Boronic Acid Catalysis: A Versatile Strategy for Direct Hydroxyl Group Functionalization

by

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Abstract

The field of organic chemistry has seen remarkable advances throughout the decades. Of all advances, catalysis is playing a crucial role, since it can lower the activation energy of normally inert starting materials for further chemical reactions. In this context, the catalytic direct activation and transformation of hydroxyl groups (–OH) is of significant value since hydroxyl groups exist in numerous commodity chemicals, pharmaceutical agents and natural products. Arylboronic acids can form covalent bonds with hydroxyl groups in a reversible manner, thus providing transient activation, which bypasses the need for wasteful, expensive and often toxic stoichiometric activating reagents. As an emerging mode of catalysis, boronic acid catalysis (BAC) has the potential to be developed into a versatile strategy for direct hydroxyl group functionalization. To this end, BAC has been applied to the direct activation of carboxylic acids, alcohols and oximes. Several new catalytic methods employing novel arylboronic acids are presented in this thesis.

Chapter 2 describes the development of a direct Friedel-Craft alkylation using π-activated alcohols *via* BAC. Owing to their high Lewis acidity, electron deficient arylboronic acids activate alcohol substrates though polarization of the C–O bond. Mechanistic investigation revealed that the catalytic reactivity of arylboronic acids is influenced by their *ortho*-substituents. Moreover, this chapter also details the discovery of a novel cationic ferrocenium boronic acid salt for the efficient Friedel-Crafts benzylation of challenging substrates.

Due to its broad functional group tolerance, BAC can potentially be employed cooperatively with other types of catalytic systems. Chapter 3 describes the development of a dual catalytic methodology, merging boronic acids and chiral amines, for the direct asymmetric allylation of branched aldehydes with allylic alcohols. Through the optimization of boronic acids and various

chiral amines, compounds containing valuable all-carbon quaternary centers can be accessed in good yield and high enantioselectivity. This research was also applied in the first catalytic and asymmetric synthesis of a key building block for the synthesis of a NK1/NK3 receptor antagonist.

Other functional groups containing hydroxyl units may also be amenable to BAC. Chapter 4 describes the discovery of a unique class of arylboronic acids with *ortho*-carboxyesters for catalysis of the Beckmann rearrangement of oximes. A broad substrate scope of oximes with various functional groups is achieved. Further investigations strongly suggest a two-step mechanism comprised of a novel boron induced oxime transesterification and a boron assisted Beckmann rearrangement.

Preface

A part of Chapter 2 of this thesis, mostly from Section 2.3 to Section 2.4, has been published as Ricardo, C. L.; Mo, X.; McCubbin, J. A.; Hall, D. G. “A Surprising Substituent Effect Provides a Superior Boronic Acid Catalyst for Mild and Metal-Free Direct Friedel-Crafts Alkylations and Prenylations of Neutral Arene” *Chem. Eur. J.* **2015**, *21*, 4218–4223. I was involved in part of the examination of the reaction scope. I was responsible for the mechanistic investigation of the higher reactivity of 2,3,4,5-tetrafluorophenyl boronic acid, which included the pKa determinations, construction of the linear curve and the catalyst recovery experiments. I assisted in the preparation of supporting information with McCubbin, J. A. and Hall, D. G. Hall, D. G. was the supervisory author and was involved with concept development.

The other part of Chapter 2 of this thesis, mostly from Section 2.5 to Section 2.10, has been published as Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J. A.; Hall, D. G. “Unsymmetrical Diarylmethanes by Ferroceniumboronic Acid Catalyzed Direct Friedel-Crafts Reactions with Deactivated Benzylic Alcohols: Enhanced Reactivity due to Ion-Pairing Effects” *J. Am. Chem. Soc.* **2015**, *137*, 9694–9703. I was responsible for the major part of the experimental work including optimization of the reaction conditions, examination of the substrate scope and mechanistic studies. I was also responsible for data collection and analysis. Dansereau, J. was an undergraduate student under my supervision and assisted in the aforementioned research. I wrote the supporting information with assistance from Yakiwchuk, J. and Hall, D. G. McCubbin, J. A. and Hall, D. G. were the supervisory author and was involved with concept development.

Chapter 3 of this thesis has been published as Mo, X.; Hall, D. G. “Dual Catalysis Using Boronic Acid and Chiral Amine: Acyclic Quaternary Carbons via Enantioselective Alkylation of Branched Aldehydes with Allylic Alcohols” *J. Am. Chem. Soc.* **2016**, *138*, 10762–10765. I was responsible for all the experimental work including optimization of the reaction conditions, catalyst synthesis and screening, examination of the substrate scope, application of the method, comparative and mechanistic studies. I was responsible for data collection and analysis. I wrote the manuscript with assistance from Hall, D. G. Hall, D. G. was the supervisory author and was involved with concept development.

The research in Chapter 4 was conducted with Morgan, T. D. R. I was responsible for the major experimental work in Chapter 4 including optimization of the reaction conditions, catalysts

synthesis, part of the mechanistic studies and a small part of the substrate scope. Morgan, T. D. R. finished the majority of the substrate scope. I was also responsible for data collection and analysis. I wrote the manuscript with assistance from Morgan, T. D. R. and Hall, D. G. Hall, D. G. was the supervisory author and was involved with concept development.

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I would also like to thank the excellent administrative and research fellows in the Department of Chemistry. Anita Weiler, Lynne Lechelt and Bonnie Gover have been very kind and wonderful. I am grateful for those individuals from the analytical labs, NMR service, mass spectrometry and the storeroom, in particular, Ed Fu, Wayne Moffat, Jing Zheng, Angelina Morales-Izquierdo Mark Miskolzie and Matthew Kingston. They devote valuable time and effort for my benefit.

My appreciation and thanks are also offered to the following individuals and organizations that helped the research described in this thesis. I would like to thank Professor J. Adam McCubbin for all the discussion and suggestion during his sabbatical in our group. I am very grateful for the help from Julien Dansereau, Dr. Carolynne Ricardo and Joshua Yakiwchuk in the Friedel-Crafts alkylation project. I am most indebted to Dr. Timothy Morgan for his effort in the Beckmann rearrangement project. Most of all, I feel extremely thankful for the funding from the following organizations: University of Alberta for a Thesis-Based Master's Recruitment Scholarship and Alberta Innovates – Health Solutions for a Graduate Studentship.

I would certainly not forget the Hall group members, past and present, for the time we spent working together. I have learnt a lot from these talented people. I am extremely thankful to Dr. Tristan Verdelet. He is kind, considerate, and mostly importantly, incredible. I would also like to thank Mike Bell, Alice Chan, Helen Clement, Vitor Cunha, Samantha Kwok, Timothy Morgan, Amar Sahloul, Olivier Soueidan, Ho-Yan Sun, Ryan Sweeney and Dr. Hayley Wan for their friendship.

Last but not least, I am extremely thankful to my family for their unconditional love and support. They are the people who are always there for me and help me through the most difficult times. I will be always grateful to them.

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List of Abbreviations

Ac	Acetyl
ACS	American Chemical Society
APIs	Active Pharmaceutical Ingredients
app	Apparent
Ar	Aryl group
BAC	Boronic Acid Catalysis
$[BAr^F_4]^-$	Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
Boc	*tert*-Butyloxycarbonyl
Bn	Benzyl
bpy	2,2'-Bipyridyl
br	Broad
br s	Broad singlet
n-Bu	Butyl
t-Bu	*tert*-Butyl
Bz	Benzoyl
calcd	Calculated
cat.	Catalyst
(*S*)-CBS	(*S*)-(−)-2-Methyl-CBS-oxazaborolidine
CFL	Compact Fluorescent Lamp
cm^{-1}	Wavenumbers
CNC	Cyanuric chloride
COD	1,5-Cyclooctadiene
CPI-Cl	Dichloridecyclopropene
Cy	Cyclohexyl
d	Doublet
DCC	N,N'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
DEAD	Diethyl azodicarboxylate

$dFCF_3ppy$	3,5-Difluoro-2-(5-(trifluoromethyl)-2-pyridinyl)
DIPEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMAPO	4-Dimethylaminopyridine N-oxide
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
dr	Diastereomeric ratio
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dq	Doublet of quartets
dt	Doublet of triplets
dtbbpy	4,4’-Di-tert-butyl-2,2’-dipyridyl
E	Electrophile
EDC·HCl	N-(3-Dimethylaminopropyl)-N’-ethylcarbodiimide hydrochloride
ee	Enantiomeric excess
EI	Electron impact
equiv	Equivalents
er	Enantiomeric ratio
ESI	Electrospray Ionization
Et	Ethyl
Fc^+	Ferrocenium cation
FDA	The Food and Drug Administration
h	Hour
HFIP	Hexafluoro-2-propanol
HMBC	Heteronuclear multiple-bond correlation spectroscopy
H-mont	Proton-exchanged montmorillonites
HOBt	Hydroxybenzotriazole
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear single-quantum correlation spectroscopy
IBX	2-Iodoxybenzoic acid
IR	Infrared Spectroscopy
IUPAC	International Union of Pure and Applied Chemistry

L	Ligand
LA	Lewis Acid
LED	Light-Emitting Diode
LiHMDS	Lithium bis(trimethylsilyl)amide
LUMO	Lowest Unoccupied Molecular Orbital
m	Multiplet
Me	Methyl
MeCN	Acetonitrile
mol	Mole
Ms	Methanesulfonyl
MS	Molecular Sieves
MTBE	Methyl *tert*-butyl ether
(*R*)-MTPA	(*R*)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetyl
NHC	*N*-Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
Ns	2-Nitrobenzenesulfonyl
Nu	Nucleophile
OMs	Mesylate
OTf	Triflate
PCC	Pyridinium chlorochromate
Ph	Phenyl
picryl	2,4,6-Trinitrophenyl
pin	Pinacolato
PMA	Phosphomolybdic acid
PMP	*para*-Methoxyphenyl
PPA	Polyphosphoric acid
ppy	2-Phenylpyridyl
i-Pr	Isopropyl
n-Pr	Propyl
PTLC	Preparative Thin Layer Chromatography
q	Quartet
qd	Quartet of doublets
qq	Quartet of quartets
qt	Quartet of triplets

quint	Quintet
rt	Room temperature
s	Singlet
sext	Sextet
t	Triplet
TAPC	Triphosphazene
TBS	*tert*-Butyldimethylsilyl
td	Triplet of doublets
temp	Temperature
TES	Triethylsilyl
Tf	Triflyl
TFA	Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMOF	Trimethyl orthoformate
TMS	Trimethylsilyl
T3P	Propylphosphonic anhydride
(*R*)-TRIP	(*R*)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
Ts	*para*-Toluenesulfonyl
TsOH	*para*-Toluenesulfonic acid
TS	Transition State
tt	Triplet of triplets
tq	Triplet of quartets
W	Wattage

Chapter 1 Introduction: Recent Advances in Catalysis for Direct Alcohol C–O bond Activation

1.1 Definition and introduction of alcohol functional group

The term hydroxyl group refers to the functional entity –OH. Unlike hydroxyl, which represents the radical OH according to IUPAC rules,[1] the hydroxyl group widely exists in a variety of compounds such as water, alcohol, phenol, oxime, hydroxamic acid, carboxylic acid and mineral acid (**Figure 1-1**). For instance, when the hydroxyl group is attached to saturated carbon atoms (sp^3C–OH or R–OH), alcohols are formed.

The chemistry of alcohols is vital and popular owing to their ready availability, prevalence in bioactive motifs, low toxicity and relatively high stability. Various alcohol products can be obtained through partial petroleum oxidation, biomass deoxygenation and other industrial processes directly from raw materials.[2] For instance, over 2.5 billion gallons of ethanol fuel was produced worldwide in 2015.[3] From there, hundreds of thousands of industrial chemicals and daily commodities can be produced *via* further chemical transformations.[4] According to the Alfa Aesar catalog, it is estimated that more than 2500 different alcohol compounds are commercially available.[5] Furthermore, approximately 65% of the biologically relevant natural products and 40% of the commercial pharmaceutical agents contain alcohol units.[6]

Chemical reactions with alcohol substrates are fundamental for many important carbon-carbon and carbon-heteroatom bond formation reactions, such as oxidation, reduction, dehydration, nucleophilic substitution, rearrangements, and many others. Versatile installation, manipulation and transformation of the alcohol functional group lie at the heart of modern synthetic organic chemistry.

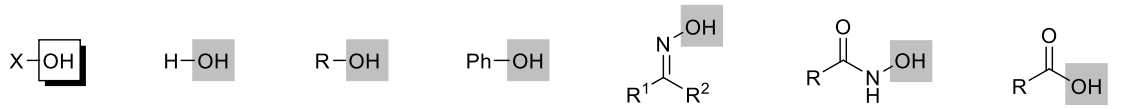
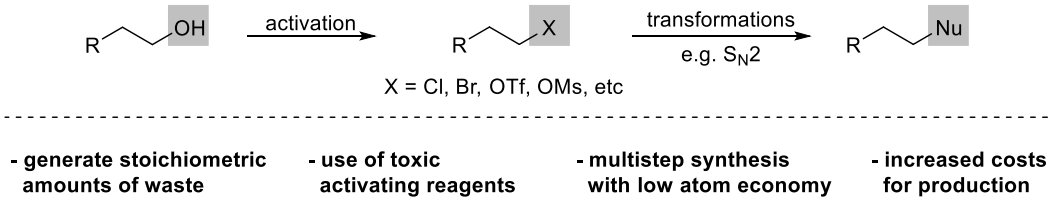


Figure 1-1. Functional entities that contain a hydroxyl group.

1.2 Traditional methods for C–O bond activation of alcohols

As one of the most important aspects of alcohol chemistry, the alcohol C–O bond activation has received great attention as it is often the key step in many widely used transformations such as nucleophilic substitutions, eliminations, and rearrangement reactions. However, the relatively inert property of the C–O bond has rendered its activation and transformation rather challenging. Research on alcohol C–O bond activation for chemical synthesis has come a long way. One of the earliest documented alcohol activation of this kind dates back to as far as 1860 when the pinacol rearrangement was reported to produce *tert*-butyl methyl ketone.[7] The use of excess strong acids certainly allows substitution or elimination to occur, however, only with structurally simple alcohols under harsh conditions. Since then, more effort has been placed on the development of methods with broader substrate scope and more controllable conditions. Common strategies follow the idea to first convert the hydroxyl group into activated species (e.g. halide, sulfonate, oxyphosphonium, etc.), then to effect the desired reactions (**Scheme 1-1**). These activation methods include, but are not limited to, the Appel reaction,[8] Mitsunobu reaction,[9] Zaitsev elimination,[10] Chugaev reaction[11] and the Grieco elimination.[12] These traditional transformations deliver great efficiency and wide applicability in the pharmaceutical industry. A survey in 2006 showed that 2% of the reactions performed in the synthesis of active pharmaceutical ingredients (APIs) directly related to the interconversion of alcohols to sulfonates or halides for further manipulation.[13] These traditional methods for alcohol C–O bond functionalization, however, are undesirable. Significant drawbacks come from the production of large amounts of waste though the activation process involving stoichiometric reagents. These activators also often display safety and toxicity problems for manufacturing. Overall, the strategy of multistep functional group interconversion exhibits fairly low atom economy and greatly increases production costs. Consequently, since 2005, the ACS Green Chemistry Institute Pharmaceutical Roundtable has ranked the activation of alcohol as one of the most important research areas.[14]



Scheme 1-1. Traditional methods for alcohol C–O bond activation and associated drawbacks.

1.3 Catalysis development for direct alcohol activation

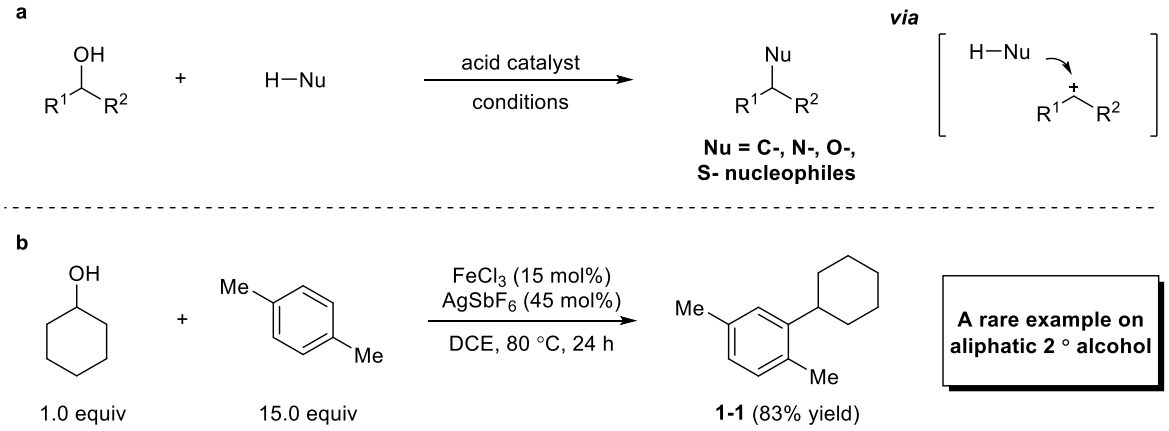
The use of catalysis in direct C–O bond activation would be an ideal solution for the alcohol functionalization since the only by-product is water. However, reactions of this kind have proven to be highly challenging. The difficulty lies in several thermodynamic and kinetic pitfalls in the activation-transformation process. The C–O bond dissociation energy is ~95 kcal/mol.[15] The energy required to break such a strong bond is rarely compensated by the formation of the new bonds, which are often weaker. Even though external energy can be supplied, the activation process faces intrinsically high activation barriers as hydroxyl groups are poor leaving groups regardless of reaction type. Furthermore, generation of water can potentially undermine the catalyst and renders the entire activation process sluggish. Successful catalytic systems must be very carefully designed. Despite all the challenges, significant progress has been made in the area of direct alcohol activation.

1.3.1 Direct alcohol activation *via* catalytic nucleophilic substitutions

1.3.1.1 Catalytic direct alcohol activation *via* S_N1 and other cationic reactions

Lewis- or Brønsted acid catalysis is one of the most popular methods for direct functionalization of tertiary and π-activated alcohols. The canonical reaction mechanism involves transient polarization of the C–O bond by coordination or protonation of the alcohol unit, formation of a relatively stable carbocation and attack of a nucleophile or other downstream cationic reaction. The use of acids, especially Lewis acids, may seem counterintuitive for direct alcohol activation where water is generated as the by-product. On the contrary, certain Lewis acids express moderate to excellent catalytic activity in the presence of water, providing that they exhibit suitable hydrolysis constant and water exchange rate constant as described by Kobayashi.[16] In fact, as Rueping and co-workers stated in their review, a number of elements, including but not limited to H, Sc, Fe, Nb, In, La, Nd, Sm, Yb, Hf, W, Ir, Pt, Au, and Bi, have shown to be able to direct Friedel-Crafts alkylation of certain alcohols.[17] Moreover, a broad range of nucleophiles are suitable such as arenes, alkenes, 1,3-diketones, nitriles, azides, amines and even boronic acids (**Scheme 1-2a**).[18] However, Lewis- or Brønsted acid catalyzed alcohol activation generally shares some limitations, namely the need to use π-activated or tertiary alcohols in most cases and the lack of methods for enantioselective control over the short-lived prochiral carbocation species. Only recently, a rare catalytic system with $FeCl_3/AgSbF_6$ was reported by Cook and co-

workers, where cyclohexanol was activated for direct Friedel-Crafts alkylation of simple arenes such as *p*-xylene (**Scheme1-2b**), affording the product **1-1** in high yield.[19] Nevertheless, transformations of the π-activated alcohols through carbocation intermediates have been extensively used to construct numerous carbon-carbon and carbon-heteroatom bonds for organic synthesis.[20]

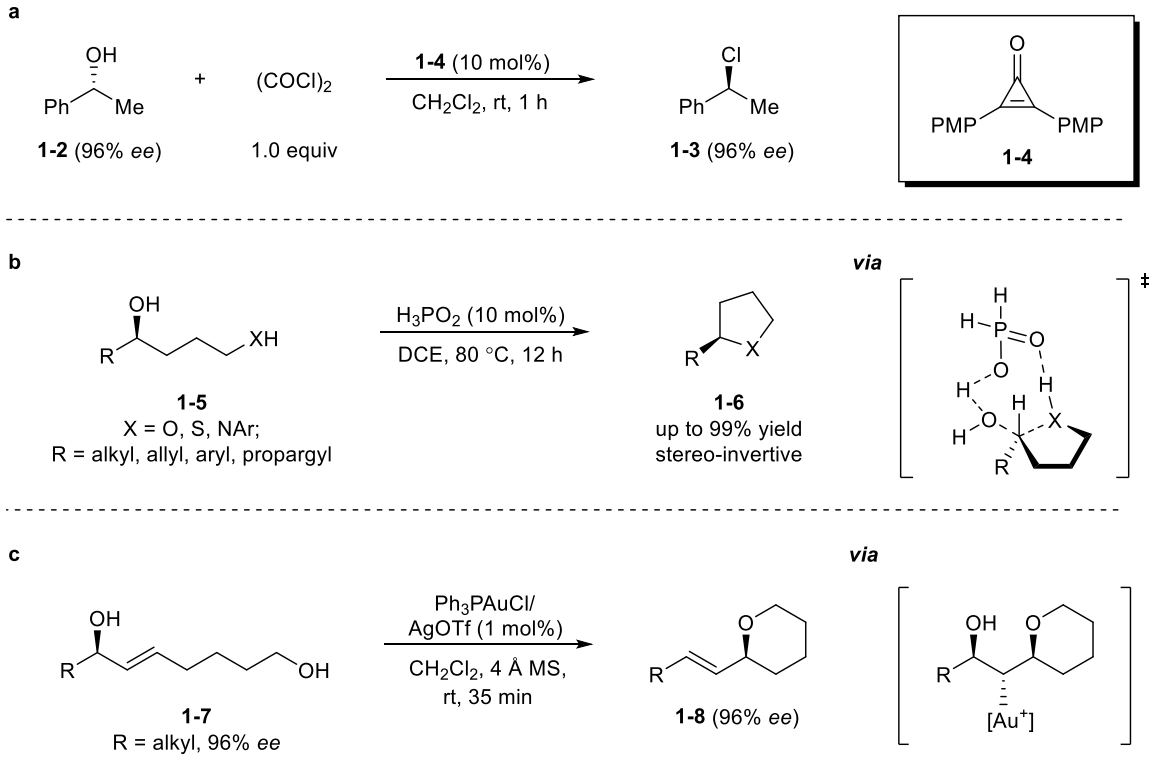


Scheme 1-2. (a) Catalytic direct alcohol activation via S_N1 and other cationic reactions. (b) A challenging Friedel-Crafts alkylation of *p*-xylene using a non-π-activated secondary alcohol.

1.3.1.2 Catalytic methods for S_N2 and S_N2' reactions

In comparison with ionization of alcohol substrates in S_N1 reactions, direct catalytic dehydrative S_N2 and S_N2' reactions are much less developed. Several catalytic variants of the Mitsunobu and Appel reactions have been reported by Toy,[21] Taniguchi,[22] Aldrich,[23] Denton[24] and Lambert,[25] respectively. For example, the optically pure alcohol **1-2** could be transformed to the chloride **1-3** with cyclopropenone **1-4** as the catalyst (**Scheme 1-3a**).[25] However, stoichiometric reagents were used to regenerate the active species for catalyst turnover in these reactions. The reported systems of this kind are not truly catalytic direct activation of alcohols and they are not discussed in detail in this section. In 2015, Samec and co-workers reported a remarkable Brønsted acid catalyzed S_N2 type reaction (**Scheme 1-3b**).[26] Starting from optically pure alcohol substrates **1-5**, the direct intramolecular nucleophilic substitution occurred with a high degree of chirality transfer in the presence of catalytic phosphinic acid. The reaction is thought to occur through a well-organized hydrogen bonding network where the phosphinic acid is associated with both the nucleophile and the leaving alcohol simultaneously. Compared with the relatively

simple S_N2 reactions, the case of S_N2' reactions are less straightforward. A gold (I) complex is known to catalyze the direct allylic alcohol substitution in a stereospecific manner as reported independently by Aponick,[27] Widenhoefer[28] and Bandini[29] (**Scheme 1-3c**). The accepted general mechanism involves the complexation of gold (I) to the alkene moiety followed by anti-addition of the internal nucleophile and anti-elimination of gold (I) and the alcohol. Thus, the cyclized product **1-8** can be obtained in high enantiomeric purity.[27]

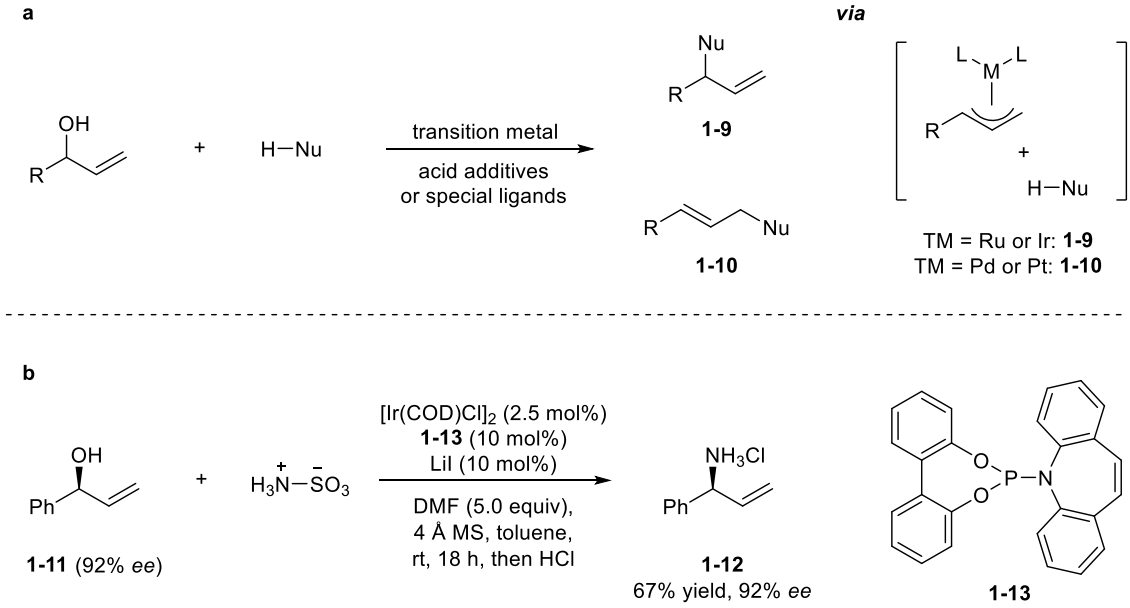


Scheme 1-3. Catalytic direct alcohol activation *via* S_N2 and S_N2' reactions: (a) cyclopropenone catalyzed chlorination of a chiral alcohol; (b) phosphinic acid catalyzed intramolecular S_N2 reaction; (c) gold catalyzed intramolecular S_N2' reaction.

1.3.2 Direct alcohol activation *via* transition metal π-allyl intermediate

Transition metal catalyzed π-allyl chemistry has received enormous attention since the 1970s when the Tsuji-Trost reaction was first introduced.[30] Variants were soon developed: use of different metals, examination of leaving groups, stereochemical control with novel ligands and construction of new carbon-carbon and carbon-heteroatom bonds.[31] Despite great progress, the direct use of allylic alcohol substrates for transition metal π-allyl chemistry is still challenging.

While a number of transition metals (Ni, Mo, Ru, Pd, Ir and Pt) were reported to be able to activate allylic alcohols directly, these methods share similar strategies (**Scheme 1-4a**).[32] The use of aqueous or protic media was shown to be beneficial for the activation process.[33] Oshima and co-workers proposed that elimination of the –OH was accelerated due to efficient hydration of the allylic alcohol in the protic environment. The newly formed hydroxide anion is thought to be sufficiently stabilized by a hydrogen-bonding network.[33] The other common strategy is the addition of Lewis- and Brønsted acids (*p*-toluenesulfonic acid, CO_2, Et_3B, $Ti(OiPr)_4$, As_2O_3, etc) to activate the alcohol unit *in situ*.[34] Polarization of the C–O bond by acidic additives enhances the rate of formation of the π-allyl intermediate. Last but not least, the use of special ligands was also proven beneficial.[35] However, most of the designed ligands display a lack of generality and dubious potential for asymmetric variants. A nice example of direct amination featuring alcohol **1-11** with an iridium catalyst combining the addition of lithium iodide and the use of special ligand **1-13** is shown in **Scheme 1-4b**.[36] Direct allylic alcohol activation *via* transition metal π-allyl chemistry remains a popular method; however, it is only applicable to this specific class of substrates.



Scheme 1-4. Direct alcohol activation *via* transition metal π-allyl intermediate: (a) general strategies; (b) a specific example of direct allylic alcohol amination with Lewis acid additive and special ligand by iridium π-allyl chemistry.

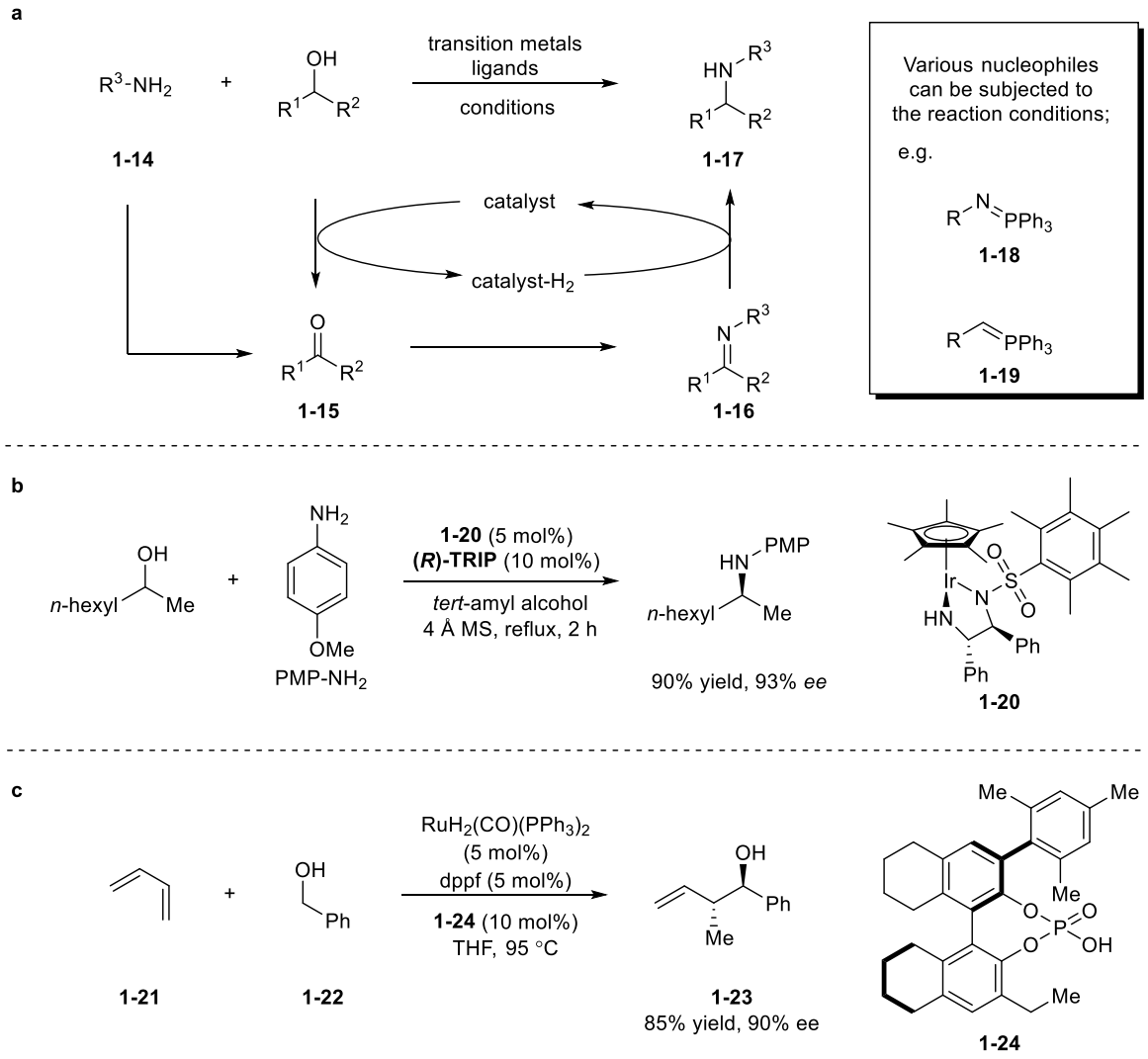
1.3.3 Direct alcohol activation *via* borrowing hydrogen strategy

The borrowing hydrogen methodology offers a different perspective for direct alcohol activation compared to the nucleophilic substitution. For an example of the alkylation of amines with alcohols, a traditional S_N2 reaction generally involves a two-step sequence: activation of the alcohols into halides followed by the nucleophilic substitution from the amines. Over alkylation is a severe problem in a regular S_N2 process. In contrast, the borrowing hydrogen strategy bypasses this problem by exploiting the redox active metal complexes and their ability to temporarily remove hydrogens from alcohols. The corresponding aldehydes or ketones can then undergo other reactions that result in new unsaturated moieties. Eventually, the reduced metal complex transfers the hydrogens back to the newly formed unsaturated species. A general reaction mechanism of the transfer hydrogenation strategy for the direct amination of alcohols with amines is described in **Scheme 1-5a**.[37]

While certain metals such as Al, Ni, Cu, Pd and Pt, were shown to be able to catalyze the reactions under heterogeneous conditions, the use of homogeneous Ru and Ir complexes is of great interest as various ligands can be introduced for asymmetric catalysis.[38] As depicted in **Scheme 1-5b**, the direct asymmetric amination of alcohols was achieved with a chiral iridium catalyst **1-20** and a chiral phosphoric acid, reported by Zhao and co-workers.[39] Recently, due to the abundance and low toxicity of iron, more research on the iron based cyclopentadienone complexes for alcohol activation with a similar mechanism was also reported.[40]

As an extension of the borrowing hydrogen strategy, direct construction of C–C bonds from alcohols can be also achieved by using carbon nucleophiles,[37] such as Wittig reagents **1-19** (**Scheme 1-5a**). Remarkably, further modification of the borrowing hydrogen method to alkenes and other unsaturated functional groups by Krische and co-workers has led to great progress in the construction of tertiary carbon centers for natural product synthesis.[41] As shown in **Scheme 1-5c**, transfer hydrogenation from alcohol **1-22** to alkene **1-21** results in homoallylic alcohol **1-23** in high yield and enantioselectivity with chiral phosphoric acid **1-24**.

The borrowing hydrogen strategy has become a popular method for direct functionalization of alcohols, in particular the direct amination of alcohols. However, as one of the drawbacks, this strategy cannot be applied to the activation of tertiary alcohols, since they cannot be oxidized into the corresponding aldehydes or ketones.

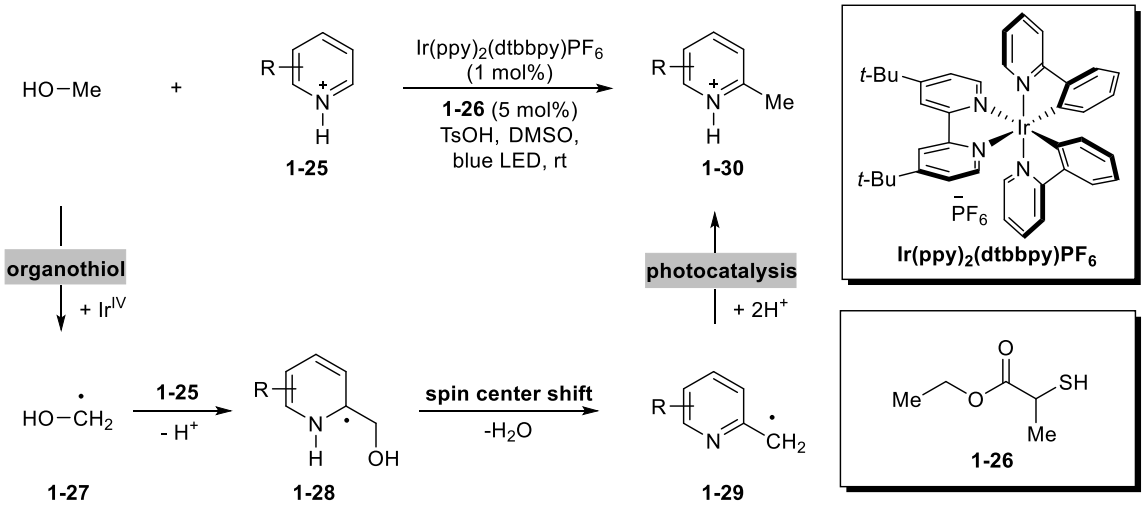


Scheme 1-5. Direct alcohol activation *via* borrowing hydrogen strategy: (a) a general reaction mechanism; (b) an example of direct asymmetric amination of alcohols; (c) transfer hydrogenation from alcohols to alkenes for the synthesis of chiral homoallylic alcohols.

1.3.4 Direct alcohol activation *via* radical process

To this day, there has been very little exploration on the direct catalytic activation of alcohols *via* radical pathways. Alcohols as alkylating reagents activated *via* a radical mechanism have only recently been reported by MacMillan and co-workers. Their approach, which combines iridium photoredox catalysis and thiol organocatalysis, mimics the key step of spin-center shift during the enzymatic reduction of ribonucleoside diphosphates into deoxyribonucleoside in DNA

biosynthesis.[42] This complicated dual catalytic system features several interesting mechanistic aspects, which are simplified as follows: (a) generation of the α-hydroxyl radical **1-27** from methanol or other alcohols by thiol **1-26** along with photocatalysis; (b) subsequent Minisci reaction of radical **1-27** to pyridinium **1-25**, affording the α-amino radical **1-28**; (c) facile spin-center shift of radical **1-28**, eliminating a molecule of water, resulting in a benzyl radical **1-29**; (d) reduction of radical **1-29** *via* photocatalysis in the presence of acids eventually leading to the alkylated product **1-30** (**Scheme 1-6**).[43] Despite the scarcity of literature precedent, alcohol activation *via* radical processes appears to be a promising area.



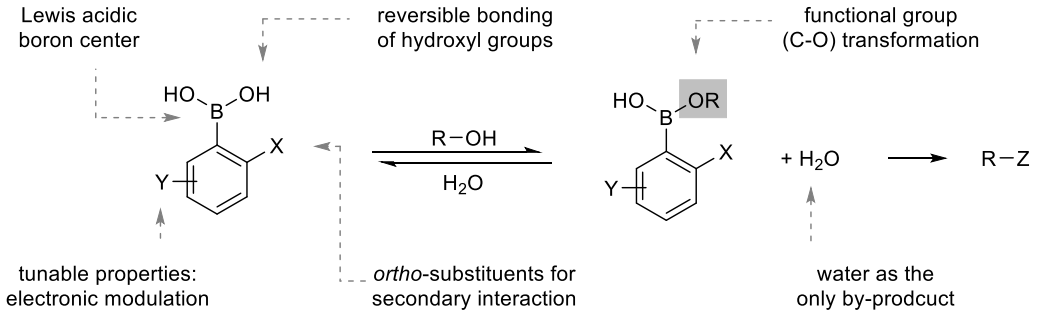
Scheme 1-6. Direct alcohol activation *via* radical process merging photocatalysis and organocatalysis.

1.4 Boronic acid catalysis (BAC)

1.4.1 Overview of boronic acid catalysis

Boronic acids or dihydroxy boranes refer to the trivalent boron containing compounds with two hydroxyl groups and one carbon substituent attached to the boron center. Boronic acids have become important building blocks for organic synthesis in recent decades. They are the key components in many important transformations such as the Nobel Prize-winning Suzuki-Miyaura cross-coupling, Matteson homologation, Chan-Lam coupling, Liebeskind-Srogl coupling, conjugate addition, stereo-retentive oxidation, amination and many other processes.[44] More recently, boronic acids have also found a unique application in drug discovery. For instance,

Bortezomib, a small molecule with an alpha-amino alkyl boronic acid unit, was approved by the FDA in 2003 for the treatment of multiple myeloma.[45] Shadowed by its spectacular versatility in organic synthesis, medicinal chemistry and material science, the potential of boronic acids in green catalysis has long been overlooked. Boronic acids are considered environmental friendly as they eventually decompose into boric acid, which possesses low toxicity. While alkylboronic acids suffer from facile aerobic decomposition, arylboronic acids express a higher degree of stability and serve as an ideal candidate for the catalytic activation of hydroxyl groups.[44] Comprised of a Lewis acidic oxophilic boron center, arylboronic acids can form covalent bonds with hydroxyl groups in a reversible manner,[46] thus providing transient polarization and activation of the C–O bond from alcohols, carboxylic acids, carbonyl groups, etc. Downstream reactions can be achieved by fine tuning the structure and properties of the aromatic ring. In addition, different *ortho*-substituents can be introduced to provide secondary directing or activating effect along with the boronic acid (**Scheme 1-7**). Herein, an overview of boronic acid catalysis (BAC) for the transformation of hydroxyl containing functional groups is presented.

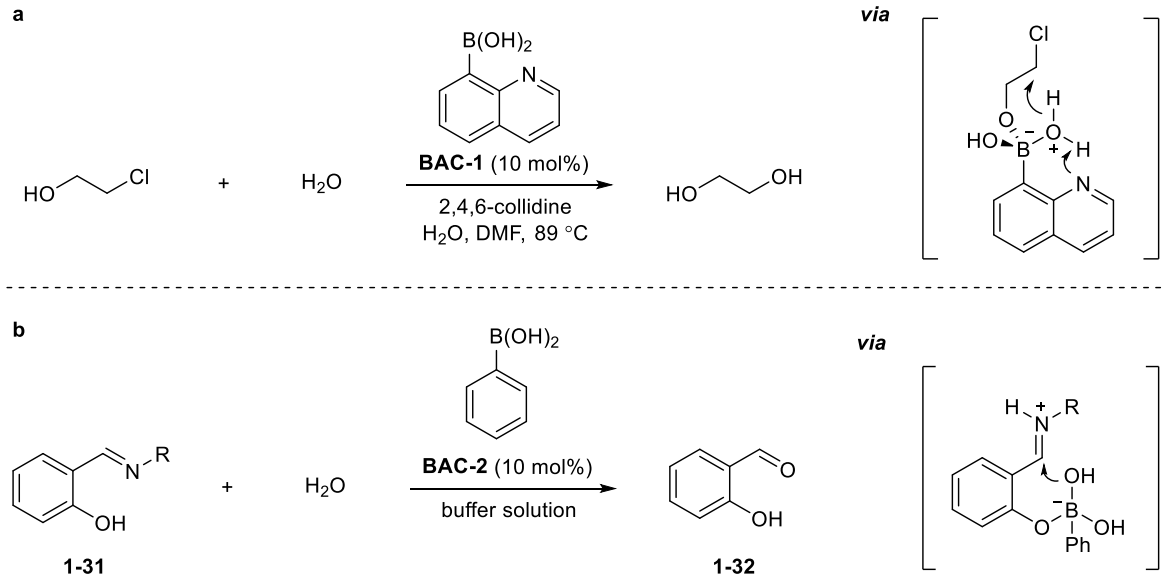


Scheme 1-7. The concept of boronic acid catalysis (BAC).

1.4.2 BAC as reaction template

Boronic acids can reversibly bind to certain substrates with hydroxyl groups *via* boronic ester or boronate formation. Taking advantage of this unique property, boronic acid catalysts can be designed as reaction templates for hydroxyl group containing compounds. In fact, the first boronic acid catalyzed reaction was discovered in this context. In 1963, Letsinger and co-workers reported that 8-quinolineboronic acid **BAC-1** could serve as a bifunctional catalyst for the hydrolysis of 2-chloroethanol. It was proposed that a tetrahedron boronate was formed which brought the substrates in close proximity. The nearby nitrogen then facilitated the

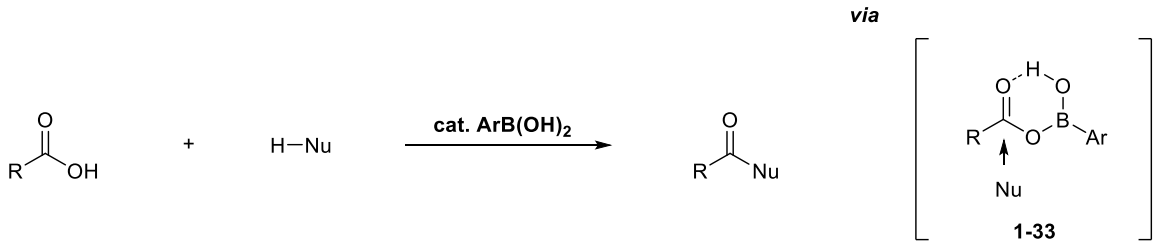
hydroxide substitution through hydrogen bonding (**Scheme 1-8a**).[47] Similarly in 1991, Philipp and co-workers reported a phenyl boronic acid catalyzed hydrolysis of salicylaldehyde imine. The *ortho*-hydroxyl group not only associated with the boronic acid but also enhanced its nucleophilicity for hydrolysis of imine **1-31** (**Scheme 1-8b**).[48]



Scheme 1-8. BAC as reaction templates for hydrolysis reactions: (a) hydrolysis of 2-chloroethanol; (b) hydrolysis of salicylaldehyde imine.

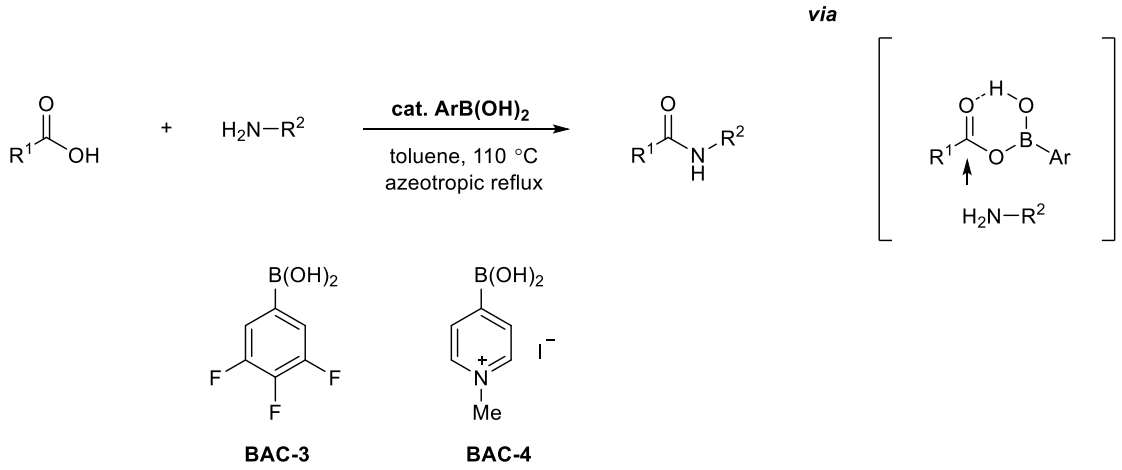
1.4.3 Activation of carboxylic acids

Boronic acid catalysis for carboxylic acid activation has received great attention in the past two decades. It is generally proposed that, when a carboxylic acid and a boronic acid interact, a mono-acyl boronic ester (**1-33**) is formed upon the removal of water, which is then activated for nucleophilic displacement (**Scheme 1-9**).[46]



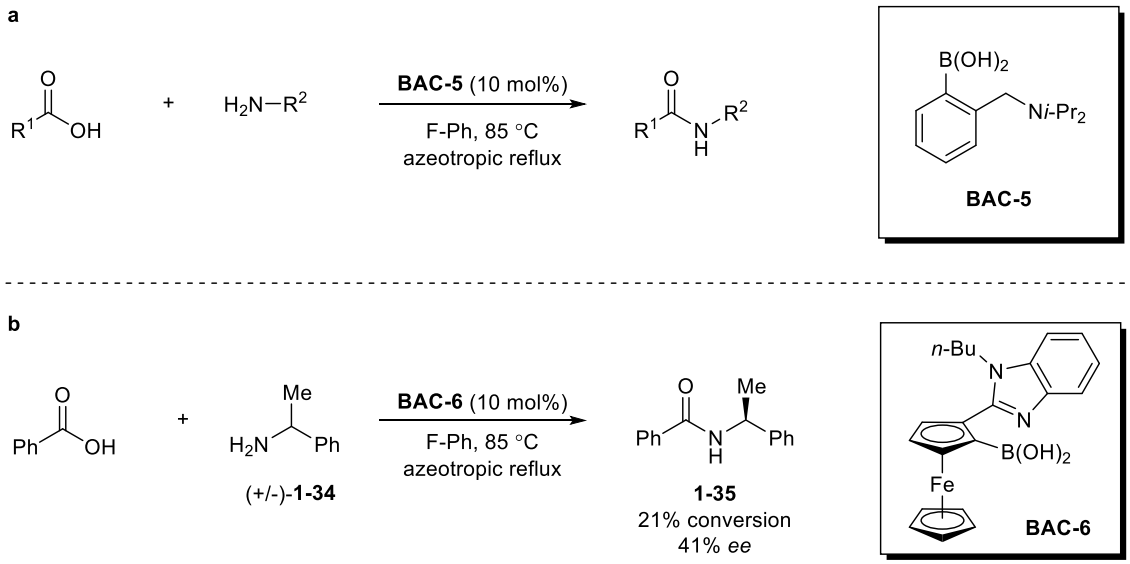
Scheme 1-9. General activation mode of carboxylic acid *via* BAC.

The use of amines as nucleophiles is prevalent due to their potential for catalytic direct amide coupling. In 1996, Yamamoto and co-workers reported the first boronic acid catalyzed direct amidation. In their report, different electron poor boronic acids were examined as they potentially increased the electrophilicity of the mono-acyl boronic ester **1-33** for direct amidation (**Scheme 1-10**). As a result, 3,4,5-trifluoropehnyl boronic acid **BAC-3** was identified as the best catalyst and displayed a high performance for amide coupling in non-polar solvent.[49] Later, the same group introduced pyridiniumboronic acid **BAC-4**, which exhibited higher activity in polar solvents.[50] Reactions with these electron poor boronic acids, however, required very high temperatures (> 110 °C) and azeotropic reflux conditions (**Scheme 1-10**).



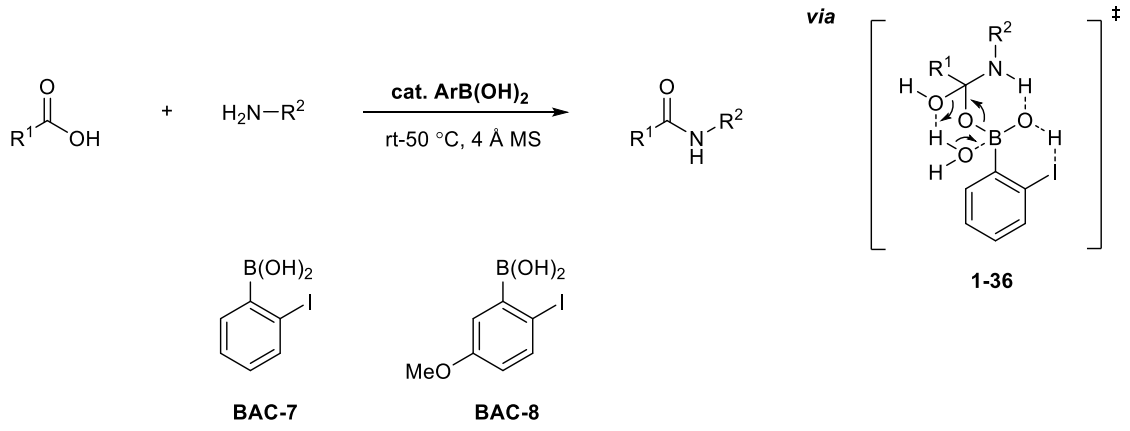
Scheme 1-10. Yamamoto's boronic acids for direct carboxylic acid amidation.

In 2006, Whiting and co-workers described an amino boronic acid **BAC-5** as catalyst for direct amidation. Reactions were performed at lower temperature (~ 85 °C) but still under azeotropic reflux. Even though the exact mechanism is unclear, it was suggested that the amino boronic acid was acting as a bifunctional catalyst which could connect the ammonium or carboxylic acid to the boronic acid by hydrogen bonding (**Scheme 1-11**).[51] This study was also significant because it showed that electron-poor boronic acids were not necessary for catalyzing the direct amidation. Shortly thereafter, the same group identified a ferrocene derived amino boronic acid **BAC-6** for the asymmetric kinetic resolution of racemic amines **1-34** *via* direct amidation (**Scheme 1-11**). Amide **1-35** was isolated with low yield but significant enantiomeric purity.[52]



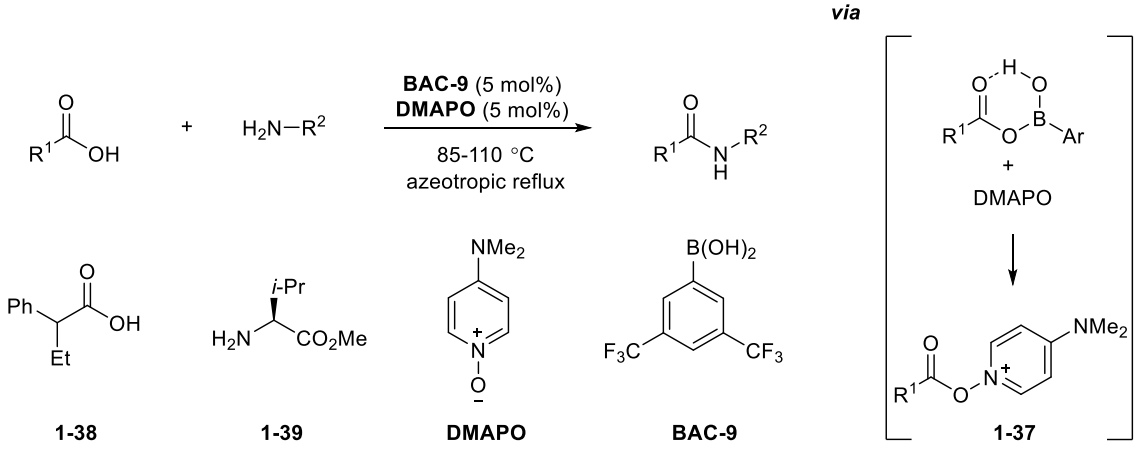
Scheme 1-11. Whiting's boronic acids for direct carboxylic acid amidation.

In 2008, Hall and co-workers introduced the *ortho*-iodophenyl boronic acid **BAC-7** as a superior catalyst. Direct amidation of aliphatic carboxylic acids and amines could be achieved at room temperature with the use of molecular sieves.[53] Later, 5-methoxy-2-iodophenylboronic acid **BAC-8** was discovered to be a more reactive catalyst by the same group.[54] DFT calculations showed that the unique reactivity probably came from the basic character of the *ortho*-iodo substituent, which may facilitate the elimination of water from orthoaminal intermediate **1-36** via halogen-hydrogen bonding (**Scheme 1-12**).[55]



Scheme 1-12. Hall's boronic acids for direct carboxylic acid amidation.

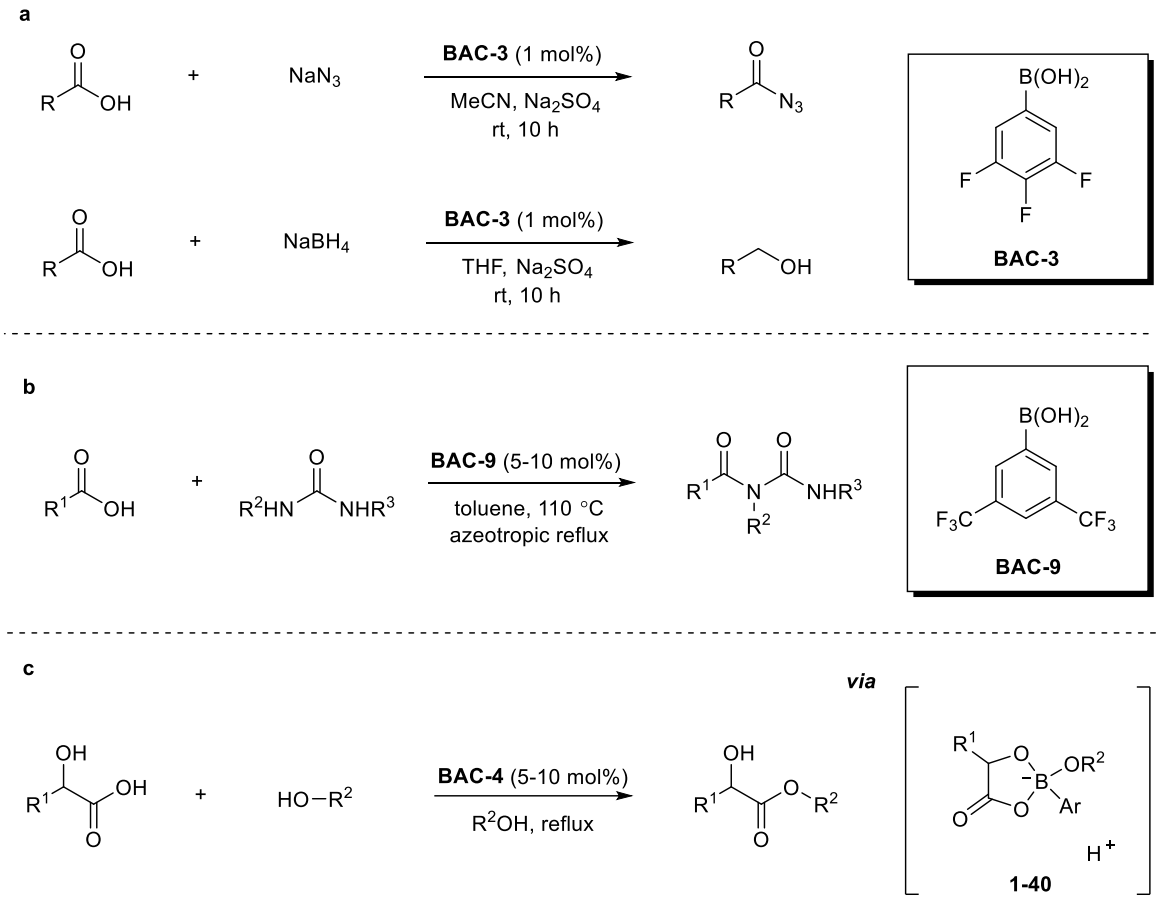
Despite great progress, boronic acid catalyzed direct amidation still faces significant limitations. The process needs water removal either by azeotropic reflux or with molecular sieves. Moreover, reactions with hindered substrates, such as α-branched carboxylic acids, acyclic secondary amines and amino acid derivatives, do not proceed well. In 2016, Ishihara and co-workers designed a cooperative catalytic system with boronic acid and an extra nucleophile DMAPO, 4-dimethylaminopyridine N-oxide, to address the limited substrate scope of direct amidation. The proposed idea featured the attack of the DMAPO to the mono-acyl boronic ester **1-33**, which resulted in a more active cationic acyl intermediate **1-37**. Indeed, the optimized system with boronic acid **BAC-9** and DMAPO performed well for a variety of challenging hindered substrates, such as **1-38** and **1-39**, affording the amide products in high yields. However, removal of water by azeotropic reflux remains an unsolved challenge (**Scheme 1-13**).[56]



Scheme 1-13. Use of DMAPO for direct amidation of challenging substrates *via* BAC.

Apart from amines, other nucleophiles can also be used in the electrophilic activation of carboxylic acid *via* boronic acid catalysis. In 2002, Tale and co-workers reported that the mono-acyl boronic ester **1-33** could be trapped by azide anion in the presence of Na_2SO_4. A variety of acyl azide products were obtained in high yield at room temperature (**Scheme 1-14a**).[57] Later, the same group described the reduction of carboxylic acids to the corresponding alcohols by $NaBH_4$. In both cases, as low as 1 mol% of boronic acid catalyst was used. Although no mechanistic studies were performed, the author suggested that the hydride could serve as a nucleophile for the reduction of the mono-acyl boronic ester **1-33** (**Scheme 1-14a**). [58] Similarly in 2004, as described by Yamamoto and co-workers, urea was examined for the direct substitution of carboxylic acid with boronic acid (**Scheme 1-14b**).[59] In 2005, Yamamoto also discovered that

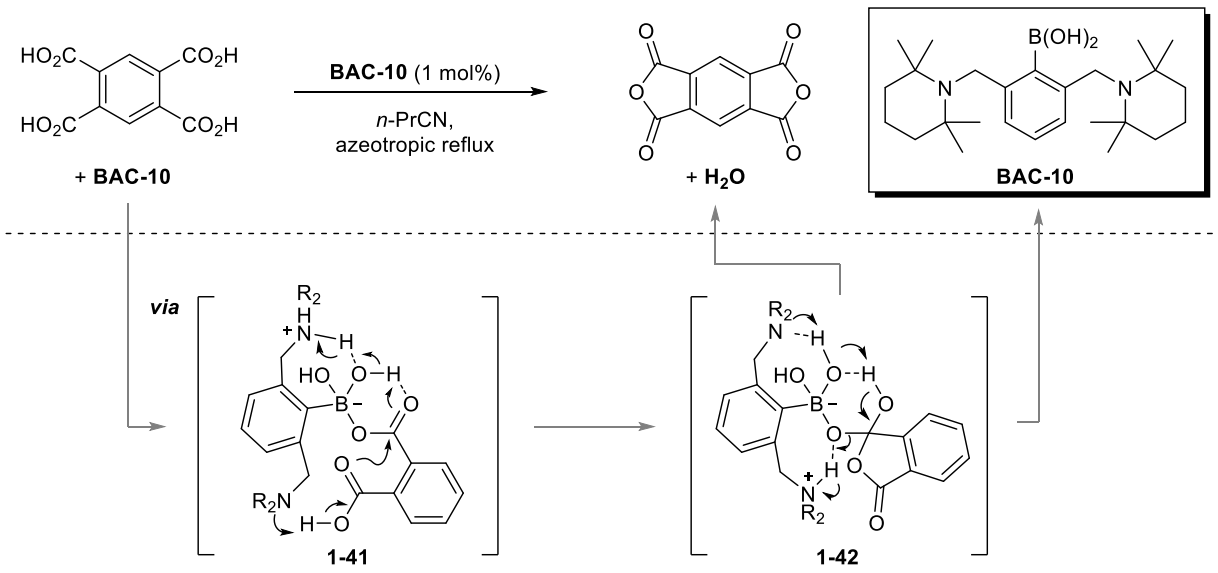
pyridiniumboronic acid **BAC-4** could be used to catalyze the direct esterification of α-hydroxycarboxylic acids with alcohols as the nucleophile. The presence of the α-hydroxyl group to the carboxylic acid was vital to the success of this esterification. An anionic acyloxyborate intermediate **1-40** was proposed for this transformation (**Scheme 1-14c**).[60]



Scheme 1-14. Direct carboxylic acid activation for reactions with other nucleophiles *via* BAC: (a) with azide and hydride; (b) with urea; (c) with alcohol.

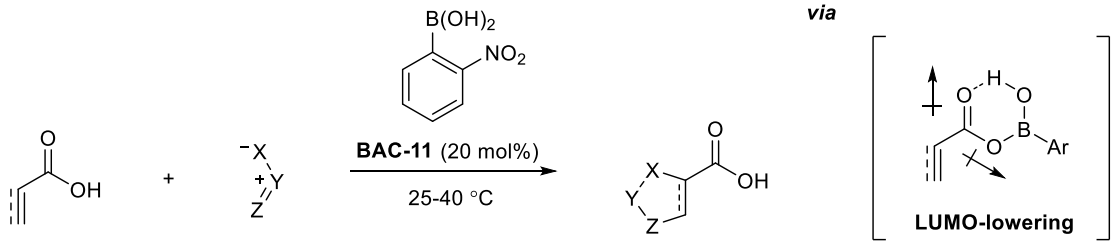
Interestingly, even carboxylic acids could act as nucleophiles in certain cases with a well-designed boronic acid. In 2011, Ishihara and co-workers introduced a bifunctional boronic acid **BAC-10** with bulky Brønsted basic sites at the 2,6-positions for intramolecular carboxylic acid dehydration (**Scheme 1-15**). The authors described the mechanistic picture shown as **1-41**, where one of the amines deprotonated the carboxylic acid as a carboxylate, rendering it more nucleophilic. The other amine unit acted as a hydrogen shuttle for the attack of the carboxylate to the mono-acyl boronic ester, which led to the intermediate **1-42**. After another proton transfer

assisted by the amine units and subsequent dehydration, the anhydride product was formed and the boronic acid was regenerated.[61]



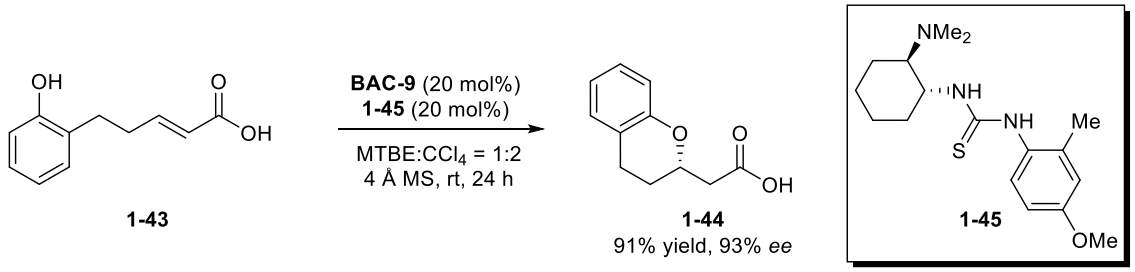
Scheme 1-15. Direct carboxylic acid activation for anhydride formation *via* BAC.

As an extension of the BAC concept, direct activation of α,β-unsaturated carboxylic acids was also explored. In 2010, Hall and co-workers identified *ortho*-nitrophenyl boronic acid **BAC-11** as a general catalyst for the dipolar cycloadditions of α,β-unsaturated carboxylic acids. Cycloadditions between acrylic/propiolic acid derivatives and azides, nitrile oxides, nitrones and dienes could be performed under mild conditions. Inspired by the common mono-acyl boronic ester intermediate **1-33** in direct amidation, it was proposed that the polarizing effect was extended to the unsaturated moieties. A LUMO-lowering transition state was proposed and further supported by NMR spectroscopic studies (**Scheme 1-16**).[62]



Scheme 1-16. Direct activation of α,β-unsaturated carboxylic acids for various dipolar cycloadditions *via* BAC.

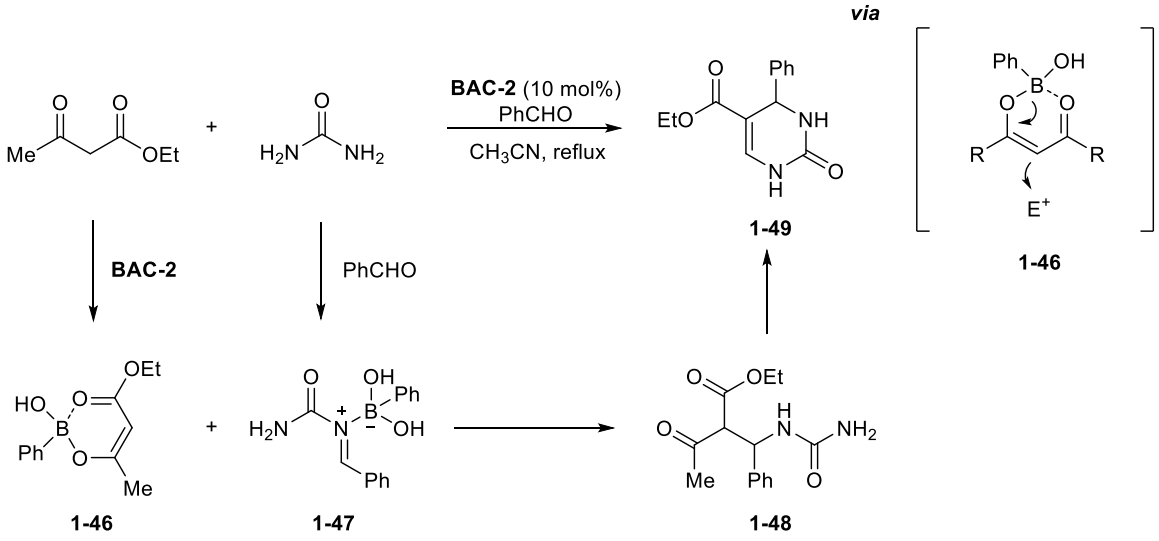
Recently in 2014, Takemoto and co-workers described a boronic acid catalyzed intramolecular oxa-Michael addition of α,β-unsaturated carboxylic acids. The asymmetric variant of the reaction was achieved with a chiral base **1-45**. In their dual catalytic system, α,β-unsaturated carboxylic acid **1-43** tethered with a nucleophilic moiety was able to cyclize under BAC activation and provide product **1-44** in high yield and high enantioselectivity. Although the exact mechanism is not clear, the authors proposed that the chiral base **1-45** was more likely to be associated to the boronate *via* hydrogen bonding rather than chelating with the boronic acid directly. (**Scheme 1-17**).[63]



Scheme 1-17. Asymmetric oxa-Michael addition of α,β-unsaturated carboxylic acid *via* BAC.

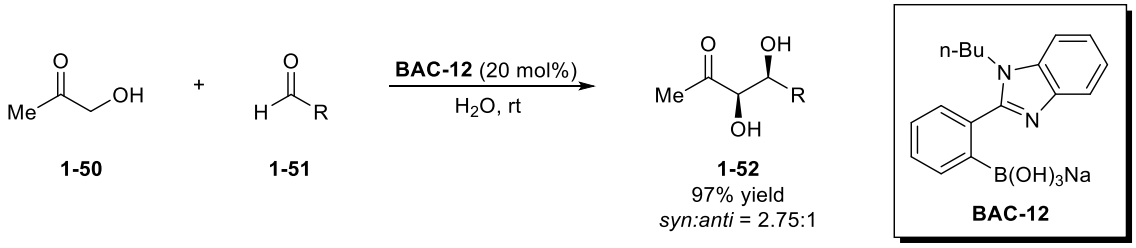
1.4.4 Activation of carbonyl groups

Boronic acid catalyzed carbonyl group functionalization involves the formation of boron enolates (e.g.**1-46**) and their nucleophilic addition to electrophiles. As early as 2006, phenyl boronic acid was identified as an efficient catalyst for the Biginelli reaction by Carboni and co-workers (**Scheme 1-18**). In their communication, a dual activation mode of the catalyst was proposed. In the key mechanistic steps, it was suggested that phenylboronic acid not only promoted the enolate formation of ethyl acetoacetate but also activated the acylimine intermediate **1-47** for nucleophilic addition. This catalytic system provided the desired 3,4-dihydropyrimidinone product **1-49** in good yield.[64]



Scheme 1-18. Direct carbonyl activation for Biginelli condensation *via* BAC.

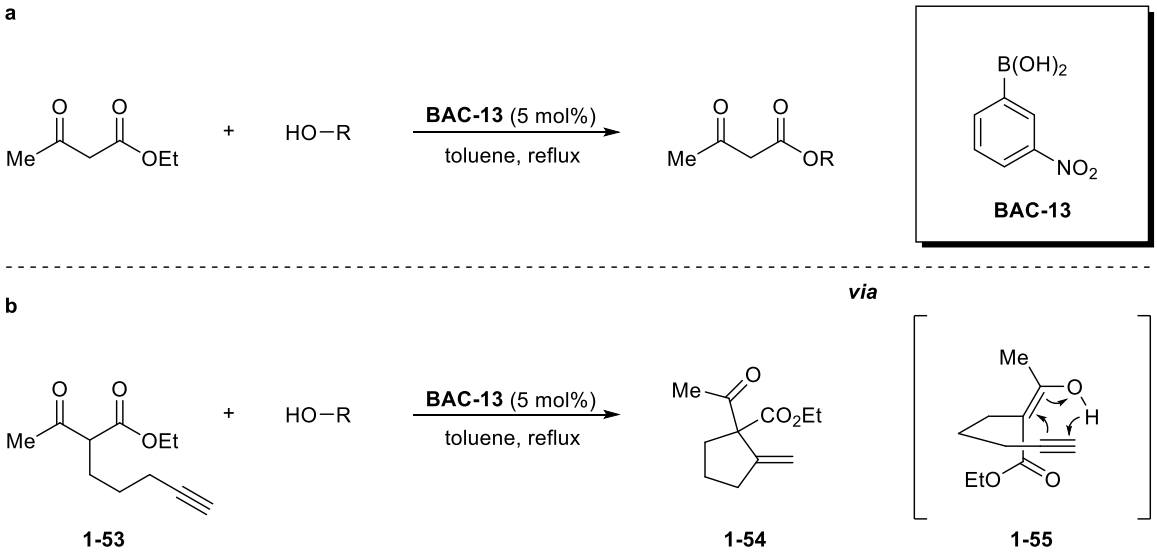
In 2008, Whiting and co-workers reported that the bifunctional aminoboronate **BAC-12** was able to catalyze the *syn*-aldol reaction of α-hydroxyl ketones such as **1-50** and aldehydes in water (**Scheme 1-19**). In their report, it was proposed that the imidazole not only helped accelerate the boron enolate formation but also held the aldehyde in position *via* hydrogen bonding for the nucleophilic attack by the enolate.[65]



Scheme 1-19. Direct carbonyl activation for aldol reaction *via* BAC.

In 2010, a boronic acid catalyzed ene carbocyclization of acetylenic dicarbonyl compounds was introduced by Dixon and co-workers.[66] As described in the report, this interesting discovery arose from the failed attempt of a transesterification with cyclohexanol and **1-53** catalyzed by 3-nitrophenyl boronic acid **BAC-13** as previously reported by Tale (**Scheme 1-20a**).[67] Instead, a cyclized ketoester **1-54** was formed. It was suggested that 3-nitrophenyl boronic acid **BAC-13**

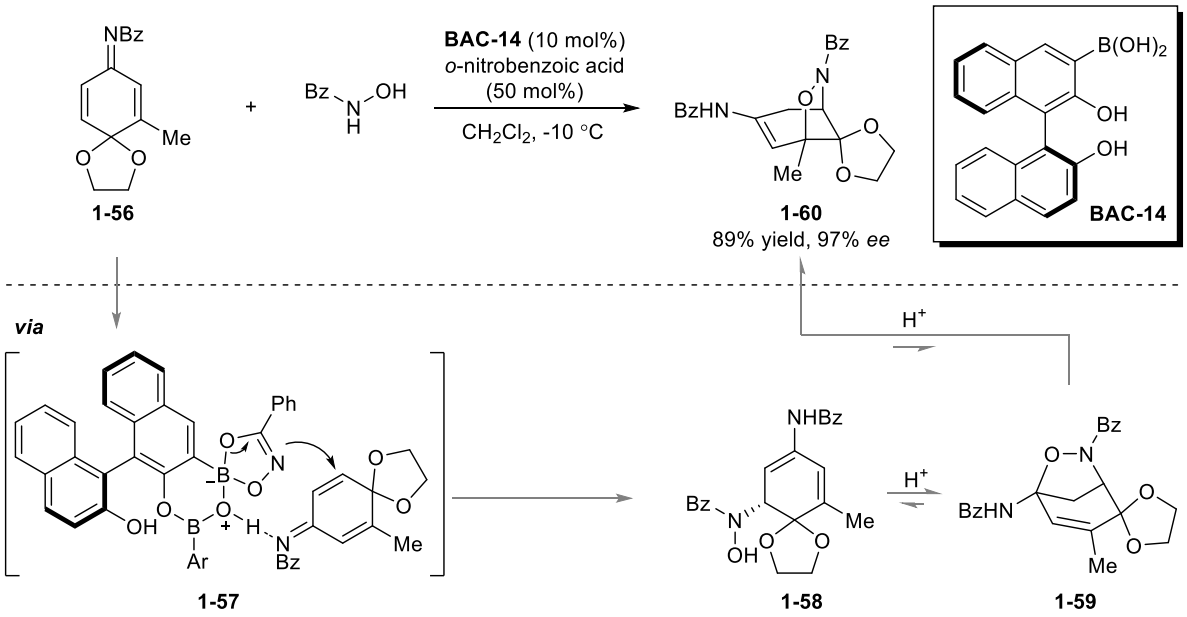
accelerated enolization of the 1,3-dicarbonyl compound. The corresponding enol then underwent an ene reaction with the alkyne moiety as described in transition structure **1-55** (**Scheme 1-20b**).[66]



Scheme 1-20. Direct carbonyl activation for transesterification and ene carbocyclization *via* BAC.

1.4.5 Activation of hydroxamic acids

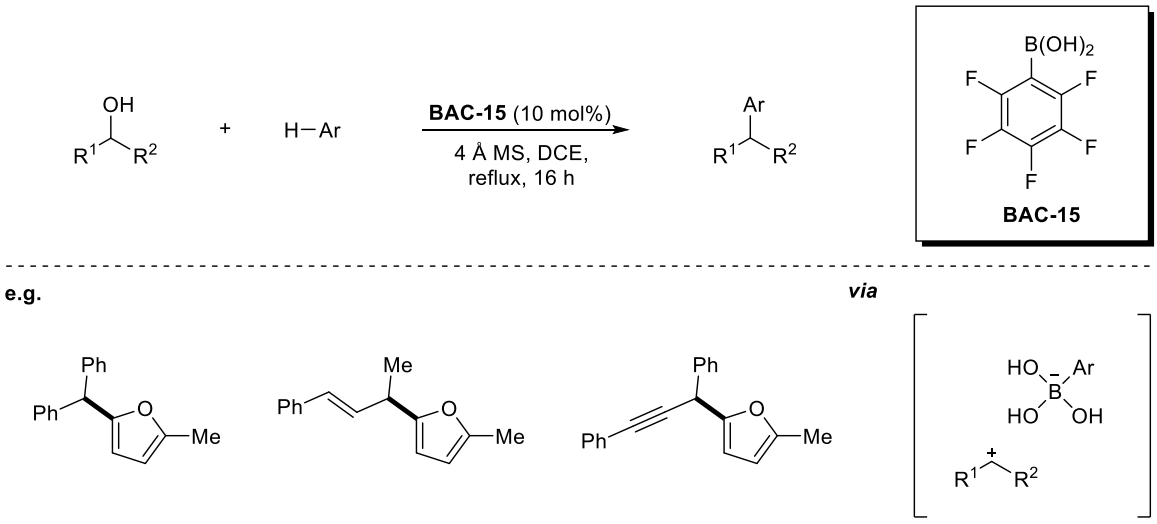
The boronic acid catalyzed direct transformation of hydroxamic acid is relatively underexplored. To the best of the author's knowledge, there is only one reported example for a reaction of this kind. In 2015, Maruoka and co-workers reported the asymmetric aza-Michael addition of hydroxamic acid to a quinone imine ketal facilitated by boronic acid catalysis. In their protocol, the chiral 3-borono-BINOL **BAC-14** was used to promote the aza-Michael addition. During this process, a rigid dimeric catalytic species **1-57**, which was comprised of a dioxazaborole and a boronate half-ester, was claimed to form based on NMR observation and MS study. It was further suggested that this dimeric species also activated the quinone imine ketal **1-56** *via* hydrogen bonding for the addition of the dioxazaborole unit, providing the Michael adduct **1-58**. In the presence of *ortho*-nitrobenzoic acid as a co-catalyst, a bicyclic product **1-60** was eventually formed with high enantioselectivity after a series of rearrangements (**Scheme 1-21**).[68]



Scheme 1-21. Direct hydroxamic acid activation for aza-Michael addition *via* BAC.

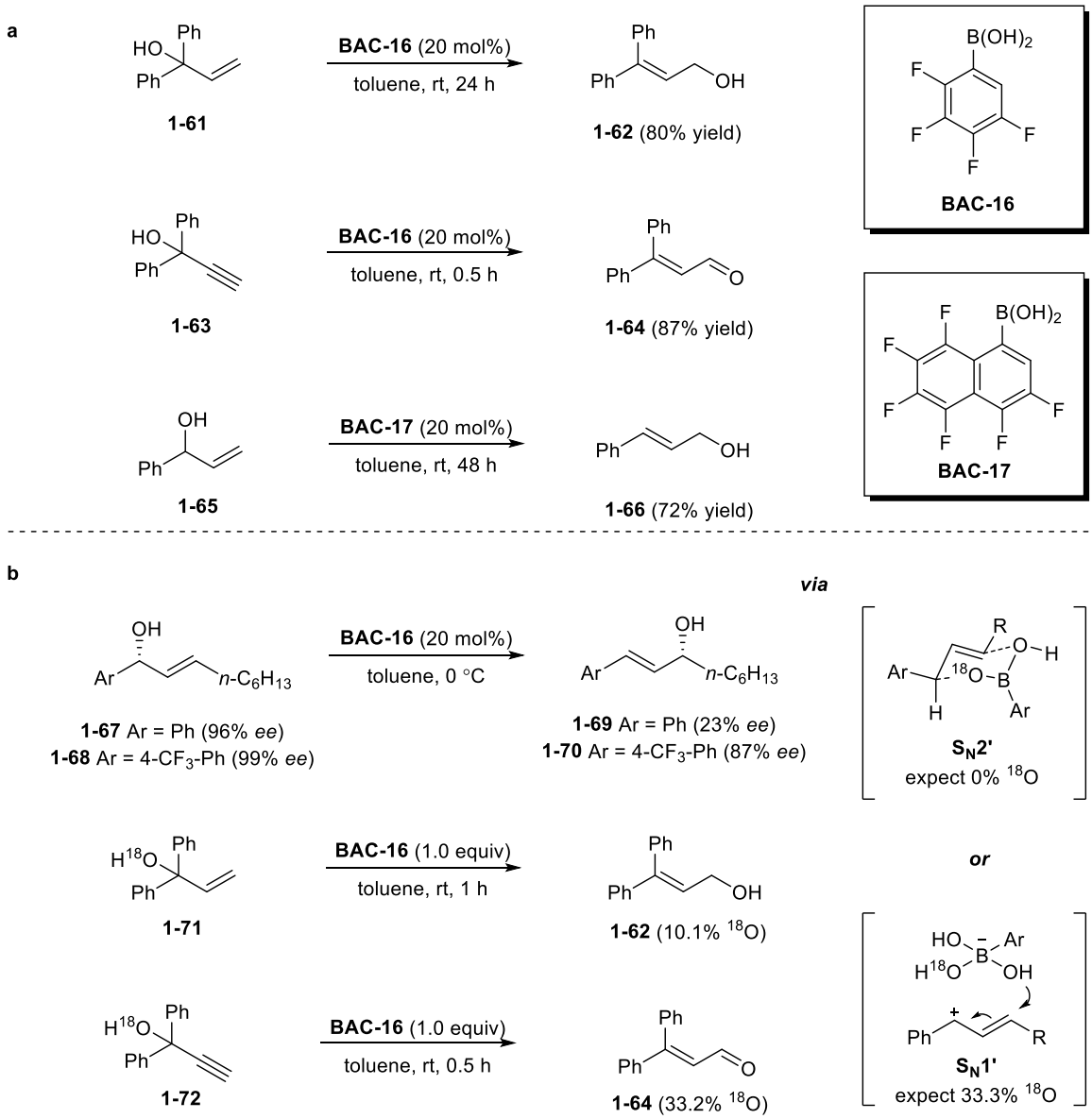
1.4.6 Activation of alcohols

Boronic acid catalysis for the direct activation of alcohols is a new and emerging area. BAC can potentially serve as a powerful method for direct activation of alcohol C–O bond. As discussed in section 1.4.1, these molecules can form reversible covalent bonds with alcohol substrates and provide transient activation. Ideally, further polarization and even cleavage of the C–O bond can be achieved by enhancing the Lewis acidity of the boronic acid. To achieve this, the most straightforward design would involve installing as many electron withdrawing groups as possible. In 2010, McCubbin and co-workers reported that pentafluorophenyl boronic acid **BAC-15** exhibited adequate Lewis acidity and was able to ionize activated allylic alcohols for direct Friedel-Crafts allylation of electron rich arenes such as furan, indole and pyrrole. This strategy was soon extended to the activation of benzylic and propargylic alcohols for the corresponding Friedel-Crafts alkylation (**Scheme 1-22**). However, the substrate scope of these reports was limited to highly ionizable alcohols and very electron rich arenes; e.g. even anisole was not nucleophilic enough to participate in the reaction. According to the authors' mechanistic study, it is suggested that stable carbocations were formed during the C–O bond activation step by the electrophilic boronic acid.[69]



Scheme 1-22. Direct alcohol activation for Friedel-Crafts alkylation *via* BAC.

In 2011, Hall and co-workers described the 1,3-transposition of allylic alcohols and the Meyer-Schuster rearrangement of propargylic alcohols by boronic acid catalysis. A variety of electron-deficient aryl boronic acids were examined. While tetrafluorophenyl boronic acid **BAC-16** was a suitable catalyst for the rearrangement of most activated allylic and propargylic alcohols, the more active hexafluoronaphthalene boronic acid **BAC-17** was needed for more challenging alcohol substrates. It is worth pointing out that, during the optimization, tetrafluorophenyl boronic acid was found to be a better catalyst compared to the pentafluorophenyl boronic acid **BAC-15**. The rationale in the original report was that “removal of one of the *ortho*-fluoride substituents could provide steric relief and accelerate the rearrangement despite the attenuation of electronic effects. “ It was found that the higher yield was obtained in less polar solvent with the absence of external nucleophiles. Generally, the reaction, which is potentially reversible, afforded the thermodynamically more stable alkenes (**Scheme 1-23a**).[70]

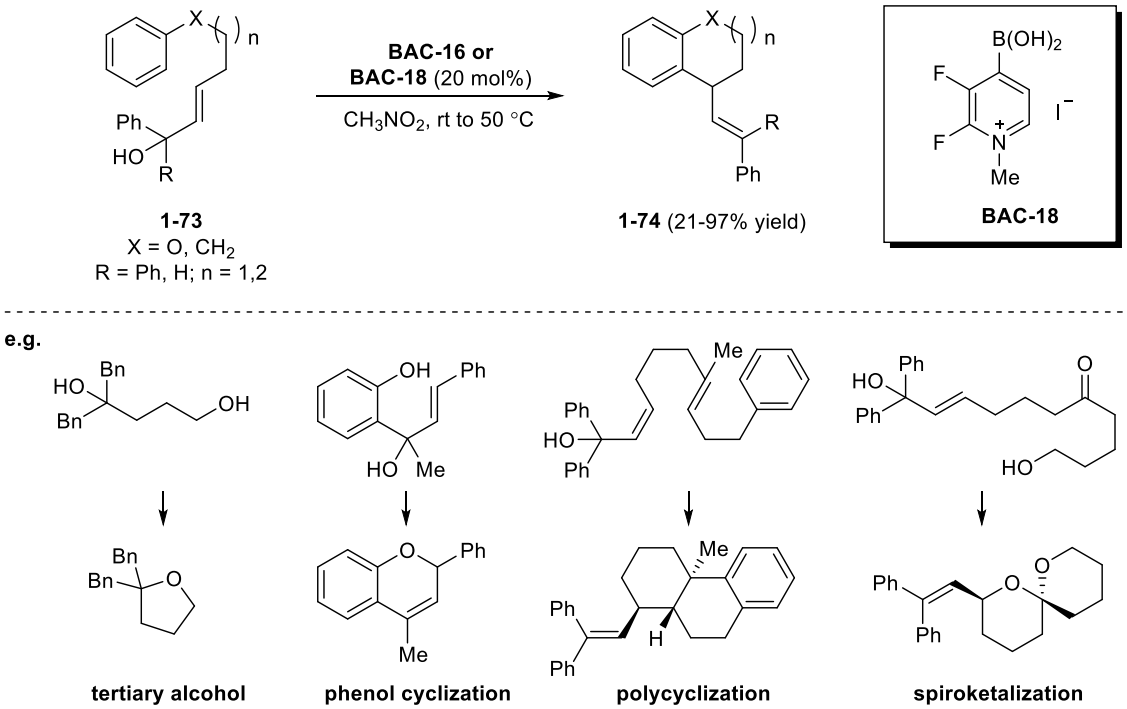


Scheme 1-23. Direct alcohol activation for 1,3-transposition *via* BAC.

