyl)-4-hydroxypiperidine-1-carboxylate (3-7j, Scheme 3-7)



The title compound was prepared using the general procedure (Method B) for the preparation of propargylic alcohols (57% yield, pale yellow oil). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.10 (q, *J* = 7.1 Hz, 2H), 3.87-3.72 (m, 2H), 3.21 (ddd, *J* = 13.3, 9.8, 3.4 Hz, 2H), 2.17 (br s, 1H), 1.87-1.60 (m, 4H), 1.46 (s. 9H), 1.38 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.0, 94.3, 79.8, 77.0, 75.0, 67.2, 40.9, 40.1, 28.7, 14.6; **IR** (Microscope, cm^{-1}) 3418, 2977, 2931, 2872, 2260, 1695, 1671, 1470, 1426; **HRMS** (EI) for $C_{14}H_{23}NO_4$: calcd. 269.1627; found 269.1621.

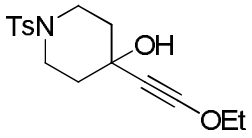
3.8.3.3.11 Benzyl 4-(ethoxyethynyl)-4-hydroxypiperidine-1-carboxylate (3-7k, Scheme 3-7)



The title compound was prepared using the general procedure (Method B) for the preparation of propargylic alcohols (60% yield, pale yellow oil). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 5.15 (s, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.96-3.82 (m, 2H), 3.32 (ddd, *J* = 13.2, 9.6, 3.4 Hz, 2H), 2.25 (br s, 1H), 1.96-1.64

(m, 4H), 1.38 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.4, 137.1, 128.7, 128.2, 128.1, 94.4, 75.0, 67.3, 66.9, 41.6, 40.8, 40.0, 14.6; **IR** (Microscope, cm^{-1}) 3417, 3064, 2955, 2929, 2873, 2259, 1700, 1680, 1473, 1433; **HRMS** (EI) for $C_{17}H_{21}NO_4$: calcd. 303.1471; found 303.1471.

3.8.3.3.12 4-(Ethoxyethynyl)-1-tosylpiperidin-4-ol (3-7l, Scheme 3-7)

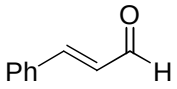


The title compound was prepared using the general procedure (Method B) for the preparation of propargylic alcohols (91% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.31 (dd, *J* = 8.5, 0.5 Hz, 2H), 3.96 (q, *J* = 7.4 Hz, 2H), 3.25 (ddd, *J* = 11.0, 6.6, 3.9 Hz, 2H), 2.96 (dt, *J* = 11.2, 3.1 Hz, 2H), 2.41 (s, 3H), 2.25-2.17 (m, 1H), 1.85 (ddd, *J* = 12.9, 6.6, 3.9 Hz, 4H), 1.24 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.7, 133.6, 129.9, 127.9, 94.2, 74.9, 65.7, 43.5, 40.7, 39.4, 21.7, 14.4; **IR** (Microscope, cm^{-1}) 3495, 2959, 2931, 2861, 2415, 2260, 1924, 1720, 1597, 1494, 1466; **HRMS** (EI) for $C_{17}H_{21}NO_4S$: calcd. 323.11914; found 323.11974.

3.8.3.4 General procedure for the boronic acid catalyzed Meyer-Schuster rearrangement of propargylic alcohols (Table 3-5 and Scheme 3-7)

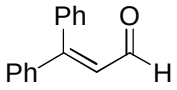
To a solution of propargylic alcohol **3-7** (0.4 mmol) in toluene (1 mL) at the indicated temperature was added aryl boronic acid **3-1k** or **3-1l** (0.08 mmol). The resulting solution was stirred at the indicated temperature for the indicated period of time. Then the resulting reaction mixture was directly purified by silica gel column chromatography (EtOAc/Hexanes = 1:20) to give the title compounds **3-8** in pure form.

3.8.3.4.1 Cinnamaldehyde (3-8a, Table 3-5)



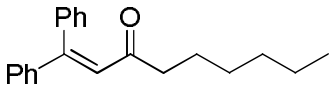
The title compound was prepared using the general procedure for the boronic acid catalyzed Meyer-Schuster rearrangement of propargylic alcohols (catalyst is **3-1l**). The reaction temperature was 50 ^{o}C and the reaction time was 6 hours (75% yield). The characterization data for this compound matched those of a previous report.[51]

3.8.3.4.2 3,3-Diphenylacrylaldehyde (3-8b, Table 3-5)



The title compound was prepared using the general procedure for the boronic acid catalyzed Meyer-Schuster rearrangement of propargylic alcohols (catalyst is **3-1k**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 0.25 hour (87% yield). The characterization data for this compound matched those of a previous report.[52]

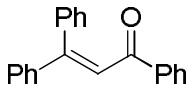
3.8.3.4.3 1,1-Diphenylnon-1-en-3-one (3-8c, Table 3-5)



The title compound was prepared using the general procedure for the boronic acid catalyzed Meyer-Schuster rearrangement of propargylic alcohols (catalyst is **3-1k**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 0.25 hour (90% yield, pale yellow oil). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42-7.28 (m, 8H), 7.23-7.18 (m, 2H), 6.59 (s, 1H), 2.24 (t, *J* = 7.3 Hz, 2H), 1.54-1.46 (m, 2H), 1.32-1.13 (m, 6H), 0.86 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.6, 153.0, 141.1, 139.1, 129.5, 129.2, 128.5, 128.4, 128.4, 128.2, 126.7, 43.2, 31.5, 28.8, 24.3, 22.4, 14.0; **IR** (Microscope, cm^{-1}) 3080, 3058, 3026, 2955, 2929,

2857, 1691, 1660, 1591, 1575, 1446; **HRMS** (EI) for $C_{21}H_{24}O$: calcd. 292.18271; found 292.18224.

3.8.3.4.4 1,3,3-Triphenylprop-2-en-1-one (3-8d, Table 3-5)



The title compound was prepared using the general procedure for the boronic acid catalyzed Meyer-Schuster rearrangement of propargylic alcohols (catalyst is **3-1k**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 1 hour (89% yield). The characterization data for this compound matched those of a previous report.[43]

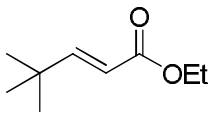
3.8.3.4.5 Ethyl cinnamate (3-8e, Table 3-5)

To a solution of propargylic alcohol **3-7e** (70 mg, 0.4 mmol) and PhSH (9 mg, 0.08 mmol) in toluene (1 mL) at room temperature was added aryl boronic acid **3-1k** (15 mg, 0.08 mmol). The resulting solution was stirred at room temperature for the 2 hours. Then the resulting reaction mixture was directly purified by silica gel column chromatography (EtOAc/Hexanes = 1:20) to give the title compound **3-8e** (59 mg, 84% yield, all *E*) in pure form.

Without PhSH (20 mol%) as additive, the same reaction gave the title product **3-8e** in 80% yield (*E* : *Z* = 4 : 3, determined by ^{1}H NMR).

The characterization data for this compound matched those of a previous report.[53]

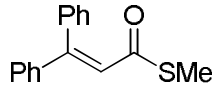
3.8.3.4.6 (*E*)-Ethyl 4,4-dimethylpent-2-enoate (3-8f, Table 3-5)



The title compound was prepared using the general procedure for the boronic acid catalyzed Meyer-Schuster rearrangement of propargylic alcohols (catalyst is **3-1l**).

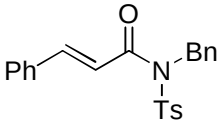
The reaction temperature was 50 ^{o}C and the reaction time was 6 hours (78% yield). The characterization data for this compound matched those of a previous report.[50]

3.8.3.4.7 *S*-Methyl 3,3-diphenylprop-2-enethioate (3-8g, Table 3-5)



The title compound was prepared using the general procedure for the boronic acid catalyzed Meyer-Schuster rearrangement of propargylic alcohols (catalyst is **3-1l**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 0.5 hour (88% yield, yellow oil). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.33 (m, 8H), 7.28-7.24 (m, 2H), 6.65 (s, 1H), 2.31 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.4, 153.4, 140.9, 138.9, 129.9, 129.6, 128.8, 128.7, 128.6, 128.2, 123.8, 12.3; **IR** (Microscope, cm^{-1}) 3358, 3079, 3058, 3027, 2925, 2853, 1952, 1886, 1807, 1725, 1677, 1591, 1572, 1490, 1445; **HRMS** (EI) for $C_{16}H_{14}OS$: calcd. 254.07654; found 254.07634.

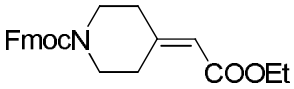
3.8.3.4.8 *N*-Benzyl-N-tosylcinnamamide (3-8h, Scheme 3-7)



The title compound was prepared using the similar procedure for the boronic acid catalyzed Meyer-Schuster rearrangement of propargylic alcohol **3-7e** with PhSH (20 mol%) as the additive (catalyst is **3-1l**). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 24 hours (80%, all *E*, determined by ^{1}H NMR). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 15.5 Hz, 1H), 7.35 (m, 12H), 7.29 (d, *J* = 15.5 Hz, 1H), 5.17 (s, 2H), 2.41 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.4, 146.4, 145.1, 137.2, 137.0, 134.7, 130.8, 129.9, 129.2, 128.9, 128.6, 128.3, 128.0, 127.8, 118.4, 49.7, 21.8; **IR** (Microscope, cm^{-1}) 3062, 3030, 2923, 2851, 1678, 1617, 1598, 1577, 1496; **HRMS** (ESI) for

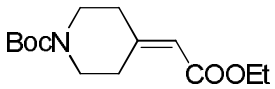
$C_{23}H_{21}NO_3SNa$: calcd. 414.11340; found 414.11350.

3.8.3.4.9 (9*H*-Fluoren-9-yl)methyl 4-(2-ethoxy-2-oxoethylidene)piperidine-1-Carboxylate (3-8i, Scheme 3-7)



The title compound was prepared using the general procedure for the boronic acid catalyzed Meyer-Schuster rearrangement of propargylic alcohols (catalyst is **3-1l**). The reaction temperature was 50 ^oC and the reaction time was 1 hour (84% yield, colorless oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.33 (td, *J* = 7.5, 1.2 Hz, 2H), 5.73 (s, 1H), 4.50 (d, *J* = 6.5 Hz, 2H), 4.26 (t, *J* = 6.5 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.62-3.44 (m, 4H), 3.00-2.86 (m, 2H), 2.32-2.14 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.2, 157.2, 155.0, 144.0, 141.4, 127.7, 127.1, 124.9, 120.0, 115.6, 67.2, 59.8, 47.4, 45.0, 44.3, 36.2, 29.4, 14.3; **IR** (Microscope, cm^{-1}) 3066, 2950, 2903, 1707, 1653, 1477, 1451, 1430; **HRMS** (EI) for $C_{24}H_{25}NO_4$: calcd. 391.1783; found 391.1792.

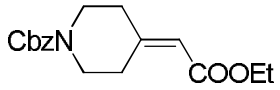
3.8.3.4.10 *tert*-Butyl 4-(2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (3-8j, Scheme 3-7)



The title compound was prepared using the general procedure for the boronic acid catalyzed Meyer-Schuster rearrangement of propargylic alcohols (catalyst is **3-1l**). The reaction temperature was 50 ^oC and the reaction time was 1 hour (75% yield, colorless oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.73-5.65 (m, 1H), 4.18-4.08 (m, 2H), 3.54-3.40 (m, 4H), 2.96-2.85 (m, 2H), 2.32-2.22 (m, 2H), 1.49-1.41 (m, 9H), 1.30-1.22 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.3, 157.8, 154.6, 115.3,

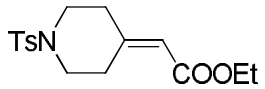
79.8, 59.7, 44.5, 36.4, 29.5, 28.4, 14.3; **IR** (Microscope, cm^{-1}) 3013, 2972, 2934, 2901, 2875, 1709, 1680, 1655, 1470, 1429, 1403; **HRMS** (ESI) for $C_{14}H_{23}NNaO_4$: calcd. 292.1519; found 292.1534.

3.8.3.4.11 Benzyl 4-(2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (3-8k, Scheme 3-7)



The title compound was prepared using the general procedure for the boronic acid catalyzed Meyer-Schuster rearrangement of propargylic alcohols (catalyst is **3-1l**). The reaction temperature was 50 ^oC and the reaction time was 1 hour (80% yield, colorless oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40-7.26 (m, 5H), 5.72 (s, 1H), 5.15 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.61-3.52 (m, 4H), 3.02-2.92 (m, 2H), 2.34-2.24 (m, 2H), 1.27 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.2, 157.1, 155.0, 136.7, 128.5, 128.0, 127.9, 115.6, 67.2, 59.8, 45.0, 44.2, 36.3, 29.4, 14.3; **IR** (Microscope, cm^{-1}) 3067, 2980, 2951, 2872, 1709, 1653, 1498, 1430; **HRMS** (EI) for $C_{17}H_{21}NO_4$: calcd. 303.1471; found 303.1464

3.8.3.4.12 .Ethyl 2-(1-tosylpiperidin-4-ylidene)acetate (3-8l, Scheme 3-7)

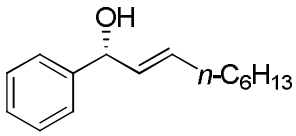


The title compound was prepared using the general procedure for the boronic acid catalyzed Meyer-Schuster rearrangement of propargylic alcohols (catalyst is **3-1l**). The reaction temperature was 50 ^oC and the reaction time was 1 hour (89% yield, colorless oil). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66-7.60 (m, 2H), 7.34-7.29 (m, 2H), 5.66-5.62 (m, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.16-3.02 (m, 6H), 2.42 (s, 3H), 2.41-2.34 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.0, 155.3, 143.7, 133.1, 129.7, 127.6, 116.0, 59.9, 47.3, 46.8, 35.8, 28.6, 21.5, 14.2;

IR (Microscope, cm^{-1}) 3091, 2978, 2928, 2911, 2848, 1712, 1657, 1598; **HRMS** (ESI) for $C_{16}H_{21}NO_4S$: calcd. 323.11914; found 323.11982.

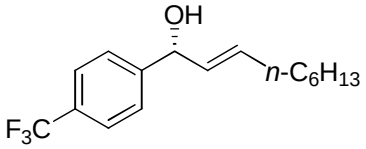
3.8.3.5 Stereochemical study of the 1,3-transposition of allylic alcohols

3.8.3.5.1 Preparation of (*R*,*E*)-1-phenylnon-2-en-1-ol (3-11, Scheme 3-9)



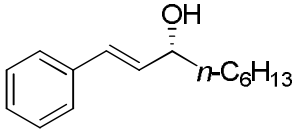
Compound **3-11** was made following a literature procedure.[12e] The characterization data for compound **3-11** matched those of a previous report.[12e] $[\alpha]_D^{20}$: –34.4 (c = 1.2, chloroform) for 96.5% ee. **HPLC (Chiralcel OD)**: 2:98 *i*-PrOH/Hexanes, 1.0 mL/minute, λ = 250 nm, T_{major} = 11.8 min, T_{minor} = 16.9 min, ee = 96.5%.

3.8.3.5.2 Preparation of (*R*,*E*)-1-(4-(trifluoromethyl)phenyl)non-2-en-1-ol (3-13, Scheme 3-9)



Compound **3-13** was made following a literature procedure.[12h] The characterization data for compound **3-13** matched those of a previous report.[12h] $[\alpha]_D^{20}$: –42.5 (c = 1.0, chloroform) for 99% ee.

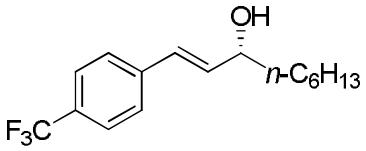
3.8.3.5.3 Boronic acid catalyzed 1,3-transposition of 3-11 (Scheme 3-9)



To a solution of allylic alcohol **3-11** (43 mg, 0.2 mmol) in toluene (1 mL) at 0 ^oC was added 2,3,4,5-tetrafluorophenyl boronic acid **3-1k** (8 mg, 0.04 mmol). The resulting solution was stirred at 0 ^oC for 8 hours. Then the resulting reaction

mixture was directly purified by silica gel column chromatography (EtOAc/Hexanes = 1:8) to give (*R*,*E*)-1-phenylnon-1-en-3-ol **3-12** (33.5 mg, 78% yield) in pure form. The characterization data for compound **3-12** matched those of a previous report.[12e] $[\alpha]_D^{20}$: –1.4 (c = 1.2, chloroform) for 23% ee. **HPLC (Chiralcel OD)**: 3:97 *i*-PrOH/Hexanes, 1.0 mL/minute, λ = 280 nm, T_{major} = 17.1 min, T_{minor} = 33.2 min, ee = 23%.

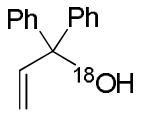
3.8.3.5.4 Boronic acid catalyzed 1,3-transposition of 3-13 (Scheme 3-9)



To a solution of allylic alcohol **3-13** (57 mg, 0.2 mmol) in toluene (1 mL) at 0 ^oC was added 2,3,4,5-tetrafluorophenyl boronic acid **3-1k** (8 mg, 0.04 mmol). The resulting solution was stirred at 0 ^oC for 8 hours. Then the resulting reaction mixture was directly purified by silica gel column chromatography (EtOAc/Hexanes = 1:8) to give (*R*,*E*)-1-(4-(trifluoromethyl)phenyl)non-1-en-3-ol **3-14** (42 mg, 74% yield) in pure form. The characterization data for compound **3-14** matched those of a previous report.[12h] $[\alpha]_D^{20}$: –7.1 (c = 1.7, chloroform) for 87% ee. **HPLC (Chiralcel OD)**: 1:99 *i*-PrOH/Hexanes, 1.0 mL/minute, λ = 230 nm, T_{major} = 18.8 min, T_{minor} = 28.7 min, ee = 87%.

3.8.3.6 ^{18}O Labeling Experiments

3.8.3.6.1 Preparation of [^{18}O]1,1-diphenylprop-2-en-1-ol (Scheme 3-11)

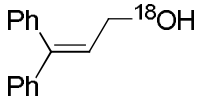


[18O] 3-5m
8.81 atom% ^{18}O

[^{18}O]1,1-Diphenylprop-2-en-1-ol ([^{18}O] **3-5m**) was made following a similar procedure to the one for the preparation of **3-5m** (83% yield). Mass spectral

analysis indicated 8.81% ^{18}O isotopic incorporation (HRMS using EI technique).

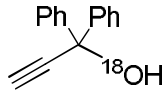
3.8.3.6.2 Boronic acid catalyzed 1,3-transposition of [^{18}O] 3-5m



0.89 atom% ^{18}O

Compound [^{18}O] **3-6m** was prepared using the general procedure for the boronic acid catalyzed 1,3-transposition of allylic alcohols (79% yield). Mass spectral analysis indicated 0.89% ^{18}O isotopic incorporation (HRMS using EI technique).

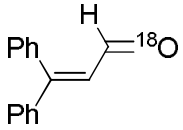
3.8.3.6.3 Preparation of [^{18}O]1,1-diphenylprop-2-yn-1-ol (Scheme 3-11)



8.53 atom% ^{18}O

[^{18}O] 1,1-Diphenylprop-2-yn-1-ol ([^{18}O] **3-7b**) was made following a a similar procedure to the one for the preparation of **3-7b** (82% yield). Mass spectral analysis indicated 8.53% ^{18}O isotopic incorporation (HRMS using EI technique).

3.8.3.6.4 Boronic acid catalyzed Meyer-Schuster rearrangement of [^{18}O] 3-7b

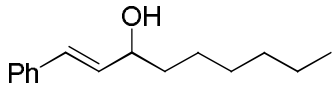


2.84 atom% ^{18}O

Compound [^{18}O] **3-8b** was prepared using the general procedure for the boronic acid catalyzed Meyer-Schuster rearrangement of propargylic alcohols (87% yield). Mass spectral analysis indicated 2.84% ^{18}O isotopic incorporation (HRMS using EI technique).

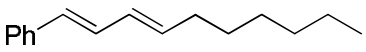
3.8.3.7 Competitive elimination reactions (Section 3.2.6)

3.8.3.7.1 (*E*)-1-phenylnon-1-en-3-ol (3-12, Scheme 3-13)



To a solution of allylic alcohol **3-11** (87 mg, 0.4 mmol) in toluene (1 mL) at room temperature was added 2,3,4,5-tetrafluorophenyl boronic acid **3-1k** (16 mg, 0.08 mmol). The resulting solution was stirred at room temperature for 2 hours. Then the resulting reaction mixture was directly purified by silica gel column chromatography (EtOAc/Hexanes = 1:10) to give (*E*)-1-phenylnon-1-en-3-ol **3-12** (68 mg, 78% yield) in pure form. The characterization data for compound **3-12** matched those of a previous report.[12e]

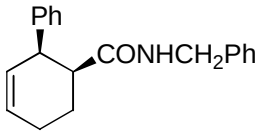
3.8.3.7.2 (1*E*,3*E*)-deca-1,3-dienylbenzene (3-18, Scheme 3-13)



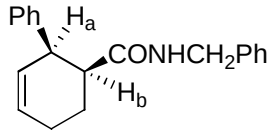
To a solution of allylic alcohol **3-11** (87 mg, 0.4 mmol) in toluene (1 mL) at room temperature was added 2,3,4,5-tetrafluorophenyl boronic acid **3-1k** (16 mg, 0.08 mmol). The resulting solution was stirred at room temperature for 48 hours. Then the resulting reaction mixture was directly purified by silica gel column chromatography (100% Hexanes) to give the diene **3-18** (69 mg, 86% yield) in pure form. The characterization data for compound **3-18** matched those of a previous report.[54]

3.8.3.8 Application to a multicatalytic tandem reaction process (Section 3.2.7)

3.8.3.8.1 *N*-Benzyl-2-phenylcyclohex-3-ene-carboxamide (3-19, Scheme 3-14)



To a mixture of the allylic alcohol **3-5y** (296 mg, 2.0 mmol) and Na_2SO_4 (284 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) at room temperature was added 2,3,4,5-tetrafluorophenyl boronic acid **3-1k** (39 mg, 0.2 mmol). The resulting solution was stirred at room temperature for 48 hours. Then acrylic acid (144 mg, 2.0 mmol) and 2-nitrophenylboronic acid **3-1d** (33 mg, 0.2 mmol) were added to the reaction mixture. The reaction mixture was stirred at room temperature for 48 hours. Benzyl amine (214 mg, 2.0 mmol), 4A molecular sieves (2.0 g), 2-iodophenylboronic acid **3-1m** (50 mg, 0.2 mmol) and CH_2Cl_2 (5 mL) were added to the reaction mixture. The reaction mixture was stirred at room temperature for 72 hours and filtered through Celite. The filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:5) to give the desired amide **3-19** (286 mg, 49% yield, *syn*:*anti* = 19:1, determined by 2D NMR) in pure form. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33-7.17 (m, 8H), 6.91-6.84 (m, 2H), 5.90-5.84 (m, 1H), 5.68 (dq, *J* = 10.0, 2.1 Hz, 1H), 5.41 (br s, 1H), 4.36 (dd, *J* = 14.9, 6.4 Hz, 1H), 4.15 (dd, *J* = 14.9, 5.1 Hz, 1H), 3.77-3.70 (m, 1H), 2.29-2.16 (m, 3H), 2.08-1.91 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.6, 144.3, 138.1, 130.0, 128.6, 128.4, 128.0, 127.4, 127.2, 127.0, 126.6, 51.3, 45.0, 43.2, 26.2, 24.6; **IR** (Microscope, cm^{-1}) 3294, 3085, 3066, 3029, 2926, 2914, 2883, 2869, 1645, 1558, 1493, 1453; **HRMS** (ESI) for $C_{20}H_{22}NO$: calcd. 292.16961; found 292.16940.



3-19

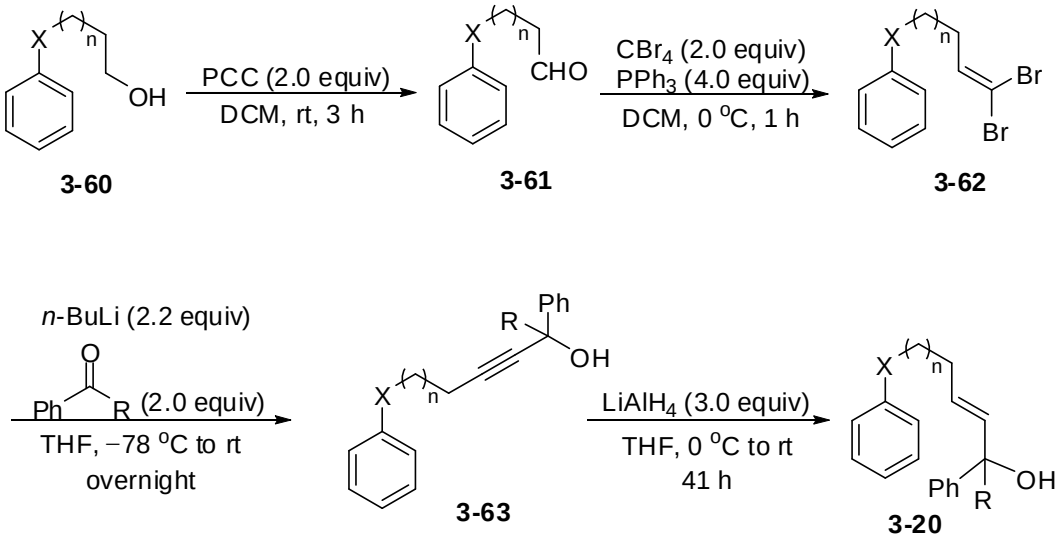
The above stereoisomer was determined by 2D-NMR spectroscopy. From HSQC and HMBC spectra, H_a and H_b (see the above figure) could be identified as 3.77-3.70 (m, 1H) and 2.29-2.16 (m, 1H) respectively. A strong correlation δ H_a ↔ H_b on the COSY spectrum shows the desired product was the indicated

regioisomer and a strong correlation δ H_a ↔ H_b on the TROESY spectrum strongly suggests that the desired product was the *syn*-stereoisomer.

3.8.4 Boronic acid catalyzed cationic cyclizations of allylic alcohols (Section 3.3)

3.8.4.1 Boronic acid catalyzed intramolecular Friedel-Crafts reaction

3.8.4.1.1 General procedure for the preparation of free allylic alcohols 3-20 (Table 3-9)



X = O, CH_2; n = 1, 2; R = Ph, H

Step 1: To a solution of pyridinium chlorochromate (4.31 g, 20.0 mmol) in CH_2Cl_2 (30 mL) at room temperature was added a solution of alcohol **3-60** (10.0 mmol) in CH_2Cl_2 (30 mL). The resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with *n*-pentane (100 mL) and filtered through Celite. The filtrate was evaporated under reduced pressure to give the crude aldehyde **3-61**. This crude aldehyde was used in the next step without any further purification.

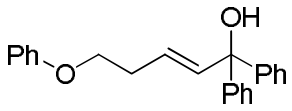
Step 2: To a solution of carbon tetrabromide (6.63 g, 20.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added a solution of triphenylphospine (10.49 g, 40.0 mmol) in CH_2Cl_2 (20 mL) dropwise. The reaction mixture was stirred at 0 °C for 10 minutes

and a solution of the crude 3-phenoxypropanal **3-61** (1.5 g, 10.0 mmol) in CH_2Cl_2 (20 mL) was added. The resulting reaction mixture was stirred at 0 ^oC for one hour. Then the reaction mixture was diluted with *n*-pentane (100 mL) and filtered through Celite. The filtrate was evaporated under reduced pressure to give the crude dibromoalkene **3-62**. This crude dibromoalkene was used in the next step without any further purification.

Step 3: To a solution of the crude (4,4-dibromobut-3-enyloxy)benzene **3-62** (6.0 mmol) in THF (30 mL) at –78 ^oC was added *n*-butyllithium (2.5 M in hexanes, 5.52 mL, 13.8 mmol) dropwise. The reaction mixture was stirred at –78 ^oC for 30 minutes and a solution of benzophenone or benzaldehyde (2.18 g, 12.0 mmol) in THF (30 mL) was added. The resulting mixture was allowed to warm to room temperature and stirred at room temperature for 12 hours. A saturated aqueous NH_4Cl solution (20 mL) was added to quench the reaction and the reaction mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:20) to give **3-63** in pure form.

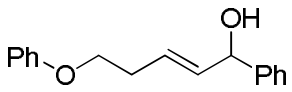
Step 4: To a solution of propargylic alcohol **3-63** (2.0 mmol) in THF (5 mL) at 0 ^oC was added $LiAlH_4$ solution (1.0 M in THF, 6.0 mL, 6.0 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 41 hours. Then the reaction mixture was cooled to 0 ^oC. EtOAc (10 mL) and $Na_2SO_4 \cdot 10H_2O$ (0.5 g) were added to the reaction mixture and the reaction mixture was stirred at 0 ^oC for 20 minutes. The reaction mixture was filtered through Celite and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:7) to give **3-20** in pure form.

3.8.4.1.1.1 (*E*)-5-Phenoxy-1,1-diphenylpent-2-en-1-ol (3-20a, Table 3-9)



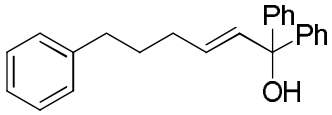
The title compound was prepared using the general procedure for the preparation of free allylic alcohols **3-20** (48% over 4 steps, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52-7.48 (m, 4H), 7.44-7.32 (m, 8H), 7.08-6.98 (m, 3H), 6.34 (tt, *J* = 15.4, 1.4 Hz, 1H), 5.84 (tt, *J* = 15.4, 6.9 Hz, 1H), 4.10 (t, *J* = 6.6 Hz, 2H), 2.69 (qd, *J* = 6.6, 1.4 Hz, 2H), 2.59 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.5, 145.9, 138.1, 129.2, 127.8, 126.9, 126.7, 125.9, 120.4, 114.3, 78.8, 66.6, 32.0; **IR** (Microscope, cm^{-1}) 3553, 3457, 3058, 3028, 2940, 1599, 1586, 1496, 1471, 1447; **HRMS** (EI) for $C_{23}H_{22}O_2$: calcd. 330.1620; found 330.1621.

3.8.4.1.1.2 (*E*)-5-Phenoxy-1-phenylpent-2-en-1-ol (3-20b, Table 3-9)



The title compound was prepared using the general procedure for the preparation of free allylic alcohols **3-20** (46% over 4 steps, yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43-7.36 (m, 4H), 7.34-7.28 (m, 3H), 6.97 (t, *J* = 7.3 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 2H), 5.94-5.82 (m, 2H), 5.23 (d, *J* = 6.0 Hz, 1H), 4.05 (t, *J* = 6.7 Hz, 2H), 2.59 (q, *J* = 6.5 Hz, 2H), 1.97 (br s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.8, 143.0, 134.8, 129.5, 128.6, 127.8, 127.7, 126.2, 120.8, 114.6, 75.0, 67.0, 32.2; **IR** (Microscope, cm^{-1}) 3380, 3061, 3029, 2927, 2873, 1600, 1587, 1497, 1471, 1453; **HRMS** (EI) for $C_{17}H_{18}O_2$: calcd. 254.1307; found 254.1304.

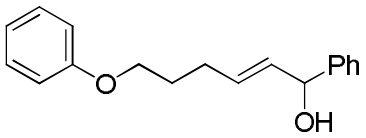
3.8.4.1.1.3 (*E*)-1,1,6-Triphenylhex-2-en-1-ol (3-20c, Table 3-9)



The title compound was prepared using the general procedure for the preparation

of free allylic alcohols **3-20** (28% over 4 steps, pale yellow oil). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47-7.20 (m, 15H), 6.18 (dt, *J* = 15.4, 1.5 Hz, 1H), 5.72 (dt, *J* = 15.5, 6.8 Hz, 1H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.36 (s, 1H), 2.24 (qd, *J* = 7.1, 1.4 Hz, 2H), 1.86-1.77 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.1, 141.9, 135.9, 130.2, 128.1, 128.0, 127.7, 126.8, 126.6, 125.4, 78.7, 35.1, 31.5, 30.6; **IR** (Microscope, cm^{-1}) 3557, 3458, 3060, 3026, 2931, 2856, 1494, 1447; **HRMS** (EI) for $C_{24}H_{24}O$: calcd. 328.1827; found 328.1832.

3.8.4.1.1.4 (*E*)-6-Phenoxy-1-phenylhex-2-en-1-ol (3-20d, Table 3-9)



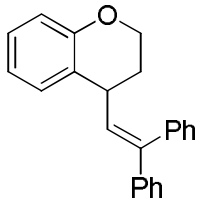
The title compound was prepared using the general procedure for the preparation of free allylic alcohols **3-20** (45% over 4 steps, yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40-7.26 (m, 7H), 7.00-6.94 (m, 1H), 6.92-6.87 (m, 2H), 5.87-5.71 (m, 2H), 5.19 (dd, *J* = 6.1, 3.0 Hz, 1H), 3.98 (t, *J* = 6.4 Hz, 2H), 2.28 (q, *J* = 6.9 Hz, 2H), 2.02 (d, *J* = 3.4 Hz, 1H), 1.96-1.87 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.6, 142.9, 132.8, 130.9, 129.0, 128.1, 127.1, 125.8, 120.2, 114.1, 74.7, 66.6, 28.29, 28.27; **IR** (Microscope, cm^{-1}) 3389, 3062, 3029, 2941, 2872, 1600, 1586, 1497, 1471; **HRMS** (EI) for $C_{18}H_{20}O_2$: calcd. 268.1463; found 268.1463.

3.8.4.1.2 General procedure for boronic acid catalyzed intramolecular Friedel-Crafts reaction (Table 3-9)

To a solution of allylic alcohol **3-20** (0.2 mmol) in nitromethane (1 mL) at room temperature was added the boronic acid catalyst **3-1** (0.04 mmol). The resulting solution was stirred at the indicated reaction temperature for a given time. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:20) to give the cyclic

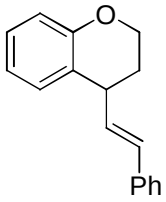
product **3-21** in pure form.

3.8.4.1.2.1 4-(2,2-Diphenylvinyl)chroman (3-21a, Table 3-9)



The title compound was prepared using the general procedure for the boronic acid catalyzed intramolecular Friedel-Crafts reaction (with **3-1k** as the catalyst). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 60 hours (97% yield, white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48-7.24 (m, 10H), 7.22-7.10 (m, 2H), 6.93-6.81 (m, 2H), 6.12 (d, *J* = 10.2 Hz, 1H), 4.34 (dt, *J* = 10.9, 4.1 Hz, 1H), 4.12-4.02 (m, 1H), 3.78-3.66 (m, 1H), 2.12-2.00 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.4, 142.7, 142.0, 139.8, 131.6, 129.7, 129.6, 128.6, 128.2, 127.8, 127.37, 127.35, 127.3, 124.9, 120.4, 116.8, 65.1, 35.5, 29.6; **IR** (Microscope, cm^{-1}) 3056, 3023, 2947, 2876, 1603, 1580, 1487, 1450; **HRMS** (EI) for $C_{23}H_{20}O$: calcd. 312.1514; found 312.1517.

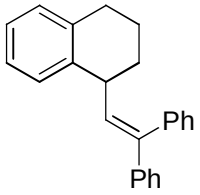
3.8.4.1.2.2 (*E*)-4-Styrylchroman (3-21b, Table 3-9)



The title compound was prepared using the general procedure for the boronic acid catalyzed intramolecular Friedel-Crafts reaction (with **3-1k** as the catalyst). The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 48 hours (79% yield, colorless oil). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.31 (m, 4H), 7.30-7.14 (m, 3H), 6.93-6.87 (m, 2H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.29 (dd, *J* = 15.7, 8.0 Hz, 1H), 4.35-4.20 (m, 2H), 3.73 (q, *J* = 6.9 Hz, 1H), 2.26-2.19 (m, 1H),

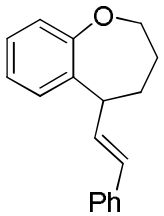
2.07-1.98 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.2, 136.7, 132.8, 131.3, 129.8, 128.2, 127.6, 127.0, 125.9, 123.4, 119.9, 116.5, 63.7, 38.2, 28.7; **IR** (Microscope, cm^{-1}) 3057, 3025, 2949, 2874, 1581, 1488, 1450; **HRMS** (EI) for $C_{17}H_{16}O$: calcd. 236.1201; found 236.1200.