Additional mechanistic studies suggested that the reaction mechanism of this unique rearrangement is highly substrate dependent. For instance, when allylic alcohols **1-67** (96% *ee*) and **1-68** (99% *ee*) were subjected to the reaction conditions, the corresponding product **1-69** and **1-70** were obtained in 23% and 87% *ee* respectively. A more sophisticated ^{18}O-labelling experiment was therefore designed. Starting from ^{18}O enriched allylic or propargylic alcohol, an S_N1' reaction mechanism should result in a statistically distributed 33.3% ^{18}O labelled product while an S_N2' reaction mechanism would lead to no ^{18}O incorporation in the rearranged product.

The experimental results showed that the rearranged product of ^{18}O labelled allylic alcohol **1-62** contained 10.1% of the ^{18}O, which suggested a high degree of S_N2' character. In the contrary, 33.2% of the rearranged aldehyde **1-64** was incorporated with ^{18}O indicated that a stable carbocation was formed in case of this activated propargylic alcohol (**Scheme 1-23b**).[70]

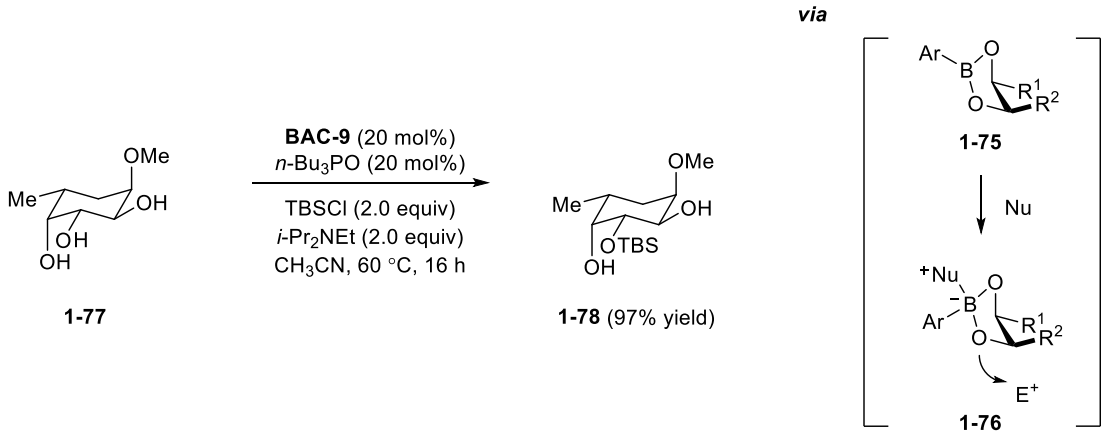
As an extension, Hall and co-workers also applied the concept of BAC from allylic alcohol transposition to direct intramolecular cyclization. A series of allylic alcohols **1-73** tethered with C–, N– and O– nucleophiles were synthesized. It was shown that tetrafluorophenyl boronic acid **BAC-16** was efficient enough to ionize the allylic alcohol in nitromethane and allowed the intramolecular nucleophilic attack without the use of desiccants under mild conditions. In certain cases where alcohol substrates were less activated, a more active catalyst, N-methyl-2,3-difluoropyridium boronic acid iodide salt **BAC-18**, was used (**Scheme 1-24**). Remarkably, the method was also successfully applied in the construction of complex molecules *via* phenol cyclization, poly cyclization and spiroketalization (**Scheme 1-24**).[71]



Scheme 1-24. Direct alcohol activation for intramolecular cyclization *via* BAC.

As a versatile strategy, BAC can also be applied to the nucleophilic activation of diols. In 2013, Taylor and co-workers described a regioselective silylation of carbohydrate derivatives by 3,5-

bis(trifluoromethyl)phenyl boronic acid **BAC-9**. Different *cis*-diol moieties were selectively protected by silyl groups by dual catalysis with boronic acid in the presence of a catalytic amount of Lewis base. As shown in **Scheme 1-25**, protection of the *cis*-diol with **BAC-9** resulted in an unreactive neutral boronic ester **1-75**. Upon addition of the Lewis base, a cyclic tetra-coordinated boronate was formed. It was this anionic boronate, **1-76**, that enhanced the nucleophilicity of one of the diol's hydroxyl groups for further silylation.[72]



Scheme 1-25. Direct diol activation for regioselective silylation of carbohydrate derivatives *via* BAC.

1.5 Thesis objective

Due to its natural abundance, benign physical properties and versatility, alcohols serve as one of the most widely used chemical substances despite the fact that they are relatively inert. How to activate and transform alcohols for synthesis is a pressing issue for the advancement of sustainable chemical synthesis. The traditional activation processes are wasteful. The use of stoichiometric activating reagents poses a great burden for the production of commodity chemicals. Thus, catalytic direct alcohol activation has become a research area that has received considerable attention over the past decades. Numerous efforts have been devoted to this area; however, great challenges are still unmet and await organic chemists.

In this context, boronic acid catalysis (BAC), as an environmentally friendly system, can potentially serve as an efficient method for catalytic direct alcohol activation. As a versatile

strategy, BAC also has the potential to serve as a general platform for transformation of other hydroxyl-containing compounds.

In light of the recent discovery of electron poor boronic acids for the direct polarization of alcohol C–O bonds and the formation of carbocations, Chapter 2 will present our efforts towards the identification of new boronic acids and the development of more general reaction conditions for direct Friedel-Crafts alkylation from π-activated alcohols. With the established reaction system, Friedel-Crafts alkylations between deactivated alcohols and neutral arenes can be achieved.

Inspired by the 1,3-transposition and intramolecular cyclization of allylic alcohols *via* BAC, it was envisioned that another carbon nucleophile, perhaps even another nucleophilic catalysis, could be introduced for trapping the cationic intermediate. Chapter 3 will present the optimization and mechanistic study towards a novel dual catalysis system uniting boronic acids and chiral amines. This catalytic system exploits the electrophilic activation of allylic alcohols *via* boronic acids and the nucleophilic activation of aldehydes by chiral amines for the synthesis of valuable enantiomerically enriched acyclic quaternary carbon center.

As an extension of the electrophilic activation of alcohol C–O bonds by BAC, the concept was expanded to direct activation of oxime N–O bonds. Chapter 4 will introduce the discovery of a class of unique boronic acids for direct Beckmann rearrangement under mild conditions. Mechanistic studies revealed a new and interesting boron induced oxime transesterification and Beckmann rearrangement process.

1.6 References

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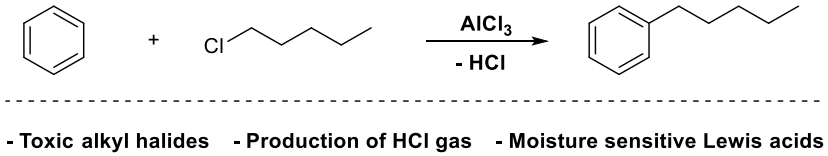
Chapter 2 Boronic Acid Catalyzed Direct Friedel-Crafts Alkylation with π-Activated Alcohols*

2.1 Introduction

Functionalization of aromatic compounds lies at the core of modern manufacturing of commodity chemicals and pharmaceutical products. Since its discovery in 1877,[1] the Friedel-Crafts alkylation has become one of the most important reactions for arene transformations.[2] In the original report, using unquantified amounts of $AlCl_3$ as a Lewis acid and amyl chloride, the product amyl benzene was produced along with hydrogen chloride gas (**Scheme 2-1**). More than a century later, Friedel-Crafts reactions using toxic alkyl halides, large excess of arenes and moisture sensitive Lewis acids are still prevalent. These conditions are far from ideal from the stand points of atom economy and environmental awareness. It is no wonder that the ACS Green Chemistry Institute Pharmaceutical Roundtable has listed Friedel-Crafts reactions as one of the most important transformations to improve.[3]

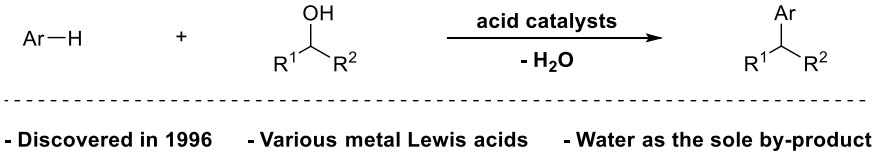


Scheme 2-1. The first electrophilic aromatic alkylation reported by Friedel and Crafts.

As a result, the search for a safer replacement of alkyl halides and milder catalytic systems is of great significance. Alcohols could potentially serve as more accessible and less toxic starting materials compared to the corresponding alkyl halides.[4] However, the consideration that alcohols could be used directly as alkylating reagents in catalytic Friedel-Crafts reaction was not realized until recently (**Scheme 2-2**). In 1996, Fukuzawa and co-workers reported the first systematic study of Friedel-Crafts alkylation using benzylic alcohols with $Sc(OTf)_3$ as the

* A version of this chapter has been published. (a) Ricardo, C. L.; Mo, X.; McCubbin, J. A.; Hall, D. G. *Chem. Eur. J.* **2015**, *21*, 4218–4223. (b) Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J. A.; Hall, D. G. *J. Am. Chem. Soc.* **2015**, *137*, 9694–9703.

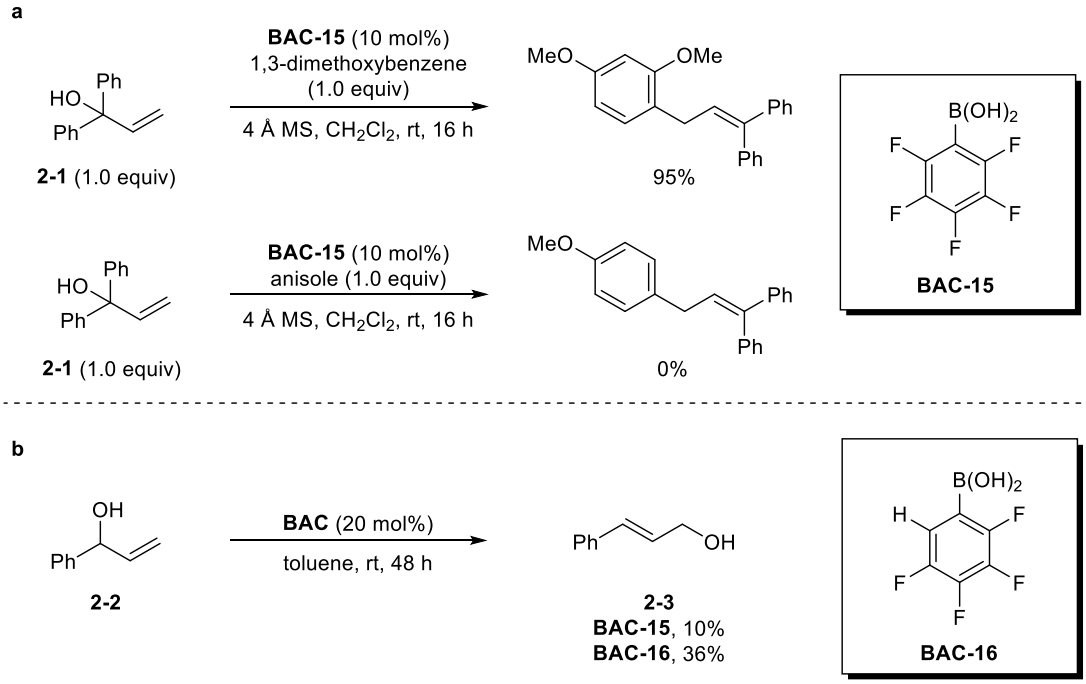
catalyst.[5] Shortly thereafter, other main group and rare metal Lewis acids (e.g. Si, Ga, In, La, Nd, Sm, Gd, Yb, and Hf) as well as some strong Brønsted acids (e.g. H-mont and HOTf) were identified as efficient catalysts for direct use of alcohol substrates in Friedel-Crafts reactions.[6] In 2005, Beller and co-workers conducted another systematic study on different transition metal chlorides (Fe, Rh, Pd, W, Ir, Pt, and Au) for direct Friedel-Crafts alkylation with alcohols.[7] Among all the Lewis acids tested, $HAuCl_4$ and $FeCl_3$ displayed superior catalytic activities.[8] Notably, $FeCl_3$ was identified as a suitable catalyst due to its great abundance.[9] Another significant advance was made by Rueping and co-workers in 2006 with the use of $Bi(OTf)_3$.[10] This highly active Lewis acid was shown capable to catalyze direct Friedel-Crafts reactions with alcohols under very low catalyst loading (0.5 mol%). Catalytic systems involving other new Lewis and Brønsted acids include $Ca(NTf_2)_2$ and $HNTf_2$, which have been slowly developed over the past several years.[11] Despite great advancement in the area of direct Friedel-Crafts alkylation with alcohols as alkyl halide surrogates, limitations still remain: (a) the use of rare, toxic and expensive metals; (b) the need for electron rich substrates; (c) harsh reaction conditions including high temperatures and often using a large excess of arenes as reaction solvents; (d) limited functional group tolerance. Thus, the search for novel and mild catalytic systems is of great value.



Scheme 2-2. Friedel-Crafts alkylation with alcohols as starting materials.

As an emerging class of organocatalysts, boronic acids could be employed as an alternative metal-free method for direct Friedel-Crafts alkylation with alcohols. Boronic acids can provide transient activation of the C–O bond by a reversible covalent interaction with alcohol substrates.[12] In comparison with strong Lewis and Brønsted acids, boronic acids have a broader functional group tolerance due to its milder acidity (pK_a 5-9).[13] In 2010, McCubbin and co-workers described the first boronic acid catalyzed direct Friedel-Crafts reaction using different allylic alcohols. This catalytic system exploited the highly Lewis acidic pentafluorophenyl boronic acid **BAC-15** for alcohol ionization and provided good yields for select arene or heteroarene substrates.[14] Even though this concept was later expanded to benzylic and propargylic

alcohols,[15] clear limitations existed: only strongly activated alcohols and highly electron rich arenes were suitable substrates (**Scheme 2-3a**). Shortly thereafter, our group described a unique 1,3-transposition[16] and intramolecular nucleophilic cyclization[17] of allylic alcohols *via* boronic acid catalysis. Surprisingly, it was found that tetrafluorophenyl boronic acid **BAC-16** exhibited higher reactivity compared to the presumably more active pentafluorophenyl boronic acid (**Scheme 2-3b**). The rationale behind this observation was not explored.



Scheme 2-3. (a) Examples and limitations of Friedel-Crafts allylation using pentafluorophenyl boronic acid **BAC-15**. (b) Observation of higher reactivity of 2,3,4,5-tetrafluorophenyl boronic acid **BAC-16** compared to **BAC-15** for the 1,3-transposition of allylic alcohol

2.2 Objective

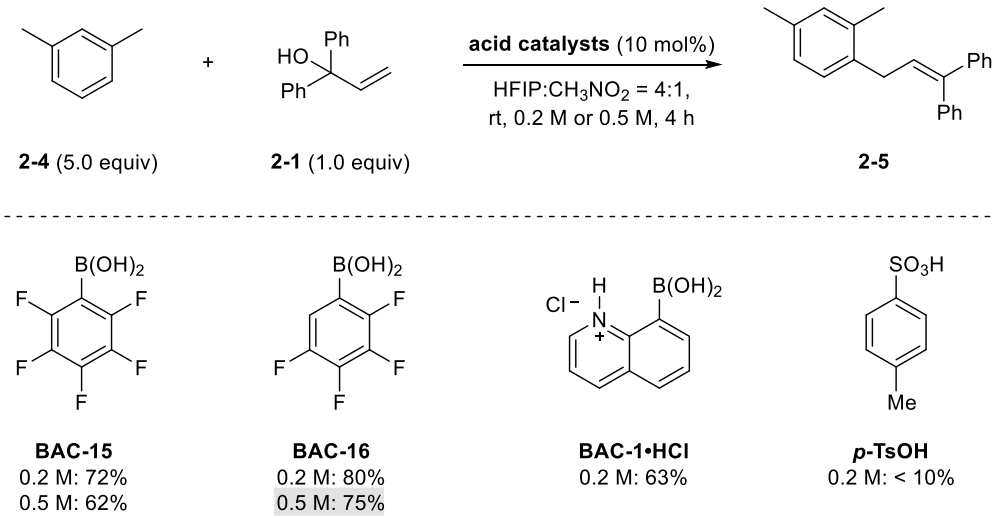
Intrigued by the higher reactivity of tetrafluorophenyl boronic acid for alcohol activation in comparison with reports by McCubbin utilizing **BAC-15**, it was believed that further investigation with **BAC-16** were merited. This chapter will discuss the efforts undertaken towards more general and mild conditions for direct Friedel-Crafts alkylation with alcohols catalyzed by boronic acids (BAC). Mechanistic studies were also performed to elucidate the improved performance of tetrafluorophenyl boronic acid (**BAC-16**) vs **BAC-15**. Further investigation provided guidance

towards the discovery of novel boronic acids and the development of new concepts to address the existing challenges in direct Friedel-Crafts alkylation with alcohols.

2.3 Reaction development of direct Friedel-Crafts alkylation with 2,3,4,5-tetrafluorophenyl boronic acid

2.3.1 Optimization of reaction conditions

The optimization of the Friedel-Crafts alkylation with **BAC-16** was performed by Dr. Carolynne L. Ricardo. Allylic alcohol **2-1** and *m*-xylene **2-4** were used for initial investigation (**Scheme 2-4**). A solvent mixture of hexafluoroisopropanol (HFIP) and nitromethane (CH_3NO_2) (v:v = 4:1) displayed great efficiency for the allylation at room temperature with different acid catalysts. A large proportion of HFIP was preferred due to its ability to stabilize the allyl carbocation intermediates.[18] Various electron poor aryl boronic acids were tested with selective examples shown in **Scheme 2-4**. Among all, 2,3,4,5-tetrafluorophenyl boronic acid **BAC-16** was identified as the optimal catalyst, affording the allylated product **2-5** in 80% yield after 4 hours. Under the same conditions, pentafluorophenyl boronic acid **BAC-15** and **BAC-1·HCl** provided slightly lower yield. In contrast, the use of strong Brønsted acid *p*-TsOH led to facile decomposition of alcohol **2-1**. With **BAC-16**, it was found that the reaction concentration could be increased to 0.5 M without significantly diminishing the yield of product **2-5** (**Scheme 2-4**).



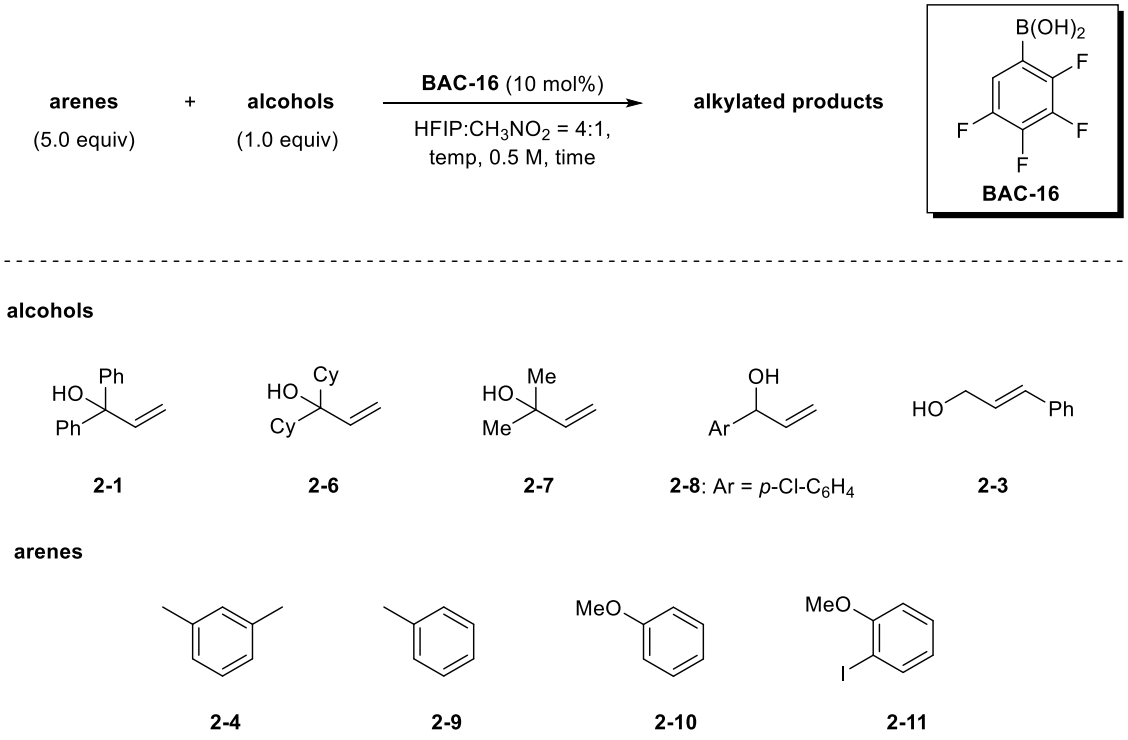
Scheme 2-4. Reaction optimization of direct Friedel-Crafts allylation with different acid catalysts.

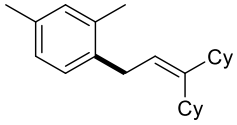
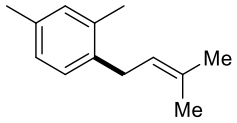
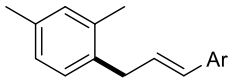
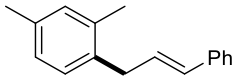
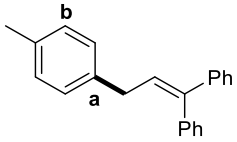
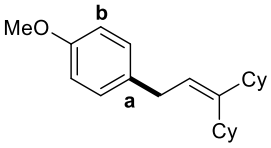
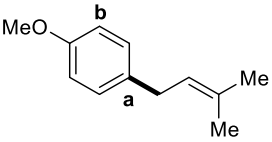
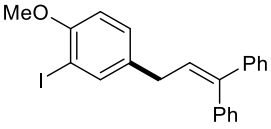
2.3.2 Substrate scope

The substrate scope of the direct Friedel-Crafts alkylation with tetrafluorophenyl boronic acid **BAC-16** was examined using the optimized reaction conditions (highlighted in **Scheme 2-4**), with a few examples (**Table 2-1**, entry 4 and **Table 2-2**, entry 2) contributed by Dr. Ricardo and Prof. J. Adam McCubbin.

2.3.2.1 Substrate scope with allylic alcohols

As shown in **Table 2-1**, a variety of activated allylic alcohols (**2-1**, **2-6** to **2-8**) were found to undergo alkylation with *m*-xylene, affording the desired products in high yield (entries 1-3) at room temperature with 10 mol% catalyst loading. It was found that the optimized conditions were also applicable for a challenging primary allylic alcohol, **2-3** (entry 4). Further examination of the arene scope showed that the protocol was applicable to a series of electron rich arenes (entries 6-8). However, little to no product was obtained when relatively electron poor arenes such as toluene **2-9** were used (entry 5). The decomposition of allylic alcohol **2-1** was observed in this case.



entry	alcohol	arene	condition	product[a]	number	yield (%)[b]
1	**2-6**	**2-4**	rt, 20 h		**2-12**	90
2	**2-7**	**2-4**	rt, 24 h		**2-13**	58
3	**2-8**	**2-4**	rt, 4 h	 Ar = *p*-Cl-C_6H_4	**2-14**	81
4[e]	**2-3**	**2-4**	rt, 1 h		**2-15**	93 (<5)[d]
5	**2-1**	**2-9**	50 °C, 24 h		**2-16**	10 (a:b = 58:42)
6	**2-6**	**2-10**	rt, 3 h		**2-17**	68 (a:b = 60:40)
7[c]	**2-7**	**2-10**	rt, 3 h		**2-18**	85 (a:b = 75:25)
8[c]	**2-1**	**2-11**	rt, 24 h		**2-19**	49

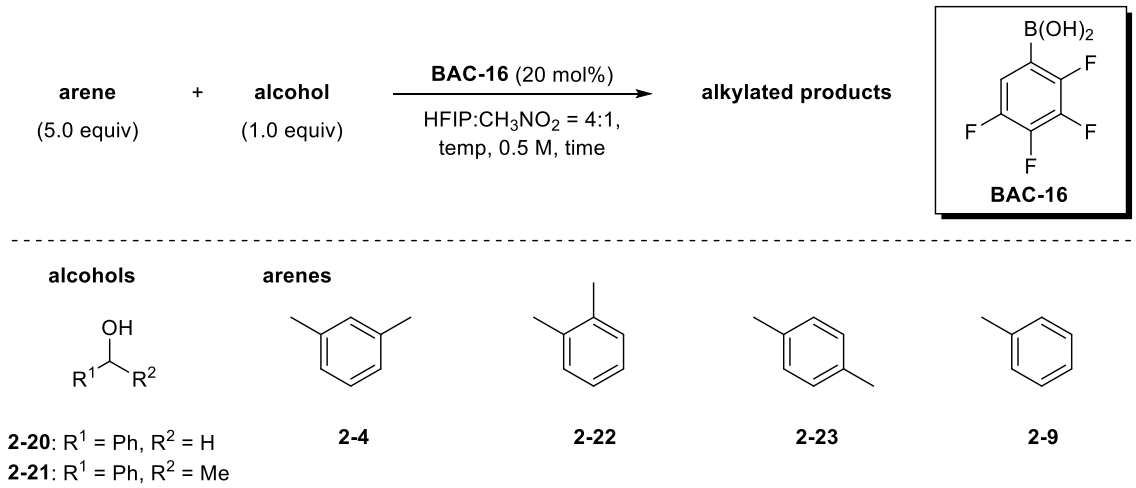
[a]Unless indicated, all the reactions were run on 1.0 mmol scale of the alcohol substrates. Ratio of the major and minor isomer was determined by ^{1}H NMR analysis of the crude. No ratio was reported when the major and minor isomer was >95:5. [b]Isolated yield. [c]Reaction was run with 20 mol% of catalyst. [d]Reaction was run with 2,3,4,5,6-pentafluorophenyl boronic acid **BAC-15** as catalyst. [e]The reaction was run by Dr. Carolynne L. Ricardo.

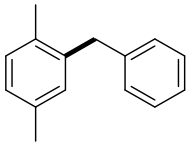
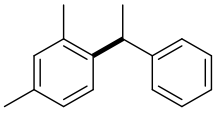
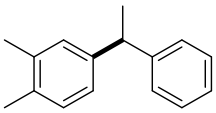
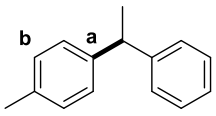
Table 2-1. Substrate scope of direct Friedel-Crafts allylation with **BAC-16**.

2.3.2.2 Substrate scope with benzylic alcohols

Benzylic alcohols were shown to be suitable alkylating reagents, with a higher catalyst loading (20 mol%) required (**Table 2-2**). Benzylation of *p*-xylene with primary benzylic alcohol **2-20**

afforded moderate yield under higher temperature (50 °C) after 24 h (entry 1). The lower efficiency for alcohol **2-20** presumably resulted from the higher activation energy required for the formation of primary benzylic carbocations. In contrast, secondary benzylic alcohol **2-21** is more activated and the alkylation was achieved in moderate to high yields under room temperature conditions (entries 2-4). Gratifyingly, upon prolonged reaction time, the benzylation of toluene (entry 4) also provided a moderate 63% yield in comparison with the low yield of the corresponding allylation with alcohol **2-1** (cf., **Table 2-1**, entry 5).



entry	alcohol	arene	condition	product[a]	number	yield (%)[b]
1	**2-20**	**2-23**	50 °C, 24 h		**2-24**	60
2[d]	**2-21**	**2-4**	rt, 1 h		**2-25**	96 (0)[c]
3	**2-21**	**2-22**	rt, 1 h		**2-26**	88
4	**2-21**	**2-9**	rt, 18 h		**2-27**	63 (a:b = 87:13)

[a]Unless indicated, all the reactions were run on 1.0 mmol scale of the alcohol substrates. Ratio of the major and minor isomer was >95:5 based on ^{1}H NMR analysis of the crude. [b]Isolated yield. [c]Reaction was run with 2,3,4,5,6-pentafluorophenyl boronic acid **BAC-15** as catalyst. [d]The reaction was run by Prof. J. Adam McCubbin.

Table 2-2. Substrate scope of direct Friedel-Crafts benzylation with **BAC-16**.

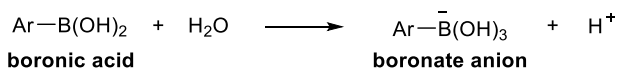
2.4 Rationale for the higher reactivity of boronic acid BAC-16 compared to BAC-15

As described in the introduction (Section 2.1), tetrafluorophenyl boronic acid (**BAC-16**) exhibited higher reactivity for the previously reported 1,3-transposition of allylic alcohol compared to **BAC-15**.[16] This intriguing observation can be seen by comparing the relevant experiments, namely entry 4 (**Table 2-1**) and entry 2 (**Table 2-2**) (from Dr. Ricardo and Prof. J. Adam McCubbin). In these experiments, low yield or no conversion was observed when pentafluorophenyl boronic acid **BAC-15** was used. Thus, further investigations were performed to rationalize the different reactivity of **BAC-15** and **BAC-16**.

2.4.1 Comparison of Lewis acidity

2.4.1.1 Direct pK_a measurement of BAC-15 and BAC-16

According to previous reports,[16,17] it appears that the ability of boronic acids to ionize alcohols correlates directly to the corresponding Lewis acidity, which is represented by their pK_a value. As shown by Wang and co-workers,[19] the number of electron withdrawing substituents on the aromatic moiety of a boronic acid correlates with a decrease in pK_a. From this point of view, the higher reactivity of tetrafluorophenyl boronic acid is counterintuitive. To compare the Lewis acidity of **BAC-15** and **BAC-16**, the pK_a measurements for these boronic acids were performed using ^{11}B NMR titration.[20] A series of boronic acid solutions at specific pH were prepared with phosphate buffers. The chemical shift of the boron signal, produced from the boronic acid and boronate equilibrium, were recorded by ^{11}B NMR. The titration curves could be plotted with pH against ^{11}B chemical shift. As a result, the pK_a of the boronic acid could be determined as the pH at the half equivalence point, when the amount of boronate and boronic acid are equal (**Scheme 2-5**). The pK_a of tetrafluorophenyl boronic acid was determined to be 6.0 (**Figure 2-1**).



$$\mathrm{p}Ka = \mathrm{pH} - \log\left(\frac{[\text{boronate}]}{[\text{boronic acid}]}\right)$$

Scheme 2-5. The pK_a measurement of boronic acids.

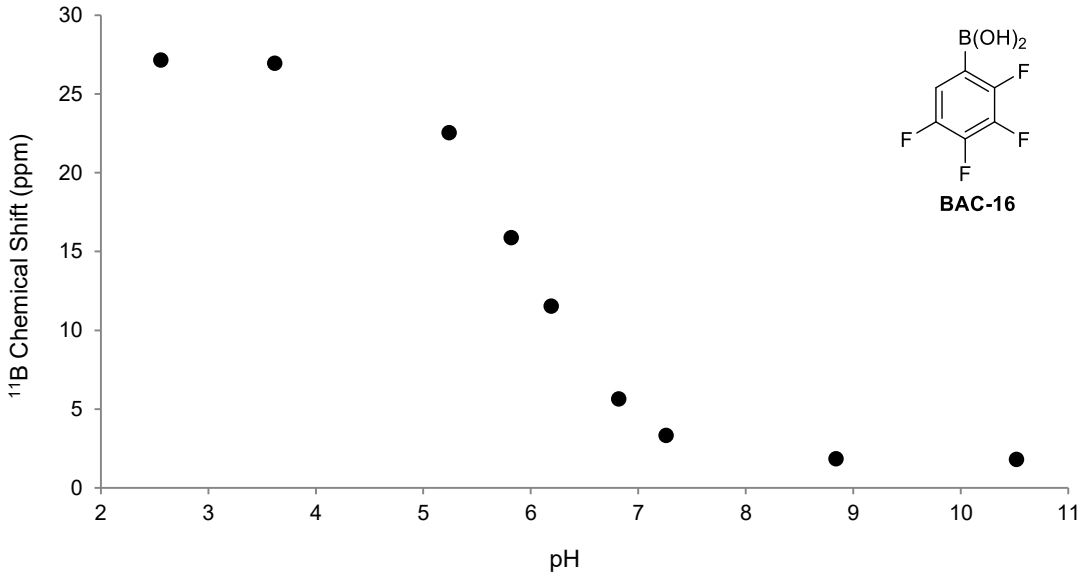
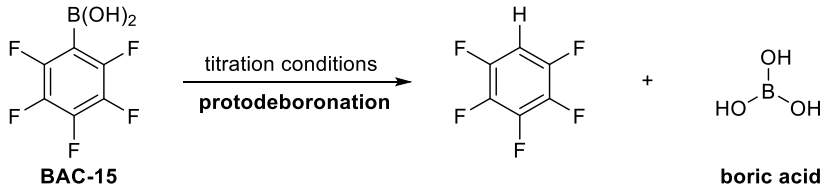


Figure 2-1. pK_a determination of 2,3,4,5-tetrafluorophenyl boronic acid *via* ^{11}B NMR titration in phosphate buffer solutions.

The direct pK_a measurement of pentafluorophenyl boronic acid by titration is difficult due to its extremely fast protodeboronation, as reported by Perrin and co-workers.[21] The attempted ^{11}B NMR titration was not successful and only boric acid was detected (**Scheme 2-6**). Consequently, an alternative and indirect method was sought.



Scheme 2-6. Facile protodeboronation of pentafluorophenyl boronic acid.

2.4.1.2 Indirect comparison – analogy using 2-fluorophenyl boronic acid and 2,6-difluorophenyl boronic acid

It is proposed that the comparison of Lewis acidity of 2-fluorophenyl boronic acid **BAC-19** and 2,6-difluorophenyl boronic acid **BAC-20** should be analogous to comparing tetrafluorophenyl

boronic acid and pentafluorophenyl boronic acid. As a result, the pK_a of **BAC-19** and **BAC-20** were measured using the ^{11}B NMR titration method. As shown in **Figure 2-2**, the pK_a of 2-fluorophenyl boronic acid was determined to be 7.9, which is consistent with the previous literature value of 7.85.[22]

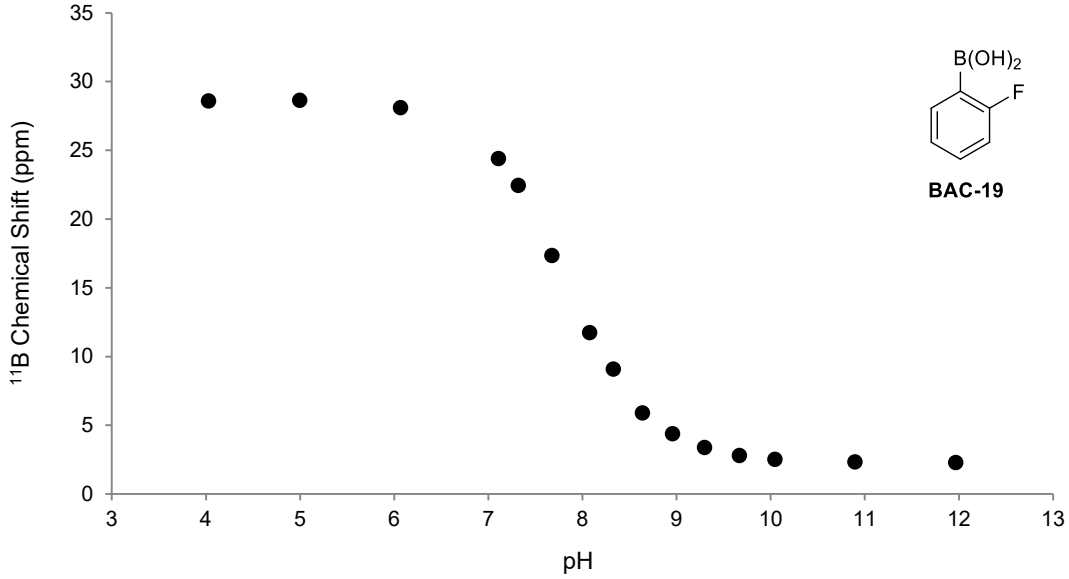


Figure 2-2. pK_a determination of 2-fluorophenyl boronic acid *via* ^{11}B NMR titration in phosphate buffer solutions.

The apparent pK_a of 2,6-difluorophenyl boronic acid was determined to be 7.2 based on the ^{11}B NMR titration curve (**Figure 2-3**). However, gradual formation of boric acid, the product of the protodeboronation, was observed at pH > 6.8. Unfortunately, the formation of boric acid influences the accuracy of the pK_a measurement. Hypothetically, at the half equivalence point, the amount of boronic acid and boronate should be equal. Instead, a deceased amount of the boronate was observed due to its simultaneous conversion to boric acid. To establish the new half equivalence point, more boronate needs to be formed, which is achieved at higher pH. Thus, the half equivalence point is shifted to a higher pH value. The apparent pK_a from **Figure 2-3** is 7.2, which means that the actual pK_a should have a lower value than 7.2 since more boronate was produced but converted into boric acid at the observed half equivalence point.

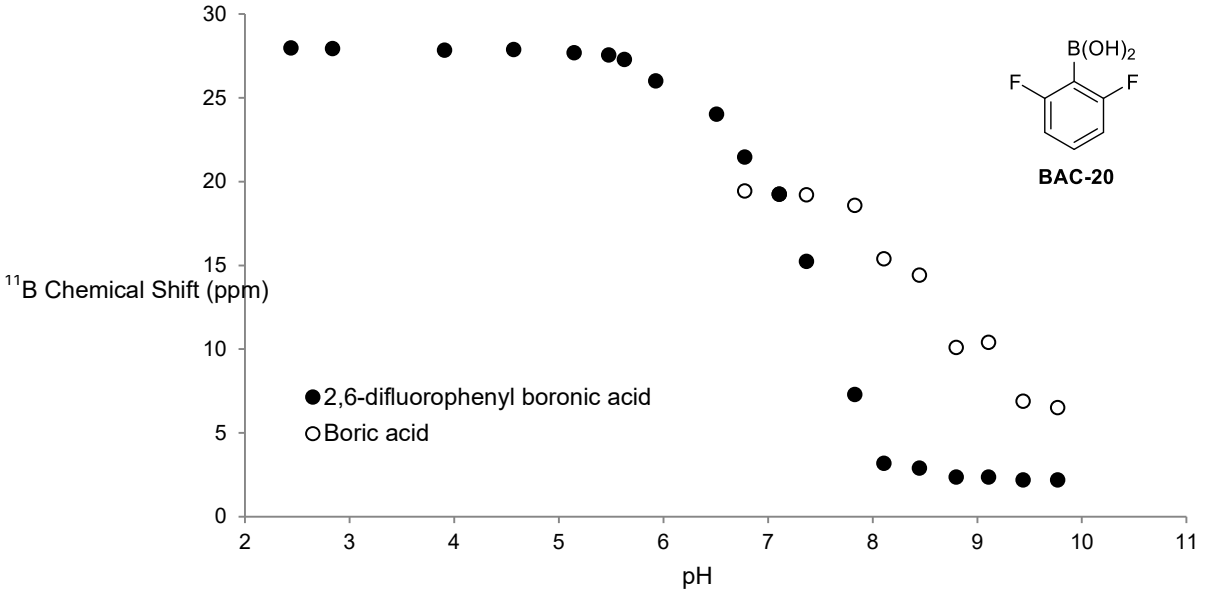


Figure 2-3. pK_a determination of 2,6-difluorophenyl boronic acid *via* ^{11}B NMR titration in phosphate buffer solutions.

Based on the ^{11}B NMR titration results, 2,6-difluorophenyl boronic acid (pK_a < 7.2) is more Lewis acidic than 2-fluorophenyl boronic acid (pK_a = 7.9). Analogously, pentafluorophenyl boronic acid should be more Lewis acidic than 2,3,4,5-tetrafluorophenyl boronic acid.

2.4.1.3 Verification using linear correlation between pKa and δ (B–O<u>H</u>)

To validate the indirect comparison described above, a correlation was established between the previously reported pK_a values[19, 22] of eight different fluorinated boronic acids (**Figure 2-4a**) and their experimental ^{1}H NMR (B-O<u>H</u>) chemical shift in anhydrous DMSO-*d6*. The resulting plot shows a high degree of linearity (R^2 = 0.98) (**Figure 2-4b**). To validate the correlation, data for tetrafluorophenyl boronic acid was excluded. Satisfactorily, the corrected linear curve predicted a pK_a of 5.9 for **BAC-16**, which is in agreement with the value of 6.0 obtained from the ^{11}B NMR titration method. The ^{1}H NMR (B-O<u>H</u>) chemical shift of the pentafluorophenyl boronic acid was measured to be 9.08 ppm in anhydrous DMSO-*d6*, which predicts a pK_a value of 3.5. Since the pK_a determination for 2,6-difluorophenyl boronic acid was not entirely accurate due to the partial protodeboronation, a predicted value of 5.5 was estimated with the linear correlation method.

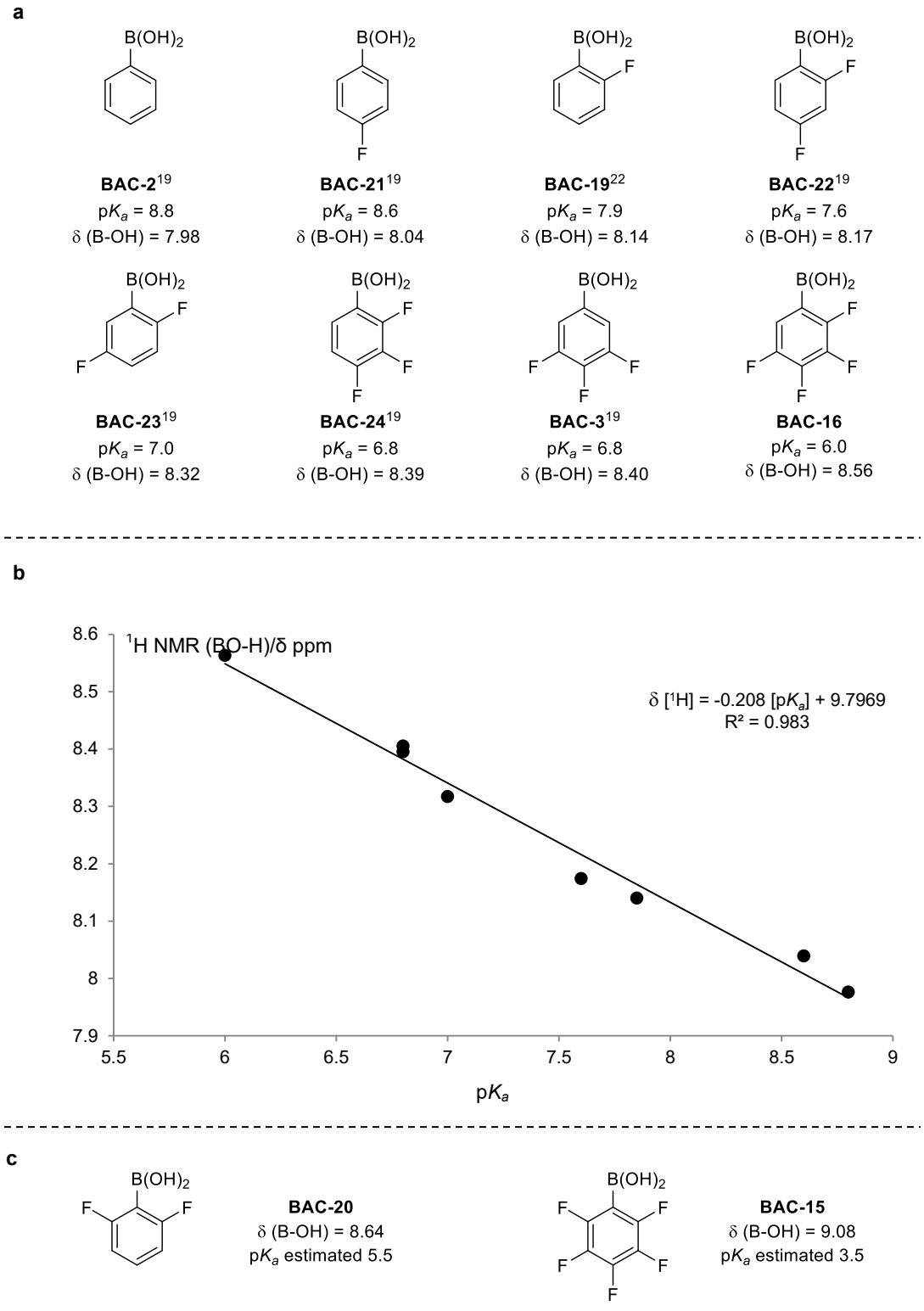
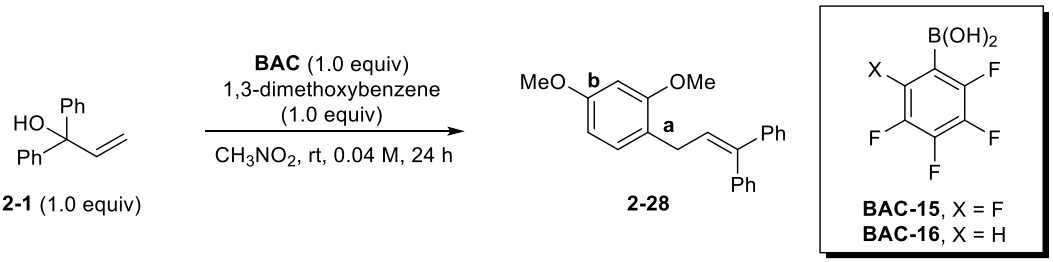


Figure 2-4. (a) Reported pK_a and ^{11}H NMR (B-OH) chemical shifts of eight different fluorinated boronic acids. (b) Linear correlation between reported pK_a and ^{11}H NMR (B-OH) chemical shifts. (c) Predicted pK_a value of **BAC-20** and **BAC-15**.

In summary, 2,3,4,5-tetrafluorophenyl boronic acid was confidently determined to be less Lewis acidic than pentafluorophenyl boronic acid. Thus, pK_a values do not explain the observed higher reactivity of **BAC-16** for alcohol activation.

2.4.2 Catalyst recovery experiments

Given the fact that pentafluorophenyl boronic acid **BAC-15** is not stable in water, it is possible that this catalyst undergoes decomposition in the reaction media, which would lead to lowered reactivity. Therefore, the stability of the catalysts was tested as follows. In an ideal situation, we would like to recover both catalysts, **BAC-15** and **BAC-16**, under the same Friedel-Crafts reaction conditions with an observable amount of product formation. Thus, highly electron rich 1,3-dimethoxybenzene and activated allylic alcohol **2-1** were selected as substrates since pentafluorophenyl boronic acid has a relatively low reactivity. An equal amount of boronic acid, alcohol and arene was used for easier isolation of the catalyst. It was also found that lower concentration was preferable to avoid decomposition of the allylic alcohol with such a high loading of boronic acid. The boronic acids were recovered by recrystallization from toluene. As shown in **Table 2-3**, both catalysts afforded the allylated product **2-28** in good conversion, with similar recovery under the same reaction conditions. Although pentafluorophenyl boronic acid did provide a slightly higher yield of 83%, it is not significant enough to overrule the previously observed lower activity. Since tetrafluorophenyl boronic acid is more reactive, it is possible that decomposition of **2-1** was preferential in the reaction using **BAC-16**, which led to lower yield.



entry	boronic acid	product yield (%)[a]	catalyst recovery (%)[b]
1	**BAC-15**	83 (a:b = 56:44)	75
2	**BAC-16**	71 (a:b = 56:44)	81

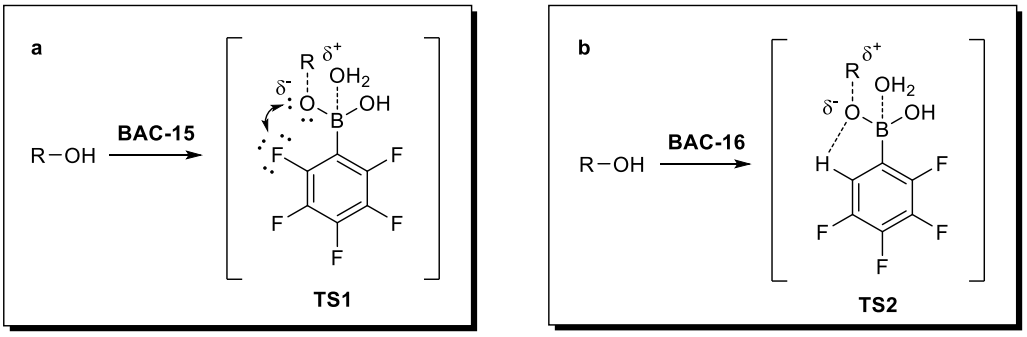
[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 4-bromobenzyl alcohol as an internal standard. [b]Boronic acids were recovered by recrystallization from toluene.

Table 2-3. Catalyst recovery experiments with **BAC-15** and **BAC-16**.

Since both catalysts were successfully recovered in similar yields under the same reaction conditions, decomposition of pentafluorophenyl boronic acid is not likely to be accountable for its relatively lower reactivity in direct alcohol activation.

2.4.3 Proposed rationale

Since comparisons of Lewis acidity and catalyst stability cannot explain the higher reactivity of 2,3,4,5-tetrafluorophenyl boronic acid, other possible explanations were proposed regarding the influence of the *ortho* substituents on the transition state of the alcohol activation process. In one possible transition state **TS1** (**Scheme 2-7a**), the presence of an extra *ortho*-fluorine increases the electronic repulsion with the lone pairs from the proximal oxygen atom, which leads to a relatively destabilized transition state as the transient negatively charged borate forms. In the other scenario with **TS2** (**Scheme 2-7b**), it is envisioned that the C–O bond cleavage could be facilitated by the *ortho*-H in the boronic acid through a weak hydrogen bond (estimated 13 kJ/mol),[23] thus dispersing the incipient negative charge. Further confirmation of these possibilities would require more in depth experimental or theoretical calculations.



Scheme 2-7. Proposed transition states and rational for the effort of *ortho*-H or F substituents.

2.5 Identification of ferrocenium boronic acid for diarylalkane synthesis

As discussed in Section 2.3.2, although 2,3,4,5-tetrafluorophenyl boronic acid is efficient for the direct allylation of electron rich and neutral arenes, the corresponding activation of benzyl alcohols is not satisfactory. For instance, when primary benzyl alcohol **2-20** or electron neutral

arene **2-9** were used with **BAC-16**, the corresponding diarylalkane compounds **2-24** and **2-27** were obtained in only moderate yield after prolonged reaction time (**Table 2-2**, entries 1 and 4). The lack of reactivity of **BAC-16** for less activated benzyl alcohol substrates is undoubtedly a limitation regarding the preparation of valuable diarylmethane or diarylalkane derivatives. As an important class of compounds, the diarylalkane scaffold is present in many pharmaceutical drug candidates and biologically active agents (**Figure 2-5**).[24] Therefore, facile access to diarylalkane compounds is highly desirable.

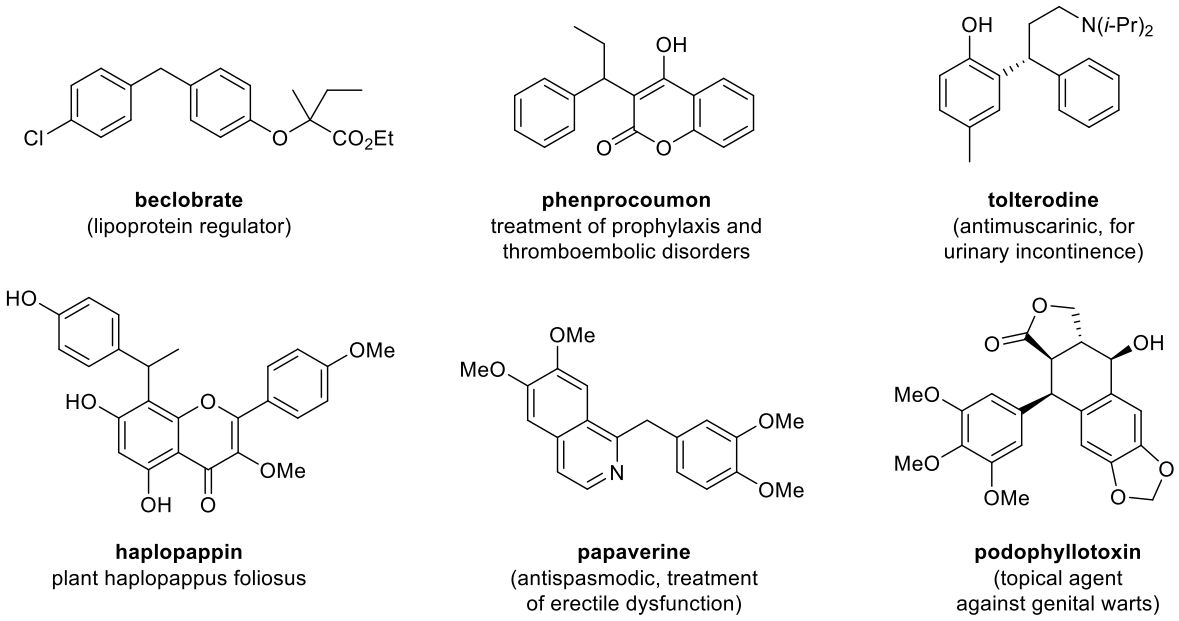
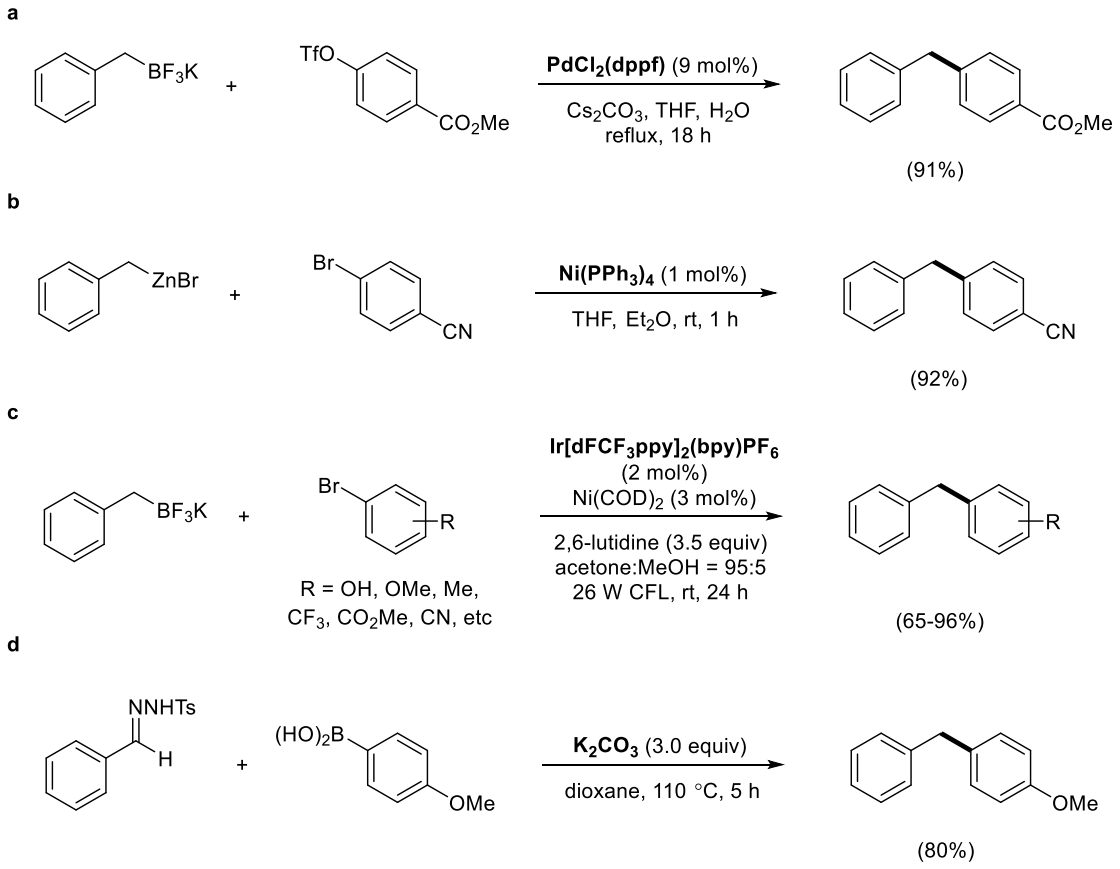


Figure 2-5. Selective examples of biological relevant diarylalkane compounds.

An overview of some of the representative preparative methods for diarylalkanes is shown in **Schemes 2-8** to **2-10**. Notably, advances have been made in the field of transition metal catalysis. With suitable aryl halides or triflates and benzyl nucleophiles, diarylalkane products can be obtained by Suzuki-Miyaura cross-coupling (**Scheme 2-8a**),[25] Negishi cross-coupling (**Scheme 2-8b**),[26] as well as other coupling reactions.[27] Furthermore, in light of the recent progress of photocatalysis, new protocols were also developed by Molander and co-workers combining iridium photoredox catalysis and nickel catalysis (**Scheme 2-8c**).[28] Diarylalkane compounds can also be prepared without the use of transition metals. Barluenga and co-workers described a method for the preparation of diarylmethanes using aryl boronic acids and tosylhydrazones as the carbene precursors with excess base (**Scheme 2-8d**).[29] Despite the

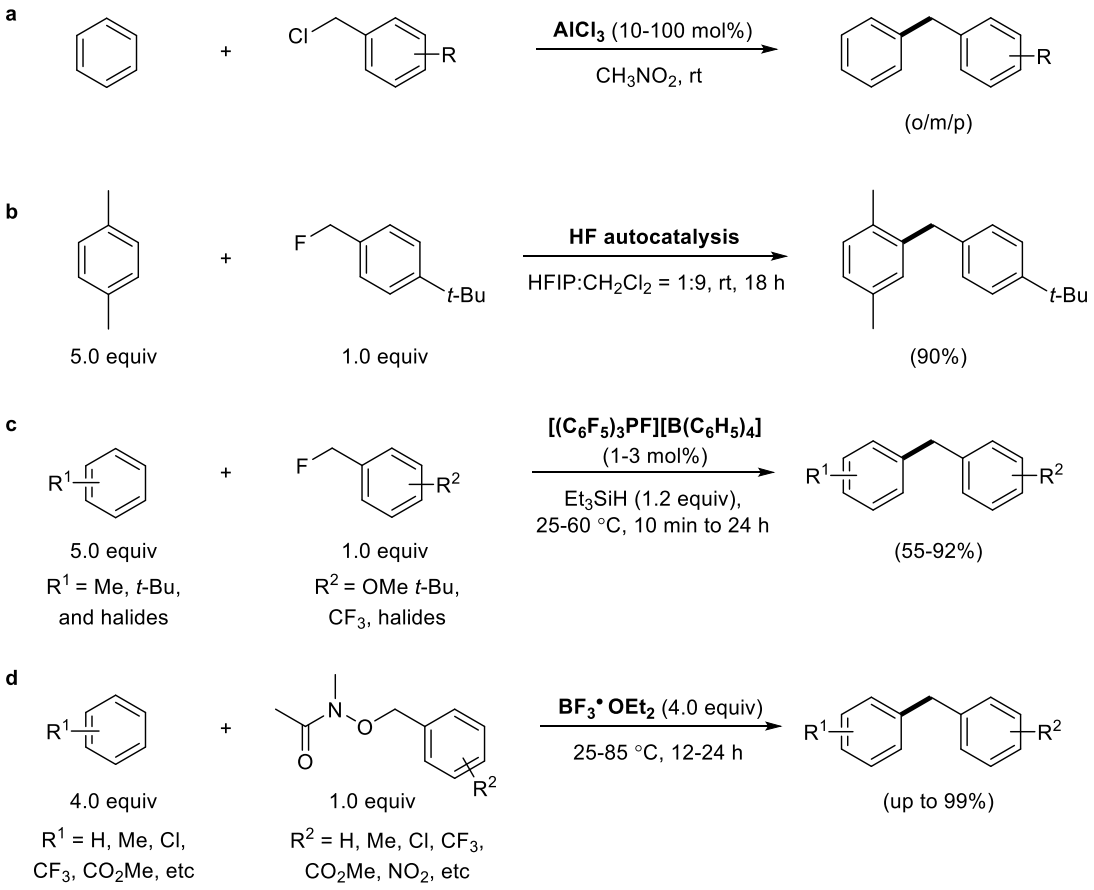
great efficiency of these methods, they require expensive and toxic metals. Moreover, the need to use pre-activation on both benzyl and aryl coupling partners is associated with low atom-economy.



Scheme 2-8. Selective methods for diarylalkane synthesis *via*: (a) Suzuki-Miyaura cross coupling (b) Negishi cross-coupling (c) dual photocatalysis and nickel catalysis (d) transition metal free carbene insertion.

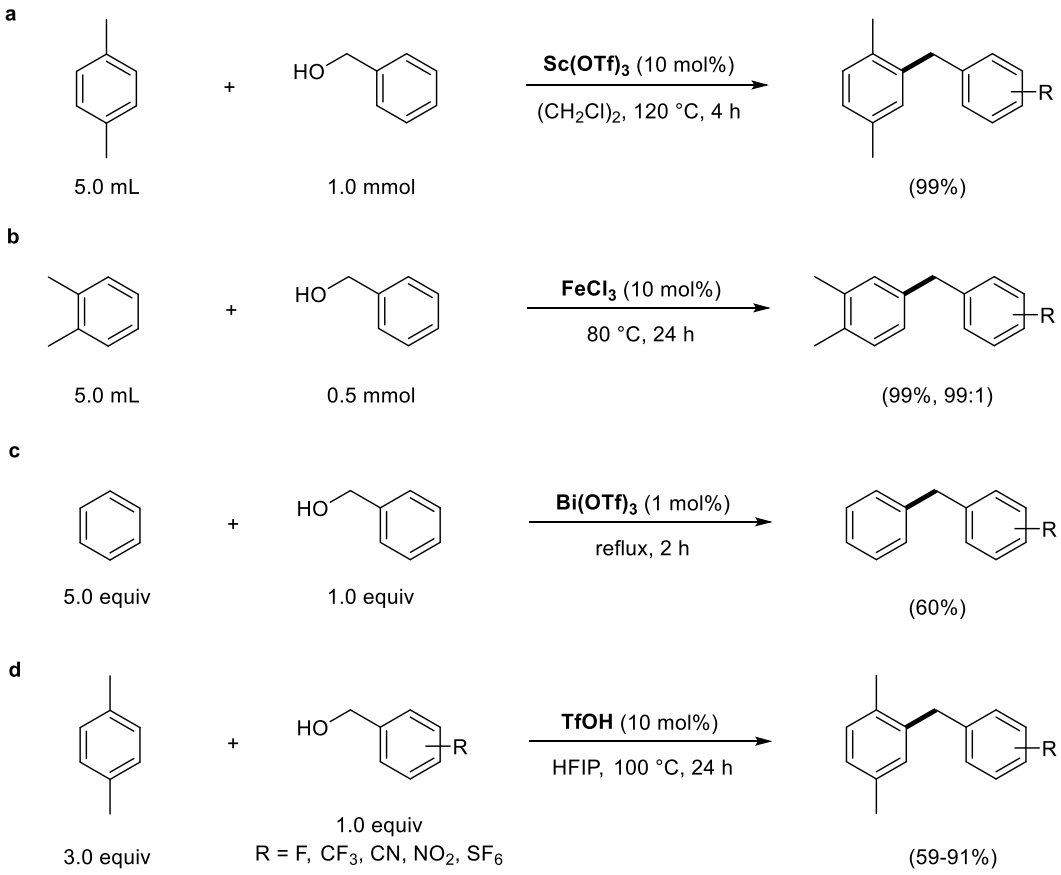
In comparison, access to diarylalkane compounds by Friedel-Crafts benzylation does not require pre-activation of the aryl coupling partners, and various arenes can be used directly. However, reactive and toxic electrophiles such as benzylic halides are still required for many of the reported methods. Friedel-Crafts alkylation with benzylic chlorides was systematically studied by Olah and co-workers a few decades ago.[30] The typical reaction conditions involved the use of a strong and moisture sensitive Lewis acid, such as $AlCl_3$. The diarylmethane compounds were produced along with hydrochloride gas as the side product (**Scheme 2-9a**).

Similarly, benzyl fluorides were also reported as effective alkylating reagents. Recently, Paquin and co-workers described a benzylation of electronically neutral arenes with hydrofluoric acid autocatalysis.[31] Benzyl fluorides were shown to be activated by HFIP for the reaction initiation. However, the production of hydrofluoric acid leads to a limitation of the scale of these reactions (**Scheme 2-9b**). As an improvement, a safer method using a phosphonium cation as the Lewis acid for benzyl fluoride activation and Et_3SiH as a fluoride scavenger was reported by Stephan and co-workers.[32] A variety of electron neutral arenes were successfully benzylated (**Scheme 2-9c**). In terms of substrate scope, the use of benzyl hydroxamates for Friedel-Crafts alkylation is rather remarkable. According to Bode and co-workers, benzyl hydroxamates could serve as excellent coupling partners upon activation with excess $BF_3{\cdot}OEt_2$. Benzylation was achieved with both activated and deactivated alcohols and arenes (**Scheme 2-9d**).[33] One limitation of these methods, however, is that the preparation of these activated benzylic species can be often hazardous and adds extra steps in the reaction sequence.



Scheme 2-9. Selective examples of diarylalkane synthesis by Friedel-Crafts alkylation from pre-activated substrate with: (a) $AlCl_3$; (b) HF autocatalysis; (c) a phosphonium cation; (d) $BF_3{\cdot}OEt_2$.

The direct activation of benzylic alcohols for Friedel-Crafts reaction is still a relatively new area of research. For example, in 1996, the first application of $Sc(OTf)_3$ as a water tolerant Lewis acid for the direct arylation of benzylic alcohols was ground breaking (**Scheme 2-10a**).[5] Since then, many other active catalysts have been discovered, such as the earth abundant $FeCl_3$ (**Scheme 2-10b**)[9] and $Bi(OTf)_3$ (**Scheme 2-10c**).[10] Despite great convenience, these catalytic systems suffer from significant limitations; (a) generally, only electron rich or neutral benzyl alcohols are suitable for ionization; (b) a large excess of arenes are often used as solvents to prevent over alkylation; (c) the methods generally do not perform well for electron deficient arene substrates. Very recently, these issues were partially addressed by Moran and co-workers. The authors reported that triflic acid can catalyze Friedel-Crafts reaction between highly electron poor benzylic alcohols and electron neutral arenes.[34] The reported protocol, however, suffers from harsh reaction conditions, requiring a strong Brønsted acid and high temperature (**Scheme 2-10d**).



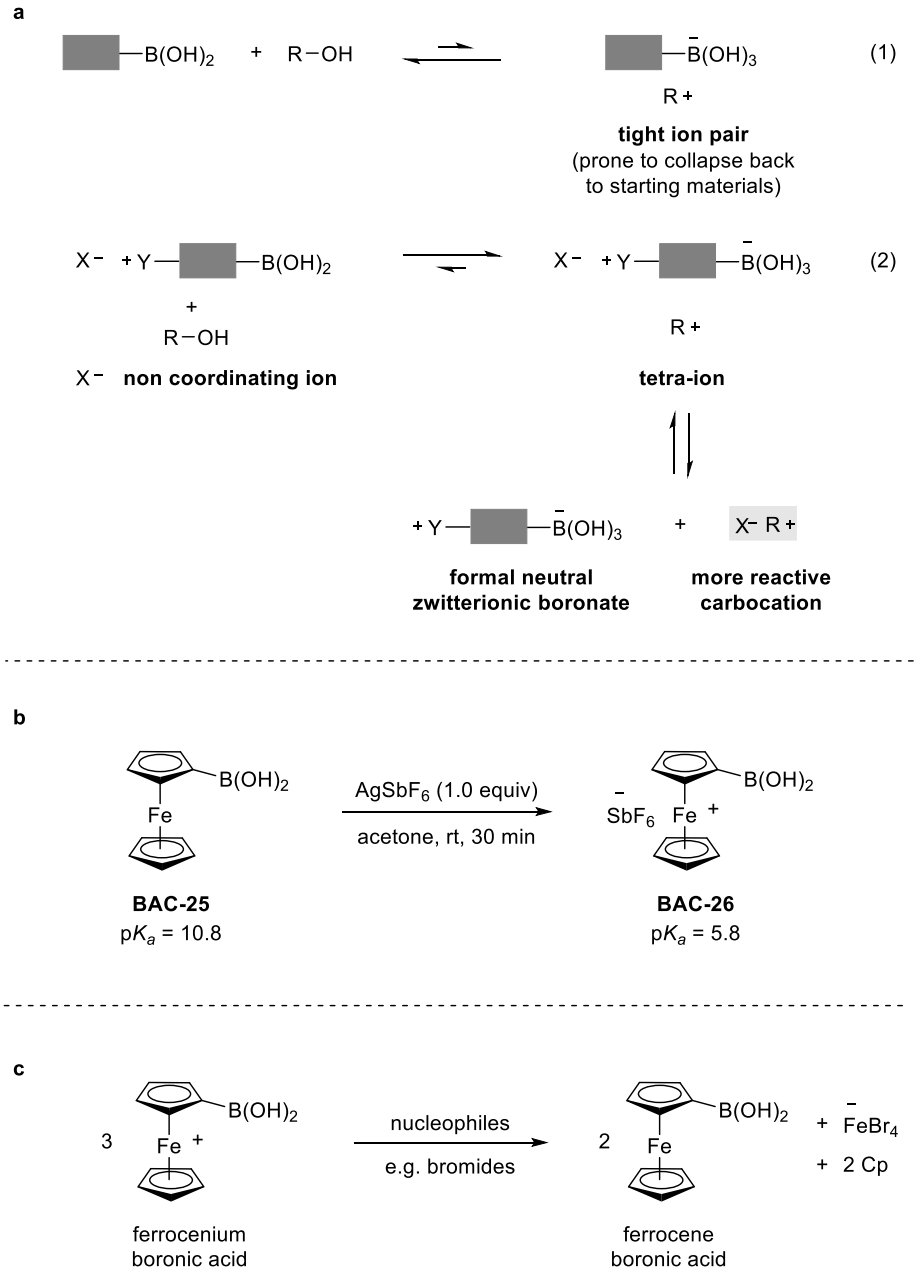
Scheme 2-10. Selective examples of diarylalkane synthesis by direct Friedel-Crafts alkylation from benzyl alcohols with acid catalysts: (a) $Sc(OTf)_3$; (b) $FeCl_3$; (c) $Bi(OTf)_3$; (d) TfOH.

In this regard, there is a need for direct Friedel-Crafts benzylation methods with a broader substrate scope (such as acid-sensitive or deactivated alcohols and arenes) under milder conditions.[35] To address these challenges, further effort in our group was devoted in a search for more reactive boronic acid catalysts for direct Friedel-Crafts benzylation.

Although existing reports suggest that the ionization power of boronic acids relates closely to their pK_a, this empirical observation does not always stand true. As previously discussed, the reactivity of boronic acids toward alcohol activation could also be influenced by the *ortho*-substituents. For example, tetrafluorophenyl boronic acid exhibited higher reactivity compared to pentafluorophenyl boronic acid, even though the latter has a lower pK_a. Thus, subtle structural features of boronic acids must also be considered when searching for more reactive catalysts. From this point of view, it was proposed that boronic acid salts with cationic aryl backbones and non-coordinating counter anions could serve as better candidates for direct alcohol activation, compared to their electron neutral counterparts. It was envisioned that a novel ion redistribution mechanism could benefit the direct Friedel-Crafts reaction. As shown in **Scheme 2-11a**, ionization of the alcohol with a neutral boronic acid results in the formation of a tight ion pair (**Scheme 2-11a**, equation 1). Association of the anionic boronate renders the carbocation less electrophilic. Furthermore, reversible interaction between the boronate and the carbocation can collapse back to the starting materials. In contrast, when a cationic boronic acid with a non-coordinating anion (X^-) is employed, ionization of the alcohol leads to the corresponding tetra-ion (**Scheme 2-11a**, equation 2). It is proposed that the corresponding tetra-ion will undergo a facile ion redistribution process emitting the formal neutral boronate. The carbocation would then be paired with the non-coordinating ion. A more exposed carbocation should exhibit higher reactivity in Friedel-Crafts reactions.

Following this proposal, ferrocene boronic acid (**BAC-25**) and ferrocenium boronic acid hexafluoroantimonate salt (**BAC-26**) were chosen as potential catalysts (**Scheme 2-11b**). Ferrocenium boronic acid could be prepared by oxidation of the parent ferrocene boronic acid with $AgSbF_6$ in acetone as reported by Osella and co-workers.[36] The pK_a of ferrocene boronic acid and ferrocenium boronic acid were measured to be 10.8 and 5.8, respectively, *via* cyclic voltammetry by Wayner and co-workers.[37] The significantly lowered pK_a of the ferrocenium boronic acid potentially results from the electrophilic 17 electron structure of this iron (III) complex, which is susceptible to decomposition by nucleophilic attack of certain nucleophiles to the ferrocenium center (**Scheme 2-11c**), according to Kortbeek and co-workers.[38] Nevertheless, taking into consideration that **BAC-26** has a similar pK_a to tetrafluorophenyl boronic acid (pK_a

6.0), ferrocenium boronic acid **BAC-26** was proposed to potentially serve as a powerful catalyst for direct Friedel-Crafts benzylation with a broader range of substrates.



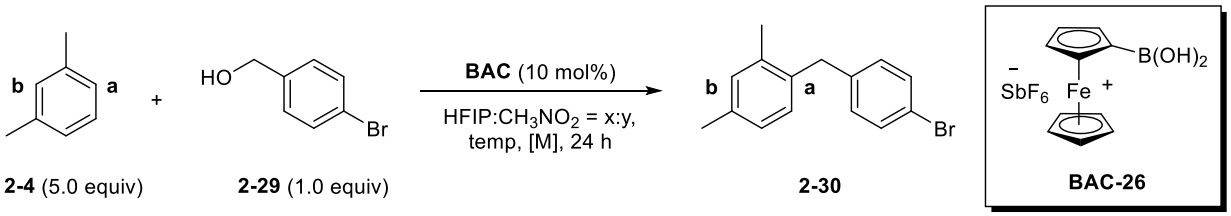
Scheme 2-11. (a) The concept of ion redistribution mechanism by cationic boronic acid salts with non-coordinating anions; (b) Preparation of ferrocenium boronic acid salt; (c) Decomposition of ferrocenium salt in the presence of nucleophiles, such as bromide.

2.6 The development of a direct Friedel-Crafts benzylation reaction with ferrocenium boronic acid hexafluoroantimonate salt†

2.6.1 Optimization of the reaction conditions

With easy access to ferrocenium boronic acid **BAC-26**, initial reaction optimization of the Friedel-Crafts benzylation was then performed (**Table 2-4**). As a starting point, 4-bromobenzyl alcohol was chosen as the alkylating reagent for several reasons: (a) the bromo substituent deactivates the benzyl alcohol, making it a challenging, yet suitable substrate to identify superior catalysts; (b) installation of the Ar–Br moiety in the diarylmethane products is beneficial for further functionalization such as cross-coupling reactions; (c) the Ar–Br bond is not stable with many existing methods using transition metal catalysts. The benzylation was performed on *m*-xylene using the previously optimized solvent mixture of 4:1 HFIP and CH_3NO_2 at 50 °C. Owing to its high polarity, nitromethane was used in small proportion in order to reduce the amount of HFIP and lower the cost. While both tetrafluorophenyl boronic acid **BAC-16** and ferrocene boronic acid **BAC-25** failed to produce any product (entries 1-2), the ferrocenium boronic acid exhibited superior reactivity, affording diarylmethane **2-30** in 87% yield (entry 3). Since the position **a** and **b** on *m*-xylene are activated by the methyl groups for nucleophilic attack, compound **2-30** was isolated as an inseparable isomeric mixture of **2-30a** and **2-30b** (a:b = 78:22) according to ^{1}H NMR analysis of the reaction crude. Isomer **2-30a** was formed as the major product due to the less steric hindrance. Unsurprisingly, the reaction efficiency was greatly influenced by the amount of HFIP; a high proportion of HFIP was more desirable (entries 4-5). Further increasing the concentration resulted in a lower yield (entry 6). Attempting the reaction at room temperature resulted in low conversion (entry 7).

† A part of this work was contributed by Julien Dansereau, who was an undergraduate researcher under the author's supervision.



entry	catalyst	solvent ratio (x:y)	T (°C)	[M]	yield (%)[a]	a:b[b]
1	**BAC-16**	4:1	50	0.5	0	-
2	**BAC-25**	4:1	50	0.5	0	-
3	**BAC-26**	4:1	50	0.5	87	78:22
4	**BAC-26**	3:1	50	0.5	78	78:22
5	**BAC-26**	2:1	50	0.5	71	78:22
6	**BAC-26**	4:1	50	1.0	74	78:22
7	**BAC-26**	4:1	rt	0.5	14	75:25

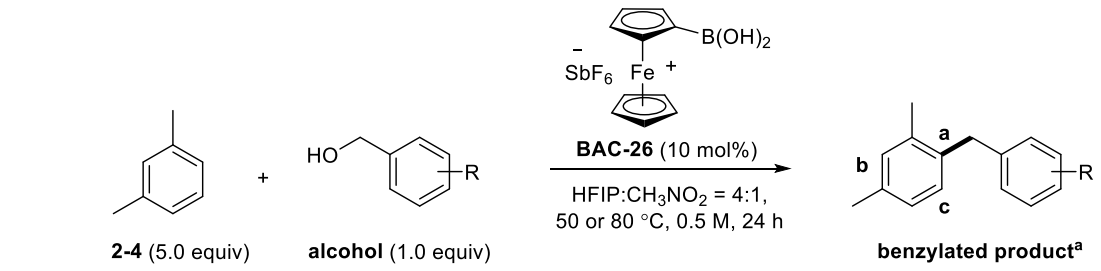
[a]Isolated yield. [b]Product ratio was determined by ^{1}H NMR analysis of the crude reaction mixture.

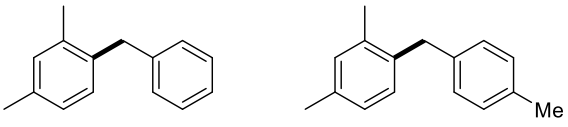
Table 2-4. Optimization of direct Friedel-Crafts benzylation with ferrocenium boronic acid.

2.6.2 Substrate scope examination

With the optimized conditions established (**Table 2-4**, entry 3), the scope of benzylic alcohol was investigated using *m*-xylene as the nucleophile (**Scheme 2-12**). Diarylmethanes **2-31** and **2-32** could be obtained in high yield, when electron neutral benzylic alcohols were used. To our satisfaction, benzylic alcohols with slightly deactivating substituents such as halides also performed well at 50 °C, affording products **2-33** to **2-36**. Gratifyingly, an activated electron rich benzylic alcohol with a methoxy group was also tolerated in the reaction. A moderate yield of **2-37** was obtained without a significant amount of the dibenzylated side product. The protocol, however, does not tolerate free amino groups, such as dimethyl amine, since product **2-38** was not observed. A possible explanation could be that a strong hydrogen bonding interaction between the solvent, HFIP (pK_a = 9.3), and the amino group might inhibit the resonance stabilization of the putative carbocation and slow down its formation. Only small amounts of products (**2-39** and **2-40**) were isolated when benzylic alcohols containing highly electron deficient arenes, such as Ar–NO_2 and Ar–CN, were used. The poor performance of these substrates is mostly likely due to the relatively high energy needed for the formation of the carbocation. Fortunately, other electron withdrawing groups on the benzylic alcohols such as –CO_2Me and –CF_3 were well tolerated. The corresponding diarylmethane products (**2-41** to **2-43**

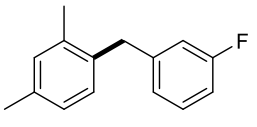
and **2-45**) were obtained in good yields. Notably, incorporation of fluorine atoms in products is highly desirable in the pharmaceutical industry. Although, the *para* substituted isomer was obtained as the major product, unfortunately, small amounts of the *ortho* isomer was also formed. This observation agrees with the classic isomeric product distribution of Friedel-Crafts benzylation. In all cases, these regioisomers cannot be separated by column chromatography under the standard conditions.



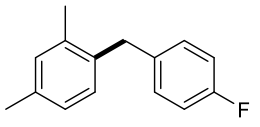


2-31
(87%, 50 °C, a:b = 82:18)

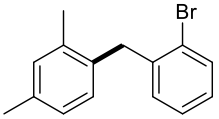
2-32
(94%, 50 °C, a:b = 83:17)



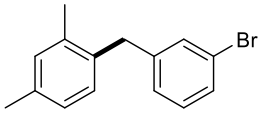
2-33
(99%, 50 °C, a:b = 78:22)



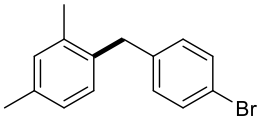
2-34
(95%, 50 °C, a:b = 75:25)



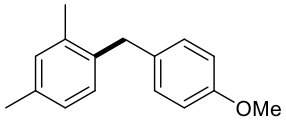
2-35
(99%, 50 °C, a:b = 81:19)



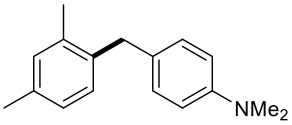
2-36
(81%, 50 °C, a:b = 82:18)



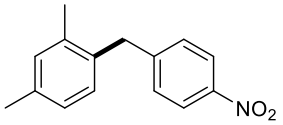
2-30
(87%, 50 °C, a:b = 78:22)
(78%, 50 °C, with $FeCl_3$)



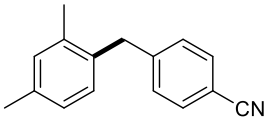
2-37
(61%, 40 °C)



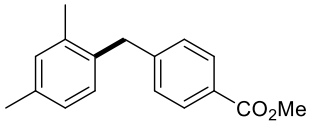
2-38
(0%, 40 °C)



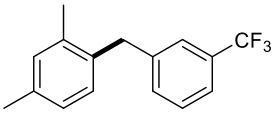
2-39
(10%, 80 °C, a:b = 81:19)



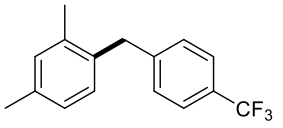
2-40
(12%, 80 °C, a:b = 77:23)



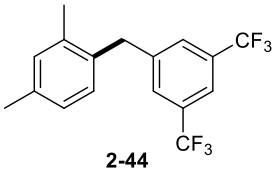
2-41
(63%, 80 °C, a:b = 76:24)



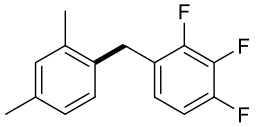
2-42
(99%, 80 °C, a:b = 81:19)



2-43
(99%, 80 °C, a:b = 81:19)



2-44
(0%, 80 °C)



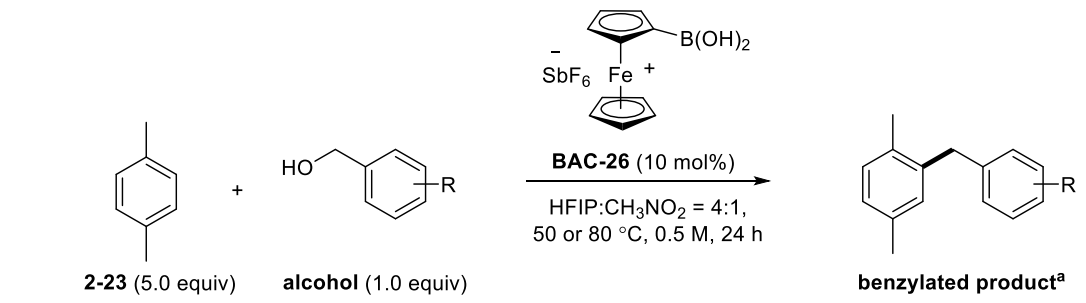
2-45
(60%, 80 °C, a:b = 77:23)

[a]Isolated yield. Product ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. For products **2-33**, **2-35**, **2-36**, **2-39** to **2-43** and **2-45**, <6% of the 5-substituted isomer c was obtained.

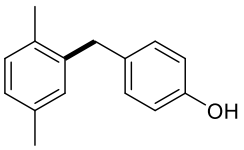
Scheme 2-12. Examination of the scope of benzylic alcohol with *meta*-xylene as nucleophile.

To better study the scope of the alcohol substrates, further efforts focused on the use of *p*-xylene to eliminate the formation of isomers (**Scheme 2-13**). Unsurprisingly, low conversion of product **2-46** was observed when the alcohol substrate with a phenolic moiety was used. It is suspected that such an electron rich benzylic alcohol is more nucleophilic than *p*-xylene and resulted in self-polymerization. Benzylic alcohols with halogenated arenes were therefore revisited and a high yield of products **2-48** to **2-52** was obtained. In contrast, only a moderate amount of product **2-53** was isolated. It is presumed that the thioether can interrupt the formation of the carbocation due to its high nucleophilicity. Remarkably, a benzylic alcohol with a carboxyester substituted arene reacted smoothly under the optimal conditions, providing product **2-54** in good yield. The highly deactivated benzylic alcohol with a nitro moiety also delivered a moderate amount of product **2-55** under more forcing conditions; reactions with substrates bearing other nitrogen functional groups resulted in low yield or no conversion to the products **2-56** to **2-59**. It is proposed that the high coordinating ability of these functional groups, such as –CN and pyridine, can possibly bind to the boronic acid or attack the iron center of the ferrocenium unit, both of which lead to catalyst deactivation.

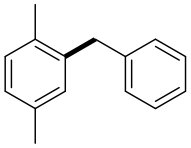
In comparison with other Lewis acids under the same reaction conditions, ferrocenium boronic acid **BAC-26** consistently delivered superior results for activation of C–O bonds. For instance, very low conversion or no product formation was observed when tetrafluorophenyl boronic acid **BAC-16** was used (**Scheme 2-13**, products **2-48**, **2-49** and **2-54**). In contrast, high yields were obtained with the ferrocenium boronic acid **BAC-26**. Although the moisture sensitive $FeCl_3$ was also an active Lewis acid and afforded diarylmethanes **2-30** and **2-54** in our reaction conditions, **BAC-26** provided a higher yield and easier reaction set up.



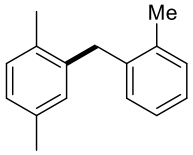
2-23 (5.0 equiv) **alcohol** (1.0 equiv) **benzylated product**[a]



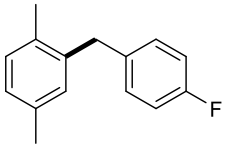
2-46
(22%, 50 °C, 48 h)



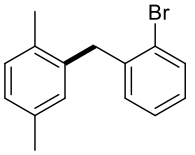
2-24
(88%, 50 °C)



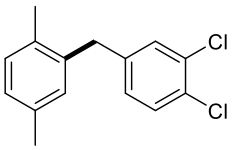
2-47
(89%, 50 °C)



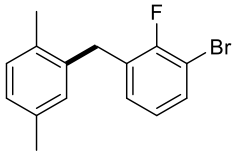
2-48 (77%, rt)
(6%, rt, with **BAC-16**)



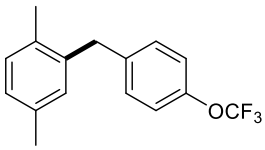
2-49 (98%, 50 °C)
(0%, 50 °C with **BAC-16**)[b]



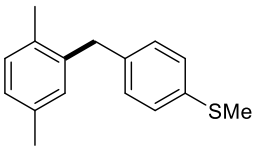
2-50
(69%, 80 °C)



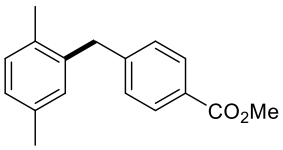
2-51
(57%, 80 °C)



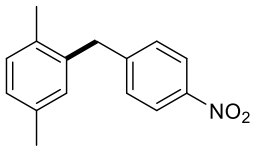
2-52
(93%, 50 °C)



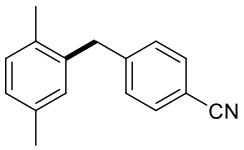
2-53
(44%, 80 °C)



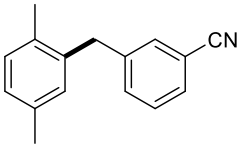
2-54 (85%, 80 °C)
(74%, 80 °C with $FeCl_3$,
0%, 80 °C with **BAC-16**)



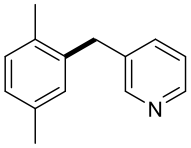
2-55
(46%, 80 °C, 48 h)[b]



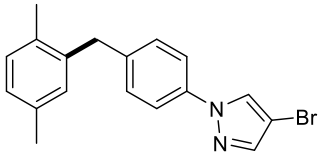
2-56
(8%, 80 °C)



2-57
(36%, 80 °C, 48 h)[b]



2-58
(0%, 80 °C)

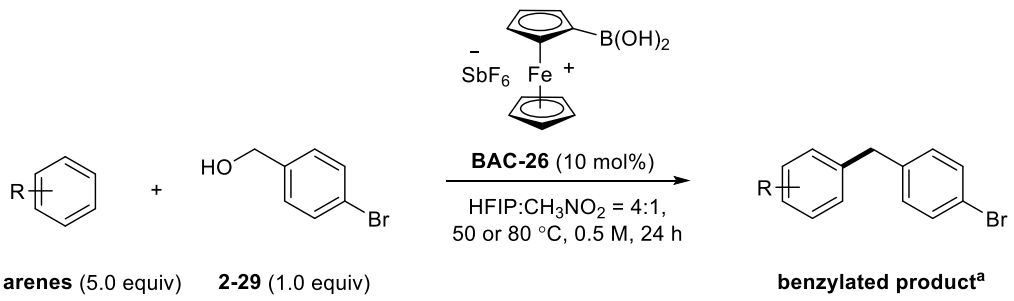


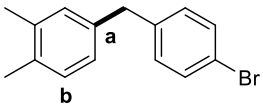
2-59
(trace, 80 °C)

[a]Isolated yield. [b]Reaction was run with 20 mol% catalyst.

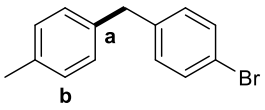
Scheme 2-13. Examination of the scope of benzylic alcohol with *para*-xylene as nucleophile.

The arene substrate scope was also performed, using 4-bromobenzyl alcohol **2-29** as the electrophile (**Scheme 2-14**). Similar to *m*-xylene, *o*-xylene underwent benzylation to provide product **2-60** in high yield. Electronically neutral arenes such as toluene and benzene, which are often sluggish coupling partners in Friedel-Crafts reactions, afforded the corresponding diarylmethanes **2-61** and **2-62** in high yields. Remarkably, even more electron poor arenes such as fluorobenzene, chlorobenzene and bromobenzene served as suitable nucleophiles using higher temperatures and longer reaction time (**2-63** to **2-65**). A modified solvent system was needed for naphthalene since it displays a very low solubility in both nitromethane and HFIP. Upon using chloroform along with HFIP, the benzylated product **2-66** was obtained in good yield. A series of electron rich aryl halides such as 4-bromoanisole, 4-bromophenol and 2-iodoanisole served as good coupling partners for the Friedel-Crafts benzylation within a short period of time. The resulting halogenated diarylmethanes **2-67** to **2-69** were obtained in high yield. While benzylation of 4-methoxy-methyl benzoate afforded product **2-70** in high yield, only a very small amount of product **2-71** was observed when 4'-methoxy-acetophone was used. This drastically decreased yield indicates that the benzylation protocol is highly sensitive to the electronic properties of the arenes. Under the optimal conditions, the reaction was also tested on drug derivatives such as ibuprofen methyl ester. As a result, the benzylated product **2-72** could be obtained in moderate yield, despite the increased steric hindrance from the arene substrate.

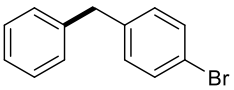




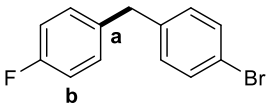
2-60 (96%, a:b = 61:39)[b]



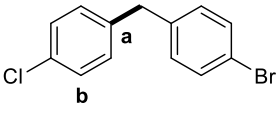
2-61 (84%, a:b = 57:43)[b]



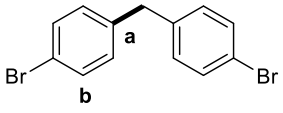
2-62 (89%)[c]



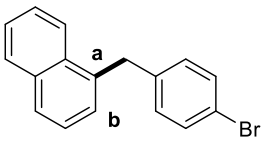
2-63 (88%, a:b = 73:27)[c,d]



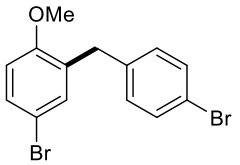
2-64 (77%, a:b = 71:29)[c,d]



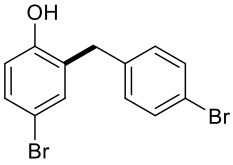
2-65 (83%, a:b = 71:29)[c,d]



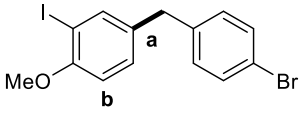
2-66 (88%, a:b = 70:30)[c,d,e]



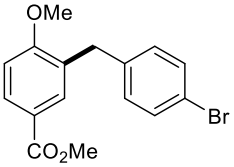
2-67 (81%)[b,f]



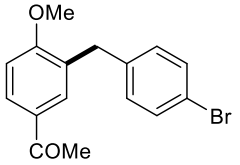
2-68 (52%)[b,g]



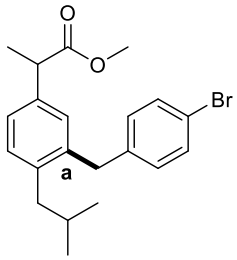
2-69 (91%, a:b = 95:5)[b]

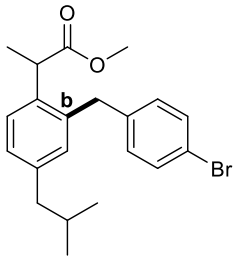


2-70 (94%)[c]



2-71 (25%)[c]





2-72 (52%, a:b = 67:33)[b,h]

[a]Isolated yield. Product ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Reaction was run at 50 °C. [c]Reaction was run at 80 °C. [d]48 h. [e]Reaction was run in HFIP:$CDCl_3$ = 4:1, 0.16 M. [f]Reaction was run with 3.0 equivalent of arenes, 2 h. The yield of was determined by ^{1}H NMR analysis of the crude reaction mixture using 1,4-dinitrobenzene as internal standard. [g]0.25 M,1.5 h. [h]Reaction was run with 3.0 equivalents of arenes.

Scheme 2-14. Examination of the arene scope with 4-bromobenzyl alcohol as the electrophile.

It is noteworthy that, some of the diarylmethanes prepared by this Friedel-Crafts benzylation protocol with catalyst **BAC-26** can hardly be synthesized using other methods (**Figure 2-6**). For example, the synthesis of **2-70** can be challenging using the traditional and photochemical cross-coupling reactions by palladium or nickel catalysis due to the presence of the aryl bromide (**Scheme 2-8a** to **Scheme 2-8c**). Although the use of the metal free cross coupling with aryl hydrazones and boronic acids (**Scheme 2-8d**) can potentially access compound **2-70**, this method has not been shown to be successful with sterically hindered substrates. Triflic acid was also described as a powerful catalyst for Friedel-Crafts benzylation very recently (**Scheme 2-10d**). However, use of a high temperature under acidic conditions could potentially hydrolyze the ester group from **2-70**.

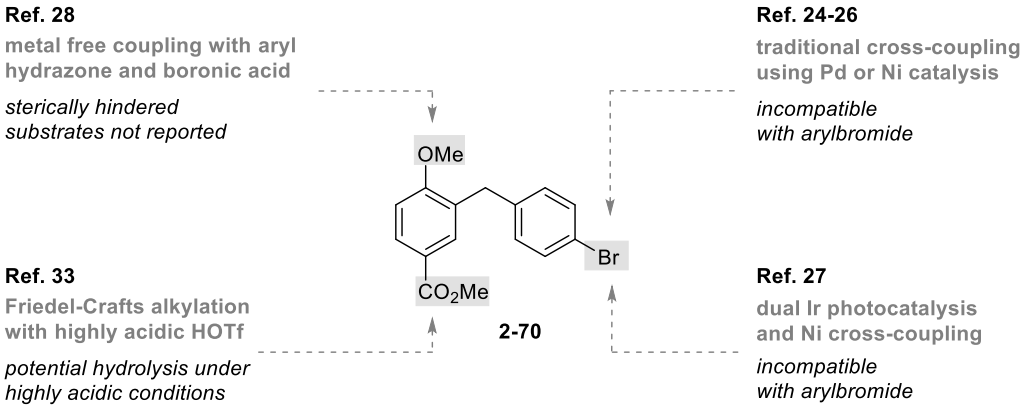
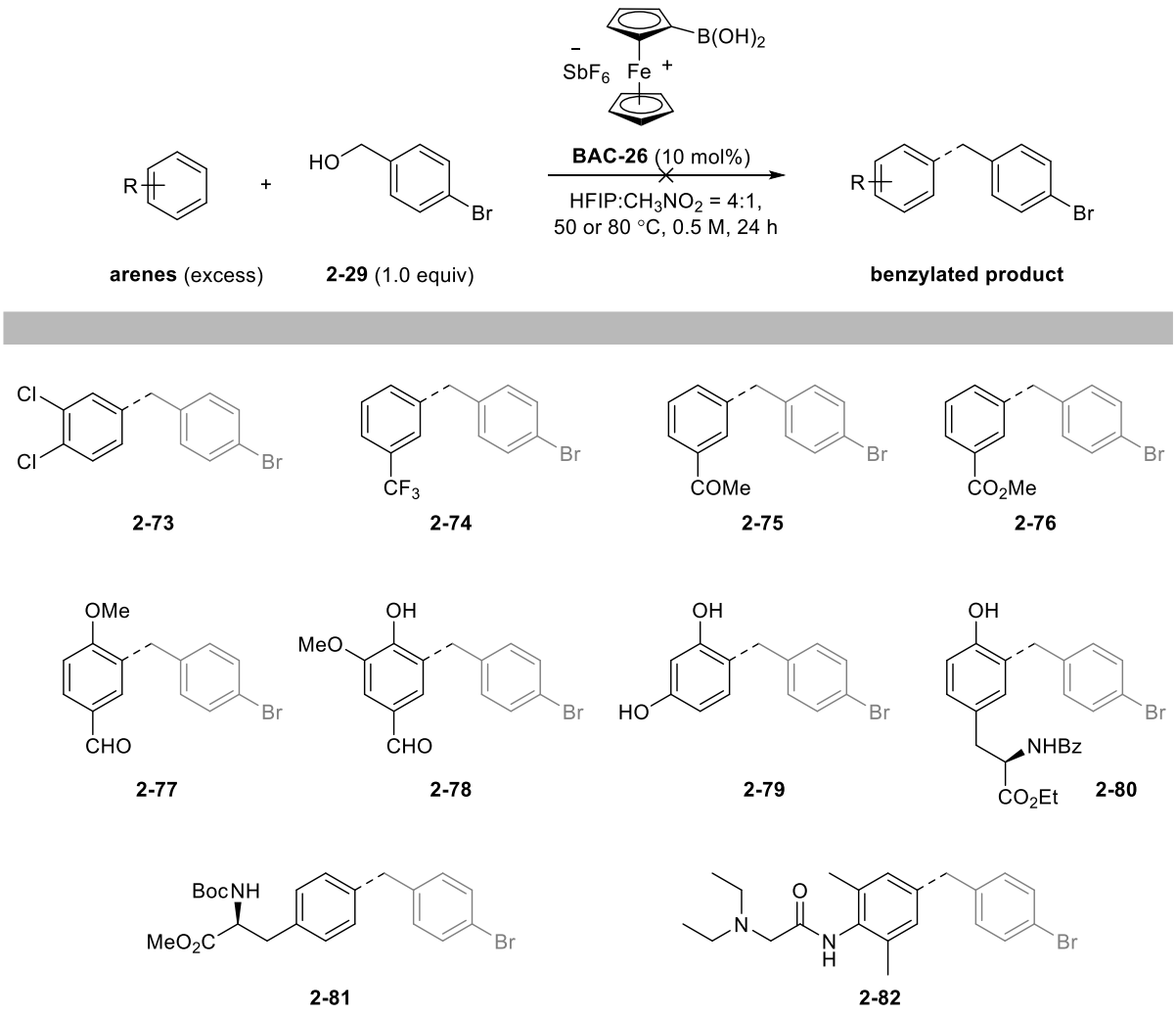


Figure 2-6. A diarylmethane compound that can hardly be prepared by other methods.

Certain aromatic compounds exhibited a lack of reactivity in the benzylations with the ferrocenium boronic acid catalyst. As shown in **Scheme 2-15**, it was found that highly electron deficient arenes, such as *ortho*-dichlorobenzene, trifluoromethylbenzene, acetophenone and methyl benzoate, are not nucleophilic enough for the standard benzylation. No products (**2-73** to **2-76**) but recovered arenes were observed under various forcing conditions with increasing catalyst loading, temperature and reaction time. Unfortunately, arenes with aldehyde groups were also inert despite the presence of electron donating groups and none of the desired products **2-77** and **2-78** were formed. Although the exact rational is unclear, it appears that compensation from the –OMe and –OH groups is not sufficient enough to overcome the electron withdrawing effect of the aldehyde. However, other possible explanations cannot be ruled out, such as catalyst deactivation resulting from oxidation of the aldehyde by the

ferrocenium unit. Arenes that do not have good solubility in HFIP and CH_3NO_2 do not undergo the benzylation. For example, despite its electron richness, resorcinol cannot be alkylated under the standard conditions due to poor solubility (**2-79**). Amino acid derivatives are also unsuitable substrates for benzylation with **BAC-26**. It is suspected that chelation from the amino ester unit to the boronic acid inhibited the catalytic activity. Similarly, an attempted benzylation of the drug lidocaine was also unsuccessful. As a result, no desired products (**2-80** to **2-82**) were observed.



Scheme 2-15. Arenes that failed to react with 4-bromobenzyl alcohol.

The synthesis of the unsymmetrical diarylmathane compounds can be achieved by two different disconnections. Although some of the electron deficient arenes display a lack of reactivity in this Friedel-Crafts benzylation, this issue can partially be addressed through synthetic planning with

another set of benzylic alcohols and arenes. For instance, the synthesis of diarylmethane **2-73** was not successful using 4-bomobenzyl alcohol and *ortho*-dichlorobenzene, owing to a lack of nucleophilicity of the *ortho*-dichlorobenzene (**Figure 2-7**, equation 1). In an alternative synthetic route using 3,4-dichlorobenzyl alcohol and bromobenzene (equation 2), the same product **2-73** was obtained in a high yield of 73%, albeit in forms of isomers. Similarly, trifluoromethylbenzene serves as an unreactive arene with 2,5-dimethylbenzyl alcohol in the Friedel-Crafts benzylation (equation 3), but the other synthetic route with different disconnection provided the product **2-83** in a high yield of 97% (equation 4). These two examples of diarylmethane synthesis using double disconnection are contributed by Joshua Yakiwchuk, a former student in the Hall group.

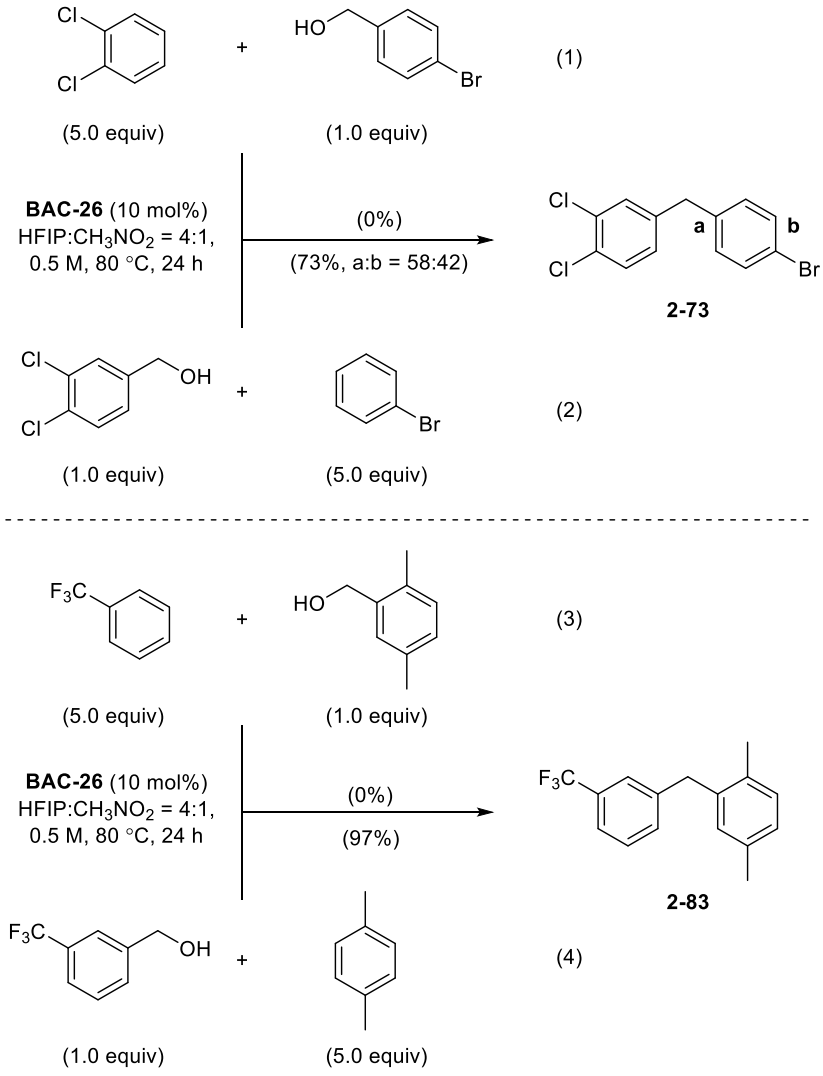
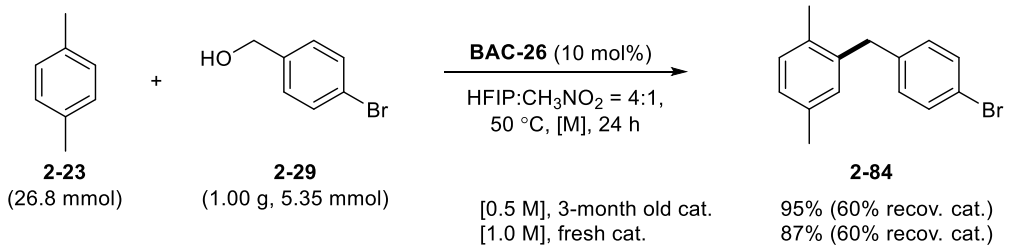


Figure 2-7. The synthesis of diarylmethane compounds with different disconnection.

2.6.3 Gram scale synthesis and catalyst recovery

As an application of the developed method, a gram scale reaction of *p*-xylene and 4-bromobenzyl alcohol was performed (**Scheme 2-16**). An excellent yield (95%) was obtained with a batch of 3-month old catalyst **BAC-26** under the standard benzylation conditions (0.5 M). The catalyst **BAC-26** was recovered in a moderate 60% yield by recrystallization from diethyl ether. Further experiments showed that the gram scale benzylation could also be achieved with good yield (87%) with freshly prepared catalyst and a higher concentration (1.0 M) for higher solvent economy.



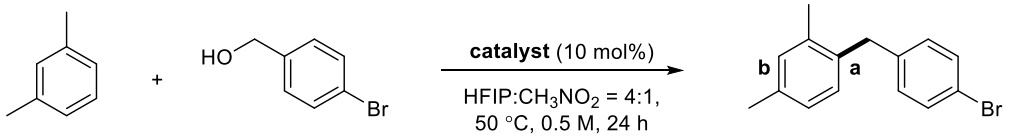
Scheme 2-16. Gram scale reactions and catalyst recovery.

2.7 Mechanistic studies

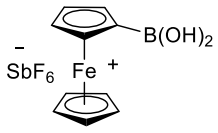
2.7.1 Examination of the important roles of the boronyl group and iron center in the ferrocenium boronic acid BAC-26

Control experiments were conducted to reveal the highly reactive nature of the ferrocenium boronic acid catalyst **BAC-26** (**Scheme 2-17**). Under the optimal conditions (**Scheme 2-17a**), benzylation of *m*-xylene with 4-bromobenzyl alcohol **2-29** afforded the diarylmethane product **2-30** in high yield (87%). As previously described, the parent neutral ferrocene boronic acid was not active at all, providing no trace of product (**Scheme 2-17b**). This comparison highlights the essential role of the cationic Fe(III) center in the catalyst. Further experiments also revealed the critical role of the boronic acid moiety for the direct Friedel-Crafts alkylation. Devoid of the boronyl moiety, ferrocenium hexafluoroantimate salt only provided very low conversion (15%) to the expected product (**Scheme 2-17c**). Complete inhibition of the catalyst upon removal of the boronic acid was not observed in this case since the 17 electron ferrocenium is electrophilic as well.[39] A moderate 45% yield of product **2-30** was obtained using the corresponding pinacol

boronic ester (**Scheme 2-17d**). This unexpected high performance of the pinacol boronic ester possibly resulted from partial hydrolysis to the free boronic acid **BAC-26**, which was supported by a further decrease of the yield with the addition of molecular sieves (**Scheme 2-17e**). It was also found that the reaction provided no product using ferrocenium boronic acid along with molecular sieves (**Scheme 2-17f**). It is possible that the boronic acid anhydride (boroxine) was formed in conjunction with the removal of water, which led to complete loss of reactivity. In order to rule out the possible formation of HF from the hexafluoroantimonate anion, a control experiment with $AgSbF_6$ was performed (**Scheme 2-17g**). A negative result was obtained, thus confirming that the presence of the SbF_6 anion alone is not responsible for the reactivity of ferrocenium boronic acid. Considering that the pK_a of ferrocenium boronic is relatively low (pK_a = 5.8), it was later sought to explore whether this catalyst was working as a Lewis acid or a Brønsted acid. Thus, comparison experiments using a stronger Brønsted acid, TFA, were performed (**Scheme 2-17h** and **2-17i**). With or without the addition of water, only trace amounts of diarylmethane **2-30** were observed. Consequently, it is reasonable to state that the ferrocenium boronic acid behaves as a Lewis acid under the reaction conditions. In conclusion, the high catalytic activity of ferrocenium boronic acid originates from its cationic electrophilic iron(III) center and its Lewis acidic, free boronic acid moiety.



2-4 (5.0 equiv) **2-29** (1.0 equiv) **2-30** (a:b = 78:22)



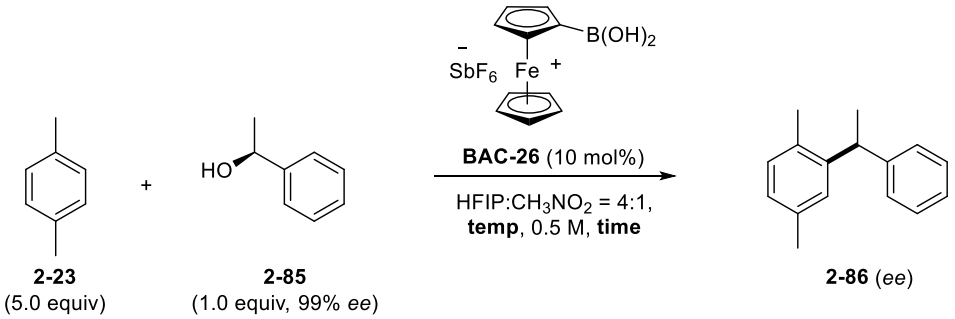
BAC-26

control	**catalyst**	**yield** (%)
a	$[CpFe(III)CpB(OH)_2]^+ SbF_6^-$ (**BAC-26**)	87
b	$[CpFe(II)CpB(OH)_2]$ (**BAC-25**)	0
c	$[CpFe(III)Cp]^+ SbF_6^-$	15
d	$[CpFe(III)CpBpin]^+ SbF_6^-$	45
e	$[CpFe(III)CpBpin]^+ SbF_6^-$ + 4 Å MS	27
f	$[CpFe(III)CpB(OH)_2]^+ SbF_6^-$ + 4 Å MS	0
g	$Ag^+ SbF_6^-$	0
h	CF_3CO_2H	trace
i	$CF_3CO_2H + H_2O$ (20 mol%)	trace

Scheme 2-17. Control experiments examining the important roles of the boronyl group and the iron center in ferrocenium boronic acid **BAC-26**.

2.7.2 Confirmation of the S_N1 mechanism

Although the previous substrate scope (**Scheme 2-12**) strongly hinted at an S_N1 mechanism and the formation of a carbocation intermediate, the S_N2 substitution could not be ruled out completely. Thus, the following experiments were designed to further confirm an S_N1 mechanism. As shown in **Scheme 2-18**, optically pure secondary benzyl alcohol **2-85** was tested with *p*-xylene under various temperatures and reaction times and the corresponding product **2-86** was isolated with full racemization in all cases. The loss of stereochemical information strongly indicates the formation of a stabilized carbocation. However, these experiments are not conclusive since secondary benzyl alcohols were not tested in the substrate scope.

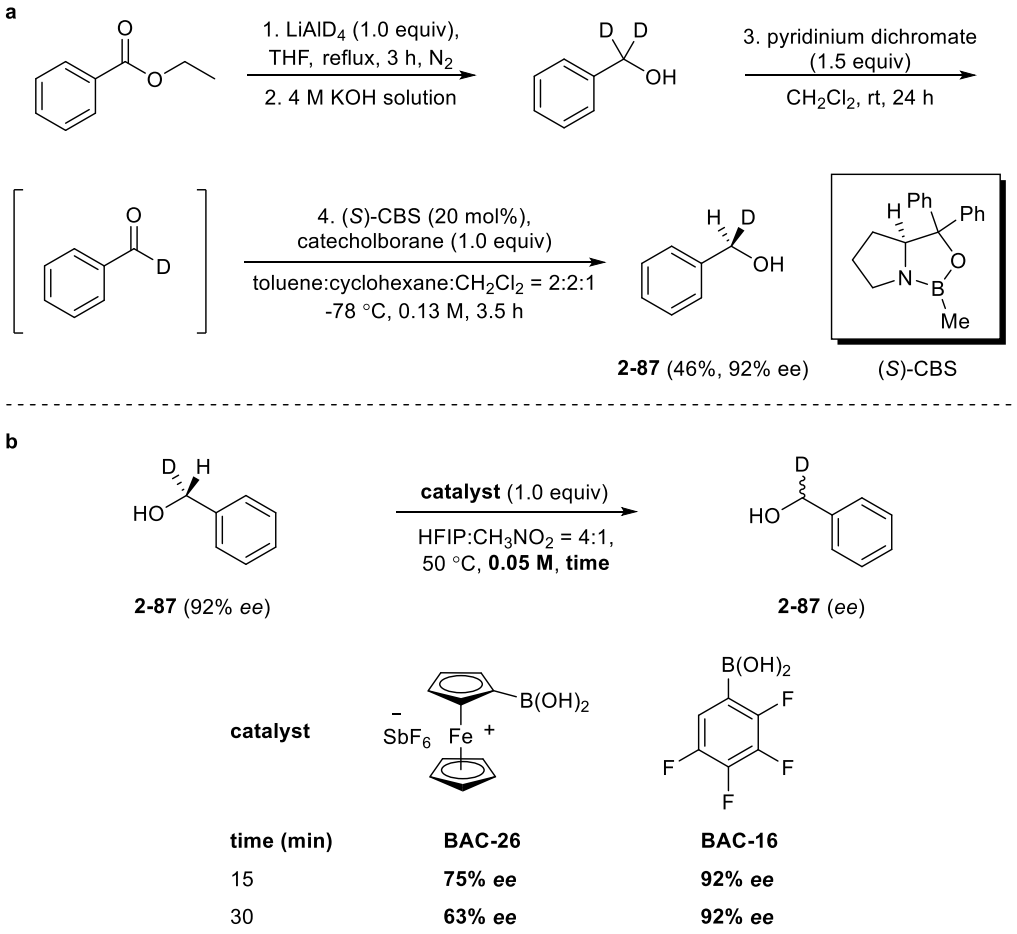


temp (°C)	**time** (h)	**yield** (%)	***ee*** **(%)**
25	20	48	0
0	20	51	0
-20	48	14	0

Scheme 2-18. Stereochemical experiments of optically pure secondary benzyl alcohol in direct Friedel-Crafts alkylation with *p*-xylene.

Subsequently, deuterium-labelling experiments were conducted. The optically pure deuterated primary benzyl alcohol **2-87** was prepared (**Scheme 2-19a**)[40,41] and subjected to the following reaction conditions with ferrocenium boronic acid and tetrafluorophenyl boronic acid (**Scheme 2-19b**). A lower concentration 0.05 M was preferable since facile decomposition of **2-87** was observed due to the strong ionizing power of ferrocenium boronic acid under the original conditions. Therefore, one equivalent of both boronic acids (**BAC-16** and **BAC-26**) was used due to the low reactivity of tetrafluorophenyl boronic acid in lower concentration. It was observed that the optical purity of **2-87** decreased drastically within 30 min of exposure to the ferrocenium

boronic acid **BAC-26**. The formation of the carbocation intermediate was therefore confirmed. Expectedly, no loss of enantiomeric excess of **2-87** was obtained when tetrafluorophenyl boronic acid was used, which suggests that ferrocenium boronic acid is more potent for direct alcohol activation.

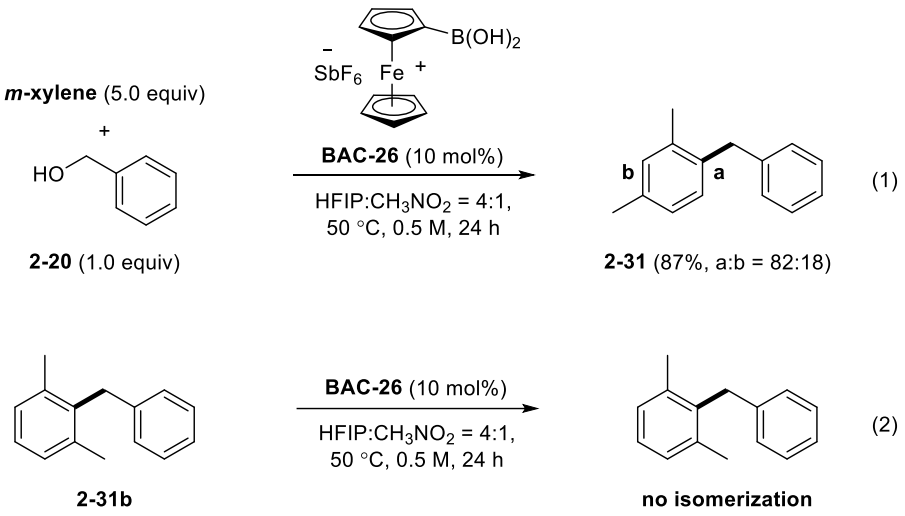


Scheme 2-19. (a) The synthesis of optically pure deuterated primary benzyl alcohol; (b) Stereochemical experiments of optically pure deuterated primary benzyl alcohol in direct Friedel-Crafts alkylation.

2.7.3 Kinetic control vs thermodynamic control

After establishing an S_N1 mechanism for the benzylation catalyzed by ferrocenium boronic acid **BAC-26**, the question of whether the benzylation is under kinetic or thermodynamic control was explored. Throughout the course of substrate scope examination, the formation of minor isomer

b (such as **2-31b**) was observed in most cases (an example is shown as **Scheme 2-20**, equation 1). The minor product **2-31b** was prepared independently according to the method of Molander and co-workers and subjected to the standard reaction conditions.[42] No isomerization of **2-31b** to the less sterically hindered product was observed after 24 h (**Scheme 2-20**, equation 2), which suggests that the isomeric product distribution is likely under kinetic control rather than thermodynamic control.

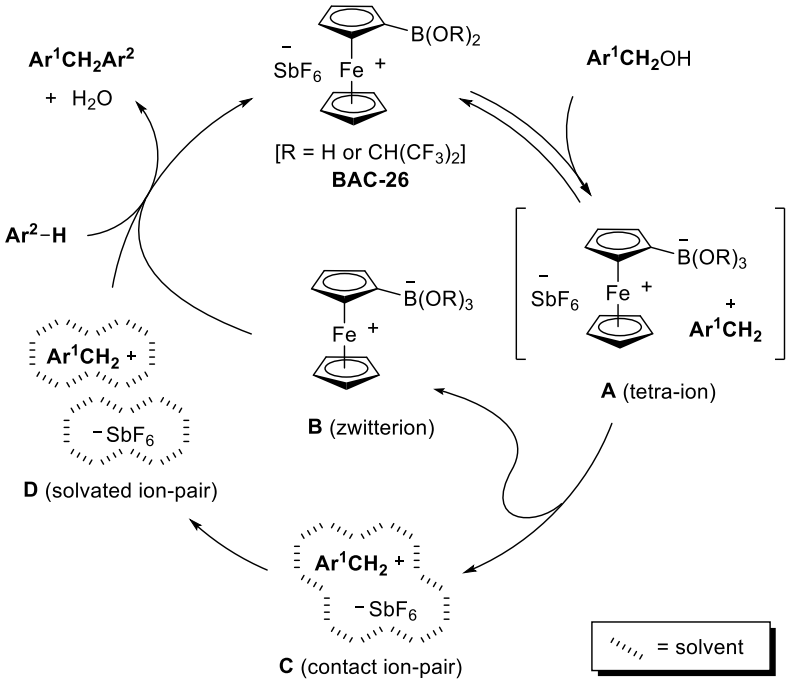


Scheme 2-20. Isomerization experiment of the minor product in reaction conditions.

2.8 Proposed mechanism

Based on observations regarding the substrate scope, control experiments and mechanistic studies, the following reaction mechanism is proposed (**Scheme 2-21**). A full ionization of the benzylic alcohol by ferrocenium boronic acid **BAC-26** is achieved in the solvent mixture of HFIP and CH_3NO_2. Although it is well known that, as a highly polar solvent, HFIP can help stabilize and solvate the carbocation, the formation of the highly Lewis acidic boronyl HFIP hemi-ester or HFIP diester [-BOR, R = $CH(CF_3)_2$] cannot be ruled out. Upon ionization of the alcohol, it is suggested that a tetra-ion species **A** is formed, which undergoes a facile decomposition into formal neutral zwitterion boronate **B** and the contact ion pair **C**. This novel ion redistribution process is thought to benefit from the cationic structure of ferrocenium boronic acid as depicted in **Scheme 2-11a**. The anion hexafluoroantimonate is prone to dissociate due to a lack of coordination to the paired carbocation, which results in the solvated ion-pair **D**. The non-

coordinating properties of the hexafluoroantimonate anion help increase the energy of the carbocation compared to the scenario where it is paired with the nucleophilic boronate (**A**). Consequently, a more electrophilic and exposed carbocation is produced for nucleophilic substitution. As discussed in the section dedicated to the arene substrate scope (**Scheme 2-14** and **Scheme 2-15**), the efficacy of the benzylation is greatly influenced by the nucleophilicity of the arenes, which supports the rate-determining step being the electrophilic substitution. Furthermore, a kinetic control of product distribution is most likely since product isomerization under the reaction conditions was not observed.



Scheme 2-21. Proposed mechanism of the ferrocenium boronic acid catalyzed direct Friedel-Crafts benzylation.

2.9 Summary

This chapter reports a study on boronic acid catalysis for direct Friedel-Crafts alkylation with alcohol substrates. Significant effort was placed on explaining the higher reactivity of tetrafluorophenyl boronic acid compared to pentafluorophenyl boronic acid for alcohol ionization. Mechanistic studies revealed the important role of the *ortho*-substituents for catalyst reactivity. Pentafluorophenyl boronic acid in fact displays a stronger Lewis acidity; however, the lower

reactivity is attributed to the stronger electronic repulsion in the alcohol C–O bond cleavage event in the presence of the additional fluoride substituent compared to the tetrafluorophenyl boronic acid. Potential hydrogen bonding stabilization from the *ortho*-H to the polarized C–O bond cannot be ruled out in the case of tetrafluorophenyl boronic acid. Further exploration of more structurally different boronic acids led to the discovery of a much more potent catalyst, ferrocenium boronic acid hexafluoroantimonate. Featuring a cationic backbone with a non-coordinating anion, ferrocenium boronic acid exhibits strong ionization ability for activated and deactivated benzylic alcohols. A diverse scope of electron neutral arenes can be benzylated under mild conditions with HFIP as the co-solvent. Control experiments highlight the importance of both the iron(III) center and the boronic acid moiety in the catalyst. An S_N1 mechanism is strongly supported by mechanistic control experiments for the direct Friedel-Craft benzylation. It is believed that a highly reactive carbocation is formed as a result of a novel ion redistribution mechanism.

2.10 Experimental

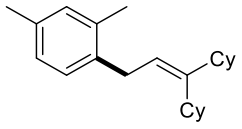
2.10.1 General information

The following materials include representative experimental procedures and details for the synthesis and isolation of compounds. Full characterization of all new compounds and partial characterization of known compounds presented in this chapter are described. Unless otherwise stated, all reactions were performed in capped regular glassware with no further precautions. Tetrahydrofuran (THF) and dichloromethane (DCM) were purified using a cartridge solvent purification system with 4 Å molecular sieves as absorbent. Acetone was dried with anhydrous magnesium sulfate before use. All other solvents were purchased as ACS reagents and used without further purification. 2,3,4,5-Tetrafluorophenyl boronic acid was synthesized according to Piers and co-workers.[43] Unless otherwise noted, all other chemicals were purchased from commercial sources and used as received. Chromatographic separations were performed on silica gel 60 using ACS grade hexanes, ethyl acetate, dichloromethane, diethylether and toluene as eluents. Preparative thin-layer chromatography (PTLC) was run on silica gel 60 F254 plates. Thin layer chromatography (TLC) was performed on silica gel 60 F254 plates, which were visualized under UV light and with $KMnO_4$ or phosphomolybdic acid (PMA) stains. ^{1}H NMR, ^{13}C NMR, ^{11}B NMR and ^{19}F NMR spectra were recorded on 400 MHz or 500 MHz instruments. The

residual solvent protons (^{1}H / $CHCl_3$) or the solvent carbon (^{13}C) were used as internal references. ^{1}H NMR data is presented as follows: chemical shifts in ppm 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; quin, quintet; sext, sextet; sept, septet; dd, doublet of doublets; m, multiplet. The error of coupling constants from ^{1}H NMR spectra is estimated to be 0.3 Hz. High-resolution mass spectra were recorded on a oaTOF analyzer. Infrared (IR) spectra were obtained using cast-film technique with frequencies expressed in cm^{-1}. The resolution of the IR instrument is 4 wavenumber. Melting points (m. p.) were measured on a melting point apparatus and are uncorrected. All the pH values were recorded on a Mettler Toledo pH meter.

2.10.2 General procedure for the Friedel-Crafts alkylation with 2,3,4,5-tetrafluorophenyl boronic acid

To a vial equipped with a stir bar, containing the alcohol and the arene dissolved in a 4:1 mixture of HFIP:CH_3NO_2 (unless otherwise noted), was added 2,3,4,5-tetrafluorophenyl boronic acid. The vial was capped and stirred for the indicated time at the stated temperature. Upon completion (as determined by periodic monitoring of the reaction by TLC), the mixture was concentrated and subjected to flash chromatography using EtOAc/hexanes as the eluent to afford the product.



2-12

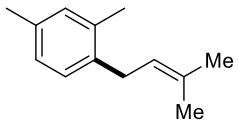
(3-(2,4-Dimethylphenyl)prop-1-ene-1,1-diyl)dicyclohexane (2-12): Prepared from allylic alcohol **2-6** (111 mg, 1.00 mmol), *m*-xylene (265 mg, 2.50 mmol) and **BAC-16** (10 mg, 0.05 mmol) at room temperature for 20 hours, followed by flash column chromatography (hexane to hexane:EtOAc = 20:1) to afford **2-12** as a yellow oil (279 mg, 90%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.01-6.97 (m, 1H), 6.93-6.89 (m, 2H), 5.15-5.12 (t, *J* = 7.1 Hz, 1H), 3.31-3.29 (d, *J* = 7.1 Hz, 3H), 2.52-2.44 (m, 1H), 2.26 (s, 3H), 2.23 (s, 3H), 1.92-1.85 (m, 1H), 1.74-1.60 (m, 8H), 1.50-1.49 (m, 2H) 1.37-1.11 (m,10H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.4, 136.9, 135.6, 134.6, 130.3, 127.9, 125.9, 119.9, 40.3, 39.8, 34.5, 34.5, 30.5, 30.3, 26.7, 26.2, 25.8, 25.7, 20.4, 18.9;

IR (Microscope, cm^{-1}): 3003, 2926, 2851, 1503, 1448;

HRMS (EI) for $C_{22}H_{34}$: calcd. 310.2661; found 310.2659.



2-13

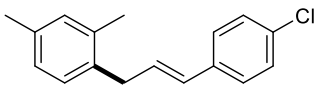
2,4-Dimethyl-1-(3-methylbut-2-en-1-yl)benzene (2-13): Prepared from allylic alcohol **2-7** (86 mg, 1.00 mmol), *m*-xylene (531 mg, 5.00 mmol) and **BAC-16** (20 mg, 0.10 mmol) at room temperature for 24 hours, followed by flash column chromatography (hexane to hexane:EtOAc = 20:1) to afford **2-13** as an oil (100 mg, 58%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.04-7.01 (m, 1H), 6.97-6.94 (m, 2H), 5.31-5.21 (m, 1H), 3.28-3.26 (d, *J* = 7.1 Hz, 2H), 2.29 (s, 3H), 2.26 (s, 3H), 1.74 (s, 3H), 1.73 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.9, 136.0, 135.4, 132.1, 131.0, 128.6, 126.6, 122.9, 31.9, 25.8, 20.9, 19.4, 17.9;

IR (Microscope, cm^{-1}): 3004, 2969, 2920, 2857, 1502, 1449;

HRMS (EI) for $C_{13}H_{17}$ $[M-H]^+$: calcd. 173.1330; found 173.1332.



2-14

(*E*)-1-(3-(4-Chlorophenyl)allyl)-2,4-dimethylbenzene (2-14): Prepared from allylic alcohol **2-8** (84 mg, 0.50 mmol), *m*-xylene (265 mg, 2.50 mmol) and **BAC-16** (10 mg, 0.05 mmol) at room

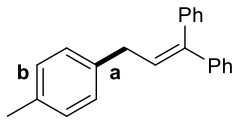
temperature for 20 hours, followed by flash column chromatography (hexane to hexane:EtOAc = 20:1) to afford **2-14** as a yellow oil (208 mg, 81%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23-7.17 (m, 4H), 7.05-7.03 (m, 1H), 6.97-6.94 (m, 2H), 6.28-6.26 (m, 2H), 3.46-3.45 (d, *J* = 3.5 Hz, 2H), 2.28 (s, 3H), 2.26 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.7, 135.6, 135.5, 134.3, 132.0, 130.6, 129.1, 128.9, 128.7, 128.1, 126.7, 126.2, 35.9, 20.4, 18.8.

IR (Microscope, cm^{-1}): 3025, 3007, 29202, 2857, 1650, 1616, 1594, 1502, 1490, 1442, 1092.27, 816;

HRMS (EI) for $C_{17}H_{17}Cl$: calcd. 256.1019; found 256.1016.



2-16

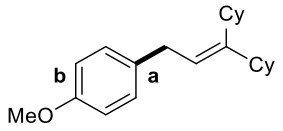
(3-(*p*-Tolyl)prop-1-ene-1,1-diyl)dibenzene (2-16): Prepared from allylic alcohol **2-1** (210 mg, 1.00 mmol), toluene (460 mg, 5.00 mmol) and **BAC-16** (20 mg, 0.10 mmol) at 50 °C for 24 hours, followed by flash column chromatography (hexane to hexane:EtOAc = 20:1) to afford **2-16** as a colorless oil (29 mg, 10%, *p*:*o* = 58:42 regioisomeric mixture).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.07 (m, 14H), 6.23 (t, *J* = 7.6 Hz, 0.57H), 6.17 (t, *J* = 7.3 Hz, 0.49H), 3.41 (d, *J* = 7.4 Hz, 1.0H), 3.40 (d, *J* = 7.4 Hz, 1H), 2.30 (s, 1.58H), 2.17 (s, 1.43H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.0, 141.7, 139.4, 138.5, 137.4, 135.8, 134.9, 129.6, 129.4, 129.3, 128.7, 128.1, 127.8, 127.6, 127.5, 126.9, 126.8, 126.6, 126.6, 126.5, 126.5, 125.7, 125.5, 35.0, 33.2, 20.5, 19.0;

IR (Microscope, cm^{-1}): 3079, 3055, 3021, 2923, 1599, 1513, 1494, 1460, 762, 701;

HRMS (EI) $C_{22}H_{20}$: calcd. 284.1565; found 284.1565.



2-17

(3-(4-Methoxyphenyl)prop-1-ene-1,1-diyl)dicyclohexane (2-17): Prepared from allylic alcohol **2-6** (222 mg, 1.00 mmol) arene **2-10** (540 mg, 5.00 mmol) and **BAC-16** (20 mg, 0.10 mmol) at room temperature for 3 hours, followed by flash column chromatography (hexane:EtOAc = 20:1) to afford **2-17a** as a yellow oil: (178 mg, 57%) and **2-17b** as a yellow oil (33 mg, 11%).

2-24a:

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.07-7.05 (m, 2H), 6.80-6.78 (m, 2H), 5.21 (t, *J* = 7.4 Hz, 1H), 3.76 (s, 3H), 3.33 (d, *J* = 7.4 Hz, 2H), 2.50-2.42 (m, 1H), 1.92-1.85 (m, 1H), 1.74-1.55 (m, 8H), 1.50-1.46 (m, 2H), 1.41-1.06 (m, 10H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.1, 150.4, 133.8, 128.6, 120.5, 113.2, 54.8, 40.2, 40.0, 34.5, 32.0, 30.6, 26.7, 26.2, 25.8, 25.7;

IR (Microscope, cm^{-1}): 2996, 2925, 2850, 1611, 1511, 1464, 1448, 1246;

HRMS (EI) for $C_{22}H_{32}O$: calcd. 312.2453; found 312.2454.

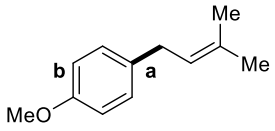
2-24b:

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20-7.15 (m, 2H), 6.94-6.87 (m, 2H), 5.28 (t, *J* = 7.5 Hz, 1H), 3.87 (s, 3H), 3.42 (d, *J* = 7.5 Hz, 2H), 2.59-2.51 (m, 1H), 1.96-1.92 (m, 1H), 1.79-1.68 (m, 8H), 1.55-1.52 (m, 2H), 1.46-1.17 (m, 10H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.9, 151.7, 131.2, 129.6, 127.2, 121.0, 120.5, 110.6, 55.9, 41.1, 41.1, 35.6, 31.6, 27.8, 27.7, 27.3, 27.0, 26.8;

IR (Microscope, cm^{-1}): 2925, 2850, 1600, 1587, 1492, 1464, 1448, 1242;

HRMS (EI) for $C_{22}H_{32}O$: calcd. 312.2453; found 312.2453.



2-18

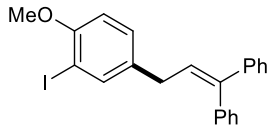
1-Methoxy-4-(3-methylbut-2-en-1-yl)benzene (2-18): Prepared from allylic alcohol **2-7** (86 mg, 1.00 mmol), arene **2-10** (540 mg, 5.00 mmol) and **BAC-16** (20 mg, 0.10 mmol) at room temperature for 3 hours, followed by flash column chromatography (hexane to hexane:EtOAc = 20:1) to afford **2-18** as a yellow oil (150 mg, 85%, *p*:*o* = 75:25 regioisomeric mixture).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.16-7.10 (m, 0.55H, minor), 7.08-7.05 (m, 1.33H, major), 6.94-6.82 (m, 0.62H, minor), 6.81-6.74 (m, 1.43H, major), 5.28 (t, *J* = 7.4 Hz, 1H), 3.81 (s, 0.71H, minor), 3.76 (s, 1.50H, major), 3.29 (d, *J* = 7.4 Hz, 0.53H, minor), 3.25 (d, *J* = 7.4 Hz, 1.50H, major), 1.72 (s, 3H), 1.69 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.2, 133.0, 131.6, 128.6, 126.3, 123.1, 122.0, 119.9, 113.3, 109.7, 54.8, 54.8, 32.9, 27.9, 25.3, 25.2, 17.3, 17.2;

IR (Microscope, cm^{-1}): 3030, 2967, 2913, 2856, 2835, 1611, 1511, 1495, 1464, 1440, 1245, 1038;

HRMS (EI) for $C_{12}H_{16}O$: calcd. 176.1201; found 176.1196.



2-19

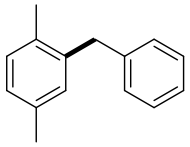
(3-(3-Iodo-4-methoxyphenyl)prop-1-ene-1,1-diyl)dibenzene (2-19): Prepared from allylic alcohol **2-1** (210 mg, 1.00 mmol), arene **2-11** (1.17 g, 5.00 mmol) and **BAC-16** (20 mg, 0.10 mmol) at room temperature for 24 hours, followed by flash column chromatography (hexane to hexane:EtOAc = 20:1) to afford **2-19** as a yellow oil (207 mg, 49%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58-7.57 (d, *J* = 2.1 Hz, 1H), 7.40-7.35 (m, 2H), 7.32-7.29 (m, 1H), 7.25-7.18 (m, 7H), 6.73-6.71 (d, *J* = 8.4 Hz, 1H), 6.20-6.13 (t, *J* = 7.6 Hz, 1H), 3.83 (s, 3H), 3.36-3.34 (d, *J* = 7.6 Hz);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.0, 142.2, 141.7, 139.2, 138.7, 134.7, 129.4, 128.8, 127.8, 127.6, 126.8, 126.8, 126.7, 126.6, 110.4, 85.6, 55.9, 34.0;

IR (Microscope, cm^{-1}): 3078, 3055, 3022, 2961, 2640, 2902, 2835, 1597 1489, 1460, 1442, 1277, 1253, 1048;

HRMS (EI) for $C_{22}H_{19}IO$: calcd. 426.0481; found 426.0482.



2-24

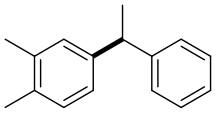
2-Benzyl-1,4-dimethylbenzene (2-24): Prepared from benzyl alcohol **2-20** (108 mg, 1.00 mmol), *p*-xylene (5.00 mmol) and **BAC-16** (39 mg, 0.20 mmol) at 50 °C for 24 hours, followed by flash column chromatography (hexane to hexane:EtOAc = 20:1) to afford **2-24** as a colorless oil (118 mg, 60%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27-7.23 (m, 2H), 7.18-7.14 (m, 1H), 7.12-7.09 (m, 2H), 7.04-7.03 (m, 1H), 6.96-6.92 (m, 2H), 3.94 (s, 2H), 2.72 (s, 3H), 2.18 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.0, 138.2, 134.9, 132.9, 130.3, 129.7, 128.2, 127.8, 126.6, 125.3, 38.9, 20.5, 18.7;

IR (Microscope, cm^{-1}): 3061, 3026, 3001, 2921, 2861, 1602, 1504, 1494, 1452, 725, 697;

HRMS (EI) $C_{15}H_{16}$: calcd. 196.1252; found 196.1253.



2-26

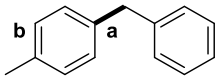
1,2-Dimethyl-4-(1-phenylethyl)benzene (2-26): Prepared from benzyl alcoohol **2-21** (122 mg, 1.00 mmol), *o*-xylene (531 mg, 5.00 mmol) and **BAC-16** (39 mg, 0.20 mmol) at room temperature for 1 hour, followed by flash column chromatography (hexane to hexane:EtOAc = 20:1) to afford **2-26** as a colorless oil (185 mg, 88%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.20 (m, 4H), 7.17-7.15 (m, 1H), 7.04-7.03 (m, 1H), 6.98-6.93 (m, 2H), 4.07 (q, *J* = 7.3 Hz, 1H), 2.21 (s, 3H), 2.20 (s 3H), 1.60 (d, *J* = 7.3 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.2, 143.4, 135.9, 133.6, 129.1, 128.5, 127.8, 127.0, 125.4, 124.4, 43.9, 21.4, 19.3, 18.8;

IR (Microscope, cm^{-1}): 30607, 3025, 2967, 2930, 2874, 1601, 1503, 1494, 1450, 699;

HRMS (EI) for $C_{16}H_{18}$: calcd. 210.1409; found 210.1409.



2-27

1-Benzyl-4-methylbenzene (2-27): Prepared from benzyl alcohol **2-20** (122 mg, 1.00 mmol), toluene (391 mg, 5.00 mmol) and **BAC-16** (39 mg, 0.20 mmol) at room temperature for 18 hours, followed by flash column chromatography (hexane to hexane:EtOAc = 20:1) to afford **2-27a** and **2-27b** as a colorless oil (123 mg, 63%, *p*:*o* = 87:13 regioisomeric mixture).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23-7.19 (m, 4H), 7.17-7.10 (m, 2H), 7.10-7.06 (m, 3H), 4.10 (q, *J* = 7.4 Hz, 1H), 2.29 (s, 3H), 16.0 (d, *J* = 7.3 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.1, 142.9, 135.0, 128.5, 127.8, 127.2, 127.1, 125.4, 43.9, 21.4, 20.4;

IR (Microscope, cm^{-1}): 3083, 3060, 3025, 2967, 2929, 2873, 1601, 1513, 1493, 1451, 699;

HRMS (EI) for $C_{15}H_{16}$: calcd. 196.1252; found 196.1252.

2.10.3 General procedure for pK_a determination of boronic acids

A phosphate buffer solution was prepared by dissolving 690 mg of NaH_2PO_4 in 5mL of D_2O and ~30 mL of H_2O in a 50 mL volumetric flask, then diluting to 50 mL total volume. In a second 25 mL volumetric flask, boronic acid 0.50 mmol was dissolved in a minimum of DMSO, and then diluted to 25 mL total volume with the buffer solution. 1 mL of the solution was added to each of nine vials, and the pH of each was adjusted with NaOH solution so that a range of pH between

~2 and ~12 was achieved. The various solutions were transferred to NMR tubes and their ^{11}B NMR spectra were recorded. The ^{11}B chemical shift was plotted against the pH (**Figure 2-1** to **Figure 2-3**) and from this the pK_a of selective boronic acids was determined.[20]

2,3,4,5-Tetrafluorophenyl boronic acid BAC-16: According to the general procedure, a solution of 2,3,4,5-tetrafluorophenyl boronic acid (99 mg, 0.50 mmol) was prepared. Different ^{11}B NMR shifts were determined at various pH, as recorded in **Table 2-5**. The titration curve was shown in **Figure 2-1**. The pK_a of 2,3,4,5-tetrafluorophenyl boronic acid was determined to be 6.0.

pH[a]	2.56	3.62	5.24	5.82	6.19	6.82	7.26	8.84	10.52
^{11}B NMR (ppm)	27.2	26.9	22.5	15.9	11.5	5.6	3.3	1.8	1.8

[a]The pH value was determined using a Mettler Toledo pH meter.

Table 2-5. Different ^{11}B NMR shifts of 2,3,4,5-tetrafluorophenyl boronic acid at various pH.

2-Fluorophenyl boronic acid BAC-19: According to the general procedure, a solution of 2-fluorophenyl boronic acid (70 mg, 0.50 mmol) was prepared. Different ^{11}B NMR shifts were determined at various pH, as recorded in **Table 2-6**. The titration curve was shown in **Figure 2-2**. The pK_a of 2-fluorophenylboronic acid was determined to be 7.9.

pH[a]	4.03	5.00	6.07	7.11	7.32	7.68	8.08	8.33	8.64
^{11}B NMR (ppm)	28.6	28.6	28.1	24.4	22.4	17.3	11.7	9.1	5.9
pH[a]	8.96	9.30	9.67	10.05	10.90	11.97			
^{11}B NMR (ppm)	4.4	3.4	2.8	2.5	2.3	2.3			

[a]The pH value was determined using a Mettler Toledo pH meter.

Table 2-6. Different ^{11}B NMR shifts of 2-fluorophenyl boronic acid at various pH.

2,6-Difluorophenyl boronic acid BAC-20: According to the general procedure, a solution of 2,6-difluorophenyl boronic acid (79 mg, 0.50 mmol) was prepared. Different ^{11}B NMR shifts were determined at various pH, as recorded in **Table 2-7**. The titration curve was shown in **Figure 2-3**. The titration curve for 2,6-difluorophenylboronic acid suggests a pK_a of 7.2. However, gradual protodeborylation was observed at pH >6.8. The increasing concentration of boric acid (and corresponding decrease in boronic acid concentration) resulting from this process would

artificially increase the observed pK_a of the boronic acid. Thus, the actual pK_a of 2,6-difluorophenylboronic acid must be lower than the observed value of 7.2.

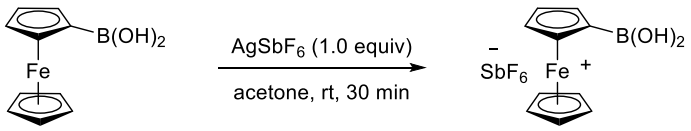
pH[a]	2.44	2.84	3.91	4.57	5.15	5.48	5.63	5.93	6.51
^{11}B NMR (ppm)[b]	28.0	27.9	27.8	27.9	27.7	27.5	27.3	26.0	24.0
pH[a]	6.78	7.11	7.37	7.83	8.11	8.45	8.80	9.11	9.44
^{11}B NMR (ppm)[b]	21.5	19.2	15.2	7.3	3.2	2.9	2.4	2.4	2.2
^{11}B NMR (ppm)[c]	19.4	19.3	19.2	18.6	15.4	14.4	10.1	10.4	6.9

[a]The pH value was determined using a Mettler Toledo pH meter. [b]The ^{11}B NMR signals of 2,6-difluorophenyl boronic acid. [c]The ^{11}B NMR signals of boric acid.

Table 2-7. Different ^{11}B NMR shifts of 2,6-difluorophenyl boronic acid at various pH.

Pentafluorophenyl boronic acid BAC-15: The pK_a of pentafluorophenyl boronic acid cannot be determined using the ^{11}B NMR titration method due to the rapid protodeborylation in the phosphate buffer solution within short period of time. Therefore, a linear correlation was established between the previously reported pK_a of eight different boronic acids and their experimental ^{1}H NMR (B-OH).[19] Specifically, these pK_a values of the select boronic acids were plotted against the chemical shifts of their hydroxyl protons (ArB(O<u>H</u>)$_2$) as measured by ^{1}H NMR of the boronic acids (6 mg) in 0.7 mL of DMSO-*d6* (**Figure 2-4a**).[22] Of note, the DMSO-*d6* was dried over 4 Å molecular sieves. A linear fit was applied to the data (R^2 = 0.98) (**Figure 2-4b**). Using the equation generated from the linear fit (δ [^{1}H] = -0.208 [pK_a] + 9.7969), extrapolation of the corresponding ^{11}B NMR chemical shift for pentafluorophenyl boronic acid (9.08 ppm) reveals an apparent pK_a of 3.5.

2.10.4 General procedure for the synthesis of ferroceniumboronic acid hexafluoroantimonate salt BAC-26



Ferrocenium boronic acid was synthesized according to the literature procedure with minor modifications as described herein.[36] Ferrocene boronic acid (690 mg, 3.00 mmol) was dissolved in 50 mL of dried acetone. The resulting mixture was stirred at room temperature for 15 min,

providing a clear orange solution. $AgSbF_6$ (1.03 g, 3.00 mmol) was then added in one pot, resulting in a dark blue solution immediately. Resulting solution was stirred at room temperature for 30 min. Reaction mixture was filtered through Celite 545 to separate the dark blue solution from the light brown silver solid. Further separation of silver was carried out by careful vacuum filtration with Fisher P5 filter paper (medium porosity) three times. The resulting filtrate was collected and concentrated under reduced pressure, affording the crude product. The crude product was transferred into a 250 mL round bottom flask equipped with stir bar and dissolved in 5-10 mL dried acetone. Crude product solution was stirred vigorously and 120 mL of Et_2O was added. Upon the addition of Et_2O, dark blue solid was formed and the resulting mixture was allowed to stir vigorously at room temperature for 15 min before subjected to filtration by Fisher P5 filter paper (medium porosity). The dark blue product was collected and dried under high vacuum for 4 h. After the indicated time, the dark blue solid was grinded into a fine powder and subjected to high vacuum overnight for further drying overnight, affording 1.00 g (72%) of ferrocenium boronic acid. The resulting product ferrocenium boronic acid was stored in a vial at ambient temperature.

^{1}H NMR and **^{13}C NMR** were not obtained in high quality due to the paramagnetism of iron (III);

^{11}B NMR (CD_3COCD_3, 128 MHz): δ 36.7;

^{19}F NMR (CD_3COCD_3, 376 MHz): δ –124.9 (m, 6F);

IR (Microscope, cm^{-1}): 3504, 3118, 1641, 1419, 1065, 1013, 861;

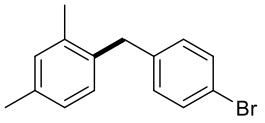
HRMS (ESI) for $C_{10}H_{11}BFeO_2$: calcd. 230.0196; found 230.0198;

Anal. Calcd for $C_{10}H_{11}BF_6FeO_2Sb$: C, 25.80; H, 2.38. Found: C, 25.78; H, 2.69.

2.10.5 General procedure for the Friedel-Crafts benzylation

To a vial equipped with a stir bar, containing benzyl alcohols and the arenes in a solvent mixture of 4:1 hexafluoroisopropanol and nitromethane, was added the ferrocenium boronic acid catalyst. The vial was capped and stirred at the stated temperature for indicated time. Upon completion, monitored by TLC, the reaction mixture was concentrated and subjected to flash column chromatography using EtOAc/hexane as the eluent to afford the product.

Only the structures of the major products are shown. The ratio of regioisomeric mixtures was assigned by ^{1}H NMR analysis of crude reaction mixtures. Only the major products are characterized for the regioisomeric mixtures > 90:10. For products that contain regioisomers, the determination of the major products on ^{13}C NMR was assigned by comparison with the existing literature reports. No assignment was made if neither the major nor the minor products were reported.



2-30

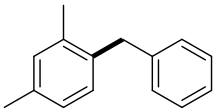
1-(4-Bromobenzyl)-2,4-dimethylbenzene (2-30): Prepared from 4-bromobenzyl alcohol (94 mg, 0.50 mmol) and *m*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (119 mg, 87%, *p*:*o* = 77:23 mixture of regioisomers).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.40 (m, 1.48H, major), 7.39-7.37 (m, 0.47H, minor), 7.15-7.09 (m, 0.79H), 7.02-7.00 (m, 3.69H), 6.92-6.90 (m, 0.51H), 4.03 (s, 0.48H, minor), 3.92 (s, 1.52H, major), 2.34 (s, 2.29H, major), 2.25 (s, 1.44H, minor), 2.21 (s, 2.27H, minor);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.8, 138.9, 137.1, 136.4, 136.2, 136.2, 135.2, 131.4, 131.4, 131.3, 130.4, 129.9, 129.6, 128.3, 126.7, 126.6, 119.7, 119.5, 38.5, 34.5, 21.0, 20.2, 19.6;

IR (Microscope, cm^{-1}): 3007, 2919, 2859, 1616, 1486, 1443, 1403, 1071, 1011, 802, 770;

HRMS (EI) for $C_{15}H_{15}Br$: calcd. 276.0337; found 276.0338.



2-31

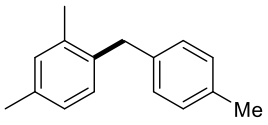
1-Benzyl-2,4-dimethylbenzene (2-31):[44] Prepared from benzyl alcohol (54 mg, 0.50 mmol) and *m*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (85 mg, 87%, *p*:*o* = 78:22 mixture of regioisomers).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30-7.23 (m, 2.32H), 7.22-7.19 (m, 1.00H), 7.16-7.14 (m, 1.60H), 7.10-7.08 (m, 0.57H), 7.50-6.98 (m, 2.69H), 4.09 (s, 0.41H, minor), 3.98 (s, 1.59, major), 2.33 (s, 2.39H, major), 2.27 (s, 1.18H, minor), 2.24 (s, 2.37, major);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.7 (major), 139.8 (minor), 137.2 (minor), 136.9 (minor), 136.4 (major), 135.9 (major), 135.9 (major), 131.1 (major), 129.9 (major), 128.7 (major), 128.4 (minor), 128.4 (major), 128.1 (minor), 127.9 (minor), 126.6 (major), 126.3 (minor), 125.8 (major), 125.7 (minor), 39.1 (major), 35.1 (minor), 21.0 (major), 20.2 (minor), 19.6 (major);

IR (Microscope, cm^{-1}): 3062, 3026, 2921, 2856, 1601, 1494, 1425, 727, 697;

HRMS (EI) for $C_{15}H_{16}$: calcd. 196.1252; found 196.1252.



2-32

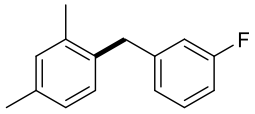
2,4-Dimethyl-1-(4-methylbenzyl)benzene (2-32):[45] Prepared from 4-methylbenzyl alcohol (61 mg, 0.50 mmol) and *m*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (99 mg, 94%, *p*:*o* = 83:17 mixture of regioisomers).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.12-7.07 (m, 2.43H), 7.05-7.01 (m, 3.21H), 7.00-6.98 (m, 0.81H), 6.95-6.93 (m, 0.33H), 4.06 (s, 0.33H, minor), 3.94 (s, 1.67H, major), 2.35 (s, 2.48H, major), 2.34 (s, 2.97H, minor), 2.28 (s, 0.97H, minor), 2.25 (s, 2.48H, major):

^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.6, 137.2, 137.1, 136.7, 136.4, 136.2, 135.8, 135.3, 135.2, 131.1, 129.8, 129.1, 129.1, 128.6, 128.1, 127.8, 126.6, 126.3, 38.6 (major), 34.6 (minor), 21.0 (major), 21.0 (major), 21.0 (minor), 20.2 (major), 19.6 (minor);

IR (Microscope, cm^{-1}): 3005, 2920, 2860, 1617, 1513, 1443, 804;

HRMS (EI) for $C_{16}H_{18}$: calcd. 210.1409; found 210.1411.



2-33

1-(3-Fluorobenzyl)-2,4-dimethylbenzene (2-33): Prepared from 3-fluorobenzyl alcohol (63 mg, 0.50 mmol) and *m*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (106 mg, 99%, *p*:o:*m* = 75:21:4 mixture of regioisomers).

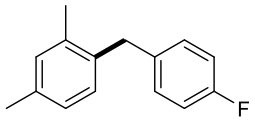
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26-7.20 (m, 1.03H), 7.15-7.09 (m, 0.69H), 7.03-6.99 (m, 2.30H), 6.94-6.92 (d, *J* = 7.7 Hz, 0.78H), 6.91-6.88 (m, 1.01H), 6.85-6.81 (m, 1.08H), 6.72-6.79 (m, 0.23H), 4.08 (s, 0.45H, minor), 3.97 (s, 1.55H, major), 2.34 (s, 2.31H, major), 2.26 (s, 1.26H, minor), 2.22 (s, 2.28H, major);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.1 (d, *J* = 245.3 Hz), 163.0 (d, *J* = 245.3 Hz), 143.4 (d, *J* = 7.0 Hz), 142.6 (d, *J* = 7.1 Hz), 137.1, 136.4, 136.3, 136.1, 135.1, 131.3, 129.9, 129.7 (d, *J* = 8.1 Hz), 129.7 (d, *J* = 8.3 Hz), 128.3, 126.7, 126.6, 124.3 (d, *J* = 2.7 Hz), 123.6 (d, *J* = 2.7 Hz), 115.5 (d, *J* = 21.2 Hz), 114.7 (d, *J* = 21.5 Hz), 112.8 (d, *J* = 21.1 Hz), 112.7 (d, *J* = 21.2 Hz), 38.8 (d, *J* = 1.5 Hz), 34.8 (d, *J* = 1.6 Hz), 21.0, 20.2, 19.6;

^{19}F NMR ($CDCl_3$, 468 MHz): δ –113.7 (m, minor), –113.8 (m, major);

IR (Microscope, cm^{-1}): 3007, 2920, 2860, 1613, 1588, 1486, 1446, 1248, 951, 769, 684;

HRMS (EI) for $C_{15}H_{15}F$: calcd. 214.1158; found 214.1153.



2-34

1-(4-Fluorobenzyl)-2,4-dimethylbenzene (2-34): Prepared from 4-fluorobenzyl alcohol (63 mg, 0.50 mmol) and *m*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a yellow oil (102 mg, 95%, *p*:o = 75:25 mixture of regioisomers).

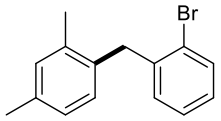
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.10-7.06 (m, 2.38H), 7.00 (m, 0.79H), 6.98-6.93 (m, 4.04H), 4.03 (s, 0.46H, minor), 3.92 (s, 1.54H, major), 2.32 (s, 2.29H, major), 2.24 (s, 1.49, minor), 2.20 (s, 2.28, major);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.3 (d, *J* = 243.7 Hz), 161.2 (d, *J* = 243.4 Hz), 137.1, 136.7, 136.3, 136.3 (d, *J* = 3.2 Hz), 136.1, 135.7, 135.3 (d, *J* = 3.2 Hz), 131.2, 130.0 (d, *J* = 7.7 Hz), 129.8, 129.1 (d, *J* = 7.4 Hz), 128.2, 126.7, 126.5, 115.1 (d, *J* = 21.1 Hz), 115.1 (d, *J* = 21.1 Hz), 38.3, 34.2, 21.0, 20.2, 19.6;

^{19}F NMR ($CDCl_3$, 376 MHz): δ –117.8 (app quin, 0.75F, major), –117.9 (app quin, 0.25F, minor);

IR (Microscope, cm^{-1}): 3038, 3005, 2921, 1604, 1508, 1444, 1222, 1157, 813, 774;

HRMS (EI) for $C_{15}H_{15}F$: calcd. 214.1158; found 214.1161.



2-35

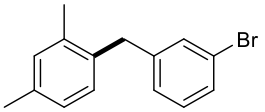
1-(2-Bromobenzyl)-2,4-dimethylbenzene (2-35): Prepared from 2-bromobenzyl alcohol (94 mg, 0.50 mmol) and *m*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (136 mg, 99%, *p*:o:*m* = 76:17:7 mixture of regioisomers).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60-7.58 (m, 1.04H), 7.20-7.16 (td, *J* = 7.4, 1.3 Hz, 0.83H, major), 7.12-7.03 (m, 2.65H), 6.98-6.96 (dd, *J* = 7.7, 1.2 Hz, 0.81H, major), 6.90-6.87 (m, 1.68H), 6.56-6.54 (m, 0.17H), 4.06 (s, 0.37H, minor), 4.02 (s, 1.67H, major), 2.33 (s, 2.43H, major), 2.21 (s, 2.41H, major), 2.20 (s, 1.10H, minor);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.0, 138.8, 138.0, 137.4, 136.6, 136.1, 136.0, 134.4, 132.6, 132.5, 131.1, 130.3, 129.6, 128.3, 128.2, 127.7, 127.5, 127.4, 126.7, 126.6, 125.2, 125.0, 39.1, 35.7, 21.0, 20.0, 19.5;

IR (Microscope, cm^{-1}): 3075, 3009, 2919, 1566, 1503, 1465, 1440, 1026, 746;

HRMS (EI) for $C_{15}H_{15}Br$: calcd. 274.0357; found 274.0356.



2-36

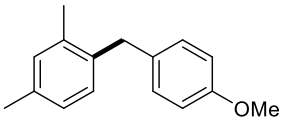
1-(3-Bromobenzyl)-2,4-dimethylbenzene (2-36): Prepared from 3-bromobenzyl alcohol (94 mg, 0.50 mmol) and *m*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (111 mg, 81%, *p*:o:*m* = 77:19:4 mixture of regioisomers).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.26 (m, 0.99H), 7.25-7.24 (m, 0.76H), 7.14-7.05 (m, 1.98H), 7.02-7.00 (m, 0.82H), 6.97-6.95 (m, 2.35H), 6.89-6.87 (m, 0.21H), 4.00 (s, 0.39H, minor), 3.89 (s, 1.61H, major), 2.28 (s, 2.40H, major), 2.20 (s, 1.23H, minor), 2.16 (2s, 2.45H, major);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.2, 142.4, 138.1, 137.1, 136.4, 136.3, 135.9, 134.9, 131.7, 131.3, 130.9, 129.9, 129.9, 129.0, 129.0, 128.3, 127.3, 126.8, 126.7, 126.5, 122.7, 122.6, 38.7, 34.7, 21.0, 20.2, 19.6;

IR (Microscope, cm^{-1}): 3008, 2919, 2858, 1592, 1567, 1473, 1442, 1071, 764, 685;

HRMS (EI) for $C_{15}H_{15}Br$: calcd. 274.0357; found 274.0356.



2-37

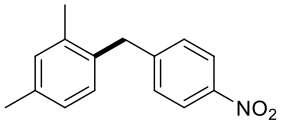
1-(4-Methoxybenzyl)-2,4-dimethylbenzene (2-37): Prepared from 4-methoxybenzyl alcohol (69 mg, 0.50 mmol) and *m*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a yellow oil (69 mg, 61%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.02-7.00 (m, 2H), 6.96-6.91 (m, 3H), 6.80-6.77 (m, 2H), 3.86 (s, 2H), 3.75 (s, 3H), 2.28 (s, 3H), 2.18 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.8, 136.4, 136.3, 135.8, 132.8, 131.1, 129.7, 129.6, 126.6, 113.8, 55.3, 38.2, 21.0, 19.6;

IR (Microscope, cm^{-1}): 3003, 2918, 2834, 1611, 1510, 1463, 1246, 1037, 810;

HRMS (EI) for $C_{16}H_{18}O$: calcd. 226.1358; found 226.1357.



2-39

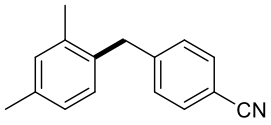
2,4-Dimethyl-1-(4-nitrobenzyl)benzene (2-39): Prepared from 4-nitrobenzyl alcohol (77 mg, 0.50 mmol) and *m*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane:EtOAc = 10:1) and isolated as a yellow oil (12 mg, 10%, *p*:o:*m* = 75:20:5 mixture of regioisomers).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.17-8.12 (m, 2.13H), 7.29-7.28 (m, 1.88H), 7.19-7.11 (m, 1.19H), 7.04-7.02 (m, 2.26H), 4.17 (s, 0.42H), 4.07 (s, 1.58H), 2.34 (s, 2.38H), 2.24 (s, 1.27H), 2.19 (s, 2.36H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.7, 148.0, 146.4, 137.0, 136.8, 136.3, 135.2, 134.1, 131.5, 130.0, 129.6, 129.3, 128.6, 128.5, 127.0, 127.0, 123.7, 123.7, 39.0, 35.1, 21.0, 20.2, 19.6;

IR (Microscope, cm^{-1}): 3104, 3076, 2921, 1597, 1512, 1345, 1112, 860;

HRMS (ESI) for $C_{15}H_{15}NO_2$ $[M+Na]^+$: calcd. 264.0995; found 264.0993.



2-40

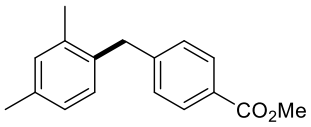
4-(2,4-Dimethylbenzyl)benzonitrile (2-40): Prepared from 4-(hydroxymethyl) benzonitrile (67 mg, 0.50 mmol) and *m*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane:EtOAc = 10:1) and isolated as a yellow oil (13 mg, 12%, *p*:o:*m* = 73:22:5 mixture of regioisomers).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.58-7.54 (m, 2.04H), 7.24-7.22 (m, 1.51H), 7.17-7.07 (m, 1.18H), 7.03-7.00 (m, 2.25H), 4.13 (s, 0.46H, minor), 4.02 (s, 1.54H, major), 2.34 (s, 2.27H, major), 2.23 (s, 1.31H, minor), 2.18 (s, 2.21H, major);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.6, 145.8, 137.1, 136.7, 136.4, 134.2, 132.3, 132.2, 131.4, 130.0, 129.4, 128.6, 128.4, 126.9, 126.9, 119.1, 109.8, 109.8, 39.2, 35.2, 21.0, 20.2, 19.6;

IR (Microscope, cm^{-1}): 3006, 2921, 2227, 1607, 1503, 1445, 812, 776;

HRMS (EI) for $C_{16}H_{15}N$: calcd. 221.1205; found 221.1207.



2-41

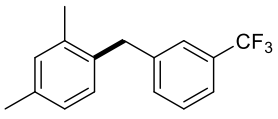
Methyl 4-(2,4-dimethylbenzyl)benzoate (2-41): Prepared from methyl 4-(hydroxymethyl) benzoate (83 mg, 0.50 mmol) and *m*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane:EtOAc = 10:1) and isolated as a colorless oil (80 mg, 63%, *p*:o:*m* = 72:23:5 mixture of regioisomers).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.97-7.93 (m, 2.10H), 7.22-7.20 (m, 1.54H), 7.16-7.09 (m, 1.23H), 7.03-6.99 (m, 2.26H), 4.13 (s, 0.48H, minor), 4.04 (s, 1.52H, major), 3.92 (s, 2.16H, major), 3.91 (s, 0.71H, minor), 2.34 (s, 2.28H, major), 2.25 (s, 1.42H, minor), 2.20 (s, 2.30H, major);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.1, 167.1, 146.3, 145.5, 137.1, 136.4, 136.3, 134.9, 131.3, 130.0, 129.8, 129.7, 128.7, 128.3, 127.9, 127.9, 127.9, 126.8, 126.7, 52.0, 39.2, 35.2, 21.0, 20.2, 19.6;

IR (Microscope, cm^{-1}): 3004, 2950, 2920, 1721, 1610, 1435, 1280, 1178, 1108, 748;

HRMS (ESI) for $C_{17}H_{18}O_2$ $[M+Na]^+$: calcd. 277.1200; found 277.1201.



2-42

2,4-Dimethyl-1-(3-(trifluoromethyl)benzyl)benzene (2-42): Prepared from 3-(trifluoromethyl) benzyl alcohol (88 mg, 0.50 mmol) and *m*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (132 mg, 99%, *p*:o:*m* = 76:18:6 mixture of regioisomers).

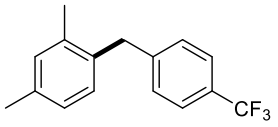
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49-7.43 (m, 1.89H), 7.41-7.34 (m, 1.32H), 7.30-7.29 (m, 0.84H), 7.15-7.10 (m, 0.94H), 7.03-7.00 (m, 2.19H), 4.13 (s, 0.46H, minor), 4.02 (s, 1.54H, major), 2.34 (s, 2.30H, major), 2.26 (s, 1.34H, minor), 2.22 (s, 2.27H, major);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 141.7, 140.9, 138.2, 137.1, 136.4, 136.3, 135.7, 134.8, 132.0, 131.3, 130.7 (q, *J* = 31.9 Hz), 129.9, 128.8, 128.3, 128.1, 127.8 (q, *J* = 263.8 Hz), 126.8, 125.4 (q, *J* = 3.7 Hz), 124.7 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.6 Hz), 122.8 (q, *J* = 3.8 Hz), 122.8 (q, *J* = 4.2 Hz), 38.9, 34.9, 21.0, 20.2, 19.6;

^{19}F NMR ($CDCl_3$, 376 MHz): δ –62.6 (s, minor), –62.6 (s, major);

IR (Microscope, cm^{-1}): 3010, 2922, 2864, 1615, 1504, 1446, 1330, 1161, 1121, 1074, 701, 658;

HRMS (EI) for $C_{16}H_{15}F_3$: calcd. 264.1126; found 264.1125.



2-43

2,4-Dimethyl-1-(4-(trifluoromethyl)benzyl)benzene (2-43): Prepared from 4-(trifluoromethyl) benzyl alcohol (88 mg, 0.50 mmol) and *m*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (132 mg, 99%, *p*:o:*m* = 76:18:6 mixture of regioisomers).

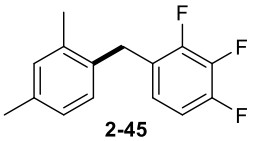
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55-7.49 (m, 2.04H), 7.32-7.30 (m, 0.12H), 7.24-7.22 (m, 1.57H), 7.14-7.08 (m, 0.94H), 7.02-6.99 (m, 2.36H), 4.12 (s, 0.39H, minor), 4.01 (s, 1.61H, major), 2.33 (s, 2.42H, major), 2.24 (s, 1.14H, minor), 2.19 (s, 2.37H, major);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.9, 144.1, 138.2, 137.1, 136.4, 136.4, 135.8, 134.8, 131.3, 129.9, 129.2, 128.9, 128.3, 128.3 (q, *J* = 32.6 Hz), 128.1, 126.8, 126.8, 126.7, 125.3 (q, *J* = 3.9 Hz), 125.3 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 271.6 Hz), 38.9, 34.9, 21.0, 20.2, 19.6;

^{19}F NMR ($CDCl_3$, 376 MHz): δ –62.3 (s, 3F).

IR (Microscope, cm^{-1}): 3008, 2922, 1619, 1417, 1326, 1162, 1123, 1067, 814;

HRMS (EI) for $C_{16}H_{15}F_3$: calcd. 264.1126; found 264.1124.



2-45

1-(2,4-Dimethylbenzyl)-2,3,4-trifluorobenzene (2-45): Prepared from 2,3,4-trifluorobenzyl alcohol (81 mg, 0.50 mmol) and *m*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (79 mg, 60%, *p*:o:*m* = 72:22:6 mixture of regioisomers).

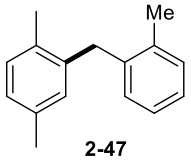
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.16-7.08 (m, 0.71H), 7.02-6.95 (m, 2.24H), 6.87-6.79 (m, 1.07H), 6.78-6.72 (m, 0.22H, minor), 6.67-6.60 (m, 0.75H, major), 6.32-6.26 (m, 0.23H, minor), 4.00 (s, 0.47H, minor), 3.93 (s, 1.53H, major), 2.32 (s, 2.29H, major), 2.21 (m, 3.71H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.7 (ddd, *J* = 247.5, 10.1, 2.8 Hz), 149.6 (ddd, *J* = 248.2, 10.0, 2.8 Hz), 139.9 (ddd, *J* = 250.7, 15.6, 15.6 Hz), 138.7, 138.2, 137.3, 136.6, 136.3, 134.3, 133.4, 131.3, 129.7, 128.4, 128.3, 126.9, 126.9, 126.5, 125.2 (dd, *J* = 13.4, 2.8 Hz), 123.5 (ddd, *J* = 7.7, 4.5, 4.3 Hz), 121.7 (ddd, *J* = 7.4, 4.4, 4.0 Hz), 111.6 (dd, *J* = 17.1, 3.9 Hz), 111.6 (dd, *J* = 16.9, 3.9 Hz), 31.1, 27.1, 21.0, 19.9, 19.4;

^{19}F NMR ($CDCl_3$, 376 MHz): δ –137.7 (m, 0.06F, minor), –137.8 (app ddt, *J* = 20.3, 9.5, 6.0 Hz, 0.71F, major); –138.0 (app ddt, *J* = 20.4, 9.5, 5.9 Hz, 0.22F, minor), –138.2 (dt, *J* = 20.3, 6.3 Hz, 0.81F, major), –138.3 (m, 0.19F, minor), –160.9 (app tdd, *J* = 22.0, 6.4, 1.7 Hz, 0.06F, minor), –161.2 (app tdd, *J* = 20.3, 7.1, 2.4 Hz, 0.71F, major), –161.4 (app tdd, *J* = 20.3, 7.1, 2.2 Hz, 0.21F, minor);

IR (Microscope, cm^{-1}): 3010, 2923, 2864, 1615, 1512, 1479, 1299, 1031, 959, 804, 679;

HRMS (EI) for $C_{15}H_{13}F_3$: calcd. 250.0969; found 250.0973.



2-47

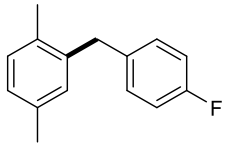
1,4-Dimethyl-2-(2-methylbenzyl)benzene (2-47): Prepared from 2-methylbenzyl alcohol (61 mg, 0.50 mmol) and *p*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexanes) and isolated as a colorless oil (93 mg, 89%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.22 (d, *J* = 6.9 Hz, 1H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.13 (t, *J* = 7.1 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.77 (s, 1H), 3.91 (s, 2H), 2.32 (s, 3H), 2.28 (s, 3H), 2.25 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.6, 138.2, 136.5, 135.4, 133.5, 130.1, 130.0, 129.9, 129.0, 126.9, 126.1, 126.0, 36.7, 21.0, 19.6, 19.1;

IR (Microscope, cm^{-1}): 3017, 2969, 2921, 1604, 1500, 1493, 1461, 743;

HRMS (EI) for $C_{16}H_{18}$: calcd. 210.1409; found 210.1409.



2-48

2-(4-Fluorobenzyl)-1,4-dimethylbenzene (2-48): Prepared from 4-fluorobenzyl alcohol (126 mg, 1.00 mmol) and *p*-xylene (530 mg, 5.00 mmol). Purified by flash column chromatography (hexane) and isolated as a light yellow oil (164 mg, 77%).

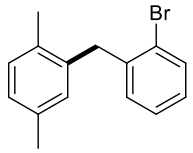
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.09-7.05 (m, 3H), 6.99-6.94 (m, 3H), 6.91 (m, 1H), 3.92 (s, 2H), 2.30 (s, 3H), 2.19 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.3 (d, *J* = 243.6 Hz), 138.5, 136.2 (d, *J* = 3.2 Hz), 135.5, 133.4, 130.7, 130.3, 130.0 (d, *J* = 7.7 Hz), 127.2, 115.1 (d, *J* = 21.1 Hz), 38.6, 21.0, 19.2;

^{19}F NMR ($CDCl_3$, 376 MHz): δ –117.7 (m, 1F);

IR (Microscope, cm^{-1}): 3115, 3001, 2922, 2862, 1603, 1508, 1444, 1222, 812;

HRMS (EI) for $C_{15}H_{15}F$: calcd. 214.1158; found 214.1156.