3.8.4.1.2.3 1-(2,2-Diphenylvinyl)-1,2,3,4-tetrahydronaphthalene (3-21c, Table 3-9)



The title compound was prepared using the general procedure for the boronic acid catalyzed intramolecular Friedel-Crafts reaction. The reaction temperature was 50 ^{o}C and the reaction time was 48 hours (50% yield with **3-1k** as the catalyst; 60% with **3-1l** as the catalyst; 72% with **3-1n** as the catalyst; pale yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46-7.22 (m, 11H), 7.18-7.09 (m, 3H), 6.17 (d, *J* = 10.3 Hz, 1H), 3.67-3.59 (m, 1H), 2.90-2.74 (m, 2H), 2.05-1.95 (m, 2H), 1.78-1.64 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.4, 141.3, 140.1, 139.2, 136.8, 133.6, 129.8, 129.20, 129.18, 128.4, 128.2, 127.2, 127.1, 127.0, 125.9, 125.7, 39.4, 30.6, 29.7, 21.8; **IR** (Microscope, cm^{-1}) 3078, 3056, 3019, 2929, 2856, 1598, 1489, 1444; **HRMS** (EI) for $C_{24}H_{22}$: calcd. 310.1722; found 310.1727.

3.8.4.1.2.4 (*E*)-5-Styryl-2,3,4,5-tetrahydrobenzo[*b*]oxepine (3-21d, Table 3-9)

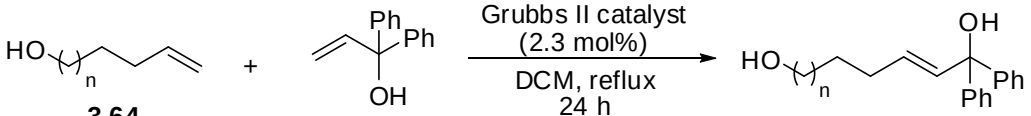


The title compound was prepared using the general procedure for the boronic acid catalyzed intramolecular Friedel-Crafts reaction. The reaction temperature was 50

^{o}C and the reaction time was 48 hours (21% yield with **3-1k** as the catalyst; 60% with **3-1n** as the catalyst; pale yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40-7.35 (m, 2H), 7.33-7.26 (m, 2H), 7.22-7.14 (m, 3H), 7.05-6.99 (m, 2H), 6.60 (dd, *J* = 15.8, 8.4 Hz, 1H), 6.35 (d, *J* = 15.9 Hz, 1H), 4.16 (ddd, *J* = 12.0, 6.3, 3.3 Hz, 1H), 3.93 (ddd, *J* = 11.5, 8.7, 2.7 Hz, 1H), 3.82-3.76 (m, 1H), 2.24-2.14 (m, 1H), 2.22-1.86 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 159.6, 137.5, 136.7, 132.2, 130.1, 129.8, 128.4, 127.7, 127.1, 126.2, 123.7, 121.9, 73.3, 47.4, 32.1, 28.6; **IR** (Microscope, cm^{-1}) 3058, 3026, 2933, 2865, 1600, 1577, 1487, 1448; **HRMS** (EI) for $C_{18}H_{18}O$: calcd. 250.1358; found 250.1355.

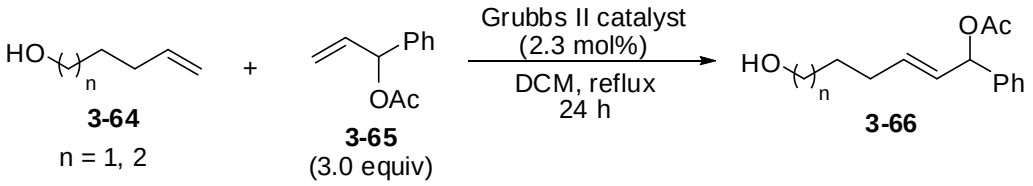
3.8.4.2 Boronic acid catalyzed heterocyclization of allylic alcohols

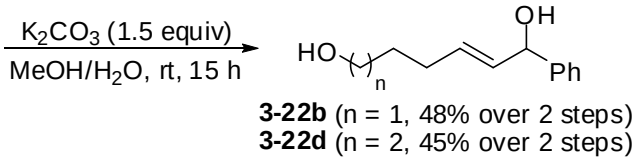
3.8.4.2.1 General procedure for the preparation of free allylic alcohols 3-22 (Table 3-10 and Scheme 3-18)



General procedure A:

A solution of alcohols **3-64** (1.0 mmol), 1,1-diphenylprop-2-en-1-ol **3-5m** (630 mg, 3.0 mmol), Grubbs II catalyst (20 mg, 0.023 mmol) in CH_2Cl_2 (2 mL) was heated under reflux for 24 hours. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:3) to give **3-22** (**3-22a**, 35%; **3-22c**, 39%; **3-22e**, 32%) in pure form.



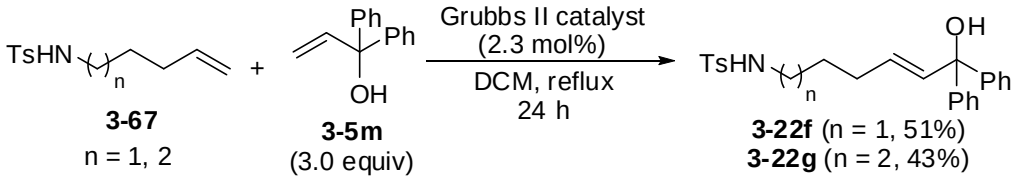


3-22b (n = 1, 48% over 2 steps)
3-22d (n = 2, 45% over 2 steps)

General procedure B:

Step 1: A solution of alcohols **3-64** (1.0 mmol), 1-phenylallyl acetate **3-65** (529 mg, 3.0 mmol), Grubbs II catalyst (20 mg, 0.023 mmol) in CH_2Cl_2 (2 mL) was heated under reflux for 24 hours. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:3) to give **3-66** in pure form.

Step 2: To a solution of the above newly-prepared allylic acetate **3-66** in MeOH/H_2O (9 mL/3 mL) was added K_2CO_3 (207 mg, 1.5 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:2) to give **3-22** (**3-22b**, 48% over 2 steps; **3-22d**, 45% over 2 steps) in pure form.

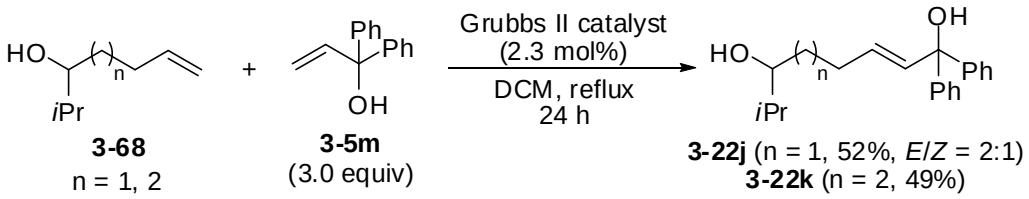


3-22f (n = 1, 51%)
3-22g (n = 2, 43%)

General procedure C:

A solution of tosylamides **3-67** (1.0 mmol), 1,1-diphenylprop-2-en-1-ol **3-5m**

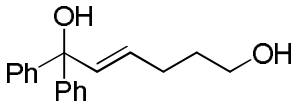
(630 mg, 3.0 mmol), Grubbs II catalyst (20 mg, 0.023 mmol) in CH_2Cl_2 (2 mL) was heated under reflux for 24 hours. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:2) to give **3-22** (**3-22f**, 51%; **3-22g**, 43%) in pure form.



General procedure D:

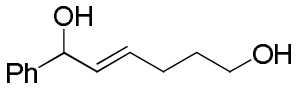
A solution of alcohols **3-68** (1.0 mmol), 1,1-diphenylprop-2-en-1-ol **3-5m** (630 mg, 3.0 mmol), Grubbs II catalyst (20 mg, 0.023 mmol) in CH_2Cl_2 (2 mL) was heated under reflux for 24 hours. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:3) to give **3-22** (**3-22j**, 52%, *E*/*Z* = 2:1; **3-22k**, 49%) in pure form.

3.8.4.2.1.1 (*E*)-1,1-Diphenylhex-2-ene-1,6-diol (3-22a, Table 3-10)



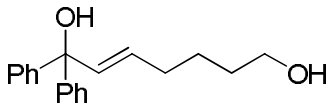
The title compound was prepared using the general procedure (procedure A) for the preparation of free allylic alcohols **3-22** (35% yield, colorless oil). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.42-7.18 (m, 10H), 6.16 (d, *J* = 15.5 Hz, 1H), 5.66 (dt, *J* = 15.5, 6.8 Hz, 1H), 3.60 (t, *J* = 6.3 Hz, 2H), 2.53 (s, 1H), 2.20 (q, *J* = 7.1 Hz, 2H), 1.64 (qnt, *J* = 6.5 Hz, 2H), 1.43 (s, 1H); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ 147.1, 136.7, 130.6, 128.4, 127.4, 127.2, 79.1, 62.6, 32.6, 29.0; **IR** (Microscope, cm^{-1}) 3374, 3085, 3058, 3026, 2936, 2879, 1599, 1491, 1447; **HRMS** (ESI) for $C_{18}H_{20}NaO_2$: calcd. 291.1356; found 291.1351.

3.8.4.2.1.2 (*E*)-1-Phenylhex-2-ene-1,6-diol (3-22b, Table 3-10)



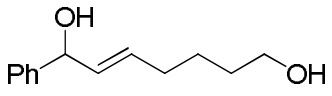
The title compound was prepared using the general procedure (procedure B) for the preparation of free allylic alcohols **3-22** (48% yield over 2 steps, colorless oil). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.40-7.31 (m, 4H), 7.29-7.23 (m, 1H), 5.81-5.73 (m, 1H), 5.71-5.64 (m, 1H), 5.14 (d, *J* = 6.6 Hz, 1H), 3.59 (t, *J* = 6.5 Hz, 2H), 2.13 (q, *J* = 7.3 Hz, 2H), 2.03 (br s, 1H), 1.66-1.59 (m, 2H), 1.41 (br s, 1H); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ 144.0, 133.4, 132.0, 128.7, 127.7, 126.5, 75.3, 62.5, 32.5, 28.9; **IR** (Microscope, cm^{-1}) 3336, 3086, 3062, 3028, 2937, 2876, 1493, 1451; **HRMS** (ESI) for $C_{12}H_{16}NaO_2$: calcd. 215.1043; found 215.1042.

3.8.4.2.1.3 (*E*)-1,1-Diphenylhept-2-ene-1,7-diol (3-22c, Table 3-10)



The title compound was prepared using the general procedure (procedure A) for the preparation of free allylic alcohols **3-22** (39% yield, colorless oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42-7.24 (m, 10H), 6.15 (dt, *J* = 15.5, 1.4 Hz, 1H), 5.66 (dt, *J* = 15.4, 6.8 Hz, 1H), 3.64 (t, *J* = 6.3 Hz, 2H), 2.52 (br s, 1H), 2.19 (qd, *J* = 7.4, 1.3 Hz, 2H), 1.63-1.43 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 146.4, 136.1, 130.6, 128.1, 127.1, 126.9, 79.0, 62.7, 32.3, 32.0, 25.4; **IR** (Microscope, cm^{-1}) 3373, 3058, 3026, 2934, 2859, 1491, 1447; **HRMS** (ESI) for $C_{19}H_{22}NaO_2$: calcd. 305.1512; found 305.1509.

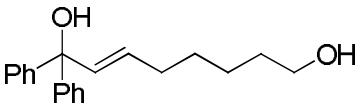
3.8.4.2.1.4 (*E*)-1-Phenylhept-2-ene-1,7-diol (3-22d, Table 3-10)



The title compound was prepared using the general procedure (procedure B) for

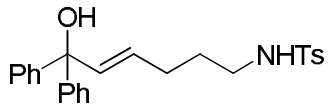
the preparation of free allylic alcohols **3-22** (45% yield over 2 steps, colorless oil). The characterization data for this compound matched those of a previous report.[55]

3.8.4.2.1.5 (*E*)-1,1-Diphenyloct-2-ene-1,8-diol (3-22e, Table 3-10)



The title compound was prepared using the general procedure (procedure A) for the preparation of free allylic alcohols **3-22** (32% yield, colorless oil). **^{1}H NMR** (125 MHz, $CDCl_3$) δ 7.39-7.36 (m, 4H), 7.34-7.28 (m, 4H), 7.27-7.22 (m, 2H), 6.11 (dt, *J* = 15.5, 1.4 Hz, 1H), 5.63 (dt, *J* = 15.4, 6.9 Hz, 1H), 3.61 (t, *J* = 6.6 Hz, 2H), 2.44 (s, 1H), 2.14 (qd, *J* = 7.0, 1.4 Hz, 2H), 1.56 (qnt, *J* = 6.9 Hz, 2H), 1.48-1.33 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 146.5, 136.0, 130.8, 128.0, 127.1, 126.9, 79.0, 62.9, 32.5, 32.2, 28.9, 25.3; **IR** (Microscope, cm^{-1}) 3373, 3085, 3059, 3027, 2931, 2856, 1599, 1491, 1447; **HRMS** (ESI) for $C_{20}H_{24}NaO_2$: calcd. 319.1669; found 319.1664.

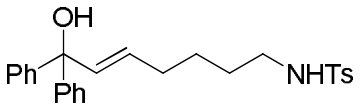
3.8.4.2.1.6 (*E*)-*N*-(6-Hydroxy-6,6-diphenylhex-4-enyl)-4-methylbenzenesulfonamide (3-22f, Table 3-10)



The title compound was prepared using the general procedure (procedure C) for the preparation of free allylic alcohols **3-22** (51% yield, colorless oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78-7.72 (m, 2H), 7.40-7.24 (m, 12H), 6.11 (dt, *J* = 15.4, 1.4 Hz, 1H), 5.55 (dt, *J* = 15.4, 6.9 Hz, 1H), 4.95 (t, *J* = 6.2 Hz, 1H), 2.94 (q, *J* = 6.8 Hz, 2H), 2.61 (s, 1H), 2.43 (s, 3H), 2.17-2.11 (m, 2H), 1.58 (qnt, *J* = 7.2 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 146.3, 143.3, 137.02, 137.01, 129.7, 129.3, 128.1, 127.14, 127.12, 126.9, 79.0, 42.6, 29.1, 29.0, 21.6; **IR** (Microscope, cm^{-1}) 3492, 3280, 3058, 3027, 2932, 2868, 1598, 1492, 1447; **HRMS** (ESI) for

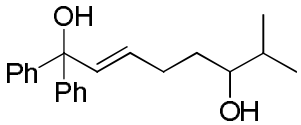
$C_{25}H_{27}NNaO_3S$: calcd. 444.1604; found 444.1600.

3.8.4.2.1.7 (*E*)-*N*-(7-Hydroxy-7,7-diphenylhept-5-enyl)-4-methylbenzenesulfonamide (3-22g, Table 3-10)



The title compound was prepared using the general procedure (procedure C) for the preparation of free allylic alcohols **3-22** (45% yield, colorless oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78-7.73 (m, 2H), 7.40-7.24 (m, 12H), 6.10 (dt, *J* = 15.5, 1.4 Hz, 1H), 5.59 (dt, *J* = 15.4, 6.8 Hz, 1H), 4.66 (t, *J* = 6.2 Hz, 1H), 2.93 (q, *J* = 6.8 Hz, 2H), 2.47 (br s, 1H), 2.44 (s, 3H), 2.09 (qd, *J* = 7.3, 1.4 Hz, 2H), 1.53-1.37 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 146.4, 143.4, 137.0, 136.4, 130.1, 129.7, 128.1, 127.1, 127.1, 126.9, 79.0, 43.0, 31.7, 29.1, 26.0, 21.5; **IR** (Microscope, cm^{-1}) 3496, 3281, 3058, 3026, 2934, 2861, 1724, 1598, 1492, 1447; **HRMS** (ESI) for $C_{26}H_{29}NNaO_3S$: calcd. 458.1760; found 458.1758.

3.8.4.2.1.8 (*E*)-7-Methyl-1,1-diphenyloct-2-ene-1,6-diol (3-22j, Scheme 3-18)

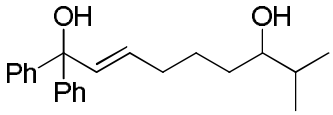


(*E*/*Z* = 2:1)

The title compound was prepared using the general procedure (procedure D) for the preparation of free allylic alcohols **3-22** (52% yield, *E*/*Z* = 2:1, inseparable, colorless oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41-7.22 (m, 10H), 6.24 (dt, *J* = 15.4, 1.4 Hz, 0.38H/1H), 6.16 (dt, *J* = 15.4, 1.5 Hz, 0.62H/1H), 5.76-5.63 (m, 1H), 3.44-3.33 (m, 1H), 2.60 (br s, 0.38H/1H), 2.43 (br s, 0.62H/1H), 2.41-2.14 (m, 2H), 1.74-1.44 (m, 3H), 1.37 (br s, 1H), 0.94 (d, *J* = 3.4 Hz, 1.14H/3H), 0.92 (d, *J* = 3.4 Hz, 1.14H/3H), 0.91 (d, *J* = 3.4 Hz, 1.86H/3H), 0.90 (d, *J* = 3.4 Hz, 1.86H/3H); **^{13}C NMR** (125 MHz, $CDCl_3$) ***E* isomer**: δ 146.4, 136.1, 130.6, 128.0,

127.1, 126.9, 79.0, 76.2, 33.6, 33.5, 28.9, 18.8, 17.1; ***Z* isomer**: δ 146.3, 139.0, 128.1, 127.2, 127.0, 126.8, 79.0, 75.8, 37.4, 33.5, 33.3, 18.8, 17.5; **IR** (Microscope, cm^{-1}) 3409, 3059, 3026, 2960, 2874, 1599, 1491, 1468, 1447; **HRMS** (ESI) for $C_{21}H_{26}NaO_2$: calcd. 333.1825; found 333.1822.

3.8.4.2.1.9 (*E*)-8-Methyl-1,1-diphenylnon-2-ene-1,7-diol (3-22k, Scheme 3-18)

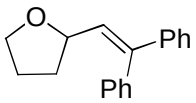


The title compound was prepared using the general procedure (procedure D) for the preparation of free allylic alcohols **3-22** (49% yield, colorless oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40-7.22 (m, 10H), 6.12 (dt, *J* = 15.5, 1.4 Hz, 1H), 5.64 (dt, *J* = 15.5, 6.8 Hz, 1H), 3.37-3.31 (m, 1H), 2.55 (br s, 1H), 2.20-2.12 (m, 2H), 1.70-1.57 (m, 2H), 1.52-1.32 (m, 4H), 0.90 (d, *J* = 3.6 Hz, 3H), 0.89 (d, *J* = 3.6 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 146.5, 136.1, 130.7, 128.0, 127.0, 126.9, 79.0, 76.6, 33.59, 33.56, 32.3, 25.6, 18.8, 17.2; **IR** (Microscope, cm^{-1}) 3405, 3059, 3026, 2957, 2934, 2872, 1599, 1491, 1447; **HRMS** (ESI) for $C_{22}H_{28}NaO_2$: calcd. 347.1982; found 347.1977.

3.8.4.2.2 General procedure for boronic acid catalyzed heterocyclizations (Table 3-10 and Scheme 3-18)

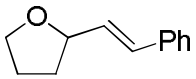
To a solution of allylic alcohol **3-22** (0.2 mmol) in nitromethane (1 mL) at room temperature was added 2,3,4,5-tetrafluorophenyl boronic acid **3-1k** (4 mg, 0.02 mmol). The resulting solution was stirred at the indicated reaction temperature for a given time. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:20) to give the cyclic product **3-23** in pure form.

3.8.4.2.2.1 2-(2,2-Diphenylvinyl)tetrahydrofuran (3-23a, Table 3-10)



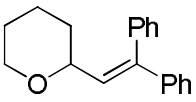
The title compound was prepared using the general procedure for the boronic acid catalyzed heterocyclizations. The reaction temperature was room temperature (25 ^{o}C) and the reaction time was 24 hours (95% yield). The reaction temperature was 50 ^{o}C and the reaction time was 16 hours (>99% yield). The characterization data for this compound matched those of a previous report.[56]

3.8.4.2.2.2 (*E*)-2-Styryltetrahydrofuran (3-23b, Table 3-10)



The title compound was prepared using the general procedure for the boronic acid catalyzed heterocyclizations. The reaction temperature was 50 ^{o}C and the reaction time was 16 hours (89% yield, pale yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40-7.35 (m, 2H), 7.33-7.27 (m, 2H), 7.24-7.20 (m, 1H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.21 (dd, *J* = 15.8, 6.6 Hz, 1H), 4.50-4.45 (m, 1H), 4.00-3.94 (m, 1H), 3.87-3.81 (m, 1H), 2.17-2.09 (m, 1H), 2.26-1.90 (m, 2H), 1.76-1.68 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 136.9, 130.5, 130.4, 128.5, 127.5, 126.4, 79.6, 68.2, 32.4, 25.9; **IR** (Microscope, cm^{-1}) 3026, 2973, 2869, 1599, 1494, 1449; **HRMS** (EI) for $C_{12}H_{14}O$: calcd. 174.1045; found 174.1040.

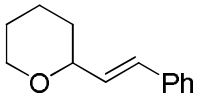
3.8.4.2.2.3 2-(2,2-Diphenylvinyl)tetrahydro-2*H*-pyran (3-23c, Table 3-10)



The title compound was prepared using the general procedure for the boronic acid catalyzed heterocyclizations. The reaction temperature was 50 ^{o}C and the reaction time was 16 hours (87% yield, white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ

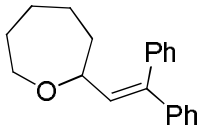
7.43-7.34 (m, 3H), 7.32-7.23 (m, 7H), 6.08 (d, *J* = 8.8 Hz, 1H), 4.03-3.97 (m, 1H), 3.87 (ddd, *J* = 10.9, 8.9, 2.5 Hz, 1H), 3.40 (ddd, *J* = 12.1, 11.6, 2.4 Hz, 1H), 1.88-1.80 (m, 1H), 1.70-1.53 (m, 3H), 1.52-1.38 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.5, 142.1, 139.6, 129.9, 129.8, 128.11, 128.08, 127.6, 127.4, 127.3, 75.7, 67.9, 32.3, 25.7, 23.2; **IR** (Microscope, cm^{-1}) 3080, 3056, 3024, 2934, 2855, 1598, 1494, 1444; **HRMS** (EI) for $C_{19}H_{20}O$: calcd. 264.1514; found 264.1515.

3.8.4.2.2.4 (*E*)-2-Styryltetrahydro-2*H*-pyran (3-23d, Table 3-10)



The title compound was prepared using the general procedure for the boronic acid catalyzed heterocyclizations. The reaction temperature was 50 ^{o}C and the reaction time was 48 hours (94% yield). The characterization data for this compound matched those of a previous report.[55]

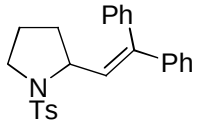
3.8.4.2.2.5 2-(2,2-Diphenylvinyl)oxepane (3-23e, Table 3-10)



The title compound was prepared using the general procedure for the boronic acid catalyzed heterocyclizations. The reaction temperature was 50 ^{o}C and the reaction time was 16 hours (62% yield, white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40-7.20 (m, 10H), 6.14 (d, *J* = 9.1 Hz, 1H), 4.04 (td, *J* = 8.9, 4.3 Hz, 1H), 3.90-3.83 (m, 1H), 3.49 (ddd, *J* = 12.1, 7.5, 3.5 Hz, 1H), 1.88-1.81 (m, 1H), 1.79-1.69 (m, 3H), 1.64-1.54 (m, 3H), 1.51-1.41 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.1, 141.8, 139.7, 130.5, 129.8, 128.1, 128.0, 127.5, 127.3, 127.2, 76.9, 67.8, 36.4, 31.2, 27.1, 25.6; **IR** (Microscope, cm^{-1}) 3080, 3056, 3023, 2928, 2854, 1599, 1494, 1444; **HRMS** (EI) for $C_{20}H_{22}O$: calcd. 278.1670; found

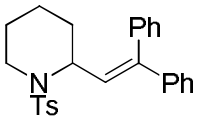
278.1670.

3.8.4.2.2.6 2-(2,2-Diphenylvinyl)-1-tosylpyrrolidine (3-23f, Table 3-10)



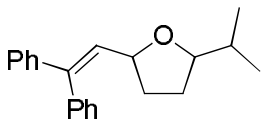
The title compound was prepared using the general procedure for the boronic acid catalyzed heterocyclizations. The reaction temperature was 50 ^{o}C and the reaction time was 16 hours (88% yield, white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48-7.36 (m, 5H), 7.32-7.24 (m, 7H), 7.14-7.10 (m, 2H), 6.12 (d, *J* = 9.4 Hz, 1H), 3.99-3.93 (m, 1H), 3.59-3.52 (m, 1H), 3.32-3.25 (m, 1H), 2.38 (s, 3H), 1.98-1.80 (m, 3H), 1.55-1.42 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.0, 141.8, 141.6, 139.5, 134.3, 130.1, 130.0, 129.4, 128.2, 128.1, 127.61, 127.55, 127.4, 127.3, 58.7, 49.6, 34.3, 24.1, 21.5; **IR** (Microscope, cm^{-1}) 3080, 3055, 3026, 2973, 2870, 1597, 1494, 1444; **HRMS** (ESI) for $C_{25}H_{25}NNaO_2S$: calcd. 426.1498; found 426.1491.

3.8.4.2.2.7 2-(2,2-Diphenylvinyl)-1-tosylpiperidine (3-23g, Table 3-10)



The title compound was prepared using the general procedure for the boronic acid catalyzed heterocyclizations. The reaction temperature was 50 ^{o}C and the reaction time was 16 hours (85% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62-7.57 (m, 2H), 7.45-7.33 (m, 3H), 7.22-7.15 (m, 7H), 6.84-6.80 (m, 2H), 5.97 (d, *J* = 9.5 Hz, 1H), 4.70-4.63 (m, 1H), 3.81-3.74 (m, 1H), 3.16-3.07 (m, 1H), 2.36 (s, 3H), 1.84-1.52 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.4, 142.2, 141.6, 138.3, 136.4, 129.01, 128.98, 128.0, 127.5, 127.2, 127.04, 126.99, 126.9, 123.6, 51.9, 41.6, 32.0, 25.1, 21.0, 19.1; **IR** (Microscope, cm^{-1}) 3438, 3054, 3028, 2939, 2862, 1598, 1492, 1444; **HRMS** (ESI) for $C_{26}H_{27}NNaO_2S$: calcd. 440.1655; found 440.1649.

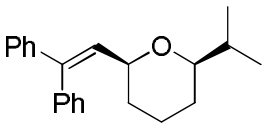
3.8.4.2.2.8 2-(2,2-Diphenylvinyl)-5-isopropyltetrahydrofuran (3-23j, Scheme 3-18)



dr = 55:45

The title compound was prepared using the general procedure for the boronic acid catalyzed heterocyclizations. The reaction temperature was 50 ^{o}C and the reaction time was 16 hours (88% yield, diastereoselectivity ratio (dr) = 55:45, dr was determined by ^{1}H-NMR of crude reaction mixture, inseparable). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38-7.20 (m, 10H), 6.08 (d, *J* = 9.0 Hz, 1H), 4.39-4.27 (m, 1H), 3.81-3.75 (m, 0.55H), 3.53 (q, *J* = 7.0 Hz, 0.45H), 2.10-1.50 (m, 5H), 0.99 (d, *J* = 6.7 Hz, 1.35H), 0.96 (d, *J* = 6.7 Hz, 1.65H), 0.90 (d, *J* = 6.7 Hz, 1.35H), 0.84 (d, *J* = 6.7 Hz, 1.65H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.2, 143.0, 142.14, 142.09, 139.54, 139.47, 130.43, 130.39, 130.05, 129.98, 128.04, 128.02, 128.00, 127.97, 127.63, 127.62, 127.32, 127.30, 127.27, 127.25, 85.0, 84.8, 76.6, 76.4, 34.1, 33.2, 33.08, 33.07, 29.8, 28.8, 19.35, 19.33, 18.3, 18.2; **IR** (Microscope, cm^{-1}) 3080, 3056, 3024, 2959, 2871, 1599, 1493, 1468, 1445; **HRMS** (EI) for $C_{21}H_{24}O$: calcd. 292.1827; found 292.1827.

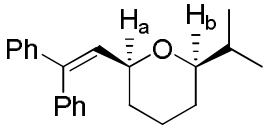
3.8.4.2.2.9 2-(2,2-Diphenylvinyl)-6-isopropyltetrahydro-2*H*-pyran (3-23k, Scheme 3-18)



dr = 95:5

The title compound was prepared using the general procedure for the boronic acid catalyzed heterocyclizations. The reaction temperature was 50 ^{o}C and the reaction time was 24 hours (90% yield, dr = 95:5, dr was determined by ^{1}H-NMR of crude reaction mixture, the major stereoisomer was determined by TROESY

experiment). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40-7.20 (m, 10H), 6.06 (d, *J* = 8.8 Hz, 1H), 3.81 (ddd, *J* = 10.7, 8.9, 2.0 Hz, 1H), 2.92 (ddd, *J* = 11.2, 6.8, 2.0 Hz, 1H), 1.86-1.79 (m, 1H), 1.73-1.65 (m, 1H), 1.62-1.54 (m, 2H), 1.51-1.33 (m, 2H), 1.25-1.16 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.9, 142.2, 139.8, 130.2, 129.9, 127.98, 127.96, 127.7, 127.4, 127.3, 82.6, 75.9, 33.3, 32.1, 27.8, 23.5, 19.0, 18.6; **IR** (Microscope, cm^{-1}) 3080, 3057, 3024, 2954, 2937, 2870, 1599, 1494, 1444; **HRMS** (EI) for $C_{22}H_{26}O$: calcd. 306.1984; found 306.1984.

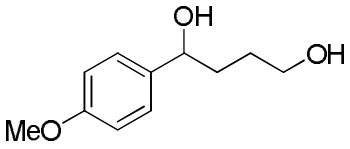


The above stereoisomer was determined by 2D-NMR spectroscopy. From ^{1}H-NMR spectrum, H_a and H_b (see the above figure) could be identified as 3.81 (ddd, *J* = 10.7, 8.9, 2.0 Hz, 1H) and 2.92 (ddd, *J* = 11.2, 6.8, 2.0 Hz, 1H) respectively. A strong correlation δ $H_a \leftrightarrow H_b$ on the TROESY spectrum strongly suggests that the desired product was the above stereoisomer.

3.8.4.3 Boronic acid catalyzed cyclization of non-allylic alcohols

3.8.4.3.1 Preparation of diols (Scheme 3-19 and Scheme 3-20)

3.8.4.3.1.1 1-(4-Methoxyphenyl)butane-1,4-diol (3-24, Scheme 3-19)

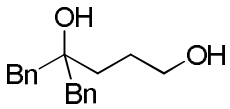


To a solution of ethyl 4-(4-methoxyphenyl)-4-oxobutanoate (945 mg, 4.0 mmol) in THF (6 mL) at 0 ^{o}C was added $LiAlH_4$ solution (1.0 M in THF, 12.0 mL, 12.0 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred at room temperature overnight. Then the reaction mixture was cooled to 0 ^{o}C. EtOAc (20 mL) and $Na_2SO_4 \cdot 10H_2O$ (0.8 g) were added to the reaction

mixture and the reaction mixture was stirred at 0 ^{o}C for 20 minutes. The reaction mixture was filtered through Celite and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 3:2) to give 1-(4-methoxyphenyl)butane-1,4-diol **3-24** (691 mg, 88% yield) in pure form.

The characterization data for this compound matched those of a previous report.[57]

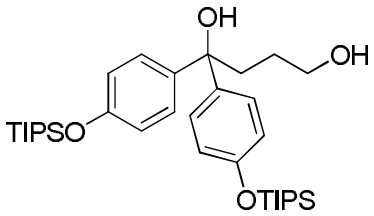
3.8.4.3.1.2 4-Benzyl-5-phenylpentane-1,4-diol (3-26, Scheme 3-19)



To a solution of magnesium (120 mg, 5.0 mmol) in THF (30 mL) was added benzyl bromide (594 μL, 5.0 mmol) dropwise. The resulting mixture was stirred at rt for 15 minutes and then cooled to –78 ^{o}C. 4-Butyrolactone (191 μL, 2.5 mmol) was added. The resulting mixture was allowed to warm to room temperature and stirred at room temperature for 12 hours. A saturated aqueous NH_4Cl solution (20 mL) was added to quench the reaction and the reaction mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:1) to give diol **3-26** (318 mg, 47% yield) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.24 (m, 10H), 3.61 (t, *J* = 6.2 Hz, 2H), 2.87 (d, *J* = 13.7 Hz, 2H), 2.84 (d, *J* = 13.7 Hz, 2H), 1.94-1.74 (m, 4H), 1.51-1.46 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.2, 130.7, 128.3, 126.6, 74.0, 63.2, 45.7, 35.1, 27.2; **IR** (Microscope, cm^{-1}) 3562, 3370, 3084, 3061, 3027, 2945, 2873, 1712, 1602, 1495, 1454; **HRMS** (ESI) for $C_{18}H_{22}NaO_2$: calcd. 293.1512; found 293.1506.

3.8.4.3.1.3 1,1-Bis(4-(triisopropylsilyloxy)phenyl)butane-1,4-diol (3-28, Scheme 3-20)

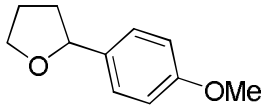


To a solution of the crude (4-bromophenoxy)triisopropylsilane (6.0 mmol) in THF (30 mL) at –78 ^{o}C was added *n*-butyllithium (2.5 M in hexanes, 2.40 mL, 6.0 mmol) dropwise. The reaction mixture was stirred at –78 ^{o}C for 30 minutes and 4-butyrolactone (457 μL, 6.0 mmol) was added. The resulting mixture was allowed to warm to room temperature and stirred at room temperature for 12 hours. A saturated aqueous NH_4Cl solution (20 mL) was added to quench the reaction and the reaction mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:9) to give diol **3-28** (1.07 g, 61% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.18 (m, 4H), 6.83-6.77 (m, 4H), 3.58 (t, *J* = 6.0 Hz, 2H), 3.23 (br s, 1H), 2.14 (br s, 1H), 2.32 (t, *J* = 7.8 Hz, 2H), 1.58-1.49 (m, 2H), 1.31-1.19 (m, 6H), 1.10 (d, *J* = 7.1 Hz, 36H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.7, 139.8, 127.3, 119.3, 77.6, 63.0, 39.1, 27.2, 17.9, 12.6; **IR** (Microscope, cm^{-1}) 3383, 2945, 2893, 2868, 1606, 1508, 1464; **HRMS** (ESI) for $C_{34}H_{58}NaO_4Si_2$: calcd. 609.3766; found 609.3767.

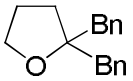
3.8.4.3.2 Boronic acid catalyzed cyclizations of non-allylic alcohols (Scheme 3-19 and Scheme 3-20)

3.8.4.3.2.1 2-(4-Methoxyphenyl)tetrahydrofuran (3-25, Scheme 3-19)



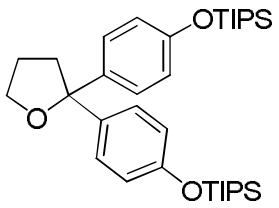
To a solution of 1-(4-methoxyphenyl)butane-1,4-diol **3-24** (39 mg, 0.2 mmol) in nitromethane (1 mL) at room temperature was added 4-borono-2,3-difluoro-1-methylpyridinium iodide **3-1n** (6 mg, 0.02 mmol). The resulting solution was stirred at 50 ^{o}C for 16 hours. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:20) to give 2-(4-methoxyphenyl)tetrahydrofuran **3-25** (33 mg, 93%) in pure form. The characterization data for this compound matched those of a previous report.[57]

3.8.4.3.2.2 2,2-Dibenzyltetrahydrofuran (3-27, Scheme 3-19)



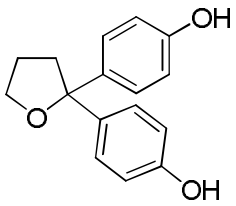
To a solution of the diol **3-26** (54 mg, 0.2 mmol) in nitromethane (1 mL) at room temperature was added 4-borono-2,3-difluoro-1-methylpyridinium iodide **3-1n** (12 mg, 0.04 mmol). The resulting solution was heated under reflux (around 101 ^{o}C) for 16 hours. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:40) to give the furan **3-27** (28 mg, 56%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31-7.20 (m, 10H), 3.61 (t, *J* = 6.7 Hz, 2H), 2.90 (d, *J* = 13.5 Hz, 2H), 2.78 (d, *J* = 13.5 Hz, 2H), 1.76 (t, *J* = 7.2 Hz, 2H), 1.41-1.32 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.2, 130.7, 127.8, 126.1, 85.3, 68.3, 46.2, 33.0, 26.2; **IR** (Microscope, cm^{-1}) 3084, 3061, 3027, 2971, 2942, 2919, 2866, 1602, 1494, 1454; **HRMS** (ESI) for $C_{18}H_{20}NaO$: calcd. 275.1406; found 275.1402.

3.8.4.3.2.3 4,4'-(Tetrahydrofuran-2,2-diyl)bis(4,1-phenylene))bis(oxy)bis (triisopropylsilane) (3-29, Scheme 3-20)



To a solution of diol **3-28** (117 mg, 0.2 mmol) in nitromethane (1 mL) at room temperature was added 4-borono-2,3-difluoro-1-methylpyridinium iodide **3-1n** (6 mg, 0.02 mmol). The resulting solution was stirred at 50 ^{o}C for 16 hours. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:60) to give furan **3-29** (103.5 mg, 91%) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28-7.23 (m, 4H), 6.85-6.80 (m, 4H), 4.05 (t, *J* = 7.1 Hz, 2H), 2.51 (t, *J* = 7.0 Hz, 2H), 1.97 (quint, *J* = 7.2 Hz, 2H), 1.33-1.23 (m, 6H), 1.13 (d, J = 7.3 Hz, 36H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.6, 138.9, 127.1, 119.3, 87.7, 67.2, 38.9, 25.6, 17.9, 12.7; **IR** (Microscope, cm^{-1}) 2945, 2892, 2868, 1606, 1507, 1464; **HRMS** (ESI) for $C_{34}H_{57}O_3Si_2$: calcd. 569.3841; found 569.3842.

3.8.4.3.2.4 4,4'-(Tetrahydrofuran-2,2-diyl)diphenol (3-30, Scheme 3-20)



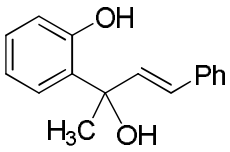
To a solution of the diol **3-28** (117 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) at room temperature was added *p*-toluenesulfonic acid monohydrate (8 mg, 0.04 mmol). The resulting solution was heated under reflux for 24 hours. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 60:1) to give the furan **3-30** (31 mg, 61%) as a white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 9.19 (br s, 2H), 7.17-7.11 (m, 4H),

6.67-6.61 (m, 4H), 3.83 (t, J = 7.2 Hz, 2H), 2.36 (t, J = 7.1 Hz, 2H), 1.79 (quint, J = 7.2 Hz, 2H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 156.2, 137.7, 127.0, 115.0, 87.5, 66.7, 38.7, 25.5; **IR** (Microscope, cm^{-1}) 3221, 2981, 2875, 1610, 1597, 1507, 1442; **HRMS** (ESI) for $C_{16}H_{17}O_3$: calcd. 257.1172; found 257.1172.

3.8.4.4 Other boronic acid catalyzed cyclizations of allylic alcohols

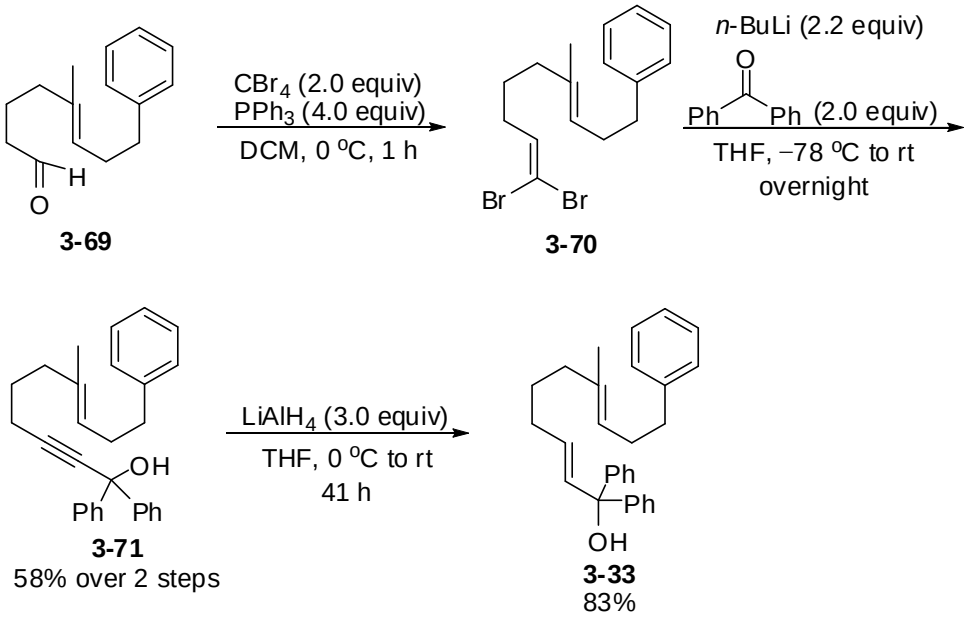
3.8.4.4.1 Preparation of allylic alcohols (Scheme 3-21)

3.8.4.4.1.1 (*E*)-2-(2-Hydroxy-4-phenylbut-3-en-2-yl)phenol (3-31, Scheme 3-21)



The title compound **3-31** was prepared using a literature procedure.[58] The characterization data for this compound matched those of a previous report.[58]

3.8.4.4.1.2 (2*E*,7*E*)-7-Methyl-1,1,10-triphenyldeca-2,7-dien-1-ol (3-33, Scheme 3-21)



Step 1: To a solution of carbon tetrabromide (663 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added a solution of triphenylphospine (1.05 g, 4.0 mmol) in CH_2Cl_2 (5

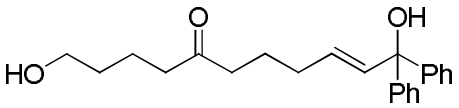
mL) dropwise. The reaction mixture was stirred at 0 ^{o}C for 10 minutes and a solution of the (*E*)-5-methyl-8-phenyloct-5-enal **3-69** (216 mg, 1.0 mmol) in CH_2Cl_2 (20 mL) was added. The resulting reaction mixture was stirred at 0 ^{o}C for one hour. Then the reaction mixture was diluted with *n*-pentane (40 mL) and filtered through Celite. The filtrate was evaporated under reduced pressure to give the crude dibromoalkene **3-70**. This crude dibromoalkene was used in the next step without any further purification.

Step 2: To a solution of the crude (*E*)-(9,9-dibromo-4-methylnona-3,8-dienyl)benzene **3-70** (1.0 mmol) in THF (5 mL) at –78 ^{o}C was added *n*-butyllithium (2.5 M in hexanes, 0.88 mL, 2.2 mmol) dropwise. The reaction mixture was stirred at –78 ^{o}C for 30 minutes and a solution of benzophenone (364 mg, 2.0 mmol) in THF (5 mL) was added. The resulting mixture was allowed to warm to room temperature and stirred at room temperature for 12 hours. A saturated aqueous NH_4Cl solution (10 mL) was added to quench the reaction and the reaction mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:45) to give (*E*)-7-methyl-1,1,10-triphenyldec-7-en-2-yn-1-ol **3-71** (229 mg, 58% over 2 steps) as a pale yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.72-7.66 (m, 4H), 7.42-7.22 (m, 11H), 5.31-5.25 (m, 1H), 2.80 (s, 1H), 2.72 (t, *J* = 7.8 Hz, 2H), 2.40 (q, *J* = 7.2 Hz, 2H), 2.34 (t, *J* = 7.2 Hz, 2H), 2.18 (t, *J* = 7.4 Hz, 2H), 1.75 (qnt, *J* = 7.2 Hz, 2H), 1.62 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 145.6, 142.3, 134.8, 128.5, 128.3, 128.2, 127.6, 126.1, 125.8, 124.7, 88.3, 83.4, 74.6, 38.8, 36.1, 30.0, 26.9, 18.4, 15.8; **IR** (Microscope, cm^{-1}) 3545, 3465, 3060, 3026, 2935, 2858, 2232, 1491, 1450; **HRMS** (EI) for $C_{29}H_{30}O$: calcd. 394.2297; found 394.2297.

Step 3: To a solution of propargylic alcohol **3-71** (197 mg, 0.5 mmol) in THF (2 mL) at 0 ^{o}C was added $LiAlH_4$ solution (1.0 M in THF, 1.5 mL, 1.5 mmol)

dropwise. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 41 hours. Then the reaction mixture was cooled to 0 ^{o}C. EtOAc (5 mL) and $Na_2SO_4 \cdot 10H_2O$ (0.3 g) were added to the reaction mixture and the reaction mixture was stirred at 0 ^{o}C for 20 minutes. The reaction mixture was filtered through Celite and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:25) to give (2*E*,7*E*)-7-methyl-1,1,10-triphenyldeca-2,7-dien-1-ol **3-33** (165 mg, 83% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46-7.40 (m, 4H), 7.40-7.27 (m, 8H), 7.26-7.18 (m, 3H), 6.13 (dt, *J* = 15.4, 1.4 Hz, 1H), 5.67 (dt, *J* = 15.4, 6.8 Hz, 1H), 5.24-5.18 (m, 1H), 2.69 (t, *J* = 7.8 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.33 (s, 1H), 2.16-2.09 (m, 2H), 2.04 (t, *J* = 7.4 Hz, 2H), 1.59 (s, 3H), 1.58-1.51 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.1, 142.0, 135.6, 135.1, 130.6, 128.1, 127.9, 127.7, 126.7, 126.6, 125.3, 123.6, 78.7, 38.8, 35.8, 31.4, 29.5, 27.0, 15.5; **IR** (Microscope, cm^{-1}) 3557, 3453, 3060, 2928, 2856, 1494, 1448; **HRMS** (EI) for $C_{29}H_{32}O$: calcd. 396.2453; found 396.2447.

3.8.4.4.1.3 (*E*)-1,11-Dihydroxy-11,11-diphenylundec-9-en-5-one (3-35, Scheme 3-21)

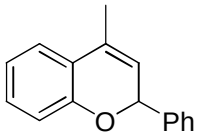


A solution of 1-hydroxydec-9-en-5-one (170 mg, 1.0 mmol), 1,1-diphenylprop-2-en-1-ol **3-5m** (630 mg, 3.0 mmol), Grubbs II catalyst (20 mg, 0.023 mmol) in CH_2Cl_2 (2 mL) was heated under reflux for 24 hours. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:1) to give the title compound **3-35** (159 mg, 45%) in pure form. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.39-7.21 (m, 10H), 6.14 (dt, *J* = 15.4, 1.3 Hz, 1H), 5.61 (dt, *J* = 15.5, 6.9 Hz, 1H), 3.54 (t, *J* = 6.2 Hz, 2H), 2.86 (br s, 1H), 2.41-2.35 (m, 4H), 2.15-2.10 (m, 2H),

1.92 (br s, 1H), 1.66 (qnt, J = 7.5 Hz, 2H), 1.63-1.54 (m, 2H), 1.51-1.44 (m, 2H); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ 211.4, 147.1, 137.1, 130.2, 128.4, 127.4, 127.2, 79.1, 62.5, 42.7, 42.2, 32.6, 32.0, 23.6, 20.2; **IR** (Microscope, cm^{-1}) 3403, 3057, 3026, 2936, 2872, 1704, 1598, 1490, 1447; **HRMS** (ESI) for $C_{23}H_{28}NaO_3$: calcd. 375.1931; found 375.1926.

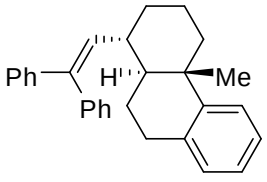
3.8.4.4.2 Other boronic acid catalyzed cyclizations (Scheme 3-21)

3.8.4.4.2.1 4-Methyl-2-phenyl-2*H*-chromene (3-32, Scheme 3-21)



To a solution of (*E*)-2-(2-hydroxy-4-phenylbut-3-en-2-yl)phenol **3-31** (48 mg, 0.2 mmol) in nitromethane (1 mL) at room temperature was added 2,3,4,5-tetrafluorophenyl boronic acid **3-1k** (8 mg, 0.04 mmol). The resulting solution was stirred at 50 ^{o}C for 16 hours. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:20) to give 4-methyl-2-phenyl-2*H*-chromene **3-33** (38 mg, 85%) in pure form. The characterization data for this compound matched those of a previous report.[58]

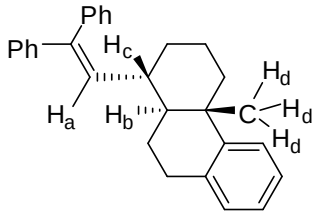
3.8.4.4.2.2 1-(2,2-Diphenylvinyl)-4a-methyl-1,2,3,4,4a,9,10,10a-octahydro-phenanthrene (3-34, Scheme 3-21)



(dr = 1:1:0.5:16)

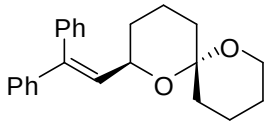
To a solution of (2*E*,7*E*)-7-methyl-1,1,10-triphenyldeca-2,7-dien-1-ol **3-33** (79 mg, 0.2 mmol) in nitromethane (1 mL) at room temperature was added 2,3,4,5-tetrafluorophenyl boronic acid **3-1k** (8 mg, 0.04 mmol). The resulting

solution was stirred at room temperature for 48 hours. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:40) to give octahydrophenanthrene **3-34** (62 mg, 82% yield, dr = 1:1:0.5:16, dr was determined by ^{1}H-NMR of crude reaction mixture, the major stereoisomer was determined by TROESY experiment) as a pale yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41-7.18 (m, 11H), 7.15-7.04 (m, 3H), 5.87 (d, *J* = 10.2 Hz, 1H), 2.90-2.85 (m, 2H), 2.36-2.28 (m, 1H), 2.26-2.20 (m, 1H), 2.03-1.95 (m, 1H), 1.76-1.64 (m, 2H), 1.63-1.56 (m, 1H), 1.52-1.38 (m, 3H), 1.31-1.20 (m, 1H), 0.94 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 148.0, 142.7, 141.1, 140.5, 135.5, 135.0, 129.7, 129.2, 128.2, 128.1, 127.0, 126.82, 126.78, 125.5, 125.3, 124.6, 47.1, 38.4, 37.8, 37.0, 33.5, 29.7, 23.1, 22.7, 21.5; **IR** (Microscope, cm^{-1}) 3079, 3057, 3024, 2927, 2861, 1598, 1491, 1444; **HRMS** (EI) for $C_{29}H_{30}$: calcd. 378.2347; found 378.2348.



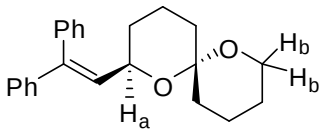
The above major stereoisomer was determined by 2D-NMR spectroscopy. From gCOSY, gHSQC, and gHMBC spectra, H_a, H_b, H_c, and H_d (see the above figure) could be identified as 5.87 (d, *J* = 10.2 Hz, 1H), 1.63-1.56 (m, 1H), 2.36-2.28 (m, 1H), and 0.94 (s, 3H) respectively. A strong correlation δ $H_a \leftrightarrow H_b$ and δ $H_c \leftrightarrow H_d$ on the TROESY spectrum strongly suggests that the desired product was the above stereoisomer.

3.8.4.4.2.3 2-(2,2-Diphenylvinyl)-1,7-dioxaspiro[5.5]undecane (3-36, Scheme 3-21)



(dr > 98:2)

To a solution of the allylic alcohol **3-35** (70 mg, 0.2 mmol) in nitromethane (1 mL) at room temperature was added 2,3,4,5-tetrafluorophenyl boronic acid **3-1k** (4 mg, 0.02 mmol). The resulting solution was stirred at 50 ^{o}C for 16 hours. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:20) to give the title compound **3-36** (56 mg, 84%, dr > 98:2, dr was determined by ^{1}H-NMR of crude reaction mixture, the major stereoisomer was determined by TROESY experiment) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40-7.19 (m, 10H), 6.12 (d, *J* = 8.9 Hz, 1H), 4.19 (ddd, *J* = 11.4, 9.0, 2.8 Hz, 1H), 3.29 (dd, *J* = 9.1, 2.3 Hz, 2H), 1.90-1.80 (m, 1H), 1.79-1.67 (m, 1H), 1.65-1.33 (m, 10H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.0, 141.6, 139.7, 130.1, 129.6, 128.2, 128.0, 127.4, 127.20, 127.16, 95.5, 67.4, 60.0, 35.8, 35.1, 31.3, 25.3, 18.5, 18.4; **IR** (Microscope, cm^{-1}) 3080, 3056, 3024, 2940, 2868, 1495, 1444; **HRMS** (EI) for $C_{23}H_{26}O_2$: calcd. 334.1933; found 334.1941.



The above major stereoisomer was determined by 2D-NMR spectroscopy. From 1H-NMR spectrum, H_a and H_b (see the above figure) could be identified as 4.19 (ddd, *J* = 11.4, 9.0, 2.8 Hz, 1H) and 3.29 (dd, *J* = 9.1, 2.3 Hz, 2H) respectively. A strong correlation δ $H_a \leftrightarrow H_b$ on the TROESY spectrum strongly suggests that the desired product was the above stereoisomer.

3.8.4.5 The stability and recyclability of boronic acid catalysts

3.8.4.5.1 The stability and recyclability of boronic acid catalyst 3-1k (Scheme 3-22)

To a solution of allylic alcohol **3-20a** (990 mg, 3.0 mmol) in nitromethane (15 mL) at room temperature was added 2,3,4,5-tetrafluorophenyl boronic acid **3-1k** (120 mg, 0.6 mmol). The resulting solution was stirred at room temperature for 60 hours. Upon evaporation of the solvent under reduced pressure, the residue was dissolved in Et_2O (20 mL). Then the resulting solution was cooled to 0 ^oC and a NaOH solution (3 N, 10 mL) was added slowly. The aqueous layer was extracted with Et_2O (2 × 20 mL) and then acidified to pH 2 with a HCl solution (6 N, 6 mL). Upon standing in an ice-bath for 30 minutes, a precipitate was formed in the aqueous solution, which was filtered and washed with hexanes (2 × 20 mL) to afford the recovered boronic acid **3-1k** (115 mg, 96% recovery yield) in pure form. The combined Et_2O layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:20) to give cyclic product **3-21a** (890 mg, 95% yield) in pure form.

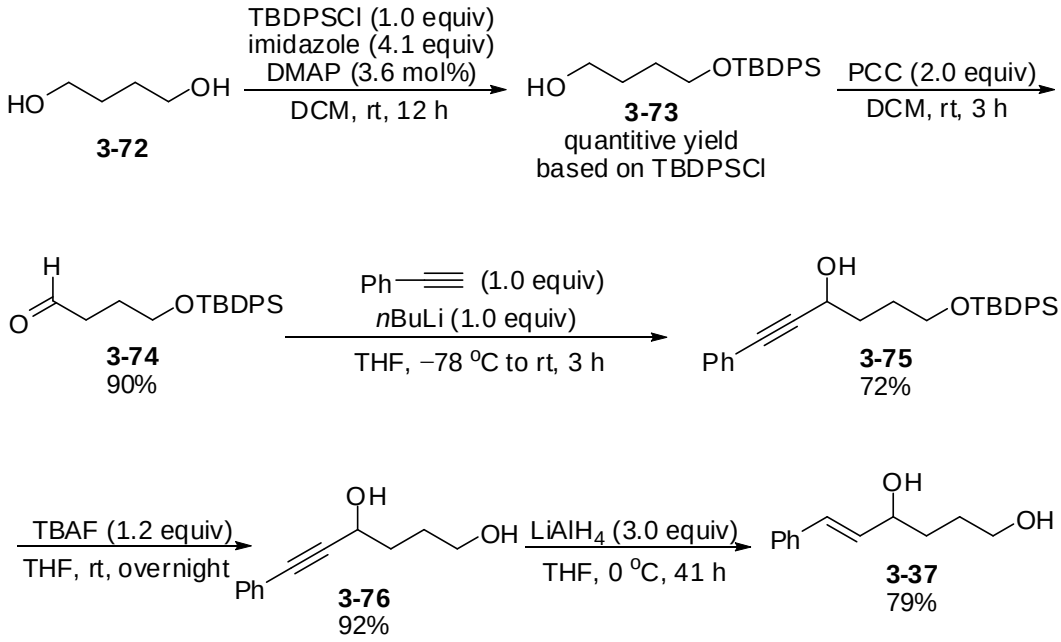
3.8.4.5.2 The stability and recyclability of boronic acid catalyst 3-1j (Scheme 3-22)

To a solution of allylic alcohol **3-20a** (990 mg, 3.0 mmol) in nitromethane (15 mL) at room temperature was added 2,3,4,5,6-pentafluorophenyl boronic acid **3-1j** (127 mg, 0.6 mmol). The resulting solution was stirred at room temperature for 60 hours. Upon evaporation of the solvent under reduced pressure, the residue was recrystallized from toluene (10 mL) to give the recovered boronic acid **3-1j** (103 mg, 81% recovery yield) in pure form. The organic filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:20) to give cyclic product **3-21a** (553 mg, 59% yield) in

pure form.

3.8.4.6 Preliminary mechanistic investigations (Scheme 3-23)

3.8.4.6.1 (*E*)-6-Phenylhex-5-ene-1,4-diol (3-37, Scheme 3-23)



Step 1: A solution of diol **3-72** (10.32 g, 114.0 mmol), TBDPS-Cl (6.40 g, 23.2 mmol), imidazole (6.48 g, 95.2 mmol), and DMAP (418 mg, 3.4 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature for 12 hours. The reaction mixture was extracted between EtOAc (150 mL) and H_2O (40 mL). The organic layer was washed with brine (3 × 20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:6) to give the title alcohol **3-73** (7.62 g, quantitive yield) in pure form.

Step 2: To a solution of pyridinium chlorochromate (8.62 g, 40.0 mmol) in CH_2Cl_2 (60 mL) at room temperature was added a solution of alcohol **3-73** (6.57 g, 20.0 mmol) in CH_2Cl_2 (30 mL). The resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with *n*-pentane (200 mL) and filtered through Celite. The filtrate was evaporated under reduced

pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:6) to give the title aldehyde **3-74** (5.88 g, 90% yield) in pure form.

Step 3: To a solution of ethynylbenzene (510 mg, 5.0 mmol) in THF (15 mL) at –78 ^{o}C was added *n*BuLi solution (2.5 M in hexanes, 2.0 mL, 5.0 mmol). The solution was allowed to warm to 0 ^{o}C over 1 hour and stirred at 0 ^{o}C for 30 minutes. Then the solution was cooled to –78 ^{o}C and the aldehyde **3-74** (1.63 g, 5.0 mmol) was added. The reaction mixture was allowed to warm to room temperature over 1 hour and stirred at room temperature for 3 hours. NH_4Cl solution (20 mL) was added to quench the reaction and the reaction mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (20 mL), saturated $NaHCO_3$ solution (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:8) to give the title propargylic alcohol **3-75** (1.54 g, 72% yield) in pure form.

Step 4: A solution of propargylic alcohol **3-75** (1.54 g, 3.6 mmol), and TBAF (1.0 M in THF, 4.3 mL, 4.3 mmol) in THF (20 mL) was stirred at room temperature overnight. The reaction mixture was extracted between Et_2O (40 mL) and H_2O (40 mL). The organic layer was washed with brine (3 × 20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 2:3) to give the title diol **3-76** (630 mg, 92% yield) in pure form.

Step 5: To a solution of propargylic diol **3-76** (571 mg, 3.0 mmol) in THF (5 mL) at 0 ^{o}C was added $LiAlH_4$ solution (1.0 M in THF, 9.0 mL, 9.0 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 41 hours. Then the reaction mixture was cooled to 0 ^{o}C. EtOAc (10 mL) and $Na_2SO_4 \cdot 10H_2O$ (0.5 g) were added to the reaction mixture

and the reaction mixture was stirred at 0 ^{o}C for 20 minutes. The reaction mixture was filtered through Celite and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:1) to give allylic alcohol **3-37** (456 mg, 79% yield) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40-7.24 (m, 5H), 6.60 (d, *J* = 16.0 Hz, 1H), 6.26 (dd, *J* = 16.0, 6.5 Hz, 1H), 4.40-4.30 (m, 1H), 3.77-3.62 (m, 2H), 3.14 (br s, 1H), 2.87 (br s, 1H), 1.84-1.67 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 136.7, 132.3, 130.1, 128.6, 127.6, 126.5, 72.7, 62.8, 34.5, 28.8; **IR** (Microscope, cm^{-1}) 3323, 3082, 3059, 3026, 2940, 2868, 1494, 1448; **HRMS** (ESI) for $C_{12}H_{16}NaO_2$: calcd. 215.1043; found 215.1038.

3.8.4.6.2 Mechanistic control reactions (eqs 1-2, Scheme 3-23)

To a solution of the allylic alcohol **3-22b** or **3-37** (38 mg, 0.2 mmol) in nitromethane (1 mL) at room temperature was added 2,3,4,5-tetrafluorophenyl boronic acid **3-1k** (4 mg, 0.02 mmol). The resulting solution was stirred at the indicated temperature for a given time. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:20) to give the product **3-23b** in pure form.

3.8.4.6.3 Mechanistic control reactions (eq 3, Scheme 3-23)

The allylic alcohol **3-38** was prepared following a literature procedure.[5]

To a solution of the allylic alcohol **3-38** (30 mg, 0.2 mmol) in nitromethane (1 mL) at room temperature was added 2,3,4,5-tetrafluorophenyl boronic acid **3-1k** (4 mg, 0.02 mmol). The resulting solution was stirred at the indicated temperature for a given time. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:8) to give the products **3-39** and **3-40** in pure form.

The characterization data for the compounds **3-39** and **3-40** matched those of a

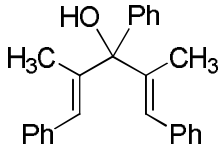
previous report.[5]

3.8.5 Boronic acid catalyzed Nazarov cyclizations (Section 3.4)

3.8.5.1 General procedure for the preparation of the divinyl alcohols 3-44 (Table 3-13)

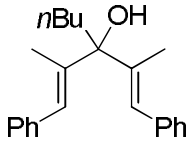
To a solution of (1*E*,4*E*)-2,4-dimethyl-1,5-diphenylpenta-1,4-dien-3-one (2.62 g, 10.0 mmol) in THF (30 mL) at –78 ^{o}C was added organolithium reagent or Grignard reagent (12.0 mmol). The reaction mixture was stirred at –78 ^{o}C for 30 minutes and then allowed to warm to 0 ^{o}C. A saturated aqueous NH_4Cl solution (20 mL) was added to quench the reaction and the reaction mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:20) to give the title allylic alcohols **3-44** in pure form.

3.8.5.1.1 (1*E*,4*E*)-2,4-Dimethyl-1,3,5-triphenylpenta-1,4-dien-3-ol (3-44a)



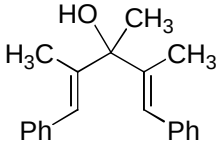
The title compound was prepared using the general procedure for the preparation of divinyl alcohols **3-44** (74% yield, yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67-7.62 (m, 2H), 7.50-7.36 (m, 11H), 7.34-7.28 (m, 2H), 6.58 (s, 2H), 2.49 (br s, 1H), 2.08 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.9, 141.0, 138.0, 129.3, 129.1, 128.22, 128.17, 128.0, 127.5, 126.7, 86.4, 16.0; **IR** (Microscope, cm^{-1}) 3566, 3468, 3056, 3023, 2979, 2956, 2921, 1599, 1491, 1446; **HRMS** (EI) for $C_{25}H_{24}O$: calcd. 340.1827; found 340.1808.

3.8.5.1.2 (*E*)-2-Methyl-1-phenyl-3-((*E*)-1-phenylprop-1-en-2-yl)hept-1-en-3-ol (3-44b)



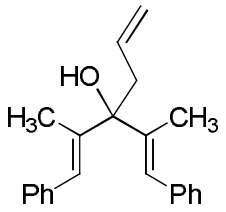
The title compound was prepared using the general procedure for the preparation of divinyl alcohols **3-44** (77% yield, pale yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47-7.38 (m, 8H), 7.35-7.30 (m, 2H), 6.86 (s, 2H), 2.11-2.04 (m, 2H), 1.92 (d, *J* = 0.9 Hz, 6H), 1.83 (br s, 1H), 1.57-1.47 (m, 4H), 1.08 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 140.7, 138.4, 129.2, 128.2, 126.4, 125.6, 81.1, 36.5, 25.9, 23.4, 14.6, 14.3; **IR** (Microscope, cm^{-1}) 3482, 3058, 3025, 2956, 2932, 2871, 1712, 1662, 1600, 1493, 1447; **HRMS** (EI) for $C_{23}H_{28}O$: calcd. 320.4678; found 320.4677.

3.8.5.1.3 (1*E*,4*E*)-2,3,4-Trimethyl-1,5-diphenylpenta-1,4-dien-3-ol (3-44c)



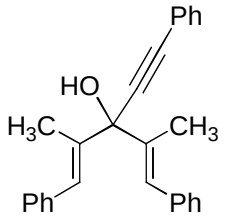
The title compound was prepared using the general procedure for the preparation of divinyl alcohols **3-44** (71% yield, yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50-7.42 (m, 8H), 7.38-7.33 (m, 2H), 6.91 (s, 2H), 2.17 (br s, 1H), 1.99 (s, 6H), 1.80 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 141.7, 138.3, 129.2, 128.3, 126.5, 125.1, 79.5, 26.4, 14.6; **IR** (Microscope, cm^{-1}) 3438, 3054, 3022, 2980, 1599, 1492, 1443; **HRMS** (EI) for $C_{20}H_{22}O$: calcd. 278.1670; found 278.1668.

3.8.5.1.4 (*E*)-2-Methyl-1-phenyl-3-((*E*)-1-phenylprop-1-en-2-yl)hexa-1,5-dien-3-ol (3-44d)



The title compound was prepared using the general procedure for the preparation of divinyl alcohols **3-44** (81% yield, yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42-7.24 (m, 10H), 6.78 (s, 2H), 5.96-5.86 (m, 1H), 5.34-5.26 (m, 2H), 2.84 (dt, *J* = 7.2, 1.1 Hz, 2H), 2.12 (br s, 1H), 1.89 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 140.1, 138.1, 133.7, 129.1, 128.1, 126.4, 125.9, 119.8, 79.8, 41.6, 14.4; **IR** (Microscope, cm^{-1}) 3469, 3057, 2978, 2922, 1492, 1443; **HRMS** (EI) for $C_{22}H_{24}O$: calcd. 304.1827; found 304.1830.

3.8.5.1.5 (1*E*,4*E*)-2,4-Dimethyl-1,5-diphenyl-3-(phenylethynyl)penta-1,4-dien-3-ol (3-44e)

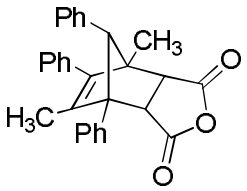


The title compound was prepared using the general procedure for the preparation of divinyl alcohols **3-44** (95% yield, yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68-7.62 (m, 2H), 7.52-7.42 (m, 11H), 7.40-7.34 (m, 4H), 2.77 (br s, 1H), 2.12 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.9, 137.8, 131.9, 129.3, 128.7, 128.5, 128.3, 127.0, 126.8, 122.7, 90.2, 87.8, 78.9, 14.1; **IR** (Microscope, cm^{-1}) 3547, 3442, 3081, 3055, 3023, 2983, 2952, 2918, 1599, 1490, 1442; **HRMS** (EI) for $C_{27}H_{24}O$: calcd. 364.1827; found 364.1818.

3.8.5.2 General procedure for boronic acid catalyzed Nazarov reaction/Diels-Alder trapping (Table 3-13)

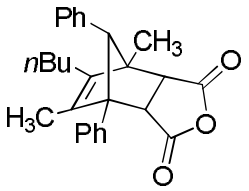
To a solution of the allylic alcohol **3-44** (0.2 mmol) and maleic anhydride or phenylmaleimide (0.2 mmol) in nitromethane (1 mL) at room temperature was added 2,3,4,5-tetrafluorophenyl boronic acid **3-1k** (4 mg, 0.02 mmol). The resulting solution was stirred at 50 ^{o}C overnight. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:10) to give the anhydride or imide **3-49** in pure form.

3.8.5.2.1 Anhydride 3-49a (Table 3-13)



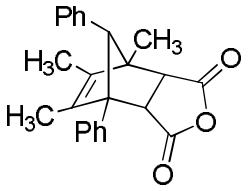
The title compound was prepared using the general procedure for boronic acid catalyzed Nazarov reaction/Diels-Alder trapping (95% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43-7.37 (m, 2H), 7.36-7.16 (m, 11H), 7.03-6.98 (m, 2H), 4.35 (d, *J* = 8.2 Hz, 1H), 3.67 (d, *J* = 8.2 Hz, 1H), 3.22 (s, 1H), 1.75 (s, 3H), 1.50 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.8, 170.2, 141.3, 139.9, 135.9, 135.4, 133.8, 130.4, 129.2, 129.2, 128.4, 128.2, 127.9, 127.58, 127.57, 127.4, 78.4, 67.8, 60.6, 54.7, 52.3, 16.5, 14.6; **IR** (Microscope, cm^{-1}) 3059, 3030, 2968, 2930, 1859, 1778, 1560, 1494, 1448; **HRMS** (EI) for $C_{29}H_{24}O_3$: calcd. 420.1726; found 420.1733.

3.8.5.2.2 Anhydride 3-49b (Table 3-13)



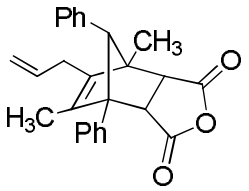
The title compound was prepared using the general procedure for boronic acid catalyzed Nazarov reaction/Diels-Alder trapping (88% yield, pale yellow solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27-7.17 (m, 6H), 7.14-7.11 (m, 2H), 6.91 (d, *J* = 7.2 Hz, 2H), 4.19 (d, *J* = 8.0 Hz, 1H), 3.51 (dd, *J* = 8.0, 0.4 Hz, 1H), 3.02 (s, 1H), 2.32-2.24 (m, 1H), 2.10-2.02 (m, 1H), 1.67 (s, 3H), 1.54 (s, 3H), 1.46-1.32 (m, 4H), 0.94 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.8, 170.3, 140.2, 136.5, 136.2, 135.5, 130.4, 129.1, 127.9, 127.8, 127.3, 127.2, 77.2, 68.3, 60.0, 54.6, 52.1, 30.8, 26.1, 23.2, 15.3, 13.8, 13.1; **IR** (Microscope, cm^{-1}) 3061, 3028, 2959, 2932, 2872, 1858, 1778, 1602, 1498, 1454; **HRMS** (EI) for $C_{27}H_{28}O_3$: calcd. 400.5094; found 400.5089.

3.8.5.2.3 Anhydride 3-49c (Table 3-13)



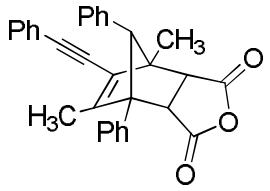
The title compound was prepared using the general procedure for boronic acid catalyzed Nazarov reaction/Diels-Alder trapping (91% yield, yellow solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30-7.16 (m, 6H), 7.09-6.95 (m, 2H), 6.83-6.77 (m, 2H), 4.34 (d, *J* = 8.0 Hz, 1H), 3.55 (d, *J* = 8.1 Hz, 1H), 2.95 (s, 1H), 1.86 (s, 3H), 1.55 (s, 3H), 1.54 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.7, 170.3, 137.3, 135.7, 135.4, 135.0, 130.4, 129.0, 128.0, 127.7, 127.4, 127.2, 77.8, 69.3, 58.9, 54.2, 50.8, 14.8, 12.6, 11.5; **IR** (Microscope, cm^{-1}) 3059, 3030, 2932, 2916, 1857, 1778, 1498, 1454; **HRMS** (EI) for $C_{24}H_{22}O_3$: calcd. 358.1569; found 358.1566.