2-49

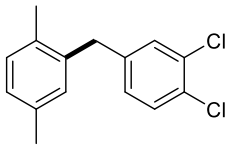
2-(2-Bromobenzyl)-1,4-dimethylbenzene (2-49): Prepared from 2-bromobenzyl alcohol (94 mg, 0.50 mmol) and *p*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a yellow oil (135 mg, 98%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.18 (td, *J* = 7.5, 1.3 Hz, 1H), 7.09 (m, 2H), 7.00 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.86 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.83 (s, 1H), 4.03 (s, 2H), 2.28 (s, 3H), 2.19 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.9, 137.3, 135.5, 133.6, 132.6, 130.6, 130.2, 130.2, 127.7, 127.4, 127.3, 125.0, 39.5, 21.0, 19.1;

IR (Microscope, cm^{-1}): 3054, 3003, 2969, 2920, 2863, 1616, 1566, 1503, 1465, 1440, 1025, 747;

HRMS (EI) for $C_{15}H_{15}Br$: calcd. 276.0337; found 276.0335.



2-50

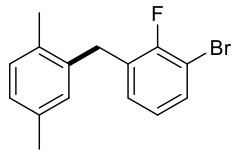
1,2-Dichloro-4-(2,5-dimethylbenzyl)benzene (2-50): Prepared from 3,4-dichlorobenzyl alcohol (89 mg, 0.50 mmol) and *p*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (102 mg, 77%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (d, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 2.1 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.94 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.89 (s, 1H), 3.89 (s, 2H), 2.30 (s, 3H), 2.17 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.9, 137.3, 135.7, 133.3, 132.3, 130.7, 130.5, 130.4, 130.2, 129.9, 128.1, 127.6, 38.6, 21.0, 19.2;

IR (Microscope, cm^{-1}): 3000, 2921, 2863, 1562, 1504, 1470, 1131, 1031, 811;

HRMS (EI) for $C_{15}H_{14}Cl_2$: calcd. 264.0472; found 264.0472.



2-51

1-Bromo-3-(2,5-dimethylbenzyl)-2-fluorobenzene (2-51): Prepared from 3-bromo-2-fluorobenzyl alcohol (103 mg, 0.50 mmol) and *p*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (83 mg, 57%).

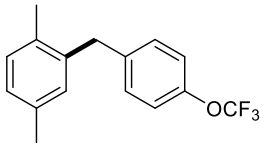
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (ddd, *J* = 8.5, 6.8, 2.7 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.98 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.92-6.84 (m, 3H), 3.97 (s, 2H), 2.30 (s, 3H), 2.20 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.7 (d, *J* = 246.1 Hz), 136.1, 135.2, 133.0, 130.8, 130.2, 129.8, 129.1 (d, *J* = 4.0 Hz), 128.8 (d, *J* = 16.8 Hz), 127.1, 124.4 (d, *J* = 4.5 Hz), 108.5 (d, *J* = 21.8 Hz), 31.8 (d, *J* = 2.9 Hz), 20.5, 18.5;

^{19}F NMR ($CDCl_3$, 468 MHz): δ –106.5 (t, 1F);

IR (Microscope, cm^{-1}): 3003, 2922, 2864, 1602, 1504, 1452, 1225, 812, 761;

HRMS (EI) for $C_{15}H_{14}BrF$: calcd. 292.0263; found 292.0260.



2-52

1,4-Dimethyl-2-(4-(trifluoro-methoxy)benzyl) benzene (2-52): Prepared from 4-(trifluoro-methoxy) benzyl alcohol (96 mg, 0.50 mmol) and *p*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (130 mg, 93%).

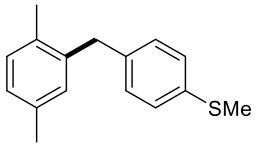
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.17-7.12 (m, 4H), 7.10-7.09 (d, *J* = 7.7 Hz, 1H), 7.02-7.01 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.95 (s, 1H), 3.97 (s, 2H), 2.33 (s, 3H), 2.21 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.5 (q, *J* = 1.7 Hz), 139.3, 138.0, 135.6, 133.4, 130.8, 130.4, 129.8, 127.4, 120.9, 120.5 (q, *J* = 256.6 Hz), 38.8, 21.0, 19.2;

^{19}F NMR ($CDCl_3$, 468 MHz): δ –57.9 (s, 3F);

IR (Microscope, cm^{-1}): 2924, 1507, 1444, 1260, 1222, 11649, 810;

HRMS (EI) for $C_{16}H_{15}F_3O$: calcd. 280.1075; found 280.1076.



2-53

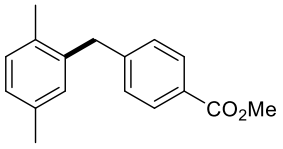
(4-(2,5-Dimethylbenzyl)phenyl)(methyl)sulfane (2-53): Prepared from 4-methylthiobenzyl alcohol (77 mg, 0.50 mmol) and *p*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (54 mg, 44%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20-7.17 (m, 2H), 7.06-7.04 (m, 3H), 6.97 (dd, 1H, *J* = 7.6, 1.4 Hz), 6.92 (s, 1H), 3.91 (s, 2H), 2.47 (s, 3H), 2.30 (s, 3H), 2.20 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.5, 137.7, 135.4, 135.4, 133.4, 130.7, 130.2, 129.3, 127.2, 127.1, 38.9, 21.0, 19.2, 16.3;

IR (Microscope, cm^{-1}): 3017, 2920, 2861, 1615, 1493, 1438, 1093, 807;

HRMS (EI) for $C_{16}H_{18}S$: calcd. 242.1129; found 242.1129.



2-54

Methyl 4-(2,5-dimethylbenzyl)benzoate (2-54): Prepared from methyl 4-(hydroxymethyl) benzoate (166 mg, 1.00 mmol) and *p*-xylene (265 mg, 5.00 mmol). Purified by flash column chromatography (hexane:EtOAc = 10:1) and isolated as a white solid (217 mg, 85%).

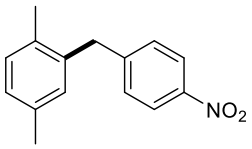
M.p. 62.1-62.4 °C;

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.96 (m, 2H), 7.21 (m, 2H), 7.08 (d, *J* = 7.5 Hz, 1H), 7.01 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.94 (s, 1H), 4.02 (s, 2H), 3.92 (s, 3H), 2.32 (s, 3H), 2.19 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.1, 146.1, 137.8, 135.6, 133.4, 130.8, 130.3, 129.7, 128.7, 128.0, 127.4, 52.0, 39.5, 21.0, 19.2;

IR (Microscope, cm^{-1}): 3000, 2950, 2921, 1723, 1610, 1504, 1435, 1280, 1109, 798;

HRMS (ESI) for $C_{17}H_{18}O_2$ $[M+Na]^+$: calcd. 277.1199; found 277.1198.



2-55

1,4-Dimethyl-2-(4-nitrobenzyl)benzene (2-55): Prepared from 4-nitrobenzyl alcohol (77 mg, 0.50 mmol) and *p*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane:EtOAc = 10:1) and isolated as a light yellow solid (56 mg, 46%).

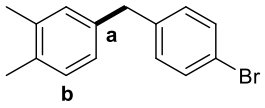
M.p. 50.9-51.1 °C;

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.15 (m, 2H), 7.29 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.03 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.94 (s, 1H), 4.07 (s, 2H), 2.33 (s, 3H), 2.19 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.5, 146.4, 136.9, 135.8, 133.4, 130.8, 130.6, 129.4, 127.8, 123.7, 39.4, 21.0, 19.2;

IR (Microscope, cm^{-1}): 3076, 3043, 2999, 2922, 2864, 1604, 15158, 1448, 1345, 1110, 858, 798, 734;

HRMS (ESI) for $C_{15}H_{15}NO_2$ $[M+Na]^+$: calcd. 264.0995; found 264.0995.



2-60

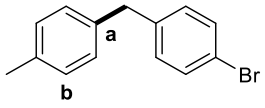
4-(4-Bromobenzyl)-1,2-dimethylbenzene (2-60): Prepared from 4-bromobenzyl alcohol (94 mg, 0.50 mmol) and *o*-xylene (265 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (132 mg, 96%, *p*:o = 61:39 mixture of regioisomers).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42-7.40 (m, 2H), 7.10-7.07 (m, 2.66H), 7.01-6.98 (m, 1.18H), 6.96 (s, 0.59H), 6.93-6.91 (m, 0.6H), 3.99 (s, 0.77H, minor), 3.89 (s, 1.23H, major), 2.31 (s, 1.15H, minor), 2.26 (s, 1,85H, major), 2.25 (s, 1.85H, major), 2.13 (s, 1.16H, minor);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.5, 139.8, 138.1, 137.9, 137.2, 136.7, 135.2, 134.5, 131.5, 131.4, 130.6, 130.4, 130.2, 129.8, 128.5, 128.0, 126.2, 125.5, 119.8, 119.7, 40.9, 39.5, 20.7, 19.8, 19.3, 15.4;

IR (Microscope, cm^{-1}): 3006, 2919, 2856, 1504, 1486, 14534, 1071, 1012, 796;

HRMS (EI) for $C_{15}H_{15}Br$: calcd. 274.0357; found: 274.0353.



2-61

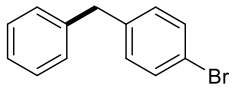
1-Bromo-4-(4-methylbenzyl)benzene (2-61):[46] Prepared from 4-bromobenzyl alcohol (94 mg, 0.50 mmol) and toluene (230 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (109 mg, 84%, *p*:o = 57:43 mixture of regioisomers).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43-7.40 (m, 1.93H), 7.21-7.17 (m, 1.40H), 7.14-7.07 (m, 3.35H), 7.03-7.01 (m, 1.05H), 3.96(s, 0.92H, minor), 3.91 (s, 1.08H, major), 2.35 (s, 1.65H), 2.25 (s, 1.32H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.4 (major), 139.4, 138.3, 137.4, 136.6 (major), 135.8 (major), 131.5, 131.5 (major), 130.6, 130.5, 130.4, 129.9, 129.3 (major), 128.8 (major), 126.7, 126.1, 119.9, 119.8, 40.9 (major), 38.9 (minor), 21.0 (major), 19.6 (minor);

IR (Microscope, cm^{-1}): 3021, 2919, 2857, 1514, 1487, 1404, 1071, 1012, 792, 742;

HRMS (EI) for $C_{14}H_{13}Br$: calcd. 260.0201; found 260.0199.



2-62

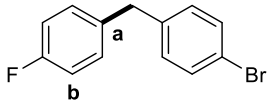
1-Benzyl-4-bromobenzene (2-62): Prepared from 4-bromobenzyl alcohol (94 mg, 0.50 mmol) and benene (195 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (111 mg, 89%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43 (m, 2H), 7.34-7.31 (m, 2H), 7.26-7.23 (m, 1H), 7.20-7.18 (m, 2H), 7.08 (m, 2H), 3.96 (s, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.5, 140.1, 131.5, 130.7, 128.9, 128.6, 126.3, 120.0, 41.3;

IR (Microscope, cm^{-1}): 3084, 3062, 3026, 2911, 2843, 1946, 1901, 1780 1603, 1487, 1453, 1072, 1012, 743;

HRMS (EI) for $C_{13}H_{11}Br$: calcd. 248.0024; found 248.0023.



2-63

1-Bromo-4-(4-fluorobenzyl)benzene (2-63):[47] Prepared from 4-bromobenzyl alcohol (94 mg, 0.50 mmol) and fluorobenzene (240 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (117 mg, 89%, *p*:o = 78:22 mixture of regioisomers).

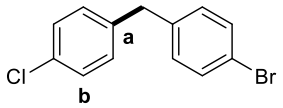
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.42 (m, 1.93H), 7.25-7.20 (m, 0.32H), 7.17-7.12 (m, 2.29H), 7.07-7.05 (m, 1.88H), 7.02-6.98 (m, 1.43H), 3.97 (s, 0.55H, minor), 3.92 (s, 1.45H, major);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.2 (d, *J* = 244.6 Hz, major), 160.9 (d, *J* = 245.7 Hz, minor), 139.9 (major), 138.9, 136.1 (d, *J* = 3.4 Hz, minor), 131.6 (major), 131.6 (minor), 130.9 (major), 130.9 (minor), 130.6, 130.5, 130.3 (d, *J* = 7.8 Hz, major), 128.2 (d, *J* = 8.1 Hz), 127.4 (d, *J* = 15.7 Hz, minor), 124.2 (d, *J* = 3.5 Hz, minor), 120.1 (major), 115.4 (d, *J* = 21.9 Hz, minor), 115.4 (d, *J* = 21.3 Hz, major), 40.5 (major), 34.3 (d, *J* = 3.0 Hz, minor);

^{19}F NMR ($CDCl_3$, 468 MHz): δ –116.9 (app sept, 0.78F, major), –117.8 (app q, 0.22F, minor);

IR (Microscope, cm^{-1}): 3041, 2916, 2856, 1602, 1509, 1488, 1228, 1012, 799, 758;

HRMS (EI) for $C_{13}H_{10}BrF$: calcd. 263.9950; found 263.9952.



2-64

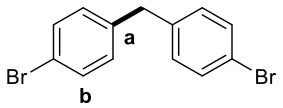
1-Bromo-4-(4-chlorobenzyl)benzene (2-64): Prepared from 4-bromobenzyl alcohol (94 mg, 0.50 mmol) and chlorobenzene (306 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (112 mg, 77%, *p*:o = 58:42 mixture of regioisomers).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.42 (m, 1.91H), 7.41-7.39 (m, 0.41H), 7.29-7.27 (m, 1.24H), 7.23-7.20 (m, 0.88H), 7.17-7.15 (m, 0.42H), 7.11-7.04 (m, 3.11H), 4.08 (s, 0.83H, minor), 3.92 (s, 1.17H, major);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.5, 138.9, 138.5, 138.0, 134.2, 132.2, 131.7, 131.6, 131.0, 130.7, 130.6, 130.2, 129.7, 128.7, 128.0, 127.0, 120.2, 120.1, 40.6, 38.7;

IR (Microscope, cm^{-1}): 3025, 2912, 2844, 1594, 1572, 1488, 1443, 1404, 1071, 1012, 783, 751;

HRMS (EI) for $C_{13}H_{10}BrCl$: calcd. 279.9655; found 279.9658.



2-65

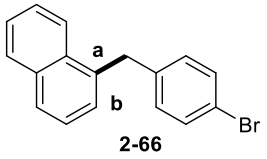
Bis(4-bromophenyl)methane (2-65):[48] Prepared from 4-bromobenzyl alcohol (94 mg, 0.50 mmol) and bromobenzene (393, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (136 mg, 83%, *p*:o = 57:43 mixture of regioisomers).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.60 (d, *J* = 8.0 Hz, 0.42H, minor), 7.45-7.43 (m, 3.03H), 7.28-7.25 (t, *J* = 7.4 Hz, 0.54H, minor), 7.17-7.12 (m, 0.86H, minor), 7.10-7.08 (m, 0.86H, minor), 7.06-7.05 (m, 2.21H, major), 4.09 (s, 0.85H, minor), 3.90 (s, 1.15H, major);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.7 (minor), 139.4 (major), 138.5 (minor), 133.0 (minor), 131.7 (major), 131.6 (minor), 131.1 (minor), 130.7 (minor), 130.6 (major), 128.2 (minor), 127.6 (minor), 124.9 (minor), 120.2 (major), 120.2 (minor), 41.2 (minor), 40.7 (major);

IR (Microscope, cm^{-1}): 3058, 3039, 2920, 2852, 1591, 1487, 1438, 1403, 1070, 1012, 779, 750;

HRMS (EI) for $C_{13}H_{10}Br_2$: calcd. 323.9149; found 323.9150.



2-66

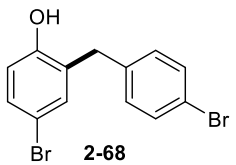
1-(4-Bromobenzyl)naphthalene (2-66):[49] Prepared from 4-bromobenzyl alcohol (94 mg, 0.50 mmol) and naphthalene (320 mg, 2.50 mmol). Purified by flash column chromatography (hexane) and isolated as a colorless oil (130 mg, 88%, a:b = 70:30 mixture of regioisomers).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94-7.86 (m, 1.36H, major), 7.82-7.77 (m, 1.54H), 7.61 (s, 0.30H, minor), 7.50-7.42 (m, 3.15H), 7.40-7.38 (m, 1.36H, major), 7.30-7.27 (m, 0.98H), 7.12 (m, 0.59H, minor), 7.08-7.06 (m, 1.35H, major), 4.40 (s, 1.40H, major), 4.10 (s, 0.60H, minor);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.0, 139.7, 137.9, 135.9, 134.0, 133.6, 132.2, 132.0, 131.6, 131.5, 130.8, 130.4, 128.8, 128.3, 127.7, 127.6, 127.5, 127.4, 127.4, 127.2, 126.1, 125.7, 125.6, 124.1, 120.1, 119.9, 41.5 (minor), 38.5 (major);

IR (Microscope, cm^{-1}): 3047, 2909, 2840, 1597, 1509, 1487, 1011, 789;

HRMS (EI) for $C_{17}H_{13}Br$: calcd. 296.0201; found 296.0203.



2-68

4-Bromo-2-(4-bromobenzyl)phenol (2-68): Prepared from 4-bromobenzyl alcohol (47 mg, 0.25 mmol) and 4-bromophenol (215 mg, 1.25 mmol). Purified by flash column chromatography (hexane:Et_2O = 10:1) and isolated as a yellow solid (45 mg, 52%).

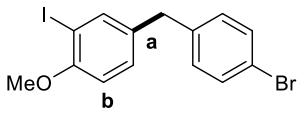
M.p. 67.7-68.0 °C;

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.43 (m, 2H), 7.24 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.21 (d, *J* = 2.3 Hz, 1H), 7.12-7.10 (m, 2H), 6.67 (d, *J* = 8.4 Hz, 1H), 4.67 (s, 1H), 3.91 (s, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.6, 138.3, 133.4, 131.7, 130.7, 130.5, 129.0, 120.4, 117.3, 113.1, 35.5;

IR (Microscope, cm^{-1}): 3339, 2966, 2927, 2850, 1608, 1582, 1486, 1431, 1240, 1116, 814;

HRMS (EI) for $C_{13}H_{10}Br_2O$: calcd. 339.9099; found 339.9102.



2-69

4-(4-Bromobenzyl)-2-iodo-1-methoxybenzene (2-69): Prepared from 4-bromobenzyl alcohol (47 mg, 0.25 mmol) and 1-iodo-2-methoxybenzene (293 mg, 1.25 mmol). Purified by flash column chromatography (hexane:DCM = 6:1) and isolated as a white solid (92 mg, 91%, *p*:o = 95:5 mixture of regioisomers).

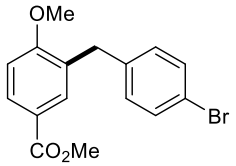
M.p. 65.7-65.9 °C;

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.60 (d, 1H, *J* = 2.2 Hz), 7.44-7.42 (m, 2H), 7.10 (dd, 1H, *J* = 8.4, 2.2 Hz), 7.06-7.04 (m, 2H), 6.76 (d, 1H, *J* = 8.4 Hz), 3.87 (s, 3H), 3.85 (s, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.7, 139.8, 139.7, 134.7, 131.6, 130.5, 129.8, 120.1, 110.9, 86.2, 56.4, 39.9;

IR (Microscope, cm^{-1}): 3021, 2962, 2939, 2909, 2837, 1597, 1486, 1458, 1249, 802;

HRMS (EI) for $C_{14}H_{12}BrIO$: calcd. 401.9116; found 401.9112.



2-70

Methyl 3-(4-bromobenzyl)-4-methoxybenzoate (2-70): Prepared from 4-bromobenzyl alcohol (47 mg, 0.25 mmol) and methyl 4-methoxybenzoate (208 mg, 1.25 mmol). Purified by flash column chromatography (hexane:Et_2O = 10:1) and PTLC (hexanes:Et_2O = 10:1) and isolated as a white solid (79 mg, 94%).

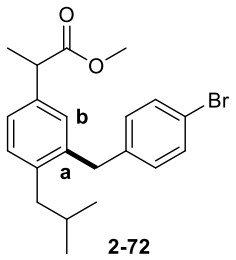
M.p. 75.7-76.0 °C;

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.82 (d, *J* = 2.1 Hz, 1H), 7.40-7.38 (m, 2H), 7.10-7.08 (m, 2H), 6.89 (d, *J* = 8.6 Hz, 1H), 3.94 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.9, 161.1, 139.4, 131.8, 131.4, 130.5, 130.2, 129.0, 122.4, 119.8, 110.0, 55.6, 51.9, 35.5;

IR (Microscope, cm^{-1}): 2952, 2933, 2844, 1708, 1604, 1503, 1437, 1264, 1123, 772;

HRMS (EI) for $C_{16}H_{15}BrO_3$: calcd. 334.0205; found 334.0208.



2-72

Methyl 2-(3-(4-bromobenzyl)-4-isobutylphenyl)propanoate (2-72): Prepared from 4-bromobenzyl alcohol (47 mg, 0.25 mmol) and methyl 2-(4-isobutylphenyl)propanoate (165 mg, 0.75 mmol). Purified by flash column chromatography (hexane:Et_2O = 10:1) and PTLC (and hexane:Et_2O = 10:1) and isolated as a light yellow oil (50 mg, 52%, 75:25 mixture of regioisomers).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.39 (m, 2.02H), 7.27-7.25 (d, *J* = 7.9 Hz, 0.26H, minor), 7.14-7.12 (m, 1.62H), 7.08-7.07 (dd, *J* = 7.9, 1.9 Hz, 0.26 H, minor), 7.00-6.98 (m, 2.73H), 6.94-

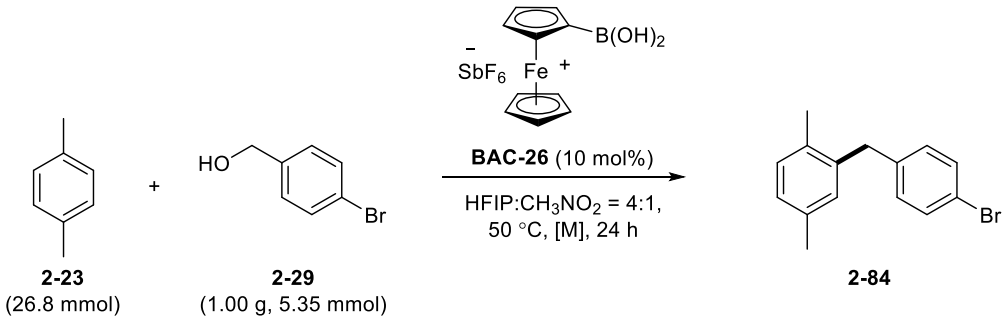
6.93 (d, J = 1.8 Hz, 0.25H), 4.04 (ABq, $\Delta\delta_{AB}$ = 0.11, J_{AB} = 16.1 Hz, 0.57H, minor), 3.97 (s, 1.52H, major), 3.85 (q, J = 7.1 Hz, 0.28H, minor), 3.68 (q, J = 7.2 Hz, 0.75H, major), 3.67 (s, 2.37H, major), 3.59 (s, 0.66H, minor), 2.45 (d, J = 7.2 Hz, 0.50H, minor), 2.43 (d, J = 7.2 Hz, 1.50H, major), 1.86 (sep, J = 6.7 Hz, 0.25H, minor), 1.81 (sep, J = 6.7 Hz, 0.83H, major), 1.47 (d, J = 7.2 Hz, 2.25H, major), 1.34 (d, J = 7.1 Hz, 0.73H, minor), 0.93-0.90 (m, 6.06H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.2, 175.1, 140.7, 140.0, 139.8, 138.9, 138.2, 138.2, 136.9, 136.6, 131.7, 131.4, 130.7, 130.4, 130.3, 129.6, 128.2, 127.1, 127.1, 125.3, 119.8, 119.8;

IR (Microscope, cm^{-1}): 2953, 2868, 1738, 1487, 1500, 1168, 1101, 796;

HRMS (EI) for $C_{21}H_{25}BrO_2$ $[M+Na]^+$: calcd. 411.0930; found 411.0929.

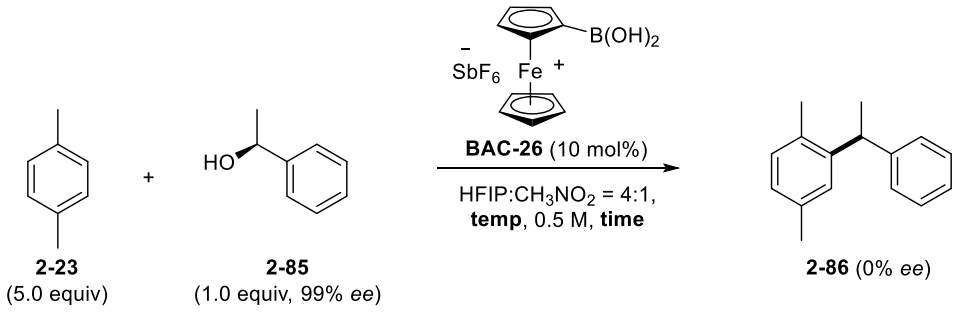
2.10.6 Procedure for gram-scale Friedel-Crafts benzylation



To a 25 mL round bottom flask equipped with a stir bar, containing 4-bromobenzyl alcohol (1.00 g, 5.35 mmol) and *p*-xylene (2.84 g, 27.8 mmol) in a solvent mixture of 4:1 hexafluoro-isopropanol and nitromethane with the indicated concentration, was added the ferrocenium boronic acid catalyst (246 mg, 0.53 mmol). The flask was capped and stirred at the 50 °C for 24 h. The reaction mixture was concentrated and the resulting viscous oil was extracted with Et_2O (30 mL × 3). During the extractions, the viscous oil solidified. The resulting organic layer was collected, concentrated and subjected to flash column chromatography with hexane as eluent. The solid (crude catalyst) was recovered by recrystallization with acetone and Et_2O.

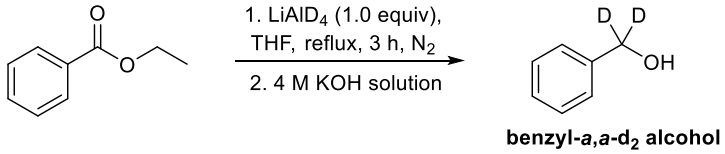
2-(4-Bromobenzyl)-1,4-dimethylbenzene (2-84) was isolated as a colorless oil which solidified slowly, the characterization matches that from a previous report as per Paquin et al.[31]

2.10.7 General procedure of Friedel-Crafts benzylation with optically pure secondary benzyl alcohol 2-85 and *p*-xylene



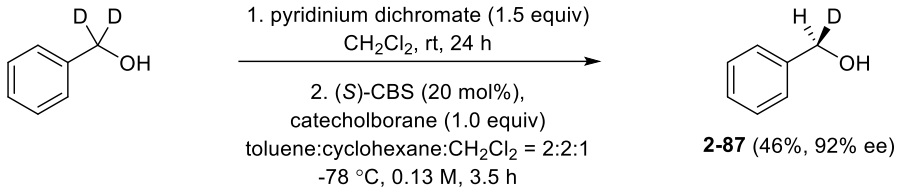
To a vial equipped with a stir bar, containing optically pure secondary benzyl alcohols **2-85** and the *p*-xylene in a solvent mixture of 4:1 hexafluoroisopropanol and nitromethane, was added the ferrocenium boronic acid catalyst. The vial was capped and stirred at the stated temperature (25 °C, 0 °C and -20 °C) for indicated time. Upon completion, monitored by TLC, the reaction mixture was concentrated and subjected to flash column chromatography using EtOAc/hexane as the eluent to afford the product. The pure product **2-86** was then subjected to chiral HPLC analysis. The characterization data of **2-86** matched that in the previous report by Rueping and co-workers.[50]

2.10.8 Synthesis of (*R*)-α-deuteriobenzyl alcohol 2-87



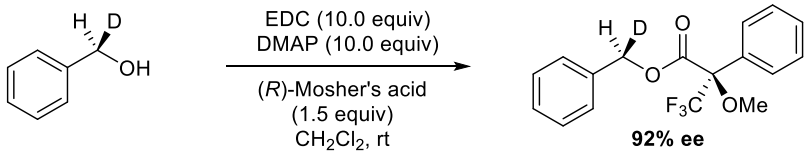
Benzyl-*a*,*a*-d$_2$ alcohol:[40] To a solution of $LiAlD_4$ (500 mg, 22.0 mmol) in THF (15 mL) in a flamed-dried flask 100 mL round bottom flask was added a solution of ethyl benzoate (3.30 g, 22.0 mmol) in THF (10 mL) at 0 °C. The reaction mixture was heated to reflux under N_2 for 3 h. The reaction mixture was then cooled down to 0 °C and quenched by 4 M KOH aqueous solution and extracted by EtOAc (20 mL × 3). Organic layer was concentrated and subjected to column chromatography (hexane:EtOAc = 3:1), affording the product benzyl-α,α-d_2 alcohol (511 mg, 21%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40-7.37 (m, 4H), 7.35-7.31 (m, 1H), 1.71 (s, 1H).



2-87 (46%, 92% ee)

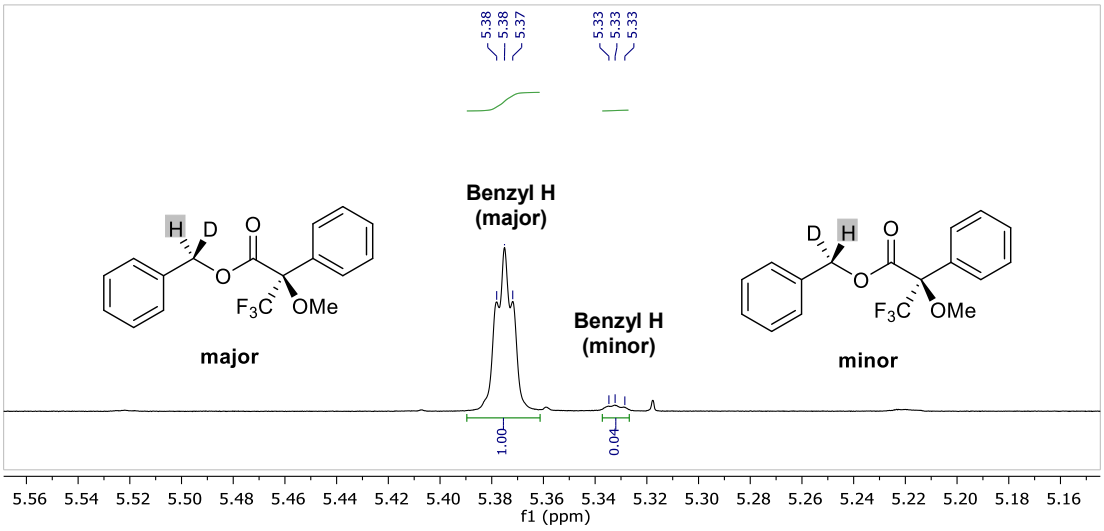
(*R*)-α-Deuteriobenzyl alcohol 2-87:[41] To a solution of benzyl-α,α-d_2 alcohol (511 mg, 4.64 mmol) in DCM (20 mL) in a flame-dried round bottom flask was added pyridinium dichromate (1.51 g, 7.00 mmol) at room temperature. Reaction mixture was stirred for 24 h before filtered through Celite 545. The filtrate was concentrated and subjected to a short silica plug with DCM and eluent. The organic layer was collected and concentrated, affording the crude benz(aldehyde-d) (312 mg, 2.91 mmol). The crude benzaldehyde-d was subjected to the next step without further purification. A solution of (*S*)-2-methyl-CBS-oxazaborolidine (242 mg, 0.87 mmol) and benzaldehyde-d in a solvent mixture of toluene-cyclohexane-dichloromethane (2:2:1, v/v) (22.4 mL) was prepared and stirred at -78 °C. A 1 M solution of catecholborane (2.2 mL, 4.36 mmol) in THF was added into the reaction over 40 min. The reaction mixture was stirred in the same temperature for 3.5 h before quenched with MeOH (10 mL) and 1 M HCl aqueous solution. The resulting mixture was washed by 1 M NaOH aqueous solution prior to drying over $MgSO_4$, filtration and concentration. The crude product was subjected to column chromatography (hexane:EtOAc = 3:1) to give (*R*)-α-deuteriobenzyl alcohol (235 mg over two steps, 46%) as a light yellow oil.



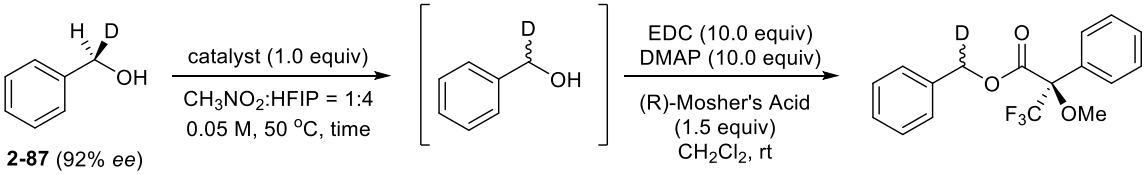
92% ee

(*R*)-MTPA ester of (*R*)-α-deuteriobenzyl alcohol:[51] To a 10 mL flamed round bottom flask was added (*R*)-Mosher's acid (44 mg, 0.19 mmol), 4-dimethylaminopyridine (153 mg, 1.25 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (240 mg, 1.25 mmol) in DCM (5 mL). Reaction mixture was stirred for 15 min before the addition of (*R*)-α-deuteriobenzyl alcohol (14 mg, 0.125 mmol). Reaction mixture was diluted with DCM after completion monitored by TLC. The resulting organic layer was washed by 1 M HCl aqueous solution, 1M NaOH solution and brine prior to drying over $MgSO_4$, filtration and concentration. The crude product was subjected to column chromatography (hexane:Et_2O = 20:1) to give the (*R*)-MTPA ester of (*R*)-α-deuteriobenzyl alcohol as colorless oil. The enantiomeric excess of the (*R*)-α-deuteriobenzyl alcohol was determined to be 92% by Mosher's ester analysis.[52]

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49-7.47 (m, 2.09H), 7.41-7.36 (m, 8.39H), 5.38 (br s, 1.00 H, major), 5.33 (br s, 0.04H, minor), 3.58 (q, *J* = 1.2 Hz, 0.05H, minor), 3.54 (q, *J* = 1.2 Hz, 3.18H, major).



2.10.9 Racemization of (*R*)-α-deuteriobenzyl alcohol 2-87

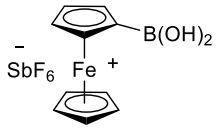
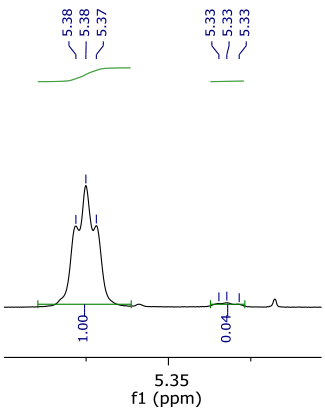
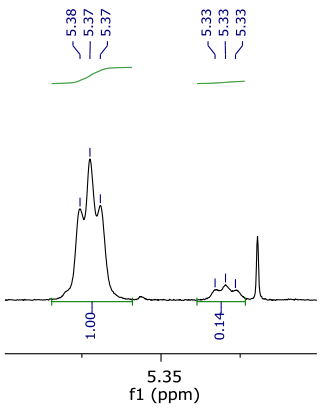
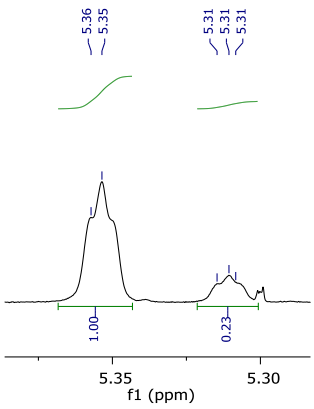
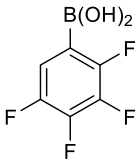
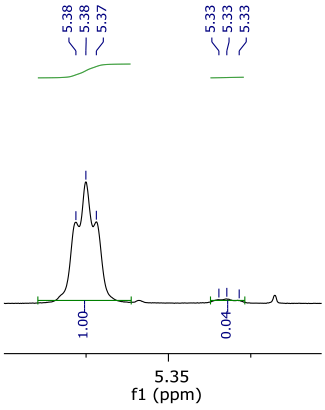
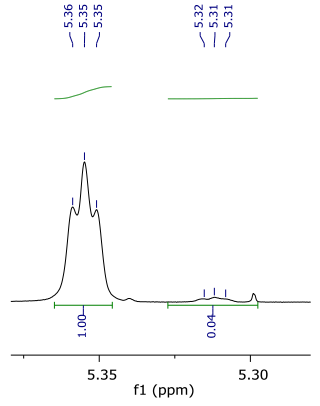
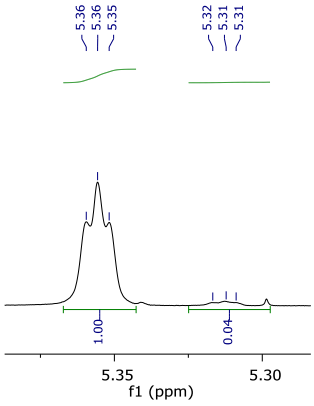


2-87 (92% *ee*)

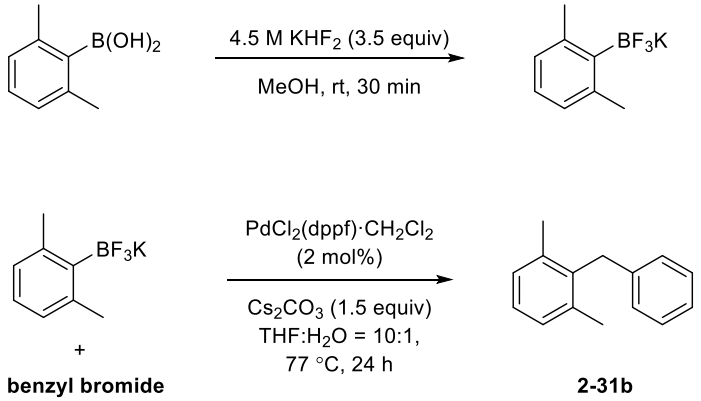
To a vial equipped with a stir bar, containing (*R*)-α-deuteriobenzyl alcohol (14 mg, 0.13 mmol) in a solvent mixture of 4:1 hexafluoro-isopropanol and nitromethane (2.5 mL), was added the ferrocenium boronic acid (58 mg, 0.13 mmol) or tetrafluorophenyl boronic acid (24 mg, 0.13 mmol). The vial was capped and stirred at 50 °C. Reaction mixture was diluted with DCM (10 mL) at indicated time (15 min and 30 min) and subjected to a short silica plug with DCM as eluent for removal of the boronic acid. The resulting organic solution was concentrated and re-dissolved in DCM (2 mL) as solution A. To a solution of 4-dimethylaminopyridine (153 mg, 1.25 mmol), (*R*)-Mosher's acid (44 mg, 0.19 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (240 mg, 1.25 mmol) in DCM (3 mL) was added solution A at room temperature. The reaction mixture was stirred at the same temperature till reaction completion monitored by TLC. Reaction mixture was diluted with DCM after completion. The resulting

organic layer was washed by 1 M HCl aqueous solution, 1 M NaOH solution and brine prior to drying over $MgSO_4$, filtration and concentration. The crude product was subjected to column chromatography (hexane:Et_2O = 20:1) to give the (*R*)-MTPA ester of α-deuteriobenzyl alcohol as a colorless oil.

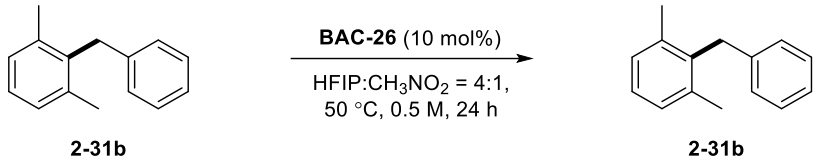
entry	catalyst	time (min)	ee (%)	yield (%)
1	BAC-26	15	75	14
2	BAC-26	30	63	22
3	BAC-16	15	92	48
4	BAC-16	30	92	48

time (min)	0	15	30
 BAC-26			
 BAC-16			

2.10.10 Isomerization experiment of diarylalkane 2-31b



Diarylalkane **2-31b** was prepared *via* Suzuki-Miyaura cross coupling according to the literature procedure by Molander and co-workers. The characterization data of **2-31b** matched those in the previous report.[42]



To a vial equipped with a stir bar, containing diarylalkane **2-31b** (37 mg, 0.19 mmol) in a solvent mixture of 4:1 hexafluoroisopropanol and nitromethane, was added the ferrocenium boronic acid catalyst (9 mg, 0.02 mmol). The vial was capped and stirred at the 50 °C for 24 h. After the indicated period of time, the reaction mixture was filtered through a silica plug with 20 mL of DCM. The crude mixture was obtained and subjected to NMR study after the removal of solvent. No isomerization of **2-31b** was observed based on the ^{1}H NMR analysis of the crude.

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Chapter 3 Dual Catalysis Merging Boronic Acid and Chiral Amine: Acyclic Quaternary Carbon Centers *via* Asymmetric Allylation of Branched Aldehydes with Allylic Alcohols[‡]

3.1 Introduction

The concept of catalyst engineering has generated many new strategies for reaction design. Dual catalysis, where two catalysts act independently to activate otherwise unreactive starting materials, has shown great potential for the rapid assembly of unconventional bonds.[1] From this perspective, it is envisioned that a more sophisticated nucleophilic system can be introduced in parallel with boronic acid catalysis (BAC). Specifically, a dual catalytic system merging boronic acid and chiral amine catalysis could lead to the facile allylation of enamines with carbocations generated from the simultaneous activation of allylic alcohols and aldehydes (**Scheme 3-1a**).[2] In this context, BAC has been successfully applied in direct 1,3-transposition,[3] intramolecular cyclization[4] and Friedel-Crafts alkylation[5] of allylic alcohols, as discussed in the previous chapters. Mechanistic studies show that electrophilic boronic acids can either partially polarize a C–O bond or completely ionize an alcohol upon a reversible co-valent interaction.[6] Furthermore, BAC displays a broader functional group tolerance due to the relatively mild acidity (pK_a 5-9) of boronic acids compared to other common Brønsted or Lewis acid catalysts.[7] As straightforward as it seems, synergistic catalysis using a Lewis acid and a Brønsted base is highly challenging due to the potential lack of chemoselectivity, outlined as follows: (a) catalyst deactivation from the acid-base interactions; (b) carbocation interception leading to 1,3-transposition and etherification of the allylic alcohol; (c) allylation of the amine catalyst; (d) facile aldol reactions and oxidation of the aldehyde substrate (**Scheme 3-1b**).

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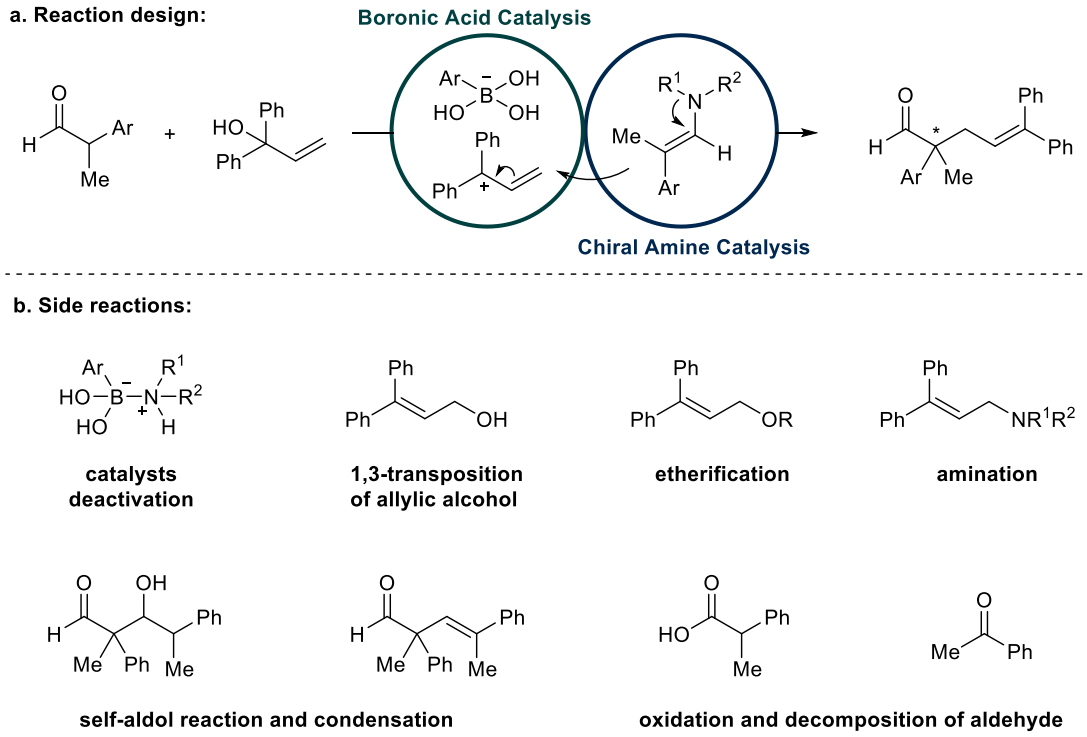
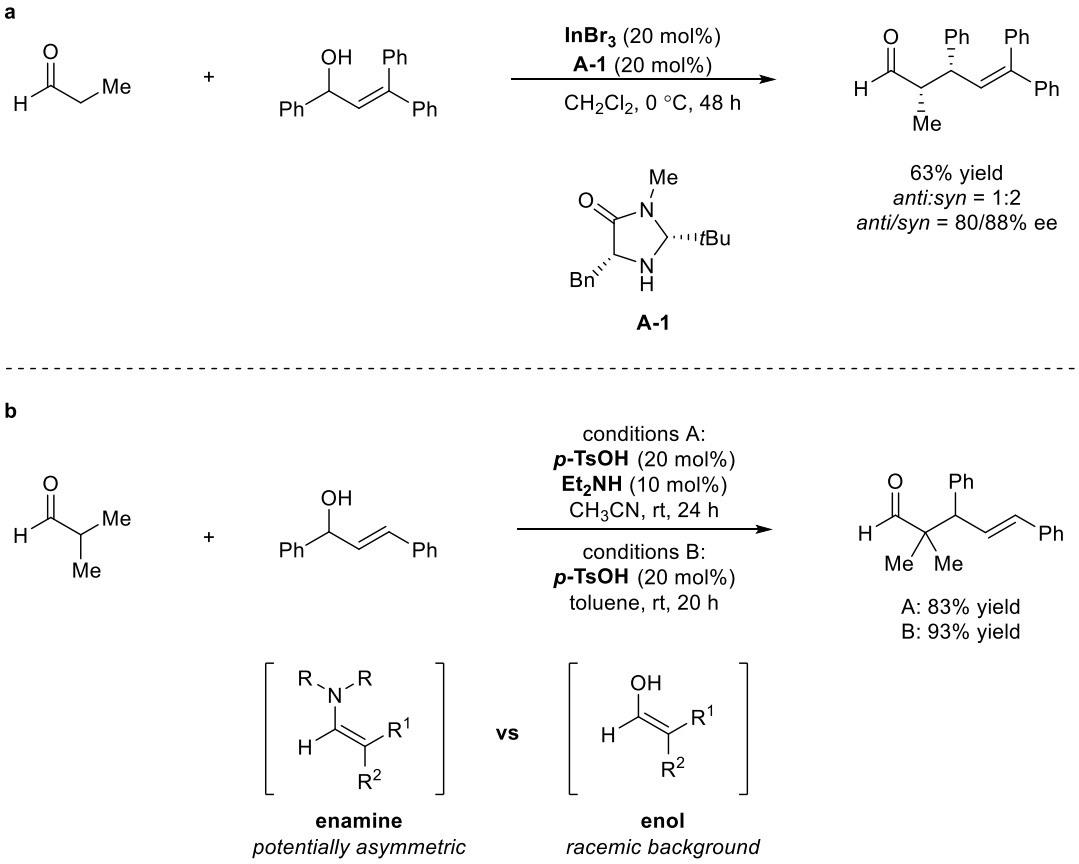


Scheme 3-1. Reaction design (a) and potential side reactions (b) of the dual catalytic asymmetric allylation merging boronic acid catalysis and chiral amine catalysis.

Despite the aforementioned challenges, progress has been made in the field of dual acid-base catalysis. In 2010, Cozzi and co-workers described a dual catalytic system using $InBr_3$ and chiral imidazolidinone catalyst, thereby addressing the potential chemoselectivity problems (**Scheme 3-2a**).[8] In their research, it was found that $InBr_3$ was able to ionize activated internal allylic alcohols, despite the presence of an amine and the production of water. Asymmetric allylation of linear aldehydes was achieved in good enantioselectivity and moderate yield. However, low diastereoselectivity was observed due to the lack of stereo-induction from the nucleophilic enamine attack to the carbocation. Moreover, no branched aldehydes were reported in the reaction scope. In fact, the development of dual catalysis for the direct asymmetric allylation of branched aldehydes with alcohols is an ongoing challenge. In 2010, Xu and co-workers described the use of diethylamine and *p*-toluenesulfonic acid (*p*-TsOH) for an effective allylation of branched aldehydes with allylic alcohols (**Scheme 3-2b**, conditions A).[9] Although the authors suggested that the dual activation of branched aldehydes and allylic alcohols occurred *via* enamines and carbocations, this proposed synergistic mechanism was

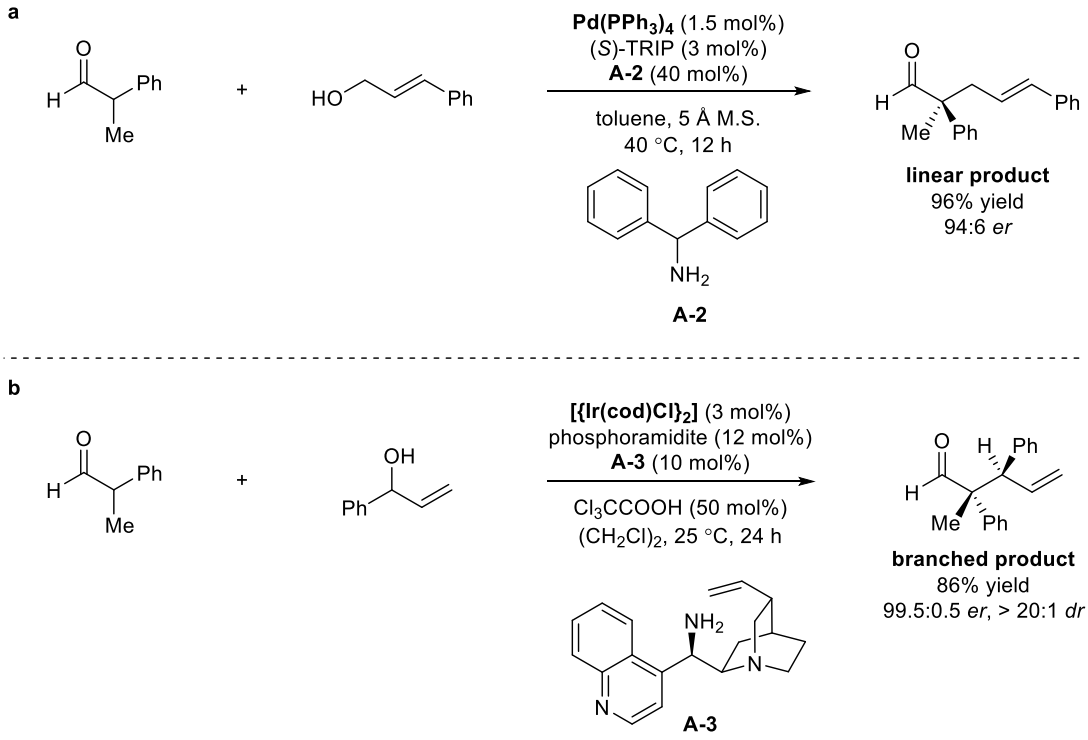
soon questioned. It was later found that the allylation was also possible without the use of an amine as reported by Chi and co-workers (**Scheme 3-2b**, conditions B).[10] It is possible that the reaction occurs through a tandem enol formation and allylation mechanism catalyzed solely by the *p*-TsOH. Consequently, no asymmetric variant was achieved in these reports due to this highly favorable racemic background reaction.



Scheme 3-2. (a) Asymmetric allylation of linear aldehydes with allylic alcohols using $InBr_3$ and an imidazolidinone catalyst **A-1**; (b) racemic allylation of branched aldehydes with *p*-TsOH.

The challenges regarding the asymmetric allylation of branched aldehydes with allylic alcohols have been partially addressed by the use of dual transition metal and chiral amine catalysis.[11] In 2011, List and co-workers described a remarkable catalytic system using palladium, a racemic amine and a chiral phosphoric acid for the preparation of acyclic quaternary carbon centers (**Scheme 3-3a**).[12] It was hypothesized that the chiral phosphoric acid not only provides transient activation of the allylic alcohol but also affords sufficient selectivity to direct attack from the

enamine *via* hydrogen bonding. Their protocol provides the linear allylated product in high yield and good enantioselectivity. As a complementary procedure, Carreira and co-workers exploited the differing regioselectivity of iridium π-allyl catalysis for the synthesis of branched allylated aldehydes bearing all carbon quaternary centers (**Scheme 3-3b**).[13] The use of a chiral ligand for iridium catalyst and a cinchona-derived primary amine afforded both good yield and high diastereo- and enantioselectivity for the desired branched products embedding an all-carbon quaternary center.



Scheme 3-3. Dual catalysis uniting transition metal and chiral amine for the allylation of branched aldehydes: (a) linear products using palladium; (b) branched products using iridium.

3.2 Objective

As highlighted in Section 3.1, the preparation of optically enriched acyclic all carbon quaternary centers remains a challenge for organic chemists.[14] Specifically, the synthesis of methyl-aryl quaternary carbons is of particular importance as they exist in a variety of natural products and biologically active molecules (**Figure 3-1**).[15] Although different strategies have been developed over the years, such as the use of chiral auxiliaries,[16] catalytic methods for the asymmetric

synthesis of compounds containing these methyl-aryl stereogenic centers are in high demand.[17] Previous synergistic catalysis using transition metals and amines displays promising results, but suffers from limited functional group tolerance (**Scheme 3-3**).[12] For instance, the traditional palladium chemistry may not be compatible with aryl halides, nitro containing compounds and functional groups with basic binding sites. The lack of generality limits the utility of these methods using transition metals. In contrast, catalytic asymmetric allylation of branched aldehydes using a Brønsted acid and a chiral amine is highly challenging due to the competing racemic enol allylation (**Scheme 3-1b**). In this regard, it was proposed that dual catalysis merging boronic acid and chiral amine catalysis could be a mild method to achieve the direct asymmetric allylation of branched aldehydes for the synthesis of valuable methyl-aryl quaternary carbon centers.

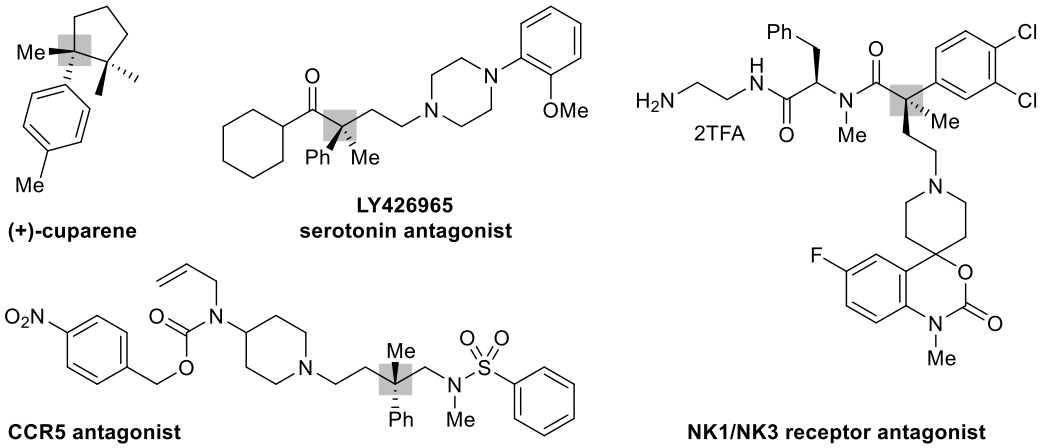


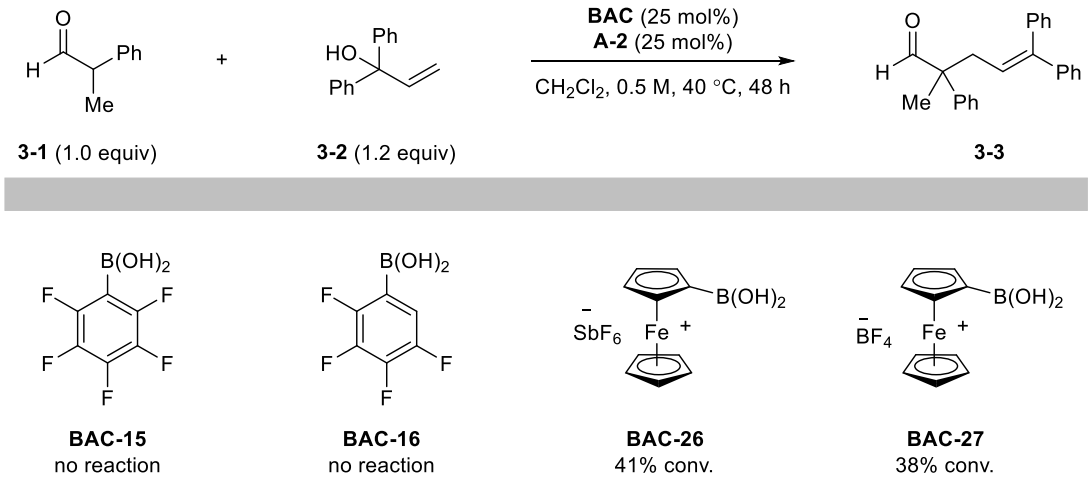
Figure 3-1. Examples of nature products and biologically active molecules containing methyl-aryl stereogenic all-carbon quaternary centers.

3.3 Optimization of the dual catalytic racemic allylation

The dual catalytic allylation of branched aldehydes with allylic alcohols merging boronic acid and amine catalysis poses great challenges for reaction development, as multiple side reactions can occur (**Scheme 3-1b**). Considering that there was no previous report on a reaction of this specific type, we first started by exploring the racemic variant.

The initial reaction optimization of the dual catalytic racemic allylation began with a screening of different boronic acids. As a starting point, branched aldehyde **3-1** and benzhydrylamine

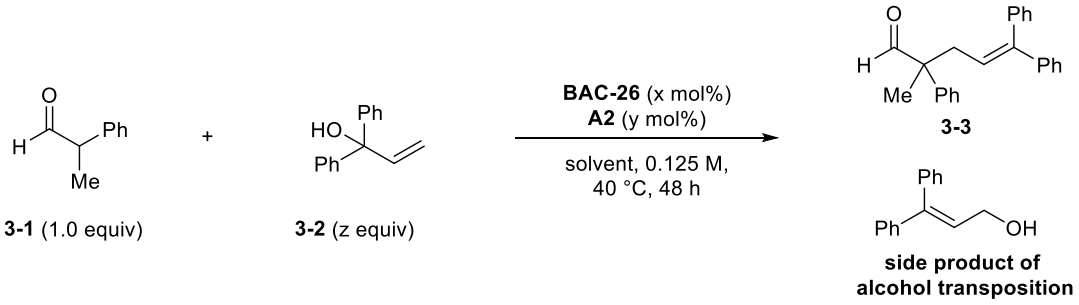
catalyst **A-2** were selected leading to reaction conditions similar to that reported by Carreira and co-workers.[13] A slight excess of allylic alcohol **3-2** was used due to the favorable 1,3-transposition reaction (**Scheme 3-1a**). Dichloromethane was chosen as the initial solvent due to its use in a similar allylation of linear aldehydes using $InBr_3$ reported by Cozzi and co-workers (**Scheme 3-2a**).[8] A one-to-one ratio of boronic acid and amine was used to minimize catalyst deactivation. With these initial experiments, it was observed that the fluorinated electron poor aryl boronic acids **BAC-15** and **BAC-16** were presumably deactivated in the presence of amine **A-2**. The desired product was not observed, instead, only recovery of both aldehyde **3-1** and alcohol **3-2** was obtained (**Scheme 3-4**). In comparison, ferrocenium boronic acid salts **BAC-26** and **BAC-27** provided moderate conversion to the allylated product **3-3**. Even though the use of SbF_6 and BF_4 anion provided similar results at this point, **BAC-26** was selected for further optimization since the SbF_6 anion is thought to be less coordinating to the allyl carbocation.



Scheme 3-4. Boronic acid screening for dual catalytic racemic allylation.

Table 3-1 summarizes the optimization of the reaction parameters using catalyst **BAC-26**. Unless otherwise stated, the major side reaction was 1,3-transposition of the allylic alcohol **3-2**.[3] In most cases, unreacted starting allylic alcohol and the rearranged allylic alcohol were observed along with the desired product. When the decomposition of **BAC-26** was observed (cf. Chapter 2, Section 2.5), reactions showed mostly aldehyde **3-1** and allylic alcohol **3-2**. A brief solvent screen was performed. It was found that polar solvents containing basic atoms were not compatible with the ferrocenium boronic acid **BAC-26**. Facile decomposition of **BAC-26** was observed in DMF, which led to no desired product (entry 1). The use of diethyl ether afforded a

low yield of product **3-3**, presumably due to the coordinating effect of the oxygen lone pair to the boronic acid moiety or the carbocation (entry 2). The allylation displayed moderate, however, inconsistent results in various chlorinated solvents (entries 3-6). Nevertheless, dichloromethane still provided the best yield (entry 6). It was suspected that the allylic alcohol **3-2** was not ionized sufficiently in dichloromethane, thus the acidic additive was sought. However, the addition of acid HBF_4 was detrimental, leading to decomposition of the allylic alcohol **3-2** (entry 7). Considering that the 1,3-transposition could not be supressed effectively by changing solvents, the loadings of both amine **A-2** and boronic acid catalysts were increased to 40 mol% along with a greater amount of the allylic alcohol substrate. As expected, a higher yield of the product **3-3** was obtained (entry 8). However, the reaction was not easily reproducible possibly due to a lack of solubility of the ferrocenium boronic salt in less polar solvents. The solid of **BAC-26** were formed in dichloromethane. It was suspected that less homogeneous boronic acid was present in the reaction media compared to the amine, which led to different degrees of ferrocenium boronic acid decomposition. A more reliable system was then developed using a solvent mixture of CH_2Cl_2:HFIP (1:1). The use of HFIP[18] increased the solubility of **BAC-26** as well as stabilized the carbocation intermediate, although a slightly lower yield was observed (entry 9).

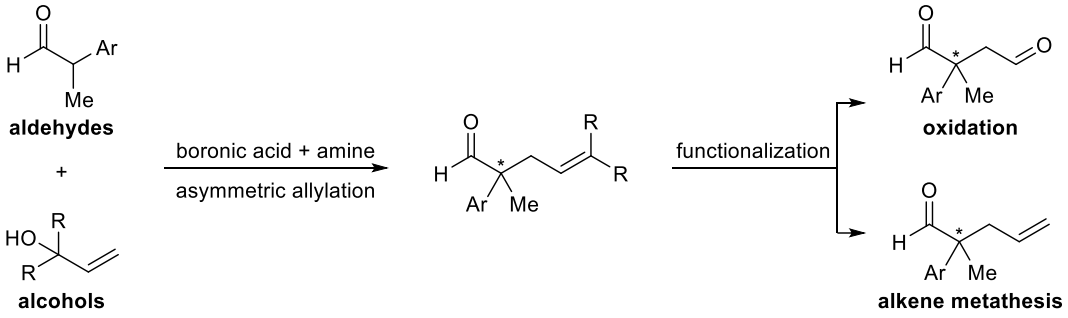


entry	z	x	y	solvent	product	yield (%)[a]
1	1.2	25	25	DMF	**3-3**	0
2	1.2	25	25	Et_2O	**3-3**	12
3	1.2	25	25	DCE	**3-3**	6
4	1.2	25	25	$CDCl_3$	**3-3**	23
5	1.2	25	25	CH_2Cl_2	**3-3**	47
6	1.2	25	25	CH_2Cl_2	**3-3**	42
7[b]	1.2	25	25	CH_2Cl_2	**3-3**	0
8	2.0	40	40	CH_2Cl_2	**3-3**	63
9	2.0	40	40	CH_2Cl_2:HFIP = 1:1	**3-3**	55

[a]Yields were determined by ^{1}H NMR analysis of reaction mixture with 1,4-dinitrobenzene as an internal standard. [b]Reaction was run with 20 mol% of HBF_4 as an additive.

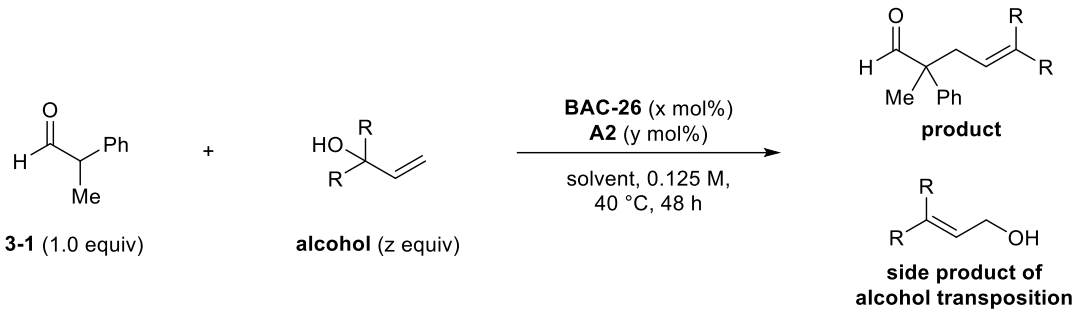
Table 3-1. Optimization of reaction conditions for dual catalytic racemic allylation-Part 1.

Since only a moderate yield of 55% could be obtained following the solvent screening (**Table 3-1, entry 9**), other strategies were considered to increase the yield of the desired reaction and suppress the undesirable 1,3-transposition of allylic alcohols (**Table 3-2**). Considering that the diarylalkene moiety of the allylated product can be designed to be further transformed to more useful functional groups by oxidation or alkene metathesis (**Scheme 3-5**), a series of allylic alcohols were then tested in hope of finding a more suitable allylic alcohol starting material.[19]



Scheme 3-5. Projected functionalization of the alkene moiety in the allylated products.

An allylic alcohol with strong electron-withdrawing substituents, such as $–CF_3$, was not suitable due to destabilization of the putative carbocation (**Table 3-2**, entry 1). Other less activated allylic alcohols such as **3-6** and **3-8** were shown to be completely unreactive even in pure HFIP (entries 2 and 3). In contrast, the use of allylic alcohols **3-10** and **3-12** with electron rich aryl groups only afforded the corresponding allylated products **3-11** and **3-13** in low yields, along with large amounts of transposition side-product (entries 4 and 5). Gratifyingly, halides at the *para* position of the aryl groups in the allylic alcohol substrates significantly increased the reaction yield (entries 6 and 7). The installation of halides at the *para* position effectively decreases the 1,3-transposition side reaction, yet still provided sufficient activation for the allylic alcohol through lone pair donation. This was confirmed by the lack of reactivity of alcohol **3-18** with fluoride at the *meta* position, which could not provide stabilization of the benzylic carbocation (entry 8). To our satisfaction, it was found that the catalyst loading could be decreased to 20 mol% with allylic alcohol **3-14** to provide an increase in yield to 80% (entry 9). Surprisingly, the allylated product **3-15** was obtained in even higher yield 88% when using a smaller proportion of HFIP (entry 10). This observation could be attributed to the over ionization of the allylic alcohol with excess HFIP, thus favoring the alcohol transposition.



entry	R	alcohol	z	x	y	solvent	product	yield (%)[a]
1	4-CF_3-C_6H_4	**3-4**	2.0	40	40	CH_2Cl_2:HFIP = 1:1	**3-5**	0
2	Cy	**3-6**	2.0	40	40	HFIP	**3-7**	0
3	Me	**3-8**	2.0	40	40	HFIP	**3-9**	0
4	4-*t*-Bu-C_6H_4	**3-10**	2.0	40	40	CH_2Cl_2:HFIP = 1:1	**3-11**	56
5	4-MeO-C_6H_4	**3-12**	2.0	40	40	CH_2Cl_2:HFIP = 1:1	**3-13**	40
6	4-F- C_6H_4	**3-14**	2.0	40	40	CH_2Cl_2:HFIP = 1:1	**3-15**	73
7	4-Cl- C_6H_4	**3-16**	2.0	40	40	CH_2Cl_2:HFIP = 1:1	**3-17**	71
8	3-F- C_6H_4	**3-18**	2.0	40	40	CH_2Cl_2:HFIP = 1:1	**3-19**	6
9	4-F- C_6H_4	**3-14**	2.0	20	20	CH_2Cl_2:HFIP = 1:1	**3-15**	80
10	4-F- C_6H_4	**3-14**	2.0	20	20	CH_2Cl_2:HFIP = 10:1	**3-15**	88

[a]Yields were determined by ^{1}H NMR analysis of reaction mixture with 1,4-dinitrobenzene as an internal standard.

Table 3-2. Optimization of reaction conditions for dual catalytic racemic allylation-Part 2.

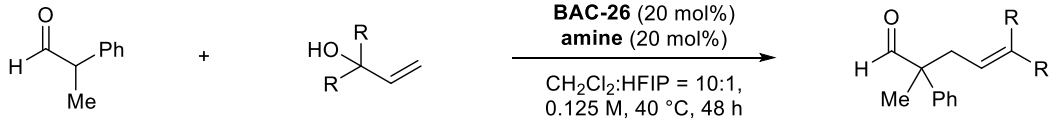
3.4 Optimization of the dual catalytic asymmetric allylation

3.4.1 Screening of primary amine

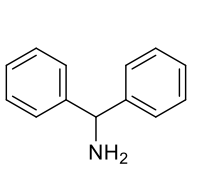
At the outset, a number of chiral primary amines with a large range of structural features were tested using the optimal racemic reaction conditions (**Table 3-2**, entry 10). Despite the lower nucleophilicity compared to secondary amines, primary amines were tested first, because they are more suitable for hindered substrates such as branched aldehydes (**Scheme 3-6**). The use of cinchona alkaloids derived amines **A-3** and **A-4** was not productive even though they were shown to display great results for a previous amination reaction of branched aldehydes.[20] In this case, coordination from all the nitrogen atoms of the amine might be strongly deactivating for the boronic acid. Similarly, reaction with a urea-amine bifunctional catalyst **A-5** gave the product **3-15** in low yield with moderate enantioselectivity.[21] Since the use of these traditional catalysts

was not fruitful, amino acids were then tested because they are widely available and easily functionalized. Unfortunately, free amino acids, such as phenylalanine, **A-6**, proved unsuitable for the direct asymmetric allylation presumably because both the amine and carboxylic acid moieties could chelate with the boronic acid. Consequently, simply protecting the carboxylic acid as the methyl ester **A-7** drastically increased the reaction yield; unfortunately the selectivity was rather low. Increasing the steric bulk of the amino ester side chain did not result in a significant change of *er* (see **A-8** and **A-10**). Interestingly, when tryptophan methyl ester **A-9** was used, a moderate improvement in selectivity (63.5:36.5 *er*) was obtained along with a low yield (30%). It appears that incorporation of one nitrogen atom can potentially increase the selectivity for the allylation; however, excess basic binding sites on the amine catalyst may deactivate the boronic acid. Based on this observation, installation of one extra nitrogen atom into the amine catalyst was attempted. While the amino amide **A-11** only gave a moderate yield with no improvement of *er*, it was found that the use of the corresponding diamine **A-12** resulted in a high yield and a substantial increase in selectivity (72.5:17.5 *er*).

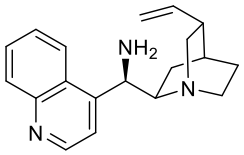
In light of the high reactivity and selectivity of **A-12**, more effort was then placed in search of the optimal 1,2-diamines.[22] A library of 1,2-diamines with various structures was prepared from amino acids due to the synthetic modularity of these substrates (**Scheme 3-7**). A series of 1,2-diamines (**A-12** to **A-17**) derived from L-*tert*-leucine were tested (**Scheme 3-7a**).[23] It was observed that reducing the steric hindrance of the tertiary amine moiety (**A-13**) further increased the selectivity, while amine **A-14** with bulkier tertiary amine side chains led to a lower *er*. Introduction of the cyclic tertiary amine (**A-15**) unit led to much lower yield with no obvious improvement of *er*. The pyrrolidine unit with high nucleophilicity could potentially deactivate the boronic acid or attack the ferrocenium scaffold. It was found that installation of less hindered *n*-butyl secondary amine unit (**A-16**) had a negative impact on the reaction yield while amine (**A-17**) with less accessible cyclohexyl amine still provided good yield but no significant improvement in *er* (**Scheme 3-6**).



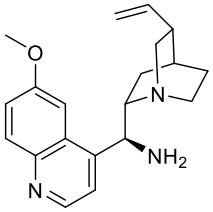
3-1 (1.0 equiv) + **3-14** R = 4-F-C_6H_4 (2.0 equiv) → **3-15** (yield[a] & *er*[b])



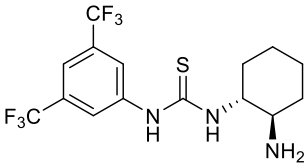
A-2 88% yield



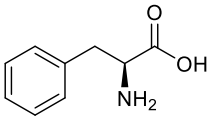
A-3 no reaction



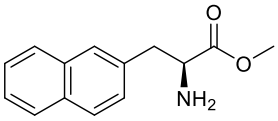
A-4 no reaction



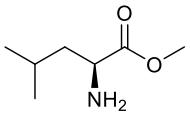
A-5 10% yield
82.5:17.5 *er*



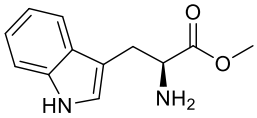
A-6 no reaction



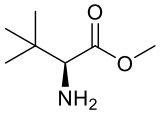
A-7 86% yield
53.5:46.5 *er*



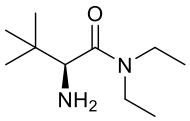
A-8 87% yield
55:45 *er*



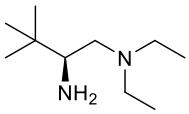
A-9 30% yield
63.5:36.5 *er*



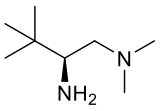
A-10 82% yield
52.5:47.5 *er*



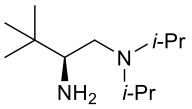
A-11 44% yield
53.5:46.5 *er*



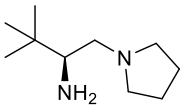
A-12 84% yield
72.5:27.5 *er*



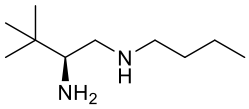
A-13 86% yield
76.5:23.5 *er*



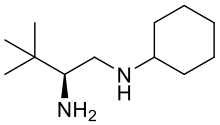
A-14[c] 36% yield
63.5:36.5 *er*



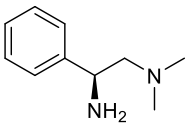
A-15 15% yield
68.5:31.5 *er*



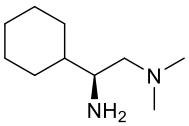
A-16 38% yield
79:21 *er*



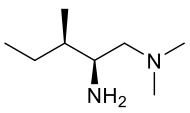
A-17[c] 80% yield
80:20 *er*



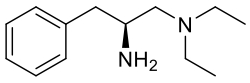
A-18[c] 74% yield
54.5:45.5 *er*



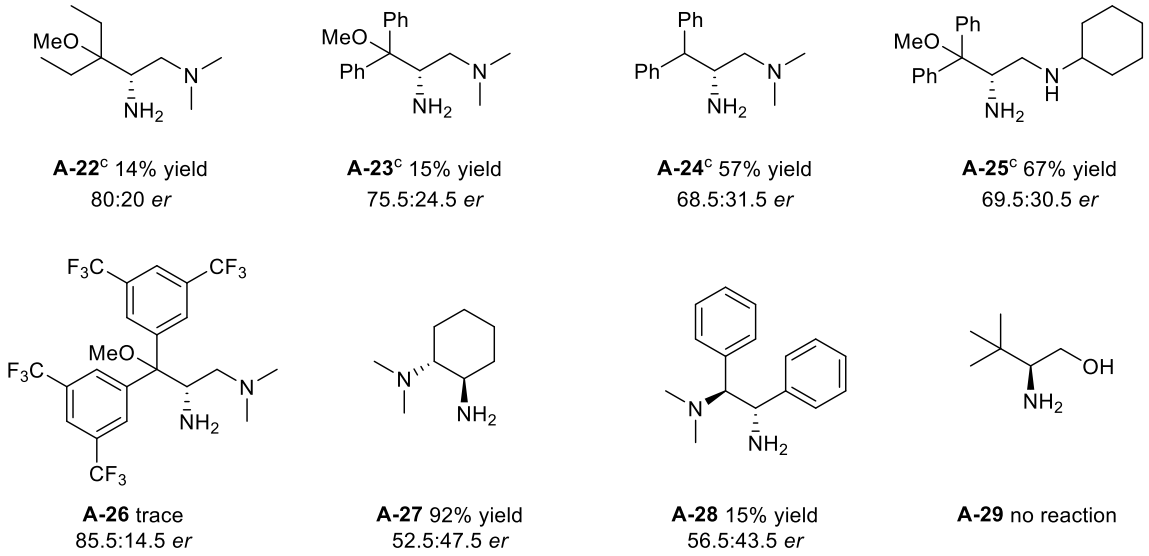
A-19 92% yield
73.5:26.5 *er*



A-20[c] 89 yield%
77.5:22.5 *er*



A-21 92% yield
55:45 *er*

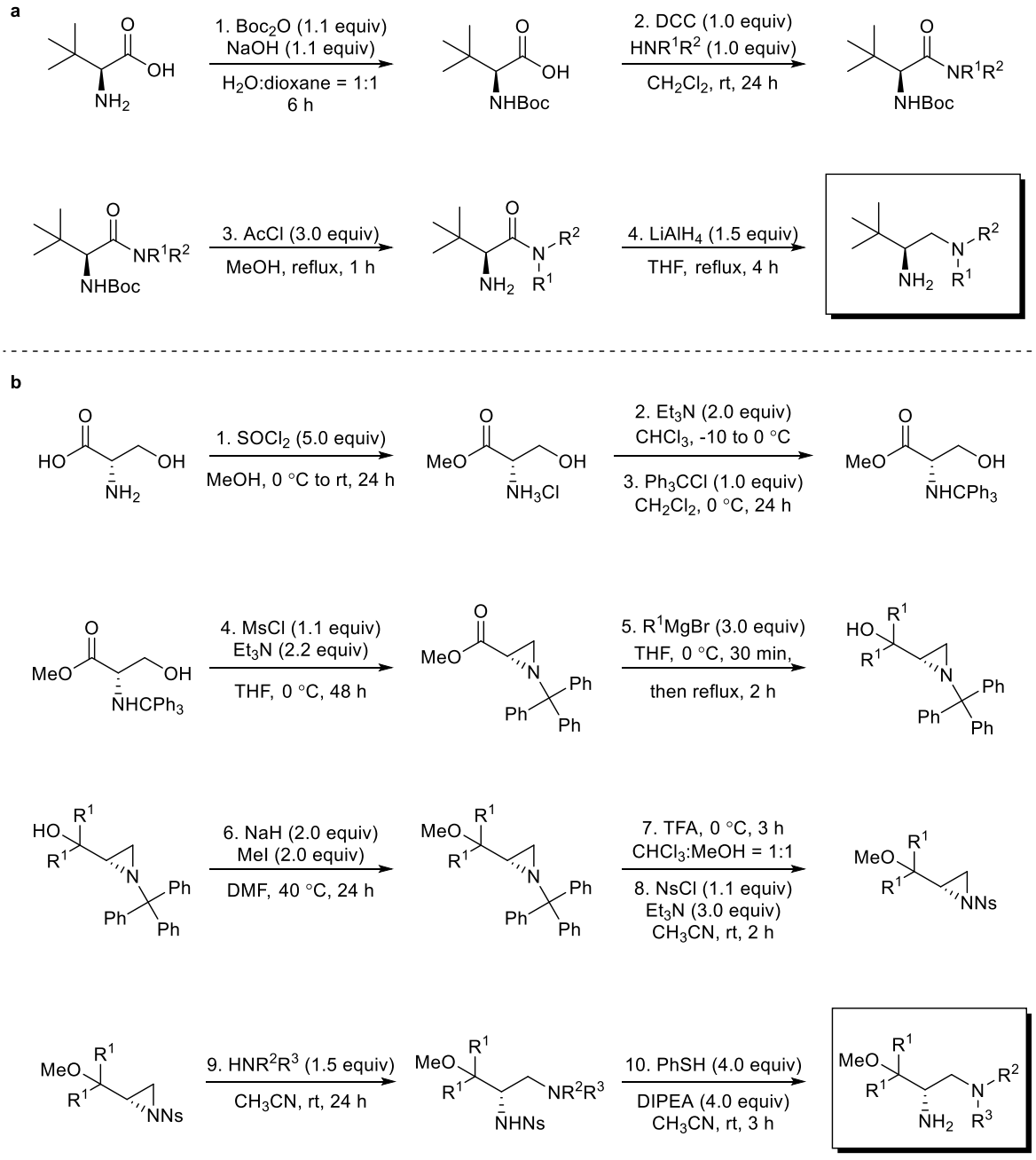


[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as an internal standard. [b]Determined by chiral HPLC analysis of the corresponding alcohol product of aldehyde reduction. [c]Reaction was in the solvent mixture of fluorobenzene:HFIP (v:v = 10:1).

Scheme 3-6. Screening of primary amines for the dual catalytic asymmetric allylation.

Compared to refining the tertiary/secondary amine unit, modification at the α-position of the primary amine was more challenging. From commercially available amino acids, 1,2-diamines **A-18** to **A-21** were prepared according to the method outlined in **Scheme 3-7a**. However, these amines did not provide the allylated product **3-15** in satisfying yield or enantioselectivity. Therefore, different 1,2-diamines with more sterically demanding substituents at the α-position of the primary amine unit were synthesized from L-serine (**Scheme 3-7b**).[24] Unfortunately, amines **A-22** and **A-23** gave the desired product in very low yield with similar *er* as compared to the conditions using **A-13**. It is possible that the primary amine units were not accessible for the branched aldehyde due to an increased steric bulk effect. Another explanation would be that the presence of a methoxy group rendered the amine less nucleophilic for enamine formation by inductive effects. Amine **A-24**, devoid of the methoxy group, afforded a much higher yield. This result is highly indicative that the reaction yield is affected by the nucleophilicity of the primary amine. Further structural modifications were not fruitful. Reaction with **A-25** gave a moderate yield and *er*. Although a superior enantioselectivity was observed when using **A-26**, the allylated product was obtained in trace amount presumably because **A-26** displayed a lack of nucleophilicity. Finally, new scaffolds were attempted using 1,2-diamines **A-27** and **A-28**, but

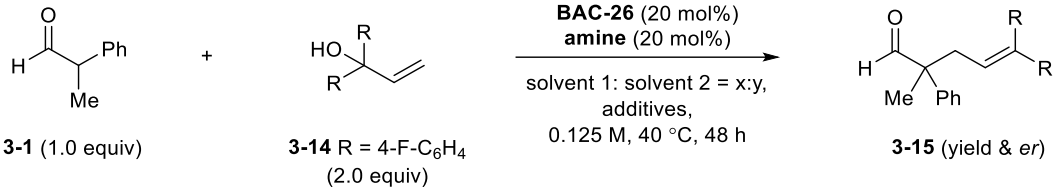
both resulted in low selectivity. The amino alcohol **A-29** was also unreactive under the reaction conditions (**Scheme 3-6**).



Scheme 3-7. General preparation methods for 1,2-diamines from amino acids: (a) from L-*tert*-leucine; (b) from L-serine.

3.4.2 Screening of conditions with primary amines

As described in the previous Section 3.4.1, structural modifications of the primary amine led to the use of 1,2-diamines, such as **A-13** and **A-19** for screening of other reaction parameters. Further solvent screening was performed primarily with **A-19** due to purification difficulties with **A-13**. In the following experiments, the desired product was observed along with different amounts of the rearranged alcohol and remaining starting material **3-14**. The amount of HFIP was explored first. It was found that, under the same reaction conditions, a lower proportion of HFIP was preferred since product **3-15** was isolated in lower *er* when DCM:HFIP (1:1) was used as solvent mixture (**Table 3-2**, entries 1-4). Replacing DCM with other solvents (entries 5-12) for the dual asymmetric allylation revealed that better yield (92%) and *er* (77.5:22.5) could be obtained in fluorobenzene (entry 7). Facile decomposition of the ferrocenium boronic acid **BAC-26** was observed when THF was used as the solvent (entry 12). Attempts to replace HFIP with other polar solvents such as trifluoroethanol (TFE) and nitromethane (CH_3NO_2) were also unsuccessful; only decomposition of **BAC-26** was observed in these cases (entries 13 and 14). A brief examination of other acid and base additives was performed. The addition of *p*-TsOH only resulted in the facile decomposition of allylic alcohols **3-14** as a result of its strong acidity (entry 15). In contrast, the use of diisopropylethylamine (DIPEA) led to decomposition of the ferrocenium unit of **BAC-26**. Consequently, the allylated product **3-15** was not observed (entry 16). Given the high sensitivity of ferrocenium boronic acid **BAC-26** in the presence of primary amines and the difficulty of structurally modifying the 1,2-diamines, further optimization of the dual catalytic asymmetric allylation of branched aldehydes with allylic alcohols using primary amines was discontinued.



entry	amine	solvent 1	solvent 2	x:y	additive	yield (%)[a]	er[b]
1	**A-19**	CH_2Cl_2	HFIP	1:1	-	81	62.5:37.5
2	**A-19**	CH_2Cl_2	HFIP	10:1	-	92	73.5:26.5
3	**A-19**	CH_2Cl_2	HFIP	20:1	-	85	75:25
4	**A-19**	CH_2Cl_2	-	-	-	n.r.	n.d.
5	**A-19**	DCE	HFIP	10:1	-	82	70:30
6	**A-19**	$CHCl_3$	HFIP	10:1	-	64	79:21
7	**A-19**	Ph-F	HFIP	10:1	-	92	77.5:22.5
8	**A-19**	Ph-H	HFIP	10:1	-	48	78.5:21.5
9	**A-19**	Ph-Me	HFIP	10:1	-	36	78:22
10	**A-19**	Ph-Cl	HFIP	10:1	-	87	77:23
11	**A-19**	Ph-CF_3	HFIP	10:1	-	86	74:26
12	**A-19**	THF	HFIP	10:1	-	n.r.	n.d.
13	**A-19**	Ph-F	TFE	10:1	-	n.r.	n.d.
14	**A-19**	Ph-F	CH_3NO_2	10:1	-	n.r.	n.d.
15	**A-13**	Ph-F	HFIP	10:1	TsOH[c]	10	n.d.
16	**A-13**	Ph-F	HFIP	10:1	DIPEA[c]	n.r.	n.d.