3.8.5.2.4 Anhydride 3-49d (Table 3-13)



The title compound was prepared using the general procedure for boronic acid catalyzed Nazarov reaction/Diels-Alder trapping (85% yield, yellow solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26-7.14 (m, 6H), 7.10-7.04 (m, 2H), 6.94-6.86 (m, 2H), 5.84-5.72 (m, 1H), 5.16-5.04 (m, 2H), 4.22 (d, *J* = 8.0 Hz, 1H), 3.52 (d, *J* = 8.0 Hz, 1H), 3.10 (dd, *J* = 15.2, 6.7 Hz, 1H), 3.01 (s, 1H), 2.88 (ddd, *J* = 15.1, 7.4, 0.7 Hz, 1H), 1.66 (s, 3H), 1.55 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.3, 169.9, 137.3, 137.1, 135.5, 134.8, 134.1, 130.1, 128.7, 127.5, 127.4, 127.0, 126.8, 116.5, 76.9, 59.4, 54.1, 51.2, 30.7, 14.9, 12.7; **IR** (Microscope, cm^{-1}) 3060, 3029, 2975, 2931, 1857, 1777, 1498, 1447; **HRMS** (ESI) for $C_{26}H_{24}NaO_3$: calcd. 407.1618; found 407.1612.

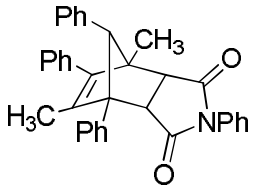
3.8.5.2.5 Anhydride 3-49e (Table 3-13)



The title compound was prepared using the general procedure for boronic acid catalyzed Nazarov reaction/Diels-Alder trapping (87% yield, yellow solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56-7.50 (m, 2H), 7.38-7.32 (m, 3H), 7.30-7.19 (m, 6H), 7.00-6.95 (m, 2H), 6.94-6.87 (m, 2H), 4.40 (d, *J* = 8.1 Hz, 1H), 3.63 (d, *J* = 8.2 Hz, 1H), 3.12 (s, 1H), 1.85 (s, 3H), 1.68 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.4, 168.8, 148.3, 134.4, 134.1, 131.4, 130.1, 128.6, 128.2, 127.9, 127.8, 127.5, 127.3, 127.2, 125.2, 122.6, 99.1, 81.6, 77.1, 69.0, 58.2, 53.5, 50.6, 14.9, 14.7; **IR** (Microscope, cm^{-1}) 3060, 3032, 2969, 2928, 1859, 1777, 1497, 1453,

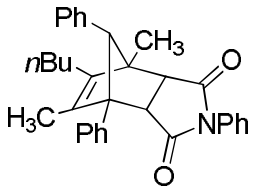
1445; **HRMS** (ESI) for $C_{31}H_{24}NaO_3$: calcd. 467.1618; found 467.1614.

3.8.5.2.6 Cycloadduct 3-49g (Table 3-13)



The title compound was prepared using the general procedure for boronic acid catalyzed Nazarov reaction/Diels-Alder trapping (58% yield, yellow solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.18 (m, 16H), 7.10-7.05 (m, 2H), 7.01-6.95 (m, 2H), 4.33 (d, *J* = 7.8 Hz, 1H), 3.60 (d, *J* = 7.8 Hz, 1H), 3.27 (s, 1H), 1.73 (s, 3H), 1.58 (s. 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.0, 175.4, 142.3, 139.1, 136.9, 136.1, 134.7, 132.1, 131.0, 129.8, 129.6, 129.4, 128.8, 128.6, 128.2, 127.8, 127.42, 127.37, 127.3, 126.9, 79.7, 68.3, 60.2, 54.4, 50.4, 16.9, 15.3; **IR** (Microscope, cm^{-1}) 3065, 3027, 2960, 2931, 2872, 2859, 1770, 1708, 1602, 1501, 1458; **HRMS** (EI) for $C_{35}H_{29}NO_2$: calcd. 495.2198; found 495.2192.

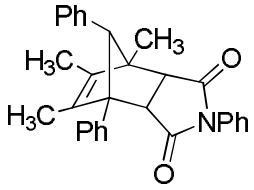
3.8.5.2.7 Cycloadduct 3-49h (Table 3-13)



The title compound was prepared using the general procedure for boronic acid catalyzed Nazarov reaction/Diels-Alder trapping (62% yield, yellow solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50-7.16 (m, 13H), 7.00-6.95 (m, 2H), 4.05 (d, *J* = 7.6 Hz, 1H), 3.38 (d, *J* = 7.6 Hz, 1H), 3.10 (s, 1H), 2.30-2.19 (m, 1H), 2.14-2.03 (m, 1H), 1.70 (s, 3H), 1.58 (s, 3H), 1.50-1.29 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.0, 175.7, 139.6, 137.5, 136.5, 135.5, 132.2, 130.8, 129.7, 129.3, 128.7, 127.9, 127.8, 127.2, 127.0, 126.7, 77.2, 68.4, 59.5,

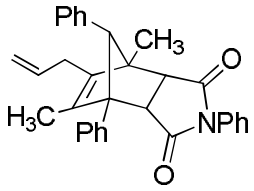
54.1, 51.1, 31.4, 26.6, 23.4, 15.9, 14.1, 13.5; **IR** (Microscope, cm^{-1}) 3062, 3026, 2958, 2932, 2872, 2860, 1770, 1708, 1600, 1500, 1455; **HRMS** (EI) for $C_{33}H_{33}NO_2$: calcd. 475.2511; found 475.2493.

3.8.5.2.8 Cycloadduct 3-49i (Table 3-13)



The title compound was prepared using the general procedure for boronic acid catalyzed Nazarov reaction/Diels-Alder trapping (60% yield, yellow solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50-7.36 (m, 3H), 7.25-7.15 (m, 8H), 7.09-7.04 (m, 2H), 6.88-6.82 (m, 2H), 4.21 (d, *J* = 7.5 Hz, 1H), 3.41 (d, *J* = 7.6 Hz, 1H), 3.02 (s, 1H), 1.88 (d, *J* = 1.1 Hz, 3H), 1.58 (s, 3H), 1.56 (d, *J* = 1.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.1, 175.7, 137.0, 136.7, 136.5, 134.2, 132.3, 130.8, 129.6, 129.4, 128.7, 128.1, 127.7, 127.3, 127.0, 126.8, 78.1, 69.3, 58.5, 53.7, 49.9, 15.5, 13.0, 11.9; **IR** (Microscope, cm^{-1}) 3078, 3057, 3023, 2978, 2953, 2922, 1718, 1640, 1600, 1492, 1444; **HRMS** (ESI) for $C_{30}H_{28}NO_2$: calcd. 434.2115; found 434.2119.

3.8.5.2.9 Cycloadduct 3-49j (Table 3-13)



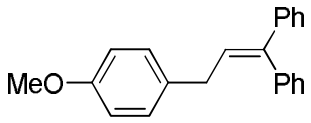
The title compound was prepared using the general procedure for boronic acid catalyzed Nazarov reaction/Diels-Alder trapping (55% yield, yellow solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51-7.36 (m, 3H), 7.27-7.15 (m, 10H), 6.99-6.94 (m, 2H), 5.87-5.75 (m, 1H), 5.11 (dq, *J* = 17.0, 1.6 Hz, 1H), 5.03 (dq, *J* = 10.0, 1.4 Hz,

1H), 4.11 (d, *J* = 7.6 Hz, 1H), 3.41 (d, *J* = 7.5 Hz, 1H), 3.10 (dd, *J* = 15.2, 6.5 Hz, 1H), 3.08 (s, 1H), 2.91 (dd, *J* = 15.1, 7.9 Hz, 1H), 1.69 (s, 3H), 1.60 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.0, 175.6, 137.3, 137.1, 136.5, 136.2, 135.3, 132.2, 131.0, 129.7, 129.3, 128.7, 128.0, 127.8, 127.3, 127.1, 126.7, 116.8, 77.6, 68.7, 59.3, 54.0, 50.6, 31.8, 15.9, 13.5; **IR** (Microscope, cm^{-1}) 3079, 3055, 3022, 2977, 2952, 2923, 2856, 1719, 1639, 1599, 1492, 1443, 1414; **HRMS** (EI) for $C_{32}H_{29}NO_2$: calcd. 459.2198; found 459.2202.

3.8.6 Boronic acid catalyzed allylic substitutions (Section 3.5)

To a solution of the allylic alcohol **3-50** (0.2 mmol) and arene or nucleophile (0.2 mmol or 1.0 mmol) in nitromethane (1 mL) at the indicated reaction temperature was added the boronic acid catalyst **3-1k** or **3-1n** (4 mg, 0.02 mmol). The resulting solution was stirred at the indicated reaction temperature for 48 hours. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography to give the desired products **3-51** or **3-53** in pure form.

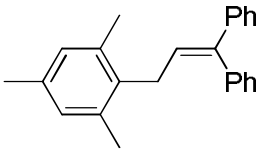
3.8.6.1 (3-(4-Methoxyphenyl)prop-1-ene-1,1-diyl)dibenzene (3-51a, Table 3-16)



The title compound was prepared using the general procedure for boronic acid catalyzed allylic substitutions (70% yield with **3-1k**, 84% with **3-1n**; yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47-7.42 (m, 2H), 7.40-7.36 (m, 1H), 7.32-7.24 (m, 7H), 7.19-7.15 (m, 2H), 6.92-6.87 (m, 2H), 6.30 (t, *J* = 7.6 Hz, 1H), 3.84 (s, 3H), 3.47 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.0, 142.5, 142.2, 139.9, 133.0, 130.0, 129.3, 128.3, 128.2, 128.1, 127.3, 127.1, 127.0, 114.0, 55.3, 35.1; **IR** (Microscope, cm^{-1}) 3079, 3055, 3026, 2952, 2932, 2906, 2833, 1610,

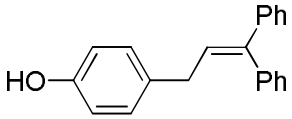
1510, 1495, 1463, 1443; **HRMS** (EI) for $C_{22}H_{20}O$: calcd. 300.1514; found 300.1517.

3.8.6.2 (3-Mesitylprop-1-ene-1,1-diyl)dibenzene (3-51b, Table 3-16)



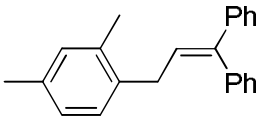
The title compound was prepared using the general procedure for boronic acid catalyzed allylic substitutions (80% yield with **3-1k**, 90% with **3-1n**; white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46-7.15 (m, 10H), 6.85 (s, 2H), 5.94 (t, *J* = 6.7 Hz, 1H), 3.45 (d, *J* = 6.7 Hz, 2H), 2.27 (s, 3H), 2.18 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.5, 142.0, 140.0, 136.4, 135.3, 134.7, 130.1, 130.0, 128.8, 128.2, 128.0, 127.4, 127.2, 126.9, 30.3, 20.8, 20.0; **IR** (Microscope, cm^{-1}) 3079, 3055, 3021, 2943, 2918, 2859, 1612, 1599, 1494, 1484, 1443; **HRMS** (EI) for $C_{24}H_{24}$: calcd. 312.1878; found 312.1873.

3.8.6.3 4-(3,3-Diphenylallyl)phenol (3-51c, Table 3-16)



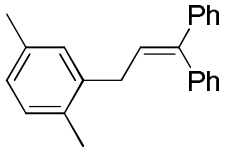
The title compound was prepared using the general procedure for boronic acid catalyzed allylic substitutions (54% yield with **3-1k**, 72% with **3-1n**; white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44-7.21 (m, 10H), 7.10-7.05 (m, 2H), 6.80-6.76 (m, 2H), 6.25 (t, *J* = 7.6 Hz, 1H), 4.72 (br s, 1H), 3.42 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.4, 142.1, 141.8, 139.4, 132.8, 129.5, 129.1, 127.9, 127.75, 127.72, 126.9, 126.7, 126.6, 114.9, 34.6; **IR** (Microscope, cm^{-1}) 3539, 3365, 3079, 3055, 3022, 2964, 2927, 1704, 1612, 1597, 1511, 1494, 1443; **HRMS** (ESI) for $C_{21}H_{17}O$: calcd. 285.1285; found 285.1285.

3.8.6.4 (3-(2,4-Dimethylphenyl)prop-1-ene-1,1-diyl)dibenzene (3-51d, Table 3-17)



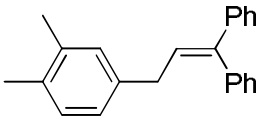
The title compound was prepared using the general procedure for boronic acid catalyzed allylic substitutions (57% yield with **3-1k**, 74% with **3-1n**; white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41-7.38 (m, 2H), 7.37-7.32 (m, 1H), 7.28-7.21 (m, 7H), 7.11-7.08 (m, 1H), 7.00-6.96 (m, 2H), 6.20 (t, *J* = 7.4 Hz, 1H), 3.42 (d, *J* = 7.4 Hz, 2H), 2.32 (s, 3H), 2.18 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.6, 142.3, 139.9, 136.2, 136.1, 135.6, 131.0, 129.9, 128.6, 128.2, 128.1, 127.7, 127.4, 127.1, 127.0, 126.6, 33.4, 20.9, 19.4; **IR** (Microscope, cm^{-1}) 3079, 3055, 3022, 2968, 2919, 2860, 1598, 1495, 1444; **HRMS** (EI) for $C_{23}H_{22}$: calcd. 298.1722; found 298.1721.

3.8.6.5 (3-(2,5-Dimethylphenyl)prop-1-ene-1,1-diyl)dibenzene (3-51e, Table 3-17)



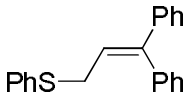
The title compound was prepared using the general procedure for boronic acid catalyzed allylic substitutions (20% yield with **3-1k**, 48% with **3-1n**; white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42-7.31 (m, 3H), 7.29-7.19 (m, 7H), 7.04-6.92 (m, 3H), 6.19 (t, *J* = 7.4 Hz, 1H), 3.40 (d, *J* = 7.4 Hz, 2H), 2.30 (s, 3H), 2.15 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.5, 142.3, 139.9, 139.0, 135.4, 133.0, 130.0, 129.9, 129.4, 128.2, 128.1, 127.5, 127.3, 127.1, 127.0, 126.8, 33.8, 21.0, 19.0; **IR** (Microscope, cm^{-1}) 3079, 3054, 3021, 2966, 2920, 2864, 1598, 1495, 1444; **HRMS** (EI) for $C_{23}H_{22}$: calcd. 298.1722; found 298.1725.

3.8.6.6 (3-(3,4-Dimethylphenyl)prop-1-ene-1,1-diyl)dibenzene (3-51f, Table 3-17)



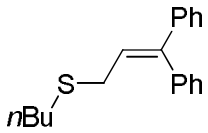
The title compound was prepared using the general procedure for boronic acid catalyzed allylic substitutions (18% yield with **3-1k**, 48% with **3-1n**; yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42-7.30 (m, 3H), 7.28-7.20 (m, 7H), 7.08-6.92 (m, 3H), 6.26 (t, *J* = 7.6 Hz, 1H), 6.18 (t, *J* = 7.4 Hz, 1H)*, 3.47 (d, *J* = 7.3 Hz, 2H)*, 3.41 (d, *J* = 7.5 Hz, 2H), 2.29 (s, 3H)*, 2.25 (s, 3H), 2.24 (s, 3H), 2.11 (s, 3H)* (*: minor isomer); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.55*, 142.53, 142.2*, 142.1, 139.92*, 139.90, 139.2*, 138.3, 136.8*, 136.6, 134.8*, 134.1, 130.0, 129.9*, 129.73, 129.72, 128.24, 128.20*, 128.1, 128.0*, 127.34*, 127.32, 127.1*, 127.0, 126.97*, 126.96, 126.7, 125.7, 125.5*, 35.5, 34.5*, 20.7*, 19.8, 19.3, 15.1* (*: minor isomer); **IR** (Microscope, cm^{-1}) 3079, 3055, 3021, 2968, 2920, 2857, 1598, 1504, 1495, 1444; **HRMS** (EI) for $C_{23}H_{22}$: calcd. 298.1722; found 298.1723.

3.8.6.7 (3,3-Diphenylallyl)(phenyl)sulfane (3-53a, Table 3-18)



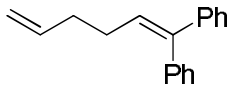
The title compound was prepared using the general procedure for boronic acid catalyzed allylic substitutions (81% yield with **3-1k**; white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38-7.16 (m, 13H), 7.11-7.07 (m, 2H), 6.16 (t, *J* = 7.8 Hz, 1H), 3.64 (d, *J* = 7.8 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 144.4, 141.9, 138.9, 135.7, 130.3, 129.9, 128.8, 128.2, 128.1, 127.5, 127.44, 127.43, 126.3, 124.2, 33.9; **IR** (Microscope, cm^{-1}) 3077, 3056, 3024, 2918, 1664, 1598, 1583, 1494, 1480, 1442; **HRMS** (EI) for $C_{21}H_{18}S$: calcd. 302.1129; found 302.1132.

3.8.6.8 Butyl(3,3-diphenylallyl)sulfane (3-53b, Table 3-18)



The title compound was prepared using the general procedure for boronic acid catalyzed allylic substitutions (84% yield with **3-1k**; colorless oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40-7.18 (m, 10H), 6.15 (t, *J* = 7.8 Hz, 1H), 3.25 (d, *J* = 7.9 Hz, 2H), 2.47-2.42 (m, 2H), 1.44-1.26 (m, 4H), 0.85 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.4, 142.0, 139.2, 130.0, 128.25, 128.15, 127.4, 127.341, 127.335, 125.5, 31.8, 30.9, 30.8, 22.0, 13.6; **IR** (Microscope, cm^{-1}) 3079, 3056, 3024, 2957, 2929, 2871, 1598, 1494, 1464, 1444; **HRMS** (EI) for $C_{19}H_{22}S$: calcd. 282.1442; found 282.1439.

3.8.6.9 Hexa-1,5-diene-1,1-diyldibenzene (3-53d, Table 3-18)



The title compound was prepared using the general procedure for boronic acid catalyzed allylic substitutions (22% yield with **3-1k**; yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39-7.15 (m, 10H), 6.08 (t, *J* = 7.1 Hz, 1H), 5.84-5.75 (m, 1H), 5.04-4.94 (m, 2H), 2.26-2.16 (m, 4H).

3.9 References

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Chapter 4

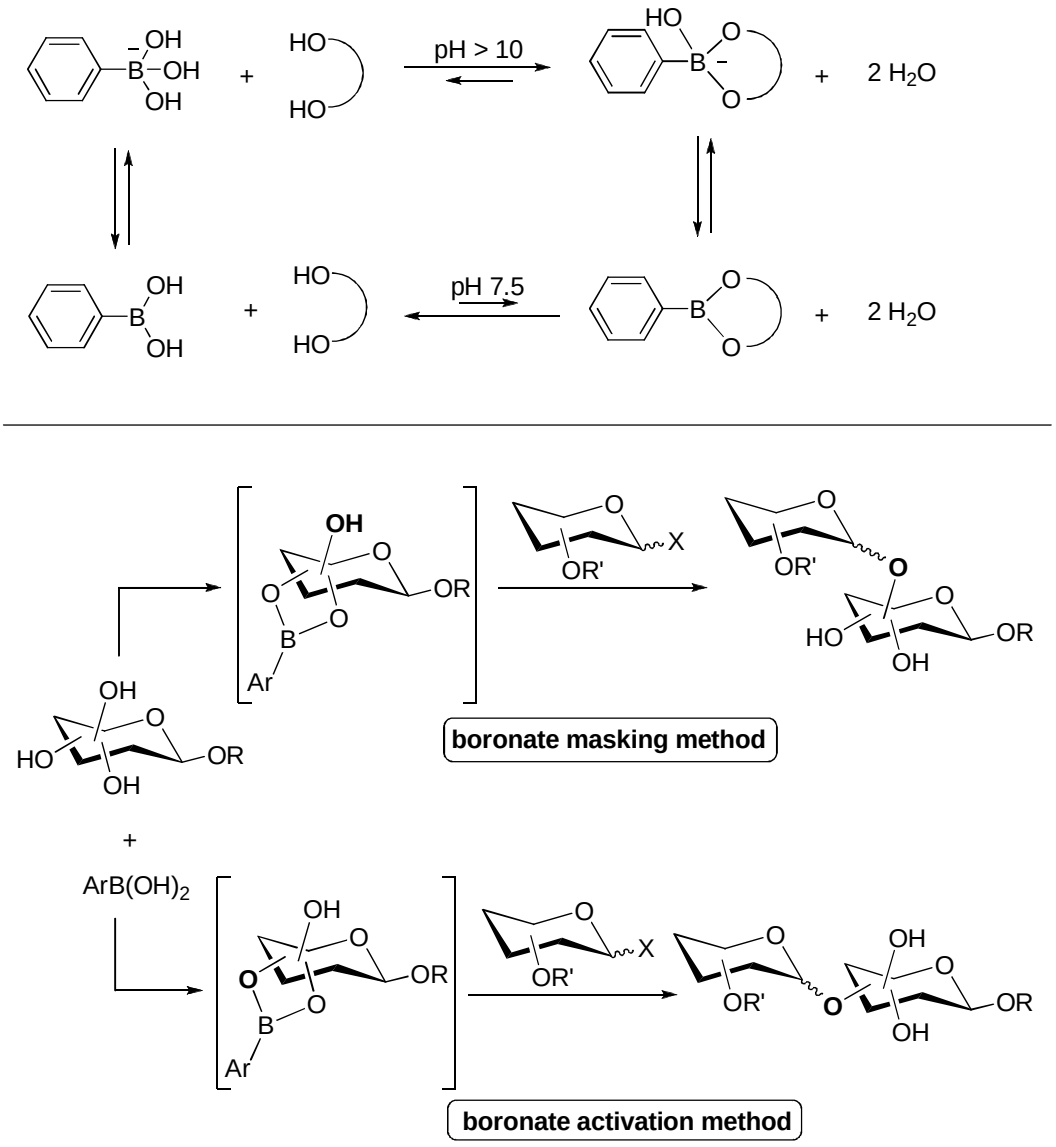
Boronic Acids as Mediators of Regioselective Glycosylation in Carbohydrate Chemistry

4.1 Introduction

Oligosaccharides play important roles in many biological processes such as cell adhesion, recognition, and migration.[1] Nature has long been recognized as an inexhaustible resource for biologically active oligosaccharides, however, the limited isolation techniques and natural supply of a growing number of interesting oligosaccharides hampers clinical development and comprehensive biological study.[2] Taking advantage of the dramatic improvements that have continuously occurred in synthetic methodology, chemical synthesis provides a powerful solution to address this issue, where a reliable and sustainable means of accessing useful amounts of the desired carbohydrates and designed analogs can be developed.[3] The construction of the O-glycosidic linkage, the key step in the synthesis of oligosaccharides, often suffers from poor regioselectivity due to the abundance of hydroxyl groups in sugar molecules.[4] Although pre-activation with stoichiometric amounts of organotin reagents[5] or introduction of protecting groups[6] have been used to address this problem, these additional operations usually result in lengthy synthetic routes and inevitably a decrease in the efficiency of the process. Moreover, toxic organotin reagents exhibit a negative impact on the environment. Thus, a greener methodology for regioselective glycosylation of fully unprotected sugars without prior activation and protection is highly desirable.

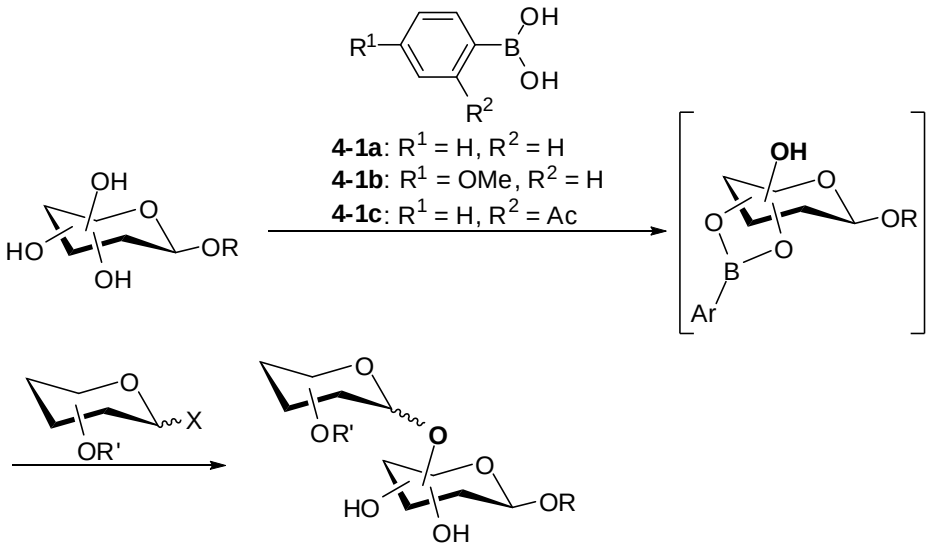
Boronic acids can form cyclic boronates with diols or sugars and the resulting boronates are susceptible to hydrolysis (**Scheme 4-1**).[7] These processes are reversible and highly pH-dependent. Taking advantage of this property, boronic

acids can be employed as transient protecting groups for unprotected sugars to achieve regioselective glycosylation (**Scheme 4-1**). On the other hand, similar to the stannylene activation method,[5] the formation of boronates may alter the nucleophilicity of the two hydroxyl groups in the 1,2-diol or 1,3-diol frameworks, biasing their potential for electrophilic attack to realize a regioselective glycosylation (**Scheme 4-1**).



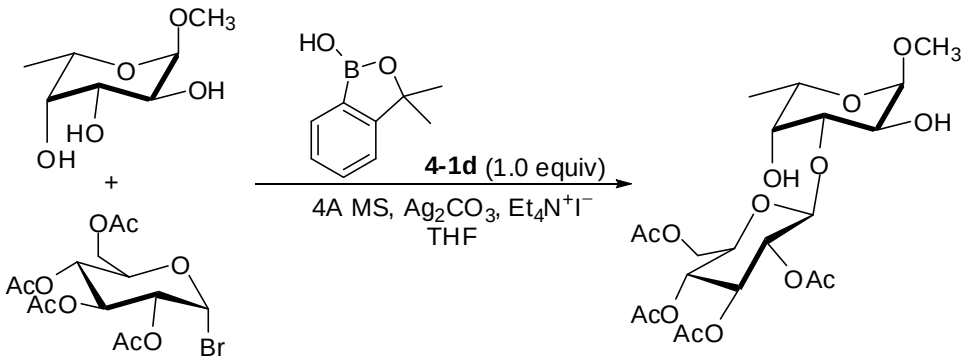
Scheme 4-1: Concept for boronic acid mediated regioselective glycosylation of fully unprotected sugars

Boronic acids as transient masks (Kaji and co-workers)[8]:



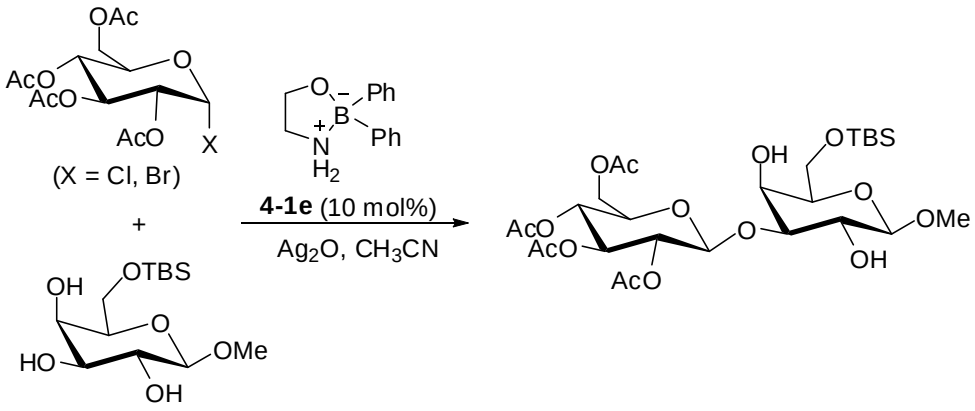
1)

Boronic acids as stoichiometric promoters (Aoyama and co-workers)[9]:



2)

Borinic acids as catalysts (Taylor and co-workers)[10]:



3)

Scheme 4-2: Organoboron compounds as mediators of regioselective glycosylation

Based on these two concepts, several organoboron compound mediated regioselective glycosylation methods were successfully developed. In 2010, Kaji and co-workers reported that phenylboronic acid **4-1a**, 4-methoxyphenylboronic acid **4-1b**, and 2-acetylphenylboronic acid **4-1c** could serve as transient masks of unprotected methyl hexopyranosides to make the glycosylation proceed at the desirable site in a highly regioselective manner (eq 1, **Scheme 4-2**).[8] Aoyama and co-workers discovered that the boroxole **4-1d** could be employed as a stoichiometric reaction activator to promote the regiospecific glycosylation of a wide range of carbohydrates.[9] This reaction was proposed to proceed *via* a tetra-coordinated boronate with the regioselectivity controlled by a combination of electronic and steric effects (eq 2, **Scheme 4-2**). Recently, Taylor and co-workers found that borinate ester **4-1e**, a precursor of diphenylborinic acid, could facilitate the same reaction in a catalytic fashion.[10] Preliminary mechanistic studies revealed that the remarkable regioselectivity was due to the enhanced nucleophilicity of the oxygen atom at the 3 position in the tetra-coordinated boronate (eq 3, **Scheme 4-2**).

Our group has long been interested in the application of diversely substituted arylboronic acids to modulate the reactivity of carboxylic acid, hydroxyl, and diol functionalities in different organic reactions.[11] In 2006, Hall and co-workers discovered for the first time the remarkable binding affinity, under physiological conditions, of benzoboroxole **4-2** towards glycopyranosides of the type found on the surfaces of cells (**Figure 4-1**).[12] This interesting finding hinted that the boroxole had the potential to control the regioselectivity of glycosylation through its unique binding ability of unprotected sugars. As part of our program aimed at exploring the use of boronic acids as catalysts and stoichiometric reaction promoters for chemical transformations,[11] in this chapter, our efforts toward boronic acid mediated regioselective glycosylation of fully unprotected sugars

will be discussed.

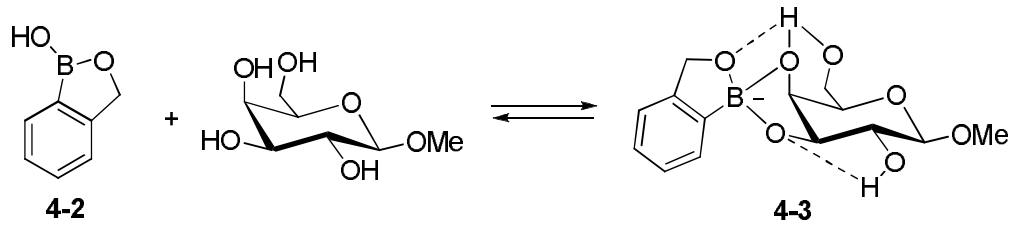
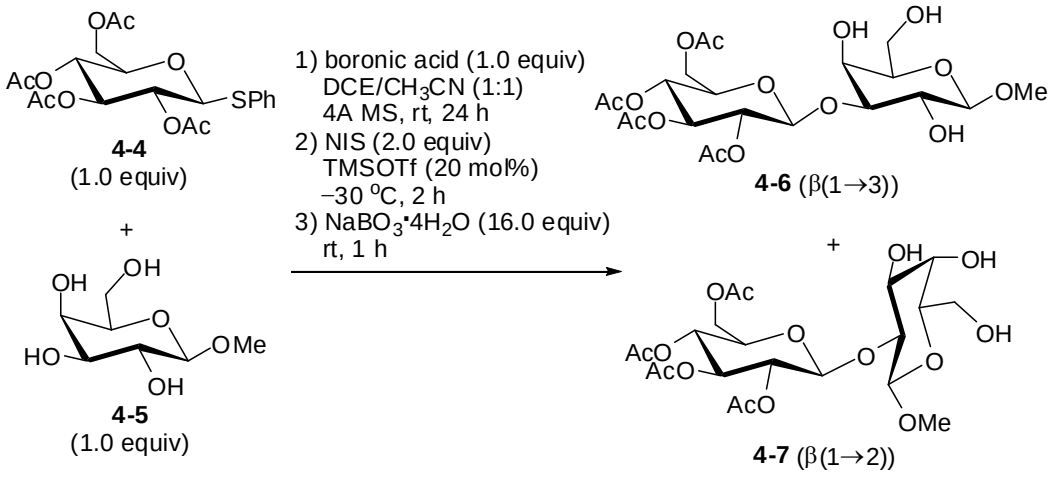


Figure 4-1: Complexation of hexopyranosides using benzoboroxole

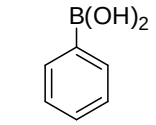
4.2 Boronic acid mediated regioselective glycosylation

Due to its stability and versatility, thioglycoside **4-4** was chosen as a donor for the glycosylation of fully unprotected methyl β-galactoside **4-5** in the presence of NIS/TMSOTf as the activators. Initially, several commercially available arylboronic acids were screened to evaluate their transient masking ability (**Scheme 4-3**). The donor **4-4**, the acceptor **4-5**, and a stoichiometric amount arylboronic acid were mixed together to form boronic ester in the presence of 4A molecular sieves at room temperature for 16 hours, then treated with glycosylation activators (NIS/TMSOTf) in a one-pot fashion affording the disaccharides **4-6** and **4-7** (**Scheme 4-3**). In all cases, β(1→3) and β(1→2)-linked disaccharides **4-6** and **4-7** were obtained as the major and minor products respectively. The selectivity of β(1→3) linkage over β(1→2) linkage is most likely due to a steric effect, where the 3-hydroxyl group is more easily accessible for the electrophilic attack than the 2-hydroxyl group. Due to the increased Lewis acidity of the boron atom, the electron-deficient arylboronic acids **4-1f** and **4-1g** could form more stable 4,6-boronates than phenylboronic acid **4-1a** and electron-rich arylboronic acid **4-1b,** thus preventing the glycosylation at the undesirable 4-OH and 6-OH positions to achieve better efficiency for glycosylation in terms of yield and β(1→3) selectivity (**Scheme 4-3**). Satisfactorily, it was found that boroxole **4-1h**, which showed remarkable binding affinity with methyl galactoside **4-5**,[12] was

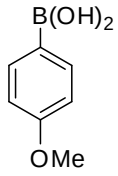
superior to phenylboronic acid **4-1a** as a transient mask for glycosylation (**Scheme 4-3**). Further optimizing the boroxole core with regards to the steric and electronic effects of ring substitution, the electron-deficient boroxoles **4-1i** and **4-1j** were identified as the best temporary protecting groups for glycosylation, providing β(1→3) disaccharide **4-6** as the only isomer in good yield (**Scheme 4-3**).



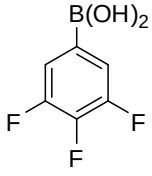
boronic acid:



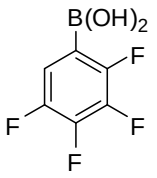
4-1a
31%
(**4-6**:**4-7** = 71:29)



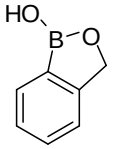
4-1b
50%
(**4-6**:**4-7** = 80:20)



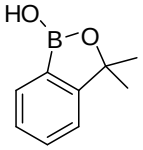
4-1f
60%
(**4-6**:**4-7** = 92:8)



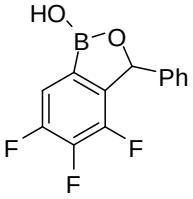
4-1g
65%
(**4-6**:**4-7** = 95:5)



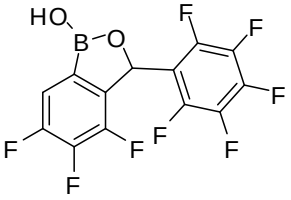
4-1h
53%
(**4-6**:**4-7** = 85:15)



4-1d
52%
(**4-6**:**4-7** = 85:15)



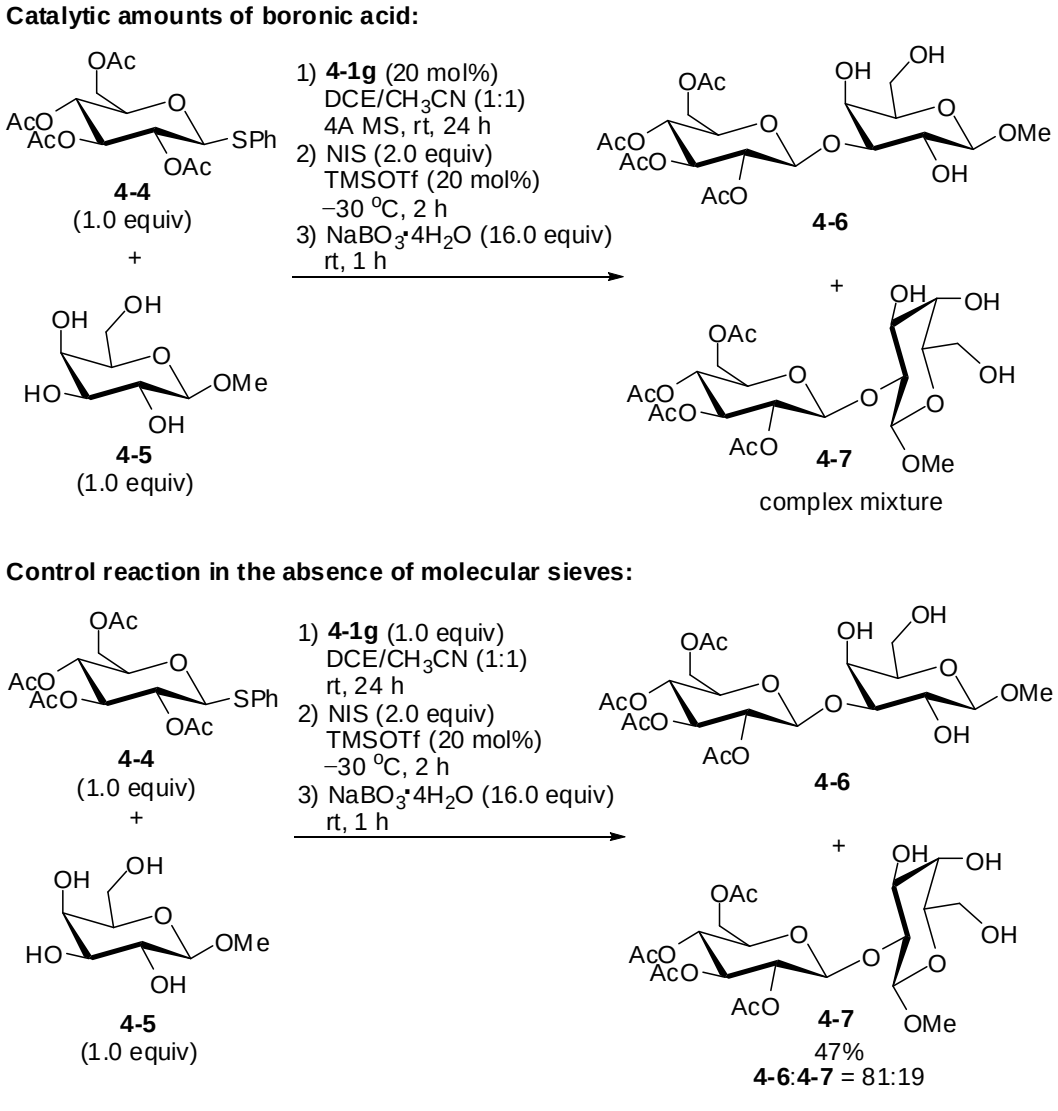
4-1i
71%
(**4-6**:**4-7** > 98:2)



4-1j
78%
(**4-6**:**4-7** > 98:2)

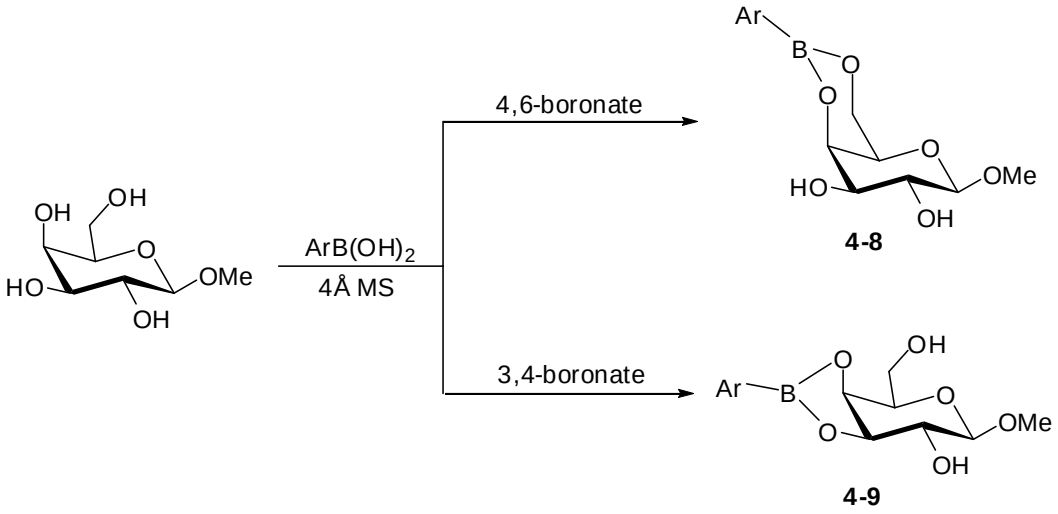
Scheme 4-3: Survey of arylboronic acids as transient masks for a "one-pot" regioselective glycosylation

To gain more mechanistic insight toward the role of the boronic acid in this regioselective glycosylation, two control experiments were conducted (**Scheme 4-4**). When the reaction was performed in the presence of a catalytic amount of boronic acid **4-1g** (20 mol%), a complex mixture was obtained. This observation suggested that boronic acid functions as a transient mask in this glycosylation protocol and therefore a substoichiometric amount of boronic acid would result in a non-selective glycosylation (top equation, **Scheme 4-4**). Moreover, the



Scheme 4-4: Control experiments for boronic acid mediated gylcosylation

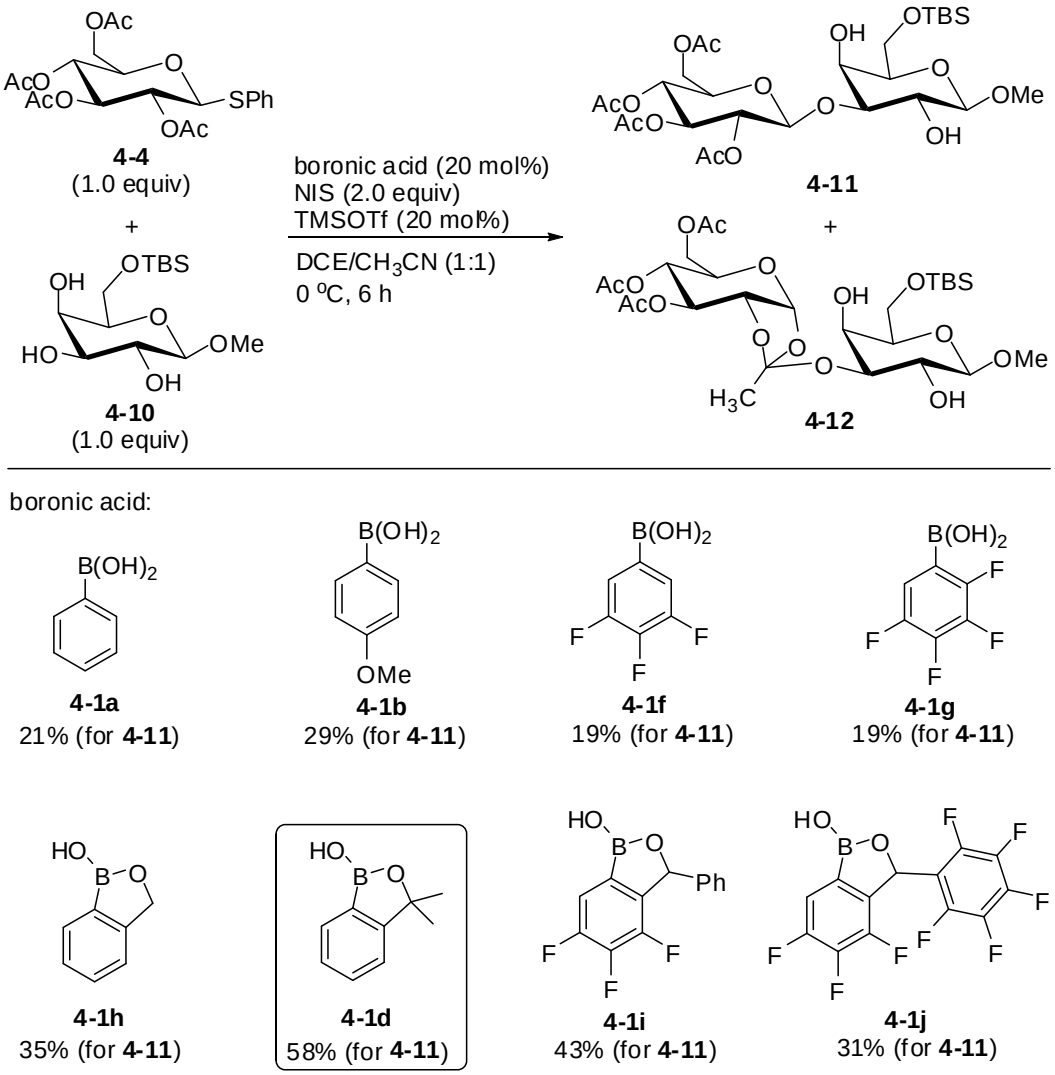
significantly lower efficiency in the absence of molecular sieves (bottom equation, **Scheme 4-4**) hinted that the formation of boronates was reversible and a dehydrating agent was crucial in order to remove the water generated in the reaction system to keep the unprotected sugar **4-5** in its boronate form.



Scheme 4-5: Proposed intermediate boronates

Since arylboronic acids bind certain 1,2- and 1,3-diols with high affinity through reversible formation of boronic esters, two possible intermediates,[7] six-membered 4,6-boronate **4-8** and five-membered 3,4-boronate **4-9** could be involved (**Scheme 4-5**). Based on the dominant β(1→3) selectivity and previous literature precedent,[8] 4,6-boronate **4-8** is most likely the intermediate for this glycosylation. The intermediate **4-8** alone, however, could not explain the enhanced selectivity of β(1→3) over β(1→2) when using an electron-deficient boroxole as the transient mask (**Scheme 4-3**). In addition, the preferred binding mode between benzoboroxoles and glycopyranosides in aqueous solvents is through a *cis*-3,4-diol.[12b] It was therefore proposed that 3,4-boronate **4-9** was also involved as a reaction intermediate where the nucleophilicity of the 3-OH could be increased leading to more β(1→3)-linked disaccharide **4-6**. Although more

experiments need to be performed to confirm this hypothesis, this interesting phenomenon suggested a possible way of using boronic acids as catalysts instead of transient masks to control the regioselectivity of glycosylation.



Scheme 4-6: Survey of arylboronic acids as catalysts for regioselective glycosylation

To eliminate the formation of the 4,6-boronate, an acceptor with the silyl-protected 6-OH **4-10** was employed for the glycosylation of thioglycoside **4-4** in the presence of NIS/TMSOTf as the activators. Different boronic acids and boroxoles were screened to assess their catalytic ability to promote this

glycosylation (**Scheme 4-6**). These reactions were performed in the absence of molecular sieves to allow for catalyst turnover. The orthoester **4-12** was the major side product and boroxoles exhibited better catalytic efficiency to suppress this side reaction compared with boronic acids leading to the β(1→3) disaccharide **4-11** in moderate yield (**Scheme 4-6**). It should be noted that all yields listed in **Scheme 4-6** are based on single experiments and they need to be reproduced in the future to confirm their reliability. Although it is not safe to draw conclusions based on these non-reproduced results at the current stage, some useful information for the design of more active catalysts can be extracted. Both electronic and steric effects from the boroxole core structure have an impact on the catalytic activity of the boroxole. Contrary to the previous observation that electron-deficient boroxole **4-1i** and **4-1j** exhibited better transient masking ability in glycosylation than the neutral boroxole **4-1h** (**Scheme 4-3**), it was found that electron-withdrawing substituents on the aromatic ring decrease the catalytic activity of boroxole in glycosylation (**Scheme 4-6**). Although the electron-deficient boroxole favored the formation of the boronate, the relatively stronger B-O bond in the boronate resulted in a more difficult catalyst turnover undermining the nucleophilicity enhancement of the 3-OH. Moreover, the boroxole **4-1d** with two vicinal methyl groups, which could effectively prevent

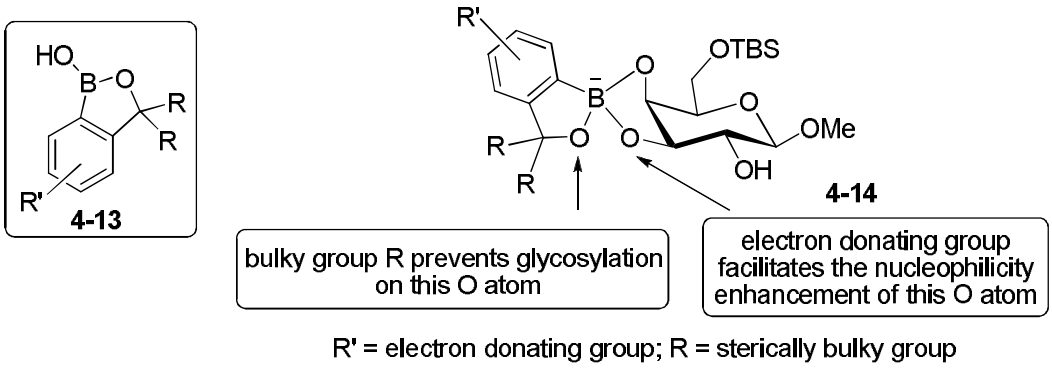
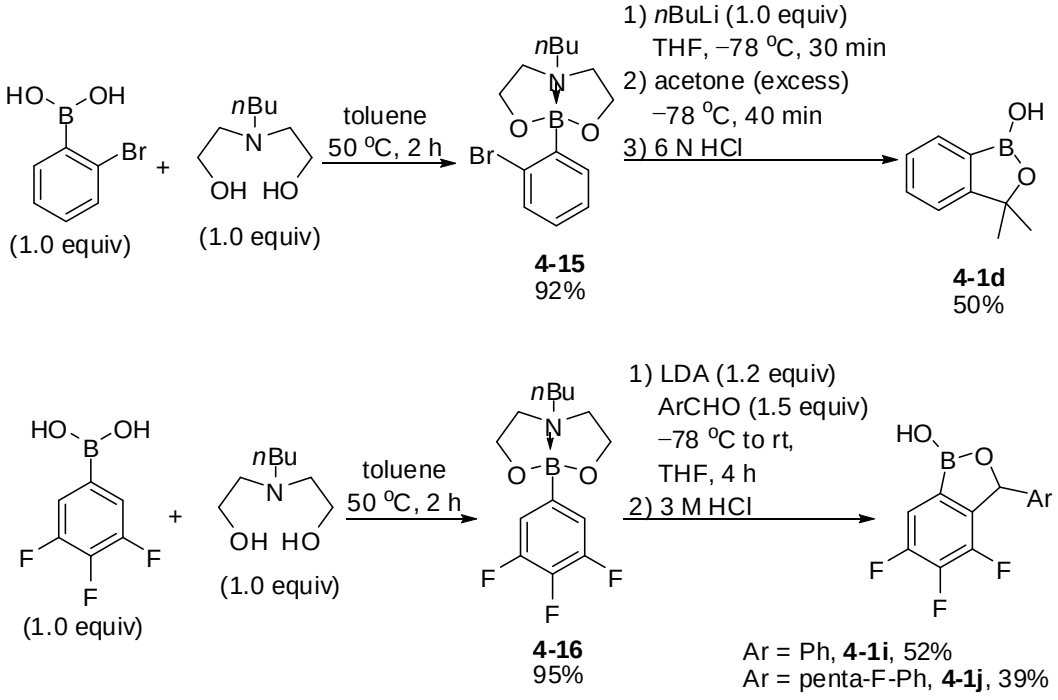


Figure 4-2: Boronic acid catalyst design for regioselective glycosylation

intermediate boronate **4-14** (**Figure 4-2**) from undergoing glycosylation reactions on the boroxole ring oxygen, further improved the yield of β(1→3) disaccharide **4-11**. This hypothesis was put forward by a literature precedent[9] and needs to be confirmed in the future by attempting to isolate side products of boroxole alkylation. Based on these observations, it can be envisioned that a boroxole **4-13** bearing an electron-donating group on the aromatic ring and two vicinal sterically hindered groups has a potential to show superior catalytic activity for regioselective glycosylation of fully unprotected sugars (**Figure 4-2**). The preparation of the newly designed boroxoles **4-13** and the evaluation of their catalytic activity will be performed in the near future.

4.3 Preparation of boroxole catalysts

One of the most common methods for synthesizing arylboronic acid involves chemoselective derivatization of simpler, free arylboronic acid or arylboronic



Scheme 4-7: Synthetic route to boroxole catalysts 4-1d, 4-1i, and 4-1j

ester.[7] As such it was considered as the strategy for the preparation of the boroxole catalysts **4-1d, 4-1i** and **4-1j**. Based on a previously reported procedure,[13] *N*-butyldiethanolamine was employed as a protective reagent for the boronic acid functionality. The resulting boronates **4-15** or **4-16** then underwent the *ortho* lithium/halogen or *ortho* lithium/hydrogen exchange followed by *in situ* trapping with the corresponding aldehydes and sequential hydrolysis to furnish the desired boroxoles **4-1d, 4-1i** and **4-1j** in synthetically useful yields (**Scheme 4-7**).

4.4 Conclusions

In summary, electron-deficient boroxoles, such as **4-1i** and **4-1j**, were found to exhibit excellent transient masking abilities for certain 1,2- and 1,3-diol frameworks in carbohydrates to achieve a regioselective glycosylation of the fully unprotected sugar **4-5** at the 3-OH position. This reaction was proposed to involve both the 4,6-boronate and the 3,4-boronate complexes as the intermediates. Based on this hypothesis, it was discovered later that boroxoles, such as **4-1d**, demonstrate moderate catalytic activity to promote the regioselective glycosylation of the silyl-protected 6-OH donor **4-10** at the 3-OH position by enhancing the nucleophilicity of 3-OH *via* a 3,4-boronate as the intermediate. Although at this stage the efficiency of our system is not as practical as that of Taylor's methodology in terms of yields and selectivities, it is probable that this issue could be addressed by developing more active catalysts. Preliminary analysis of electronic and steric effects of the boroxole core structure revealed that a boroxole **4-13** bearing an electron-donating group on the aromatic ring and two vicinal sterically hindered groups could potentially possess superior catalytic activity for the regioselective glycosylation of unprotected or partially protected sugars. Research on the preparation of the newly designed boroxoles of type **4-13** along with the evaluation of their catalytic activity for regioselective glycosylation is still in progress.

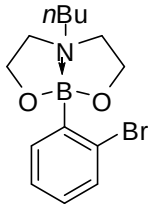
4.5 Experimental

4.5.1 General information

Unless otherwise stated, all reactions were performed under an argon atmosphere using flame-dried glassware. Toluene, THF and dichloromethane were treated using the Fisher Scientific-MBraun MB SPS* double-column solvent purification system prior to use. Acetonitrile and 1,2-dichloroethane were distilled from CaH_2. Et_2O was distilled from sodium with benzophenone as an indicator. Acetone was distilled from 4A molecular sieves. All commercially available aldehydes were purified by Kugelrohr distillation prior to use. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and was visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on Varian INOVA-400, MERCURY-400, INOVA-500, and VNMRS-500 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. ^1H NMR data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; sex, sextet; dd, doublet of doublets; td, triplet of doublets; ddd, doublet of doublet of doublets; m, multiplet.. High-resolution mass spectra (HRMS) were recorded by the University of Alberta mass spectrometry services laboratory using electron impact (EI) or electrospray ionization (ESI) techniques. Infrared spectra (IR) were obtained on a Nicolet Magna-IR with frequencies expressed in cm^{-1}. X-ray crystallographic analyses were performed using a Bruker P4/RA/SMART 1000 CCD diffractometer. Powdered 4A molecular sieves (<5 micron, Aldrich) were dried overnight in a vacuum oven (250 ^oC) prior to use.

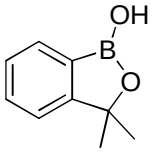
4.5.2 Preparation of boroxole catalysts (Scheme 4-7)

4.5.2.1 2-(2-Bromophenyl)-6-butyl-1,3,6,2-dioxazaborocane (4-15)



Compound **4-15** was made following a literature procedure (92% yield).[13] The characterization data for compound **4-15** matched those of a previous report.[13]

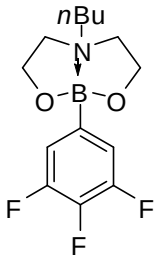
4.5.2.2 3,3-Dimethylbenzo[*c*][1,2]oxaborol-1(3*H*)-ol (4-1d)



To a solution of boronate **4-15** (326 mg, 1.00 mmol) in THF (4 mL) at –78 °C was added *n*BuLi solution (2.5 M in hexanes, 0.5 mL, 1.2 mmol) in a dropwise fashion. The solution was stirred at –78 °C for 30 minutes. Then acetone (1 mL) was slowly added and the resulting mixture was stirred at –78 °C for 40 minutes. HCl (6 M, 0.5 mL) was added to quench the reaction and the reaction mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:6) to give the title boroxole **4-1d** (80 mg, 50% yield) as a white solid. **^{1}H NMR** (500 MHz, DMSO-d_6 with one drop D_2O) δ 7.63 (d, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.28 (t, *J* = 7.2 Hz, 1H), 1.40 (s, 6H); **^{13}C NMR** (125 MHz, DMSO-d_6 with one drop D_2O) δ 161.9, 130.6, 130.3, 126.8, 120.4, 82.6, 29.0; **^{11}B NMR** (160 MHz, DMSO-d_6 with one drop D_2O) 31.5; **IR** (Microscope, cm^{-1}) 3357, 3066, 2975, 2927, 1609, 1481, 1453, 1420; **HRMS** (ESI) for $C_9H_{11}{}^{11}BNaO_2$: calcd. 185.0746; found

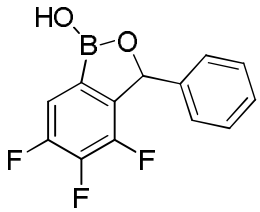
185.0745. The structure of this compound was also confirmed by X-ray crystallography.[14]

4.5.2.3 6-Butyl-2-(3,4,5-trifluorophenyl)-1,3,6,2-dioxazaborocane (4-16)



Compound **4-16** was made following a literature procedure (95% yield, white solid).[13] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.22-7.12 (m, 2H), 4.19-4.02 (m, 4H), 3.12-2.92 (m, 4H), 2.31-2.22 (m, 2H), 1.56-1.43 (m, 2H), 1.14 (sex, *J* = 7.4 Hz, 2H), 0.82 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.7, 139.1, 116.1, 63.0, 59.8, 57.4, 26.7, 20.0, 13.5; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –137.4 (dd, *J* = 19.9, 8.5 Hz, 2F), –163.5 (td, *J* = 20.0, 7.2 Hz, 1F); **^{11}B NMR** (128 MHz, $CDCl_3$) 8.2; **IR** (Microscope, cm^{-1}) 2972, 2958, 2936, 2873, 2855, 1609, 1582, 1525, 1469, 1459; **HRMS** (EI) for $C_{14}H_{19}{}^{11}BF_3NO_2$: calcd. 301.14609; found 301.14694.

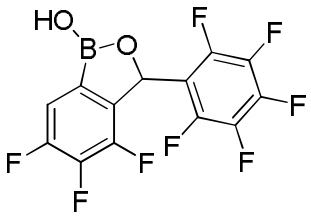
4.5.2.4 4,5,6-Trifluoro-3-phenylbenzo[*c*][1,2]oxaborol-1(3*H*)-ol (4-1i)



To a mixture of diisopropylamine (121 mg, 1.20 mmol) in THF (2 mL) at –78 °C was added *n*BuLi solution (2.5 M in hexanes, 0.5 mL, 1.2 mmol) in a dropwise fashion. The solution was stirred at –78 °C for 30 minutes. A solution of boronate **4-16** (301 mg, 1.00 mmol) in THF (10 mL) was then added dropwise and the resulting mixture was stirred at –78 °C for 30 minutes. Benzaldehyde (159 mg,

1.50 mmol) was added. The reaction mixture allowed to warm to room temperature and further stirred at room temperature for 4 hours. HCl (3 M, 0.5 mL) was added to quench the reaction and the reaction mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:8) to give the title boroxole **4-1i** (140 mg, 53% yield) as a white solid. **^{1}H NMR** (500 MHz, DMSO-d_6 with one drop D_2O) δ 7.59-7.53 (m, 1H), 7.36-7.28 (m, 3H), 7.23-7.17 (m, 2H), 6.31 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6 with one drop D_2O) δ 151.2, 145.4, 141.2, 139.4, 138.9, 129.08, 129.07, 127.2, 114.2, 79.6; **^{19}F NMR** (469 MHz, DMSO-d_6 with one drop D_2O) δ –134.1 (m, 1F), –139.8 (dd, *J* = 21.0, 5.3 Hz, 1F), –157.4 (dt, *J* = 20.3, 5.3 Hz, 1F); **^{11}B NMR** (160 MHz, DMSO-d_6 with one drop D_2O) 32.1; **IR** (Microscope, cm^{-1}) 3379, 3066, 3035, 1631, 1605, 1507, 1486, 1456; **HRMS** (EI) for $C_{13}H_7{}^{11}BF_3O_2$: calcd. 263.04913; found 263.04922.

4.5.2.5 4,5,6-Trifluoro-3-(perfluorophenyl)benzo[*c*][1,2]oxaborol-1(3*H*)-ol (4-1j)



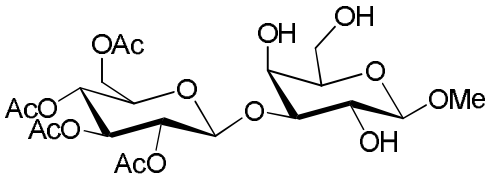
Compound **4-1j** was made following a procedure similar to that used for **4-1i** (39% yield, pale yellow solid). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 (t, *J* = 6.6 Hz, 1H), 6.64 (s, 1H), 4.82 (br s, 1H); **^{11}B NMR** (128 MHz, $CDCl_3$) 32.3; **IR** (Microscope, cm^{-1}) 3382, 3066, 1640, 1507, 1489, 1459; **HRMS** (EI) for $C_{13}H_3{}^{11}BF_8O_2$: calcd. 354.00984; found 354.00978.

4.5.3 Preparation of glycosyl donor and acceptor

Glycosyl donor **4-4**[15] and glycosyl acceptor **4-10**[16] were prepared following literature procedures. The characterization data for compounds **4-4** and **4-10** matched those of previous reports.[15,16]

4.5.4 Boronic acid mediated regioselective glycosylation

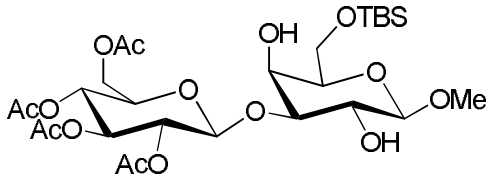
4.5.4.1 Methyl-3-O-(2',3',4',6'-tetra-O-acetyl-*β*-*D*-glucopyranosyl)-*α*-*D*-galactopyranoside (4-6)



A mixture of thioglycoside **4-4** (44 mg, 0.1 mmol), unprotected methyl hexopyranoside **4-5** (19 mg, 0.1 mmol), boronic acid **4-1** (0.1 mmol), 4A molecular sieves (200 mg) in a mixed solvent of DCE and CH_3CN (1:1, 5 mL) was stirred at room temperature for 16 hours. NIS (46 mg, 0.2 mmol) was then added to the reaction mixture at room temperature. The resulting mixture was cooled to –30 ^oC and TMSOTf (5 mg, 0.02 mmol) was added. The reaction mixture was stirred at –30 ^oC for 2 hour, and treated with aqueous $Na_2S_2O_3$ solution (10%, five drops) to quench the reaction. The resulting mixture was filtered through Celite, and the filtrate was treated with $NaBO_3 \cdot 4H_2O$ (25 mg, 1.6 mmol) and H_2O (3 mL) under stirring at room temperature for 1 hour. The resulting mixture was washed with aqueous $NaHCO_3$ solution (5%, 20 mL), water (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/MeOH = 60:1) to give the disaccharide **4-6** as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.24 (app t, *J* = 9.6 Hz, 1H, *H*-3'), 5.10 (app t, *J* = 9.5 Hz, 1H, *H*-4'), 5.04 (dd, *J* = 9.7, 7.9 Hz, 1H, *H*-2'), 4.91 (d, *J* = 7.9 Hz, 1H, *H*-1'), 4.26 (dd,

J = 12.3, 2.9 Hz, 1H, *H*-6a'), 4.17 (d, *J* = 7.5 Hz, 1H, *H*-1), 4.14 (dd, *J* = 12.3, 6.0 Hz, 1H, *H*-6b'), 4.05 (dd, *J* = 3.1, 0.9 Hz, 1H, *H*-4), 3.92 (dd, *J* = 11.6, 6.6 Hz, 1H, *H*-6a), 3.85 (dd, *J* = 11.7, 4.7 Hz, 1H, *H*-6b), 3.75 (ddd, *J* = 9.7, 7.5, 2.4 Hz, 1H, *H*-2), 3.73 (ddd, *J* = 9.7, 6.0, 2.9 Hz, 1H, *H*-5'), 3.60 (dd, *J* = 9.7, 3.1 Hz, 1H, *H*-3), 3.53 (s, 3H, OCH_3), 3.49 (ddd, *J* = 6.6, 4.7, 0.9 Hz, 1H, *H*-5), 2.70 (br s, 1H, C_6-O*H*), 2.54 (dd, *J* = 2.4, 1.6 Hz, 1H, C_4-O*H*), 2.33 (d, *J* = 2.4, 1H, C_2-O*H*), 2.09 (s, 3H, OCOCH_3), 2.05 (s, 3H, OCOCH_3), 2.03 (s, 3H, OCOCH_3), 2.02 (s, 3H, OCOCH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.7, 170.4, 170.0, 169.6, 101.6, 99.5, 82.5, 73.9, 72.5, 72.4, 72.0, 70.4, 69.5, 68.7, 62.7, 62.2, 56.9, 26.0, 20.9, 20.8, 20.7; **IR** (Microscope, cm^{-1}) 3540, 2928, 2857, 1748, 1443; **HRMS** (ESI) for $C_{21}H_{32}NaO_{15}$: calcd. 547.1639; found 547.1636.

4.5.4.2 Methyl-6-*O*-tert-butyldimethylsilyl-3-O-(2',3',4',6'-tetra-O-acetyl-*β*-*D*-glucopyranosyl)-*α*-*D*-galactopyranoside (4-11)



To a solution of thioglycoside **4-4** (44 mg, 0.1 mmol), glycosyl acceptor **4-10** (31 mg, 0.1 mmol), boronic acid (0.02 mmol), NIS (46 mg, 0.2 mmol) in a mixed solvent DCE/CH_3CN (1:1, 5 mL) at 0 ^oC was added TMSOTf (5 mg, 0.02 mmol). The resulting mixture was stirred at 0 ^oC for 6 hours. Aqueous $Na_2S_2O_3$ solution (10%, five drops) was added to quench the reaction. Then, $NaBO_3$·$4H_2O$ (25 mg, 1.6 mmol) and H_2O (3 mL) was added and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was washed with aqueous $NaHCO_3$ solution (5%, 20 mL), water (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/MeOH = 80:1) to give the disaccharide **4-11**

in pure form. The characterization data for compound **4-11** matched those of a previous report.[10]

4.6 References

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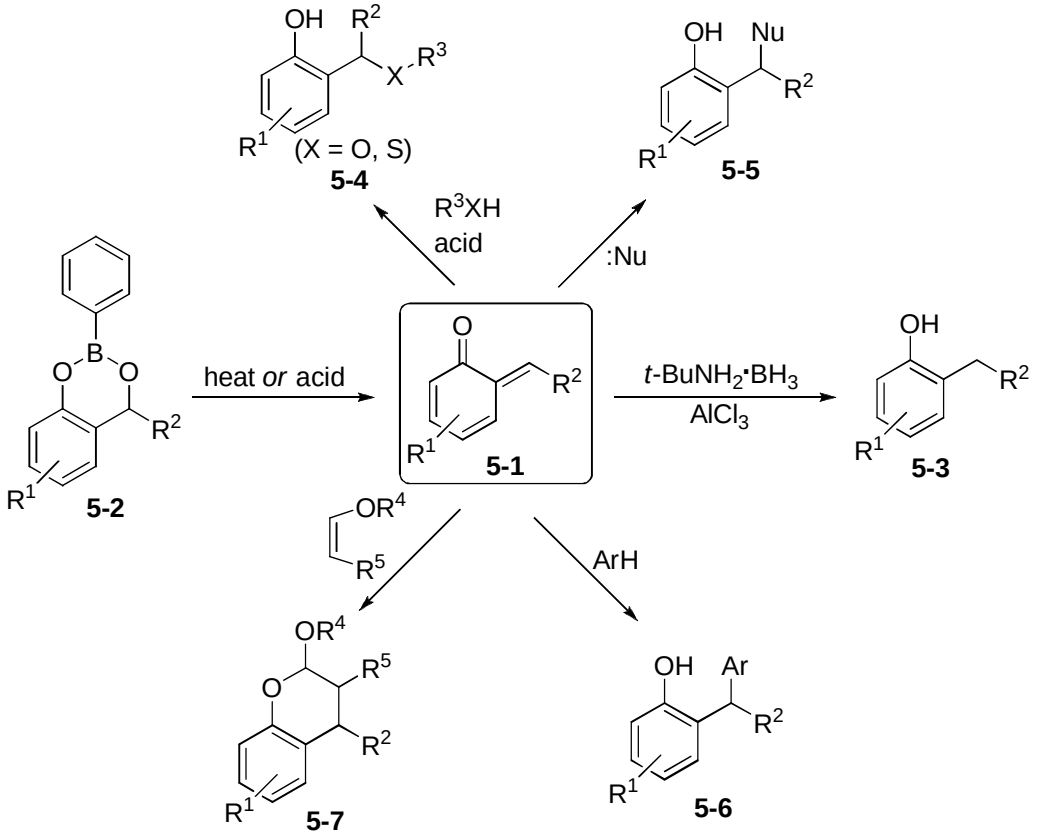
Chapter 5

Boronic Acids as Stoichiometric Promoters in the Nagata Reaction

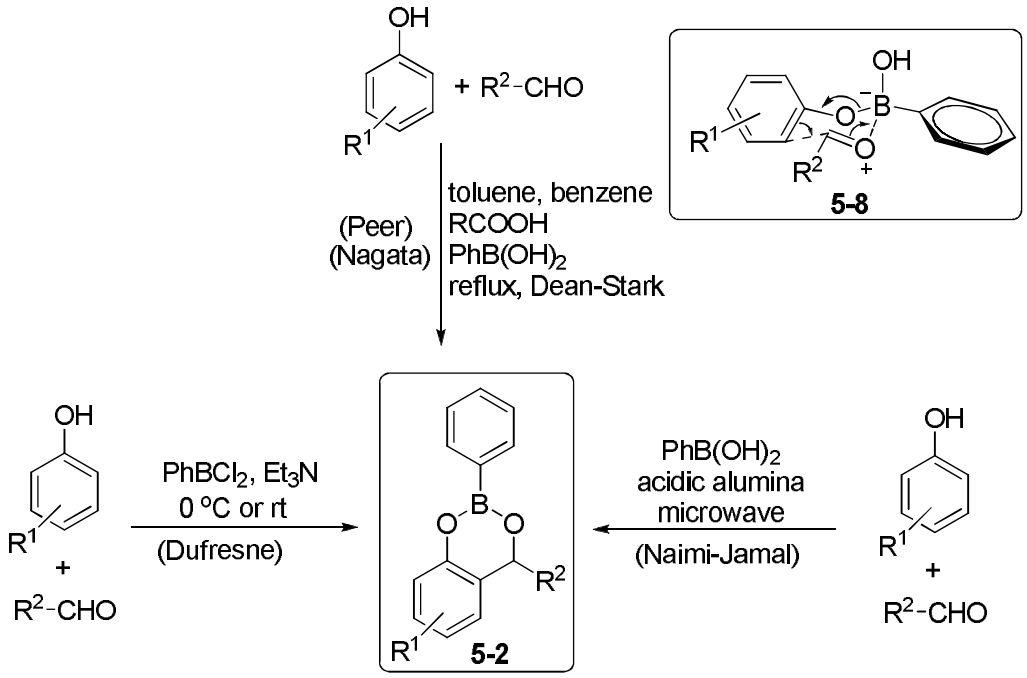
5.1 Introduction

Ortho-Quinone methides **5-1** (**Scheme 5-1**) are versatile motifs in organic synthesis, as they are known to be very reactive intermediates with applications in the total synthesis of natural products.[1] Following their generation, *ortho*-quinone methides **5-1** can undergo a wide variety of chemical transformations. For instance, they can be reduced to give *o*-alkylphenols **5-3**[2b] or they can be trapped by alcohol, thiol and carbon nucleophiles to generate phenol derivatives **5-4** and **5-5**.[2a,b] A Friedel-Crafts reaction between **5-1** and aromatic compounds furnishes



Scheme 5-1: 2-Aryl-1,3,2-aryldioxaborin 5-2 as versatile synthetic intermediates

the corresponding phenols **5-6**.[2a] Moreover, intermediates **5-1** can also be fused with different dienophiles inter- and intramolecularly to deliver the hetero-Diels-Alder cycloadducts **5-7**.[2b] A major issue with *ortho*-quinone methides **5-1** is their high reactivity, therefore, they are usually produced from a stable precursor *in situ* and used directly in the synthesis. 2-Aryl-1,3,2-aryldioxaborins **5-2** are very stable at room temperature, however, they can generate *ortho*-quinone methides **5-1** under thermolytic or acidic conditions.[2]



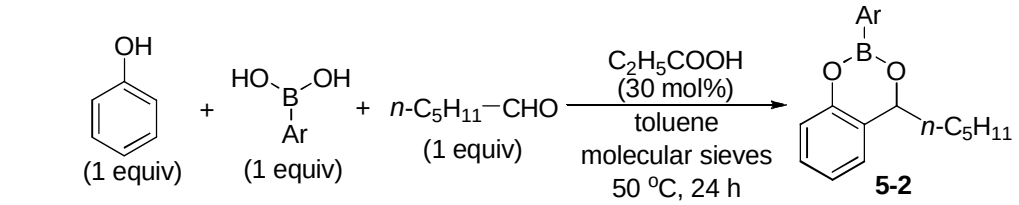
Scheme 5-2: Several reported approaches to 2-phenyl-1,3,2-aryldioxaborin 5-2

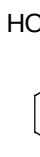
Surprisingly, only a few approaches for the preparation of 2-aryl-1,3,2-aryldioxaborins **5-2** have been reported until now (**Scheme 5-2**). In all these developed methods, the phenylboronic acid was employed as a stoichiometric promoter to mediate the *ortho*-hydroxyalkylation of phenols with aldehydes. The process was presumed to involve the formation of intermediate **5-8**, which then undergoes a formal 3,3-rearrangement to furnish the desired

product 2-aryl-1,3,2-aryldioxaborins **5-2** (**Scheme 5-2**). The Peer group synthesized **5-2** from a three-component condensation of phenylboronic acid, phenol and paraformaldehyde by employing a carboxylic acid as the catalyst under reflux in benzene.[3] The Nagata group later modified the reaction conditions (refluxing toluene) to extend the substrate scope to various aldehydes.[4] The harsh reaction conditions, however, hampered further applications to sensitive, polymerizable aldehydes. Dufresne and co-workers developed a novel dichlorophenylborane as a phenylboronic acid surrogate to perform this reaction smoothly at 0 ^{o}C or room temperature.[5] The high cost and sensitivity to humidity of this surrogate limited its general application. Recently, Naimi-Jamal and co-workers reported that microwave irradiation can promote the transformation to **5-2** on the surface of acidic alumina, which results in environmentally harmful acidic alumina waste.[6] An effective approach to synthesize **5-2** under simple and practical conditions at room temperature was envisioned. As part of our program aimed at exploring the use of boronic acids as catalysts and promoters for amidation,[7a] cycloadditions of unsaturated carboxylic acids,[7b,7c] 1,3-transpositions of allylic and propargylic alcohols,[7d] and cationic cyclizations of allylic alcohols,[7e] an efficient construction of 2-aryl-1,3,2- aryldioxaborin (**2**) catalyzed by $ZrCl_4$ under mild ambient conditions will be introduced in this chapter.[7f]

5.2 Optimization of reaction conditions

Initially, different commercially available arylboronic acids were screened under a modified procedure with the use of 4A molecular sieves instead of a Dean-Stark apparatus for continuous removal of water from the reaction system. Interestingly, electron-deficient 3,5-bis(trifluoromethyl)phenylboronic acid **5-9** was identified as the most active one amongst over 70 boronic acids (**Scheme 5-3**). It reacted with phenol and hexanal to deliver the desired aryldioxaborin **5-2** in 10% yield promoted by propionic acid at 50 ^{o}C with 4A molecular sieves.