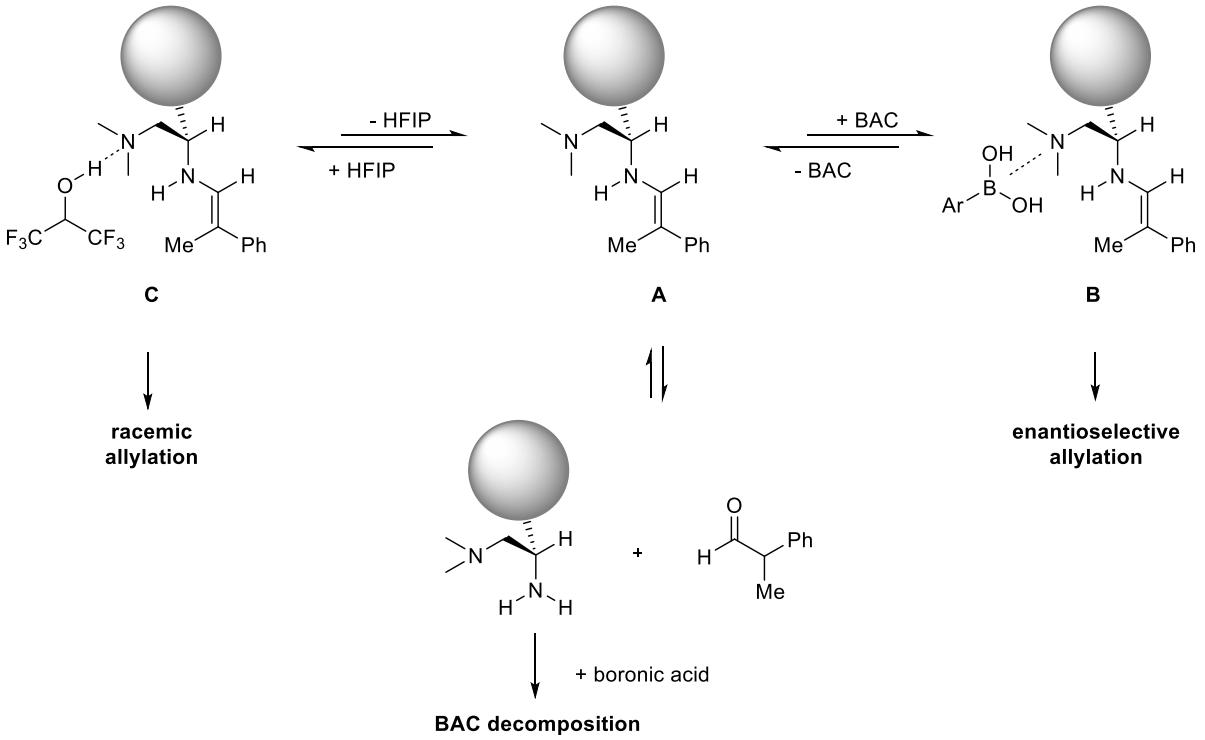
[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as an internal standard. [b]Determined by chiral HPLC analysis of the corresponding alcohol product of aldehyde reduction. [c]Reaction was run with 20 mol% of the indicated additive.

Table 3-3. Screening of solvents and additives for dual catalytic allylation with primary amine.

3.4.3 Proposed interaction of catalysts, starting materials and HFIP

To explain the observed experimental results, a possible model for the interaction between the primary amine, aldehyde, and boronic acid in HFIP is proposed (**Scheme 3-8**). Condensation of the primary amine and aldehyde leads to the formation of the desired reactive enamine **A**. Since amino ester **A-10** provided almost no selectivity for the allylation compared to **A-13**, a reversible interaction of the boronic acid and the tertiary amine moiety from the enamine is proposed to bring the catalysts into close proximity for the enantioselective allylation (shown as **B**). Although the nature of this interaction is not clear, presumably occurring through hydrogen bonding or acid-base interactions, it is expected to partially influence the enantioselectivity since increasing

the steric hindrance of the amine led to lower *er* (**Scheme 3-6**, **A-12**, **A-13** and **A-14**). Considering the similar pK_a of HFIP (9.3) and a protonated tertiary ammonium (10.8), a reversible interaction between HFIP and the tertiary amine moiety from the enamine through hydrogen bonding cannot be excluded (shown as **C**). Occupancy of the tertiary amine unit by HFIP instead of the boronic acid might favor the racemic attack to the allyl carbocation, since the use of increased amount of HFIP led to a lower *er* (**Table 3-3**, entries 1-3). It is believed that the use of HFIP is critical, not only for stabilization of the allyl carbocation, but also for stabilization of the catalyst **BAC-26**. Facile decomposition of **BAC-26** was observed without HFIP (**Table 3-3**, entry 4). This suggests that the hydrogen bonding between HFIP and the enamine could partially inhibit the decomposition of ferrocenium boronic acid by the 1,2-diamine.

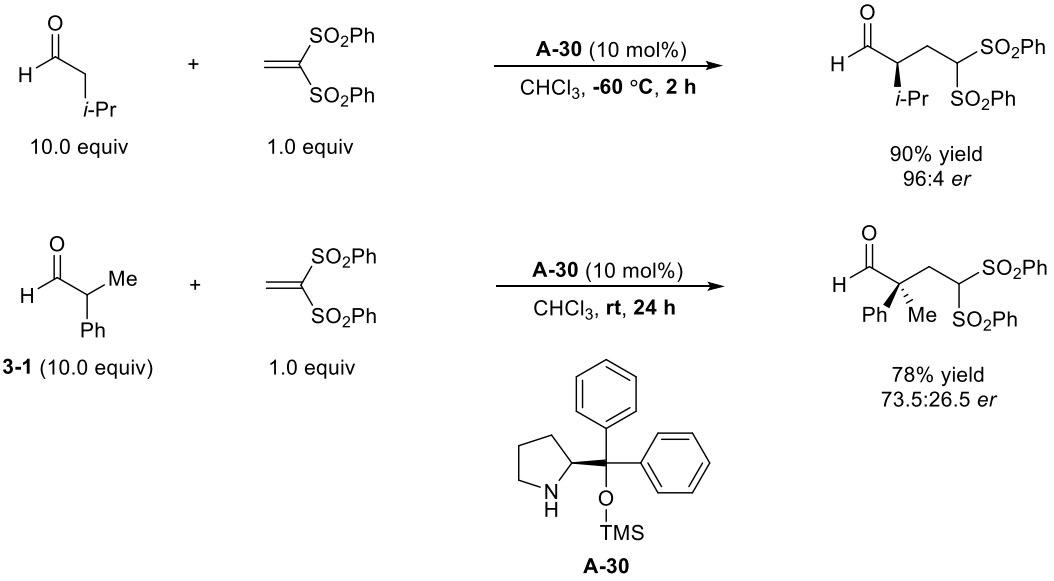


Scheme 3-8. Proposed interaction between chiral 1,2-diamine, aldehyde, HFIP and boronic acid.

3.4.4 Screening of cyclic secondary amines

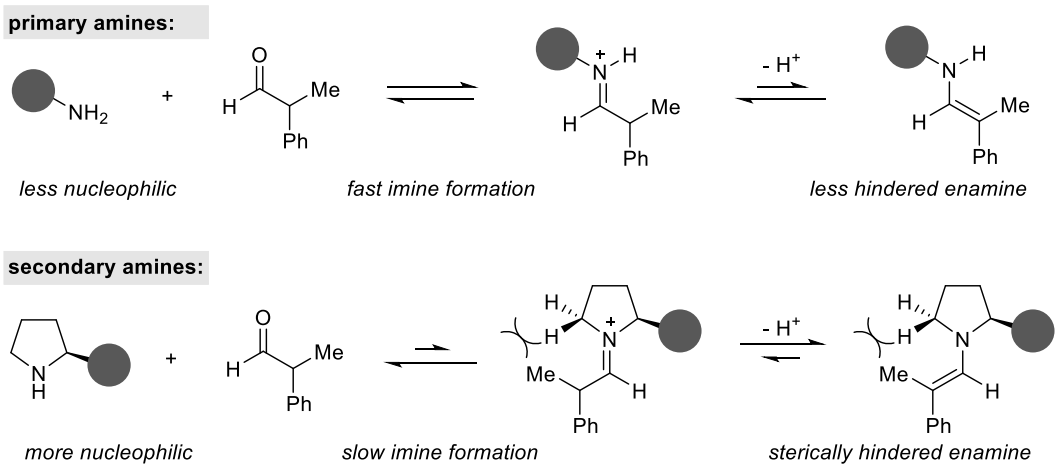
Despite many reports on successful functionalization of linear aldehydes using cyclic secondary amine catalyst, similar reactions with branched aldehydes have met greater challenges. An

example for a direct comparison of the catalytic reactivity of chiral cyclic secondary amines with both linear and branched aldehydes is given in **Scheme 3-9**. With the same chiral secondary amine **A-30**, α-alkylation of the linear aldehydes with vinyl sulfones provided the alkylated products in high yield and enantioselectivity, while a much inferior result was obtained using α branched aldehyde **3-1**.[25]



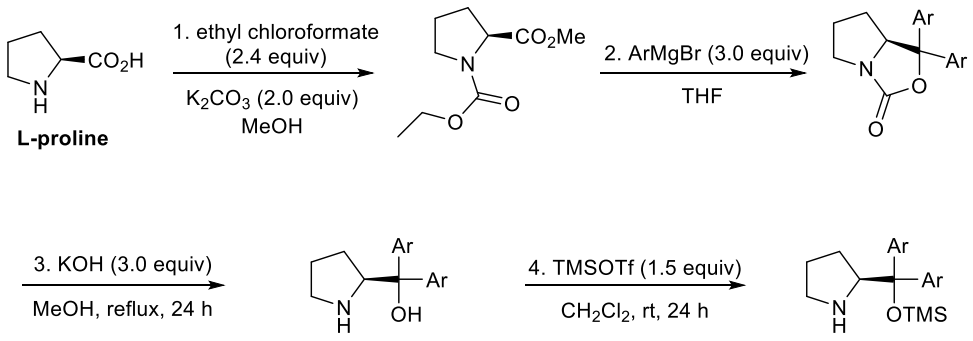
Scheme 3-9. A specific example of comparison of α-functionalization of linear and branched aldehydes using chiral secondary amine **A-30**.

The low efficiency of these cyclic secondary amines in the functionalization of α-branched aldehydes has been attributed to the relatively slow formation of the enamine intermediates in comparison with primary amines. Although cyclic secondary amines are more nucleophilic than primary amines,[26] these chiral secondary amines are much more sterically hindered and thus less suitable for condensation with α-branched aldehydes (**Scheme 3-10**).[20] Nevertheless, chiral secondary amines, such as the Jørgensen's catalyst (**A-31**, **Scheme 3-12**),[27] were investigated for the dual catalytic asymmetric allylation system of interest with **BAC-26**.

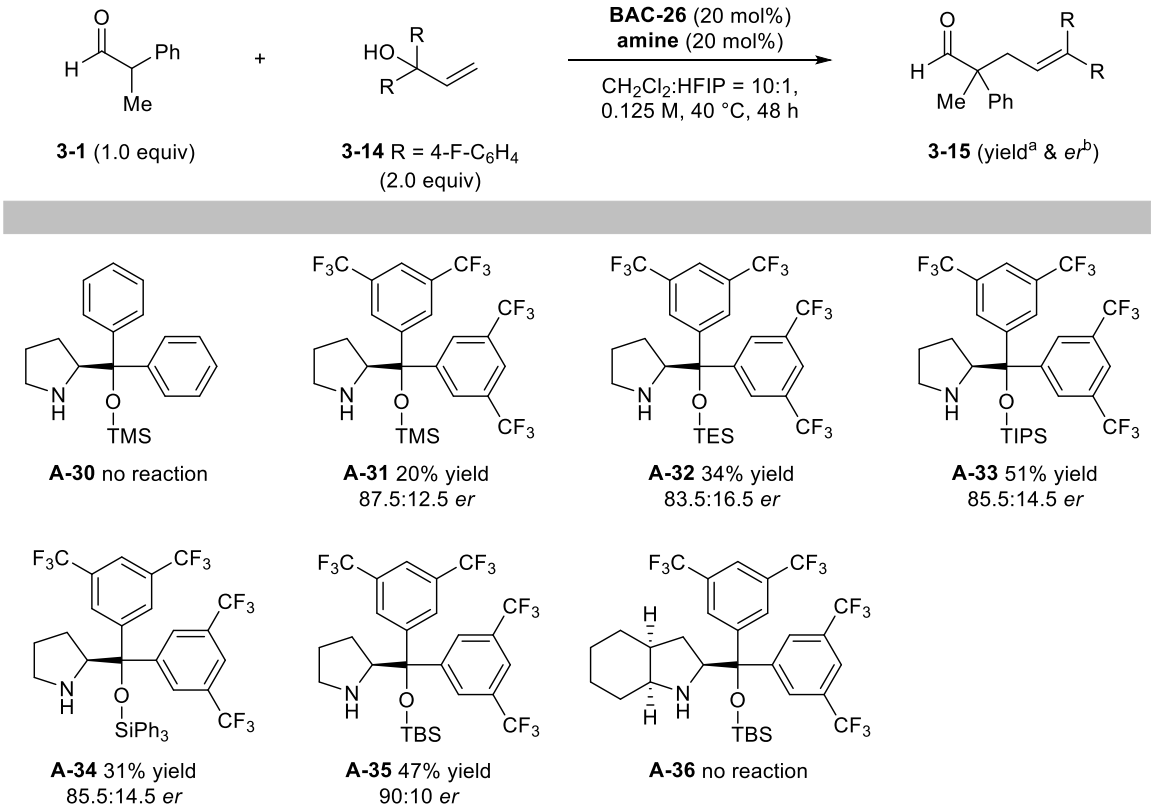


Scheme 3-10. Comparison of the efficiency of primary amines and cyclic secondary amines in the condensation with branched aldehydes.

Following the synthetic sequence from L-proline described in **Scheme 3-11**, secondary amines **A-30** to **A-36** were prepared (**Scheme 3-12**). Unsurprisingly, when secondary amine **A-30** was used, no desired product was observed. It is possible that the amine of **A-30** is too nucleophilic, which led to deactivation of the boronic acid since both starting branched aldehyde **3-1** and allylic alcohol **3-2** were recovered. The use of a less nucleophilic amine **A-31** gave a low yield, but a relatively high *er* of product **3-15**. Encouraged by this result, secondary amines with different silyl protecting groups were then synthesized and tested (**A-32** to **A-36**). While the product **3-15** was obtained in only a moderate yield of 47%, allylation with **A-35** provided the highest enantioselectivity (90:10 *er*) of all the amines tested. As expected, the more sterically hindered **A-36** was not reactive in the allylation reaction, with only recovered branched obtained.



Scheme 3-11. Representative preparation method for the synthesis of the Jørgensen's amines.



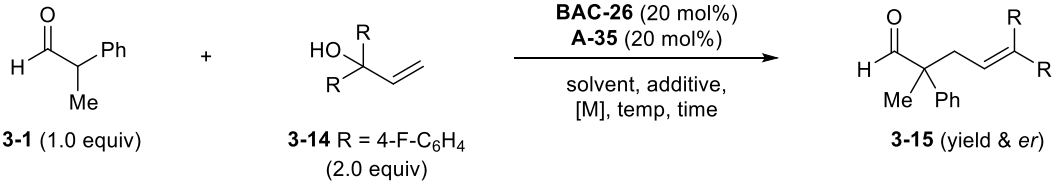
[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as an internal standard. [b]Determined by chiral HPLC analysis of the corresponding alcohol product of aldehyde reduction.

Scheme 3-12. Screening of secondary amines for the dual catalytic asymmetric allylation.

3.4.5 Screening of conditions with secondary amine A-35

With amine **A-35** in hand, other reaction parameters such as the reaction solvent, temperature, time, and the effect of additives, concentration were examined (**Table 3-4**). The most significant side product was still the rearranged alcohol in these attempts. The use of a toluene and HFIP mixture (10:1) as a promising solvent system was quickly identified (entries 1-6) providing product **3-15** in good *er* (95.5:4.5), albeit, in low yield 32%. Since a satisfactory *er* was obtained, more effort was put into increasing the reaction yield. It was soon discovered that neither changing the temperature nor prolonging the reaction time helped improve the formation of the product (entries 7-9). The low yield of **3-15** was attributed to the sluggish enamine formation between **A-35** and the hindered branched aldehyde. Different additives such as water, acetic acid[28] and Et_3N were reported to promote a faster enamine formation and equilibrium. However, no improvement of the yield was observed (entries 10-12). Due to the sensitivity of the dual

catalytic system, efforts towards identifying an additive to promote faster enamine formation were discontinued. Finally, a slightly increased yield was observed when a higher concentration was used (entries 13 and 14).



3-1 (1.0 equiv) **3-14** R = 4-F-C_6H_4 (2.0 equiv) **3-15** (yield & *er*)

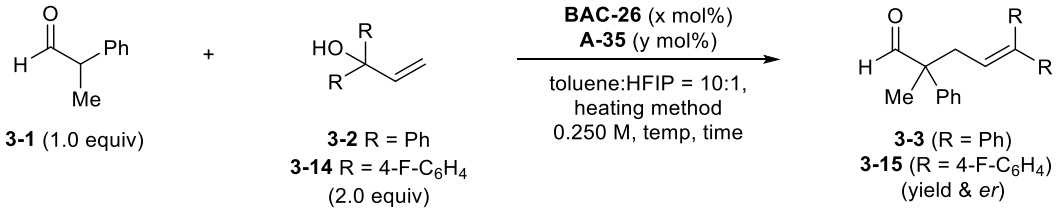
entry	solvent	T (°C)	t (h)	[M]	additive[c]	yield (%)[a]	er[b]
1	CH_2Cl_2:HFIP = 10:1	40	48	0.125	-	47	90:10
2	DCE:HFIP = 10:1	40	48	0.125	-	40	88.5:11.5
3	Ph-F:HFIP = 10:1	40	48	0.125	-	36	93:7
4	Ph-Me:HFIP = 10:1	40	48	0.125	-	32	95.5:4.5
5	Ph-Me:HFIP = 1:1	40	48	0.125	-	18	n.d.
6	Ph-Me	40	48	0.125	-	4	n.d.
7	Ph-Me:HFIP = 10:1	60	48	0.125	-	26	92.5:7.5
8	Ph-Me:HFIP = 10:1	25	48	0.125	-	14	n.d.
9	Ph-Me:HFIP = 10:1	40	144	0.125	-	36	n.d.
10	Ph-Me:HFIP = 10:1	40	48	0.125	H_2O[c]	24	93:7
11	Ph-Me:HFIP = 10:1	40	48	0.125	AcOH[d]	29	93.5:6.5
12	Ph-Me:HFIP = 10:1	40	48	0.125	Et_3N[d]	n.r.e	n.d.
13	Ph-Me:HFIP = 10:1	40	48	0.050	-	17	n.d.
14	Ph-Me:HFIP = 10:1	40	48	0.250	-	36	95:5

[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as an internal standard. [b]Determined by chiral HPLC analysis of the corresponding alcohol product of aldehyde reduction. [c]Reaction was run with 100 mol% of the indicated additive. [d]Reaction was run with 20 mol% of the indicated additive. [e]Decomposition of **BAC-26** was observed.

Table 3-4. Screening of other reaction parameters in the asymmetric allylation with secondary amine-Part 1.

Further attempts to improve the reaction yield with **A-35** are listed in **Table 3-5**. To obtain a better conversion, the catalyst ratio was re-examined. Unfortunately, increasing the amount of either boronic acid or amine resulted in lowered or no conversion to the desired product. The use of excess boronic acid promoted a faster 1,3-rearrangement of **3-14** and supressed the reactivity of the amine (**Table 3-5**, entries 1 and 2). The presence of excess amine also afforded low yields (entries 3 and 4). These results suggested that a 1:1 ratio of both catalysts had to be maintained. Thus, a higher yield (42%) of **3-15** was obtained with 30 mol% of both catalysts

(entry 5). As described by Bräse and co-workers, faster enamine formation of branched aldehydes with secondary amines can be achieved under microwave irradiation conditions.[29] When applied to the asymmetric allylation, this protocol led to a slightly increased yield of **3-15**, the reaction time was reduced to 12 hours (entry 6). Since all the previous attempts were somewhat less productive (**Table 3-5**, entries 1-6), the allylic alcohol was then re-examined. Considering that the enamine formation was sluggish, it was thought that the use of a more ionizable allylic alcohol could potentially compensate for the low concentration of the enamine partner. Indeed, a two-fold catalytic turnover was observed when allylic alcohol **3-2** was used. The corresponding product **3-3** was isolated in moderate yield and good *er* (entry 7). At this point, the optimization of the dual-catalyzed asymmetric allylation was concluded.



entry	alcohol	x	y	heating method	T (°C)	t (h)	yield (%)[a]	er[b]
1[c]	**3-14**	40	20	oil bath	40	48	22	n.d.
2[c]	**3-14**	100	20	oil bath	40	48	n.r.	n.d.
3[c]	**3-14**	20	40	oil bath	40	48	17	n.d.
4[c]	**3-14**	20	100	oil bath	40	48	11	n.d.
5	**3-14**	30	30	oil bath	40	48	42	95:5
6	**3-14**	30	30	microwave	60	12	47	94:6
7	**3-2**	30	30	microwave	60	12	60[d]	94:6

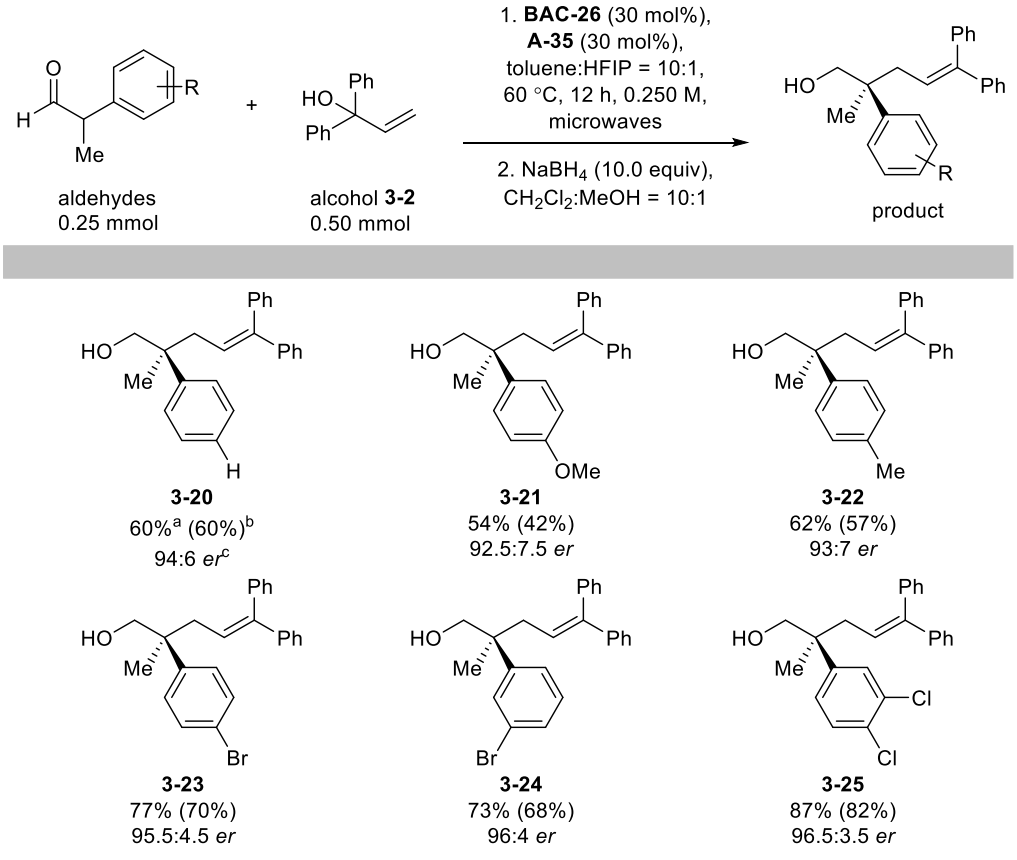
[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as an internal standard. [b]Determined by chiral HPLC analysis of the corresponding alcohol product after aldehyde reduction. [c]Reaction was run in 0.125 M concentration. [d]Isolated yield of product **3-3**.

Table 3-5. Screening of other reaction parameters in the asymmetric allylation with secondary amine-Part 2.

3.5 Scope of the dual catalytic asymmetric allylation

With the optimized conditions for the dual-catalyzed asymmetric allylation in hand (**Table 3-5**, entry 7), the substrate scope for the branched aldehydes was examined (**Scheme 3-13**, **3-14** and **3-16**). The allylated aldehydes were reduced to the corresponding alcohol for isolation purpose. When branched aldehydes with electron rich arenes were used, the allylated products

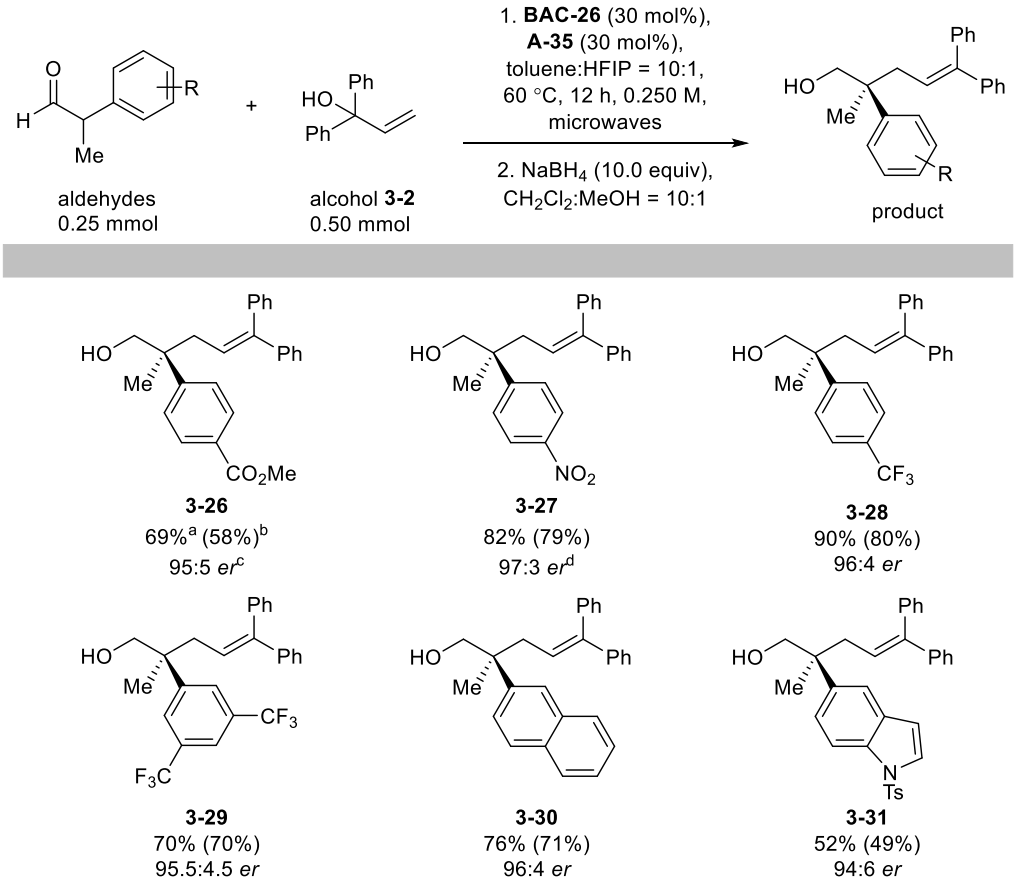
3-21 and **3-22** were isolated in moderate yield. It is suspected that these electron rich aldehydes are less electrophilic, which leads to slow enamine formation and lower yields. Moreover, the *E*/*Z* enamine equilibrium is also slow, since the α-proton of the aldehydes are less acidic, which resulted in a lower enantioselectivity (**Scheme 3-17a**). Although List and co-workers have reported better results with allylated aldehydes similar to **3-21** and **3-22**,[12] it was satisfying to find that our dual catalytic method displays a broader functional group tolerance. Branched aldehydes with haloaryl substituents (such as –Cl and –Br) served as good coupling partners in the protocol. The chlorinated and brominated products **3-23** to **3-25** were isolated in good yield and high *er* (up to 96.5:3.5). The construction of these all carbon quaternary centers with halogenated arenes is amenable to further functionalization using cross-coupling reactions. To the best of our knowledge, palladium and enamine dual catalysis has not been achieved for the asymmetric allylation of branched aldehydes with brominated arenes.[11,12]



[a]Yield of the first step were determined by ^{1}H NMR analysis of the reaction crude mixture with 1,4-dinitrobenzene as an internal standard. [b]Isolated yield over two steps of the alcohol product of aldehyde reduction. [c]Determined by chiral HPLC analysis of the alcohol product.

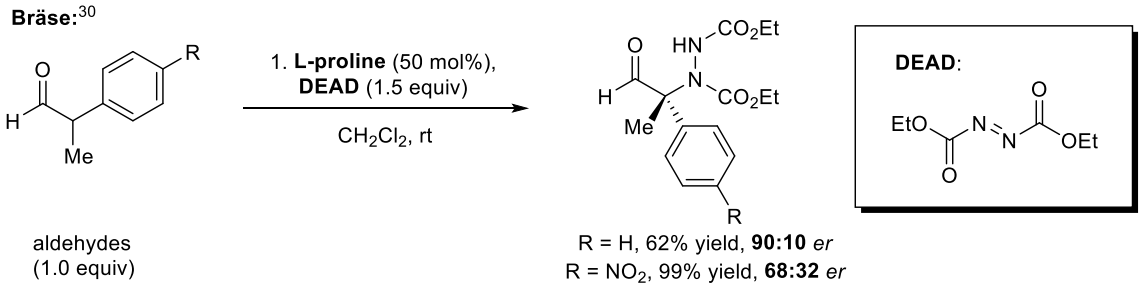
Scheme 3-13. Scope of branched aldehydes for the dual catalytic asymmetric allylation-Part 1.

Moreover, as highly challenging substrates, branched aldehydes with aryl units bearing electron withdrawing groups (–CO_2Me, –NO_2 and –CF_3) were also suitable substrates in our reaction protocol. As previously examined by Bräse and co-workers (**Scheme 3-15**),[30] asymmetric functionalization of these aldehydes generally suffers from a severe racemic background reaction due to facile enol isomerization from the increased acidity of the α-protons (**Scheme 3-17b**).[29] In our case, such a background enol allylation was not observed. Thus, products **3-26** to **3-29** were isolated in high enantiomeric excess. In addition, the asymmetric allylation performed well with aldehydes containing extended arene systems such as a naphthyl group (**3-30**). An aldehyde with a protected indolyl group also gave moderate yield and good *er* of product **3-31**, which demonstrates the applicability of our method to substrates with heterocycles and increased functionalities.



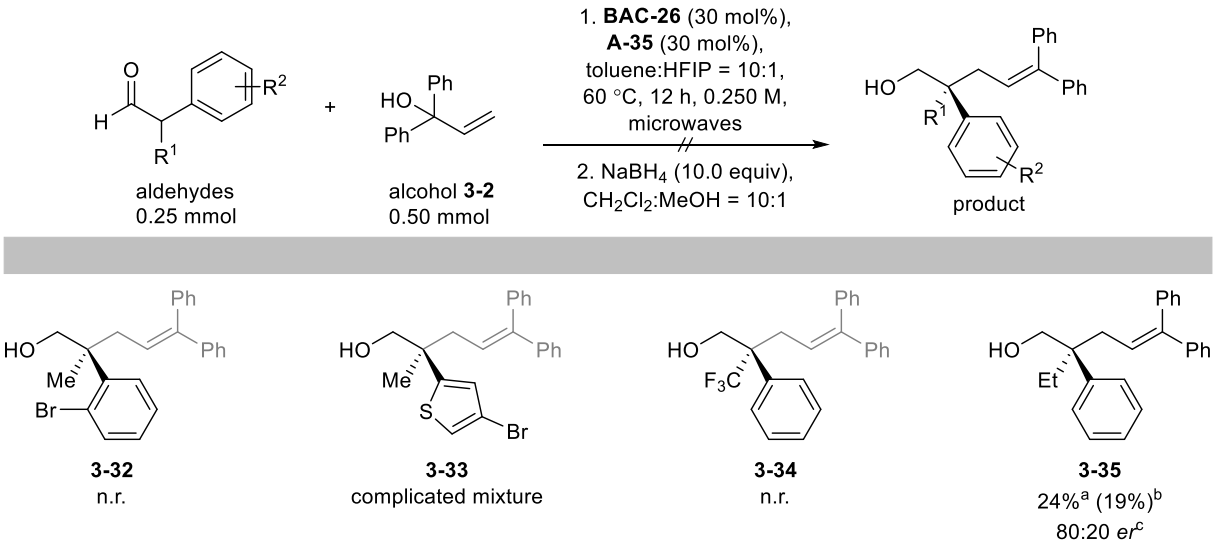
[a]Yield of the first step were determined by ^{1}H NMR analysis of the reaction crude mixture with 1,4-dinitrobenzene as an internal standard. [b]Isolated yield over two steps of the alcohol product of aldehyde reduction. [c]Determined by chiral HPLC analysis of the alcohol product. [d]Enantiomeric ratio of **3-27** was obtained by Mosher's acid analysis of the reduced alcohol product.

Scheme 3-14. Scope of branched aldehydes for the dual catalytic asymmetric allylation-Part 2.



Scheme 3-15. Difficult α-functionalization of branched aldehydes with electron poor arenes.

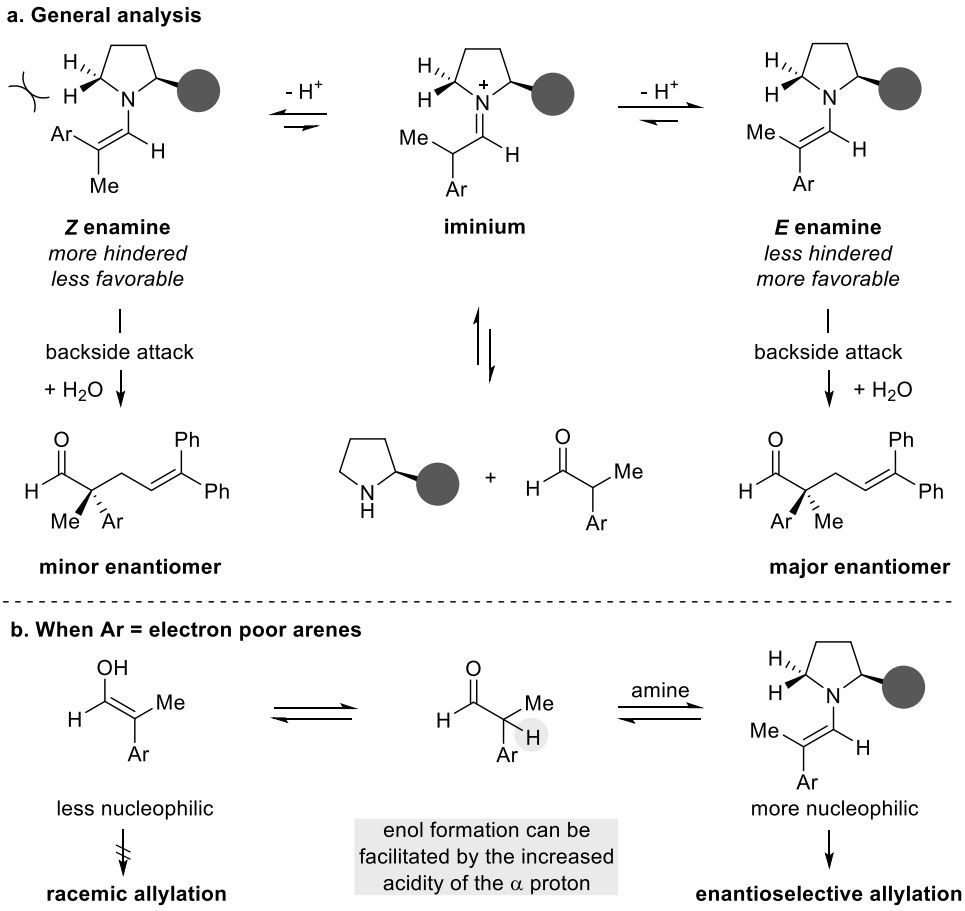
Substrates that are too sterically hindered did not perform well in the reaction. For instance, when a branched aldehyde with an aryl unit bearing an *ortho*-bromo substituent was used, the desired product **3-32** was not observed. The starting aldehyde was not consumed. Similarly, a branched aldehyde with an ethyl side chain also exhibited poor reactivity providing a low yield and low *er* of the product **3-35** (19%, 80:20). A branched aldehyde with a thiophene moiety provided a complicated mixture in the reaction conditions, which could result from the oxidation of the thiophene unit by the ferrocenium cation. It was also discovered that an aldehyde with a trifluoromethyl side chain was not suitable for the allylation due to the lack of nucleophilicity of the corresponding enamine; product **3-34** was not formed.



[a]Yield of the first step were determined by ^{1}H NMR analysis of the reaction crude mixture with 1,4-dinitrobenzene as an internal standard. [b]Isolated yield over two steps of the alcohol product of aldehyde reduction. [c]Determined by chiral HPLC analysis of the alcohol product.

Scheme 3-16. Scope of branched aldehydes for the dual catalytic asymmetric allylation-Part 3.

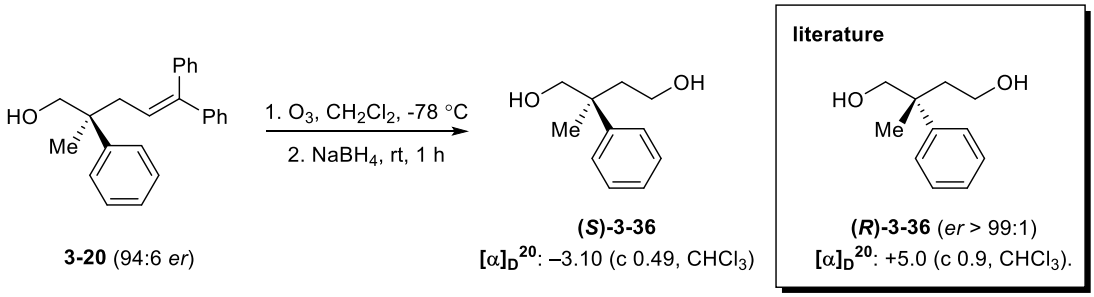
Based on the observations of the current system for allylation of branched aldehydes, a general analysis is proposed in **Scheme 3-17a**. Condensation of the aldehydes and the chiral secondary amine can result in both *E* and *Z* enamines. With decreased steric hindrance, the *E* enamine is the thermodynamically favored species.[28] Allylation of the allylic carbocation by the *E* enamine provides the major enantiomer. A faster equilibrium between the *E* and *Z* enamine will result in higher reaction yield and selectivity. Nucleophilic attack from the enamine to the carbocation occurs at the backside of the enamine presumably, since the front face, as depicted in **Scheme 3-17a**, is shielded. With more acidic α-protons, branched aldehydes with electron poor arenes are presumed to undergo a faster equilibrium favoring the *E* enamine, which afforded a higher reaction efficacy. Although the enol allylation can also be facilitated due to the increased acidity of α-protons, such a racemic background allylation is not observed (**Scheme 3-17b**). This effect is attributed to the lower nucleophilicity of the corresponding enols compared to the enamine and the relative low concentration of the allylic carbocation in solution.



Scheme 3-17. Stereochemical analysis of the dual catalytic asymmetric allylation using **A-35**.

3.6 Determination of the absolute stereochemistry

In order to determine the absolute stereochemistry of the products of this dual catalytic asymmetric allylation, derivatization of compound **3-20** to compound **3-36** by sequential ozonolysis and reduction was performed. The absolute configuration of compound **3-36** was determined as **(*S*)** according to a chemical correlation with the known compound **(*R*)-3-36** reported by Aggarwal and co-workers (**Scheme 3-18**).[31] The absolute configuration of all other compounds was assigned by analogy based on a uniform reaction mechanism. The obtained **(*S*)** configuration of the allylated product supports a nucleophilic attack from the *E* enamine to the carbocation, as illustrated in **Scheme 3-17**.

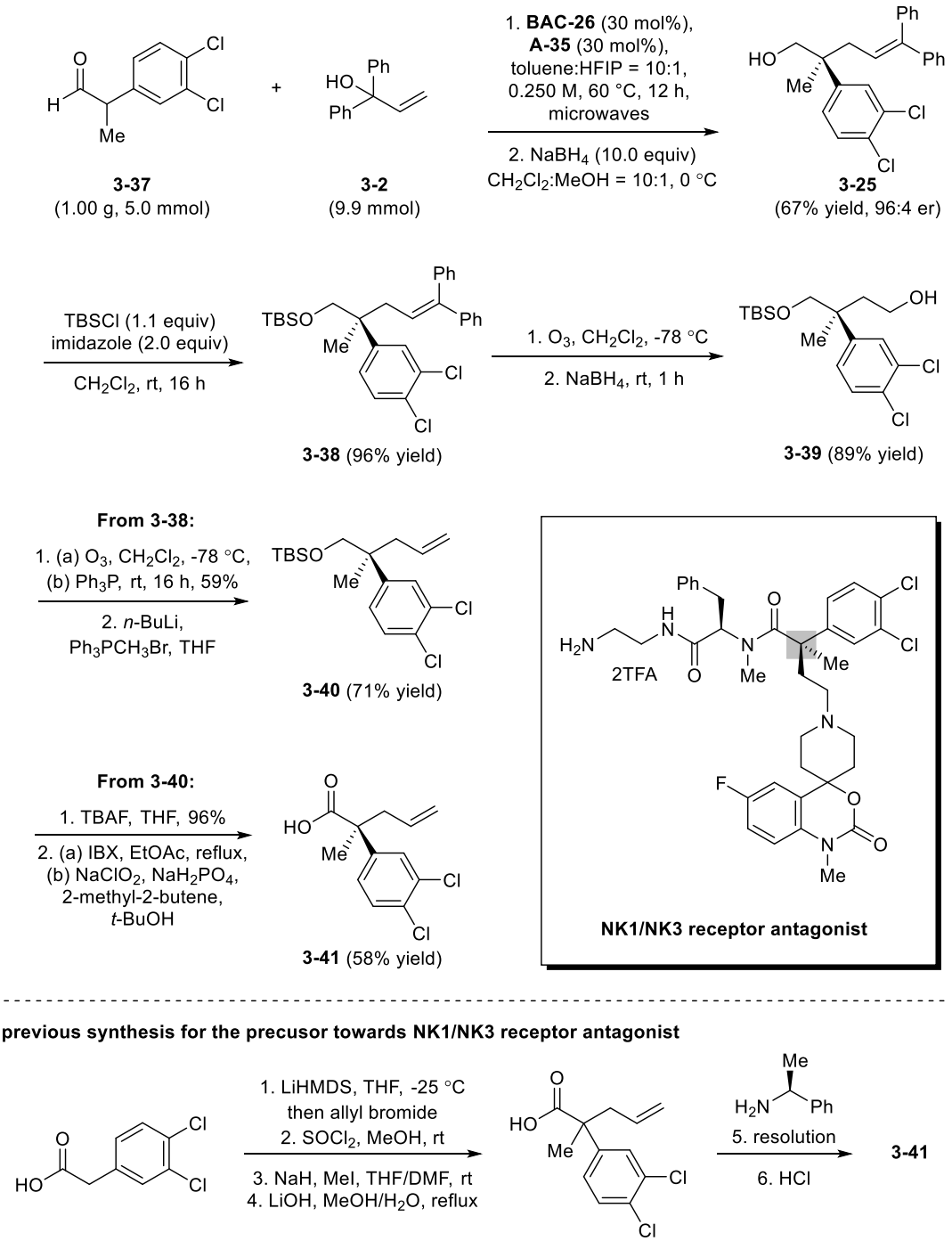


Scheme 3-18. Determination of absolute stereochemistry of allylated products.

3.7 Application of the dual catalytic asymmetric allylation

To demonstrate the application of the dual catalytic asymmetric allylation, a gram-scale synthesis was performed using branched aldehyde **3-37** (1.00 g, 4.95 mmol) and allylic alcohol **3-2**. Gratifyingly, the allylated product **3-25** was isolated in a comparable yield and excellent enantioselectivity after two steps (**Scheme 3-19**). The slight loss of yield could possibly arise from a less sufficient stirring mechanics and heat transfer on a large scale. The application of the method was further demonstrated through the first catalytic asymmetric synthesis of a precursor for an NK1/NK3 receptor antagonist.[15] Protection of compound **3-25** with TBSCl afforded the silyl ether **3-38** in a near-quantitative yield. Upon ozonolysis, the diphenyl alkene moiety of compound **3-38** was successfully removed and after a reductive work up, chiral alcohol **3-39** was obtained. The diphenyl alkene moiety of **3-38** could also be converted into a new alkene by sequential ozonolysis and Wittig olefination, providing product **3-40**. Further deprotection of the TBS group and Pinnick oxidation of **3-40** provided chiral acid **3-41**. Both **3-39**

and **3-41** could serve as convenient synthetic precursors for the NK1/NK3 receptor antagonist (**Scheme 3-19**). For comparison, a previously reported synthetic sequence to obtain compound **3-41** by resolution of a diastereomeric salt is also presented in **Scheme 3-19**.[15]

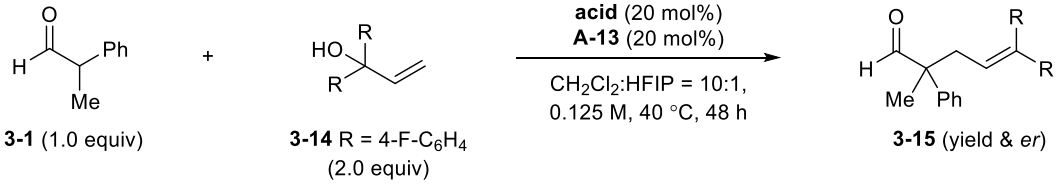


Scheme 3-19. Application of the dual catalytic asymmetric allylation: gram-scale reaction and the synthesis of precursor **3-41** for NK1/NK3 receptor antagonist.

3.8 Comparison and mechanistic studies of the dual catalytic asymmetric allylation

3.8.1 Comparison experiments with other acid catalysts

During the course of the comprehensive reaction optimization process, comparison experiments between ferrocenium boronic acid **BAC-26** and other acid catalysts against were performed at various stages to assess the potential advantages of our method *via* BAC. These results are listed in **Table 3-6**, **3-7** and **3-8**, which demonstrate the superior reactivity of **BAC-26**. With primary amine **A-13**, asymmetric allylation using $InBr_3$ only provided the product **3-15** in a low yield of 15% with no enantioselectivity (**Table 3-6**, entry 2).[8] It is possible that the facile chelation of 1,2-diamine **A-13** with $InBr_3$ inhibited its Lewis acidity for the ionization of the allylic alcohol. Since *p*-TsOH is also known to promote similar reactions,[9] a direct comparison with **BAC-26** (entry 1) was also conducted under the same reaction conditions. Although the reaction with *p*-TsOH provided a moderate 60% yield of product **3-15**, a drastically decreased enantioselectivity was observed under these Brønsted acidic conditions, possibly due to the racemic background enol allylation (entry 3).



3-1 (1.0 equiv) **3-14** R = 4-F-C_6H_4 (2.0 equiv) **3-15** (yield & *er*)

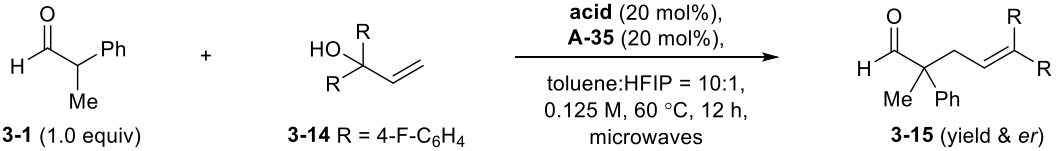
entry	acid	yield (%)[a]	er[b]
1	**$InBr_3$**	15	50:50
2	**BAC-26**	86	76.5:23.5
3	***p*-TsOH**	60	59.5:40.5

[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as an internal standard. [b]Determined by chiral HPLC analysis of the corresponding alcohol product of aldehyde reduction.

Table 3-6. Comparison experiments with other acid catalysts using primary amine **A-13**.

Similar comparison experiments using secondary amine **A-35** were also performed (**Table 3-7**). Ferrocenium boronic acid **BAC-26** still provided the highest yield (32%, entry 1) compared to

$InBr_3$ (21%, entry 2), *p*-TsOH (<5%, entry 3), tetrafluorophenyl boronic acid **BAC-16** (12%, entry 4) and pentafluorophenyl boronic acid **BAC-15** (5%, entry 5).



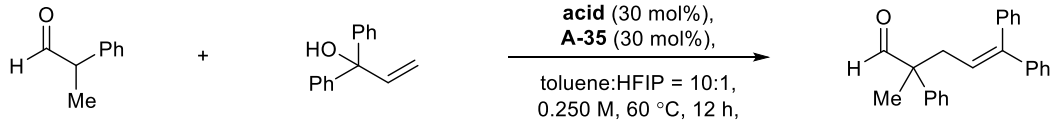
3-1 (1.0 equiv) + **3-14** R = 4-F-C_6H_4 (2.0 equiv) → **3-15** (yield & *er*)

entry	acid	yield (%)[a]	er[b]
1	**BAC-26**	32	95.5:4.5
2	**$InBr_3$**	21	93:7
3	***p*-TsOH**	<5	n.d.
4	**BAC-16**	12	n.d.
5	**BAC-15**	5	n.d.

[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as an internal standard. [b]Determined by chiral HPLC analysis of the corresponding alcohol product of aldehyde reduction.

Table 3-7. Comparison experiments with other acid catalysts with secondary amine **A-35** Part 1.

Lastly, other acid catalysts for the asymmetric allylation were also tested with the optimal conditions (**Table 3-8**). Notably, the conditions used in **Table 3-8** differ from that in **Table 3-7**. While decent yield and high enantioselectivity was achieved with **BAC-26** (entry 1), reactions using $FeCl_3$ and TFA[32] afforded low yield and slightly lower *er* (entry 2 and 3). The performance of these strong Lewis or Brønsted acid could be attributed to the high tendency of catalyst deactivation with the amine.



3-1 (1.0 equiv) + **3-2** (2.0 equiv) → **3-3** (yield & *er*)

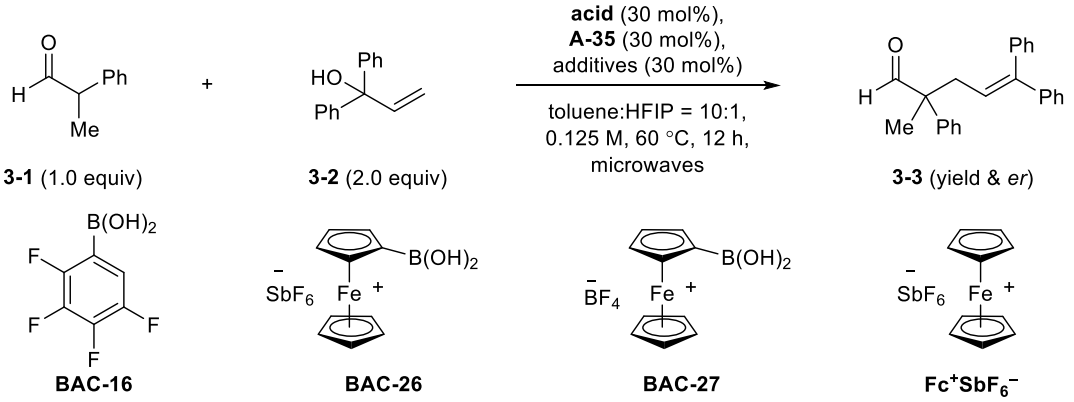
entry	acid	yield (%)[a]	er[b]
1	**BAC-26**	60	94:6
2	**$FeCl_3$**	17	92:8
3	**TFA**	18	88:12

[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as an internal standard. [b]Determined by chiral HPLC analysis of the corresponding alcohol product of aldehyde reduction.

Table 3-8. Comparison experiments with other acid catalysts with secondary amine **A-35** Part 2.

3.8.2 Mechanistic controls of the dual catalytic asymmetric allylation

Mechanistic controls were performed to reveal the nature and the effective components of the novel ferrocenium boronic acid **BAC-26** (**Table 3-9**). As discussed in Chapter 2, it is proposed that the superior reactivity of **BAC-26** can be partially attributed to the non-coordinating anion SbF_6, which induces an ion exchange mechanism. Therefore, the SbF_6 anion was replaced with other anions in the ferrocenium boronic acid salt, which should result in a significant change in the yield. As expected, when the reaction was performed with **BAC-27** (containing the BF_4 anion) or an iodide additive, a lower yield and *er* of product **3-3** was obtained (entries 1-3). Without a boronic acid moiety present in the structure, the reaction using ferrocenium salt ($\mathbf{Fc^+SbF_6^-}$) also afforded the product **3-3**, however, with no catalytic turnover (entry 4). Although this result confirms the critical role of the boronic acid, cooperative activation of the alcohol from the electrophilic ferrocenium and the boron center cannot be ruled out. Moreover, the superior activity of **BAC-26** does not come from the possible protodeboronation of the catalyst since the combined use of $\mathbf{Fc^+SbF_6^-}$ and boric acid or **BAC-16** also provided low yield (entries 5 and 6).



entry	acid	additives	yield (%)[a, b]	er[c]
1	**BAC-26**	-	60 (60)	94:6
2	**BAC-27**	-	43 (34)	93:7
3	**BAC-26**	$(n\text{-Bu})_4NI$	32 (26)	89:11
4	$\mathbf{Fc^+SbF_6^-}$	-	35	93:7
5	$\mathbf{Fc^+SbF_6^-}$	boric acid	38 (38)	93.5:6.5
6	$\mathbf{Fc^+SbF_6^-}$	**BAC-16**	32 (32)	94:6

[a]Yields were determined by ^1H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as an internal standard. [b]Isolated yield in parentheses indicates product obtained over two steps after reduction of the aldehyde into corresponding alcohol. [c]Determined by chiral HPLC analysis of the corresponding alcohol product of aldehyde reduction.

Table 3-9. Investigation of the active components in **BAC-26** for the dual asymmetric allylation.

3.8.3 ^{11}B NMR studies of the dual catalytic asymmetric allylation

The possible interaction between boronic acid **BAC-26** and amine **A-35** was explored through ^{11}B NMR study and mass spectrum analysis. The ferroceniumboronic acid SbF_6 salt **BAC-26** (17 mg) was dissolved in the reaction solvents (10:1 toluene-*d8*:HFIP, 0.6 mL) without the amine and was subjected to ^{11}B NMR analysis, as shown in **Figure 3-2**. According to the previous study (see Chapter 2, section 2.10.4), the peak at 37.9 ppm is attributed to the free boronic acid of **BAC-26**. In addition, the peak at 18.1 ppm is assigned as a non-fully-ionized half boronate. While the exact structure of this species remains unclear, it is proposed that it originates from the weak coordination of HFIP to the boronic acid, although the formation of the boroic anhydride cannot be ruled out.

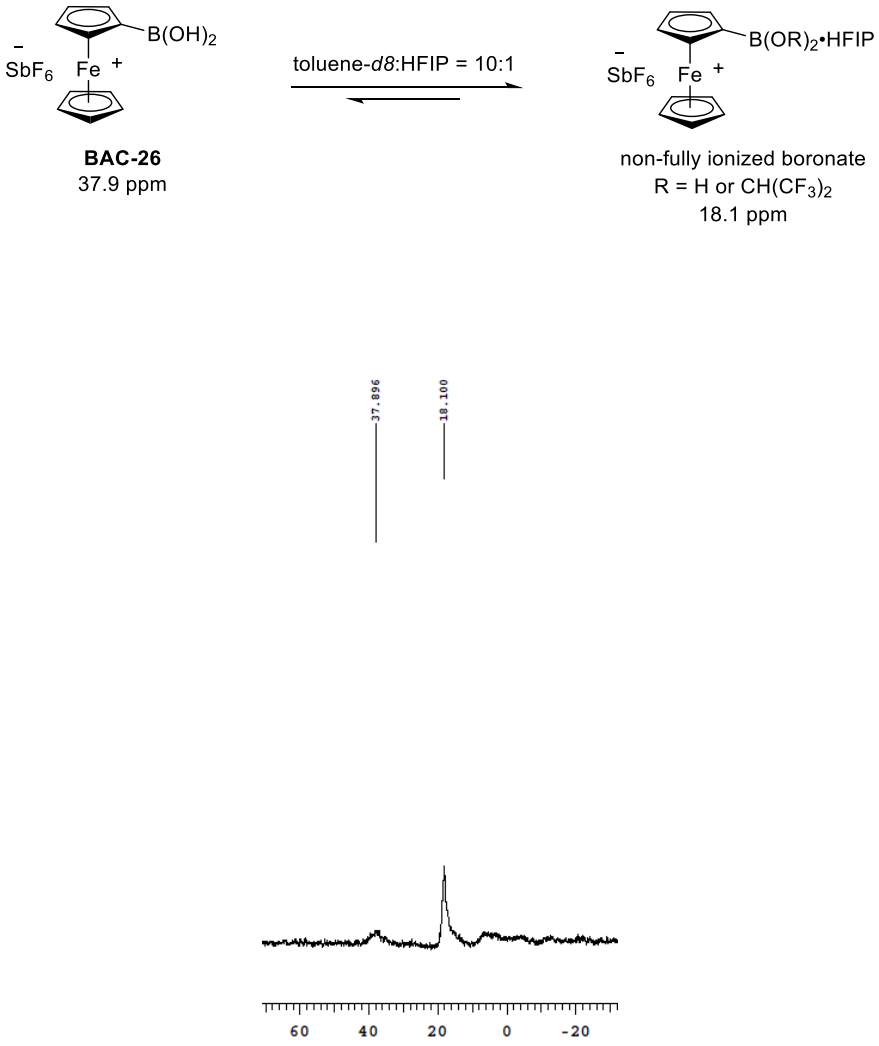
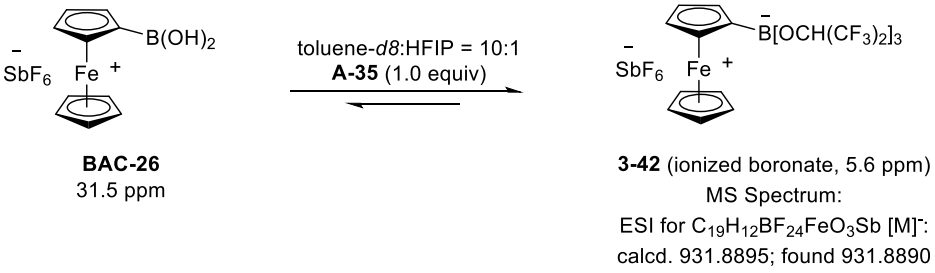


Figure 3-2. ^{11}B NMR spectrum of **BAC-26** in reaction solvent (10:1 toluene-*d8*:HFIP).

When 1.0 equivalent of the amine **A-35** was introduced to the aforementioned solution of **BAC-26** (17 mg) in the reaction solvents (10:1 toluene-*d8*:HFIP, 0.6 mL) and subjected to the ^{11}B NMR study, the peak at 18.1 ppm (**Figure 3-2**) disappeared and a new peak at 5.6 ppm was evident (**Figure 3-3**). The structure of this newly formed species was assigned to be the tri(hexafluoroisopropoxy) borate complex **3-42**, as observed by MS analysis of the mixture. Although the base-triggered formation of complex **3-42** seemed favorable, it is believed that a slow equilibrium between **BAC-26** and the complex **3-42** was established since the peak (31.5 ppm) of the free boronic acid was also observed.



BAC-26
31.5 ppm

3-42 (ionized boronate, 5.6 ppm)
MS Spectrum:
ESI for $C_{19}H_{12}BF_{24}FeO_3Sb$ $[M]^-$:
calcd. 931.8895; found 931.8890

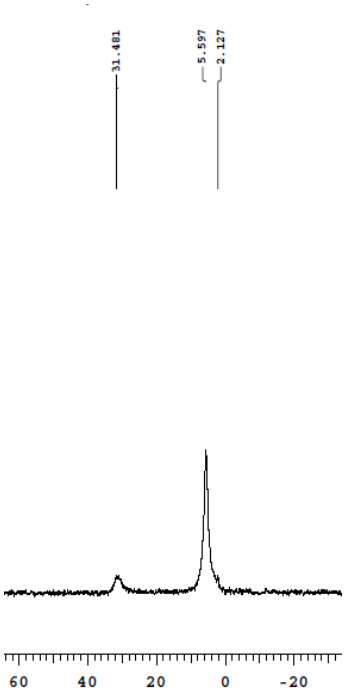


Figure 3-3. ^{11}B NMR spectrum of **BAC-26** with 1.0 equiv **A-35** in reaction solvent (10:1 toluene-*d8*:HFIP).

Later, the reaction solution of branched aldehyde **3-1**, allylic alcohol **3-2**, **BAC-26** and **A-35** was studied by ^{11}B NMR before subjecting the content to the microwave thermal reactor. As shown in **Figure 3-4**, no significant difference was observed when both aldehyde and alcohol were added compared to **Figure 3-3**. However, it was discovered that post-reaction, the ferrocenium boronic acid **BAC-26** and the complex **3-42** were largely consumed and transferred into other unidentifiable species after the reaction (**Figure 3-5**). At this point, it is not clear whether these species resulted from the complexation of **BAC-26** with the remaining starting materials, product or water by-product. Another possible rationale would be a slow decomposition of **BAC-26** in the presence of **A-35**.

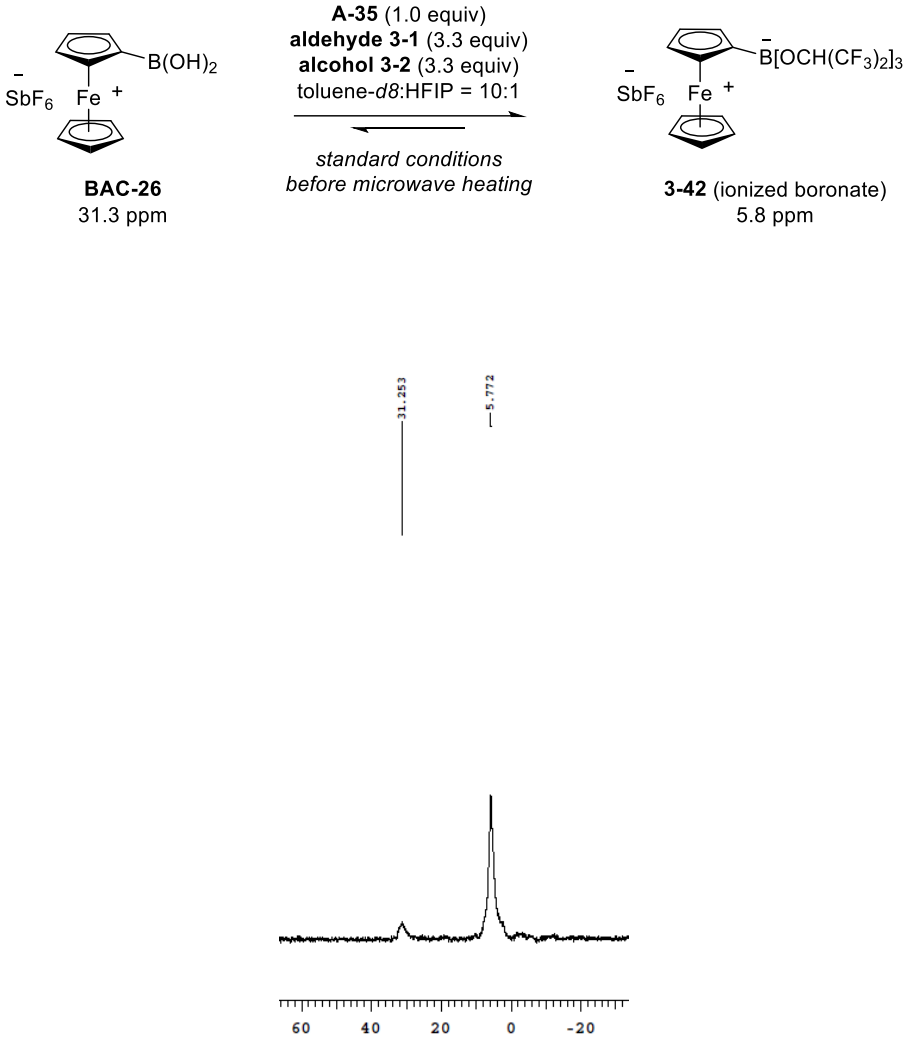


Figure 3-4. ^{11}B NMR spectrum of reaction mixture (**Table 3-4**, entry 7) before the thermal microwave-promoted reaction (10:1 toluene-*d8*:HFIP).

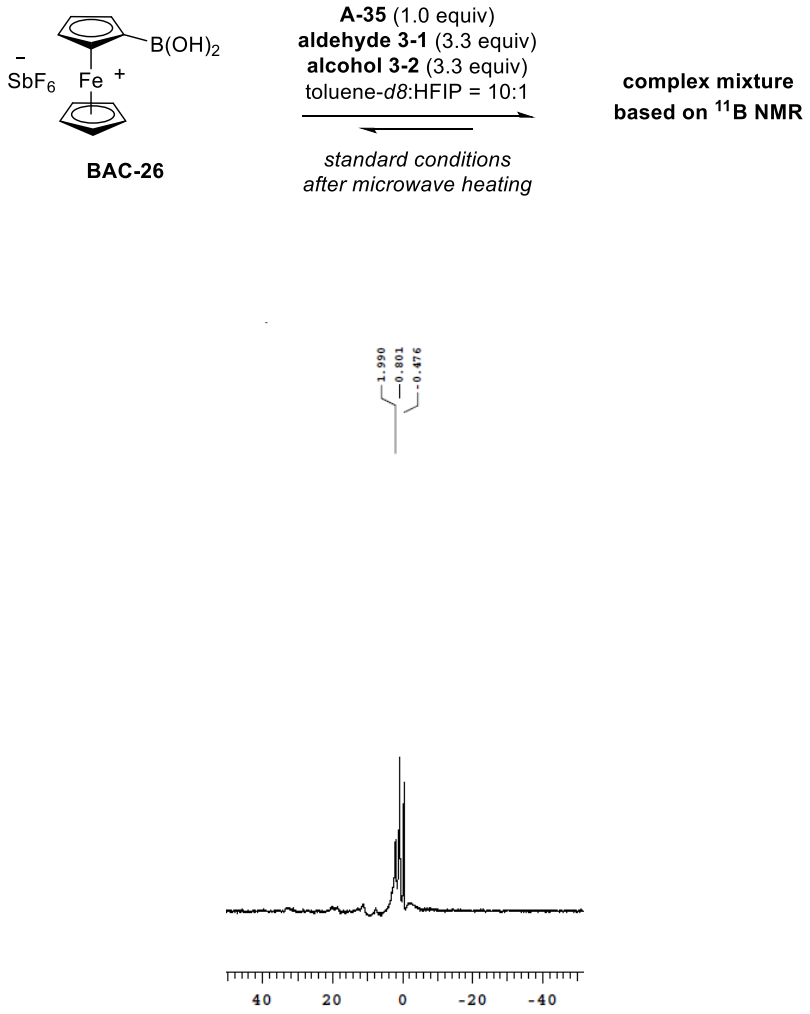
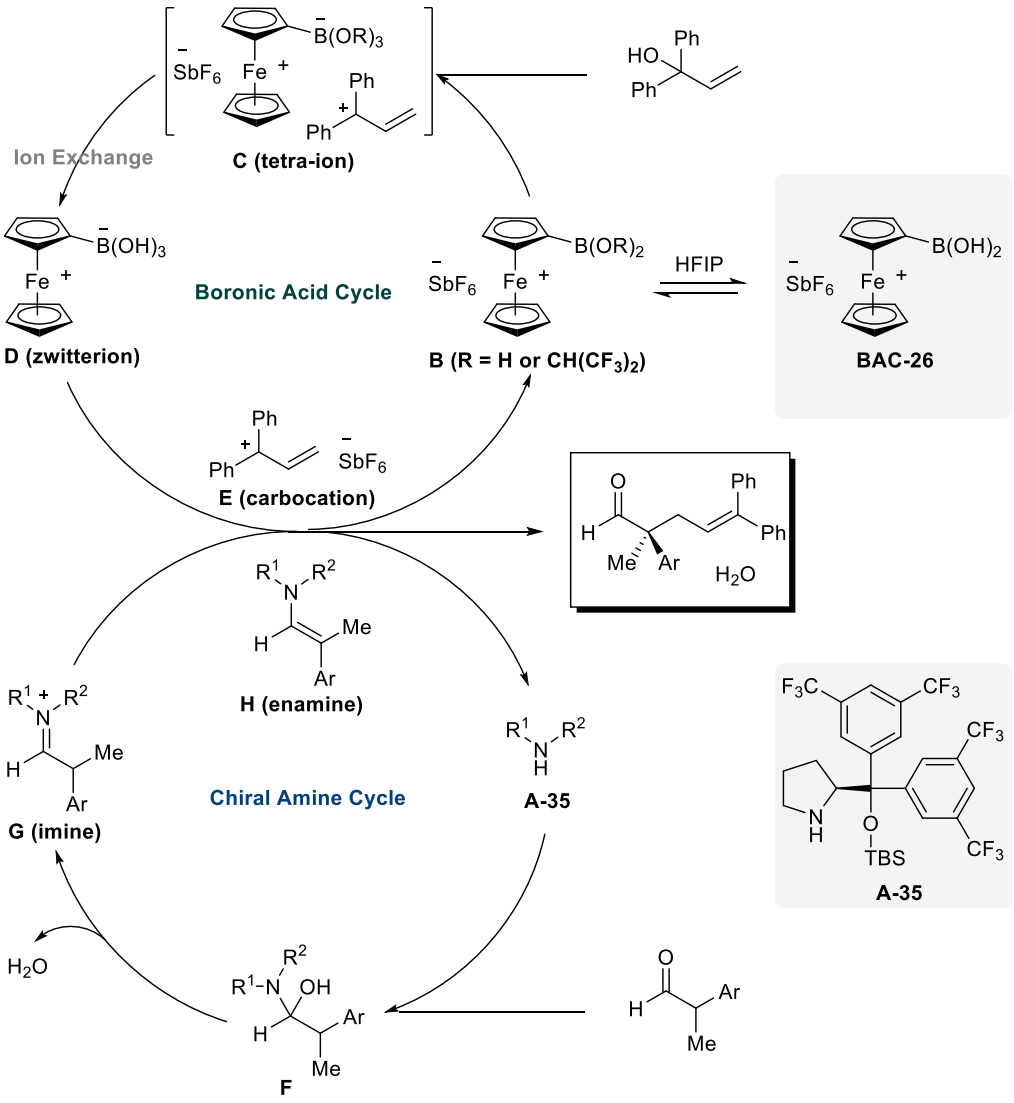


Figure 3-5. ^{11}B NMR spectrum of reaction mixture (**Table 3-4**, entry 7) after the thermal microwave-promoted reaction for 12 h (10:1 toluene-*d8*:HFIP).

3.9 Proposed mechanism

Based on the previous results, a S_N1 mechanism for the dual catalytic asymmetric allylation of branched aldehydes is proposed in **Scheme 3-20**. In the boronic acid cycle, it is suggested that HFIP not only stabilizes the carbocation but also increases the electrophilicity of the boron center by a reversible covalent exchange (**Figure 3-2**). Due to the ionic nature of **BAC-26**, a facile ion exchange mechanism (see **Table 3-9**) is proposed for the formation of carbocation **E**. In the chiral amine cycle, condensation of the amine and aldehyde leads to the formation of

reactive enamine **H**. The rigid structure of **A-35** provides excellent control for the nucleophilic attack of enamine **H** to the carbocation **E**, providing the allylated product (**Scheme 3-20**).



Scheme 3-20. Proposed mechanism of the dual catalytic asymmetric allylation.

3.10 Summary

In summary, this chapter describes efforts towards the first successful dual catalytic asymmetric allylation of branched aldehydes with allylic alcohols merging boronic acid catalysis and chiral amine catalysis. This noble metal-free strategy provides optically enriched all carbon quaternary centers in good yield and high enantioselectivity. It exhibits good functional group tolerance and

serves as a complementary method to the existing transition metal catalyzed methods. The method was successfully applied to gram-scale for the first catalytic asymmetric preparation of an important building block for an NK1/NK3 receptor antagonist. The reaction mechanism is proposed to go through allylation of the enamine *via* a carbocation intermediate, which stems from the dual activation of the allylic alcohol and aldehyde by a Lewis acidic boronic acid and a Lewis basic chiral amine.

3.11 Experimental

3.11.1 General information

The following materials include representative experimental procedures and details for the synthesis and isolation of compounds. Full characterization of all new compounds and partial characterization of known compounds presented in this chapter are described. Unless otherwise stated, all reactions were performed in capped regular glassware under nitrogen atmosphere with no further precautions. Tetrahydrofuran (THF) and dichloromethane (DCM) were purified using a cartridge solvent purification system with 4 Å molecular sieves as absorbent. All other solvents were purchased as ACS reagents and used without further purification. Unless otherwise noted, all other chemicals were purchased from commercial sources and used as received. Chromatographic separations were performed on silica gel 60 using ACS grade hexanes, ethyl acetate, dichloromethane, diethylether, *tert*-butyl methyl ether and methanol as eluents. Preparative thin-layer chromatography (PTLC) was run on silica gel 60 F 254 plates. Thin layer chromatography (TLC) was performed on silica gel 60 F254 plates, which were visualized under UV light and with $KMnO_4$, *p*-anisaldehyde, ninhydrin or phosphomolybdic acid (PMA) stains. ^{1}H NMR, ^{13}C NMR, ^{11}B NMR and ^{19}F NMR spectra were recorded on 400 MHz, 500 MHz or 700 MHz instruments. The residual solvent protons (^{1}H / $CHCl_3$) or the solvent carbon (^{13}C) were used as internal references. ^{1}H NMR data is presented as follows: chemical shifts in ppm 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; quin, quintet; sext, sextet; sept, septet; dd, doublet of doublets; m, multiplet. The error of coupling constants from ^{1}H NMR spectra is estimated to be 0.3 Hz. High-resolution mass spectra were recorded by the University of Alberta mass spectrometry services laboratory using either electron impact (EI) or electrospray ionization (ESI) techniques. Infrared (IR)

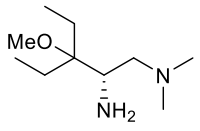
spectra were obtained using cast-film technique with frequencies expressed in cm^{-1}. The resolution of the IR instrument is 4 wavenumbers. Optical rotations were measured using a 1 mL cell with a 10 cm length on a polarimeter by University of Alberta analytical and instrumentation laboratory. Melting points (m. p.) were measured on a melting point apparatus and are uncorrected. The enantiomeric ratio for chiral compounds were determined using an HPLC instrument with Chiralcel-OD, IC, IB, or Chiralpak-AS columns as specified in the following individual procedures.

3.11.2 Synthesis and characterization of amines and boronic acids

Amines **A-2**, **A-6 to A-10** are commercially available from Sigma-Aldrich and were used directly. Cinchona based amines **A-2** and **A-3** were synthesized according to a procedure by Connon and co-workers.[33] Aminourea derivatives **A-4** was prepared according to Jacobsen and co-workers.[21] Chiral 1,2-diamines and amino alcohol **A-11** to **A-21**,[23] **A-14**,[24a,b,e] **A-23** to **A-23**,[24b] **A-24**,[24b-d] **A-25** to **A-26**,[24b] **A-27** to **A-28**,[34] and **A-29**[24e] were synthesized based on the known procedures as indicated in the references. Secondary amines **A-30** to **A-36** were prepared according to a general procedure by Lin and co-workers.[35]

Ferrocenium boronic acids salt **BAC-26**, **BAC-27** and ferrocenium hexafluoroantimonate salt $\mathbf{Fc^{+}SbF_6^{-}}$ were synthesized according to the procedure from Chapter 2, Section 2.10.4. Tetrafluorophenyl boronic acid **BAC-16** was prepared based on the known procedure by Starichenko and co-workers.[36] Pentafluorophenyl boronic acid **BAC-15** is commercially available from Sigma-Aldrich and was used directly.

Characterizations of new compounds **A-22**, **A-24** to **A-26** and **A-36** are shown as follows.



A-22

(*S*)-3-Ethyl-3-methoxy-N^1,N^1-dimethylpentane-1,2-diamine (A-22):

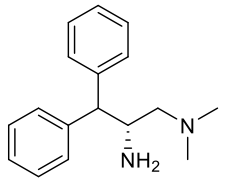
^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.23 (s, 3H), 3.00 (dd, *J* = 10.7, 2.5 Hz, 1H), 2.34 (dd, *J* = 12.1, 10.7 Hz, 1H), 2.24 (s, 6H), 2.21 (ddd, *J* = 12.1, 2.5, 0.7 Hz, 1H), 1.64-1.57 (m, 6H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 79.4, 62.1, 53.2, 49.7, 46.0, 25.3, 24.8, 8.6, 8.4;

IR (Microscope, cm^{-1}): 3238, 2926, 2851, 1672, 1464, 1082;

HRMS (ESI) for $C_{10}H_{25}N_2O$ $[M+H]^+$: calcd. 189.1961; found 189.1960;

$[\alpha]_D^{20}$: +0.9 (c 0.13, $CHCl_3$).



A-24

(*R*)-*N*^{1},*N*^{1}-Dimethyl-3,3-diphenylpropane-1,2-diamine (A-24):

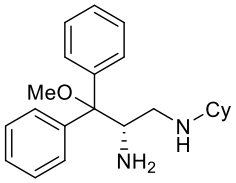
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.39 (m, 2H), 7.35-7.26 (m, 6H), 7.24-7.15 (m, 2H), 3.80 (ddd, *J* = 10.1, 9.6, 2.8 Hz, 1H), 3.71 (d, *J* = 9.6 Hz, 1H), 2.28 (dd, *J* = 12.1, 10.1 Hz, 1H), 2.25 (s, 6H), 2.12 (dd, *J* = 12.2, 2.8 Hz, 1H), 1.82 (br s, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.7, 142.6, 128.7, 128.6, 128.4, 128.1, 126.6, 126.4, 64.6, 58.0, 51.4, 45.7;

IR (Microscope, cm^{-1}): 3386, 3313, 3027, 2970, 2826, 1950, 1597, 1493, 1454;

HRMS (ESI) for $C_{17}H_{23}N_2$ $[M+H]^+$: calcd. 255.1856; found 255.1855;

$[\alpha]_D^{20}$: –54.7 (c 0.82, CH_2Cl_2).



A-25

(*S*)-*N*^{1}-Cyclohexyl-3-methoxy-3,3-diphenylpropane-1,2-diamine (A-25):

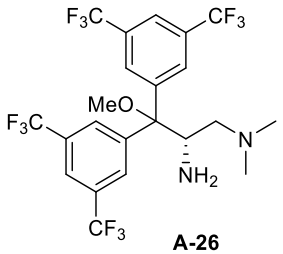
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43-7.39 (m, 2H), 7.38-7.27 (m, 8H), 3.88 (dd, *J* = 9.6, 2.4 Hz, 1H), 2.98 (dd, *J* = 11.6, 2.4 Hz, 1H), 2.93 (s, 3H), 2.28 (dddd, *J* = 10.8, 10.8, 3.9, 3.9 Hz, 1H), 1.86-1.83 (m, 1H), 1.78 (dd, *J* = 11.5, 9.6 Hz, 1H), 1.72-1.65 (m, 3H), 1.59-1.57 (m, 1H), 1.48 (br s, 3H), 1.24-1.09 (m, 3H), 1.09-0.99 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.0, 134.0, 129.3, 129.3, 127.7, 127.7, 127.5, 127.4, 86.2, 57.1, 55.6, 51.2, 49.7, 33.6, 33.5, 26.2, 25.1, 25.0;

IR (Microscope, cm^{-1}): 3383, 3306, 3057, 2927, 2852, 1600, 1493, 1447, 1074;

HRMS (ESI) for $C_{22}H_{31}N_2O$ $[M+H]^+$: calcd. 339.2431; found 339.2435;

$[\alpha]_D^{20}$: +26.8 (c 0.77, $CHCl_3$).



A-26

(*S*)-3,3-Bis(3,5-bis(trifluoromethyl)phenyl)-3-methoxy-*N*^{1},*N*^{1}-dimethylpropane-1,2-diamine (A-26):

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90 (s, 2H), 7.88 (s, 4H), 3.94 (dd, *J* = 10.4, 2.3 Hz, 1H), 3.04 (s, 3H), 2.41 (dd, *J* = 12.3, 2.2 Hz, 1H), 2.23 (s, 6H), 1.57 (dd, *J* = 12.3, 10.4 Hz, 1H), 1.35 (br s, 2H);

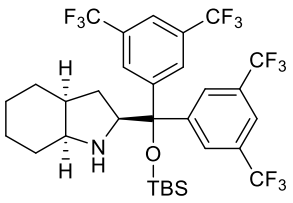
^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.7, 142.4, 131.6 (q, *J* = 33.9 Hz), 131.1 (q, *J* = 32.7 Hz), 129.3, 129.0, 123.2 (q, *J* = 272.7 Hz), 123.1 (q, *J* = 272.7 Hz), 122.2 (q, *J* = 3.8 Hz), 121.9 (q, *J* = 3,8 Hz), 84.31, 62.06, 52.12, 51.60, 46.08;

^{19}F NMR ($CDCl_3$, 476 MHz): δ –62.7 (s, 6F), –62.8 (s, 6F);

IR (Microscope, cm^{-1}): 3101, 2949, 2829, 1623, 1466, 1372, 1279, 1173, 1135;

HRMS (ESI) for $C_{22}H_{21}F_{12}N_2O$ $[M+H]^+$: calcd. 557.1457; found 557.1459;

$[\alpha]_D^{20}$: +4.8 (c 0.81, $CHCl_3$).



A-36

(2*S*,3a*S*,7a*S*)-2-(Bis(3,5-bis(trifluoromethyl)phenyl)((*tert*-butyldimethylsilyl)oxy)methyl) octahydro-1*H*-indole (A-36):

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.03 (s, 2H), 7.90 (d, *J* = 4.6 Hz, 2H), 7.78 (s, 2H), 4.27 (dd, *J* = 9.0, 7.3 Hz, 1H), 3.20 (m, 1H), 2.09-1.98 (m, 1H), 1.92-1.82 (m, 1H), 1.42-1.33 (m, 1H), 1.31-1.23 (m, 1H), 1.19-0.96 (m, 7H), 0.94 (s, 9H), -0.10 (m, 1H), -0.27 (s, 3H), -0.46 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.7, 145.3, 131.5 (q, *J* = 33.9 Hz), 130.3 (q, *J* = 32.7 Hz), 129.9, 129.4, 123.4 (q, *J* = 272.7 Hz), 123.1 (q, *J* = 272.7 Hz), 122.1, 121.5, 82.8, 62.9, 57.0, 36.4, 32.9, 29.2, 27.4, 25.8, 24.1, 21.0, 18.7, -2.9, -3.5;

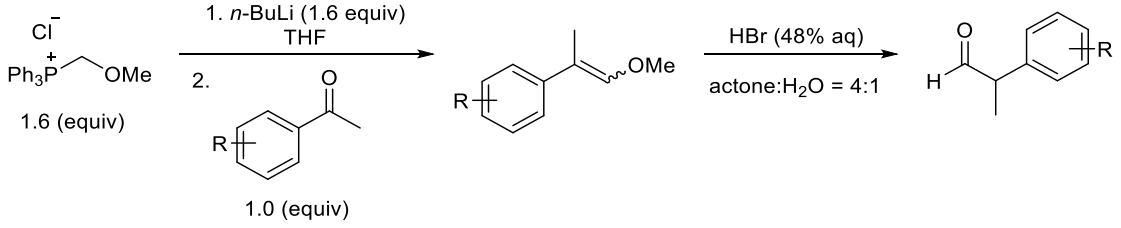
^{19}F NMR ($CDCl_3$, 476 MHz): δ –62.8 (s, 6F), –62.9 (s, 6F);

IR (Microscope, cm^{-1}): 2934, 2862, 1623, 1473, 1373, 1278, 1175, 1136;

HRMS (ESI) for $C_{31}H_{36}F_{12}NOSi$ $[M+H]^+$: calcd. 694.2369; found 694.2359;

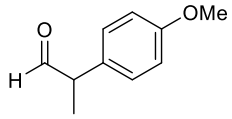
$[\alpha]_D^{20}$: +0.2 (c 1.73, $CHCl_3$).

3.11.3 Synthesis and characterization of branched aldehydes



(Methoxymethyl)triphenylphosphonium chloride (2.74 g, 8.00 mmol) was suspended in 20 mL of anhydrous THF in a 100 mL round bottom flask. The resulting mixture was then cooled to 0 °C

and stirred for 15 min. *n*-BuLi (3.2 mL of 2.5 M solution in hexane, 8.00 mmol) was added to the suspension slowly under inert atmosphere over 10 min to give a dark red solution. After stirring at 0 °C for 30 min, the reaction mixture was warmed to room temperature. After continuous stirring for 1 h, the dark red solution was cooled to 0 °C and a solution of ketone (5.00 mmol) in 10 mL of anhydrous THF was added slowly over 10 min. The reaction mixture was then allowed to stir at room temperature overnight. When the reaction was complete as monitored by TLC, 50 mL of H_2O was added to quench the reaction. The resulting mixture was extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with 50 mL of brine, dried over $MgSO_4$, filtered and concentrated. The methyl enol ether product was obtained after flash column chromatography. The methyl enol ether was dissolved in a solvent mixture of acetone and H_2O (v:v = 4:1, 0.9 M). The resulting mixture was then cooled to 0 ° C under inert atmosphere. Concentrated HBr (48%, 1 mL) was added slowly to the solution. The reaction was warmed to room temperature and stirred until completion monitored by TLC. If the reaction was not complete after 24 h, 0.5 mL of concentrated HBr was added every 4 h until all the methyl enol ether was consumed. The reaction mixture was then quenched and neutralized by saturated aq. $NaHCO_3$ solution and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with 50 mL of brine, dried over $MgSO_4$, filtered and concentrated. The branched aldehyde was obtained after flash column chromatography using the solvent mixture indicated below.

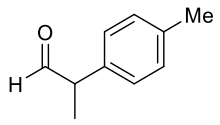


3-43

2-(4-Methoxyphenyl)propanal (3-43): Prepared from 4′-methoxyacetophenone (751 mg, 5.00 mmol) using the general procedure. Purified by flash column chromatography (50:1 to 25:1 hexane:Et_2O) and isolated as a colorless oil (157 mg, 19%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.65 (d, *J* = 1.5 Hz, 1H), 7.15-7.11 (m, 2H), 6.94-6.90 (m, 2H), 3.81 (s, 3H), 3.58 (qd, *J* = 7.1, 1.5 Hz, 1H), 1.42 (d, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.1, 159.0, 129.6, 129.3, 114.5, 55.3, 52.2, 14.7.

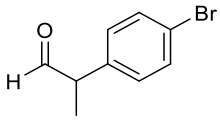


3-44

2-(*p*-Tolyl)propanal (3-44): Prepared from 4′-methylacetophenone (671 mg, 5.00 mmol) using the general procedure. Purified by flash column chromatography (50:1 to 25:1 hexane:Et_2O) and isolated as a colorless oil (316 mg, 43%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.67 (d, *J* = 1.5 Hz, 1H), 7.19 (m, 2H), 7.13-7.08 (m, 2H), 3.60 (qd, *J* = 7.1, 1.5 Hz, 1H), 2.35 (s, 3H), 1.43 (d, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.2, 137.3, 134.7, 129.8, 128.2, 52.6, 21.1, 14.7.

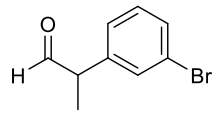


3-45

2-(4-Bromophenyl)propanal (3-45): Prepared from 4′-bromoacetophenone (995 mg, 5.00 mmol) using the general procedure. Purified by flash column chromatography (50:1 to 25:1 hexane:Et_2O) and isolated as a colorless oil (422 mg, 40%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.66 (d, *J* = 1.3 Hz, 1H), 7.59-7.42 (m, 2H), 7.16-6.99 (m, 2H), 3.60 (qd, *J* = 7.1, 1.3 Hz, 1H), 1.44 (d, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.3, 136.7, 132.2, 130.0, 121.6, 52.4, 14.6.