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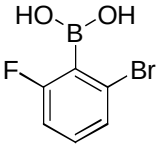

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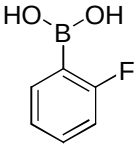

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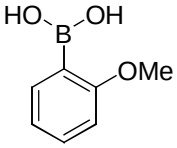

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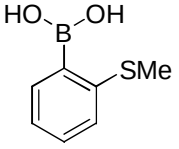

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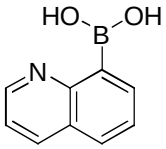

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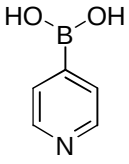

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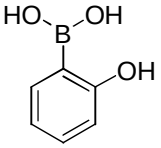

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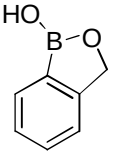

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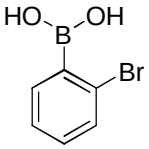

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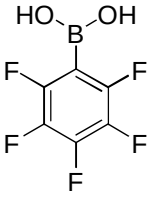

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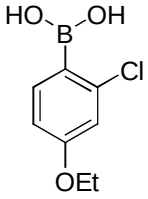

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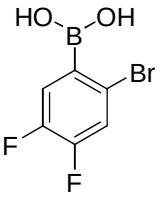

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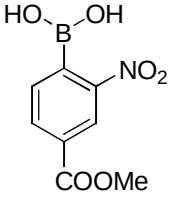

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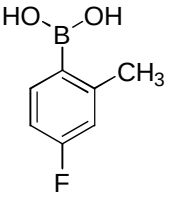

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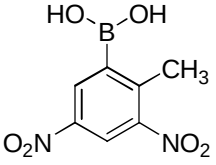

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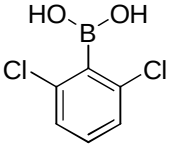

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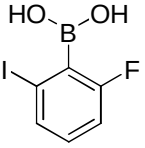

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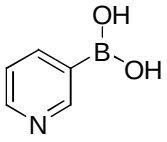

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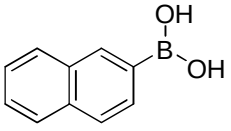

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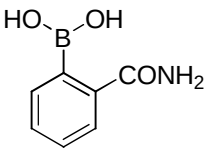

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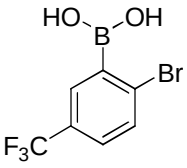

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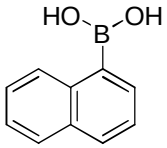

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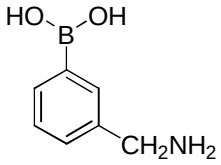

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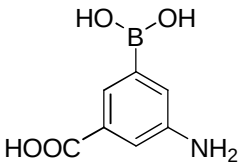

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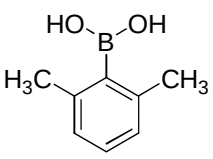

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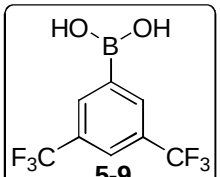

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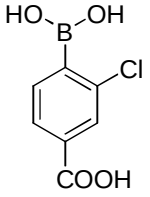

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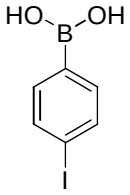

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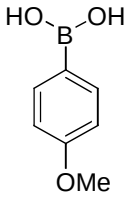

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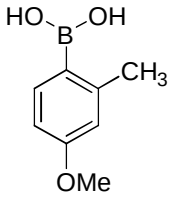

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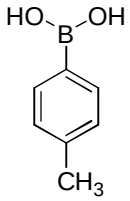

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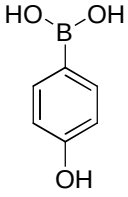

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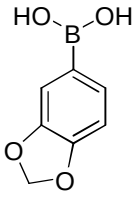

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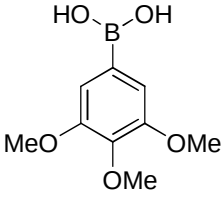

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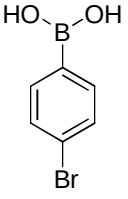

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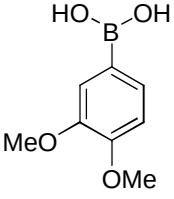

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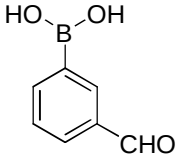

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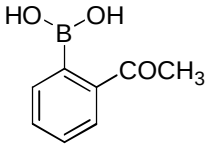

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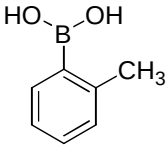

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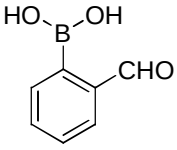

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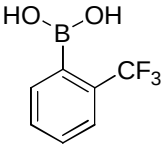

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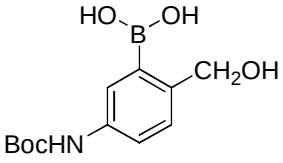

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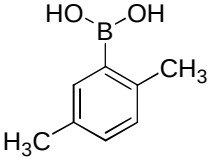

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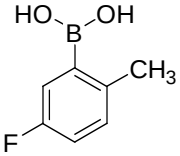

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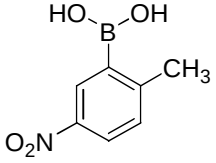

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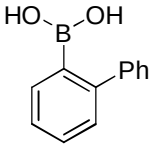

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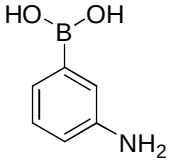

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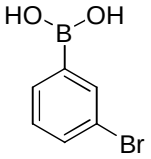

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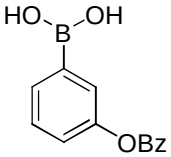

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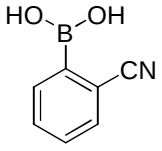

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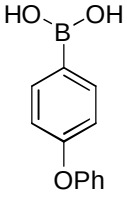

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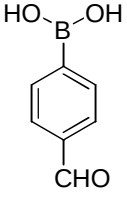

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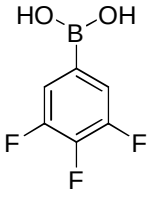

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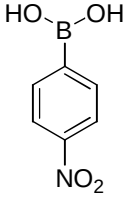

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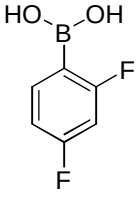

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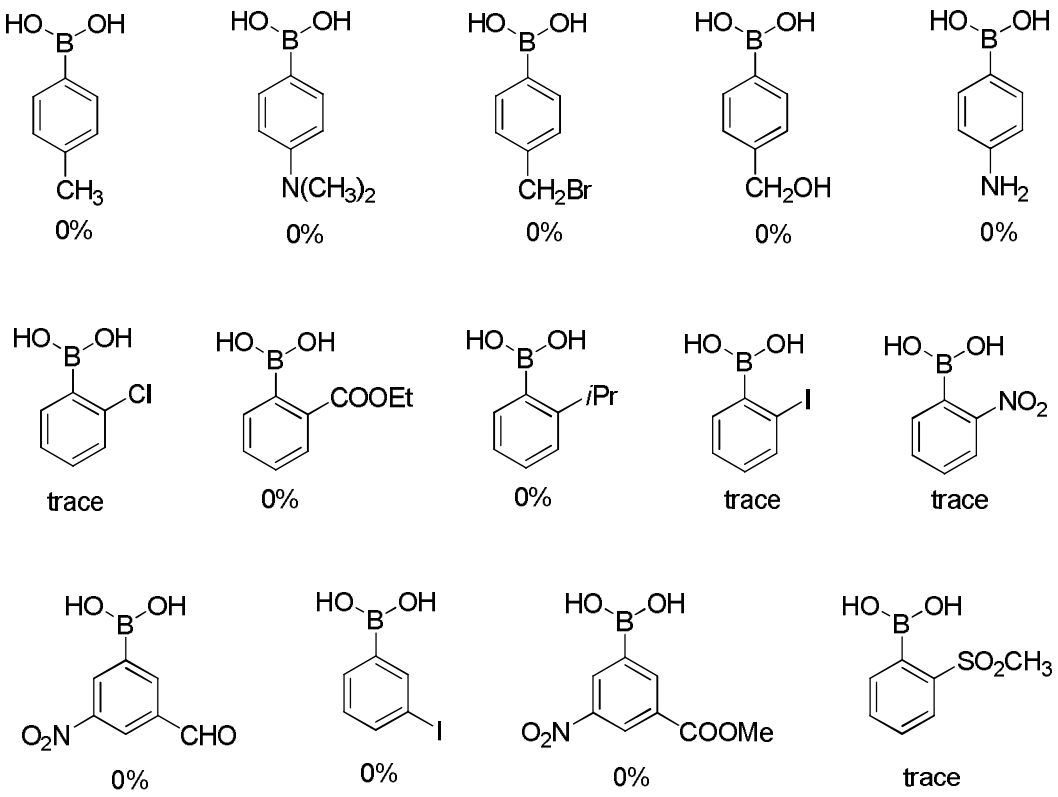
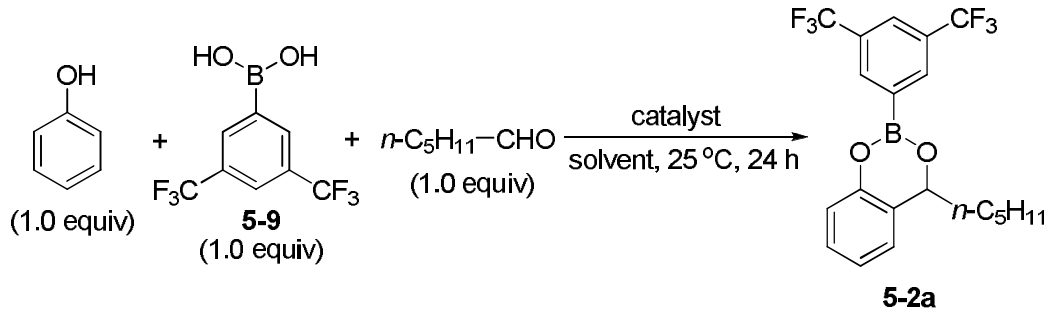


Scheme 5-3: Survey of arylboronic acids in a model Nagata reaction

Inspired by this intriguing result, we examined different reaction conditions. Several common dehydrating additives or anhydrides were selected to scavenge the water produced from the condensation reaction (entries 1–5, **Table 5-1**), and $MgSO_4$ led to the best yield of product **5-2a** at room temperature. Unfortunately, the reaction was not Brønsted acid dependent so the reaction yield could not be improved by varying the Brønsted acid (entries 6–8, **Table 5-1**). It was assumed that the reaction mechanism involves a formal 3,3-rearrangement pathway (**A**, **Figure 5-1**),[4] and Lewis acid catalyzed formal 3,3-rearrangements are well documented in the literature.[8] In the event, $Cu(OTf)_2$ was found to improve the reaction yield (entry 9, **Table 5-1**), and dichloromethane was found to give the best result after further screening of various solvents (entries 10–20, **Table 5-1**).



Entry	Additive	Catalyst[a]	Solvent	Yield[b] (%)
1	4A molecular sieves	C_2H_5COOH	toluene	0
2	Na_2SO_4 (5.0 equiv)	C_2H_5COOH	toluene	trace
3	$MgSO_4$ (5.0 equiv)	C_2H_5COOH	toluene	10
4	Ac_2O (1.0 equiv)	C_2H_5COOH	toluene	5
5	Tf_2O (1.0 equiv)	C_2H_5COOH	toluene	8
6	$MgSO_4$ (5.0 equiv)	CH_3COOH	toluene	trace
7	$MgSO_4$ (5.0 equiv)	CCl_3COOH	toluene	13
8	$MgSO_4$ (5.0 equiv)	CF_3COOH	toluene	nd[c]
9	$MgSO_4$ (5.0 equiv)	$Cu(OTf)_2$	toluene	30
10	**$MgSO_4$ (5.0 equiv)**	**$Cu(OTf)_2$**	**CH_2Cl_2**	**33**
11	$MgSO_4$ (5.0 equiv)	$Cu(OTf)_2$	MeOH	0
12	$MgSO_4$ (5.0 equiv)	$Cu(OTf)_2$	CH_3CN	0
13	$MgSO_4$ (5.0 equiv)	$Cu(OTf)_2$	THF	10
14	$MgSO_4$ (5.0 equiv)	$Cu(OTf)_2$	acetone	0
15	$MgSO_4$ (5.0 equiv)	$Cu(OTf)_2$	EtOH	0
16	$MgSO_4$ (5.0 equiv)	$Cu(OTf)_2$	DMF	0
17	$MgSO_4$ (5.0 equiv)	$Cu(OTf)_2$	EtOAc	trace
18	$MgSO_4$ (5.0 equiv)	$Cu(OTf)_2$	Et_2O	5
19	$MgSO_4$ (5.0 equiv)	$Cu(OTf)_2$	DCE	20
20	$MgSO_4$ (5.0 equiv)	$Cu(OTf)_2$	1,4-dioxane	3

[a]For Brønsted acids, 30 mol% catalyst loading was used; for Lewis acids, 5 mol% catalyst loading was used. [b]Isolated yields of product purified by recrystallization of crude mixture from diethyl ether/*n*-pentane (1:3). [c]A complex mixture was obtained.

Table 5-1: Optimization of reaction conditions in a model Nagata reaction

Furthermore, different Lewis acids were tested to further improve the reaction rate at room temperature (entries 1–17, **Table 5-2**). To our satisfaction, $ZrCl_4$ (5 mol%) gave the best yield (entry 11, **Table 5-2**). In addition, a re-examination of dehydrating agents and solvents was performed to ensure the optimal combination [$ZrCl_4$ (5 mol%), $MgSO_4$ (5.0 equiv), and DCM] (entries 18–22, **Table 5-2**). It was also found that excess hexanal (3.0 equiv) was essential to drive the reaction to completion (entry 23, **Table 5-2**). Control experiments showed that no desired product was formed in the absence of Lewis acid or **5-9** as the reactant. The detailed mechanism towards how the Lewis acid catalyzes the formation of 2-aryl-1,3,2-aryldioxaborins **5-2** is unclear. This reaction is proposed to proceed through a closed six-membered chairlike transition state **B** (**Figure 5-1**), which is based on our previous mechanistic studies of Lewis acid-catalyzed allylborations.[9] In this transition state, the electron- deficient aryl substituent of **5-9** combined with Lewis acid coordination renders the boron atom more electrophilic to further favor aldehyde activation.

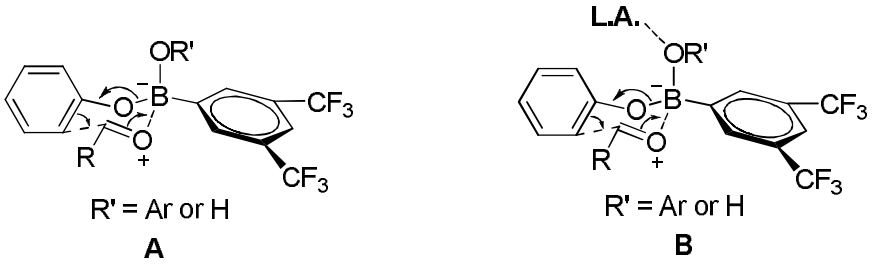
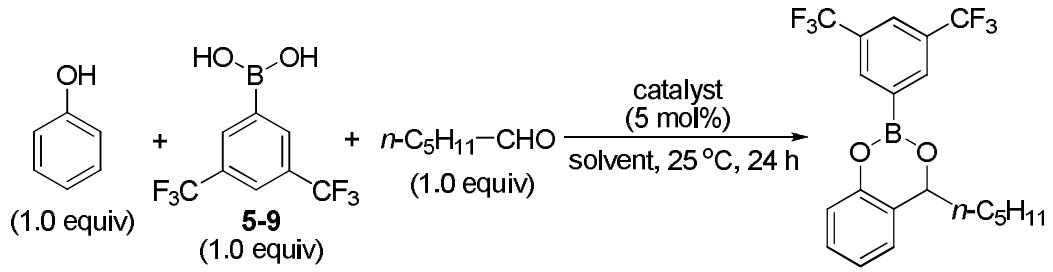


Figure 5-1: Proposed intermediates A (left, without Lewis acid catalysis) and B (right, with Lewis acid catalysis) for the formation of 2-aryl-1,3,2-aryldioxaborins 5-2.



5-2a

Entry	Additive	Catalyst	Solvent	Yield[a] (%)
1	$MgSO_4$ (5.0 equiv)	$Cu(OTf)_2$	CH_2Cl_2	33
2	$MgSO_4$ (5.0 equiv)	$Sc(OTf)_3$	CH_2Cl_2	25
3	$MgSO_4$ (5.0 equiv)	$Al(OTf)_3$	CH_2Cl_2	17
4	$MgSO_4$ (5.0 equiv)	$Mg(OTf)_2$	CH_2Cl_2	19
5	$MgSO_4$ (5.0 equiv)	AgOTf	CH_2Cl_2	8
6	$MgSO_4$ (5.0 equiv)	$Eu(OTf)_3$	CH_2Cl_2	37
7	$MgSO_4$ (5.0 equiv)	$Yb(OTf)_3$	CH_2Cl_2	42
8	$MgSO_4$ (5.0 equiv)	$ZnBr_2$	CH_2Cl_2	trace
9	$MgSO_4$ (5.0 equiv)	$SnCl_2$	CH_2Cl_2	6
10	$MgSO_4$ (5.0 equiv)	$FeCl_3$	CH_2Cl_2	13
11	**$MgSO_4$ (5.0 equiv)**	**$ZrCl_4$**	**CH_2Cl_2**	**53**
12	$MgSO_4$ (5.0 equiv)	$Ce(OTf)_3$	CH_2Cl_2	11
13	$MgSO_4$ (5.0 equiv)	CuCl	CH_2Cl_2	23
14	$MgSO_4$ (5.0 equiv)	$Cu(OAc)_2$	CH_2Cl_2	23
15	$MgSO_4$ (5.0 equiv)	$Zn(OAc)_2$	CH_2Cl_2	31
16	$MgSO_4$ (5.0 equiv)	$CrCl_2$	CH_2Cl_2	5
17	$MgSO_4$ (5.0 equiv)	CuBr	CH_2Cl_2	13
18	$MgSO_4$ (5.0 equiv)	$ZrCl_4$	toluene	48
19	$MgSO_4$ (5.0 equiv)	$ZrCl_4$	Et_2O	trace
20	$MgSO_4$ (5.0 equiv)	$ZrCl_4$	EtOAc	7
21	4A molecular sieves	$ZrCl_4$	CH_2Cl_2	trace
22	Na_2SO_4 (5.0 equiv)	$ZrCl_4$	CH_2Cl_2	31
23[b]	**$MgSO_4$ (5.0 equiv)**	**$ZrCl_4$**	**CH_2Cl_2**	**60**

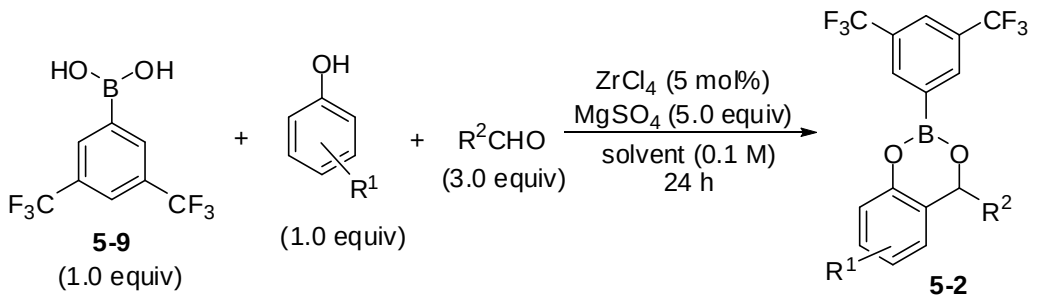
[a]Isolated yields of product purified by recrystallization of crude mixture from diethyl ether/*n*-pentane (1:3). [b]Hexanal (3.0 equiv) was used.

Table 5-2: Optimization of Lewis Acids in a model Nagata reaction

5.3 Substrate scope for $ZrCl_4$ catalyzed Nagata reaction

With the optimized conditions in hand, more synthetically useful phenols and aldehydes were investigated (**Table 5-3**). Aliphatic, and electron-poor aromatic aldehydes are tolerated (entries 1–3 and entries 5–8, **Table 5-3**). Linear aldehydes proceeded to react smoothly under optimized conditions (entries 1, 2, **Table 5-3**). For the more hindered aldehydes, it was necessary to use 1,2-dichloroethane as a solvent at elevated temperature (50 ^{o}C) (entry 3, **Table 5-3**). No desired product was observed with pivalaldehyde neither in the crude reaction mixture nor after work up (entry 4, **Table 5-3**). This lack of reactivity is likely a result of steric hindrance. Compared to aliphatic aldehydes, benzaldehyde gave the desired product **5-2e** in moderate yield even at 50 ^{o}C (entry 5, **Table 5-3**). It was found that the electronic properties of substituents played an important role for the reactivity. Thus, electron-withdrawing aromatic aldehydes delivered products **5-2f**–**5-2h** in good yields under optimized conditions (entries 6–8, **Table 5-3**), and electron-donating aromatic aldehydes showed lower reactivity (entry 9).

We next examined the substrate scope of this methodology with a panel of substituted phenols in the presence of hydrocinnamaldehyde as a model aldehyde. 1-Naphthol and 2-naphthol gave the aryldioxaborins **5-2j** and **5-2k** in good yields (entry 10 and 11, **Table 5-3**). Interestingly, only one regioisomer was obtained with 2-naphthol both in crude reaction mixture and after work up, which revealed that the 1-position of 2-naphthol is more reactive than the 3-position. The reactivity of substituted phenols was found to be dependent on the electronic properties of the substituents. Electron-rich phenols gave the desired aryldioxaborins **5-2l**–**5-2o** in excellent yields (entries 12–15, **Table 5-3**). An example of halogen (Cl) substituted phenol gave the desired product **5-2p** in good yield under elevated temperature (entry 16, **Table 5-3**). The electron-poor 4-nitro-phenol, however, showed no reactivity (entry 17, **Table 5-3**).



Entry	R^1 =	R^2 =	Solvent	Temp (^oC)	Product	Yield[a] (%)
1	H	*n*-C_5H_{11}	CH_2Cl_2	25	**5-2a**	60
2	H	$PhCH_2CH_2$	CH_2Cl_2	25	**5-2b**	68
3	H	$(C_2H_5)_2CH$	DCE	50	**5-2c**	63
4	H	$(CH_3)_3C$	DCE	50	**5-2d**	0
5	H	Ph	DCE	50	**5-2e**	36
6	H	2-$NO_2C_6H_4$	CH_2Cl_2	25	**5-2f**	76
7	H	3-$NO_2C_6H_4$	CH_2Cl_2	25	**5-2g**	58
8	H	4-$NO_2C_6H_4$	CH_2Cl_2	25	**5-2h**	71
9	H	4-$MeOC_6H_4$	DCE	50	**5-2i**	trace
10	Naph[b]	$PhCH_2CH_2$	CH_2Cl_2	25	**5-2j**	80
11	Naph[c]	$PhCH_2CH_2$	CH_2Cl_2	25	**5-2k**	75
12	2-CH_3	$PhCH_2CH_2$	CH_2Cl_2	25	**5-2l**	70
13	4-CH_3	$PhCH_2CH_2$	CH_2Cl_2	25	**5-2m**	78
14	2-OMe	$PhCH_2CH_2$	CH_2Cl_2	25	**5-2n**	83
15	4-OMe	$PhCH_2CH_2$	CH_2Cl_2	25	**5-2o**	87
16	4-Cl	$PhCH_2CH_2$	DCE	50	**5-2p**	53
17	4-NO_2	$PhCH_2CH_2$	DCE	50	**5-2q**	0

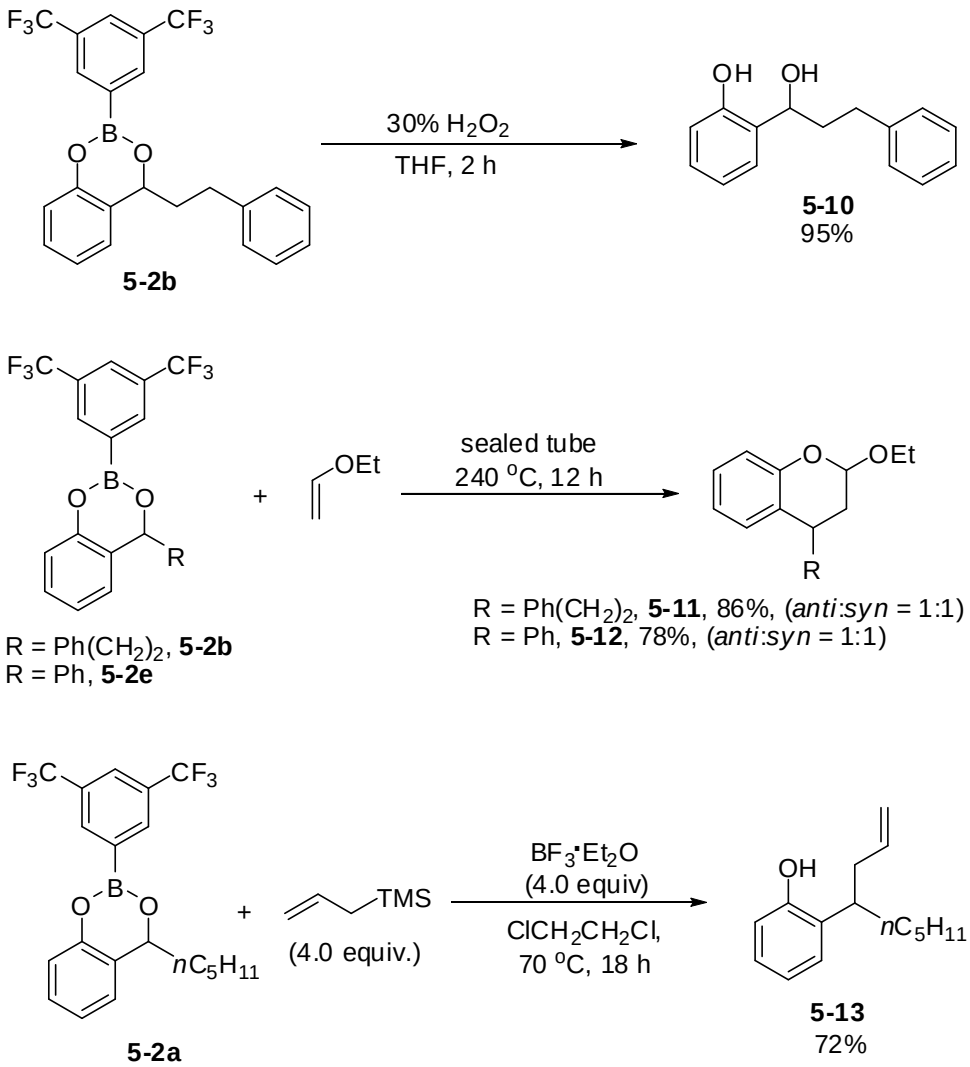
[a]Isolated yields of product purified by recrystallization of crude mixture from diethyl ether/*n*-pentane (1:3). [b]Substituted phenol: 1-naphthol. [c]Substituted phenol: 2-naphthol.

Table 5-3: Substrate scope studies for $ZrCl_4$-catalyzed three-component condensation

Although the mechanism of this new catalytic process remains to be elucidated, the substrate scope hinted that the electronic properties of substituents have a large impact on the reactivity of all three reactants. The electron-withdrawing CF_3 groups make boronic acid **3-9** more acidic, thus favoring the formation of six-membered chair-like transition state **B** (**Figure 5-1**). The improved nucleophilicity of the phenols with electron-donating groups and the increased electrophilicity of the aldehydes decorated with electron-withdrawing groups combine to favor the formal 3,3-rearrangement process.

5.4 Synthetic applications of 2-aryl-1,3,2-aryldioxaborins 5-2

Further applications of 2-aryl-1,3,2-aryldioxaborins **5-2** to the preparation of more synthetically and biologically useful derivatives are shown in **Scheme 5-4**. The substituted saligenol **5-10** was obtained by hydrolytic oxidation (30% H_2O_2) of dioxaborin **5-2b** in excellent yield.[2] Thermolysis of the dioxaborin **5-2b** or **5-2e** gave the corresponding *ortho*-quinone methides **5-1** as the intermediates, which were trapped by ethyl vinyl ether to afford the desired 2-ethoxy chromans **5-11** or **5-12** in good yields.[2] Finally, Michael addition of allyl trimethylsilane to the *ortho*-quinone methide generated *in situ* from dioxaborin **5-2a** in the presence of boron trifluoride etherate at 70 ^{o}C gave the desired 2-substituted phenol **5-13** in good yield.[2]



Scheme 5-4: Synthetic applications of 2-aryl-1,3,2-aryldioxaborins 5-2

5.5 Conclusions

In summary, an efficient $ZrCl_4$ catalyzed *ortho*-hydroxyalkylation of phenols with aldehydes promoted by 3,5-bis(trifluoromethyl)phenyl boronic acid **5-9**, leading to the formation of 2-aryl-1,3,2-aryldioxaborins **5-2** was investigated and optimized. The reaction afforded the desired aryldioxaborins **5-2** in good to excellent yields under mild conditions at room temperature. The electron-deficient boronic acid promoter **5-9** was essential. Electron-rich phenols react faster, and both alkyl and aryl aldehydes are suitable substrates. Although the detailed

mechanism of the Lewis acid catalyzed formation of **5-2** is not clear until now, this reaction was proposed to proceed through a formal 3,3-rearrangement pathway *via* a closed six-membered chair-like transition state **B** (**Figure 5-1**). In this transition state, the Lewis acid and the electron-deficient boronic acid **5-9** activates the aldehyde in a similar fashion to our previous reported Lewis acid-catalyzed allylboration.[9] The resulting aryldioxaborins **5-2** can be elaborated to produce synthetically useful substituted saligenols, 2-ethoxy chromans and 2-substituted phenols.

5.6 Experimental

5.6.1 General information

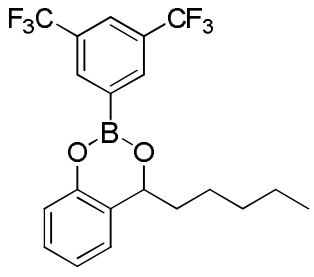
Unless otherwise stated, all reactions were performed under an argon atmosphere using flame-dried glassware. Toluene, acetonitrile, 1,2-dichloroethane and dichloromethane were distilled from CaH_2. THF and Et_2O were distilled from sodium with benzophenone as an indicator. Acetone was distilled from 4 Å molecular sieves. Anhydrous DMF and absolute EtOH were commercially available. All commercially available aldehydes were purified by Kugelrohr distillation prior to use. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and was visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on Varian INOVA-400 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. ^1H NMR data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet. High-resolution mass spectra (HRMS) were recorded by the University of Alberta mass spectrometry services laboratory using electron impact (EI) technique. Infrared spectra (IR) were obtained on a Nicolet Magna-IR with frequencies expressed in cm^{-1}.