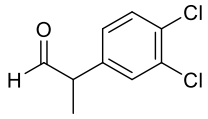


3-46

2-(3-Bromophenyl)propanal (3-46): Prepared from 3′-bromoacetophenone (995 mg, 5.00 mmol) using the general procedure. Purified by flash column chromatography (50:1 to 30:1 hexane:Et_2O) and isolated as a colorless oil (262 mg, 25%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.67 (d, *J* = 1.4 Hz, 1H), 7.44 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H), 7.37 (t, *J* = 1.8 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.16-7.11 (m, 1H), 3.61 (qd, *J* = 7.1, 1.4 Hz, 1H), 1.44 (d, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.2, 140.0, 131.4, 130.7, 130.6, 126.9, 123.1, 52.6, 14.6.

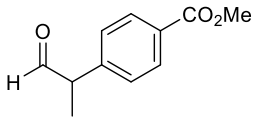


3-37

2-(3,4-Dichlorophenyl)propanal (3-37): Prepared from 3′,4′-dichloroacetophenone (3.02 g, 16.0 mmol) using the general procedure. Purified by flash column chromatography (30:1 hexane:Et_2O) and isolated as a light yellow oil (1.96 g, 61%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.66 (d, *J* = 1.3 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 2.1 Hz, 1H), 7.05 (dd, *J* = 8.3, 2.1 Hz, 1H), 3.61 (qd, *J* = 7.1 Hz, 1.3 Hz, 1H), 1.45 (d, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 199.7, 137.9, 133.2, 131.8, 131.0, 130.3, 127.6, 52.0, 14.6.

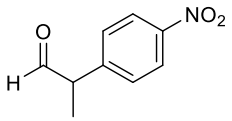


3-47

Methyl 4-(1-oxopropan-2-yl)benzoate (3-47): Prepared from methyl 4-acetylbenzoate (1.28 g, 7.20 mmol) using the general procedure. Purified by flash column chromatography (10:1 hexane:EtOAc) and isolated as a light yellow oil (170 mg, 12%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.70 (d, *J* = 1.3 Hz, 1H), 8.08-8.01 (m, 2H), 7.32-7.27 (m, 2H), 3.92 (s, 3H), 3.71 (qd, *J* = 7.1, 1.3 Hz, 1H), 1.48 (d, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.2, 166.7, 142.9, 130.3, 129.5, 128.3, 53.0, 52.2, 14.6.

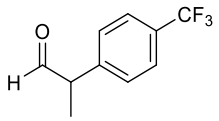


3-48

2-(4-Nitrophenyl)propanal (3-48): Prepared from 4′-nitroacetophenone (1.20 g, 7.20 mmol) using the general procedure. Purified by flash column chromatography (4:1 hexane:EtOAc) and isolated as an orange-red oil (273 mg, 31%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.72 (d, *J* = 1.2 Hz, 1H), 8.28-8.21 (m, 2H), 7.42-7.37 (m, 2H), 3.79 (qd, *J* = 7.2, 1.2 Hz, 1H), 1.52 (d, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 199.3, 147.4, 145.1, 129.2, 124.2, 52.7, 14.7.



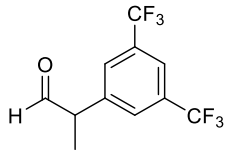
3-49

2-(4-(Trifluoromethyl)phenyl)propanal (3-49): Prepared from 4′-(trifluoromethyl) acetophenone (941 mg, 5.00 mmol) using the general procedure. Purified by flash column chromatography (100:1 hexane:Et_2O) and isolated as a colorless oil (871 mg, 86%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.70 (d, *J* = 1.3 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 3.1 (qd, *J* = 7.1, 1.3 Hz, 1H), 1.49 (d, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.1, 141.8, 129.9 (q, *J* = 32.7 Hz), 128.7, 126.0 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.7 Hz), 52.8, 14.6;

^{19}F NMR ($CDCl_3$, 476 MHz): δ –62.6 (s, 3F).



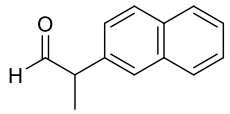
3-50

2-(3,5-Bis(trifluoromethyl)phenyl)propanal (3-50): Prepared from 2-(3,5-bis(trifluoromethyl) phenyl)propanal (1.28 g, 5.00 mmol) using the general procedure. Purified by flash column chromatography (30:1 hexane:Et_2O) and isolated as a light yellow oil (446 mg, 33%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.74 (d, *J* = 1.1 Hz, 1H), 7.84 (s, 1H), 7.67 (s, 2H), 3.82 (qd, *J* = 7.3, 1.1 Hz, 1H), 1.55 (d, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 199.0, 140.3, 132.4 (q, *J* = 32.7 Hz), 128.5, 123.1 (q, *J* = 272.7 Hz), 121.7 (sept, *J* = 3.8 Hz), 52.4, 14.7;

^{19}F NMR ($CDCl_3$, 476 MHz): δ –62.9 (s, 6F).

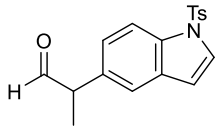


3-51

2-(Naphthalen-2-yl)propanal (3-51): Prepared from 2-acetylnaphthalene (851 mg, 5.00 mmol) using the general procedure. Purified by flash column chromatography (30:1 hexane:Et_2O) and isolated as a white solid (750 mg, 82%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.77 (d, *J* = 1.4 Hz, 1H), 7.91-7.79 (m, 3H), 7.70-7.64 (m, 1H), 7.54-7.46 (m, 2H), 7.33 (dd, *J* = 8.4, 1.8 Hz, 1H), 3.81 (qd, *J* = 7.0, 1.4 Hz, 1H), 1.55 (d, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.0, 135.2, 133.6, 132.7, 128.9, 127.7, 127.7, 127.2, 126.4, 126.2, 126.1, 53.1, 14.7.

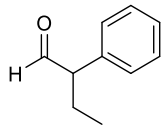


3-52

2-(1-tosyl-1*H*-indol-5-yl)propanal (3-52): Prepared from 1-(1-tosyl-1*H*-indol-5-yl) ethanone (1.04 g, 3.32 mmol) using the general procedure. Purified by flash column chromatography (6:1 hexane:EtOAc) and isolated as a light yellow viscous oil (625 mg, 58%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.67 (d, *J* = 1.5 Hz, 1H), 7.98 (d, *J* = 8.6 Hz, 1H), 7.79-7.73 (m, 2H), 7.58 (d, *J* = 3.7 Hz, 1H), 7.36 (d, *J* = 1.8 Hz, 1H), 7.25-7.19 (m, 2H), 7.14 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.63 (dd, *J* = 3.7, 0.8 Hz, 1H), 3.69 (qd, *J* = 7.0, 1.5 Hz, 1H), 2.35 (s, 3H), 1.46 (d, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.0, 145.1, 135.3, 134.2, 132.7, 131.4, 129.9, 127.0, 126.9, 124.9, 121.0, 114.1, 108.7, 52.8, 21.6, 14.9.



3-53

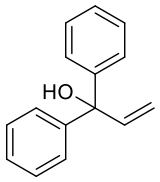
2-Phenylbutanal (3-53): Prepared from propiophenone (671 mg, 5.00 mmol) using the general procedure. Purified by flash column chromatography (30:1 hexane:Et_2O) and isolated as a colorless oil (233 mg, 31%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.68 (d, *J* = 2.1 Hz, 1H), 7.40-7.34 (m, 2H), 7.33-7.28 (m, 1H), 7.22-7.17 (m, 2H), 3.41 (ddd, *J* = 8.4, 6.9, 2.1 Hz, 1H), 2.18-2.05 (m, 1H), 1.84-1.70 (m, 1H), 0.91 (dd, *J* = 7.4, 7.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.0, 136.3, 129.0, 128.8, 127.5, 60.9, 23.0, 11.7.

3.11.4 Synthesis and characterization of allylic alcohols

Allylic alcohols were prepared according to Xia and co-workers from the corresponding ketone substrates and vinyl magnesium bromide solution in THF.[37]

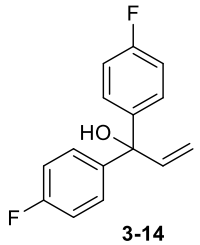


3-2

1,1-Diphenylprop-2-en-1-ol (3-2):

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45-7.39 (m, 4H), 7.35 (m, 4H), 7.31-7.24 (m, 2H), 6.58-6.51 (m, 1H), 5.39-5.35 (m, 1H), 5.34 (m, 1H), 2.30 (s, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.8, 143.5, 128.2, 127.3, 126.9, 114.0, 79.4.



3-14

1,1-Bis(4-fluorophenyl)prop-2-en-1-ol (3-14):

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39-7.29 (m, 4H), 7.05-6.95 (m, 4H), 6.45 (dd, *J* = 17.1, 10.6 Hz, 1H), 5.33 (dd, *J* = 10.6, 1.0 Hz, 1H), 5.28 (dd, *J* = 17.1, 1.0 Hz, 1H), 2.24 (s, 1H);

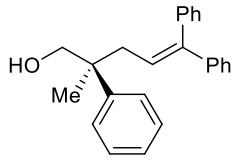
^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.0 (d, *J* = 246.5 Hz), 143.2, 141.4 (d, *J* = 3.8 Hz), 128.7 (d, *J* = 8.1 Hz), 115.0 (d, *J* = 21.4 Hz), 114.5, 78.7;

^{19}F NMR ($CDCl_3$, 476 MHz): δ –115.26 (tt, *J* = 8.6, 5.4 Hz, 2F).

3.11.5 General procedure for dual catalytic asymmetric allylation

To a 2-5 mL microwaves glass vessel charged with a stir bar under a stream of N_2, was added ferrocenium boronic acid **BAC-26** (35 mg, 0.075 mmol) followed by 0.1 mL HFIP. The mixture was allowed to stir at room temperature for 5 min. Allylic alcohol **3-2** (105 mg, 0.50 mmol), amine catalyst **A-35** (48 mg, 0.075 mmol) and branched aldehyde (0.25 mmol) in 1 mL of toluene was added to the reaction mixture under N_2. The microwaves vessel was then sealed

and heated up to 60 °C in a Biotage™ microwave reactor (absorption level: normal, 30 W) for 12 h. After the indicated time, the reaction mixture was diluted with 5 mL of DCM and run through a silica plug with 50 mL of DCM as eluent. The crude mixture was obtained after removal of DCM. To a 50 mL of round bottom flask charged with the crude mixture, was added 20 mL of DCM and 2 mL of MeOH followed by $NaBH_4$ (95 mg, 2.50 mmol) at 0 °C. The reaction mixture was then allowed to warm up to room temperature and stirred for 2 h before quenching with 20 mL saturated aqueous NH_4Cl solution. The resulting mixture was extracted with DCM (3 × 10 mL). The combined organic layers were then washed with brine, dried over and, filtered and concentrated. The reduced allylation product was obtained after flash column chromatography using the solvent mixture indicated below.



3-20

2-Methyl-2,5,5-triphenylpent-4-en-1-ol (3-20): Prepared from aldehyde **3-1** (34 mg, 0.25 mmol) using the general procedure. Purified by flash column chromatography (10:1 to 5:1 hexane:EtOAc), PTLC (5:1 hexane:EtOAc) and isolated as a light yellow solid (49 mg, 59.7%).

M.p. 69-71 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43-7.30 (m, 7H), 7.28-7.16 (m, 4H), 7.15-7.10 (m, 2H), 7.09-7.04 (m, 2H), 5.88 (dd, *J* = 7.3, 7.3 Hz, 1H), 3.71 (dd, *J* = 10.9, 4.8 Hz, 1H), 3.57 (dd, *J* = 10.8, 7.0 Hz, 1H), 2.65 (dd, *J* = 14.9, 6.9 Hz, 1H), 2.44 (dd, *J* = 14.9, 7.8 Hz, 1H), 1.39 (s, 3H), 1.16 (dd, *J* = 6.2, 6.2 Hz, 1H);

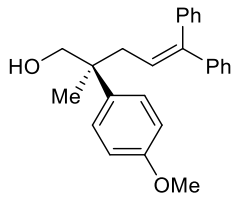
^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.4, 143.5, 142.7, 140.1, 130.0, 128.5, 128.3, 128.1, 127.2, 127.1, 126.9, 126.8, 126.4, 125.5, 71.9, 44.2, 38.2, 22.2;

IR (Microscope, cm^{-1}): 3570, 3431, 3056, 3024, 2965, 2931, 1599, 1496, 1444;

HRMS (EI) for $C_{24}H_{24}O$: calcd. 328.1827; found 328.1826;

$[\alpha]_D^{20}$: +7.57 (c 2.64, $CHCl_3$);

HPLC (Chiralpak AS): 5:95 *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 254 nm, T_{major} = 18.0 min, T_{minor} = 15.1 min, *er* = 94:6.



3-21

2-(4-Methoxyphenyl)-2-methyl-5,5-diphenylpent-4-en-1-ol (3-21): Prepared from aldehyde **3-43** (41 mg, 0.25 mmol) using the general procedure. Purified by flash column chromatography (10:1 to 5:1 hexane:EtOAc), PTLC (5:1 hexane:EtOAc) and isolated as a light yellow viscous liquid (38 mg, 42%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40-7.36 (m, 2H), 7.34-7.30 (m, 1H), 7.26-7.17 (m, 5H), 7.14-7.12 (m, 2H), 7.08-7.06 (m, 2H), 6.91-6.85 (m, 2H), 5.90-5.85 (dd, *J* = 10.9, 10.7 Hz, 1H), 3.81 (s, 3H), 3.66 (d, *J* = 10.9 Hz, 1H), 3.52 (d, *J* = 10.7 Hz, 1H), 2.61 (dd, *J* = 14.9, 6.8 Hz, 1H), 2.40 (dd, *J* = 14.8, 7.8 Hz, 1H), 1.35 (s, 3H), 1.14 (br s, 1H);

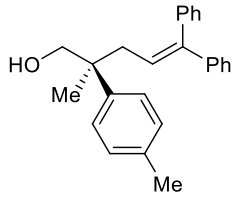
^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.0, 143.4, 142.7, 140.2, 136.3, 130.0, 128.3, 128.0, 127.9, 127.2, 127.0, 126.9, 125.6, 113.9, 72.1, 55.3, 43.6, 38.3, 22.3;

IR (Microscope, cm^{-1}): 3438, 3024, 2959, 2932, 1610, 1514, 1443, 1251, 1032;

HRMS (EI) for $C_{25}H_{26}O_2$: calcd. 358.1933; found 358.1935;

$[\alpha]_D^{20}$: +8.14 (c 1.92, $CHCl_3$);

HPLC (Chiralpak AS): 5:95 *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 254 nm, T_{major} = 33.2 min, T_{minor} = 22.4 min, *er* = 93:7.



3-22

2-Methyl-5,5-diphenyl-2-(p-tolyl)pent-4-en-1-ol (3-22): Prepared from aldehyde **3-44** (37 mg, 0.25 mmol) using the general procedure. Purified by flash column chromatography (10:1 hexane:EtOAc) and isolated as a light yellow viscous liquid (49 mg, 57%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40-7.38 (m, 2H), 7.36-7.30 (m, 1H), 7.27-7.12 (m, 9H), 7.10-7.08 (m, 2H), 5.90 (dd, *J* = 7.7, 6.9 Hz, 1H), 3.69 (dd, *J* = 10.9, 5.5 Hz, 1H), 3.54 (dd, *J* = 10.9, 7.4 Hz, 1H), 2.63 (dd, *J* = 14.9, 6.8 Hz, 1H), 2.43 (dd, *J* = 14.9, 7.8 Hz, 1H), 2.36 (s, 3H), 1.37 (s, 3H), 1.17 (dd, *J* = 6.6, 6.6 Hz, 1H);

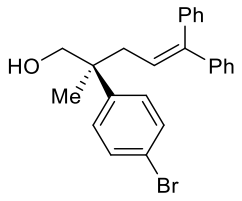
^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.4, 142.8, 141.3, 140.2, 135.8, 130.0, 129.3, 128.3, 128.1, 127.2, 127.0, 126.9, 126.7, 125.7, 71.99, 43.9, 38.2, 22.2, 20.9;

IR (Microscope, cm^{-1}): 3579, 3375, 3055, 3025, 2965, 2923, 2827, 1598, 1515, 1494, 1444, 1032;

HRMS (EI) for $C_{25}H_{26}O$: calcd. 342.1984; found 342.1986;

$[\alpha]_D^{20}$: +7.22 (c 3.83, $CHCl_3$);

HPLC (Chiralpak AS): 5:95 *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 254 nm, T_{major} = 15.0 min, T_{minor} = 13.2 min, *er* = 93:7.



3-23

2-(4-Bromophenyl)-2-methyl-5,5-diphenylpent-4-en-1-ol (3-23): Prepared from aldehyde **3-45** (53 mg, 0.25 mmol) using the general procedure. Purified by flash column chromatography (10:1 to 5:1 hexane:EtOAc), PTLC (5:1 hexane:EtOAc) and isolated as a light yellow viscous liquid (70 mg, 70%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49-7.43 (m, 2H), 7.41-7.36 (m, 2H), 7.35-7.30 (m, 1H), 7.24-7.15 (m, 5H), 7.14-7.10 (m, 2H), 7.09-7.04 (m, 2H), 5.85 (dd, *J* = 7.4, 7.4 Hz, 1H), 3.66 (dd, *J* = 11.0, 5.6 Hz, 1H), 3.54 (dd, *J* = 11.0, 7.2 Hz, 1H), 2.62 (dd, *J* = 14.9, 7.0 Hz, 1H), 2.42 (dd, *J* = 14.9, 7.7 Hz, 1H), 1.36 (s, 3H), 1.19 (dd, *J* = 6.5, 6.5 Hz, 1H);

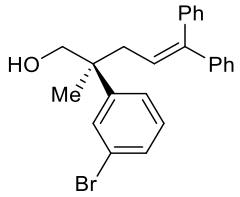
^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.9, 143.7, 142.6, 140.0, 131.5, 129.9, 128.7, 128.3, 128.1, 127.2, 127.1, 127.1, 124.9, 120.3, 71.6, 44.1, 38.0, 22.1;

IR (Microscope, cm^{-1}): 3582, 3375, 3056, 3025, 2929, 2877, 1598, 1492, 1443, 1008;

HRMS (EI) for $C_{24}H_{23}BrO$: calcd. 406.0932; found 406.0925;

$[\alpha]_D^{20}$: +12.65 (c 5.11, $CHCl_3$);

HPLC (Chiralpak AS): 5:95 *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 254 nm, T_{major} = 17.4 min, T_{minor} = 16.2 min, *er* = 95.5:4.5.



3-24

2-(3-Bromophenyl)-2-methyl-5,5-diphenylpent-4-en-1-ol (3-24): Prepared from aldehyde **3-46** (53 mg, 0.25 mmol) using the general procedure. Purified by flash column chromatography (10:1 to 5:1 hexane:EtOAc), PTLC (5:1 hexane:EtOAc) and isolated as a yellow viscous liquid (69 mg, 68%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45 (t, *J* = 1.7 Hz, 1H), 7.42-7.36 (m, 3H), 7.36-7.31 (m, 1H), 7.25-7.18 (m, 5H), 7.14-7.10 (m, 2H), 7.08-7.06 (m, 2H), 5.84 (dd, *J* = 7.4, 7.4 Hz, 1H), 3.67 (d, *J* = 11.1 Hz, 1H), 3.55 (d, *J* = 10.9 Hz, 1H), 2.61 (dd, *J* = 14.9, 7.2 Hz, 1H), 2.42 (dd, *J* = 14.9, 7.6 Hz, 1H), 1.37 (s, 3H), 1.22 (br s, 1H);

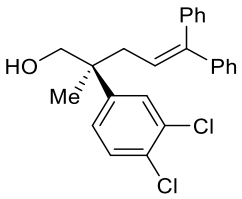
^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.2, 144.0, 142.6, 139.9, 130.2, 130.0, 129.9, 129.5, 128.4, 128.1, 127.2, 127.2, 127.1, 125.6, 124.8, 122.9, 71.6, 44.4, 38.1, 22.1;

IR (Microscope, cm^{-1}): 3585, 3379, 3028, 2973, 2927, 1593, 1562, 1476, 1443, 1031;

HRMS (EI) for $C_{24}H_{23}BrO$: calcd. 406.0932; found 406.0935;

$[\alpha]_D^{20}$: +8.99 (c 4.57, $CHCl_3$);

HPLC (Chiralpak AS): 3:97 *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 230 nm, T_{major} = 25.1 min, T_{minor} = 23.1 min, *er* = 96:4.



3-25

2-(3,4-Dichlorophenyl)-2-methyl-5,5-diphenylpent-4-en-1-ol (3-25): Prepared from aldehyde **3-37** (51 mg, 0.25 mmol) using the general procedure. Purified by flash column chromatography (10:1 to 5:1 hexane:EtOAc) and isolated as a yellow solid (81 mg, 82%).

M.p. 50-52 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.37 (m, 4H), 7.37-7.31 (m, 1H), 7.28-7.19 (m, 3H), 7.14-7.12 (m, 3H), 7.11-7.05 (m, 2H), 5.85 (dd, *J* = 7.4, 7.4 Hz, 1H), 3.65 (d, *J* = 10.9 Hz, 1H), 3.54 (d, *J* = 10.8 Hz, 1H), 2.61 (dd, *J* = 14.9, 7.3 Hz, 1H), 2.43 (dd, *J* = 14.9, 7.6 Hz, 1H), 1.37 (s, 3H), 1.30 (br s, 1H);

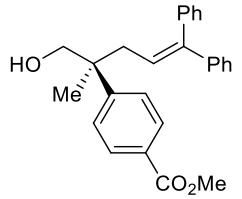
^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.3, 144.3, 142.5, 139.8, 132.5, 130.4, 130.2, 129.9, 129.2, 128.4, 128.2, 127.2, 127.2, 126.5, 124.4, 71.4, 44.1, 37.9, 22.1;

IR (Microscope, cm^{-1}): 3595, 3367, 3055, 3023, 2967, 2933, 1598, 1555, 1473, 1444, 1028;

HRMS (EI) for $C_{24}H_{22}Cl_2O$: calcd. 396.1048; found 396.1045;

$[\alpha]_D^{20}$: +12.39 (c 7.57, $CHCl_3$);

HPLC (Chiralpak AS): 2.5:97.5 *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 254 nm, T_{major} = 27.4 min, T_{minor} = 24.8 min, *er* = 96.5:3.5.



3-26

Methyl 4-(1-hydroxy-2-methyl-5,5-diphenylpent-4-en-2-yl)benzoate (3-26): Prepared from aldehyde **3-47** (48 mg, 0.25 mmol) using the general procedure. Purified by flash column

chromatography (5:1 to 3:1 hexane:EtOAc), PTLC (3:1 hexane:EtOAc) and isolated as a light yellow viscous liquid (56 mg, 58%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.03-7.97 (m, 2H), 7.42-7.36 (m, 4H), 7.34-7.30 (m, 1H), 7.21-7.17 (m, 3H), 7.11-7.19 (m, 2H), 7.05-6.99 (m, 2H), 5.81 (dd, *J* = 7.4, 7.4 Hz, 1H), 3.92 (s, 3H), 3.73 (dd, *J* = 11.0, 5.9 Hz, 1H), 3.59 (dd, *J* = 11.0, 7.2 Hz, 1H), 2.66 (dd, *J* = 14.9, 7.2 Hz, 1H), 2.45 (dd, *J* = 14.8, 7.7 Hz, 1H), 1.40 (s, 3H), 1.14 (dd, *J* = 7.1, 5.9 Hz, 1H);

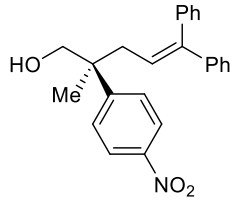
^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.0, 150.2, 144.0, 142.5, 139.9, 129.9, 129.7, 128.3, 128.2, 128.1, 127.1, 127.1, 127.1, 126.9, 124.7, 71.6, 52.1, 44.6, 38.1, 22.2;

IR (Microscope, cm^{-1}): 3488, 3056, 3025, 2951, 2876, 1722, 1610, 1437, 1283, 1117;

HRMS (EI) for $C_{26}H_{26}O_3$: calcd. 386.1882; found 386.1882;

$[\alpha]_D^{20}$: +12.36 (c 5.74, $CHCl_3$);

HPLC (Chiralcel IB): 25:75 *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 254 nm, T_{major} = 6.2 min, T_{minor} = 7.1 min, *er* = 95:5.



3-27

2-Methyl-2-(4-nitrophenyl)-5,5-diphenylpent-4-en-1-ol (3-27): Prepared from aldehyde **3-48** (45 mg, 0.25 mmol) using the general procedure. Purified by flash column chromatography (5:1 to 3:1 hexane:EtOAc) and isolated as a yellow viscous liquid (74 mg, 79%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.21-8.13 (m, 2H), 7.50-7.44 (m, 2H), 7.42-7.29 (m, 3H), 7.25-7.15 (m, 3H), 7.13-7.06 (m, 2H), 7.06-6.98 (m, 2H), 5.81 (t, *J* = 7.4, 7.4 Hz, 1H), 3.75 (d, *J* = 11.0 Hz, 1H), 3.63 (d, *J* = 10.9 Hz, 1H), 2.69 (dd, *J* = 14.9, 7.3 Hz, 1H), 2.50 (dd, *J* = 14.9, 7.6 Hz, 1H), 1.43 (s, 3H), 1.31 (br s, 1H);

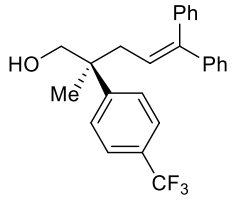
^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.0, 146.4, 144.5, 142.3, 139.7, 129.8, 128.4, 128.2, 127.9, 127.3, 127.3, 127.1, 124.0, 123.4, 71.2, 44.8, 38.0, 22.3;

IR (Microscope, cm^{-1}): 3579, 3430, 3055, 3024, 2968, 2930, 1602, 1517, 1444, 1347, 1032;

HRMS (EI) for $C_{24}H_{23}N_3O_3$: calcd. 373.1678; found 373.1678;

$[\alpha]_D^{20}$: +17.26 (c 0.69, $CHCl_3$);

The enantiomeric ratio of chiral compound **3-27** was determined by (*R*)-Mosher's acid derivatization due to a difficult HPLC separation (see below).



3-28

2-Methyl-5,5-diphenyl-2-(4-(trifluoromethyl)phenyl)pent-4-en-1-ol (3-28): Prepared from aldehyde **3-49** (51 mg, 0.25 mmol) using the general procedure. Purified by flash column chromatography (10:1 hexane:EtOAc), PTLC (5:1 hexane:EtOAc) and isolated as a yellow viscous liquid (79 mg, 80%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.41-7.30 (m, 3H), 7.25-7.16 (m, 3H), 7.11-7.08 (m, 2H), 7.07-7.02 (m, 2H), 5.84 (dd, *J* = 7.4, 7.4 Hz, 1H), 3.73 (dd, *J* = 11.6, 3.6 Hz, 1H), 3.60 (dd, *J* = 11.0, 5.4 Hz, 1H), 2.66 (dd, *J* = 14.8, 7.2 Hz, 1H), 2.47 (dd, *J* = 14.8, 7.7 Hz, 1H), 1.41 (s, 3H), 1.19 (br s, 1H);

^{13}C NMR ($CDCl_3$, 175 MHz): δ 149.0, 144.1, 142.4, 139.8, 129.8, 128.5 (q, *J* = 33.4 Hz), 128.3, 128.1, 127.2, 127.1, 127.1, 127.1, 125.3 (q, *J* = 3.5 Hz), 124.5, 124.2 (q, *J* = 272.8 Hz), 71.4, 44.4, 38.0, 22.1;

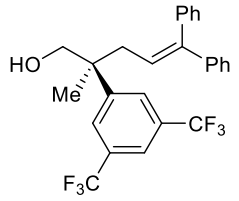
^{19}F NMR ($CDCl_3$, 476 MHz): δ –62.4 (s, 3F);

IR (Microscope, cm^{-1}): 3583, 3376, 3080, 3056, 3024, 2930, 1618, 1599, 1444, 1328, 1167, 1124;

HRMS (EI) for $C_{25}H_{23}F_3O$: calcd. 396.1701; found 396.1697;

$[\alpha]_D^{20}$: +9.53 (c 4.53, $CHCl_3$);

HPLC (Chiralcel OD): 10:90 *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 254 nm, T_{major} = 12.0 min, T_{minor} = 14.6 min, *er* = 96:4.



3-29

2-(3,5-Bis(trifluoromethyl)phenyl)-2-methyl-5,5-diphenylpent-4-en-1-ol (3-29): Prepared from aldehyde **3-50** (68 mg, 0.25 mmol) using the general procedure. Purified by flash column chromatography (10:1 hexane:EtOAc) and isolated as a yellow viscous liquid (82 mg, 70%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77 (m, 3H), 7.42-7.32 (m, 3H), 7.25-7.18 (m, 3H), 7.10-7.06 (m, 2H), 7.06-7.01 (m, 2H), 5.80 (dd, *J* = 7.4, 7.4 Hz, 1H), 3.77 (d, *J* = 12.3 Hz, 1H), 3.64 (d, *J* = 10.0 Hz, 1H), 2.67 (dd, *J* = 14.9, 7.6 Hz, 1H), 2.51 (dd, *J* = 14.9, 7.3 Hz, 1H), 1.46 (s, 3H), 1.34 (br s, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.9, 144.9, 142.3, 139.6, 131.5 (q, *J* = 33.9 Hz), 129.7, 128.4, 128.2, 127.3, 127.3, 127.2, 127.2, 123.7, 123.5 (q, *J* = 272.2 Hz), 120.4 (sept, *J* = 3.8 Hz), 70.9, 44.5, 38.0, 22.3;

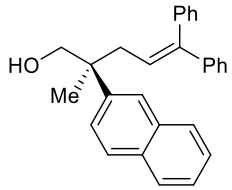
^{19}F NMR ($CDCl_3$, 476 MHz): δ –62.6 (s, 6F);

IR (Microscope, cm^{-1}): 3592, 3405, 3059, 3030, 2975, 2924, 1620, 1599, 1495, 1445, 1376, 1278, 1174, 1135;

HRMS (EI) for $C_{26}H_{22}F_6O$: calcd. 464.1575; found 464.1574;

$[\alpha]_D^{20}$: +10.09 (c 3.71, $CHCl_3$);

HPLC (Chiralcel OD): 5:95 *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 254 nm, T_{major} = 13.5 min, T_{minor} = 15.3 min, *er* = 95.5:4.5.



3-30

2-Methyl-2-(naphthalen-2-yl)-5,5-diphenylpent-4-en-1-ol (3-30): Prepared from aldehyde **3-51** (46 mg, 0.25 mmol) using the general procedure. Purified by flash column chromatography (10:1 to 5:1 hexane:EtOAc), PTLC (5:1 hexane:EtOAc) and isolated as a light yellow solid (67 mg, 71%).

M.p. 73-74 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.85-7.83 (m, 3H), 7.78 (s, 1H), 7.54-7.46 (m, 3H), 7.42-7.39 (m, 2H), 7.37-7.34 (m, 1H), 7.21-7.12 (m, 5H), 7.11-6.99 (m, 2H), 5.92 (dd, *J* = 7.3, 7.3 Hz, 1H), 3.80 (d, *J* = 11.0 Hz, 1H), 3.65 (d, *J* = 11.0 Hz, 1H), 2.79 (dd, *J* = 14.9, 6.9 Hz, 1H), 2.53 (dd, *J* = 14.9, 7.8 Hz, 1H), 1.51 (s, 3H), 1.23 (br s, 1H);

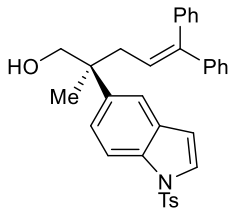
^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.6, 142.6, 141.8, 140.2, 133.4, 132.1, 130.0, 128.3, 128.2, 128.1, 128.1, 127.4, 127.2, 127.1, 127.0, 126.1, 125.9, 125.8, 125.4, 125.0, 71.9, 44.4, 38.1, 22.3;

IR (Microscope, cm^{-1}): 3577, 3401, 3056, 3022, 2966, 2928, 2875, 1631, 1598, 1506, 1443, 1376, 1031;

HRMS (EI) for $C_{28}H_{26}O$: calcd. 378.1984; found 378.1984;

$[\alpha]_D^{20}$: +2.06 (c 3.85, $CHCl_3$);

HPLC (Chiralpak AS): 5:95 *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 254 nm, T_{major} = 22.4 min, T_{minor} = 19.2 min, *er* = 96:4.



3-31

2-Methyl-5,5-diphenyl-2-(1-tosyl-1*H*-indol-5-yl)pent-4-en-1-ol (3-31): Prepared from aldehyde **3-52** (82 mg, 0.25 mmol) using the general procedure. Purified by flash column chromatography (6:1 to 3:1 hexane:EtOAc) and isolated as a white solid (64 mg, 49%).

M.p. 49-52 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (d, *J* = 8.7 Hz, 1H), 7.76 (m, 2H), 7.54 (d, *J* = 3.6 Hz, 1H), 7.44 (d, *J* = 1.6 Hz, 1H), 7.35-7.23 (m, 5H), 7.20-7.14 (m, 5H), 7.00 (m, 3H), 6.61 (d, *J* = 3.7 Hz, 1H), 5.82 (dd, *J* = 7.4, 7.4 Hz, 1H), 3.71 (dd, *J* = 10.9, 5.6 Hz, 1H), 3.56 (dd, *J* = 10.9, 7.7 Hz, 1H), 2.64 (dd, *J* = 14.8, 7.1 Hz, 1H), 2.42 (dd, *J* = 14.8, 7.7 Hz, 1H), 2.30 (s, 3H), 1.41 (s, 3H), 1.08 (dd, *J* = 7.6, 5.7 Hz, 1H);

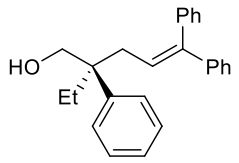
^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.9, 143.6, 142.7, 140.0, 139.4, 135.4, 133.4, 131.0, 129.9, 128.2, 128.0, 127.1, 127.0, 126.9, 126.8, 126.5, 125.3, 123.5, 119.7, 113.4, 109.2, 72.1, 44.2, 38.5, 22.4, 21.6;

IR (Microscope, cm^{-1}): 3575, 3452, 3055, 3023, 2969, 2926, 1597, 1577, 1494, 1461, 1371, 1264, 1172, 1132;

HRMS (EI) for $C_{33}H_{29}NO_2S$ $[M-H_2O]^+$: calcd. 503.1919; found 503.1922;

$[\alpha]_D^{20}$: +24.88 (c 0.79, $CHCl_3$);

HPLC (Chiralcel IB): 25:75 *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 254 nm, T_{major} = 8.6 min, T_{minor} = 9.2 min, *er* = 94:6.



3-35

2-Ethyl-2,5,5-triphenylpent-4-en-1-ol (3-35): Prepared from aldehyde **3-53** (37 mg, 0.25 mmol) using the general procedure. Purified by flash column chromatography (10:1 to 5:1 hexane:EtOAc), PTLC (5:1 hexane:EtOAc) and isolated as a yellow viscous liquid (16 mg, 19%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.32 (m, 5H), 7.31-7.29 (m, 2H), 7.25-7.15 (m, 6H), 7.11-7.06 (m, 2H), 5.92 (dd, *J* = 7.4, 7.4 Hz, 1H), 3.78 (d, *J* = 5.3 Hz, 2H), 2.58 (d, *J* = 7.2 Hz, 2H), 1.84-1.72 (m, 2H), 0.99 (dd, *J* = 6.6 Hz, 1H), 0.66 (dd, *J* = 7.4, 7.4 Hz, 3H);

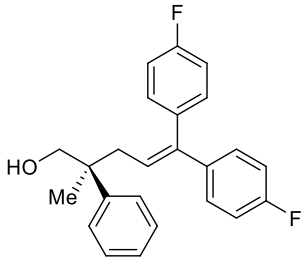
^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.8, 143.5, 142.8, 140.0, 129.9, 128.5, 128.3, 128.1, 127.2, 127.2, 127.0, 126.9, 126.2, 125.6, 67.4, 47.0, 34.3, 27.7, 8.1;

IR (Microscope, cm^{-1}): 3587, 3426, 3055, 3023, 2964, 2928, 2879, 1599, 1496, 1444, 1032;

HRMS (EI) for $C_{25}H_{26}O$: calcd. 342.1984; found 342.1977;

$[\alpha]_D^{20}$: +0.07 (c 0.84, $CHCl_3$);

HPLC (Chiralpak AS): 5:95 *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 254 nm, T_{major} = 14.4 min, T_{minor} = 12.5 min, *er* = 80:20.



3-54

5,5-Bis(4-fluorophenyl)-2-methyl-2-phenylpent-4-en-1-ol (3-54): Prepared from aldehyde **3-1** (34.0 mg, 0.25 mmol) and allylic alcohol **3-14** (123 mg, 0.50 mmol) with general procedure. Purified by flash column chromatography (10:1 to 5:1 hexane:EtOAc) and isolated as a light yellow oil (47 mg, 52.0%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.28 (m, 4H), 7.27-7.22 (m, 1H), 7.08-7.01 (m, 4H), 7.00-6.95 (m, 2H), 6.91-6.85 (m, 2H), 5.79 (dd, *J* = 7.3, 7.3 Hz, Hz, 1H), 3.71 (d, *J* = 11.0 Hz, 1H), 3.56 (d, *J* = 10.9 Hz, 1H), 2.62 (dd, *J* = 14.8, 7.0 Hz, 1H), 2.39 (dd, *J* = 14.8, 7.7 Hz, 1H), 1.37 (s, 3H), 1.16 (br s, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.1 (d, *J* = 246.4 Hz), 161.9 (d, *J* = 245.1 Hz), 144.15, 141.54, 138.7 (d, *J* = 3.2 Hz), 135.8 (d, *J* = 3.4 Hz), 131.5 (d, *J* = 7.9 Hz), 128.7 (d, *J* = 7.9 Hz), 128.6, 126.8, 126.5, 125.8, 115.3 (d, *J* = 21.3 Hz), 114.9 (d, *J* = 21.4 Hz), 72.0, 44.2, 38.2, 22.1;

^{19}F NMR ($CDCl_3$, 476 MHz): δ –115.0 (ddd, *J* = 14.1, 8.2, 6.0 Hz, 1F), –115.7 (ddd, *J* = 13.9, 8.6, 5.5 Hz, 1F);

IR (Microscope, cm^{-1}): 3386, 3056, 2965, 2931, 1894, 1602, 1508, 1223, 840;

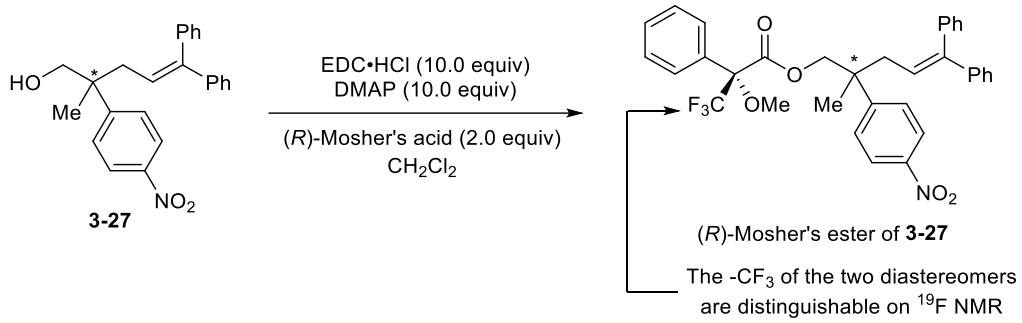
HRMS (EI) for $C_{24}H_{22}F_2O$: calcd. 328.18271; found 328.18263;

$[\alpha]_D^{20}$: +10.28 (c 0.84, $CHCl_3$);

HPLC (Chiralpak AS): 5:95 *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 254 nm, T_{major} = min, T_{minor} = min, *er* = 94:6.

3.11.6 Enantiomeric ratio determination of compound 3-27

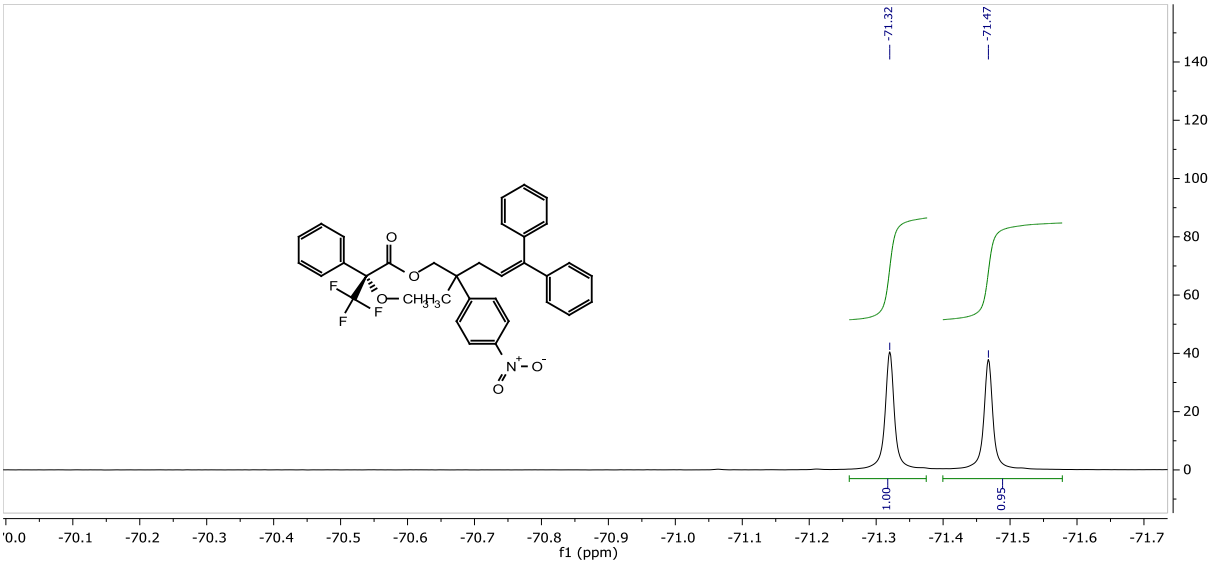
The enantiomeric ratio of chiral compound **3-27** was determined by comparison of the diastereomeric ratio of the corresponding (*R*)-Mosher's ester due to a difficult separation of racemic **3-27** with chiral HPLC. Both racemic and chiral **3-27** were subjected to the following procedure for the synthesis of the corresponding (*R*)-Mosher's ester.



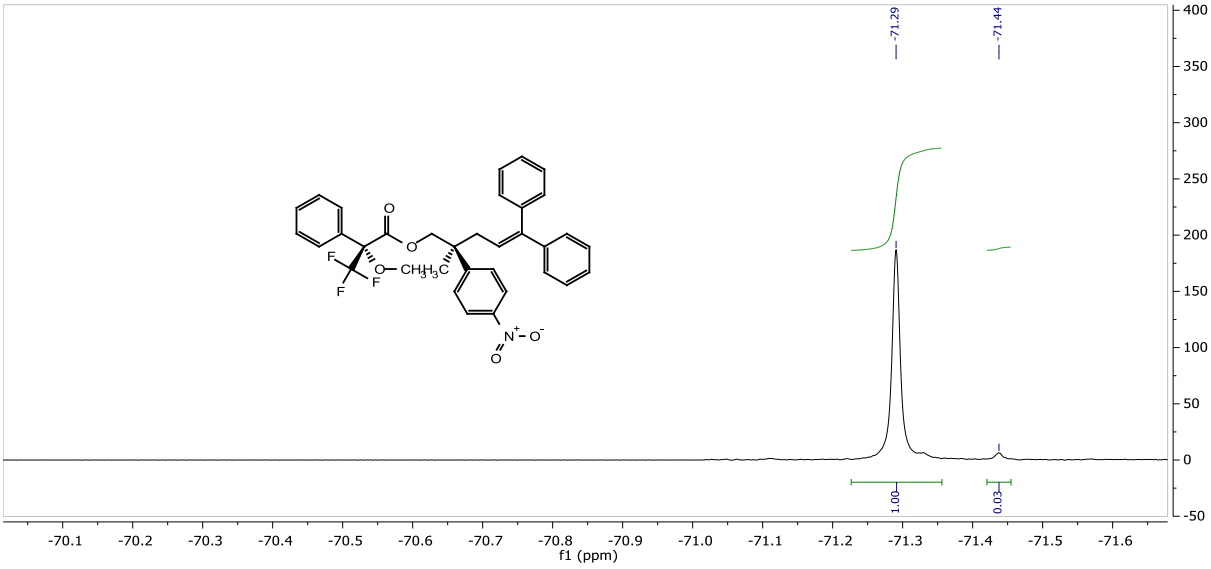
(*R*)-Mosher's ester of compound 3-27: To a 10 mL flamed round bottom flask was added (*R*)-Mosher's acid (14 mg, 0.06 mmol), 4-dimethylaminopyridine (37 mg, 0.30 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (58 mg, 0.30 mmol) in DCM (0.5 mL). Reaction mixture was stirred for 15 min before the addition of compound **3-27** (11 mg, 0.03 mmol) in DCM (0.5 mL). Reaction mixture was diluted with 10 mL DCM after 96 h. The resulting organic layer was washed by 1 M HCl aqueous solution, 1M NaOH solution and brine prior to drying over $MgSO_4$, filtration and concentration. The crude product was subjected to column chromatography (hexane:EtOAc = 4:1) to give the (*R*)-MTPA ester of compound **3-27** as a light yellow oil.

^{19}F NMR ($CDCl_3$, 476 MHz): δ_{major} = –71.3 ppm, δ_{minor} = –71.4 ppm, dr = 97:3, *er* (compound **3-27**) = 97:3.

Racemic:

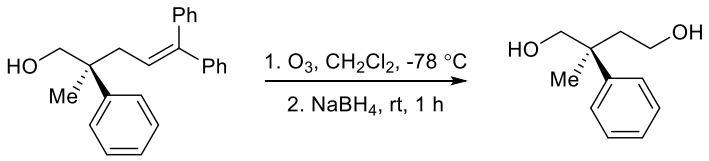


Optically enriched:



3.11.7 Determination of absolute stereochemistry

The absolute configuration of compound **3-20** was determined as **(*S*)** by chemical correlation with the known compound **(*R*)-3-36** by Aggarwal and co-workers.[31] All other absolute configurations were assigned by analogy based on a uniform reaction mechanism.



3-20 (94:6 er) **(*S*)-3-36**

(*S*)-2-Methyl-2-phenylbutane-1,4-diol (3-36): To a flame-dried 5 mL round bottom flask charged with a stir bar, was added a solution of compound **3-20** (13 mg, 0.04 mmol) in 3 mL of DCM/MeOH (v:v = 1:1). The solution was cooled down to -78 °C and stirred for 10 min. Ozone was bubbled through the alkene solution until a blue color persisted for 5 min. Nitrogen was bubbled through the solution to get rid of the excess ozone for 10 min. The reaction was then quenched with sodium borohydride (14 mg, 0.38 mmol) at -78 °C before warming up to room temperature. The reaction mixture was stirred at room temperature for another 1 h. Upon completion, 15 mL of water was added and the resulting mixture was extracted with DCM (3 × 10 mL). The combined organic layers were washed by 10 mL brine, dried over $MgSO_4$, filtered

and concentrated. Pure product was isolated as a colorless oil (5 mg, 72%) after flash column chromatography (5:1 to 1:1 hexane:EtOAc).

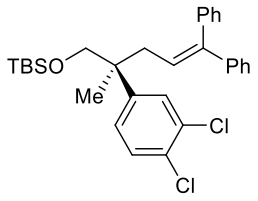
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40-7.32 (m, 4H), 7.25-7.20 (m, 1H), 3.79 (d, *J* = 11.2 Hz, 1H), 3.74-3.67 (m, 2H), 3.58 (dt, *J* = 10.8, 6.3 Hz, 1H), 2.09-1.79 (m, 4H), 1.36 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.2, 128.6, 126.4, 126.4, 71.3, 59.5, 42.5, 41.6, 23.3;

$[\alpha]_D^{20}$: –3.10 (c 0.49, $CHCl_3$);

Lit. $[\alpha]_D^{20}$: +5.0 (c 0.90, $CHCl_3$ for (*R*) enantiomer, er > 99:1).[31]

3.11.8 Derivatization of compound 3-25



3-38

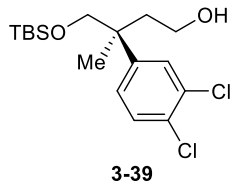
(*S*)-*tert*-Butyl ((2-(3,4-dichlorophenyl)-2-methyl-5,5-diphenylpent-4-en-1-yl)oxy) dimethyl silane (3-38): To a 25 mL round bottom flask charged with a stir bar, was added a solution of chiral alcohol **3-25** (500 mg, 1.26 mmol) in 2 mL of DCM followed by imidazole (172 mg, 2.52 mmol). The reaction mixture was then cooled down to 0 °C and stirred for 10 min. A solution of *tert*-butyldimethylsilyl chloride (190 mg, 1.39 mmol) in 2 mL of DCM was added slowly to the flask. White solid precipitated upon the complete addition. The reaction mixture was allowed to warm up to room temperature and stirred overnight. Upon completion, 15 mL of water was added and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed by 20 mL brine, dried over $MgSO_4$, filtered and concentrated. Pure product was isolated as a yellow oil (623 mg, 96%) after flash column chromatography (40:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39-7.29 (m, 5H), 7.23-7.16 (m, 3H), 7.12-7.08 (m, 3H), 7.07-7.03 (m, 2H), 5.82 (dd, *J* = 7.4, 7.4 Hz, 1H), 3.51 (d, *J* = 9.7 Hz, 1H), 3.46 (d, *J* = 9.7 Hz, 1H), 2.60 (dd, *J* = 15.0, 7.2 Hz, 1H), 2.43 (dd, *J* = 15.0, 7.6 Hz, 1H), 1.29 (s, 3H), 0.79 (s, 9H), -0.09 (s, 3H), -0.10 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.1, 143.8, 142.6, 140.0, 131.9, 129.9, 129.8, 129.6, 129.5, 128.2, 128.1, 127.1, 127.0, 127.0, 126.6, 125.1, 71.6, 44.0, 37.8, 25.8, 22.1, 18.1, -5.6, -5.7;

IR (Microscope, cm^{-1}): 3080, 3958, 3024, 2929, 2956, 2856, 1598, 1555, 1472, 1257, 1105;

$[\alpha]_D^{20}$: +22.01 (c 1.67, $CHCl_3$).



3-39

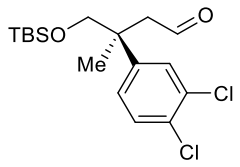
(*S*)-4-((tert-Butyldimethylsilyl)oxy)-3-(3,4-dichlorophenyl)-3-methylbutan-1-ol (3-39): To a flame-dried 5 mL round bottom flask charged with a stir bar, was added a solution of compound **3-38** (46 mg, 0.09 mmol) in 3 mL of DCM/MeOH (v:v = 1:1). The solution was cooled down to -78 °C and stirred for 10 min. Ozone was bubbled through the alkene solution until a blue color persisted for 5 min. Nitrogen was bubbled through the solution to get rid of the excess ozone for 10 min. The reaction was then quenched with sodium borohydride (34 mg, 0.90 mmol) at -78 °C before warming up to room temperature. The reaction mixture was stirred at room temperature for another 1 h. Upon completion, 15 mL of water was added and the resulting mixture was extracted with DCM (3 × 10 mL). The combined organic layers were washed by 20 mL brine, dried over $MgSO_4$, filtered and concentrated. Pure product was isolated as a colorless oil (29 mg, 89%) after flash column chromatography (8:1 to 1:1 hexane:MTBE).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44 (d, *J* = 2.3 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.18 (dd, *J* = 8.5, 2.3 Hz, 1H), 3.65-3.58 (m, 2H), 3.55-3.47 (m, 2H), 1.99 (dd, *J* = 6.9. 6.9 Hz, 2H), 1.30 (s, 3H), 0.86 (s, 9H), -0.00 (s, 3H), -0.01 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.4, 132.2, 130.0, 129.9, 128.9, 126.0, 71.6, 59.3, 42.2, 41.5, 25.8, 22.4, 18.2, -5.6, -5.7;

IR (Microscope, cm^{-1}): 3353, 2954, 2930, 2885, 2857, 1555, 1473, 1388, 1257, 1098, 1028;

$[\alpha]_D^{20}$: –1.04 (c 1.54, $CHCl_3$).



3-55

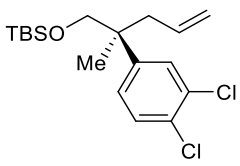
(*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-3-(3,4-dichlorophenyl)-3-methylbutanal (3-55): To a flame-dried 5 mL round bottom flask charged with a stir bar, was added a solution of compound **3-38** (46 mg, 0.09 mmol) in 2 mL of DCM. The solution was cooled down to -78 °C and stirred for 10 min. Ozone was bubbled through the alkene solution until a blue color persisted for 5 min. Nitrogen was bubbled through the solution to get rid of the excess ozone for 10 min. The reaction was then quenched with triphenylphosphine (58 mg, 0.22 mmol) at -78 °C before warming up to room temperature. The reaction mixture was stirred at room temperature for another 16 h. Upon completion, the solvent was removed in vacuo to afford the crude mixture. Pure product was isolated as a colorless oil (19 mg, 59%) after flash column chromatography (100:1 to 40:1 hexane:MTBE).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.59 (t, *J* = 2.6 Hz, 1H), 7.48 (d, *J* = 2.3 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.20 (dd, *J* = 8.5, 2.3 Hz, 1H), 3.67 (d, *J* = 9.8 Hz, 1H), 3.57 (d, *J* = 9.8 Hz, 1H), 2.81 (dd, *J* = 16.1, 2.7 Hz, 1H), 2.70 (dd, *J* = 16.0, 2.6 Hz, 1H), 1.42 (s, 3H), 0.87 (s, 9H), -0.01 (s, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.6, 144.9, 132.5, 130.6, 130.2, 128.9, 126.0, 71.3, 51.6, 42.2, 25.8, 23.1, 18.2, -5.7, -5.7;

IR (Microscope, cm^{-1}): 2955, 2930, 2889, 2857, 2739, 1722, 1473, 1141;

$[\alpha]_D^{20}$: +3.67 (c 0.92, $CHCl_3$).



3-40

(*S*)-*tert*-Butyl((2-(3,4-dichlorophenyl)-2-methylpent-4-en-1-yl)oxy)dimethylsilane (3-40): To a suspension of methyltriphenylphosphonium bromide (250 mg, 0.70 mmol) in 5 mL of THF was added *n*-BuLi solution (318 µL of 2.2 M solution in hexane, 0.70 mmol) at 0 °C under inert

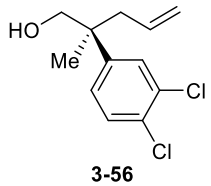
atmosphere to give a light orange solution. The reaction mixture was warmed up to room temperature and stirred for 1 h before the addition of compound **3-55** (168 mg, 0.47 mmol) solution in 5 mL of THF. After full consumption of the aldehyde, 10 mL of water was added to quench the reaction. The resulting mixture was then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed by 20 mL of brine, dried over $MgSO_4$, filtered and concentrated. Pure product was isolated as a colorless oil (119 mg, 71%) after flash column chromatography (100:1 haxane:Et_2O).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44 (d, *J* = 2.2 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.18 (dd, *J* = 8.5, 2.3 Hz, 1H), 5.59-5.47 (m, 1H), 5.05-4.95 (m, 2H), 3.55 (d, *J* = 9.6 Hz, 1H), 3.52 (d, *J* = 9.6 Hz, 1H), 2.51 (dd, *J* = 14.0, 6.8 Hz, 1H), 2.35 (dd, *J* = 14.0, 7.7 Hz, 1H), 1.24 (s, 3H), 0.85 (s, 9H), -0.04 (s, 3H), -0.05 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.5, 134.2, 131.8, 129.7, 129.6, 129.3, 126.5, 117.8, 71.0, 42.9, 42.5, 25.8, 22.0, 18.2, -5.6, -5.7;

IR (Microscope, cm^{-1}): 3078, 2955, 2929, 2857, 1640, 1556, 1472, 1257, 1101;

$[\alpha]_D^{20}$: +19.79 (c 0.48, $CHCl_3$).



3-56

(*S*)-2-(3,4-Dichlorophenyl)-2-methylpent-4-en-1-ol (3-56): To a 10 mL round bottom flask charged with a stir bar and compound **3-40** (119 mg, 0.33 mmol) in 5 mL THF, was added tetrabutylammonium fluoride solution (0.5 mL of 1.0 M solution in THF, 0.50 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before warming up to room temperature. After 24 h, 10 mL of saturated NH_4Cl aqueous solution was added to quench the reaction. The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 20 mL of brine, dried over $MgSO_4$, filtered and concentrated. Pure product was isolated as a colorless oil (77.0 mg, 96%) with flash column chromatography (10:1 to 5:1 hexane:EtOAc).

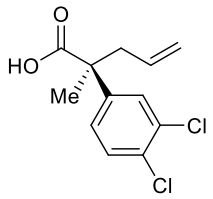
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44 (d, *J* = 2.3 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.21 (dd, *J* = 8.5, 2.3 Hz, 1H), 5.62-5.51 (m, 1H), 5.09-5.00 (m, 2H), 3.73 (d, *J* = 10.9 Hz, 1H), 3.61 (d, *J* = 11.0

Hz, 1H), 2.50 (dd, *J* = 13.9, 6.7 Hz, 1H), 2.35 (dd, *J* = 14.0, 7.8 Hz, 1H), 1.37 (br s, 1H), 1.31 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.5, 133.7, 132.5, 130.3, 130.2, 129.1, 126.3, 118.3, 71.2, 43.1, 42.8, 21.9;

IR (Microscope, cm^{-1}): 3368, 3076, 2976, 2926, 2881, 1640, 1557, 1474, 1386, 1141, 1028;

$[\alpha]_D^{20}$: +23.72 (c 0.65, $CHCl_3$).



3-41

(*S*)-2-(3,4-Dichlorophenyl)-2-methylpent-4-enoic acid (3-41): To a suspension of IBX (482 mg, 1.72 mmol) in 2 mL of EtOAc in a 10 mL round bottom flask, was added a solution of compound **3-56** (70 mg, 0.29 mmol) in 2 mL of EtOAc under inert atmosphere. The reaction was then heated up to 80 °C and stirred for 16 h. After full consumption of the starting material, the reaction mixture was cooled down to 0 °C for 15 min and then filtered. The filter cake was washed with EtOAc (3 × 5 mL). The combined organic layers were concentrated and gave the crude aldehyde, which was subjected to next step without further purification. The crude aldehyde product was dissolved in 9 mL of 1:1 mixture of *tert*-butanol and 2-methyl-2-butene at 0 °C. Sodium chlorite (52 mg, 0.57 mmol) and sodium phosphate monobasic monohydrate (79 mg, 0.57 mmol) in 1 mL of water was added slowly to the aldehyde solution. The reaction mixture was stirred at 0 °C until full consumption of the aldehyde as monitor by TLC. After 1 h, 10 mL of 1 M HCl was added to quench the reaction. The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered and concentrated. Pure product was isolated as a light yellow oil (43 mg, 58%) after flash column chromatography (10:1 to 3:1 hexane:EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46 (d, *J* = 2.3 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.22 (dd, *J* = 8.5, 2.3 Hz, 1H), 5.58 (ddt, *J* = 16.5, 10.6, 7.2 Hz, 1H), 5.10 (m, 1H), 5.08 (m, 1H), 2.78 (dd, *J* = 13.9, 7.4 Hz, 1H), 2.66 (dd, *J* = 13.8, 7.1 Hz, 1H), 1.55 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 180.3, 142.5, 132.8, 132.6, 131.4, 130.4, 128.6, 126.0, 119.5, 49.3, 43.3, 22.1;

IR (Microscope, cm^{-1}): 3080, 2982, 2927, 2637, 1703, 1642, 1559, 1475, 1385, 1272, 1030;

HRMS (ESI) for $C_{12}H_{11}Cl_2O_2$ $[M-H]^-$: calcd. 257.0142; found 257.0143;

$[\alpha]_D^{20}$: +36.07 (c 3.51, $CHCl_3$).

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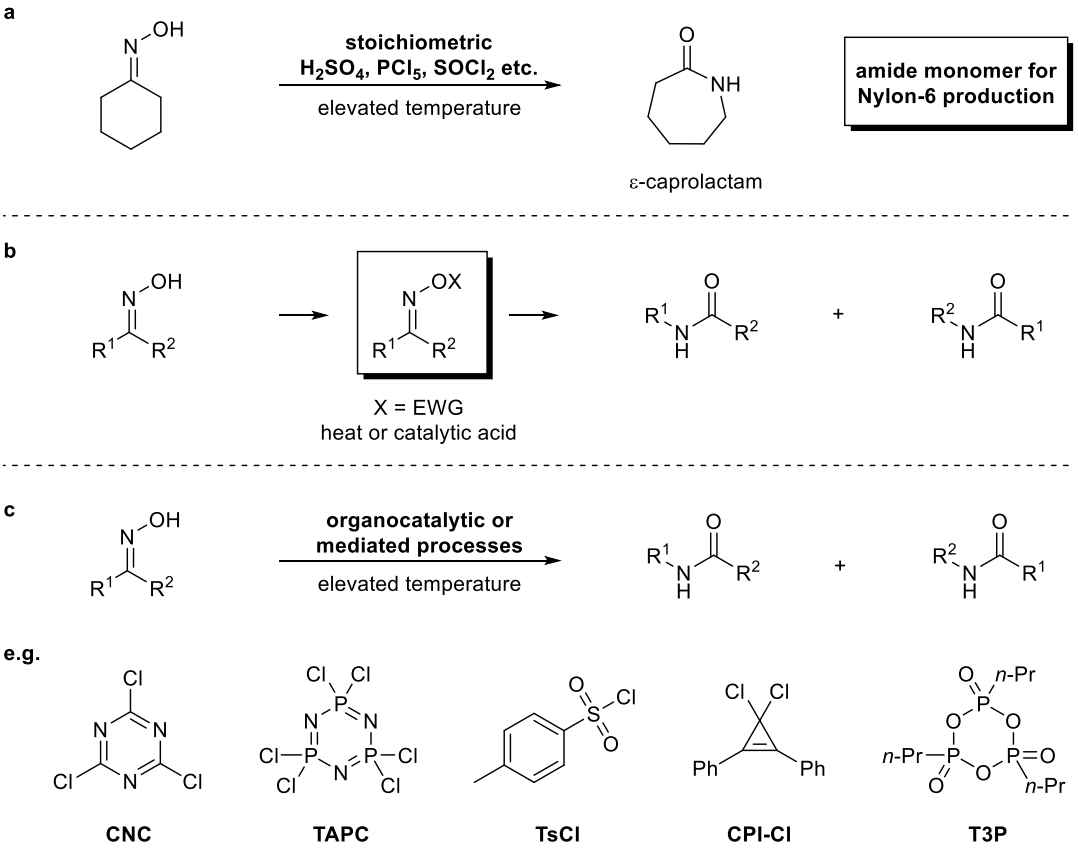
Chapter 4 Boronic Acid Catalyzed Beckmann Rearrangement

4.1 Introduction

As described in the previous chapters, boronic acid catalysis (BAC) displays diverse applications in the area of direct activation of alcohol C–O bonds.[1] By taking advantage of the ability of boronic acids to form covalent bonds with alcohols in a reversible manner, successful benzylation of arenes and asymmetric allylation of branched aldehydes were achieved with π-activated alcohol substrates.[2] It can be envisioned that this transient activation could be expanded to other hydroxyl-containing functional groups, such as N–OH. In this regard, the direct activation of oxime N–OH bonds for the Beckmann rearrangement is particularly attractive. The Beckmann rearrangement has received great attention since its discovery in 1886.[3] Empowered by its ability to transform an oxime into an amide, this reaction has not only been extensively studied in academic laboratories, but also has been applied in industrial synthesis. Notably, the Beckmann rearrangement is exploited for the transformation of cyclohexanone to ε-caprolactam, which is the amide monomer to produce synthetic fabric material, such as Nylon-6.[4] Moreover, it is widely used in the production of pharmaceutical agents and in the field of natural product synthesis.[5]

Traditionally, the Beckmann rearrangement of free oximes requires high temperatures with stoichiometric amounts of strong Brønsted or Lewis acids, such as concentrated sulfuric acid, polyphosphoric acid (PPA), phosphorus pentachloride (PCl_5), thionyl chloride ($SOCl_2$) and hydroxylamine sulfonic acid.[6] These methods not only use harsh conditions leading to great limitations on suitable substrates, but also generate large amounts of by-products (**Scheme 4-1a**). In this regard, various stoichiometric or sub-stoichiometric methods with milder Lewis acid were developed, such as $HgCl_2$,[7] $Yb(OTf)_3$,[8] $[RhCl(COD)]_2$,[9] $BiCl_3$,[10] $Cu(OAc)_2$,[11] $In(NO_2)_3$,[12] iodine,[13] $FeCl_3$-$AgSbF_6$[14] and bromodimethyl sulfonium bromide–$ZnCl_2$.[15] However, many of these milder promoters still require refluxing conditions. Although milder conditions using oxime derivatives (e.g. O-picryl oxime ethers, O-sulfonyl or O-acetyl oxime ester) were studied,[16] the need for pre-activation of the oxime adds extra synthetic steps and renders this strategy less attractive (**Scheme 4-1b**). From this perspective, organocatalysis presents itself as a mild

alternative for the direct Beckmann rearrangement with the potential for broader substrate tolerance. Previously reported organocatalyzed or mediated systems include the use of cyanuric chloride (CNC),[17] triphosphazene (TAPC),[18] TsCl,[19] dichloridecyclopropene (CPI-Cl)[20] and propylphosphonic anhydride (T3P).[21] Despite their efficiency, elevated temperature or extra Brønsted/Lewis acid are generally required by these chlorine or phosphorus based catalytic systems. Moreover, the toxicity of these reagents, such as cyanuric chloride, places limitations on their application (**Scheme 4-1c**).



Scheme 4-1. (a) The traditional Beckmann rearrangement with strong acid under elevated temperature; (b) Beckmann rearrangement under milder conditions *via* oxime ester formation; (c) Reported organocatalytic or mediated Beckmann rearrangement.

4.2 Objective

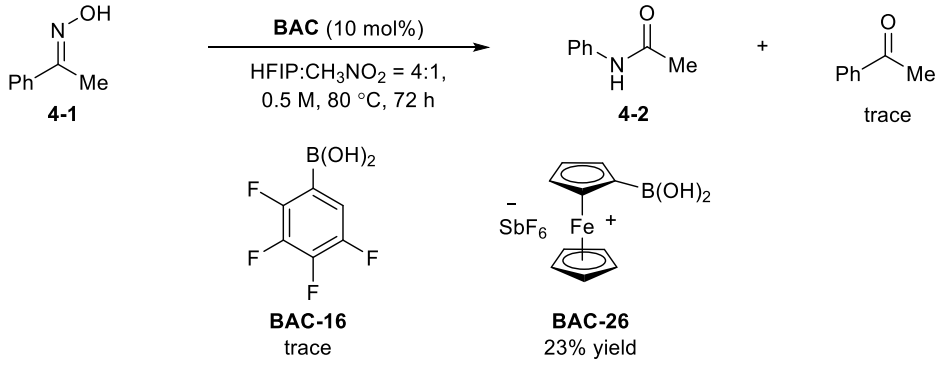
After 130 years of development, the Beckmann rearrangement still suffers from limitations such as the use of relative harsh conditions, inert atmosphere, anhydrous conditions and the lack of

platforms for potential asymmetric variants. This chapter will describe our efforts towards the development of an organocatalytic Beckmann rearrangement under relatively mild conditions using boronic acid catalysis.

4.3 Optimization of Beckmann rearrangement *via* BAC

4.3.1 Initial attempts with BAC-16 and BAC-26

Based on our previous observations, electron poor arylboronic acids generally exhibit a higher polarization effect on alcohol C–O bonds. At the outset of this project, it was assumed that the same idea could be applicable to the N–O bonds of oximes. Therefore, the direct Beckmann rearrangement of oxime **4-1** was attempted with boronic acids **BAC-16** and **BAC-26** under the previously optimized solvent mixture HFIP:CH_3NO_2 (4:1) for the direct Friedel-Craft benzylation. Unfortunately, it was found that the previously optimal electron poor boronic acids did not result in any significant conversion of oxime **4-1** to the desired product **4-2**, even under high temperatures and prolonged reaction times (**Scheme 4-2**). In both cases, the oxime **4-1** was recovered along with trace amount of the hydrolyzed acetophenone. Decomposition of the ferrocenium boronic acid **BAC-26** was observed when oxime **4-1** was present.

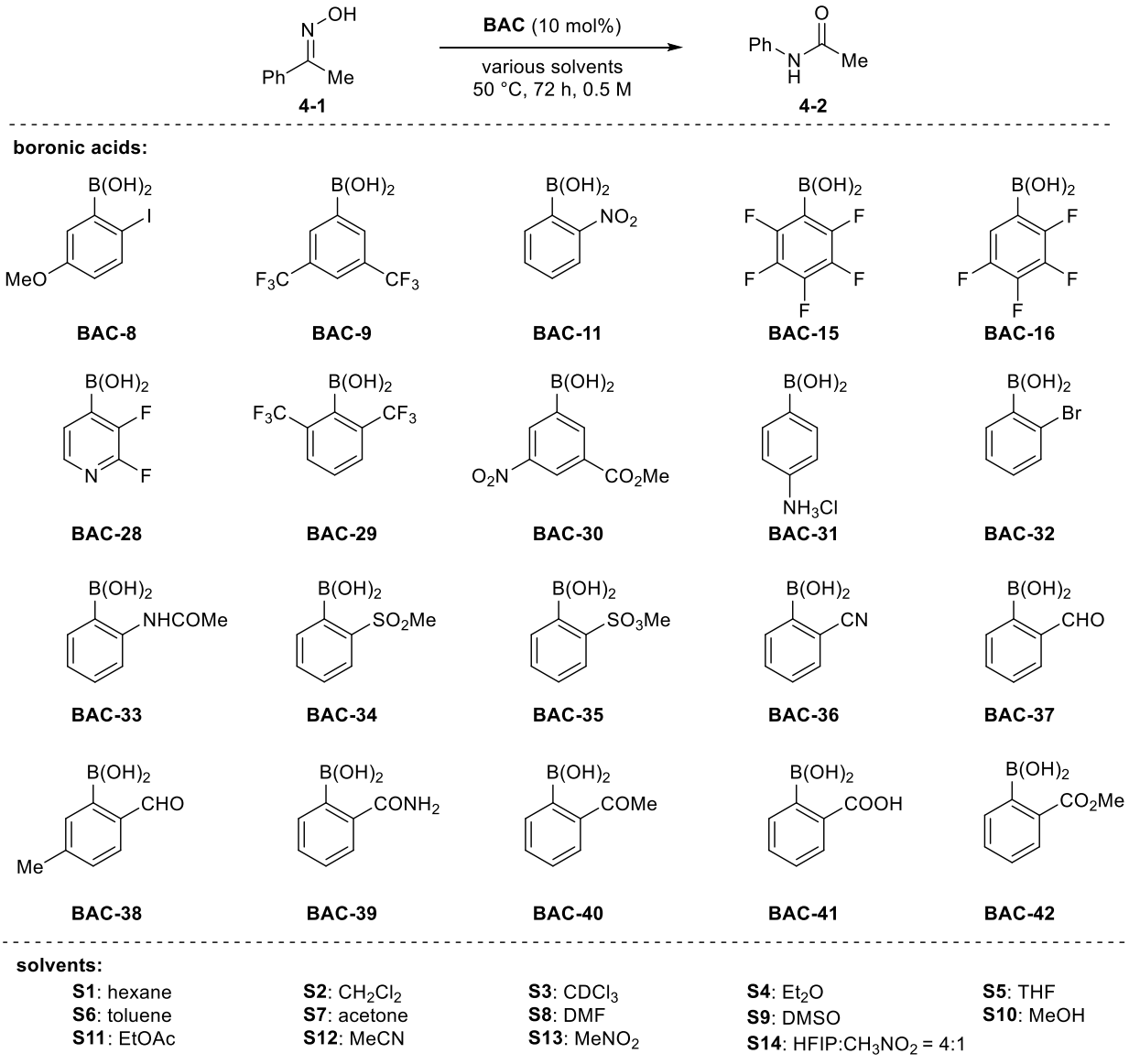


Scheme 4-2. Initial attempts of Beckmann rearrangement with electron poor boronic acids.

4.3.2 Screening of different boronic acids

Since the initial attempts to catalyze the Beckmann rearrangement with **BAC-16** and **BAC-26** were not successful, we turned our efforts to the screening of other boronic acids and different

solvents. A number of boronic acids were selected for screening; particularly a diversity of *ortho*-substituted arylboronic acids, as well as those previously shown to be reactive in various transformations (**Scheme 4-3**). Thus, along with 14 different solvents, over 250 experiments were performed for reaction evaluation. Reactions that showed significant amounts of product on thin layer chromatography (TLC) were subjected to further ^{1}H NMR analysis; the reactions were otherwise discarded. The results are presented in **Table 4-1**. In most cases, the starting oxime **4-1** was recovered along with a trace amount of the acetophenone when no desired reaction took place.



Scheme 4-3. Various boronic acids and solvents screened in the Beckmann rearrangement of **4-1**.

yield (%)[a]	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14
BAC-8	×	×	×	×	×	×	×	×	×	×	×	×	×	×
BAC-9	×	×	×	×	×	×	×	×	×	×	×	×	×	×
BAC-11	×	×	×	×	×	×	×	×	×	×	×	×	×	×
BAC-15	×	×	×	×	×	×	×	×	×	×	×	×	×	×
BAC-16	×	×	×	×	×	×	×	×	×	×	×	×	×	×
BAC-28	×	×	×	×	×	×	×	×	×	×	×	×	×	×
BAC-29	×	×	×	×	×	×	×	×	×	×	×	×	×	×
BAC-30	×	×	×	×	×	×	×	×	×	×	×	×	×	×
BAC-31	×	×	×	×	×	×	×	×	×	×	×	×	×	×
BAC-32	×	×	×	×	×	×	×	×	×	×	×	×	×	×
BAC-33	×	×	×	×	×	×	×	×	×	×	×	×	×	×
BAC-34	×	×	×	×	×	×	×	×	×	×	×	×	×	×
BAC-35	-	-	-	-	-	-	-	-	-	-	-	-	-	×
BAC-36	×	×	×	×	×	×	×	×	×	×	×	×	×	×
BAC-37	×	×	×	×	×	×	×	×	×	×	×	×	×	8
BAC-38	×	×	×	×	×	×	×	×	×	×	×	×	×	13
BAC-39	×	×	×	×	×	×	×	×	×	×	×	×	×	18
BAC-40	×	×	×	×	×	×	×	×	×	×	×	×	×	×
BAC-41	×	×	×	×	×	×	×	×	×	×	×	×	×	9
BAC-42	×	×	×	×	×	×	×	×	×	×	×	×	×	100

[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as an internal standard. Reaction with trace or no product was marked as "×". The reaction that was not run was marked as "-".

Table 4-1. Boronic acid and preliminary solvent screening for the Beckmann rearrangement.

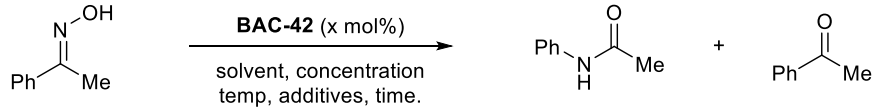
As shown in **Table 4-1**, most of the experiments afforded negative results with no desired amide product obtained; mostly oxime **4-1** and trace acetophenone from oxime hydrolysis were recovered. Yet, a noticeable amount of product was detected with five different boronic acids in the solvent mixture of HFIP:CH_3NO_2 (v:v = 4:1). While most of these boronic acids (**BAC-37**, **38**, **39** and **41**) only provided low conversion to amide **4-2**, boronic acid **BAC-42** with an *ortho* methyl carboxyester substituent gave full conversion to the desired amide product **4-2**. In light of this discovery, we decided to explore other reaction parameters such as solvent, concentration, temperature and additives to improve the efficiency of the BAC Beckmann rearrangement.

4.3.3 Optimization of other reaction parameters

Considering that a high yield was obtained during the initial boronic acid screening (**Table 4-1**), the optimization of the reaction conditions was performed with the following objectives: (a) minimizing the use of HFIP; (b) decreasing the amount of the boronic acid catalyst loading.

4.3.3.1 Solvent optimization to decrease the amount of HFIP

Even though the use of HFIP is generally beneficial to many cationic reactions,[22] its use is less desirable due to its higher cost in comparison to other solvents. To decrease the amount of HFIP, differing ratios of HFIP:CH_3NO_2 were explored at various concentrations (**Table 4-2**). As expected, decreasing the amount of HFIP led to lower conversion to the product. The use of at least 50% HFIP was required to obtain high conversion at 50 °C (entries 1-4). Since a large proportion of HFIP is inevitable, we sought to decrease the amount of solvent by increasing the concentration (entries 5-6). The reaction provided decent yield with up to 1.0 M of oxime **4-1** in the HFIP:CH_3NO_2 1:1 mixture after 72 hours (entry 5). Moreover, the reaction time could be shortened to 24 hours by increasing the amount of catalyst to 20 mol% (entry 7). However, lowering the temperature (entry 8) and decreasing the reaction time to 5 hours with or without molecular sieves (entry 9) were unsuccessful. All in all, the conditions of entry 7 best minimize the amount of HFIP. Moreover, no pre-drying of solvent or inert atmosphere is required.



4-1 (0.5 mmol) **4-2** trace

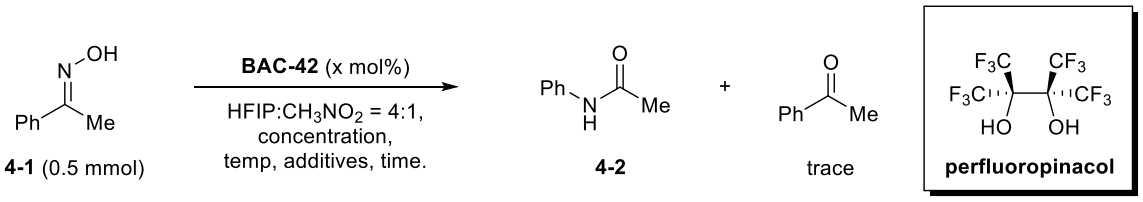
entry	x	solvent (x:y)	[M]	T (°C)	t (h)	yield (%)[a]
1	10	HFIP:CH_3NO_2 (4:1)	0.5	50	72	100
2	10	HFIP:CH_3NO_2 (2:1)	0.5	50	72	93
3	10	HFIP:CH_3NO_2 (1:1)	0.5	50	72	79
4	10	HFIP:CH_3NO_2 (1:4)	0.5	50	72	60
5	10	HFIP:CH_3NO_2 (1:1)	1.0	50	72	79
6	10	HFIP:CH_3NO_2 (1:1)	2.0	50	72	45
7	20	HFIP:CH_3NO_2 (1:1)	1.0	50	24	84
9	20	HFIP:CH_3NO_2 (1:1)	1.0	rt	24	26
8	20	HFIP:CH_3NO_2 (1:1)	1.0	50	5	59 (70)[b]

[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as an internal standard. [b]Reaction was run with 100 mg 4 Å MS.

Table 4-2. Evaluation of other parameters to decrease the amount of HFIP solvent.

4.3.3.2 Optimization of the boronic acid stoichiometry

As detailed in **Table 4-3**, efforts were also placed on developing conditions that minimize the amount of boronic acid and achieve the rearrangement under mild conditions. Similar to the previous observation, as the reaction concentration increased, the yield of amide **4-2** slightly decreased (entries 1-3). The rearrangement still provided a good yield of 87% under 1.0 M concentration of oxime **4-1** with 10 mol% of **BAC-42** (entry 2). It was soon discovered that higher reaction temperature was unnecessary; the reaction could be performed in ambient conditions without sacrificing the reaction yield (entry 4). Although a moderate, 72% yield of the amide was obtained within 24 hours (entry 5), a very low conversion to **4-2** was observed when 5 mol% of **BAC-42** was used (entry 6). Since altering the other reaction parameters was unfruitful, the effect of additives was explored next. Inspired by the need for a large amount of HFIP, it was suspected that HFIP might form a boronic ester with **BAC-42**. This way, a more electrophilic HFIP boronic ester could be accountable for the unique reactivity of **BAC-42**. Thus, 5 mol% of perfluoropinacol was used as an additive to mimic the proposed effect of HFIP, with a more favorable cyclic boronic ester. Gratifyingly, a high isolated yield (93%) of amide **4-2** was achieved with only 5 mol% of **BAC-42** (entry 7). Decreasing the reaction time below 24 hours resulted in a substantially lower conversion (entry 8).



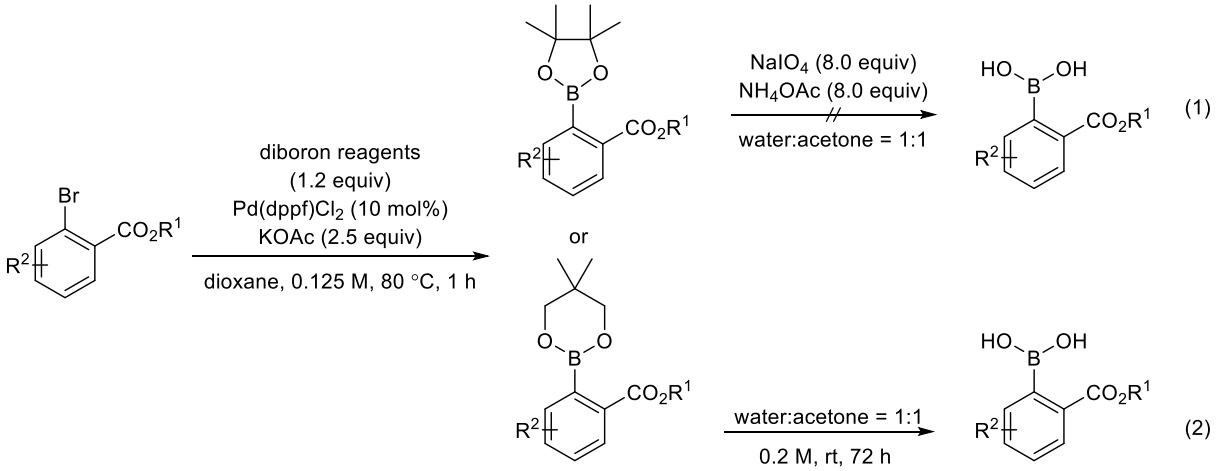
entry	x	[M]	T (°C)	t (h)	additive	yield (%)[a]
1	10	0.5	50	72	-	100
2	10	1.0	50	72	-	87
3	10	2.0	50	72	-	78
4	10	1.0	rt	72	-	86
5	10	1.0	rt	24	-	72
6	5	1.0	rt	24	-	43
7	5	1.0	rt	24	perfluoropinacol[b]	93[d]
8	5	1.0	rt	6	perfluoropinacol[b]	37[c]

[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as internal standard. [b]The reaction was run with 5 mol% perfluoropinacol. [c]Isolated yield.

Table 4-3. Evaluation of other parameters to decrease the amount of boronic acid.

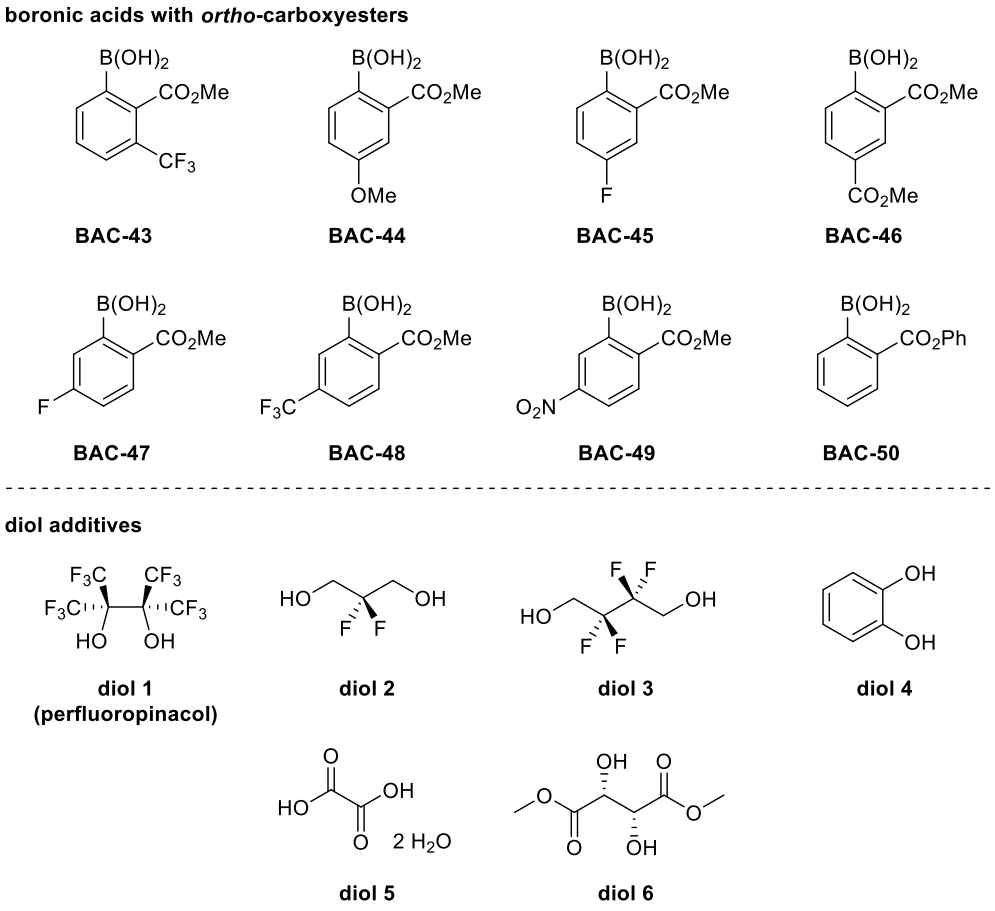
4.3.3.3 Structural optimization of arylboronic acids with an *ortho*-carboxyester

Encouraged by the preliminary results described in Section 4.3.3.2, an investigation of further structural modifications of the boronic acids and other diol additives was conducted. Although preparative methods for boronic acids with *ortho*-carboxyester units exist, only a handful of these boronic acids are commercially available due to their challenging synthesis. After careful considerations, the synthetic routes shown in **Scheme 4-4** were identified and attempted. Although the method listed in equation (1) seemed more feasible, deprotection of the pinacol boronic ester turned out to be difficult under classical conditions. As a result, the method illustrated in equation (2) was adopted for the preparation of boronic acids from the corresponding bromo arenes with *ortho*-carboxyester substituents *via* Miyaura borylation and sequential deprotection. Boronic acids **BAC-44**, **BAC-49** and **BAC-50** were prepared for further evaluation in the Beckmann rearrangement (**Scheme 4-5**).



Scheme 4-4. Synthetic routes for the preparation of different boronic acids with *ortho*-carboxyester.