Powdered 4A molecular sieves (<5 micron, Aldrich) were dried overnight in a vacuum oven (138 ^{o}C) prior to use. 2-Nitrophenylboronic acid was made following a literature procedure.[10] 2-Iodophenylboronic acid was prepared based on previous reported literature by our group.[7a] The other substituted arylboronic acids were obtained from commercial sources.

5.6.2 General procedure

A mixture of 3,5-bis(trifluoromethyl)phenylboronic acid (258 mg, 1.00 mmol), substituted phenol (1.0 mmol), aldehyde (3.0 mmol), $MgSO_4$ (600 mg, 5.00 mmol) and $ZrCl_4$ (12 mg, 0.05 mmol) in dichloromethane (10 mL) or 1,2-dichloroethane (10 mL) was stirred at 25 ^{o}C or 50 ^{o}C for 24 hours. The reaction mixture was filtered to remove $MgSO_4$. The filtrate was diluted with dichloromethane (30 mL) and washed with H_2O (30 mL). The aqueous phase was further extracted with dichloromethane (2 × 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was recrystallized from diethyl ether/*n*-pentane (1:3) to afford the title 2-aryl-1,3,2-aryldioxaborin **5-2** in pure form.

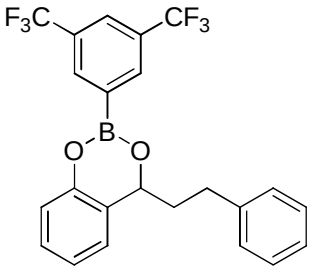
5.6.2.1 2-(3,5-Bis(trifluoromethyl)phenyl)-4-pentyl-4*H*-benzo[*d*][1,3,2] dioxaborinine (5-2a, Table 5-3)



The title compound was prepared using the general procedure for $ZrCl_4$-catalyzed formation of 2-aryl-1,3,2-aryldioxaborins. The solvent was dichloromethane and the reaction temperature was 25 ^{o}C (60% yield, white solid). **^{1}H NMR** (400 MHz,

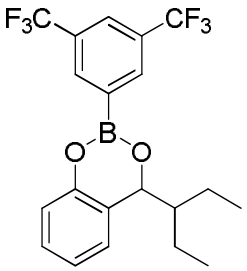
$CDCl_3$) δ 8.40 (s, 2H), 8.00 (s, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.15-7.08 (m, 2H), 7.06 (d, *J* = 7.6 Hz, 1H), 5.33 (dd, *J* = 7.2, 4.2 Hz, 1H), 2.02-1.81 (m, 2H), 1.60-1.44 (m, 2H), 1.42-1.26 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.4, 134.2, 131.0 (q, J_{C-F} = 32.8 Hz), 128.9, 126.0, 125.5, 124.9, 123.7, 123.6 (q, J_{C-F} = 272.9 Hz), 118.0, 73.6, 39.4, 31.6, 23.9, 22.6, 14.0; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 26.4; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –63.3; **IR** (Microscope, cm^{-1}) 3053, 2956, 2935, 2861, 1618, 1590; **HRMS** (EI) for $C_{20}H_{19}BF_6O_2$: calcd. 416.13824; found 416.13754.

5.6.2.2 2-(3,5-Bis(trifluoromethyl)phenyl)-4-phenethyl-4*H*-benzo[*d*][1,3,2] dioxaborinine (5-2b, Table 5-3)



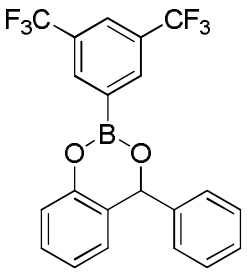
The title compound was prepared using the general procedure for $ZrCl_4$-catalyzed formation of 2-aryl-1,3,2-aryldioxaborins. The solvent was dichloromethane and the reaction temperature was 25 ^oC (68% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (s, 2H), 8.03 (s, 1H), 7.34-7.06 (m, 9H), 5.39 (dd, *J* = 7.5, 3.7 Hz, 1H), 2.94-2.82 (m, 2H), 2.42-2.32 (m, 1H), 2.30-2.18 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.4, 141.0, 134.2, 131.0, 129.0, 128.5, 128.4, 126.1, 125.5, 125.4, 124.9, 123.8, 123.6, 118.1, 72.7, 40.6, 30.6; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 26.9; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –63.2; **IR** (Microscope, cm^{-1}) 3088, 3063, 3031, 2964, 2936, 2899, 2871, 1951, 1916, 1875, 1835, 1799, 1619, 1588; **HRMS** (EI) for $C_{23}H_{17}BF_6O_2$: calcd. 450.12259; found 450.12317.

5.6.2.3 2-(3,5-Bis(trifluoromethyl)phenyl)-4-(pentan-3-yl)-4*H*-benzo[*d*][1,3,2]dioxaborinine (5-2c, Table 5-3)



The title compound was prepared using the general procedure for $ZrCl_4$-catalyzed formation of 2-aryl-1,3,2-aryldioxaborins. The solvent was 1,2-dichloroethane and the reaction temperature was 50 ^oC (63% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (s, 2H), 8.00 (s, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.11 (t, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 7.7 Hz, 1H), 5.44 (d, *J* = 2.4 Hz, 1H), 1.70-1.54 (m, 3H), 1.40-1.28 (m, 1H), 1.26-1.15 (m, 1H), 1.12 (t, *J* = 7.2 Hz, 3H), 0.82 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.1, 134.2, 131.0 (q, $J_{C\text{-}F}$ = 33.2 Hz), 128.8, 125.6, 125.4, 124.9, 123.7, 123.6 (q, $J_{C\text{-}F}$ = 272.8 Hz), 117.9, 74.8, 50.0, 22.3, 20.4, 12.1, 12.0; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 26.5; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –63.3; **IR** (Microscope, cm^{-1}) 2966, 2936, 2879, 1618, 1590; **HRMS** (EI) for $C_{20}H_{19}BF_6O_2$: calcd. 416.13824; found 416.13862.

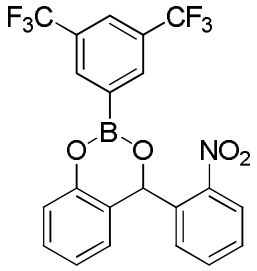
5.6.2.4 2-(3,5-Bis(trifluoromethyl)phenyl)-4-phenyl-4*H*-benzo[*d*][1,3,2]dioxaborinine (5-2e, Table 5-3)



The title compound was prepared using the general procedure for $ZrCl_4$-catalyzed formation of 2-aryl-1,3,2-aryldioxaborins. The solvent was 1,2-dichloroethane

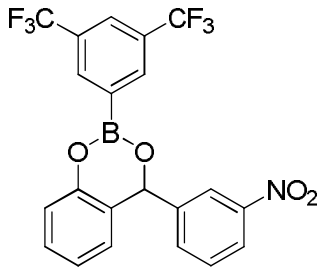
and the reaction temperature was 50 °C (36% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46 (s, 2H), 8.03 (s, 1H), 7.47-7.37 (m, 5H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.33 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.1, 142.1, 134.4, 131.0, 129.4, 129.0, 128.8, 127.5, 127.1, 125.2, 125.0, 123.9, 123.6, 118.2, 75.8; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 27.0; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –63.2; **IR** (Microscope, cm^{-1}) 3070, 3041, 2909, 1956, 1706, 1613, 1589, 1509; **HRMS** (EI) for $C_{21}H_{13}BF_6O_2$: calcd. 422.09128; found 422.08958.

5.6.2.5 2-(3,5-Bis(trifluoromethyl)phenyl)-4-(2-nitrophenyl)-4*H*-benzo[*d*][1,3,2]dioxaborinine (5-2f, Table 5-3)



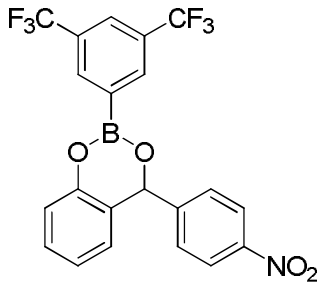
The title compound was prepared using the general procedure for $ZrCl_4$-catalyzed formation of 2-aryl-1,3,2-aryldioxaborins. The solvent was dichloromethane and the reaction temperature was 25 °C (76% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (s, 2H), 8.03-7.97 (m, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.99 (s, 1H), 6.94 (d, *J* = 7.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.2, 148.5, 136.4, 134.6, 133.8, 131.3, 130.4, 130.1, 129.8, 127.1, 125.4, 124.9, 124.3, 123.7, 123.6, 118.5, 71.0; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 26.9; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –63.3; **IR** (Microscope, cm^{-1}) 3082, 1618, 1591, 1532; **HRMS** (EI) for $C_{21}H_{12}BF_6NO_4$: calcd. 467.07635; found 467.07577.

5.6.2.6 2-(3,5-Bis(trifluoromethyl)phenyl)-4-(3-nitrophenyl)-4*H*-benzo[*d*][1,3,2]dioxaborinine (5-2g, Table 5-3)



The title compound was prepared using the general procedure for $ZrCl_4$-catalyzed formation of 2-aryl-1,3,2-aryldioxaborins. The solvent was dichloromethane and the reaction temperature was 25 ^oC (58% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 (s, 2H), 8.28-8.22 (m, 2H), 8.01 (s, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.44 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.6, 148.0, 143.8, 134.4, 133.6, 131.1, 130.1, 130.1, 126.8, 125.3, 124.3, 123.8, 123.6, 123.5, 122.6, 118.6, 74.8; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 27.0; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –63.2; **IR** (Microscope, cm^{-1}) 3089, 1879, 1618, 1591, 1534; **HRMS** (EI) for $C_{21}H_{12}BF_6NO_4$: calcd. 467.07635; found 467.07578.

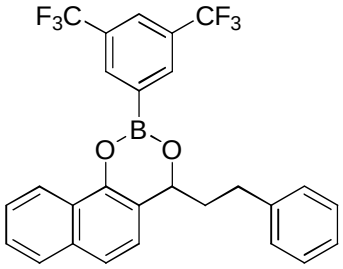
5.6.2.7 2-(3,5-Bis(trifluoromethyl)phenyl)-4-(4-nitrophenyl)-4*H*-benzo[*d*][1,3,2]dioxaborinine (5-2h, Table 5-3)



The title compound was prepared using the general procedure for $ZrCl_4$-catalyzed formation of 2-aryl-1,3,2-aryldioxaborins. The solvent was dichloromethane and

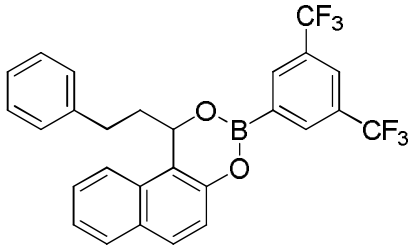
the reaction temperature was 25 °C (71% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 (s, 2H), 8.28 (d, *J* = 8.8 Hz, 2H), 8.03 (s, 1H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.45 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.4, 148.1, 148.0, 134.4, 131.2, 130.1, 128.4, 126.7, 125.3, 124.2, 124.2, 123.6, 123.5, 118.6, 74.7; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 27.5; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –63.2; **IR** (Microscope, cm^{-1}) 3082, 2817, 2849, 2454, 1926, 1711, 1618, 1610, 1589, 1523; **HRMS** (EI) for $C_{21}H_{12}BF_6NO_4$: calcd. 467.07636; found 467.07656.

5.6.2.8 2-(3,5-Bis(trifluoromethyl)phenyl)-4-phenethyl-4*H*-naphtho[1,2-*d*] [1,3,2]dioxaborinine (5-2j, Table 5-3)



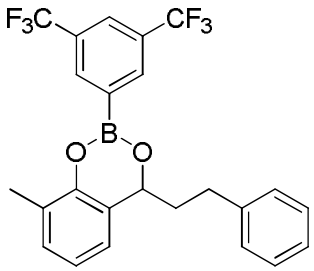
The title compound was prepared using the general procedure for $ZrCl_4$-catalyzed formation of 2-aryl-1,3,2-aryldioxaborins. The solvent was dichloromethane and the reaction temperature was 25 °C (80% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 (s, 2H), 8.43 (d, *J* = 8.2 Hz, 1H), 8.06 (s, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.30-7.20 (m, 4H), 7.18-7.11 (m, 2H), 5.52 (dd, *J* = 7.4, 3.7 Hz, 1H), 2.87 (t, *J* = 7.8 Hz, 2H), 2.49-2.40 (m, 1H), 2.33-2.23 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.5, 141.1, 134.2, 133.9, 131.1 (q, $J_{C\text{-}F}$ = 33.2 Hz), 128.6, 128.5, 127.7, 126.9, 126.6, 126.1, 125.0, 124.9, 123.6 (q, $J_{C\text{-}F}$ = 272.8 Hz), 123.5, 122.5, 121.5, 119.4, 73.2, 40.4, 30.6; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 26.6; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –63.2; **IR** (Microscope, cm^{-1}) 3063, 3029, 2926, 1619, 1604, 1580, 1511; **HRMS** (EI) for $C_{27}H_{19}BF_6O_2$: calcd. 500.13824; found 500.13877.

5.6.2.9 3-(3,5-Bis(trifluoromethyl)phenyl)-1-phenethyl-1*H*-naphtho[2,1-*d*] [1,3,2]dioxaborinine (5-2k, Table 5-3)



The title compound was prepared using the general procedure for $ZrCl_4$-catalyzed formation of 2-aryl-1,3,2-aryldioxaborins. The solvent was dichloromethane and the reaction temperature was 25 ^oC (75% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48 (s, 2H), 8.07 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.9 Hz, 1H), 7.53-7.43 (m, 3H), 7.38-7.18 (m, 6H), 5.92 (dd, *J* = 8.4, 2.9 Hz, 1H), 2.97 (t, *J* = 7.5 Hz, 2H), 2.52-2.42 (m, 1H), 2.33-2.23 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.2, 140.9, 134.2, 131.1, 130.8, 129.8, 129.5, 129.0, 128.6, 128.5, 127.1, 126.2, 125.0, 124.6, 123.7, 121.6, 118.8, 117.9, 71.1, 39.8, 31.0; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 26.4; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –63.1; **IR** (Microscope, cm^{-1}) 3065, 3028, 2926, 2860, 1618, 1602, 1518; **HRMS** (EI) for $C_{27}H_{19}BF_6O_2$: calcd. 500.13824; found 500.13947.

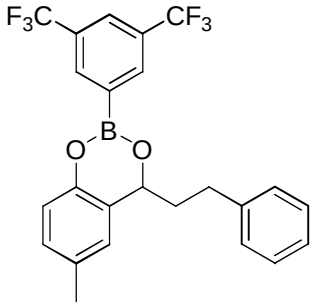
5.6.2.10 2-(3,5-Bis(trifluoromethyl)phenyl)-8-methyl-4-phenethyl-4*H*-benzo [*d*][1,3,2]dioxaborinine (5-2l, Table 5-3)



The title compound was prepared using the general procedure for $ZrCl_4$-catalyzed formation of 2-aryl-1,3,2-aryldioxaborins. The solvent was dichloromethane and the reaction temperature was 25 ^oC (70% yield, white solid). **^{1}H NMR** (400 MHz,

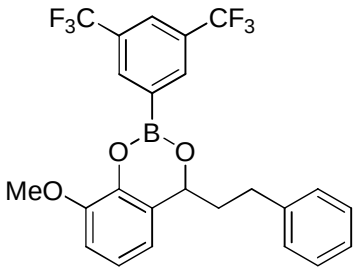
$CDCl_3$) δ 8.39 (s, 2H), 8.01 (s, 1H), 7.30-7.20 (m, 4H), 7.16 (t, *J* = 7.0 Hz, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 7.4 Hz, 1H), 5.35 (dd, *J* = 7.6, 3.9 Hz, 1H), 2.92-2.78 (m, 2H), 2.44 (s, 3H), 2.38-2.27 (m, 1H), 2.26-2.16 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.5, 141.1, 134.1, 131.0, 130.3, 128.5, 128.5, 127.2, 126.1, 125.1, 125.0, 123.6, 123.3, 123.0, 72.9, 40.8, 30.7, 15.6; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 26.5; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –63.2; **IR** (Microscope, cm^{-1}) 3030, 2927, 1617; **HRMS** (EI) for $C_{24}H_{19}BF_6O_2$: calcd. 464.13824; found 464.13791.

5.6.2.11 2-(3,5-Bis(trifluoromethyl)phenyl)-6-methyl-4-phenethyl-4*H*-benzo [*d*][1,3,2]dioxaborinine (5-2m, Table 5-3)



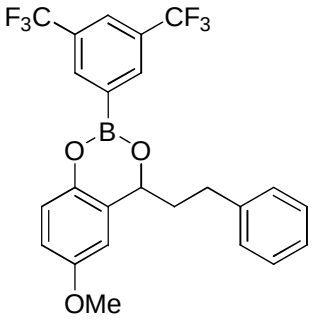
The title compound was prepared using the general procedure for $ZrCl_4$-catalyzed formation of 2-aryl-1,3,2-aryldioxaborins. The solvent was dichloromethane and the reaction temperature was 25 ^{o}C (78% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.40 (s, 2H), 8.02 (s, 1H), 7.32-7.22 (m, 4H), 7.17 (t, *J* = 6.5 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.86 (s, 1H), 5.34 (dd, *J* = 7.7, 3.6 Hz, 1H), 2.88-2.80 (m, 2H), 2.40-2.28 (m, 4H), 2.26-2.16 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.2, 141.2, 134.2, 133.3, 130.9, 129.6, 128.5, 128.5, 126.1, 125.8, 125.1, 124.8, 123.7, 117.8, 72.9, 40.9, 30.9, 21.0; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 26.5; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –63.2; **IR** (Microscope, cm^{-1}) 3088, 3061, 2958, 2930, 2866, 1871, 1833, 1618, 1504; **HRMS** (EI) for $C_{24}H_{19}BF_6O_2$: calcd. 464.13824; found 464.13736.

5.6.2.12 2-(3,5-Bis(trifluoromethyl)phenyl)-8-methoxy-4-phenethyl-4*H*-benzo[*d*][1,3,2]dioxaborinine (5-2n, Table 5-3)



The title compound was prepared using the general procedure for $ZrCl_4$-catalyzed formation of 2-aryl-1,3,2-aryldioxaborins. The solvent was dichloromethane and the reaction temperature was 25 ^oC (83% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43 (s, 2H), 8.01 (s, 1H), 7.30-7.13 (m, 5H), 7.06 (t, *J* = 8.1 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 5.37 (dd, *J* = 7.5, 3.9 Hz, 1H), 3.98 (s, 3H), 2.92-2.80 (m, 2H), 2.39-2.29 (m, 1H), 2.27-2.17 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.8, 141.1, 138.1, 134.3, 131.1 (q, $J_{C\text{-}F}$ = 33.2 Hz), 128.6, 128.5, 126.4, 126.1, 125.0, 123.8, 123.7 (q, $J_{C\text{-}F}$ = 272.9 Hz), 117.1, 111.7, 72.7, 56.2, 40.6, 30.6; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 26.3; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –63.2; **IR** (Microscope, cm^{-1}) 3062, 3024, 2939, 2869, 2842, 1829, 1618, 1591; **HRMS** (EI) for $C_{24}H_{19}BF_6O_3$: calcd. 480.13315; found 480.13336.

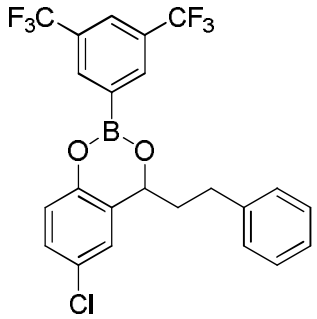
5.6.2.13 2-(3,5-Bis(trifluoromethyl)phenyl)-6-methoxy-4-phenethyl-4*H*-benzo[*d*][1,3,2]dioxaborinine (5-2o, Table 5-3)



The title compound was prepared using the general procedure for $ZrCl_4$-catalyzed formation of 2-aryl-1,3,2-aryldioxaborins. The solvent was dichloromethane and

the reaction temperature was 25 °C (87% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.37 (s, 2H), 8.00 (s, 1H), 7.30-7.20 (m, 4H), 7.16 (t, *J* = 7.0 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.58 (d, *J* = 2.9 Hz, 1H), 5.34 (dd, *J* = 7.7, 3.9 Hz, 1H), 3.81 (s, 3H), 2.92-2.80 (m, 2H), 2.39-2.29 (m, 1H), 2.26-2.16 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.8, 142.3, 141.1, 134.1, 130.9 (q, $J_{C\text{-}F}$ = 33.2 Hz), 128.6, 138.5, 126.2, 126.1, 124.9, 123.6 (q, $J_{C\text{-}F}$ = 272.9 Hz), 118.8, 114.0, 110.7, 72.8, 55.8, 40.5, 30.6; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 26.3; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –63.1; **IR** (Microscope, cm^{-1}) 3057, 3022, 3004, 2955, 2920, 2863, 2845, 1621, 1601, 1594, 1500; **HRMS** (EI) for $C_{24}H_{19}BF_6O_3$: calcd. 480.13315; found 480.13282.

5.6.2.14 2-(3,5-Bis(trifluoromethyl)phenyl)-6-chloro-4-phenethyl-4*H*-benzo [*d*][1,3,2]dioxaborinine (5-2p, Table 5-3)

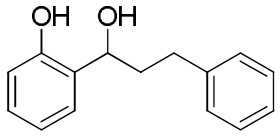


The title compound was prepared using the general procedure for $ZrCl_4$-catalyzed formation of 2-aryl-1,3,2-aryldioxaborins. The solvent was 1,2-dichloroethane and the reaction temperature was 50 °C (53% yield, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.36 (s, 2H), 8.01 (s, 1H), 7.31-7.20 (m, 5H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 5.32 (dd, *J* = 7.8, 3.6 Hz, 1H), 2.93-2.79 (m, 2H), 2.38-2.28 (m, 1H), 2.26-2.16 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.0, 140.7, 134.2, 131.1 (q, $J_{C\text{-}F}$ = 33.2 Hz), 129.1, 128.9, 128.6, 128.4, 127.1, 126.2, 126.1 (q, $J_{C\text{-}F}$ = 272.9 Hz), 125.4, 125.1, 119.6, 72.3, 40.4, 30.6; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 26.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ

–63.2; **IR** (Microscope, cm^{-1}) 3028, 2927, 1619; **HRMS** (EI) for $C_{23}H_{16}BClF_6O_2$: calcd. 484.08362; found 484.08378.

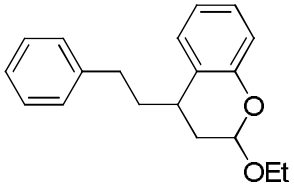
5.6.3 Synthetic applications of 5-2

5.6.3.1 2-(1-Hydroxy-3-phenylpropyl)phenol (5-10, Scheme 5-4)



A mixture of the dioxaborin **5-2b** (225 mg, 0.5 mmol), 30% H_2O_2 solution (0.5 mL), and THF (2.0 mL) was stirred at 25 ^oC for 2 hours. Then the reaction mixture was poured into ice water (10 mL) and extracted with Et_2O (3 × 10 mL). The extracts were washed with saturated $NaHSO_3$ solution (10 mL) to decompose the excess H_2O_2. The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was recrystallized from *n*-pentane to afford the title 2-(1-hydroxy-3-phenylpropyl)phenol **5-10** (108 mg, 95%) in pure form. The characterization data for this compound matched those of a previous report.[11]

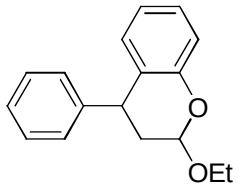
5.6.3.2 2-Ethoxy-4-phenethylchroman (5-11, Scheme 5-4)



A solution of dioxaborin **5-2b** (225 mg, 0.5 mmol) in ethyl vinyl ether (2 mL) was placed in a heavy-walled Pyrex tube equipped with a Teflon stopper. The solution was degassed for 2 minutes and then sealed under argon. The tube was heated at 240 ^oC for 12 hours. Upon cooling, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/Hexanes = 1:30) to give the title 2-ethoxy-4-phenethylchroman **5-10** (121

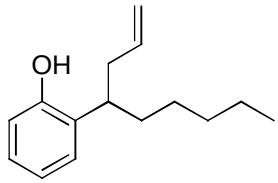
mg, 86%, *syn*:*anti* = 1:1) in pure form. The characterization data for this compound matched those of a previous report.[11]

5.6.3.3 2-Ethoxy-4-phenylchroman (5-12, Scheme 5-4)



This compound was prepared following a similar procedure as describe for **5-11** from **5-2e**. The characterization data for this compound matched those of a previous report.[12]

5.6.3.4 2-(Non-1-en-4-yl)phenol (5-13, Scheme 5-4)



To a solution of dioxaborin **5-2a** (208 mg, 0.5 mmol) and allyltrimethylsilane (228 mg, 2.0 mmol) in dichloroethane (5 mL) was added boron trifluoride etherate (284 mg, 2.0 mmol) at room temperature. The mixture was warmed to 70 ^{o}C and stirred at 70 ^{o}C for 18 hours. The resulting solution was cooled, poured into an aqueous solution of ammonium acetate (20%, 15 mL), and extracted with EtOAc (3 × 15 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/Hexanes = 1:15) to give the title 2-(non-1-en-4-yl)phenol **5-12** (79 mg, 72%) in pure form. The characterization data for this compound matched those of a previous report.[13]

5.7 References

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Chapter 6

Thesis Summary, Conclusions and Future Perspectives

6.1 Thesis summary and conclusions

The research that has been discussed throughout the chapters of this thesis revolves around the applications of diversely substituted arylboronic acids as organocatalysts, transient masks or stoichiometric mediators in promoting synthetically useful chemical transformations in a milder and "greener" fashion. Unlike other organocatalysts which were developed for activating ketone or aldehyde functionalities, arylboronic acids offer a new and unique mode for the activation of carboxylic acids, alcohols and diols through reversible formation of boronate adducts.

Encouraged by its previous successful application in direct amidations between carboxylic acids and amines, the strategy of carboxylic acid activation with *ortho*-substituted phenylboronic acid catalysis was further expanded to a variety of cycloadditions of unsaturated carboxylic acids. Successful reactions include Diels-Alder cycloadditions between substituted acrylic acid or propiolic acid and different dienes, azide-alkyne cycloaddition, nitrile oxide-alkyne (alkene) cycloaddition and nitrone-alkyne (alkene) cycloaddition with a broad spectrum of substrate scopes in excellent yield and regioselectivity. Preliminary ^{13}C-NMR studies suggested that the boronic acid catalyst provides activation by lowering the LUMO of the unsaturated carboxylic acid likely *via* a monoacylated hemiboronic ester intermediate through internal H-bonding.

Beyond carboxylic acid activation, electron deficient arylboronic acids demonstrated excellent catalytic activity for facilitating the complete or partial ionization of allylic alcohols, allowing their direct nucleophilic substitution in an

atom- and step-economical fashion. The effectiveness and versatility of this hydroxyl activation concept using boronic acid catalysis was convincingly demonstrated by its successful applications to a broad range of classical chemical transformations, including 1,3-transpositions of allylic alcohols, Meyer-Schuster rearrangement of propargylic alcohols, a variety of cationic cyclizations of allylic alcohols, Nazarov cyclizations/Diels-Alder trapping of divinyl alcohols, and allylic substitutions. Preliminary mechanistic investigations suggested that 1,3-transpositions of propargylic alcohols and cationic cyclizations of allylic alcohols proceed through an S_N1' pathway *via* a carbocation (open transition state) and 1,3-transpositions of allylic alcohols were controlled by two possible, substrate-dependent pathways, an S_N1' pathway and an S_N2' pathway (cyclic chair-like transition state).

Owing to their remarkable binding affinity with complex glycopyranosides, benzoboroxoles were found to exhibit exceptional transient masking ability and moderate catalytic activity for certain 1,2- and 1,3-diol frameworks in carbohydrates to achieve the regioselective glycosylation of fully or partially unprotected sugars at the 3-OH position. Although the detailed mechanism explaining how boroxoles activate the 1,2-diol system in carbohydrates is still not clear until now, the enhanced nucleophilicity of the 3-OH in the proposed 3,4-boronate intermediate is most likely responsible for the observed 3-OH regioselectivity in this glycosylation. Further analysis of electronic and steric effects of the boroxole core structure offers a potential direction in developing more active boroxole catalysts for regioselective glycosylation of fully or partially unprotected sugars.

Other than their use as organocatalysts, arylboronic acids could potentially serve as templates in important chemical transformations due to their unique capability

of exchanging alcohols reversibly. In this context, an efficient $ZrCl_4$ catalyzed *ortho*-hydroxyalkylation of phenols with aldehydes promoted by 3,5-bis(trifluoromethyl)phenylboronic acid leading to the formation of 2-aryl-1,3,2-aryldioxaborins, stable *o*-quinomethane precursors, was investigated and optimized. In this protocol, 3,5-bis(trifluoromethyl)phenylboronic acid and magnesium sulfate were used as the requisite promoter and dehydrating agent respectively, allowing this reaction to proceed smoothly under milder reaction conditions compared with the corresponding high-temperature variant. Even though further experiments are required to fully elucidate the detailed mechanism of Lewis acid catalyzed formation of 2-aryl-1,3,2-aryldioxaborins, this reaction was proposed to proceed through a formal 3,3-rearrangement pathway *via* a closed six-membered chair-like transition state.

6.2 Future perspectives

Although the first example of boronic acid catalysis has been known for almost half a century, when thought of as an area of catalysis the concept is still in its infancy. I believe that boronic acid catalysis will grow rapidly in the near future and be recognized as a powerful tool for activating carboxylic acids, alcohols, and diols. As our research in this thesis illustrates, boronic acid catalysis brings about several benefits, specifically (i) activating carboxylic acids, alcohols, and diols without recourse to prior activation and protection operations, thus allowing direct functionalizations in a step- and atom-economical fashion; (ii) demonstrating excellent catalytic efficiency and remarkable functional group tolerance compared with well established Lewis acid, Brønsted acid, and transition metal catalyzed variants; (iii) employing generally non-toxic, air-stable, recyclable, and easy-to-handle arylboronic acids as organocatalysts under unusually mild reaction conditions, therefore providing an environmentally friendly alternative to existing methods. Although this thesis presents significant advances made in the field of

boronic acid catalysis, there are certainly some ongoing projects where progress could be made: (i) developing superior catalysts for allylic substitutions of unactivated arenes (Chapter 3) and regioselective glycosylation of unprotected sugars (Chapter 4); (ii) investigating the degree of ionization of the substrate **3-22b** in "cationic" cyclizations using stereochemical study and ^{18}O labeling experiment that were performed for the 1,3-transposition of allylic alcohols (Chapter 3); (iii) trying "cationic" cyclizations using ionic liquid as the solvent (Chapter 3); (iv) attempting to develop efficient glycosylation system for more challenging substrates such as α-configured monosaccharides (acceptor) and armed donor (Chapter 4). The remaining challenges for boronic acid catalysis include stereoselective transformations. The design and preparation of chiral binaphthyl-derived boronic acids could lead to asymmetric catalysis applications for the chemical transformations discussed in this thesis. For the carbocation chemistry in Chapter 3, since carbocations are likely intermediates, it can be envisaged that for reactions where stereogenic centers are formed, boronate anion exchange with chiral counter-anions (such as chiral phosphoric anion) may offer a possible way of controlling the stereoselectivity. Moreover, cooperative catalysis by merging boronic acid catalysis with other modes of catalysis such as enamine or *N*-heterocyclic carbene catalysis could be a potential research topic in this area. Such applications along with the exploration of other reactions susceptible to boronic acid catalysis are the next challenges to be tackled in the Hall group.