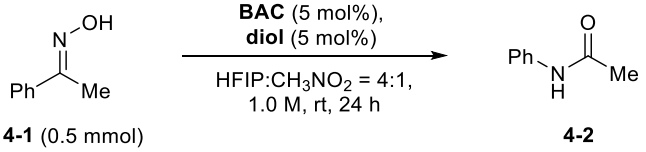
With a small library of arylboronic acids and a variety of diol additives in hand (**Scheme 4-5**), a third panel of reaction conditions was examined. The results are shown in **Table 4-4**. Unsurprisingly, perfluoropinacol (**diol 1**) exhibited general improvement for reaction yields with different boronic acids. Other fluorinated diols such as **diol 2** and **3** did not display the same effect, presumably due to a less favorable boronic ester formation and a weaker inductive effect from fewer fluorine substituents. The use of electron poor **diols 4** to **6** was also less effective. Of note, the addition of oxalic acid shut down the reaction drastically (**Table 4-4**).



Scheme 4-5. Screening of different boronic acids with *ortho*-carboxyesters substituents and diols.

As shown in **Table 4-4**, while the effect of different substituents on the arylboronic acid cannot be generalized at this point, the electron rich **BAC-44** gave the worst result of all the boronic acids examined. Certain electron poor boronic acids, such as **BAC-46** to **BAC-49** tended to provide higher yield of amide **4-2**, especially when no additive was used. It is also worth mentioning that **BAC-43** with a *meta*-CF_3 group was completely inactive despite the electron deficient nature of the boron center. The lack of reactivity of **BAC-43** was attributed to the increased steric hindrance next to the *ortho*-carboxyester moiety. This result strongly suggests that there is possibly an interaction between the oxime and the ester moiety, and oxime transesterification may be involved. This observation also led us to explore the synthesis and evaluation of **BAC-50** with an *ortho*-phenoxy ester. It was proposed that if such an oxime transesterification occurred, replacement of the methoxy ester with the phenoxy ester should

lead to a faster reaction since the phenoxy group is a better leaving group. Indeed, when **BAC-50** was employed as the catalyst with perfluoropinacol, a quantitative yield was observed within only 6 h at room temperature (**Table 4-4**).



4-1 (0.5 mmol) **4-2**

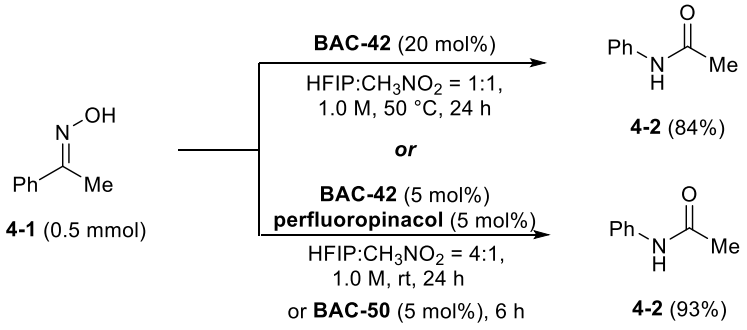
yield (%)[a]	no diols	diol 1	diol 2	diol 3	diol 4	diol 5	diol 6
BAC-42	43	90	24	41	52	10	30
BAC-43	×	×	×	×	×	×	×
BAC-44	45	48	27	34	47	×	28
BAC-45	46	74	42	45	55	×	30
BAC-46	78	84	40	83	86	19	63
BAC-47	51	78	43	61	63	20	43
BAC-48	83	78	37	72	78	×	52
BAC-49	80	63	-	-	-	-	-
BAC-50	76[b]	94[b]	-	-	-	-	-

[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as internal standard. Reaction with trace or no product was marked as ×. The reaction that was not run was marked as "-". [b]The reaction time was 6 h.

Table 4-4. Screening of the third panel of boronic acids and diol additives.

4.3.4 Summary of reaction optimization

To summarize the entire optimization process, a brief description of the optimal reaction conditions is displayed in **Scheme 4-6**.

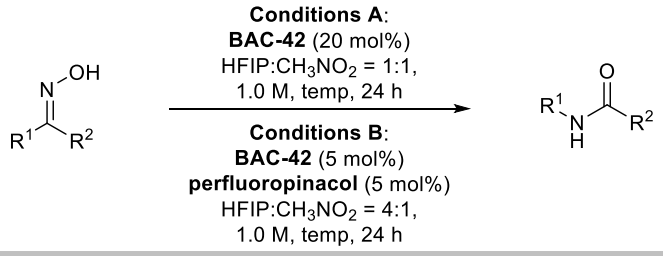


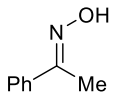
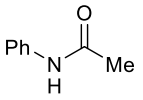
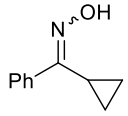
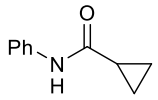
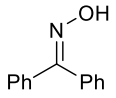
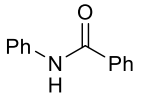
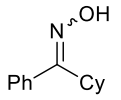
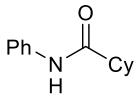
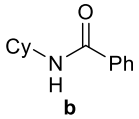
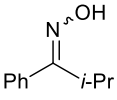
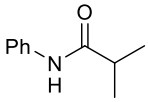
4-1 (0.5 mmol)

Scheme 4-6. Optimal conditions for the boronic acid catalyzed Beckmann rearrangement.

4.4 Substrate scope

Although **BAC-50** showed higher reactivity, **BAC-42** was selected first to examine the scope of the Beckmann rearrangement due to its availability from commercial sources. The substrate scope of this reaction was mostly performed by Dr. Timothy D. R. Morgan, as indicated in the footnotes. Examples that are not labelled in each table are run by the author of this thesis. As shown in **Scheme 4-7**, most of the aryl-aryl and aryl-alkyl oximes (**4-1** to **4-9**) underwent the Beckmann rearrangement at ambient conditions, affording the amide products **4-2** to **4-10** in high yields.

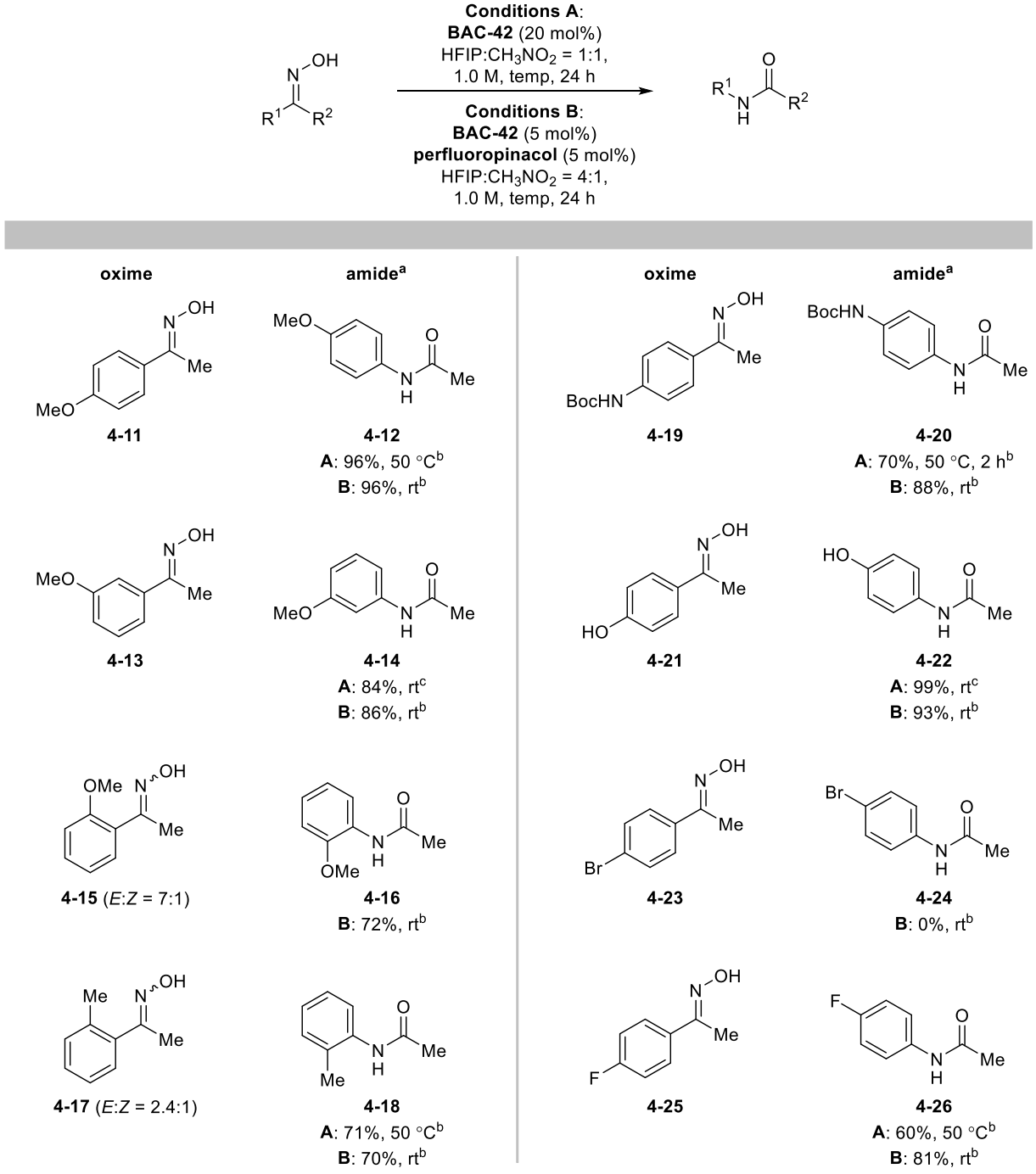


oxime	amide[a]	oxime	amide[a]
 **4-1**	 **4-2** **A**: 84%, 50 °C **B**: 93%, rt	 **4-7** (*E*:*Z* = 2.8:1)	 **4-8** **A**: 80%, 50 °C[b] **B**: 90%, rt[b]
 **4-3**	 **4-4** **A**: 87%, 50 °C[b] **B**: 94%, rt[b]	 **4-9** (*E*:*Z* = 1.2:1)	 **a**  **b** **4-10** **A**: 97%, 50 °C; **a**:**b** = 3:1[c] **B**: 93%, rt, **a**:**b** = 3:1[b]
 **4-5** (*E*:*Z* = 1:1)	 **4-6** **A**: 92%, rt[c] **B**: 90%, rt[b]		

[a]Isolated yields. [b]The reaction was accomplished by Dr. Timothy D. R. Morgan. [c]The Reaction was run with 20 mol% perfluoropinacol.

Scheme 4-7. Substrate scope for the Beckmann rearrangement catalyzed with **BAC-42**-Part 1.

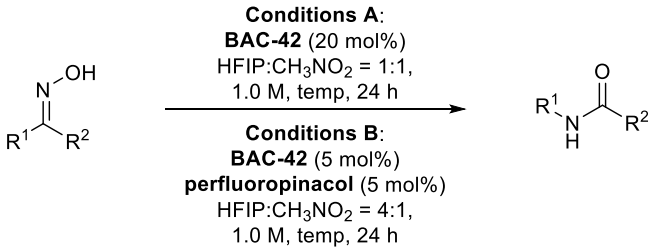
Aryl-alkyl oximes with different electronic properties and substitution patterns could serve as suitable substrates (**Scheme 4-8**). When electron rich oximes (**4-11**, **4-13** and **4-15**) were subjected to the reaction, the corresponding amides (**4-12**, **4-14** and **4-16**) were isolated in good yield. Slightly lower yields of amide **4-16** and **4-18** were obtained due to the steric hindrance of the corresponding oximes. Remarkably, the acid and temperature sensitive amide **4-20** was also obtained in high yield under the mild reaction conditions. Notably, rearrangement of a substrate with a free phenol moiety proceeded smoothly without protection (**4-22**). Oxime **4-23** with a brominated arene did not undergo the rearrangement with **BAC-42**, presumably due to the electron deficient nature of the oxime and the disfavored cationic transition state in the Beckmann rearrangement. Gratifyingly, we were glad to find that the fluorinated variant **4-25** afforded the amine **4-26** in good conversion.

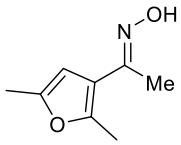
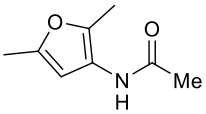
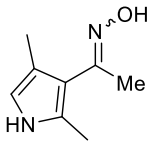
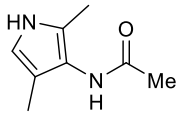
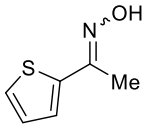
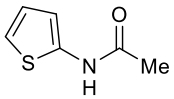
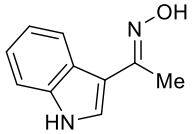
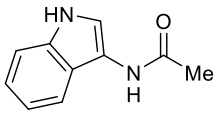
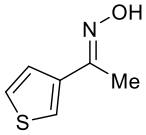
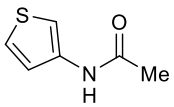
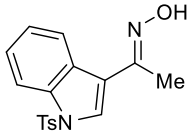
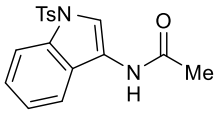
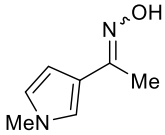
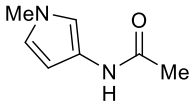
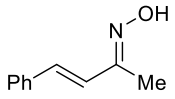
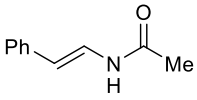


[a]Isolated yields. [b]The reaction was accomplished by Dr. Timothy D. R. Morgan. [c]The Reaction was run with 20 mol% perfluoropinacol.

Scheme 4-8. Substrate scope for the Beckmann rearrangement catalyzed with **BAC-42**-Part 2.

Gratifyingly, this mild procedure displays excellent functional group tolerance. Heteroaromatic oximes (**4-27** to **4-39**) are suitable and provided the corresponding amides **4-28** to **4-40**, including the unprotected pyrrole, **4-36**, and indole, **4-40**. When oxime **4-29** was subjected to the reaction, the amide product **4-30** was not observed. The failure of this substrate presumably results from the steric hindrance posed by the *ortho* sulfur atom in oxime **4-29**. The reaction using oxime **4-39** was run at 50 °C with 10 mol% catalyst loading due to the lack of solubility of the substrate. The reaction using oxime **4-35** afforded a complicated mixture and the amide **4-36** was isolated in a moderate yield of 46%. The alkenyl-alkyl oxime **4-41** was also applied to the standard reaction conditions and afforded amide **4-42** in moderate yield (49%). The lower yield of **4-36** and **4-42** in the reaction could be attributed to the instability of these amides under the reaction conditions or column conditions with silica.



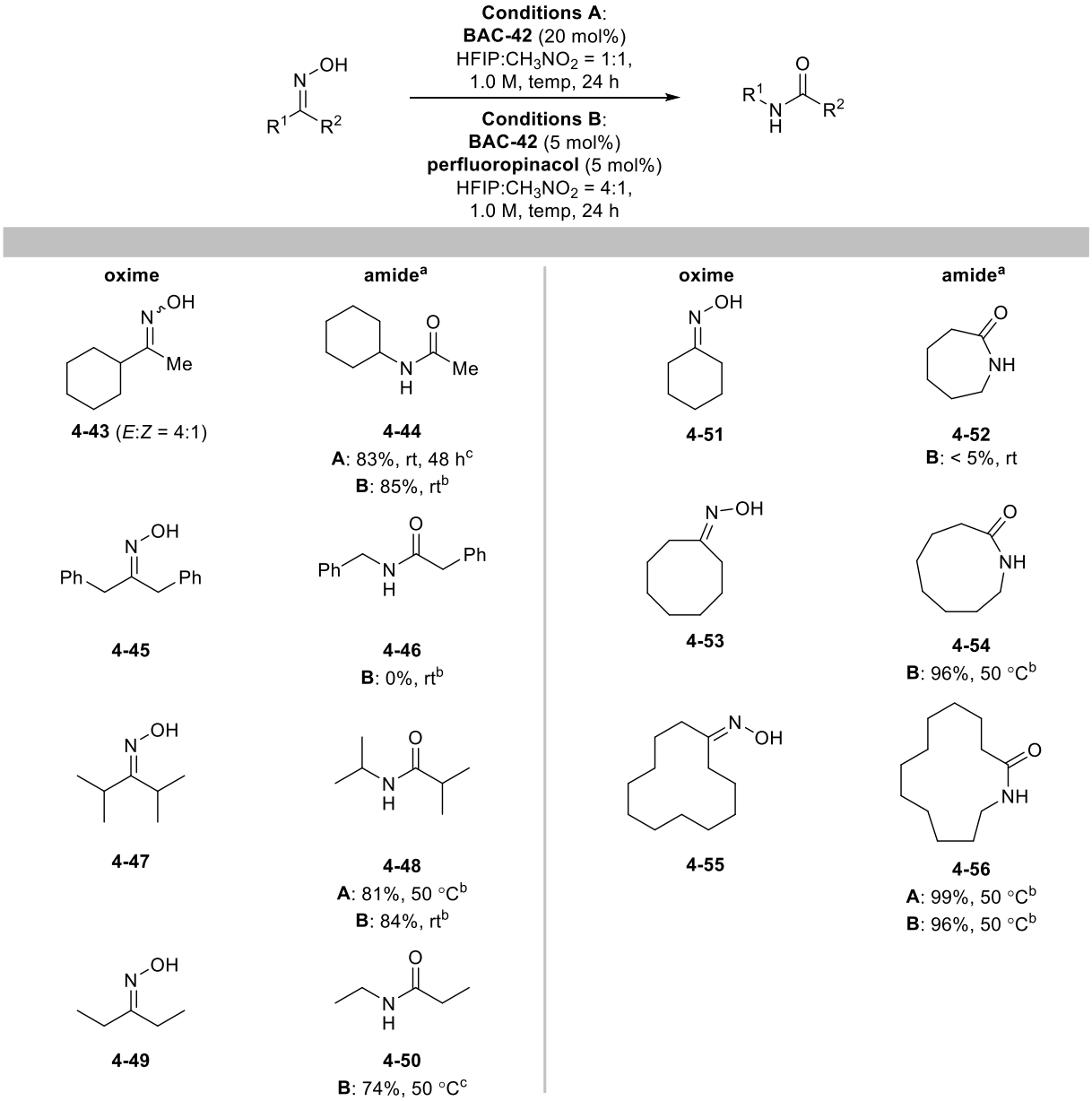
oxime	amide[a]	oxime	amide[a]
 **4-27**	 **4-28** **A**: 99%, 50 °C[b]	 **4-35** (*E*:*Z* = 5:1)	 **4-36** **A**: 43%, 50 °C
 **4-29** (*E*:*Z* = 2.2:1)	 **4-30** **B**:0%, rt[b]	 **4-37**	 **4-38** **A**: 93%, 50 °C **B**: 80%, rt
 **4-31**	 **4-32** **A**: 86%, 50 °C[b] **B**: 94%, rt[b]	 **4-39**	 **4-40** **A**: 90%, 80 °C **B**: 99%, 50 °C[c]
 **4-33** (*E*:*Z* = 1:1)	 **4-34** **A**: 99%, 50 °C **B**: 87%, rt	 **4-41**	 **4-42** **A**: 48%, 50 °C[b] **B**: 49%, rt[b]

[a]Isolated yields. [b]The reaction was accomplished by Dr. Timothy D. R. Morgan. [c]The Reaction was run with 10 mol% perfluoropinacol.

Scheme 4-9. Substrate scope for the Beckmann rearrangement catalyzed with **BAC-42**-Part 3.

Higher reaction temperatures (50 °C) or increased catalyst loading (10 mol% of **BAC-42**) were generally needed for the less reactive alkyl-alkyl oximes. The amides **4-44** to **4-56** were isolated

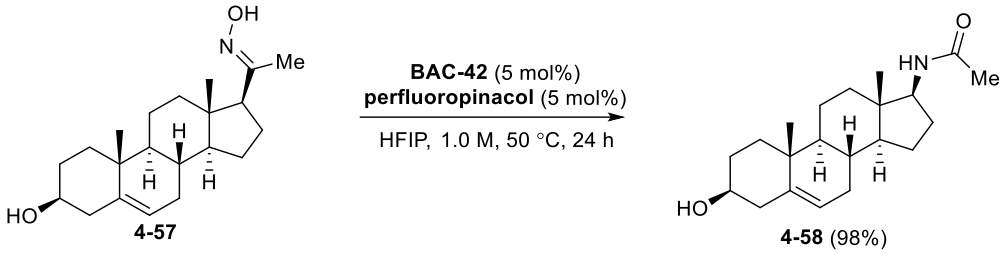
in good yield with the exception of amide **4-46** and ε-caprolactam **4-52**. The low yield of amide **4-46** presumably resulted from the low solubility of oxime **4-45** in the reaction solvent. The cyclohexanone oxime **4-51**, which is notorious for its reluctance in the organocatalyzed Beckmann rearrangement,[17,18,19] exhibited low reactivity. The low yield of **4-52** is presumably due to the ring stain of the ring expansion in the rearrangement. A more detailed discussion is given in Section 4.8.3.



[a]Isolated yields. [b]The reaction was accomplished by Dr. Timothy D. R. Morgan. [c]The Reaction was run with 10 mol% perfluoropinacol.

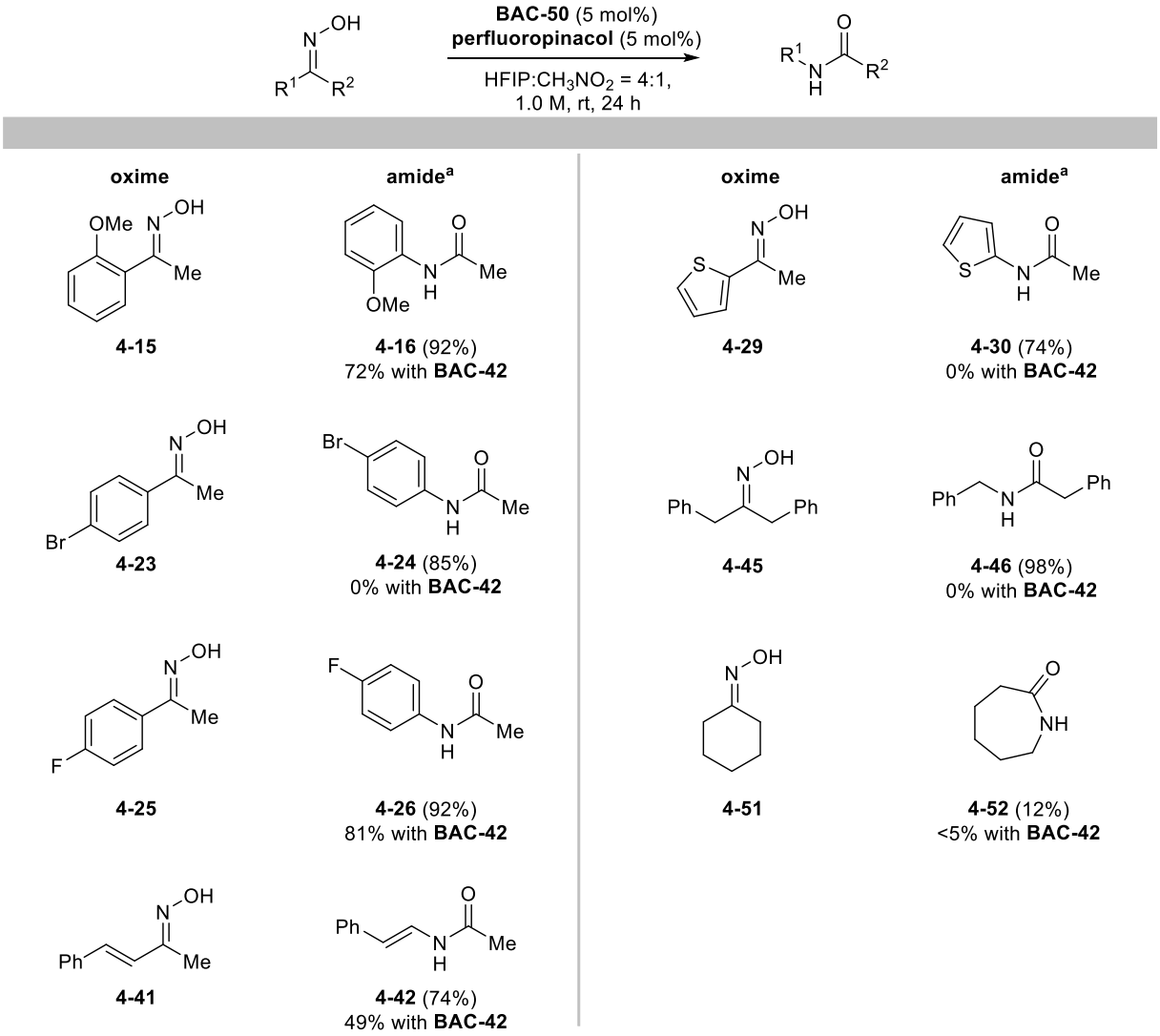
Scheme 4-10. Substrate scope for the Beckmann rearrangement catalyzed with **BAC-42**-Part 4

Satisfactorily, the pharmaceutically relevant substrate pregnenolone oxime **4-57** underwent the rearrangement and provided amide **4-58** in near quantitative yield. Pure HFIP was used as the solvent due to the lack of solubility of **4-57** in nitromethane (**Scheme 4-11**).



Scheme 4-11. Substrate scope for the Beckmann rearrangement catalyzed with **BAC-42**-Part 5

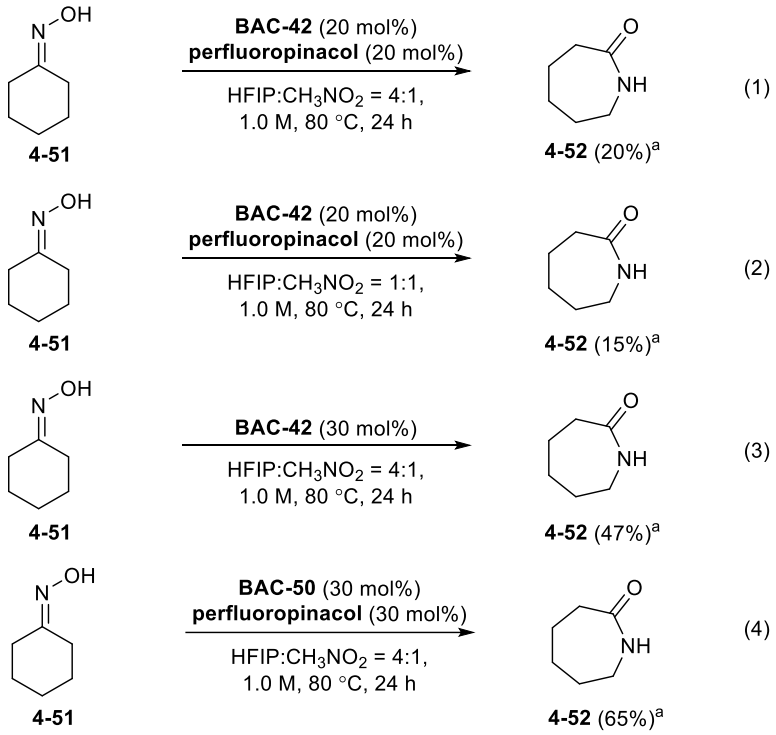
Some of the oximes that provided poor conversions with catalyst **BAC-42** were re-examined with **BAC-50**, since it displayed a higher reactivity towards the Beckmann rearrangement of **4-1** (**Table 4-4**). Satisfactorily, a significant increase in yield was observed in all cases. Especially, oximes **4-23**, **4-29** and **4-45**, which were shown to be completely unreactive with **BAC-42**, provided high yields of the amides **4-24** and **4-46**. The rearrangement of cyclohexanone oxime **4-51**, however, remained sluggish (12%) with mostly recovered starting material (**Scheme 4-12**).



[a]Isolated yields. All the examples herein were accomplished by Dr. Timothy D. R. Morgan.

Scheme 4-12. Substrate scope for the direct Beckmann rearrangement catalyzed with **BAC-50**.

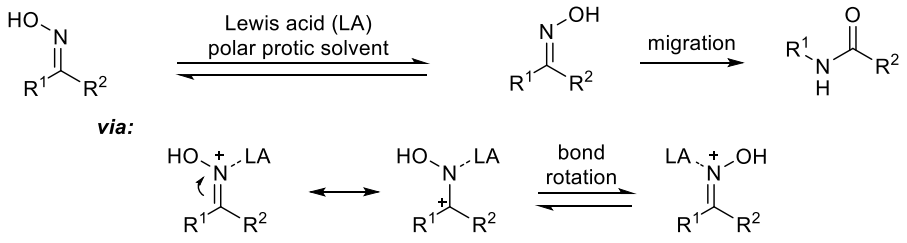
Considering that the Beckmann rearrangement of cyclohexanone oxime **4-51** is of great interest for the production of Nylon-6 in fabric industry, more experiments were attempted to improve the reaction yield of ε-caprolactam **4-52** from cyclohexanone oxime **4-51** (**Scheme 4-13**). However, no significant improvement was observed with an increase in catalyst loading or a change of the solvent ratio. Using **BAC-42**, the highest conversion (47%) was obtained with conditions of equation 3. A higher conversion of 65% was obtained using **BAC-50** and perfluoropinacol at 80 °C (equation 4).



[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as an internal standard.

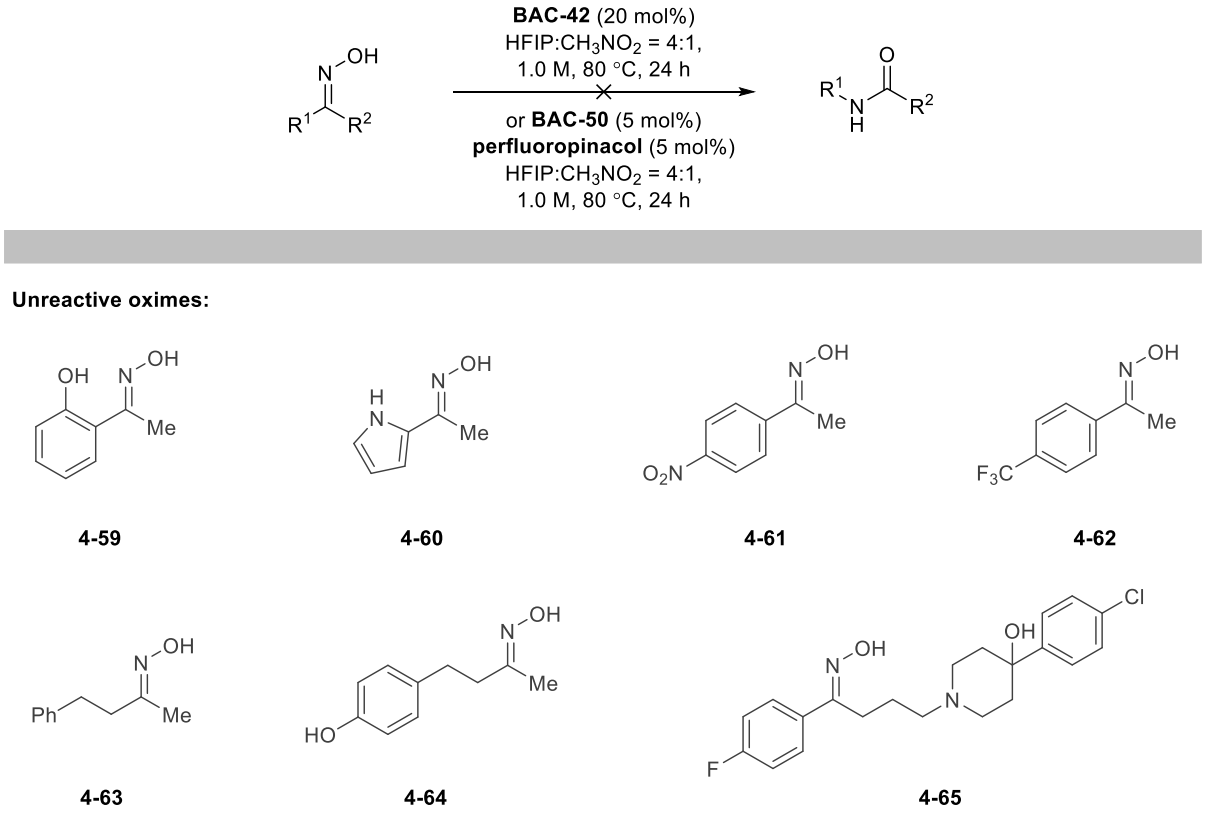
Scheme 4-13. Further attempts at the Beckmann rearrangement of cyclohexanone oxime **4-51**.

It is worth mentioning that several oximes were synthesized and isolated as mixtures of *E*/*Z* isomers and used directly for the Beckmann rearrangement (e.g. **4-5**, **4-7**, **4-9**, **4-15**, **4-17**, **4-29**, **4-33**, **4-35** and **4-43**). In almost all cases, the apparently non-stereospecific Beckmann rearrangement was observed, giving a major amide product in accordance with the more favorable migratory aptitude of R^1 and R^2. This result is suspected to originate from an oxime *E*/*Z* interconversion prior to the rearrangement due to the presence of a Lewis acidic boron compound in protic solvent (**Scheme 4-14**).[6]



Scheme 4-14. *E*/*Z* isomer interconversion of oximes in the presence of protic solvents.

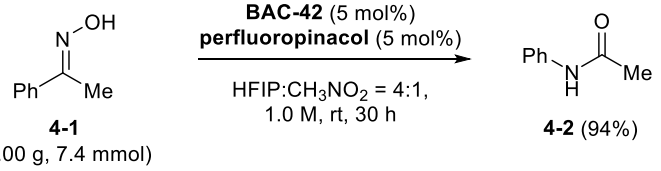
Although most substrates displayed moderate to good conversion under the optimal conditions, certain oximes were completely unreactive in this protocol, as shown in **Scheme 4-15**. For instance, when oximes **4-59** and **4-60** were reacted, no amide formation was observed. The lack of reactivity of these substrates is attributed to the favorable chelating effect between the oxime nitrogen and the hydroxyl or free amino groups *ortho* to oxime, which could lead to deactivation of the boronic acid catalyst. Substrates with highly electrophilic aromatic rings, such as **4-61** and **4-62**, also provided no desired amide products. It is believed that the electron poor nature of these oximes disfavors the cationic transition state in the Beckmann rearrangement. Similarly, oximes **4-63** and **4-64** with methyl and primary alkyl groups did not rearrange, presumably due to the lack of stabilization for the transition state from the primary alkyl groups. Oxime **4-65**, which is derived from the drug haloperidol, failed to deliver the amide product presumably because of chelating effects from functional groups embedded in the complex structure (e.g. oxime, amine and alcohol).



Scheme 4-15. Unreactive oximes in the boronic acid catalyzed Beckmann rearrangement.

4.5 Gram scale synthesis

To further display the practical usefulness of this protocol, a gram scale synthesis was conducted. Gratifyingly, the rearrangement of oxime **4-1** scaled up 15 times, still afforded amide **4-2** with a very good isolated yield (94%). However, a longer reaction time of 30 hours was required (**Scheme 4-16**).



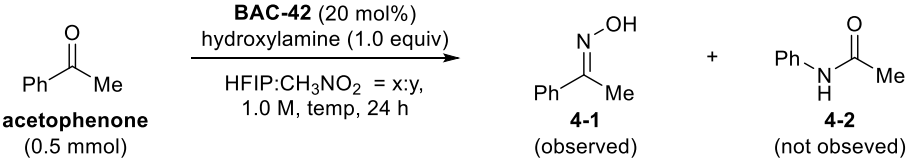
Scheme 4-16. Gram scale synthesis of amide **4-2** *via* the BAC Beckmann rearrangement procedure.

4.6 Attempts for a one-pot Beckmann rearrangement from ketones

In light of the successful development of the Beckmann rearrangement of oximes with **BAC-42** and **BAC-50**, attempts were made to achieve a one-pot rearrangement from the ketone and hydroxyl amine. While the one-pot Beckmann rearrangement is very attractive, there has been very little success demonstrated for this process. The challenge lies in the incompatible conditions for the sequential oximation and rearrangement. While the oximation normally proceeds in basic aqueous-ethanol solution, the Beckmann rearrangement often requires the use of acidic and anhydrous environment. Existing literature precedence of Beckmann rearrangements from ketones include the use of excess formic acid,[23] oxalic acid,[24] TFA,[25] ZnO,[26] TiO_2[27] and a report using catalytic amount of $FeCl_3 \cdot 6H_2O$.[28] All of these methods require high temperatures (100-170 °C). Thus, we were interested in evaluating the possibility of a one-pot Beckmann rearrangement with boronic acid catalysis under mild conditions.

At the outset, 50 wt% of hydroxylamine in water was used directly with acetophenone as a compromise of the contradictory reaction condition requirements. Although oxime **4-1** was formed in good conversion, amide **4-2** was not observed in different solvent conditions in the presence of **BAC-42** (**Table 4-5**, entries 1-2). The presence of excess water seemingly inhibits

the sequential Beckmann rearrangement. Consequently, the use of desiccants was considered. Unfortunately, the addition of molecular sieves and *ortho* methyl formate ester (TMOF) at various conditions only led to oxime **4-1** (entries 3-7). Lastly, to avoid introducing water, a reaction with hydroxylamine hydrochloride and sodium acetate was attempted (entry 8). However, the desired amide **4-2** was not observed and only acetophenone was recovered. Efforts to overcome these initial challenges are underway.



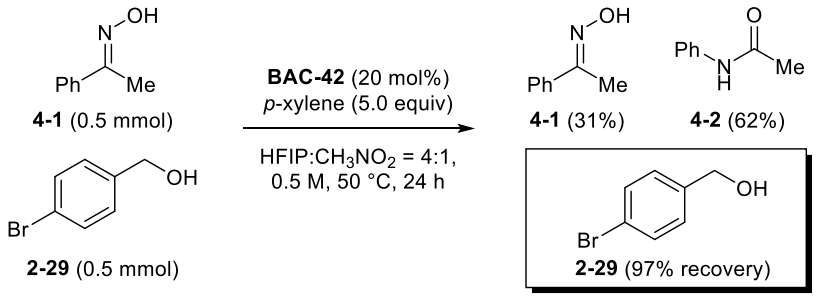
entry	hydroxylamine	x:y	T (°C)	additives	yield (%)[a]
1	NH_2OH 50 wt.% in H2O	1:1	50	-	n.r.
2	NH_2OH 50 wt.% in H2O	4:1	50	-	n.r.
3	NH_2OH 50 wt.% in H2O	1:1	50	100 mg 4 Å MS	n.r.
4	NH_2OH 50 wt.% in H2O	4:1	50	100 mg 4 Å MS	n.r.
5	NH_2OH 50 wt.% in H2O	1:1	50	3.0 equiv TMOF	n.r.
6	NH_2OH 50 wt.% in H2O	4:1	50	3.0 equiv TMOF	n.r.
7	NH_2OH 50 wt.% in H2O	4:1	80	3.0 equiv TMOF	n.r.
8[b]	$NH_2OH \cdot HCl$	4:1	80	-	n.r.

[a]In all cases, oxime **4-1** was formed in different amounts along with leftover acetophenone.
[b]Reaction was run with 1.0 equiv of NaOAc.

Table 4-5. Efforts towards a one-pot Beckmann rearrangement from acetophenone *via* BAC.

4.7 Application in orthogonal catalysis

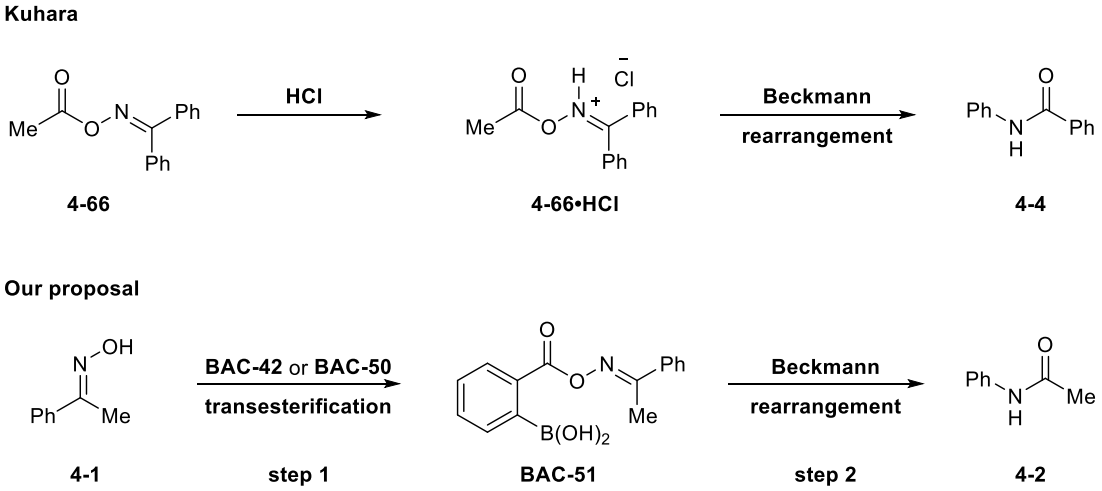
Electron-poor arylboronic acids, such as **BAC-26**, have been previously shown to be excellent catalysts for direct alcohol activation in Friedel-Crafts reaction (cf. Chapter 2). In this regard, we were interested in exploring the possibility of using arylboronic acids with *ortho*-carboxyesters as chemoselective catalysts for the activation of the oxime N–OH bond. As shown in **Scheme 4-17**, oxime **4-1** was selectively activated and transformed into amide **4-2** in the presence of alcohol **2-29** and *p*-xylene under the standard Friedel-Craft benzylation conditions. Although only a moderate yield of **4-2** was isolated due to deviation from the optimal Beckmann rearrangement conditions, almost full recovery (97%) of alcohol **2-29** was obtained. This initial result emphasizes the potential of **BAC-42** in orthogonal catalysis.



Scheme 4-17. Application of **BAC-42** in orthogonal catalysis.

4.8 Mechanistic studies

The unique reactivity of arylboronic acids with *ortho*-carboxyesters in the Beckmann rearrangement prompted us to propose the formation of the boronic acid oxime ester, **BAC-51**, as a reactive intermediate (**Scheme 4-18**). Oxime acetates have been shown to undergo the Beckmann rearrangement in the presence of a strong acid according to Kuhara in the early 1900s.[16] A two-step reaction mechanism, in which the oxime transesterification is followed by the Beckmann rearrangement, is proposed as shown in **Scheme 4-18**. Mechanistic studies were conducted to further prove the existence of oxime ester **BAC-51** and elucidate the role of the boronic acid in both the transesterification and the Beckmann rearrangement.

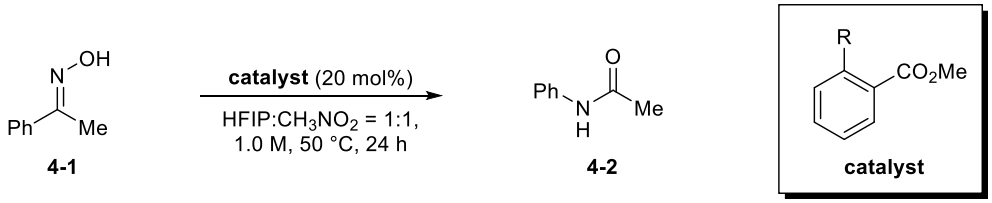


Scheme 4-18. Proposed key steps in the boronic acid catalyzed Beckmann rearrangement.

4.8.1 Exploration of the oxime transesterification hypothesis

4.8.1.1 Control experiments to examine the oxime transesterification

A series of control experiments were performed to rationalize the transesterification step. As shown in **Table 4-6**, rearrangement with **BAC-42** gave 84% yield under the optimized reaction conditions (entry 1). In contrast, the reaction using methyl benzoate **4-67** gave no amide product (entry 2). Furthermore, control experiments replacing the boronic acid moiety with other electron withdrawing groups such as $–NO_2$ (**4-68**) and $–CF_3$ (**4-69**) also led to no formation of product **4-2** (entries 3-4). It is likely that the Lewis acidic character of the boron triggers the transesterification. Surprisingly, protecting the free boronic acid as a pinacol boronic ester, **4-70**, led to failure to catalyze the rearrangement (entry 5). This result indicates a possible exchange of the B–OH bond with HFIP for the formation of an HFIP boronic ester. A more electrophilic boron center from the HFIP boronic ester could account for the oxime transesterification.



entry	R	number	yield (%)[a]
1	$B(OH)_2$	**BAC-42**	84
2	H	**4-67**	n.r.
3	NO_2	**4-68**	n.r.
4	CF_3	**4-69**	n.r.
5	Bpin	**4-70**	n.r.

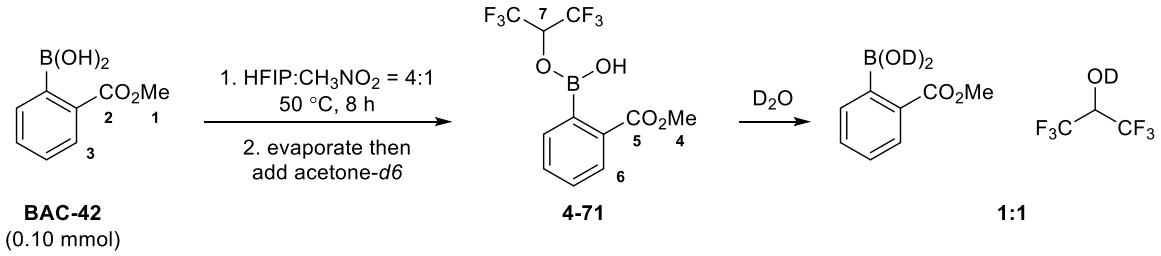
[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as internal standard.

Table 4-6. Control experiments to support the oxime transesterification hypothesis.

4.8.1.2 Evaporation experiment to examine the role of HFIP

Inspired by the intriguing results of **Table 4-6**, more studies were performed to explore the possible interaction between the boronic acid and HFIP for the transesterification. Considering that a direct observation of the HFIP boronic ester in solution is difficult by ^{1}H NMR and less quantitative by ^{11}B NMR, the following evaporation experiments were designed. Catalyst **BAC-**

42 was subjected to a solvent mixture of HFIP:CH_3NO_2 (v:v = 4:1) and stirred for the indicated period of time. Afterwards, all the solvent was removed and the crude compound **4-71** was obtained, which is proposed to be the mono HFIP boronic ester (**Scheme 4-19**).



Scheme 4-19. Evaporation experiment to explore the role of HFIP.

Both ^{1}H NMR (**Figure 4-1**) and ^{11}B NMR (**Figure 4-3**) studies of the crude material **4-71** in anhydrous acetone-*d6* showed a complicated mixture. The septet at 5.0 ppm was assigned to the methine proton from HFIP while several new septet signals appear between 5.4 ppm to 5.6 ppm (**Figure 4-1**), which represent different hexafluoroisopropoxy methine protons and indicate the formation of **4-71**. However, assignment of all the peaks on ^{1}H NMR proved to be challenging at this stage and was thus not pursued further. Nevertheless, multiple peaks at 30.1, 20.7 and 17.3 ppm in ^{11}B NMR spectra suggested the existence of at least three boron species with different ionization states (either trigonal neutral or weakly coordinated half boronate, **Figure 4-3**). It is unlikely that a meaningful amount of fully ionized boronate anion is formed since no major peak is observed below 10 ppm.

Afterwards, one drop of D_2O was added to the NMR tube charged with crude **4-71**. The sample was then subjected to the same NMR studies. As a result, the previous complicated mixture was resolved into clean spectra on both ^{1}H NMR (**Figure 4-2**) and ^{11}B NMR (**Figure 4-4**). Recovery of **BAC-42** and HFIP (1:1 ratio) was clearly observed, which supports the formation of the mono HFIP boronic ester **4-71** in the reaction media. According to the previous observations, the boronic acid catalyzed Beckmann rearrangement requires the use of HFIP (**Table 4-1**) and becomes more efficient when an increasing proportion of HFIP is used (**Table 4-2**). It is proposed that a large quantity of HFIP is necessary to ensure the formation of **4-71** which serves as a reactive species for the oxime transesterification, when perfluoropinacol is not used as an additive. Moreover, as a highly polar solvent, HFIP is known to facilitate reactions that go through cationic intermediates/transition states, such as the Beckmann rearrangement.

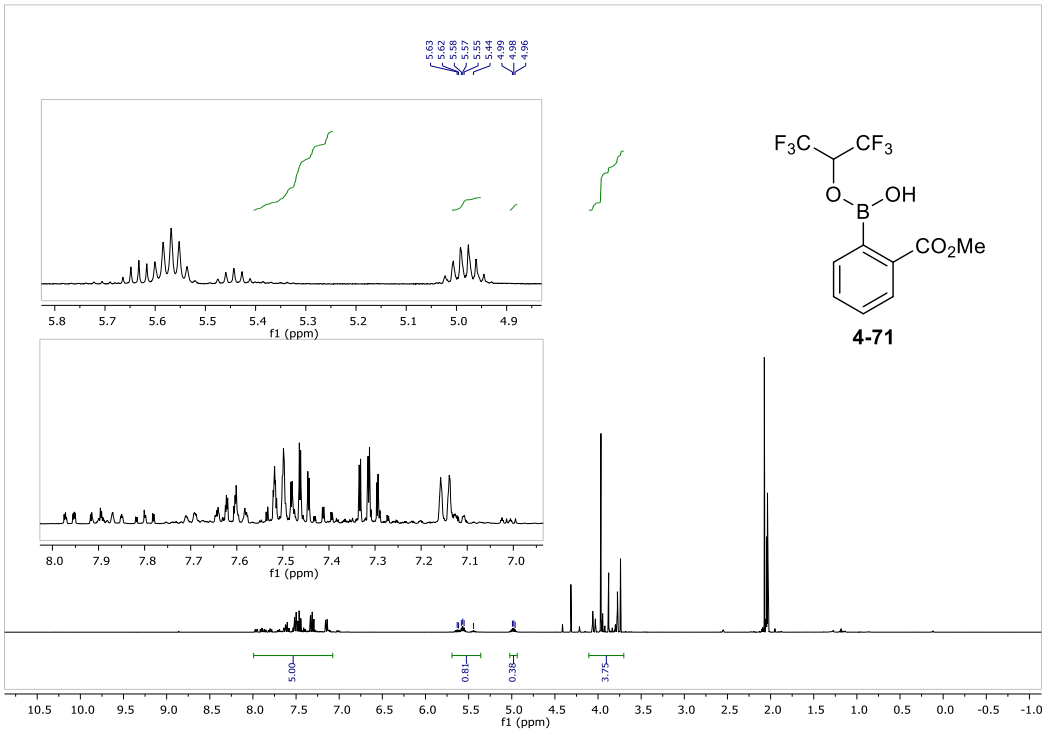


Figure 4-1. ^{1}H NMR spectrum spectrum of mixture **4-71** in anhydrous acetone-*d6*.

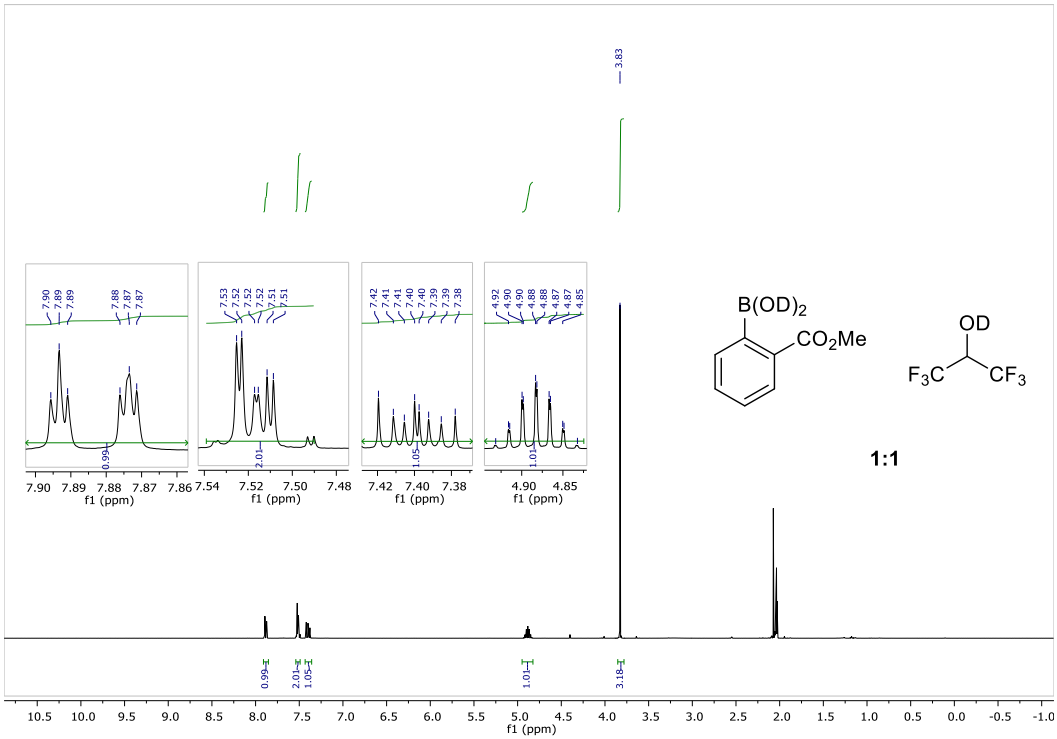


Figure 4-2. ^{1}H NMR spectrum of mixture **4-71** in anhydrous acetone-*d6* with D_2O.

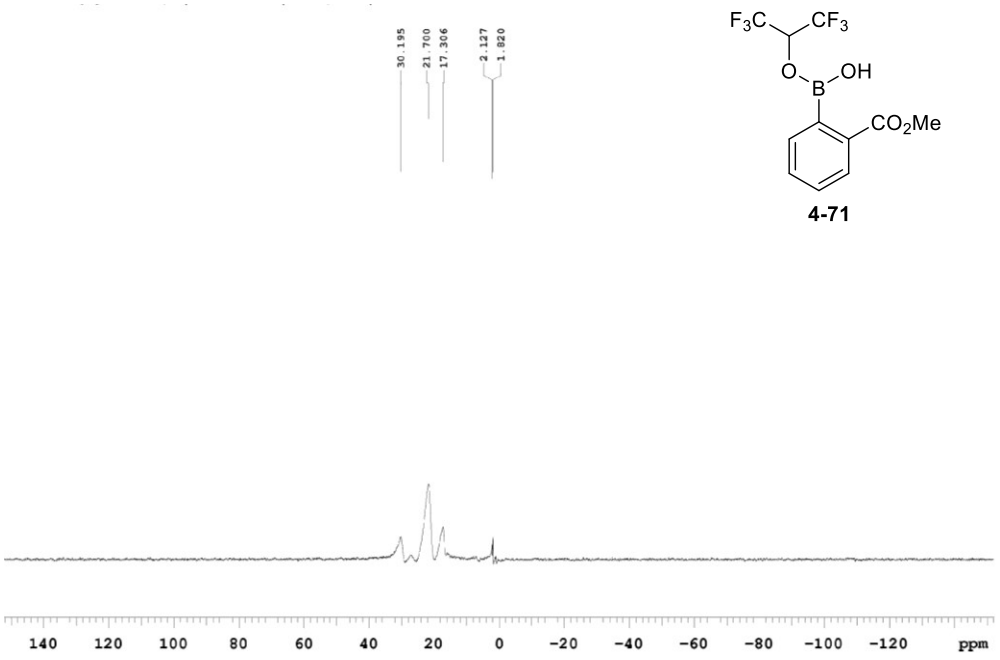


Figure 4-3. ^{11}B NMR spectrum of mixture **4-71** in anhydrous acetone-*d6*.

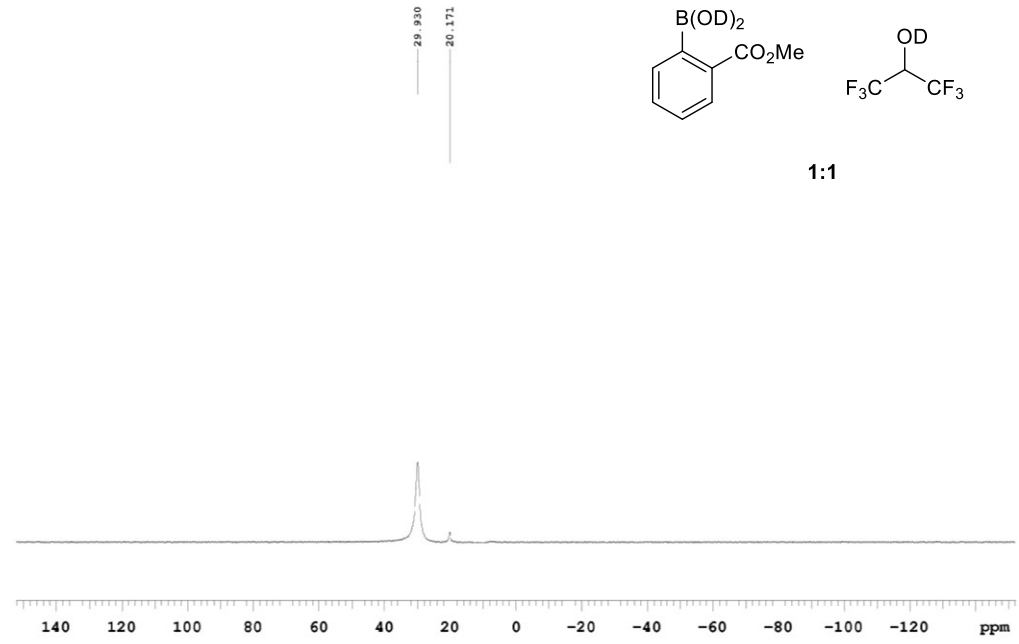
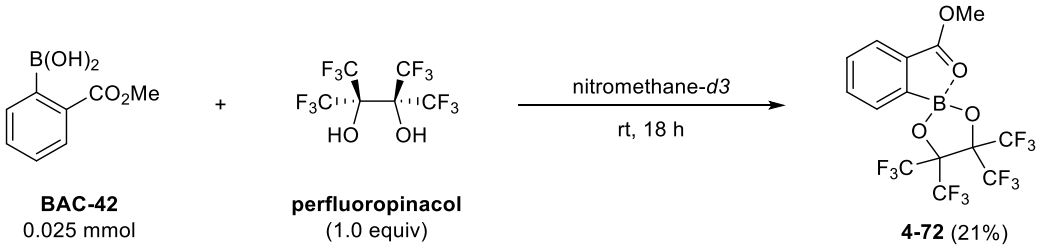


Figure 4-4. ^{11}B NMR spectrum of mixture **4-71** in anhydrous acetone-*d6* with D_2O.

4.8.1.3 Examination of the role of perfluoropinacol

We were also interested in exploring the interaction of **BAC-42** with perfluoropinacol, since the use of catalytic perfluoropinacol accelerated the reaction. In this regard, a one-to-one ratio of catalyst **BAC-42** and perfluoropinacol were dissolved in nitromethane-*d3* and stirred at room temperature before being subjected to ^{1}H NMR, ^{11}B NMR and ^{19}F NMR spectroscopic studies (**Scheme 4-20**). The relevant individual spectra of **BAC-42** (**Figure 4-5** and **Figure 4-7**) and perfluoropinacol (**Figure 4-9**) were recorded for reference. Overall, analysis of the spectra suggests that the formation of perfluoropinacol boronic ester **4-72** does occur, but in a low proportion.



Scheme 4-20. Exploration of the interaction between **BAC-42** and perfluoropinacol at a one-to-one ratio in nitromethane-*d3*.

In comparison to **Figure 4-5**, a new major peak at 4.5 ppm was observed from the ^{1}H NMR of the reaction mixture (**Figure 4-6**), which was assigned to the H8 methyl protons of complex **4-72**. The clear downfield shift of H8 from **4-72** compared to H1 of **BAC-42** originates from a polarization of the carboxyester moiety by coordination to a more electrophilic boron center in **4-72**. Meanwhile, the aromatic region showed new signals as a result of the formation of **4-72**. The assignment of the aromatic signals of **4-72** was confirmed by ^{13}C NMR, HSQC and HMBC analysis of the titration end point of **BAC-42** and perfluoropinacol with HFIP (**Figure 4-13** to **Figure 4-15**). More direct evidence of the coordination from the methyl ester to the perfluoropinacol boronic ester **4-72** is shown in **Figure 4-8**. The ^{11}B NMR signal at 15.0 ppm strongly suggests a non-fully ionized tetrahedral boron center, which supports the formation of internal coordination in **4-72**. Similarly, a new signal at -69.9 ppm on the ^{19}F NMR of the reaction mixture (**Scheme 4-20**) was also evident (**Figure 4-10**) when compared to the spectrum of perfluoropinacol at -71.0 ppm (**Figure 4-9**).

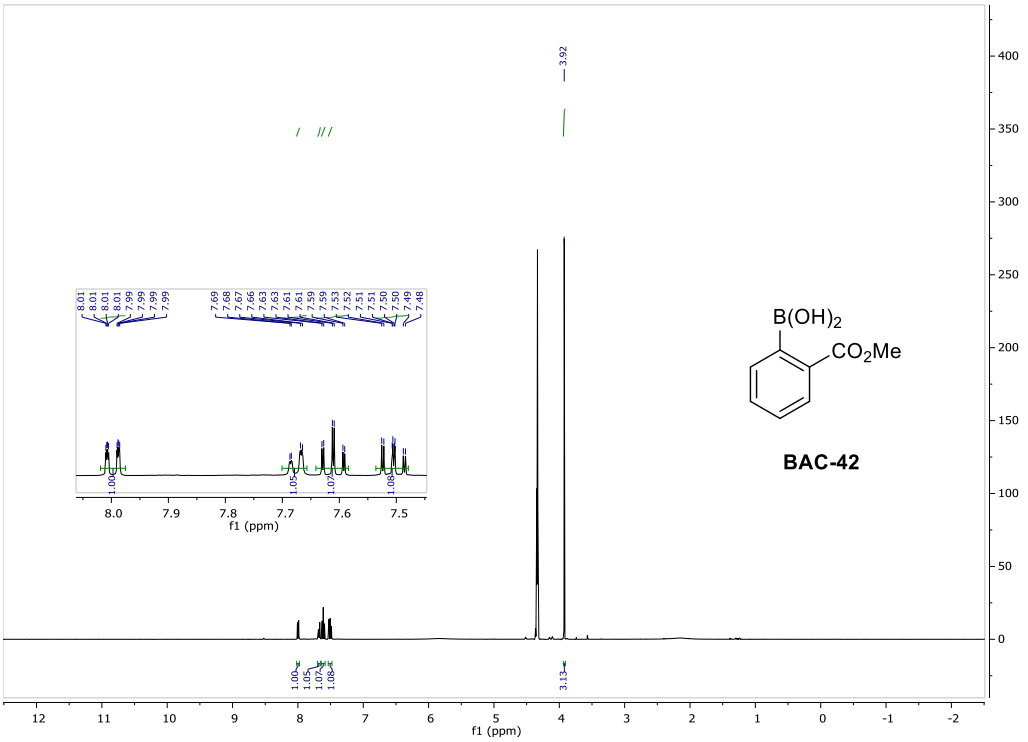


Figure 4-5. ^{1}H NMR spectrum of **BAC-42** in nitromethane-*d3*.

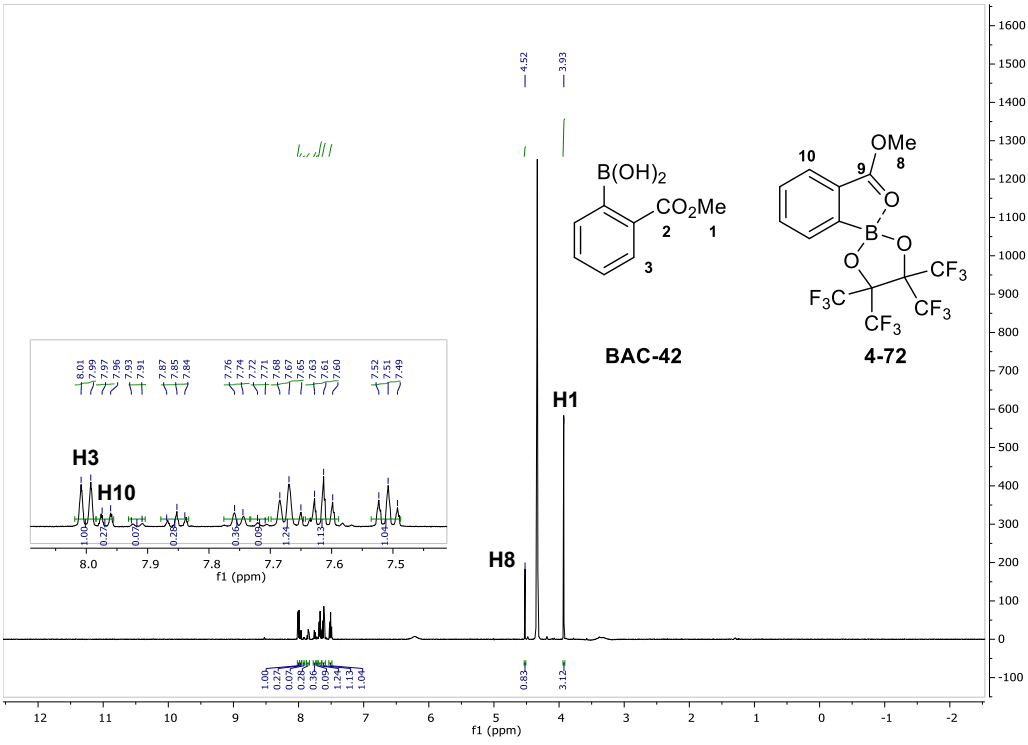


Figure 4-6. ^{1}H NMR spectrum of the equimolar reaction mixture of **BAC-42** and perfluoropinacol.

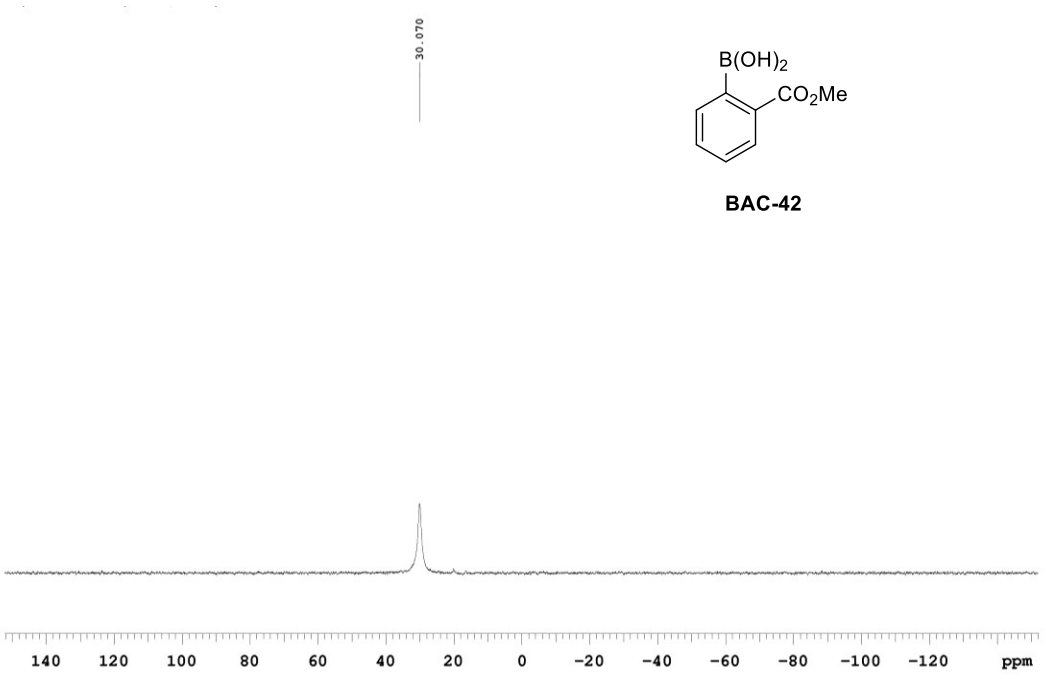


Figure 4-7. ^{11}B NMR spectrum of **BAC-42** in nitromethane-*d3*.

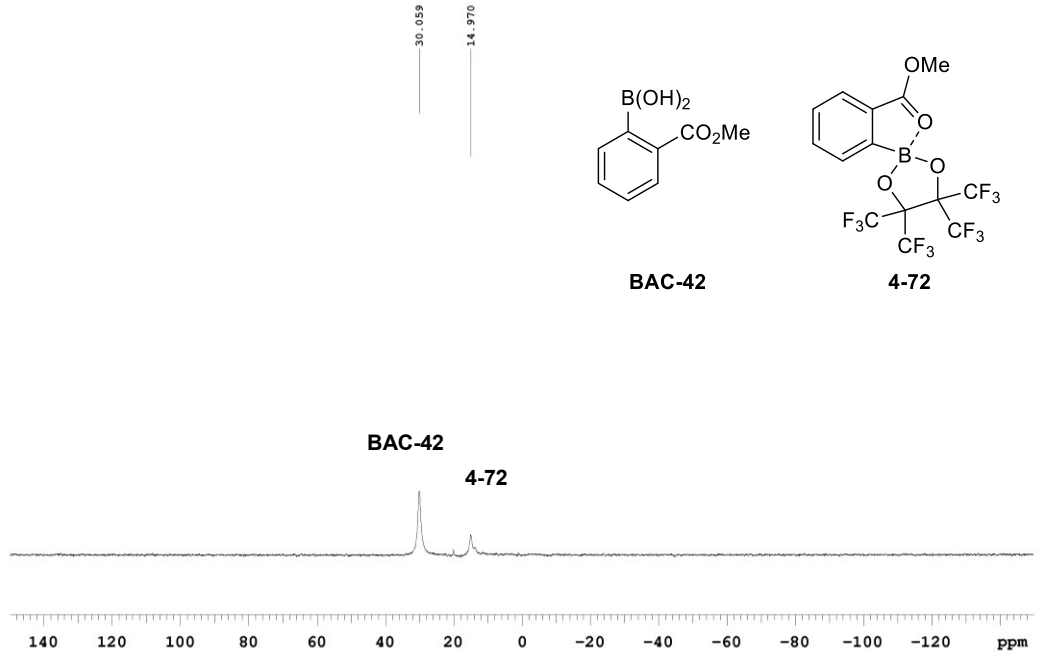


Figure 4-8. ^{11}B NMR spectrum of the equimolar reaction mixture of **BAC-42** and perfluoropinacol.

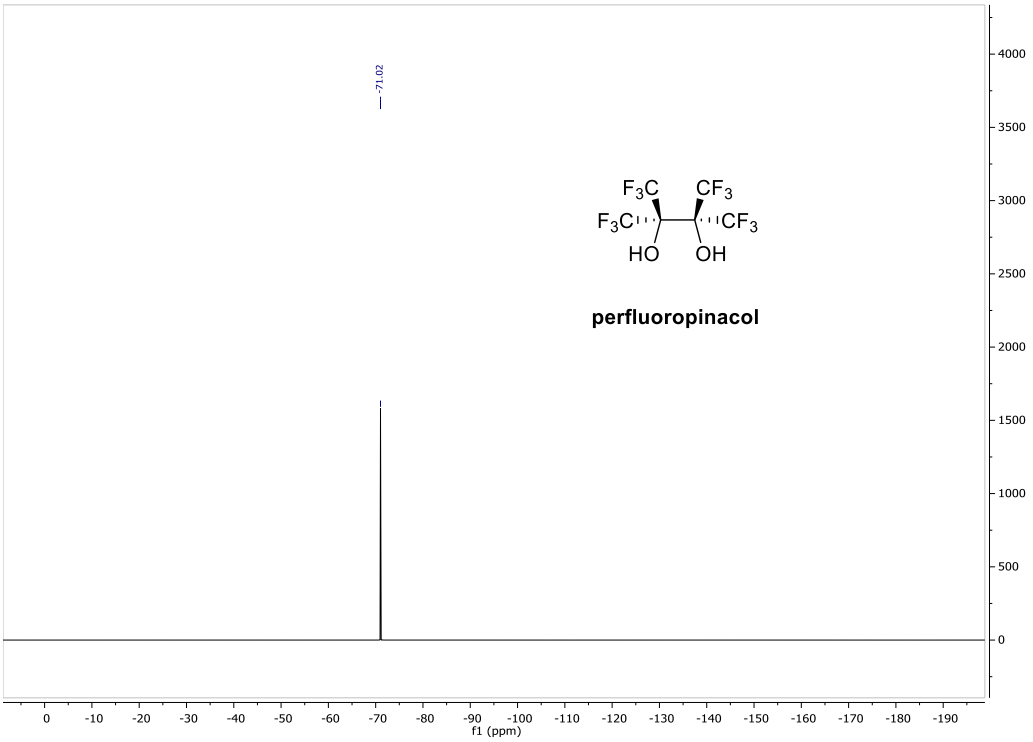


Figure 4-9. ^{19}F NMR spectrum of perfluoropinacol in nitromethane-*d3*.

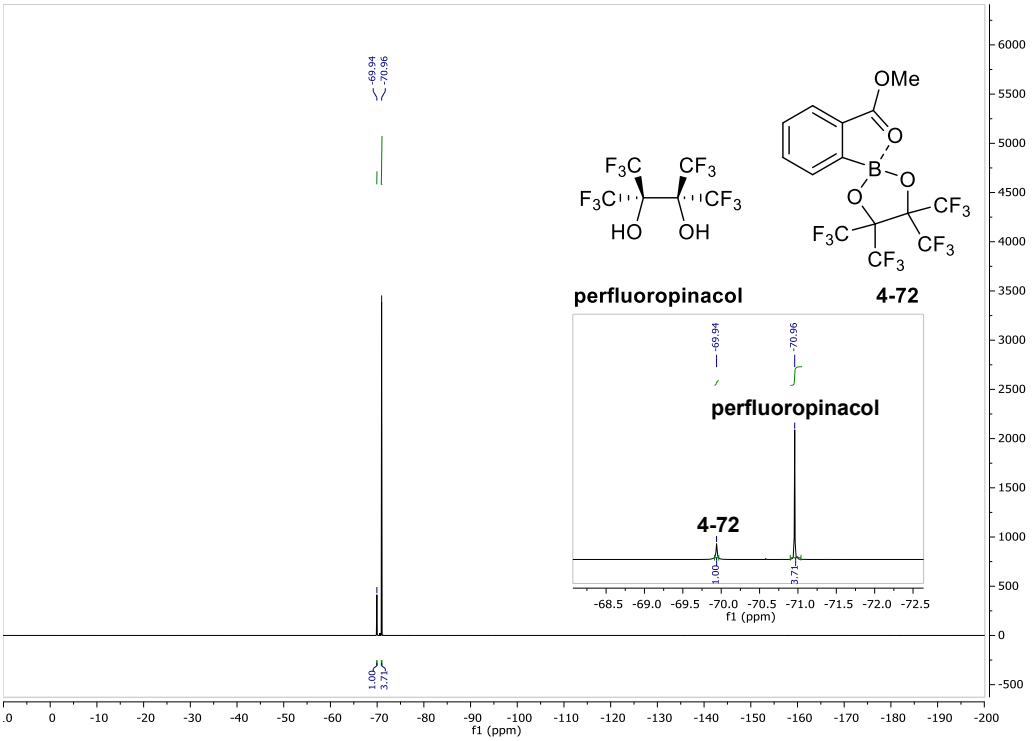
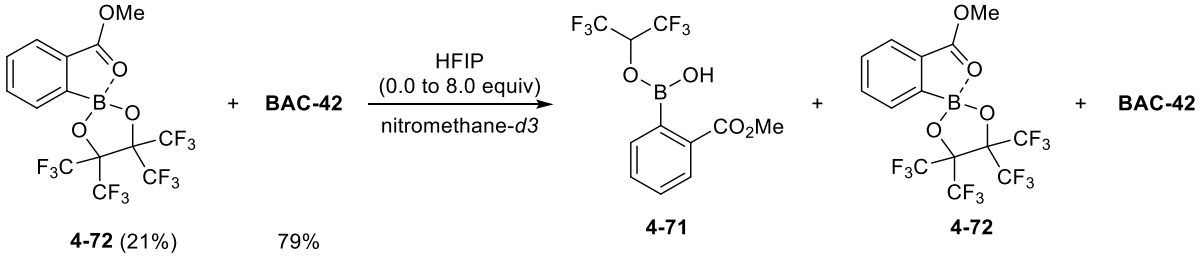


Figure 4-10. ^{19}F NMR spectrum of the equimolar reaction mixture of **BAC-42** and perfluoropinacol.

The reaction mixture of **BAC-42** and perfluoropinacol from **Scheme 4-20** was titrated with 0.0 to 8.0 equivalents of HFIP (**Scheme 4-21**). The corresponding ^{1}H NMR, ^{11}B NMR and ^{19}F NMR spectra at various HFIP equivalence were recorded. Formation of the boronic ester **4-71** was observed as more HFIP was added. As shown in **Figure 4-11** and **Figure 4-12**, a new set of peaks (H4, H6 and H7) from **4-71** gradually appeared with increasing amounts of HFIP, while the proton signals (H1 and H3) from **BAC-42** slowly weakened. Despite the consumption of **BAC-42**, no obvious quantitative changes of **4-72** were observed throughout the titration, which suggests that the perfluoropinacol boronic ester **4-72** is relatively stable in the titration conditions used.



Scheme 4-21. Titration of the reaction mixture of **BAC-42** and perfluoropinacol with varying amounts of HFIP.

At the titration end point, the ^{13}C NMR, HSQC and HMBC experiments of the reaction mixture were also performed. The relevant proton and carbon signals from **BAC-42**, **4-71** and **4-72** were assigned based on analysis of these spectra (**Figure 4-13** to **Figure 4-15**). In terms of ^{13}C NMR (**Figure 4-13**), three different carbonyl signals at 182.8, 169.4 and 169.3 ppm were distinguishable and identified as C9, C5 and C2 from **4-72**, **4-71** and **BAC-42**, respectively. The assignments are further confirmed by the correlations found by HSQC (**Figure 4-14**) and HMBC experiments (**Figure 4-15**), e.g. (H1, C1) (H1, C2), (H4, C4), (H4, C5), (H8, C8) and (H8, C9). The apparent downfield shift of C9 from **4-72** is attributed to the strong polarization of the carboxyester by coordination of the carbonyl to the highly Lewis acidic boron center. Although a similar downfield shift and polarization of C5 was also found in **4-71**, such an effect was not as strong as that in **4-72**.

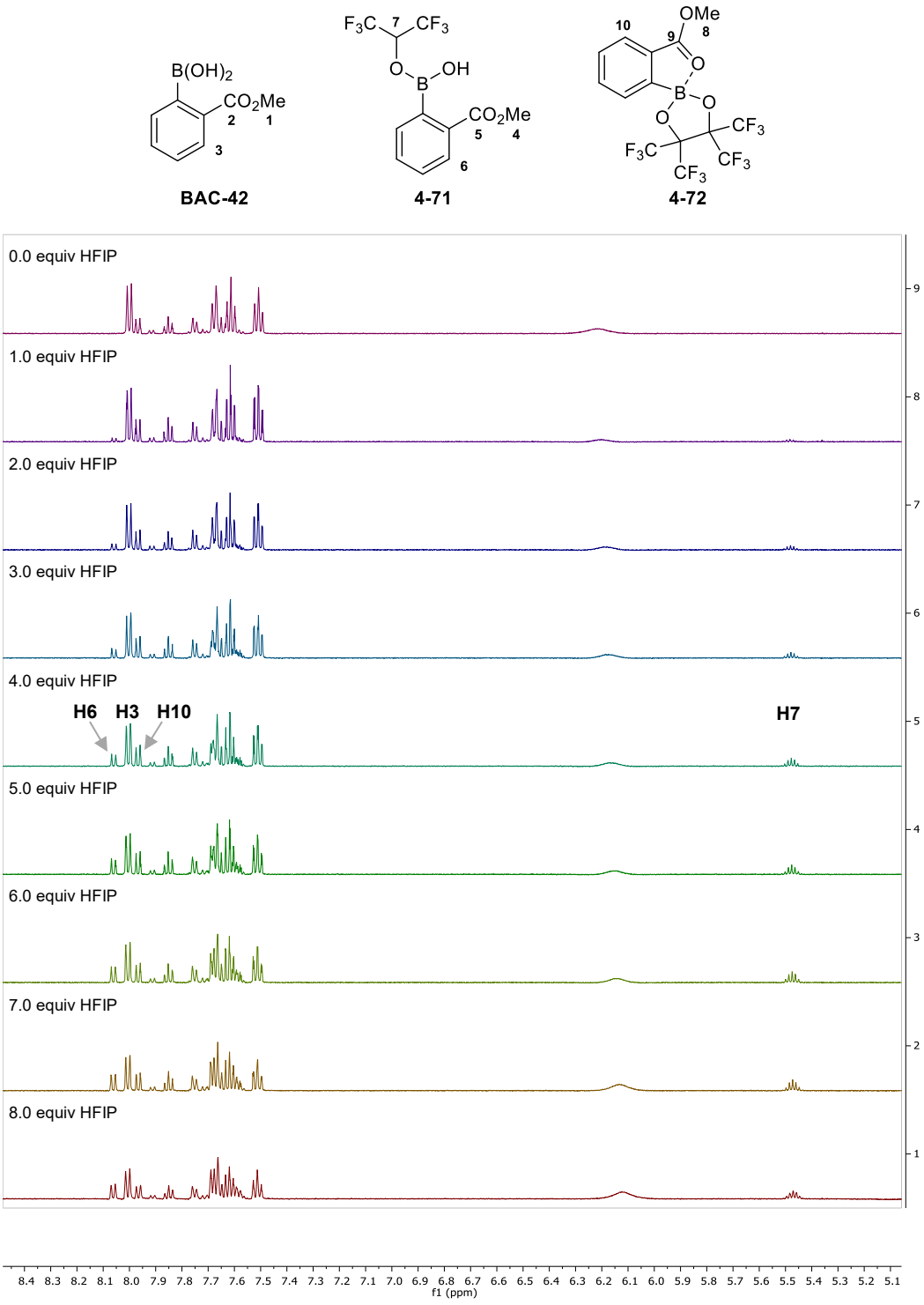


Figure 4-11. Titration of the reaction mixture of **BAC-42** and perfluoropinacol with varying amounts of HFIP by ^{1}H NMR-Part 1 (8.5–5.0 ppm).

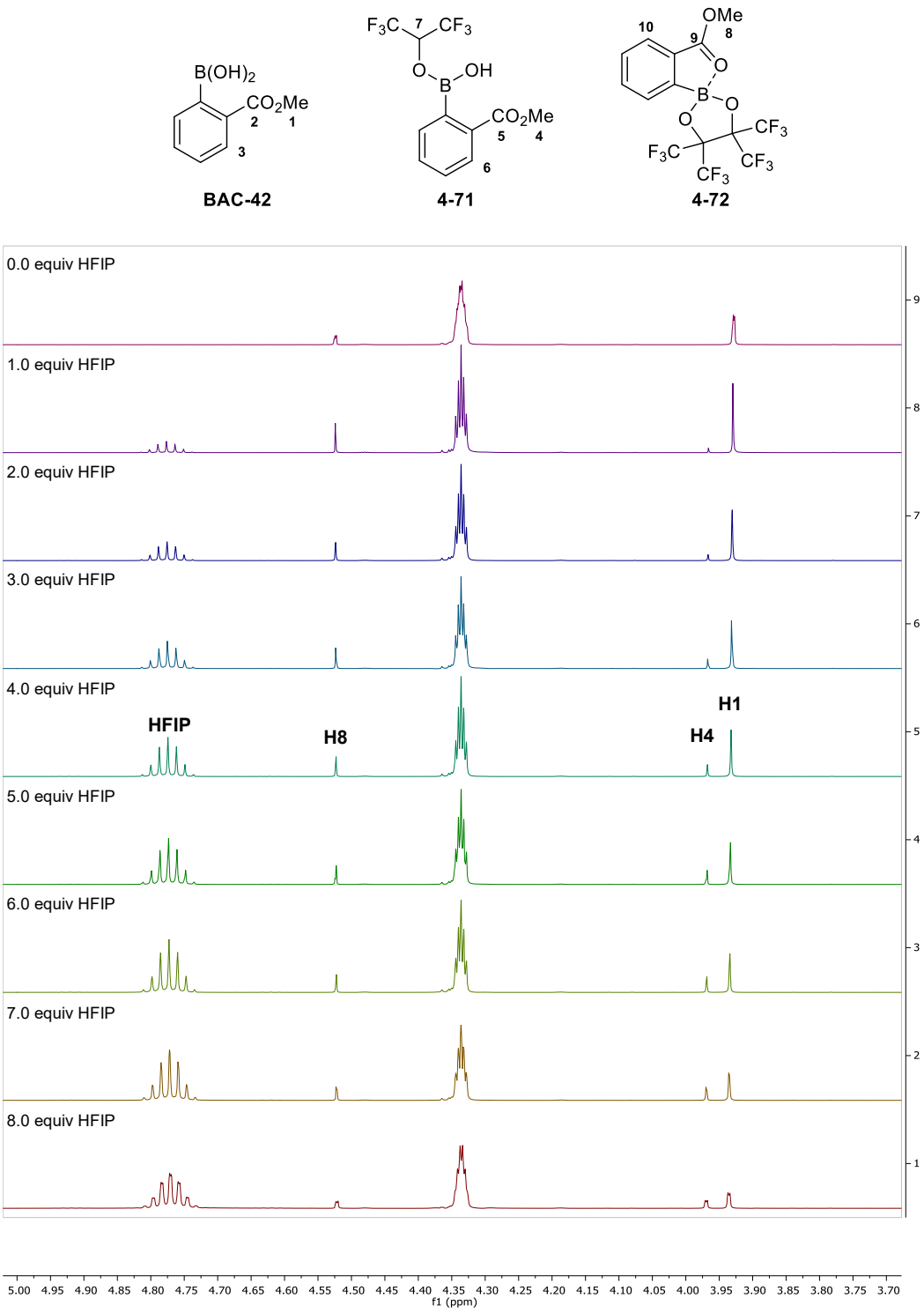


Figure 4-12. Titration of the reaction mixture of **BAC-42** and perfluoropinacol with varying amounts of HFIP by ^{1}H NMR-Part 2 (5.0–3.7 ppm).

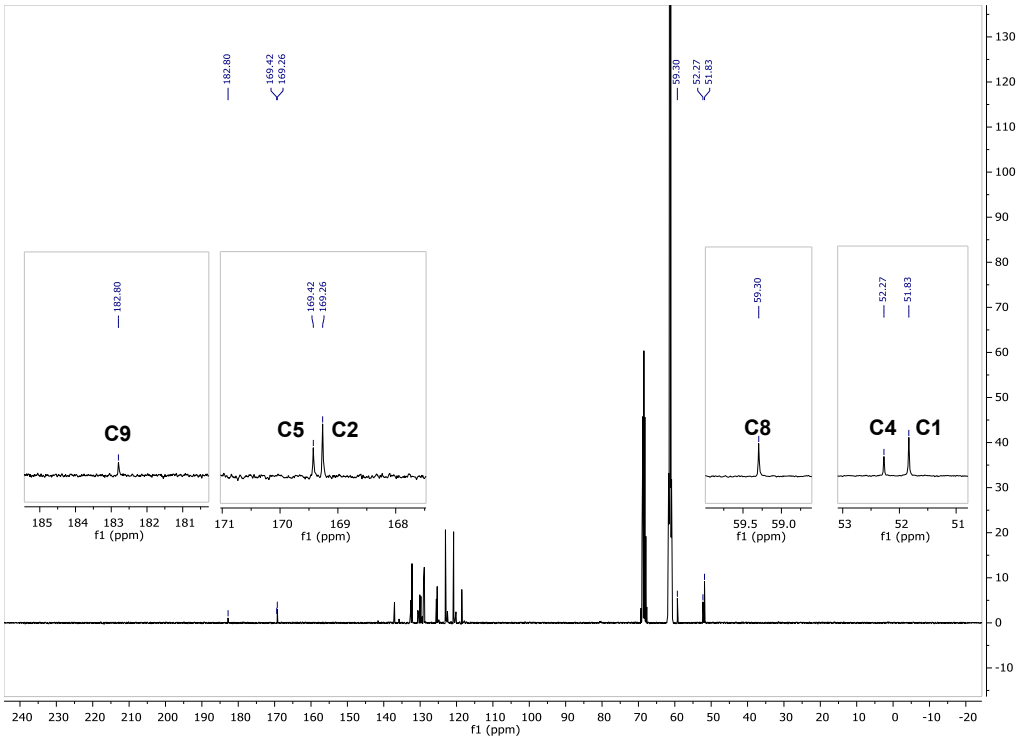


Figure 4-13. ^{13}C NMR spectrum of the titration end point of **BAC-42**, **4-71** and **4-72** with HFIP.