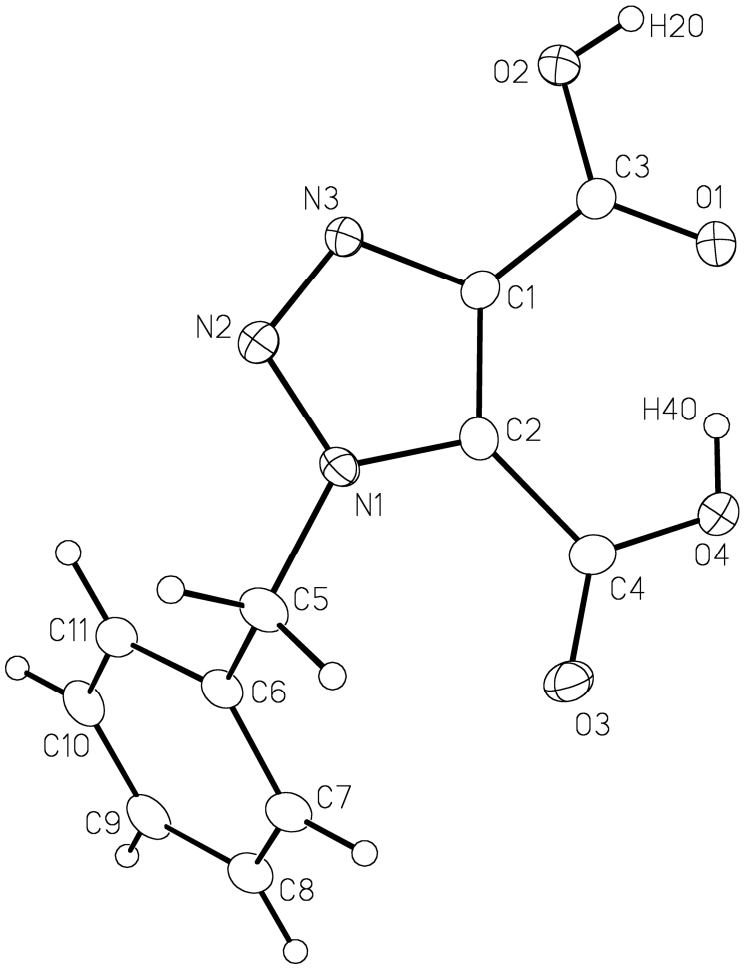
Appendix 1: X-ray Crystallographic data for 2-13o

XCL Code: DGH0902 **Date:** 12 June 2009

Compound: 1-Benzyl-1*H*-1,2,3-triazole-4,5-dicarboxylic acid

Formula: $C_{11}H_9N_3O_2$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta:

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Phone: +1 780 492 2485; **Fax:** +1 780 492 8231

X-Ray Crystallography Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta, T6G 2G2, Canada

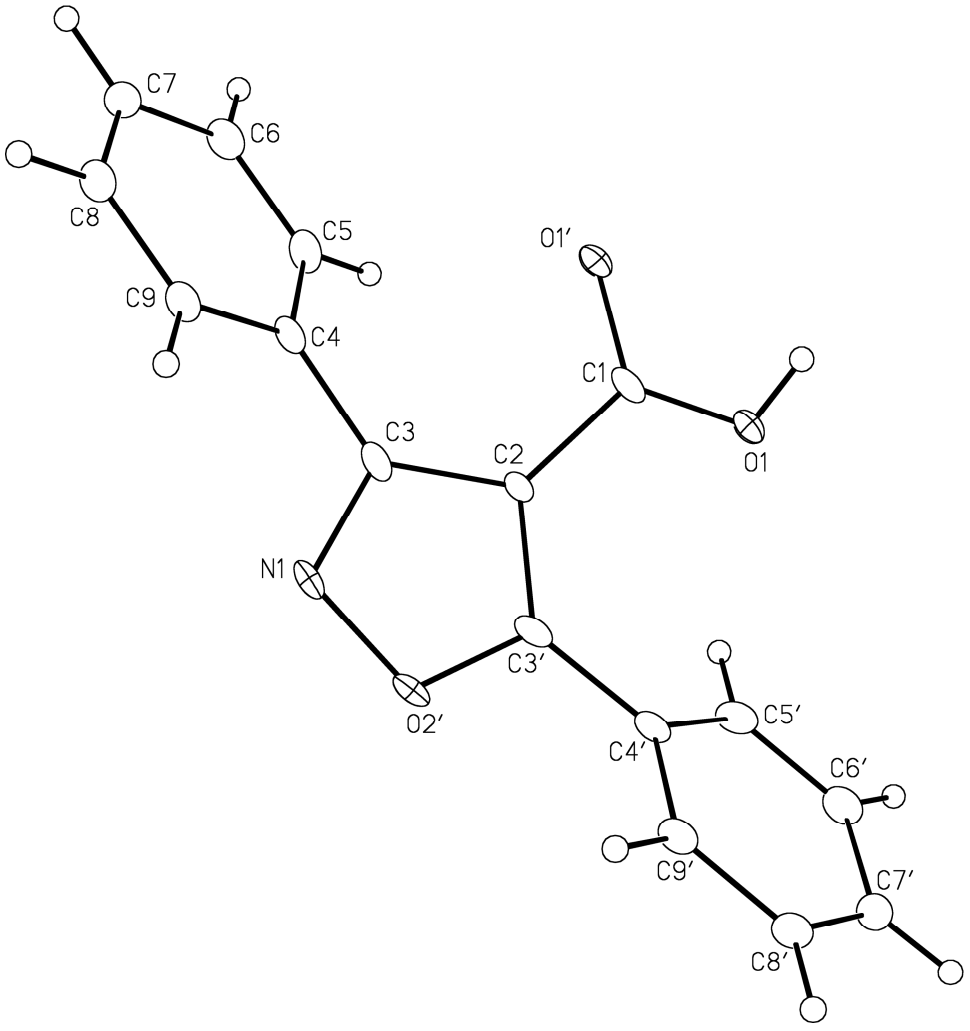
Appendix 2: X-ray Crystallographic data for 2-18d

XCL Code: DGH0901 **Date:** 11 August 2009

Compound: 3,5-diphenylisoxazole-4-carboxylic acid

Formula: $C_{16}H_{11}NO_3$

Supervisor: D. G. Hall **Crystallographer:** M. J. Ferguson



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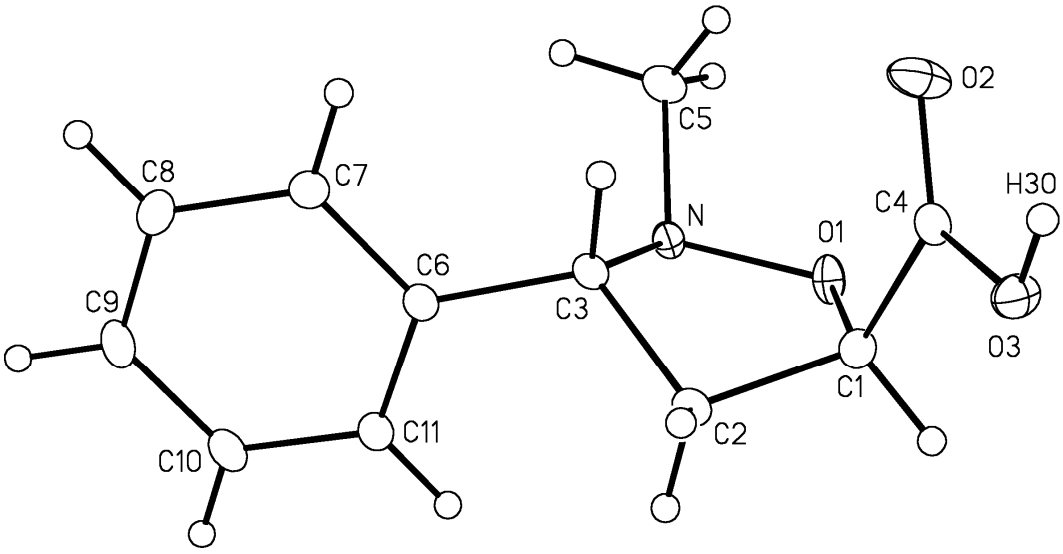
Appendix 3: X-ray Crystallographic data for 2-24a

XCL Code: DGH0906 **Date:** 19 August 2009

Compound: 2-Methyl-3-phenylisoxazolidine-5-carboxylic acid

Formula: $C_{11}H_{13}NO_3$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



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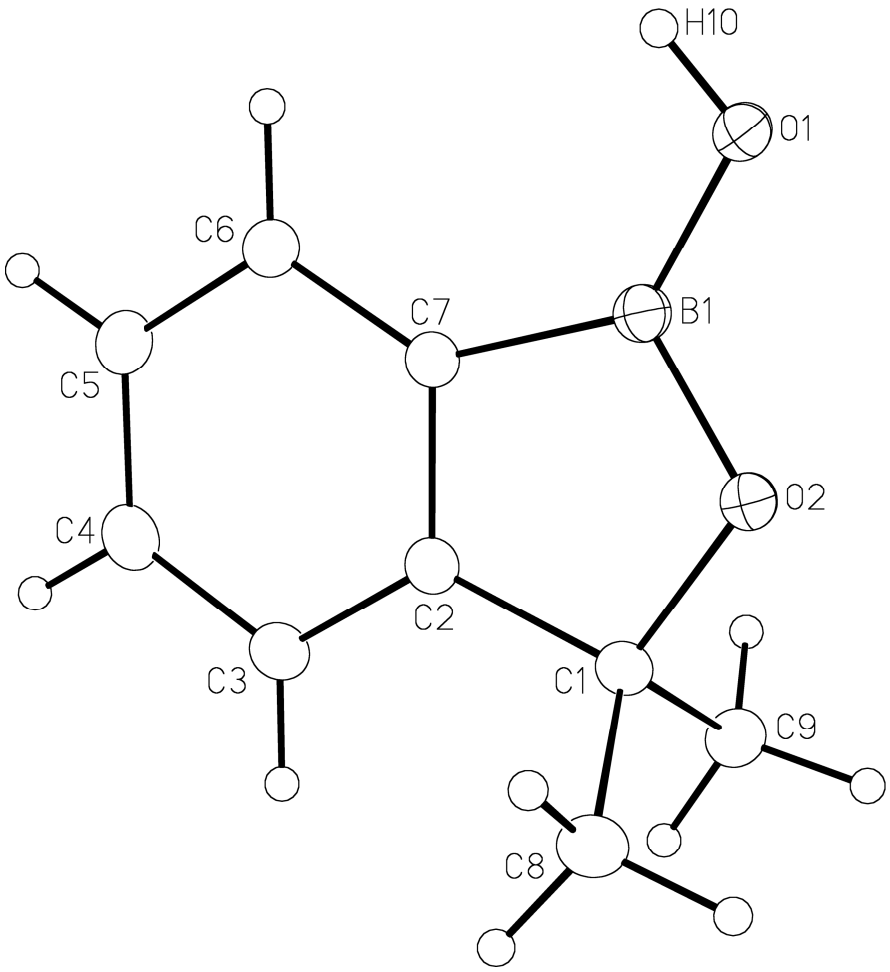
Appendix 4: X-ray Crystallographic data for 4-1d

XCL Code: DGH0812 **Date:** 17 June 2008

Compound: 3,3-dimethyl-2,1-benzoxaborol-1(3*H*)-ol

Formula: $C_9H_{11}BO_2$

Supervisor: D. G. Hall **Crystallographer:** M. J. Ferguson



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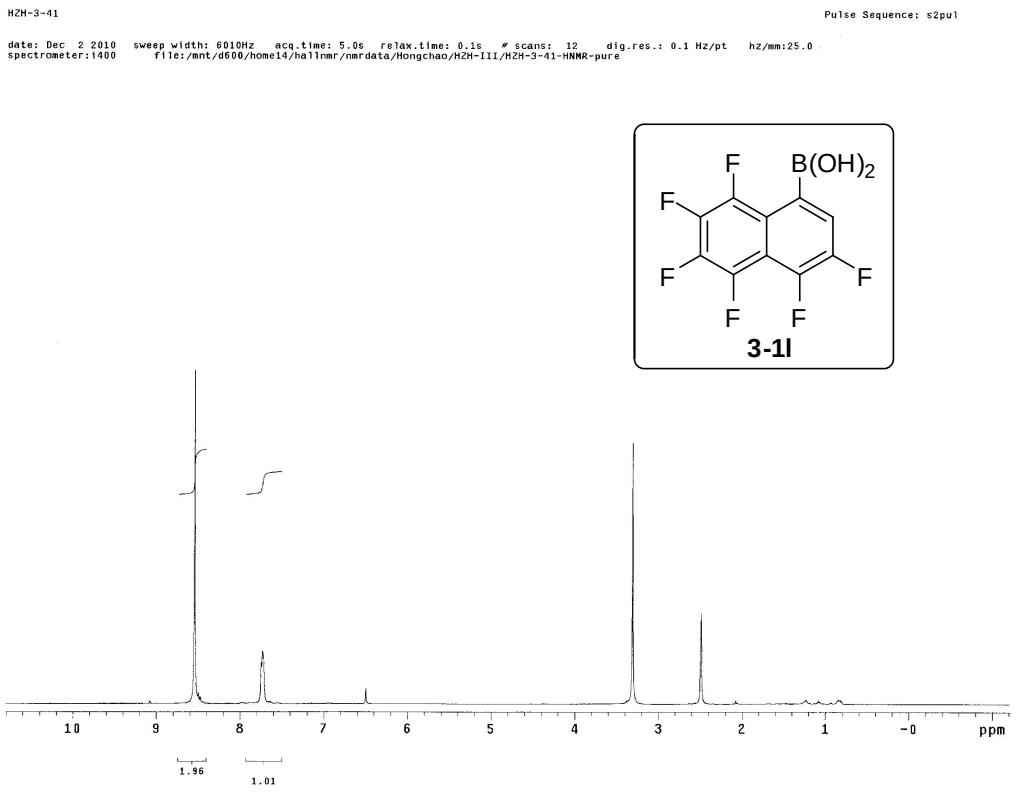
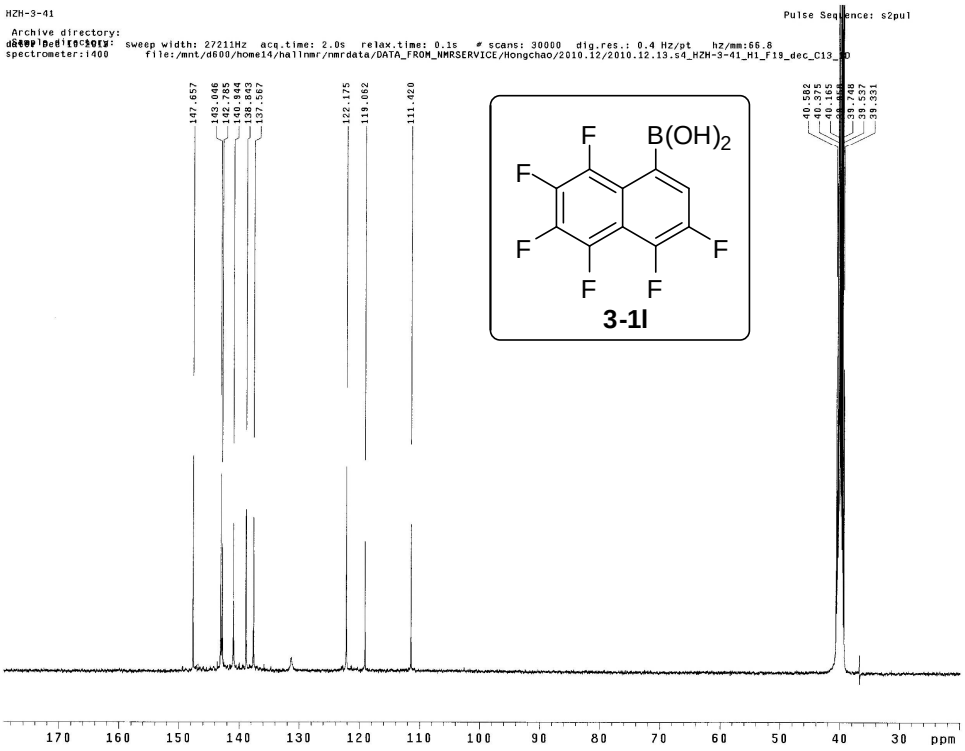
X-Ray Crystallography Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta, T6G 2G2, Canada

Appendix 5: Copies of NMR spectra for new boronic acid catalysts

^{1}H-, ^{13}C-, ^{11}B- and ^{19}F-NMR of 3-1l in DMSO-d_6 at 25 ^{o}C





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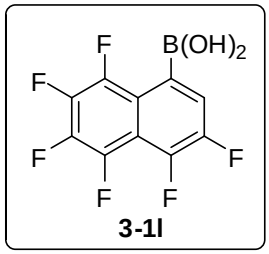
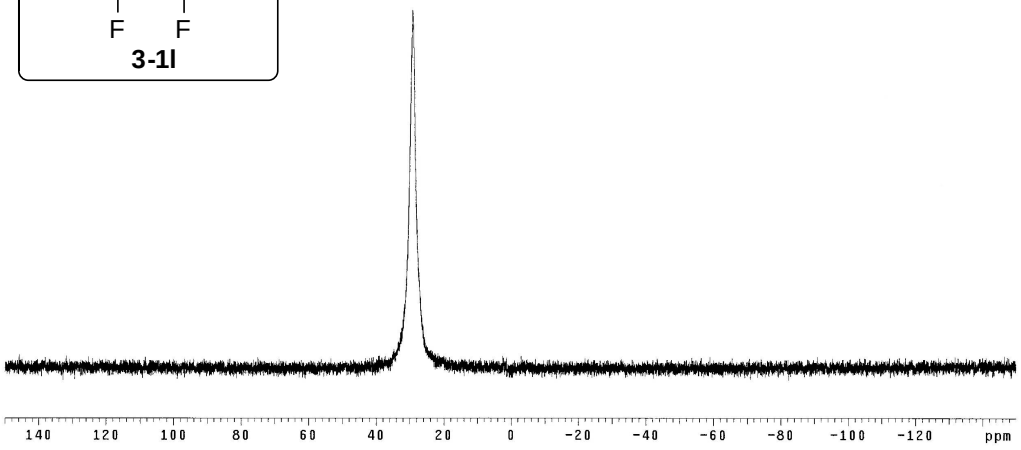
spectrometer:i400 file:/mnt/d600/home14/hallnmr/nmrdata/Hongchao/HZH-III/HZH-3-41-BNMR-pure

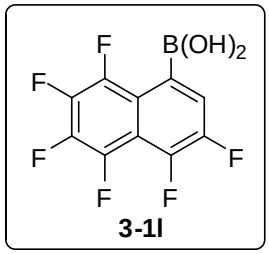


3-1l



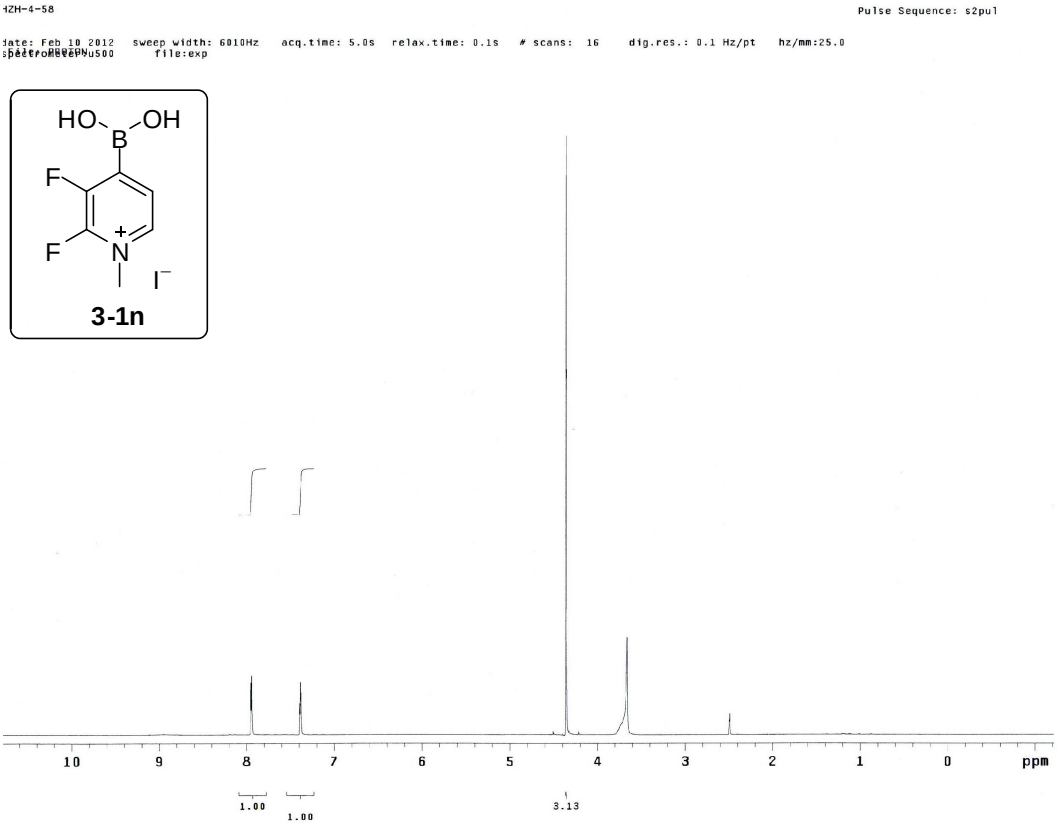
HZH-3-41 Pulse Sequence: s2pul

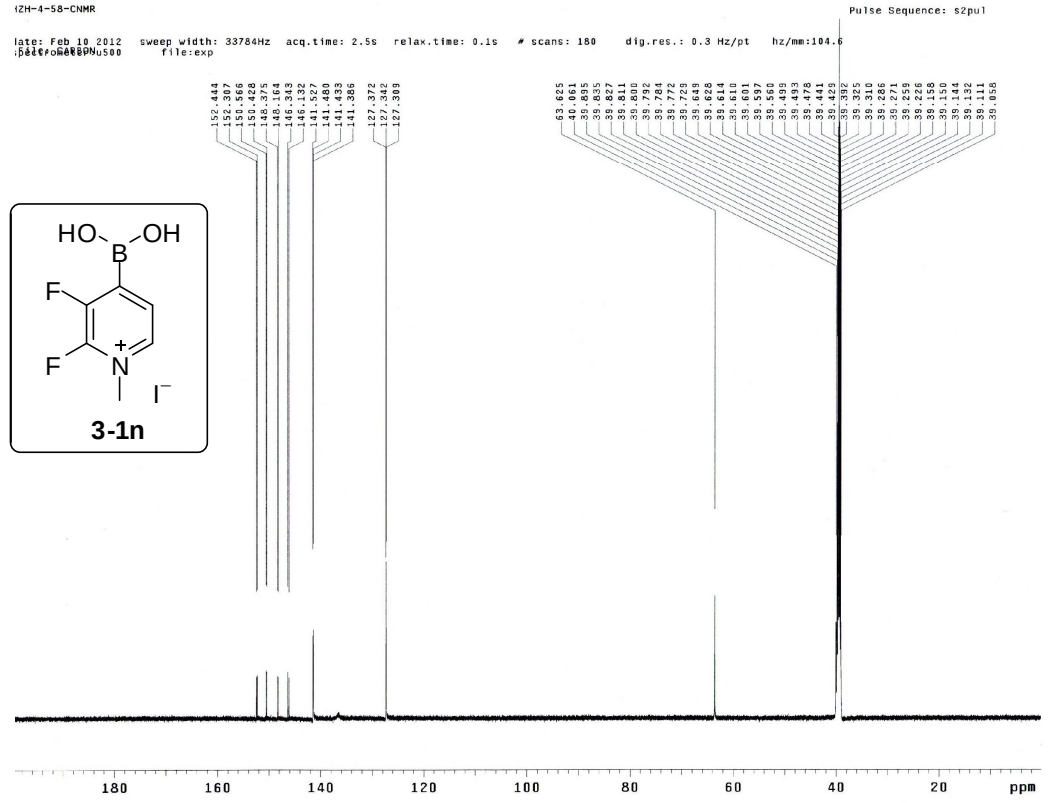
Sample directory:
date: Dec 9 2010 sweep width: 79208Hz acq.time: 3.0s relax.time: 0.1s # scans: 32 dig.res.: 0.3 Hz/pt hz/mm:62.8
spectrometer:i400 file:/mnt/d600/home14/hallnmr/nmrdata/DATA_FROM_NMRSERVICE/Hongchao/2010.12/2010.12.09.s4_HZH-3-41_f19_1D

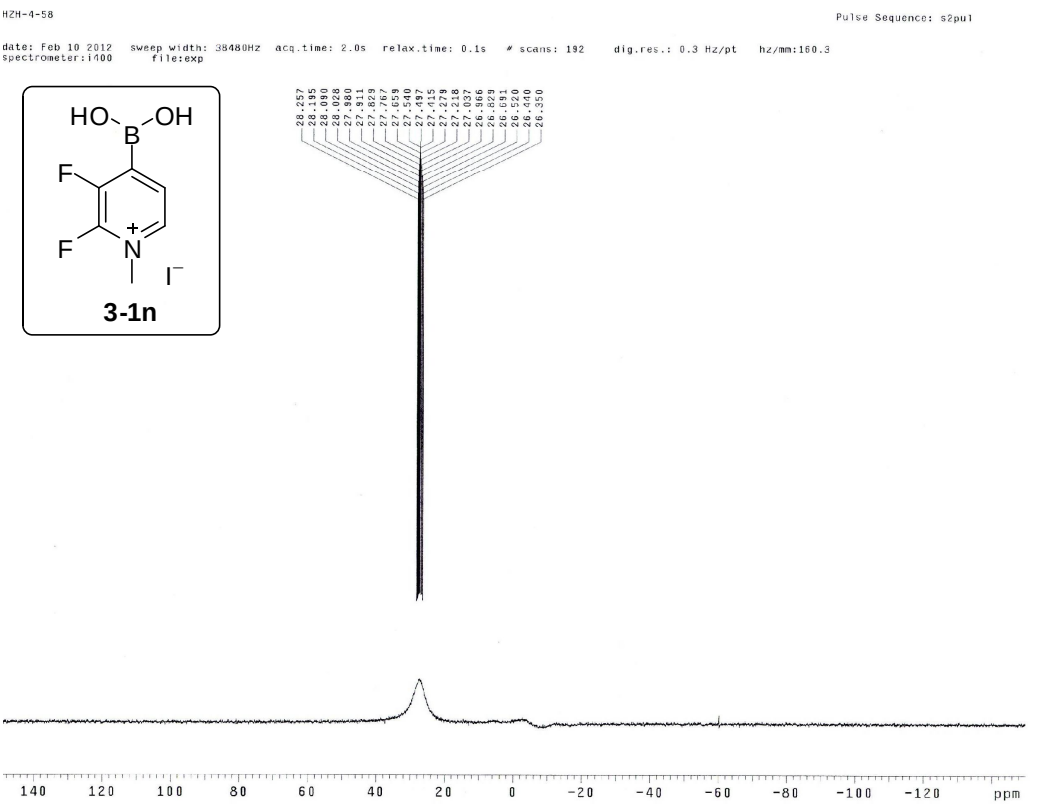


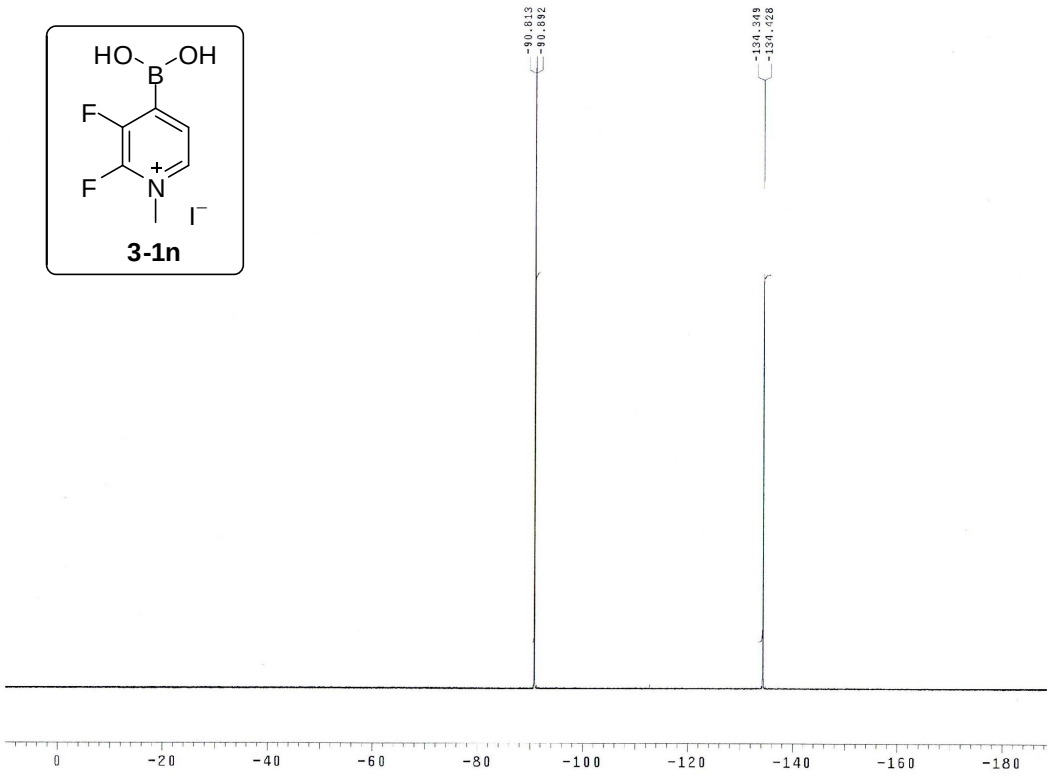
3-1l

^{1}H-, ^{13}C-, ^{11}B- and ^{19}F-NMR of 3-1n in DMSO-d_6 (one drop D_2O) at 25 ^{o}C

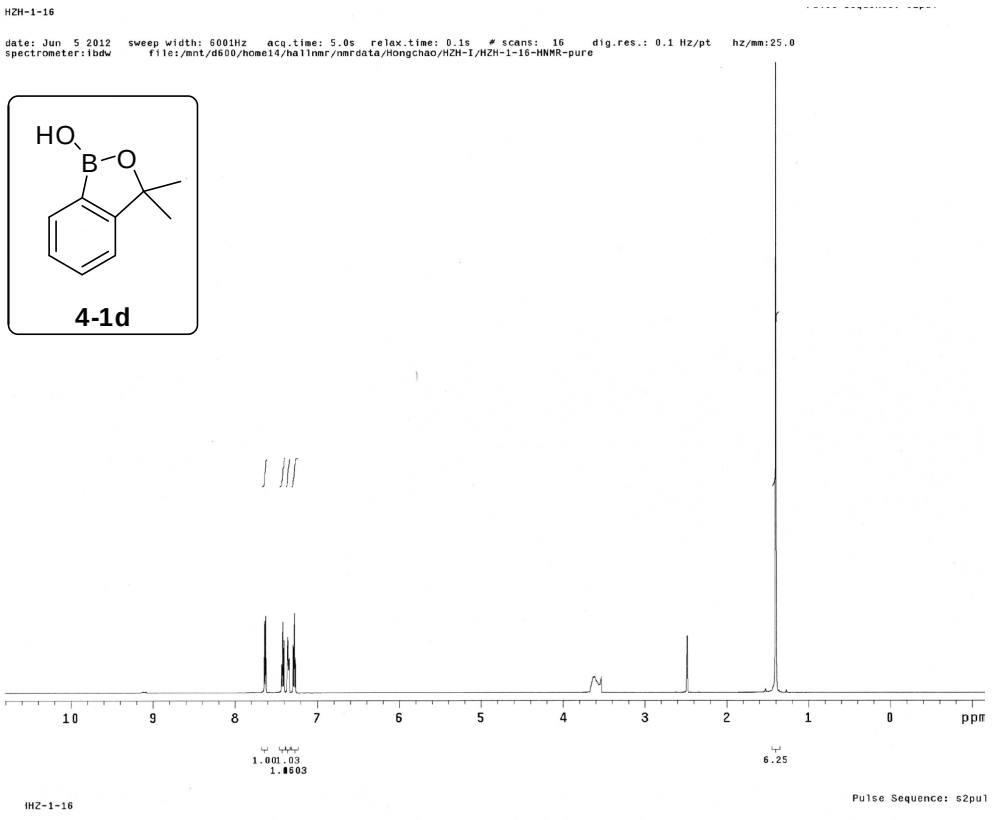





HZH-4-58
Pulse Sequence: s2pul
date: Feb 10 2012 sweep width: 38480Hz acq.time: 2.0s relax.time: 0.1s # scans: 192 dig.res.: 0.3 Hz/pt hz/mm:160.3
spectrometer:i400 file:exp
HO
B
OH
F
F
N
I⁻
3-1n
28.257
28.195
28.090
28.028
27.980
27.911
27.829
27.767
27.659
27.540
27.497
27.415
27.278
27.218
27.037
26.966
26.829
26.691
26.550
26.460
26.350
140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 ppm

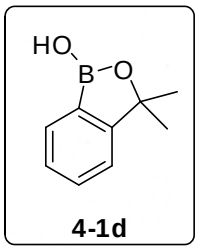

HO
B
OH
F
F
N
I⁻
3-1n
-90.813
-90.892
-134.349
-134.428
0 -20 -40 -60 -80 -100 -120 -140 -160 -180

^{1}H-, ^{13}C- and ^{11}B-NMR of 4-1d in DMSO-d_6 (one drop D_2O) at 25 ^{o}C

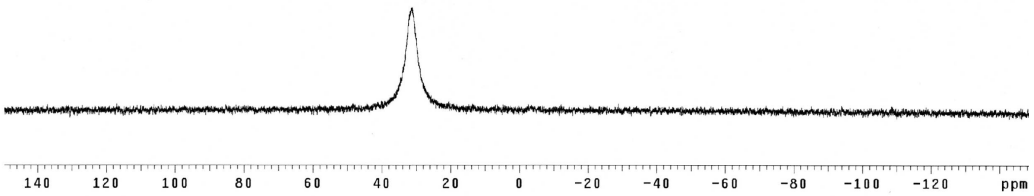


HZH-1-16

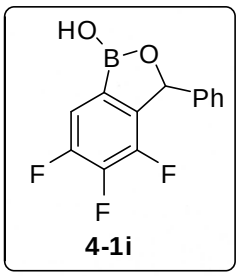
date: Jun 5 2012 sweep width: 47847Hz acq.time: 2.0s relax.time: 0.1s # scans: 36 dig.res.: 0.4 Hz/pt hz/mm:199.4
spectrometer:ibdw file:/mnt/d600/home14/hallnmr/nmrdata/Hongchao/HZH-I/HZH-1-16-BNMR-pure



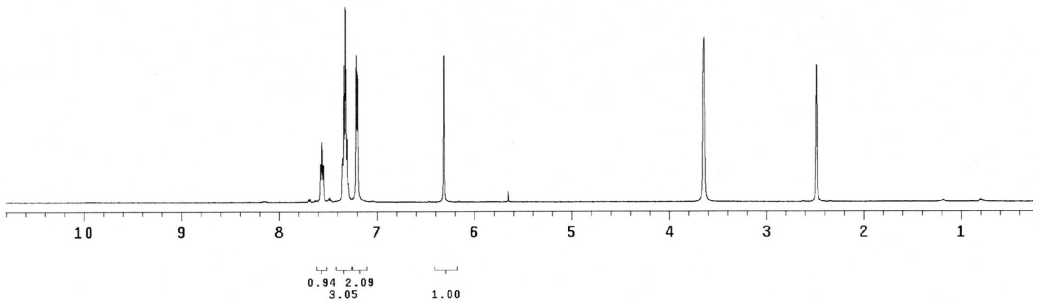
4-1d

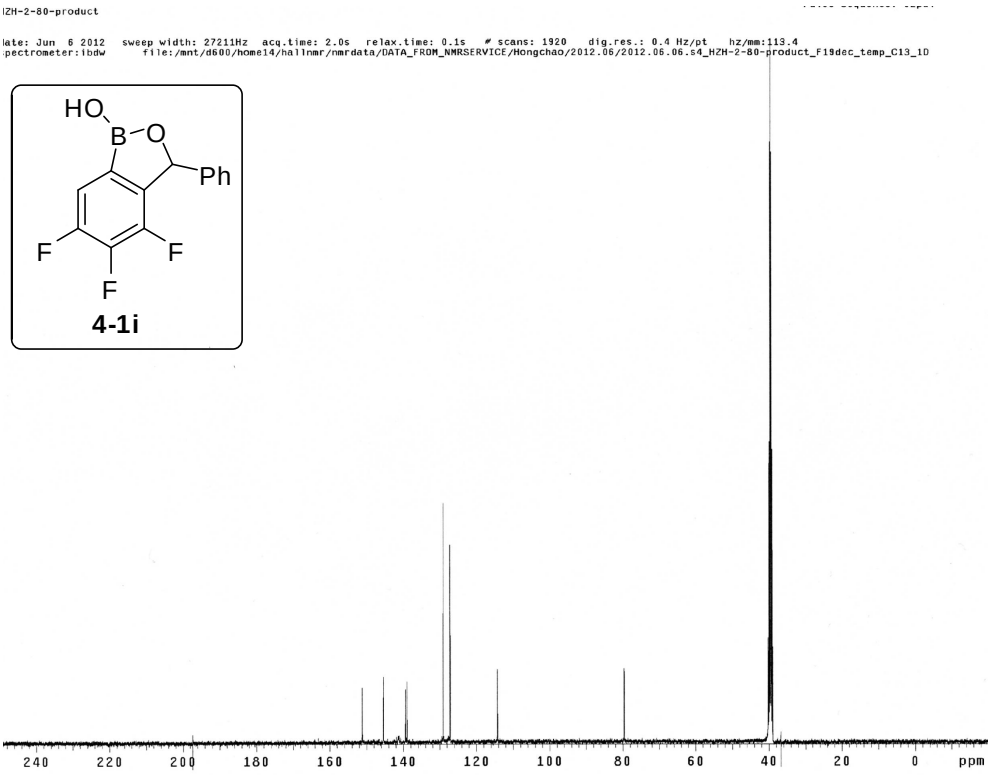


^{1}H-, ^{13}C-, ^{11}B- and ^{19}F-NMR of 4-1i in DMSO-d_6 (one drop D_2O) at 25 ^{o}C

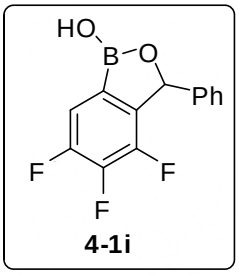


4-1i

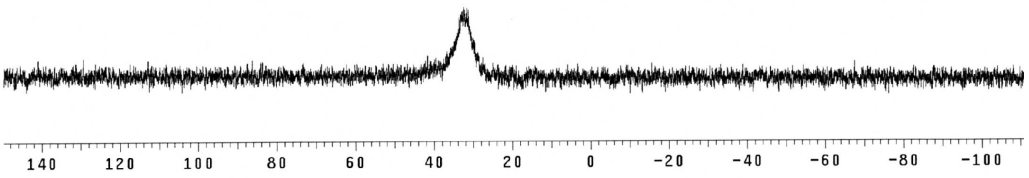


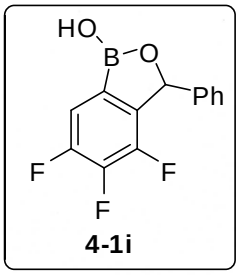


4-1i

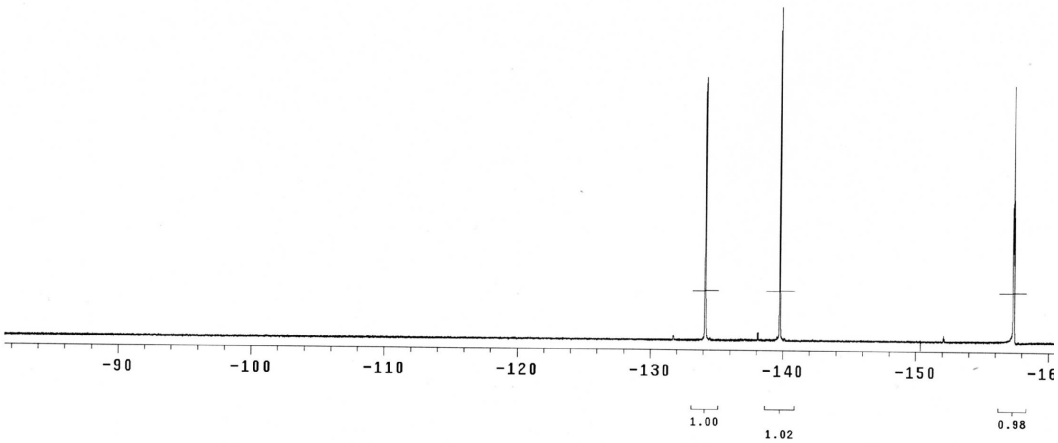

HO
B
O
Ph
F
F
F

4-1i


140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100


HO
B
O
Ph
F
F
F

4-1i


-90
-100
-110
-120
-130
-140
-150
1.00
1.02
0.98