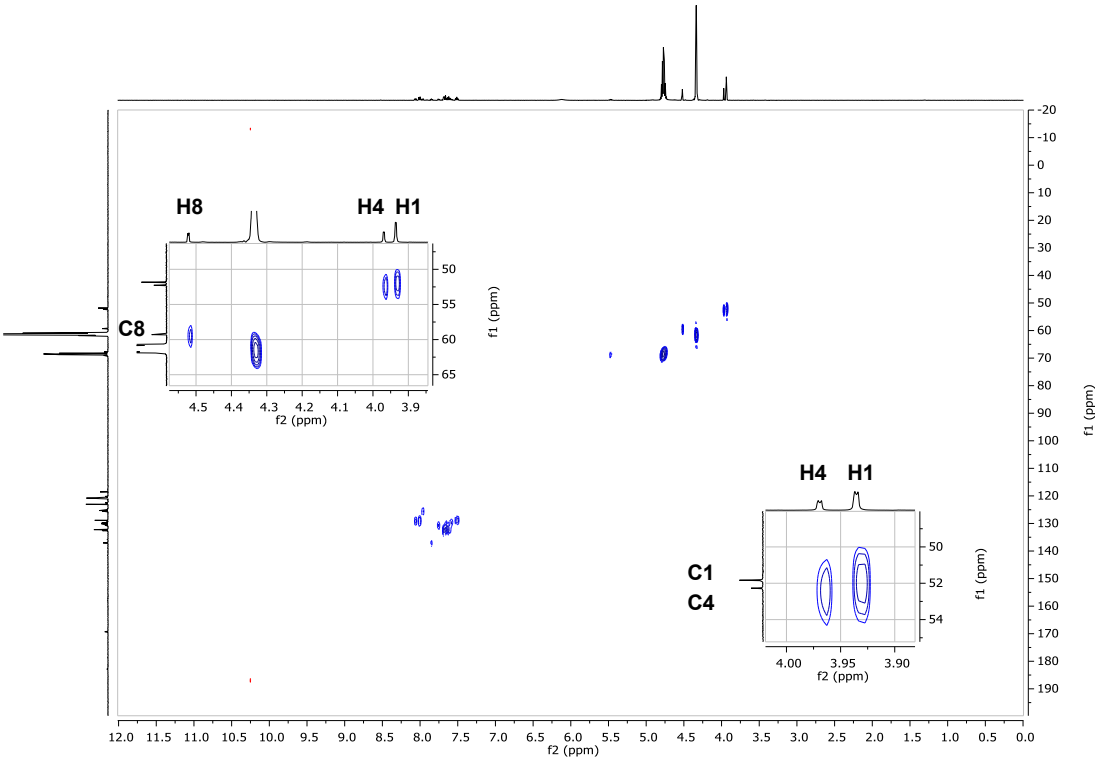


Figure 4-14. HSQC spectrum of the titration end point of **BAC-42**, **4-71** and **4-72** with HFIP.

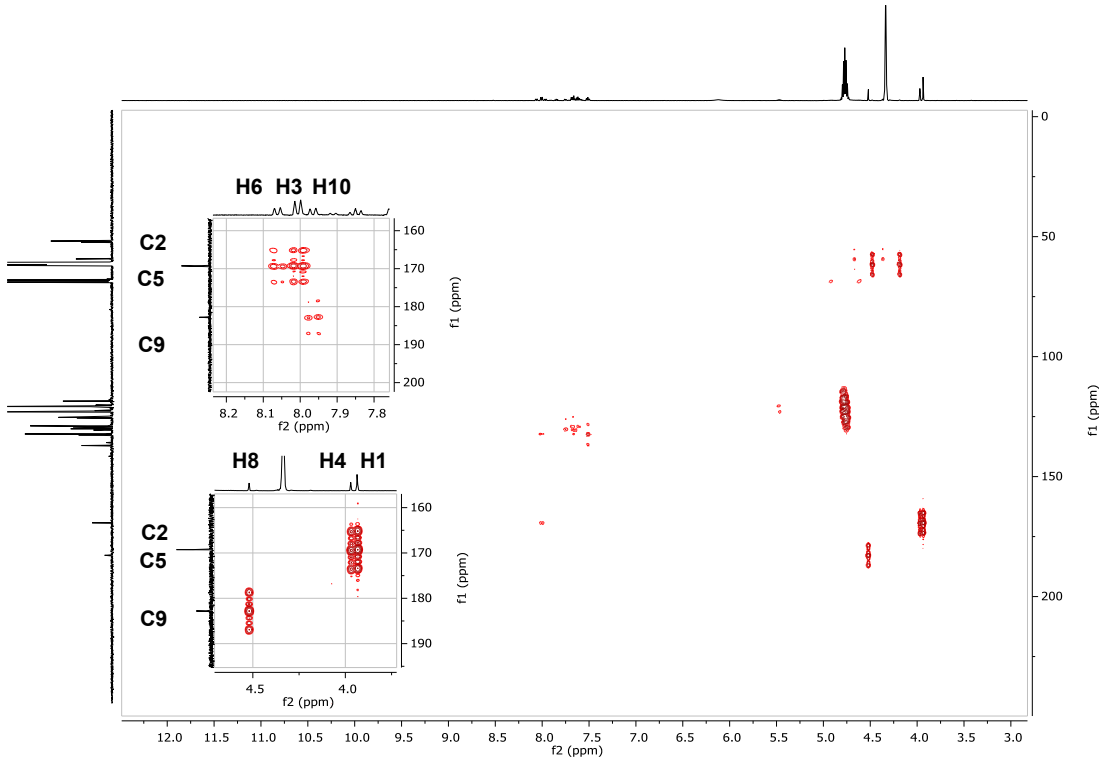
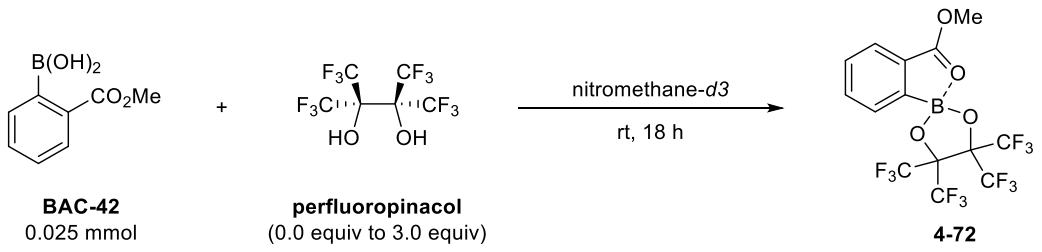


Figure 4-15. HMBC spectrum of the titration end point of **BAC-42**, **4-71** and **4-72** with HFIP.

The intermediacy of boronic ester **4-72** was also supported by the following experiments. **BAC-42** with various amounts of perfluoropinacol were dissolved in nitromethane-*d3* and stirred at room temperature for the same amount of time (**Scheme 4-22**). These reaction mixtures were then subjected to ^{11}B NMR spectroscopic studies. As the amounts of perfluoropinacol increased, the boron signal at 15.0 ppm enhanced, which suggests that more of the boronic ester **4-72** was formed (**Figure 4-16**).



BAC-42
0.025 mmol

perfluoropinacol
(0.0 equiv to 3.0 equiv)

4-72

Scheme 4-22. Reactions of one equivalent of **BAC-42** with various amounts of perfluoropinacol.

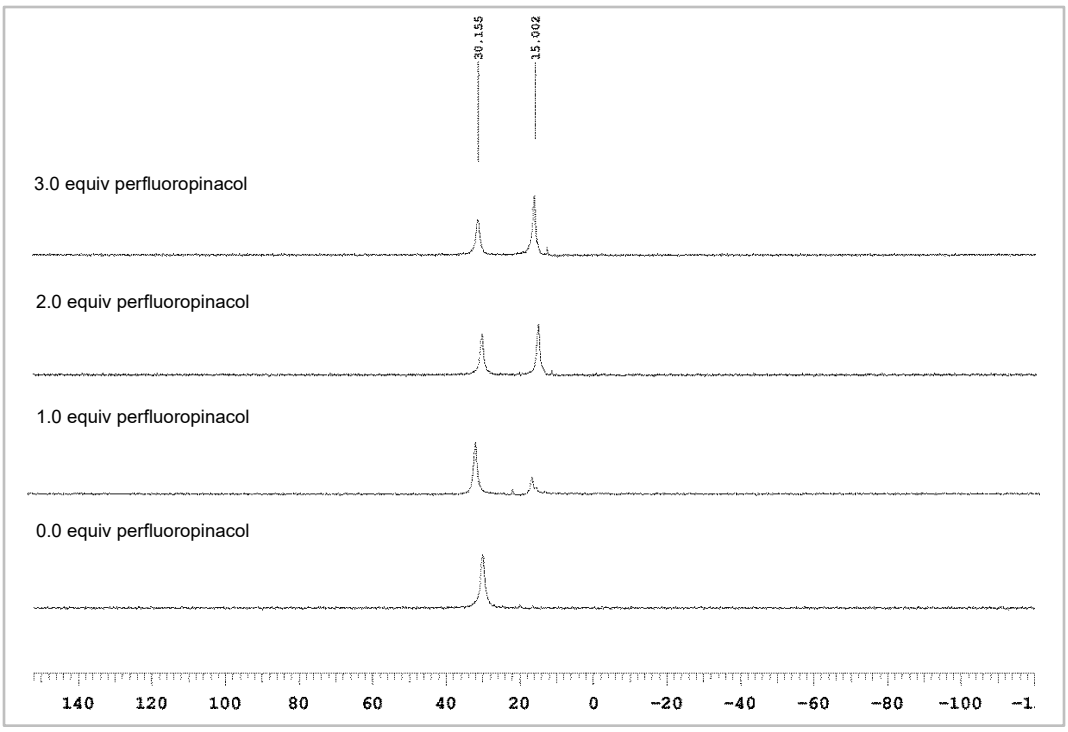
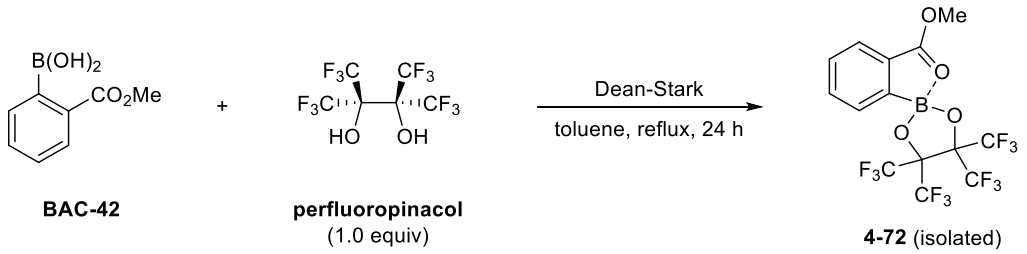


Figure 4-16. ^{11}B NMR spectrum of **BAC-42** and various amounts of perfluoropinacol in nitromethane-*d3*.

Although the previous experiments suggest that the boronic ester **4-72** was formed in nitromethane, more efforts were placed to support its intermediacy in the actual reaction solvent (HFIP:CH_3NO_2 v:v = 4:1). Specifically, boronic ester **4-72** was prepared independently as shown in **Scheme 4-23**. The characterization of **4-72** by ^{1}H NMR and ^{11}B NMR (**Figure 4-17** and **4-18**) confirmed the previous observation of new peaks in **Figures 4-6** and **4-8**.



Scheme 4-23. The synthesis of complex **4-72** from **BAC-42** and perfluoropinacol.

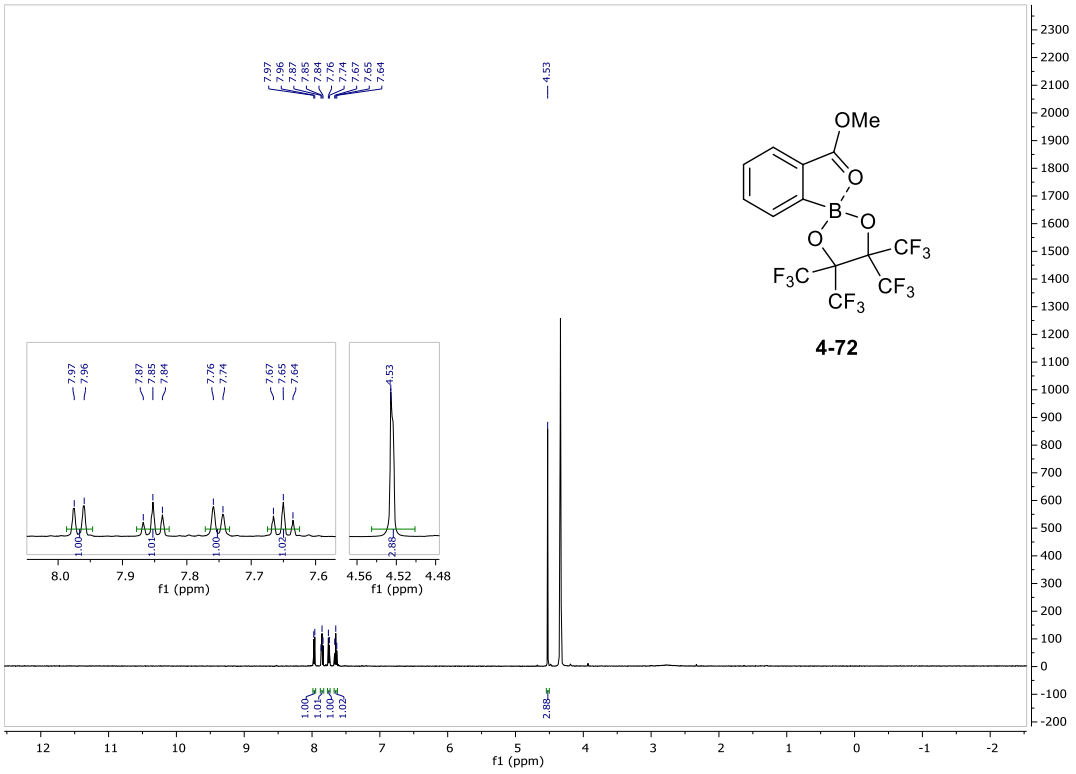


Figure 4-17. ^{1}H NMR spectrum of compound **4-72** in nitromethane-*d3*.

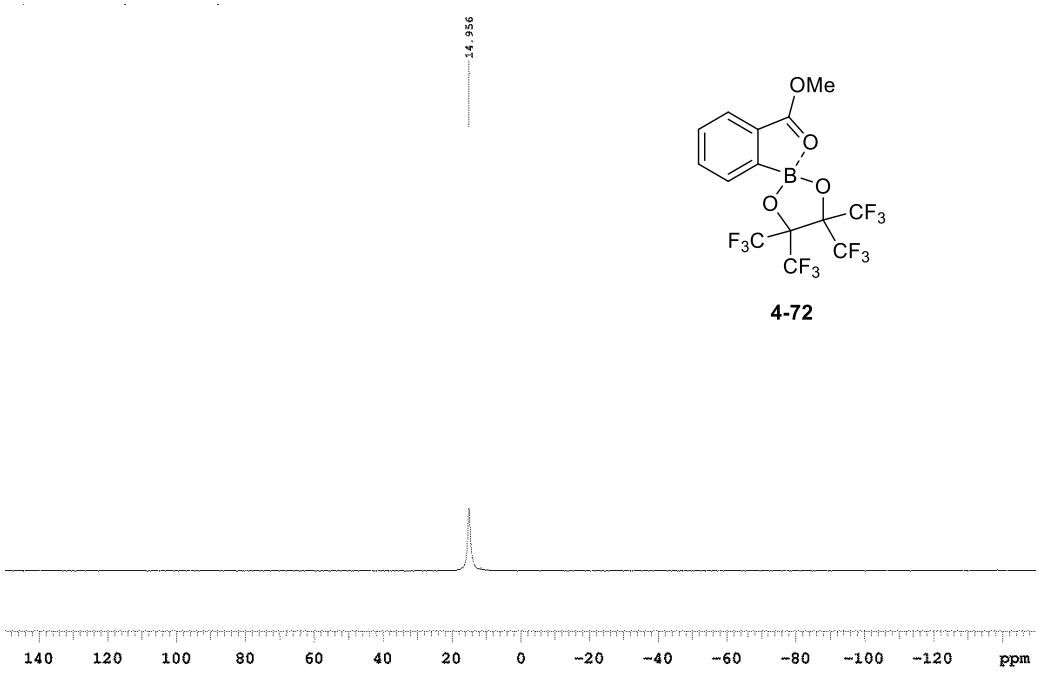
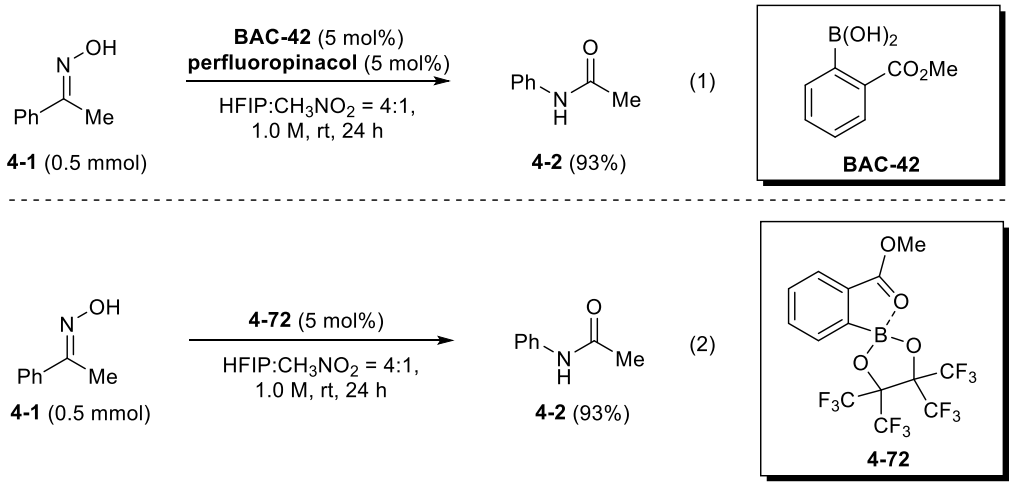


Figure 4-18. ^{11}B NMR spectrum of compound **4-72** in nitromethane-*d3*.

Furthermore, the catalytic reactivity of compound **4-72** was confirmed with oxime **4-1** in the actual reaction solvent (**Scheme 4-24**, equation 2). Full conversion of oxime **4-1** was observed after 24 hours and amide **4-2** was isolated in 93% yield, which is consistent with the optimal conditions where perfluoropinacol is added directly with **BAC-42** in the reaction (**Scheme 4-24**, equation 1). This observation supports that boronic ester **4-72** is formed in the optimal reaction conditions (**Scheme 4-24**, equation 1) when HFIP is present.



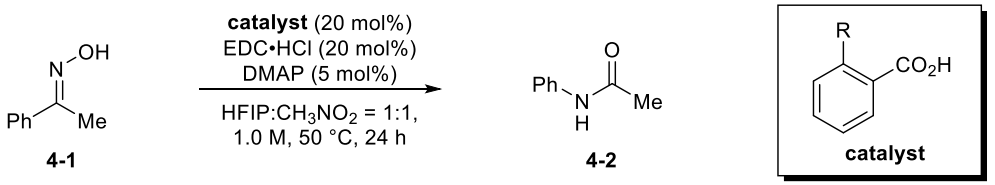
Scheme 4-24. Evaluation of the catalytic reactivity of boronic ester **4-72**.

In light of these observations, the following mechanistic picture is proposed: the oxime transesterification is facilitated due to the highly electrophilic ester, which is polarized by the Lewis acidic perfluoropinacol and/or HFIP boronic ester.

4.8.2 Studies to support the boron-assisted Beckmann rearrangement

With a clear role of the boronic acid moiety for the oxime transesterification, more studies were conducted to identify the exact role of the boronic acid in the actual Beckmann rearrangement. As described in **Table 4-1**, 2-carboxyphenyl boronic acid **BAC-41** displayed very low reactivity for the direct Beckmann rearrangement, possibly due to a relatively slow transesterification. In this regard, higher conversion of the product should be obtained with **BAC-41** in the presence of suitable coupling reagents. Indeed, when oxime **4-1** was subjected to the coupling conditions with catalytic EDC·HCl and DMAP along with **BAC-41**, a moderate yield (52%) of the amide

product **4-2** was observed (**Table 4-7**, entry 1). Surprisingly, the reaction using protected pinacol boronic ester **4-73** also gave amide **4-2** in moderate yield 33% (entry 2). However, devoid of the boronic acid, benzoic acid **4-74** resulted in no product, which highlights the important role of the boronyl group in the rearrangement (entry 3). It was also discovered that the *ortho* boronic acid moiety could not be replaced by other electron withdrawing groups. Under the same carboxylic acid coupling conditions, the use of 2-nitro/trifluoromethyl benzoic acid (**4-75** and **4-76**) provided no formation of the product (entries 4 and 5) after 24 h. Overall; these observations indirectly confirm that the presence of Lewis acidic boron center triggers the Beckmann rearrangement.



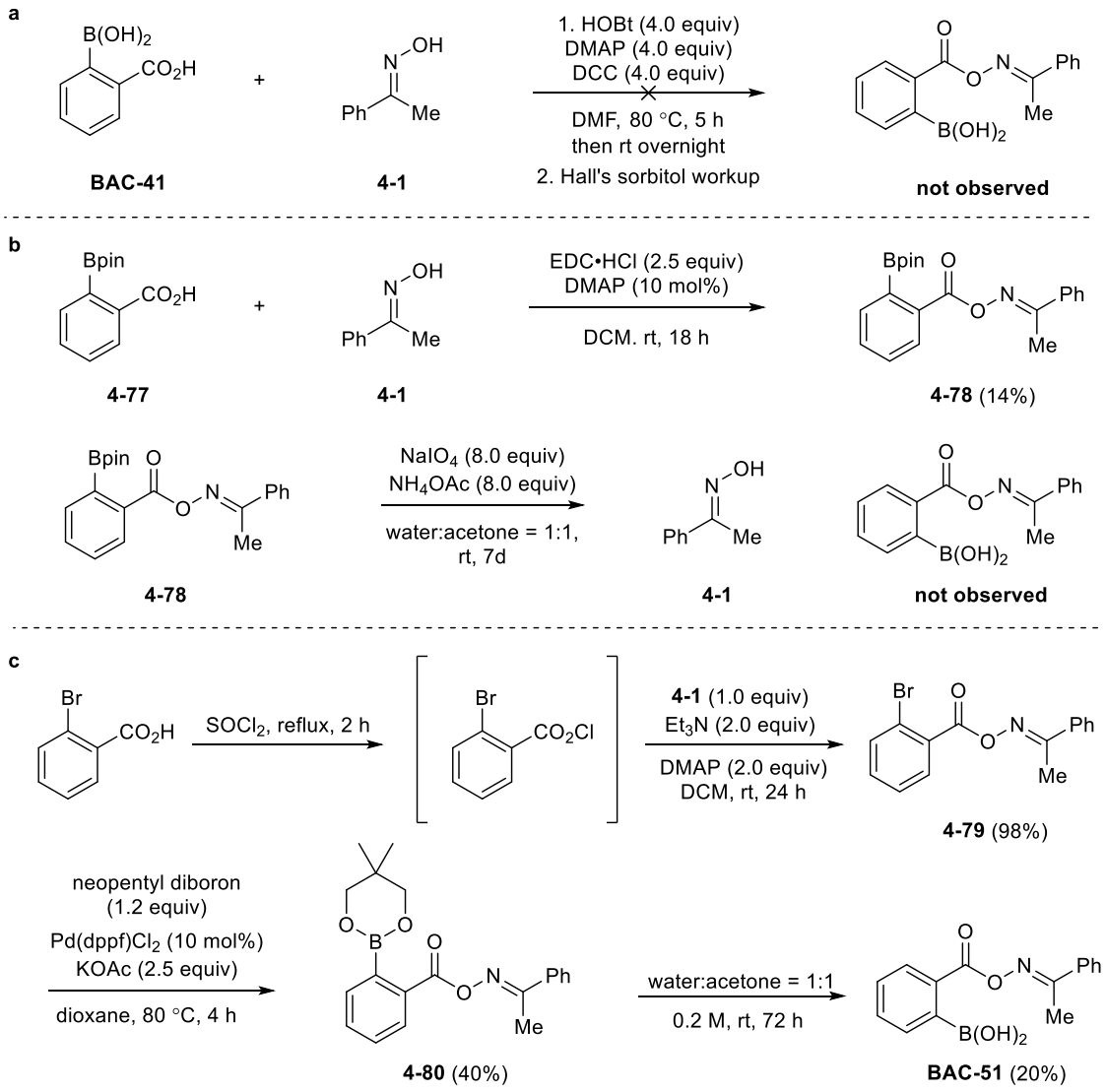
entry	R	number	yield (%)[a]
1	$B(OH)_2$	**BAC-41**	52
2	Bpin	**4-73**	33
3	H	**4-74**	n.r.
4	NO_2	**4-75**	n.r.
5	CF_3	**4-76**	n.r.

[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as an internal standard.

Table 4-7. Control experiments to support the boron assisted Beckmann rearrangement.

To support the intermediacy of the oxime ester and provide direct evidence of the boron assisted Beckmann rearrangement, effort was placed into the synthesis of **BAC-51** and evaluation of its catalytic activity for the direct Beckmann rearrangement (**Scheme 4-25**). At the outset, the direct coupling of **BAC-41** and oxime **4-1** was attempted with DCC, HOBt and DMAP using the sorbitol work-up, as previously described by Hall and co-workers.[29] Unfortunately, no desired product was obtained (**Scheme 4-25a**). While direct coupling of the oxime was not successful, a second strategy was proposed to protect **BAC-41** into the corresponding pinacol ester **4-77** to allow the sequential oxime coupling and deprotection (**Scheme 4-25b**). Although a low yield of **4-78** was obtained, enough material was isolated for further use. However, the deprotection of such a sterically hindered pinacol boronic ester **4-78** was unproductive. Only oxime **4-1**, from the hydrolysis, was observed after a long reaction time. Due to the inefficient

synthesis of the boronic ester with route b, an alternative method using Miyaura borylation and sequential deprotection method was designed. As described in **Scheme 4-25c**, the brominated oxime ester **4-79** was prepared in high yield using a more robust esterification method *via* the acid chloride. Since the pinacol boronic ester **4-78** could not be successfully deprotected, installation of a more labile protecting group was attempted. Miyaura borylation of bromoarene **4-79** afforded the corresponding neopentyl boronic ester **4-80** in a moderate yield of 40%. Gratifyingly, product **4-80** was stable enough to be isolated by column chromatography. The free boronic acid **BAC-51** was successfully obtained upon hydrolysis of **4-80**, albeit in low yield.

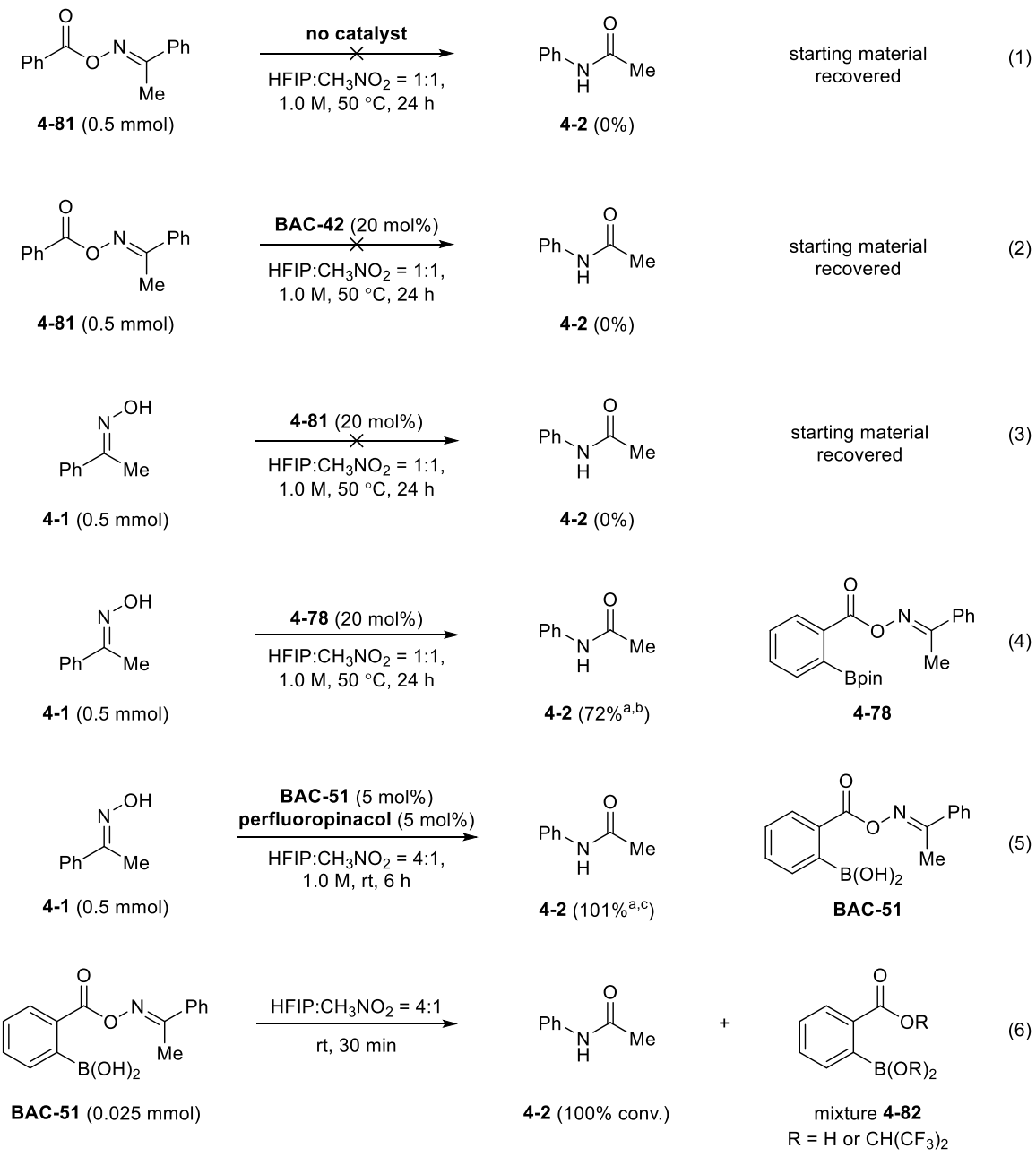


Scheme 4-25. Synthesis of oxime ester BAC-51: (a) *via* a direct coupling method; (b) by a boronic acid protection-coupling-deprotection sequence; (c) with the Miyaura borylation and deprotection method.

With **BAC-51** successfully prepared, control experiments to provide direct evidence of the Lewis acidic boron assisted Beckmann rearrangement were performed. As described in **Scheme 4-26**, oxime ester **4-81** was prepared independently and subjected to several studies. It was found that no rearrangement occurred using **4-81** with or without catalyst **BAC-42** (equation 1 and 2). In addition, compound **4-81** showed no catalytic activity in the actual reaction (equation 3). These three experiments establish the ineffectiveness of oxime ester **4-81** in the reaction media without the *ortho* boronyl group. Following these negative controls, reactions using oxime esters **4-78** and **BAC-51** with *ortho* boronyl groups were conducted. Similar to the result described in **Table 4-7** entry 2, catalyst **4-78** with protected pinacol boronic ester afforded amide **4-2** in moderate yield (**Scheme 4-26**, equation 4). This appears somewhat contradictory to the reaction with **4-42**, in which no product was formed (**Table 6**, entry 5). The observation indicates that, while a free boronic acid is needed to form a highly Lewis acidic boronic ester with HFIP or perfluoropinacol for the initial transesterification, the downstream Beckmann rearrangement only requires the presence of a boronyl group. However, hydrolysis or exchange with HFIP of pinacol boronic ester **4-78** under the reaction conditions (equation 4) cannot be excluded at this point. When **BAC-51** was subjected to the optimal conditions, a high yield of the amide **4-2** was obtained after only 6 h (**Scheme 4-26**, equation 5). Over 100% of **4-2** was measured, since catalyst **BAC-51** could produce an extra 5% of product theoretically. Self-rearrangement of **BAC-51** was also observed in the reaction solvent without the addition of oxime **4-1**, yielding amide **4-2** and complex side products (**Scheme 4-26**, equation 6). These side products were studied by ^{1}H NMR, ^{13}C NMR and HMBC analysis and eventually concluded to be **4-82**, a mixture of the HFIP carboxy ester (**4-82a**) and HFIP boronic ester (**4-82b**).

The elucidation of mixture **4-82** was concluded as follows in (**Figure 4-19**). While the peaks at 4.4 ppm represent the remaining solvent HFIP and nitromethane, two other distinct septet peaks 6.0 ppm and 5.3 ppm were observed, which were produced from the methine protons in two different hexafluoro isopropoxy moieties. From the ^{13}C NMR spectra, two major and identifiable carbonyl peaks at 169.2 and 166.6 ppm are present (**Figure 4-20**). The carbonyl signal at 166.6 ppm was assigned as C12 from the HFIP carboxy ester **4-82a**, as a correlation was found between proton H11 (6.0 ppm) and C12 (166.6 ppm). The carbon signal at 169.2 ppm was assigned as C16 from amide **4-2**, as it is correlated to the methyl group H15 (2.2 ppm). In contrast, no correlation was found between H13 (5.3 ppm) and any other carbonyl signal, which supports formation of the HFIP boronic ester **4-82b**, as illustrated in **Figure 4-20** and **Figure 4-21**.

In summary, these experiments (**Table 4-7** and **Scheme 4-26**) support the intermediacy of **BAC-51** in the reaction conditions and a boron-assisted Beckmann rearrangement.



[a]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as an internal standard. [b]Maximum yield is 120%. [c]Maximum yield is 105%.

Scheme 4-26. Control experiments to support the intermediacy of **BAC-51**.

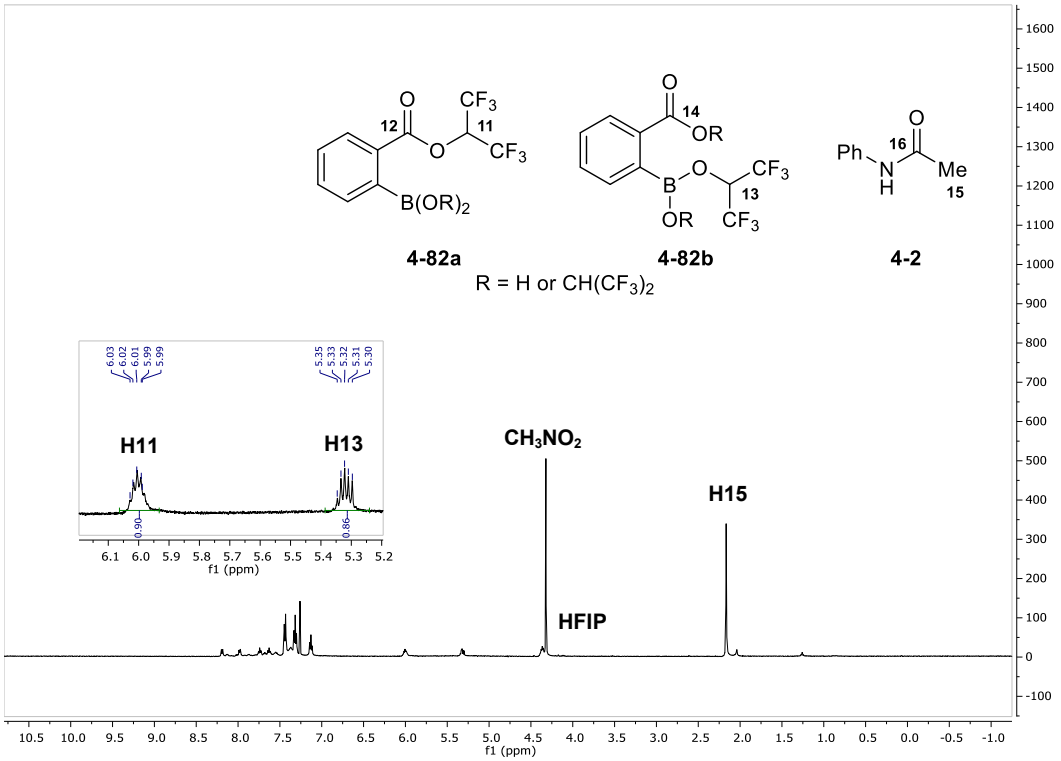


Figure 4-19. ^{1}H NMR spectrum of mixture **4-82** from the Beckmann rearrangement of **BAC-51**.

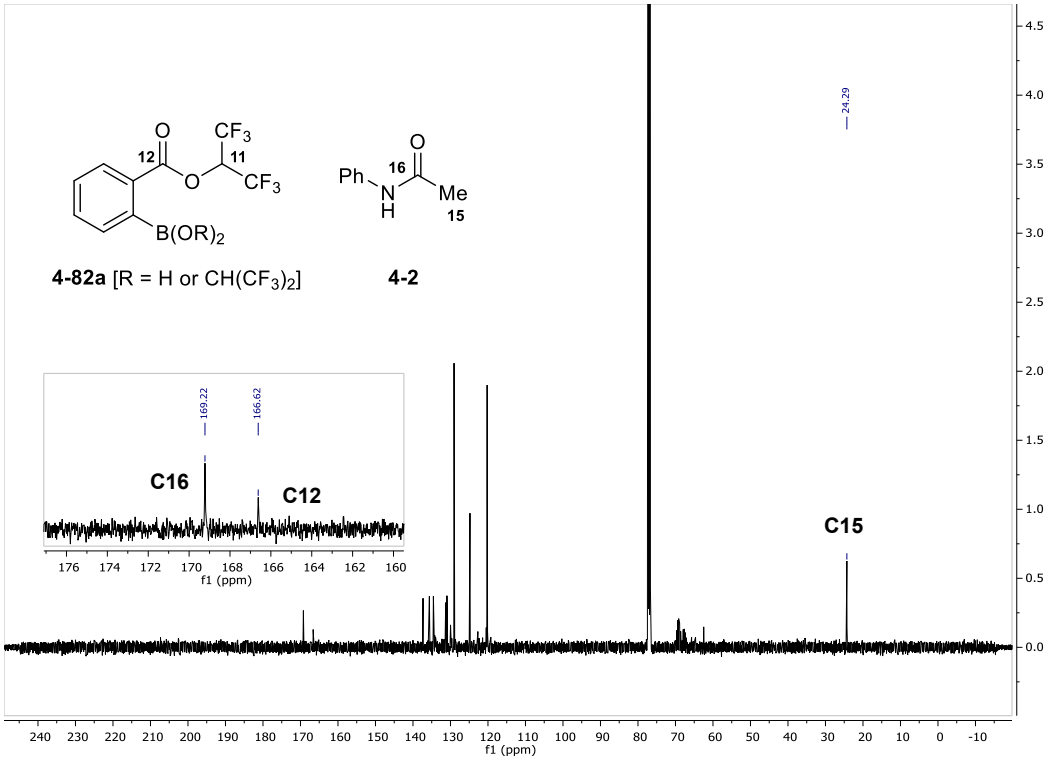


Figure 4-20. ^{13}C NMR spectrum of mixture **4-82** from the Beckmann rearrangement of **BAC-51**.

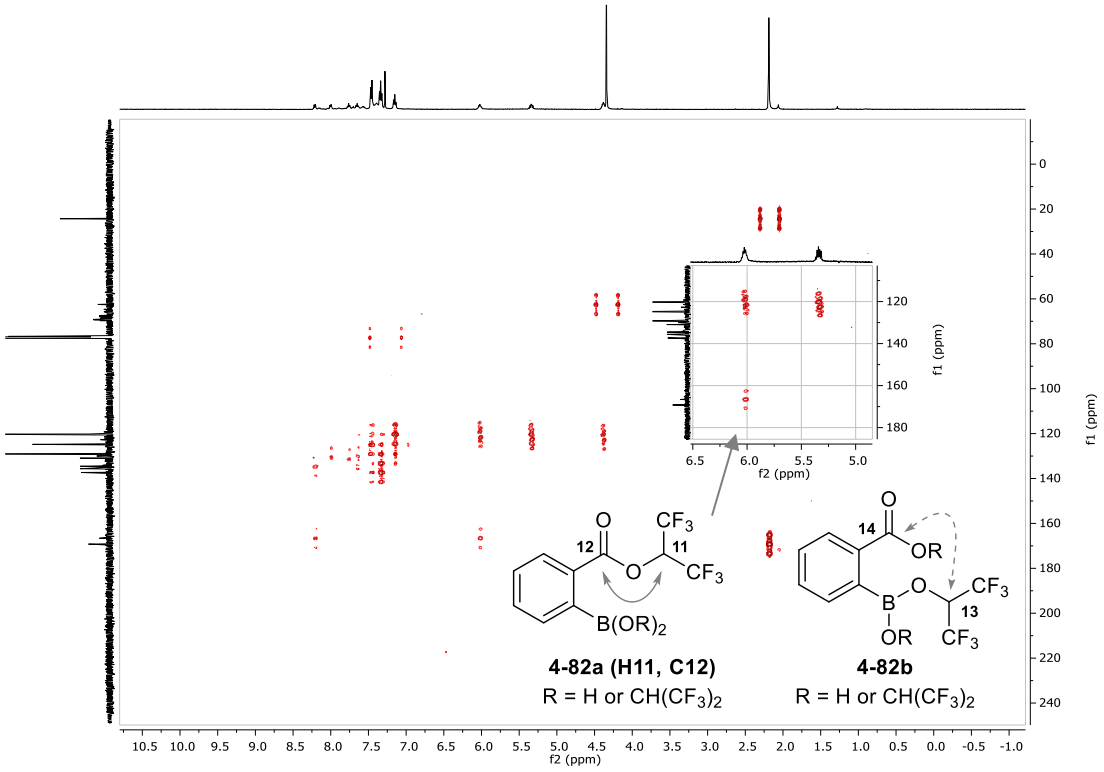
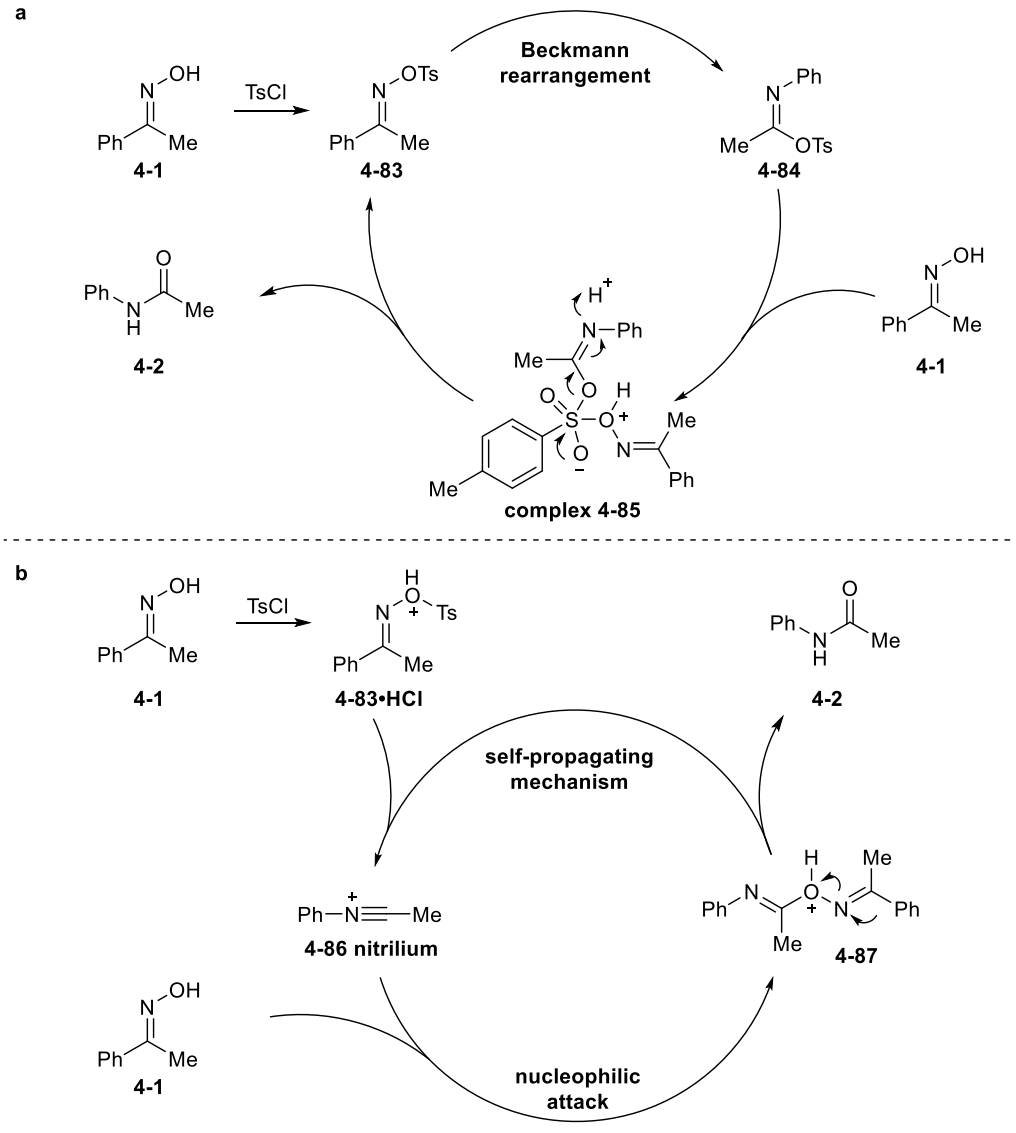


Figure 4-21. HMBC spectrum of mixture **4-82** from the Beckmann rearrangement of **BAC-51**.

4.8.3 Catalytic vs self-propagating mechanism

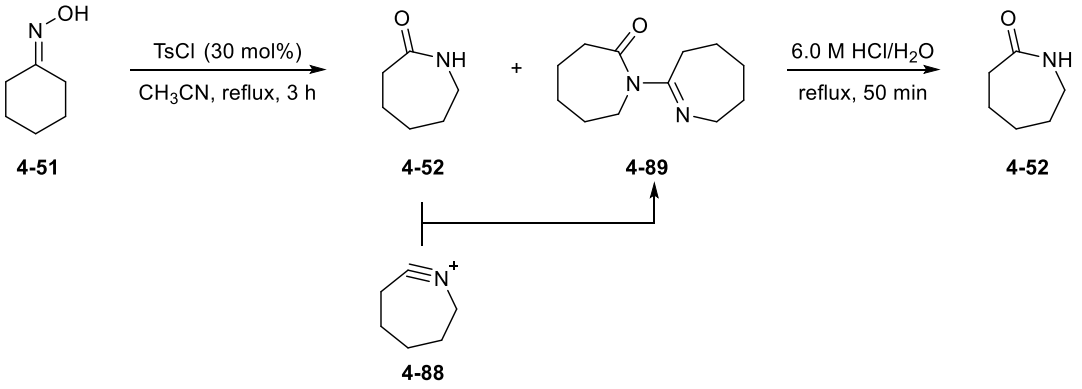
Although a number of chloride electrophiles, such as CNC, TsCl, TAPC and CPI-Cl (**Scheme 4-1c**), were reported to catalyze the Beckmann rearrangement, whether these protocols are truly organocatalytic or not is still under debate.[20] With TsCl as an example, a truly organocatalytic system is commonly proposed to involve: first the Beckmann rearrangement of **4-83** to **4-84** and then turnover through complex **4-85** (in some other cases, a Meisenheimer complex) to regenerate the catalytic species **4-83** and release the product (**Scheme 4-27a**).[19]



Scheme 4-27. Previously proposed mechanisms for organocatalytic Beckmann rearrangement: (a) catalytic mechanism; (b) self-propagating mechanism.

In contrast, DFT calculations by Eriksson and co-workers strongly suggest a self-propagating mechanism involving the formation of a nitrilium ion **4-86** (**Scheme 4-27b**). Nucleophilic attack of the oxime to the nitrilium ion results in a dimeric complex **4-87**, which undergoes Beckmann rearrangement and regeneration of the active nitrilium species.[30]

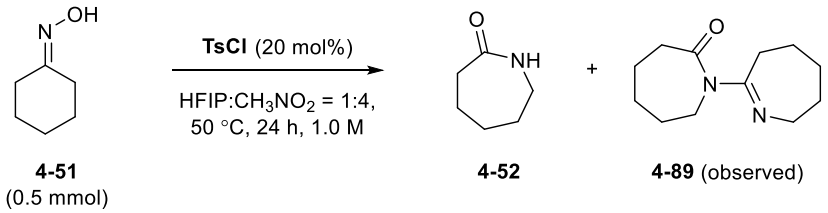
Recently, experimental explorations from Ishii[18] and Deng[31] also support the self-propagating mechanism in the organocatalytic systems using chloride electrophiles. In Deng's report,[31] efforts were also undertaken to explain why cyclohexanone oxime **4-51** is not a good substrate in the organocatalytic systems. According to their calculation and experiments, a dimeric compound **4-89**, which results from the nucleophilic attack of ε-caprolactam **4-52** to the nitrilium ion **4-88**, severely inhibits the rearrangement (**Scheme 4-28**). Upon acidic reflux conditions, this dimeric compound can be hydrolyzed back to the desired product **4-52**. The same observation was also reported by Ishii and co-workers.[18]

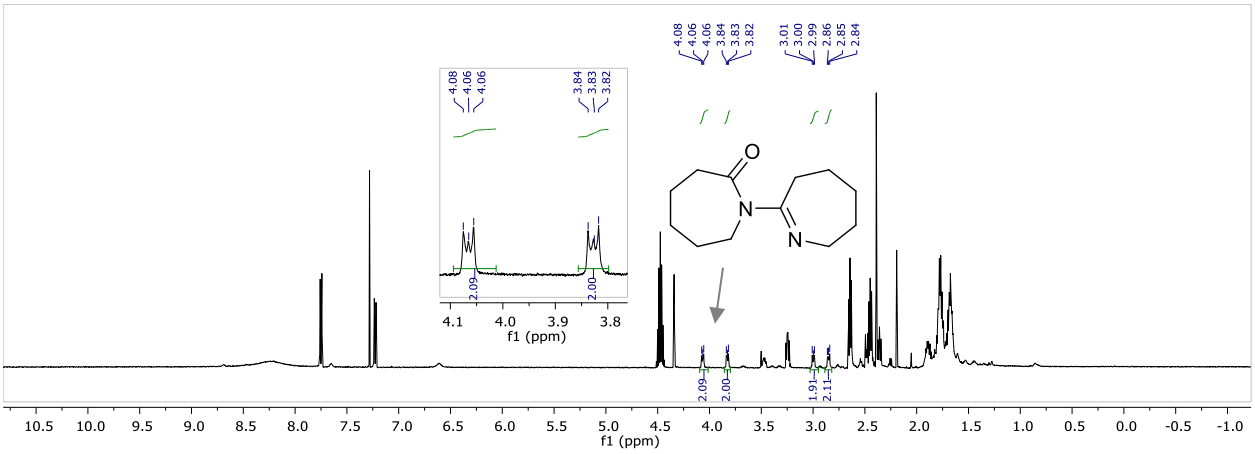


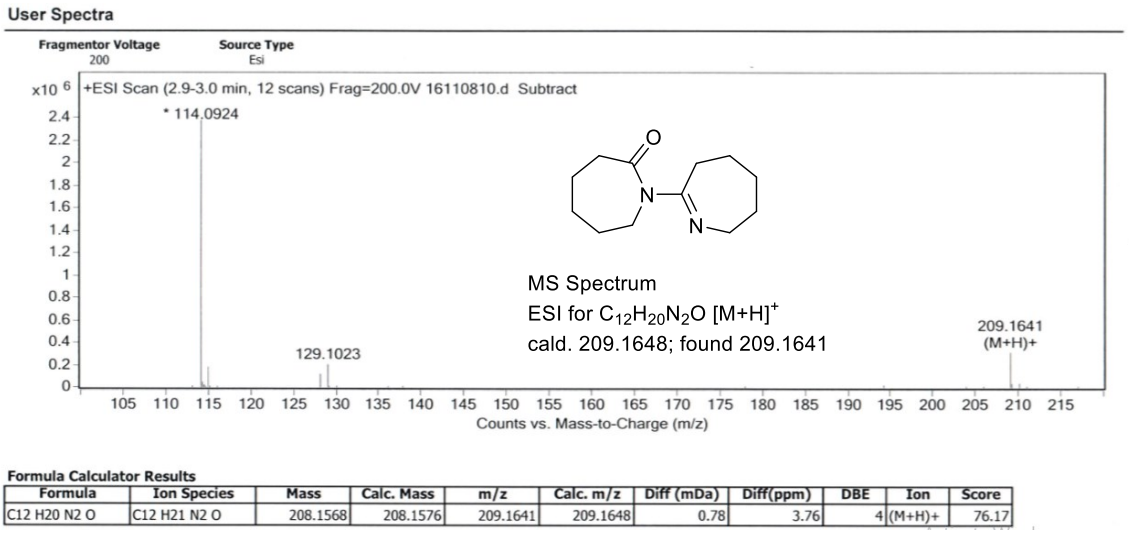
Scheme 4-28. Explanation of low reactivity of cyclohexanone oxime in organocatalytic or mediated system by Deng.

In order to further explore the nature of the Beckmann rearrangement with boronic acid catalysis, reactions with cyclohexanone oxime using TsCl and **BAC-42** under the same conditions were performed. Indeed, the dimeric compound **4-89** was observed on both ^{1}H NMR and HRMS in the rearrangement with TsCl in our solvent system (**Scheme 4-29**), which strongly suggests the formation of nitilium ion **4-88** (**Scheme 4-28**). Using catalyst **BAC-42** under the same conditions, the amide **4-52** was afforded in low yield, however, dimer **4-89** was not detected upon ^{1}H NMR and HRMS analysis (**Scheme 4-30**). Arguably, these results suggest that the BAC Beckmann

rearrangement does not go through a self-propagating mechanism. Rather, it could be considered a truly catalytic process.



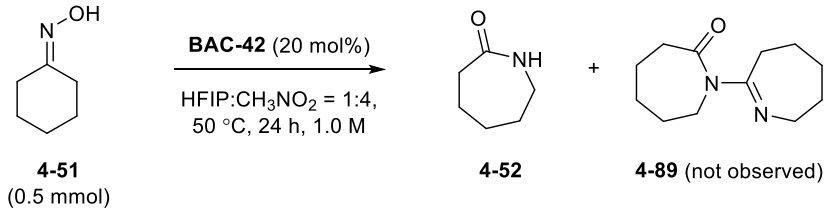


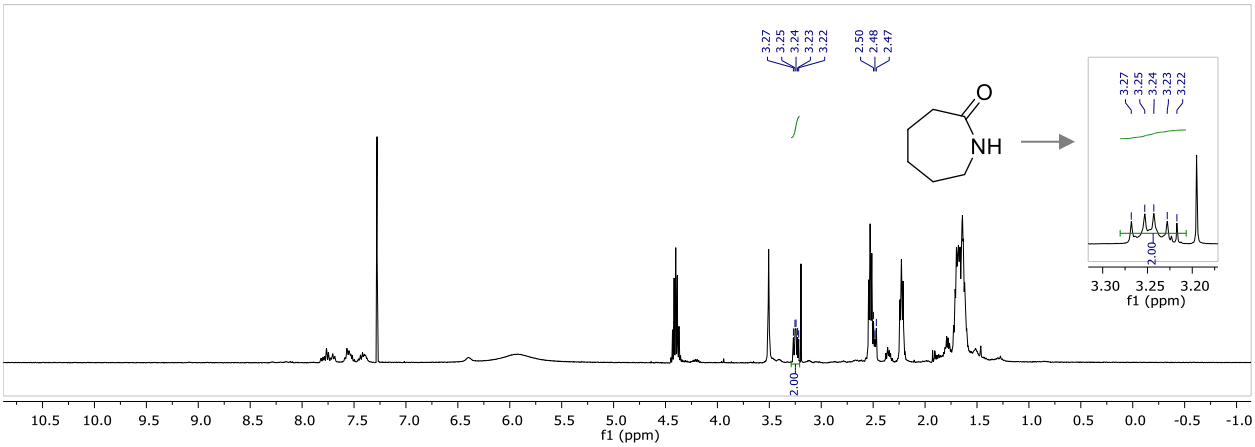


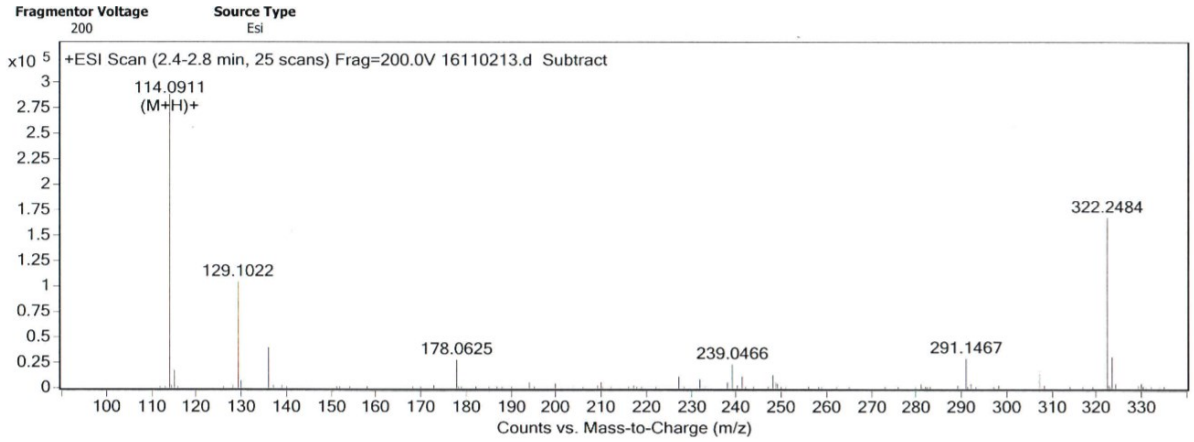
Formula Calculator Results

Formula	Ion Species	Mass	Calc. Mass	m/z	Calc. m/z	Diff (mDa)	Diff(ppm)	DBE	Ion	Score
C12 H20 N2 O	C12 H21 N2 O	208.1568	208.1576	209.1641	209.1648	0.78	3.76	4	(M+H)+	76.17

Scheme 4-29. ^{1}H NMR and HRMS analysis of reaction crude for cyclohexanone oxime using TsCl.







Formula Calculator Results

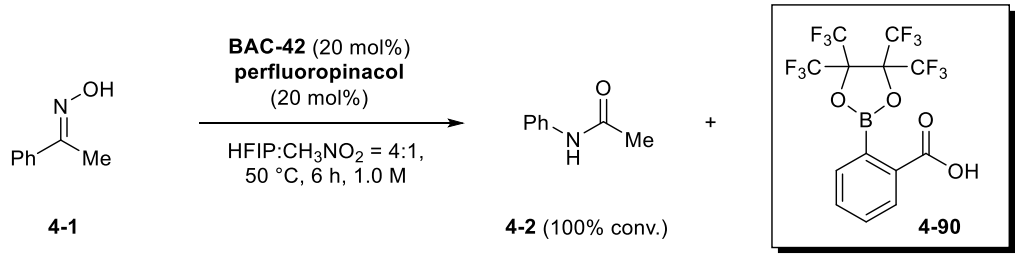
Formula	Ion Species	Mass	Calc. Mass	m/z	Calc. m/z	Diff (mDa)	Diff(ppm)	DBE	Ion	Score
C6 H11 N O	C6 H12 N O	113.0838	113.0841	114.0911	114.0913	0.22	1.95	2	(M+H)+	79.64

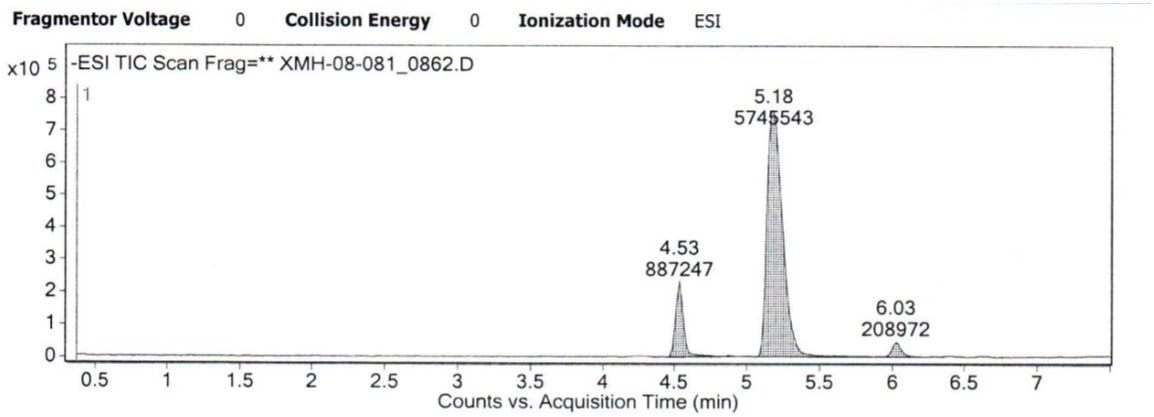
Scheme 4-30. ^{1}H NMR and HRMS analysis of reaction crude for cyclohexanone oxime using **BAC-42**.

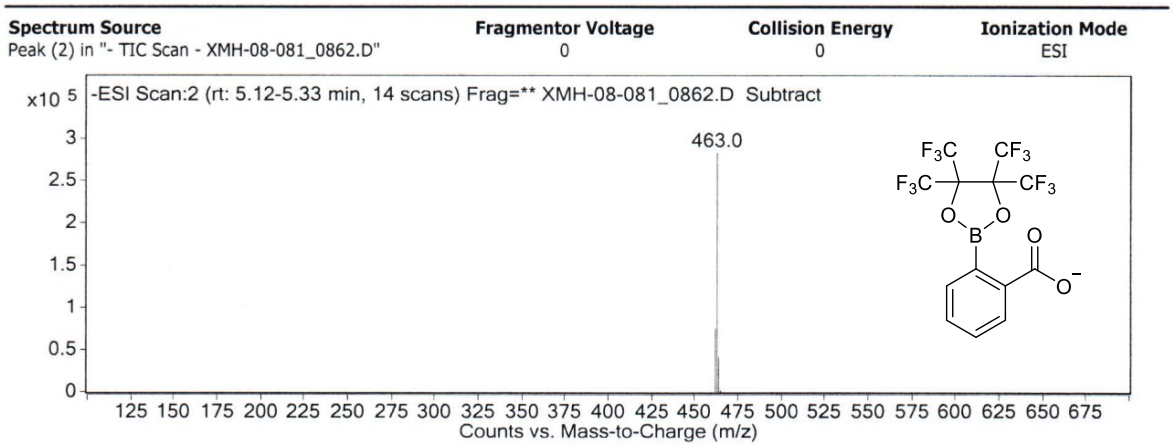
4.8.4 Degradation of the boronic acid

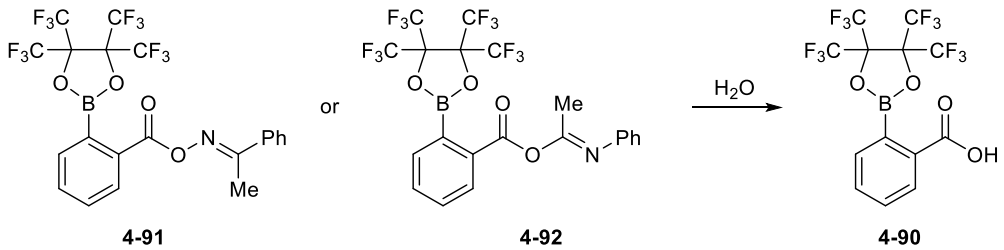
The fate of the boronic acid catalyst was studied by UPLC-MS analysis. A higher catalyst loading was employed for better detection of possible degradation products. As shown in

Scheme 4-31, the only identifiable compound was carboxylic acid **4-90**, which is suspected to be the side product from hydrolysis of the reactive intermediates **4-91** or **4-92**.





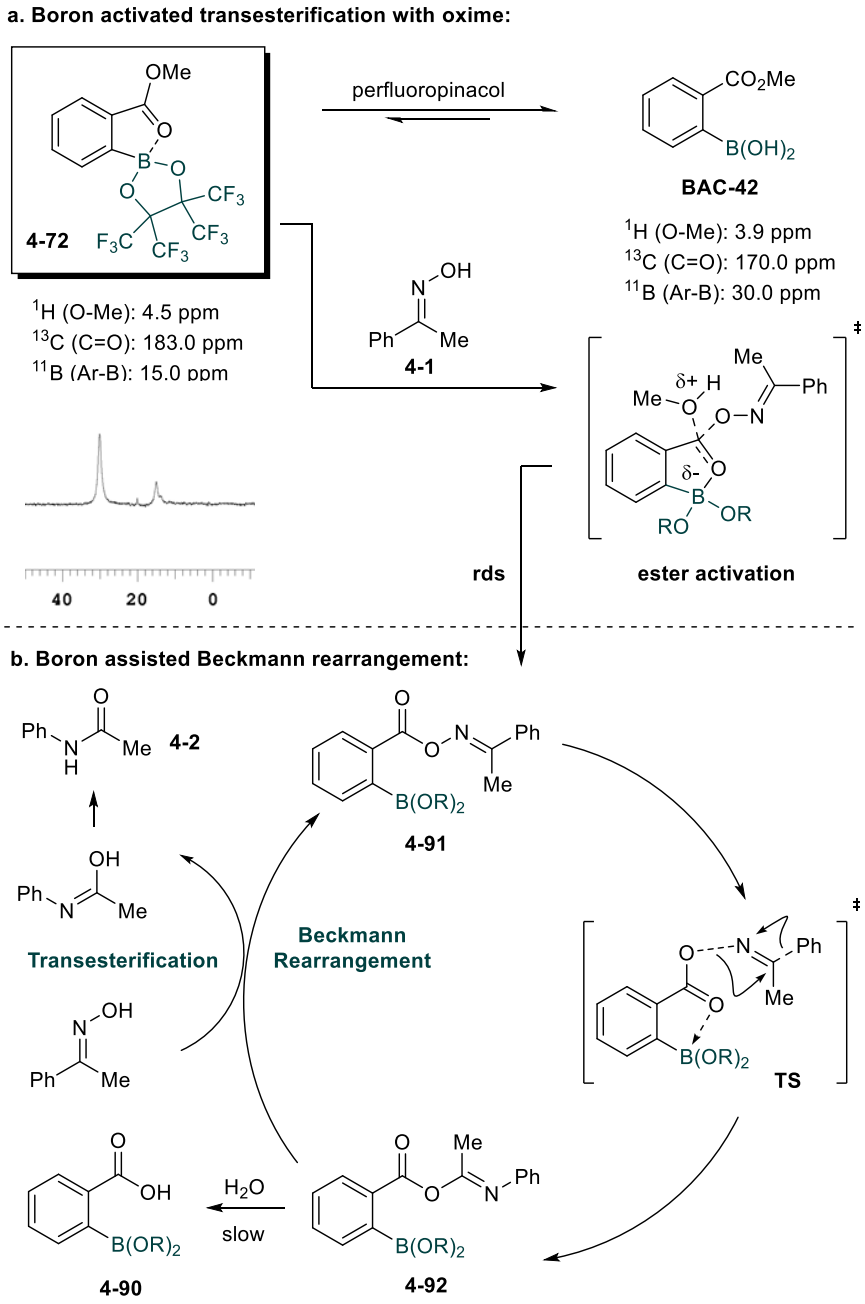




Scheme 4-31. UPLC-MS study of degradation of catalyst **BAC-42**.

4.9 Proposed mechanism

According to the mechanistic investigations described in Section 4.8, the proposed overall reaction mechanism is detailed in **Scheme 4-32**.



Scheme 4-32. Proposed mechanism for the boronic acid catalyzed Beckmann rearrangement.

As shown in **Scheme 4-31**, when **BAC-42** or **BAC-50** is subjected to the reaction solvent with perfluoropinacol, a highly electrophilic boronic ester **4-72** is formed, which strongly polarizes the *ortho*-carboxyester and triggers the oxime transesterification, affording intermediate **4-91**. This unique boron activated oxime transesterification is proposed to be the slowest step, an assertion supported by the more reactive nature of **BAC-50** bearing –OPh as a better leaving group. Presumably, the *ortho* boron from **4-91** induces the Beckmann rearrangement by polarizing the N–O bond through coordination of the oxime ester oxygen (**TS**). The nature of this rearrangement is, however, unclear at this moment. The stepwise self-propagating mechanism is unlikely, since no dimeric compound **4-89** is formed, which rules out the formation of the nitrilium ion. The dispute of the self-propagating mechanism is also supported by the fact that oxime ester **BAC-51** rearranged to amide **4-2** without the presence of extra oxime **4-1** (**Scheme 4-26**, equation 6). A concerted mechanism is proposed for the Beckmann rearrangement with **4-91** as a true catalytic species. Afterwards, the rearranged oxime ester **4-92** can under another oxime transesterification and release the amide product **4-2**. In the end, when all of the oxime is consumed, slow hydrolysis of **4-91** or **4-92** eventually leads to side product **4-90**.

4.10 Summary

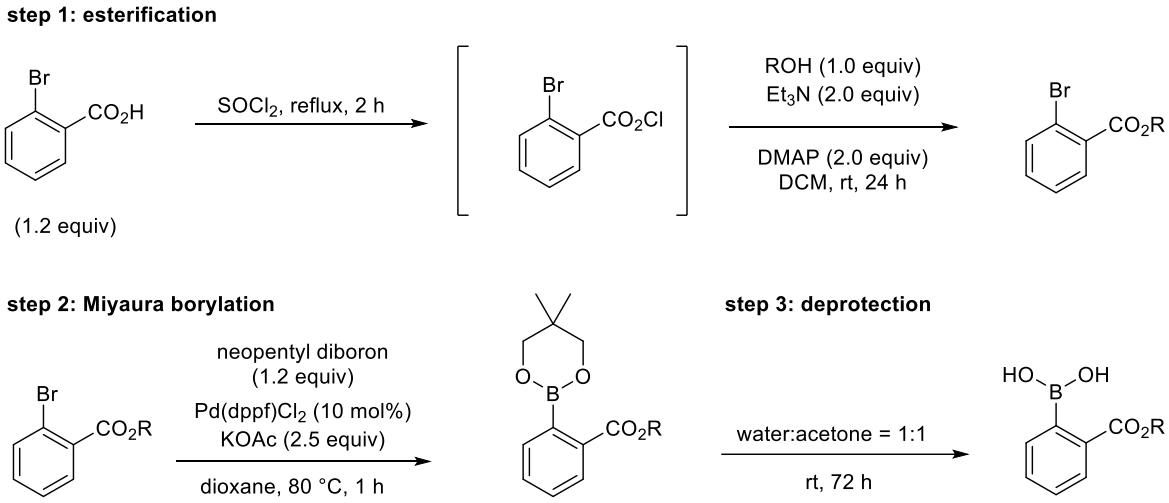
In conclusion, Chapter 4 describes our efforts towards the discovery and development of *ortho*-carboxyester arylboronic acids **BAC-42** and **BAC-50** as novel catalysts for the direct Beckmann rearrangement. This protocol is operationally simple; it does not require pre-drying of solvents or inert atmospheric conditions. Under the optimal conditions, oximes with various functional groups are tolerated and transformed into the amide products at ambient temperature. Further mechanistic studies indicate the critical functions of the boron moiety in mediating the oxime transesterification and inducing the concerted Beckmann rearrangement. This research is not only significant for direct N–OH bond activation, but also provides further guidance for boronic acid catalyst design in regard to the development of other reactions of oximes, direct S_N2 reactions and eliminations of alcohols.

4.11 Experimental

4.11.1 General methods

The following sections include representative experimental procedures and details for the synthesis and isolation of compounds. Full characterization of all new compounds and partial characterization of known compounds presented in this chapter are described. Unless otherwise stated, all reactions were performed in capped regular glassware with no further precautions to exclude air or moisture. Toluene, tetrahydrofuran (THF), dimethylformamide (DMF) and dichloromethane (DCM) were purified using a cartridge solvent purification system with 4 Å molecular sieves as absorbent. Acetonitrile and dimethyl sulfoxide (DMSO) were dried over activated molecular sieves before use. All other solvents (including HFIP and nitromethane) were purchased as ACS reagents and used without further purification or drying. 2-Methoxycarbonyl phenylboronic acid was purchased from Combi-Blocks (6:1 boronic acid: boroxine in anhydrous $CDCl_3$) and used as received. Unless otherwise noted, all other chemicals were purchased from commercial sources and used as received. Chromatographic separations were performed on silica gel 60 using ACS grade hexanes, ethyl acetate, dichloromethane, acetone, *tert*-butyl methyl ether and methanol as eluents. Thin layer chromatography (TLC) was performed on silica gel 60 F254 plates, which were visualized under UV light and with $KMnO_4$, iodine or phosphomolybdic acid (PMA) stains. ^{1}H NMR, ^{13}C NMR, ^{11}B NMR and ^{19}F NMR spectra were recorded on 400 MHz, 500 MHz or 700 MHz instruments. The residual solvent protons (^{1}H / $CHCl_3$) or the solvent carbon (^{13}C) were used as internal references. ^{1}H NMR data is presented as follows: chemical shifts in ppm 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; quin, quintet; sext, sextet; sept, septet; dd, doublet of doublets; m, multiplet. The error of coupling constants from ^{1}H NMR spectra is estimated to be 0.3 Hz. High-resolution mass spectra were recorded by the University of Alberta mass spectrometry services laboratory using either electron impact (EI) or electrospray ionization (ESI) techniques. Infrared (IR) spectra were obtained using cast-film technique with frequencies expressed in cm^{-1}. The resolution of the IR instrument is 4 wavenumbers. Melting points (m.p.) were measured on a melting point apparatus and are uncorrected.

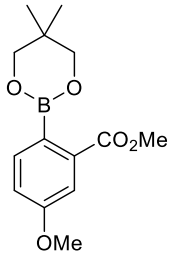
4.11.2 Synthesis and characterization of boronic acids



Step 1: To a flame-dried 15 mL round bottom flask charged with a stir bar was added 2-bromo benzoic acid (1.20 g, 6.00 mmol) and 6 mL $SOCl_2$. The mixture was brought up to reflux for 2 h under nitrogen. After the indicated time, the reaction was cool down to room temperature before the removal of excess $SOCl_2$ by vacuum. The resulting crude 2-bromo benzoyl chloride was dissolved in 5 mL of DCM and used without further purification. To another flame-dried 25 mL round bottom flask charged with triethylamine (1.02 g, 10.0 mmol) and DMAP (1.22 g, 10.0 mmol) in 15 mL DCM was added the alcohol (5.00 mmol) in one-pot. The reaction mixture was then cool down to 0 °C and allowed to stir for 10 min. To the alcohol solution was added 2-bromo benzoyl chloride solution carefully over a period of 15 min. The reaction was warmed up to room temperature and stirred overnight. The crude 2-bromo benzoate was obtained after the removal of DCM. The pure product was isolated by flash column chromatography.

Step 2: To a flame-dried 15 mL round bottom flask with a stir bar was added $Pd(dppf)C_{l2}$ (146 mg, 0.20 mmol), neopentyl diboron (542 mg, 2.40 mmol) and KOAc (491 mg, 5.00 mmol) in 12 mL freshly distilled dioxane under nitrogen. Upon stirring, a solution of the bromo benzoate in dioxane (4 mL) from step 1 was added dropwise. After the addition, the reaction mixture was allowed to heat up to 80 °C and monitored by TLC. The borylation generally went to completion within 1 to 4 h. Upon cooling down to room temperature, the crude mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed by water (1 × 20 mL) brine (1 × 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. The boronic ester product was isolated by flash column chromatography.

Step 3: In a 15 mL round bottom flask charged with a stir bar, a solution of the boronic ester from step 2 in a solvent mixture of water:acetone (v:v = 1:1, 0.1 M) was prepared. The reaction was allowed to stir at room temperature for 72 h before removal of acetone by vacuum. The aqueous layer was then extracted with EtOAc (3 × 10 mL). The combined organic layers was washed by water (6 × 10 mL) and brine (1 × 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. The pure boronic acid was obtained after recrystallization from hexane:DCM (v:v = 1:1) mixture.



4-93

Methyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5-methoxybenzoate (4-93): Prepared from methyl 2-bromo-5-methoxybenzoate (490 mg, 2.00 mmol) using the general procedure, step 2. Purified by flash column chromatography (8:1 to 3:1 hexane:EtOAc) and isolated as a yellow oil (351 mg, 63%).

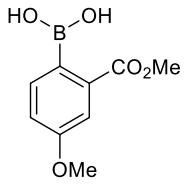
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45 (d, *J* = 8.2 Hz, 1H), 7.40 (d, *J* = 2.5 Hz, 1H), 7.04 (dd, *J* = 8.2, 2.6 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.78 (s, 4H), 1.10 (s, 6H);

^{13}C NMR ($CDCl_3$, 175 MHz): δ 171.7, 162.5, 137.7, 135.7, 120.7, 116.1, 75.3, 58.0, 55.1, 34.5, 24.7 (The boron-bound carbon was not detected due to quadrupolar relaxation of boron);

^{11}B NMR ($CDCl_3$, 160 MHz): δ 28.1;

IR (Microscope, cm^{-1}): 3000, 2959, 2888, 2837, 1722, 1605, 1477, 1317, 1288, 1133;

HRMS (EI) for $C_{14}H_{19}BO_5$: calcd. 278.1326; found 278.1320.



BAC-44

4-Methoxy-2-(methoxycarbonyl)phenylboronic acid (BAC-44): Prepared from neopentyl boronic ester **4-93** (350 mg, 1.25 mmol) using the general procedure, step 3. Purified by recrystallization (1:1 hexane:DCM) and isolated as a white solid (65 mg, 25%).

M.p. 95-96 °C;

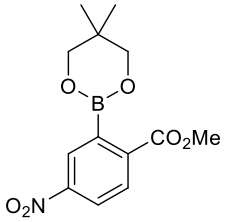
^{1}H NMR (CD_3COCD_3 + 1 drop D_2O, 500 MHz): δ 7.58 (d, *J* = 8.2 Hz, 1H), 7.43 (d, *J* = 2.6 Hz, 1H), 7.11 (dd, *J* = 8.2, 2.6 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H);

^{13}C NMR (CD_3COCD_3 + 1 drop D_2O, 125 MHz): δ 169.5, 160.8, 135.7, 135.5, 118.3, 115.2, 55.7, 52.5 (The boron-bound carbon was not detected due to quadrupolar relaxation of boron);

^{11}B NMR (CD_3COCD_3 + 1 drop D_2O, 160 MHz): δ 29.7;

IR (Microscope, cm^{-1}): 3363, 3172, 3013, 2956, 2850, 1688, 1600, 1562, 1438, 1385, 1291; 1053;

HRMS (ESI) for $C_9H_{11}BO_5$ $[M-H]^-$: calcd. 209.0627; found 209.0626.



4-94

Methyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-4-nitrobenzoate (4-94): Prepared from methyl 2-bromo-4-nitrobenzoate (520 mg, 2.00 mmol) using the general procedure, step 2. Purified by flash column chromatography (7:1 to 1:1 hexane:EtOAc) and isolated as a yellow solid (300 mg, 51%).

M.p. 75-76 °C;

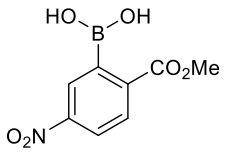
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.35 (d, *J* = 2.3 Hz, 1H), 8.22 (dd, *J* = 8.6, 2.3 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 3.97 (s, 3H), 3.81 (s, 4H), 1.13 (s, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.5, 149.6, 138.6, 129.7, 126.6, 123.6, 72.7, 53.0, 31.9, 22.1 (The boron-bound carbon was not detected due to quadrupolar relaxation of boron);

^{11}B NMR ($CDCl_3$, 128 MHz): δ 27.4;

IR (Microscope, cm^{-1}): 3083, 2960, 2895, 1728, 1610, 1528, 1480, 1302.57, 1254, 1140;

HRMS (EI) for $C_{13}H_{16}BNO_6$: calcd. 293.1071; found 293.1070.



BAC-49

2-(Methoxycarbonyl)-5-nitrophenylboronic acid (BAC-49): Prepared from neopentyl boronic ester **4-94** (147 mg, 0.50 mmol) using the general procedure, step 3. Purified by recrystallization (1:1 hexane:DCM) and isolated as a yellow solid (34 mg, 30%, decomposed upon heating).

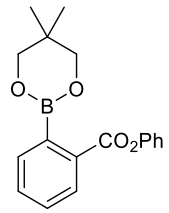
^{1}H NMR (CD_3COCD_3 + 1 drop D_2O, 500 MHz): δ 8.32 (d, *J* = 2.3 Hz, 1H), 8.25 (dd, *J* = 8.6, 2.4 Hz, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 3.91 (s, 3H);

^{13}C NMR (CD_3COCD_3 + 1 drop D_2O, 125 MHz): δ 167.6, 150.6, 139.2, 130.9, 127.2, 123.9, 53.0 (The boron-bound carbon was not detected due to quadrupolar relaxation of boron);

^{11}B NMR (CD_3COCD_3 + 1 drop D_2O, 160 MHz): δ 29.2;

IR (Microscope, cm^{-1}): 3448, 3082, 2958, 2868, 1713, 1610, 1529, 1480, 1349, 1312, 1141;

HRMS (ESI) for $C_8H_8BNO_6$: calcd. 225.0445; found 225.0444.



4-95

Phenyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (4-95): Prepared from 2-bromo benzoic acid (1.20 g, 6.00 mmol) and phenol (471 mg, 5.00 mmol) using the general procedure, step 1 and 2. Purified by flash column chromatography (5:1 hexane:EtOAc) and isolated as a yellow oil (510 mg, 82% for step 2).

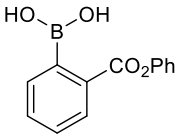
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.13 (d, *J* = 7.8 Hz, 1H), 7.64-7.56 (m, 2H), 7.51-7.39 (m, 3H), 7.32-7.19 (m, 3H), 3.76 (s, 4H), 1.06 (s, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.1, 151.1, 132.5, 132.5, 131.7, 129.5, 129.4, 128.7, 125.9, 121.8, 72.5, 31.8, 22.1 (The boron-bound carbon was not detected due to quadrupolar relaxation of boron);

^{11}B NMR ($CDCl_3$, 128 MHz): δ 28.1;

IR (Microscope, cm^{-1}): 3059, 2963, 2932, 2890, 1727, 1598, 1484, 1416, 1314, 1270, 1196, 1163;

HRMS (ESI) for $C_{18}H_{20}BO_4$ $[M+H]^+$: calcd. 311.1449; found 311.1450.



BAC-50

2-(Phenoxycarbonyl)phenylboronic acid (BAC-50): Prepared from neopentyl boronic ester **4-95** (500 mg, 1.61 mmol) using the general procedure, step 3. Purified by recrystallization (2:1 hexane:DCM) and isolated as a white solid (125 mg, 32%).

M.p. 127-129 °C;

^{1}H NMR (CD_3COCD_3 + 1 drop D_2O, 500 MHz): δ 8.07 (ddd, *J* = 7.8, 1.1, 0.7 Hz, 1H), 7.64-7.56 (m, 2H), 7.50 (ddd, *J* = 7.8, 6.8, 1.9 Hz, 1H), 7.47-7.42 (m, 2H), 7.33-7.20 (m, 3H);

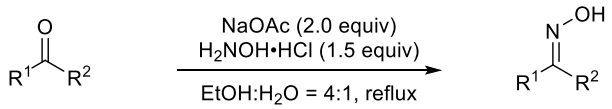
^{13}C NMR (CD_3COCD_3 + 1 drop D_2O, 125 MHz): δ 167.1, 152.2, 133.2, 132.9, 132.9, 130.2, 130.2, 129.0, 126.6, 122.7 (The boron-bound carbon was not detected due to quadrupolar relaxation of boron);

^{11}B NMR (CD_3COCD_3 + 1 drop D_2O, 160 MHz): δ 30.2;

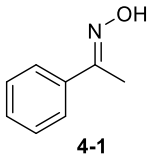
IR (Microscope, cm^{-1}): 3456, 3101, 3047, 3021, 1741, 1705, 1599, 1485, 1363, 1269, 1197;

HRMS (ESI) for $C_{13}H_{10}BO_4$ $[M-H]^-$: calcd. 241.0678; found 241.0676.

4.11.3 Synthesis and characterization of oximes



To a 100 mL round bottom flask charged with a stir bar, sodium acetate (1.64 g, 20.0 mmol,) and hydroxylamine hydrochloride (1.04 g, 15.0 mmol), was added a solution of the ketone (0.3 M) in ethanol/water (4:1). The reaction mixture was then heated to reflux until all the ketone starting material was consumed as indicated by TLC. After reflux, the reaction was allowed to cool to room temperature. The crude mixture was obtained after removal of excess ethanol. To the crude mixture was added 20 mL of water. The resulting aqueous solution was extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with water (2 × 20 mL) and brine (1 × 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. The oxime product was used directly in the next step. In certain cases, the oxime product was obtained after flash column chromatography or recrystallization using the indicated solvent mixture.

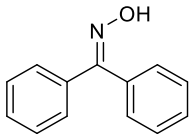


4-1

Acetophenone oxime (4-1)[20]: Prepared from acetophenone (1.20 g, 10.0 mmol) using general procedure. Isolated as a white solid (1.20 g, 88%) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.03 (br s, 1H), 7.67-7.65 (m, 2H), 7.49-7.30 (m, 3H), 2.34 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.1, 136.5, 129.3, 128.5, 126.1, 12.3.

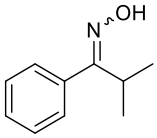


4-3

Benzophenone oxime (4-3)[20]: Prepared from benzophenone (911 mg, 5.00 mmol). Isolated as a white solid (953 mg, 97%) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.63 (s, 1H), 7.50-7.45 (m, 5H), 7.44-7.41 (m, 2H), 7.40-7.36 (m, 1H), 7.35-7.32 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.1, 136.2, 132.7, 129.5, 129.2, 129.1, 128.3, 128.2, 127.9.

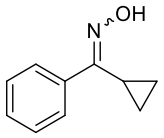


4-5

Isobutyrophenone oxime (4-5)[17]: Prepared from isobutyrophenone (0.75 mL, 5.00 mmol). Isolated as a white solid (752 mg, 92%, 1:1 mixture of *E*/*Z* isomers) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.99 (s, 1H), 8.64 (s, 1H), 7.44-7.40 (m, 2H), 7.39-7.33 (m, 6H), 7.29-7.27 (m, 1H), 3.61 (septet, *J* = 7.1 Hz, 1H), 2.84 (septet, *J* = 6.9 Hz, 1H), 1.22 (d, *J* = 7.1 Hz, 6H), 1.14 (d, *J* = 6.9 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.1, 163.5, 135.8, 133.7, 128.51, 128.46, 128.2, 128.1, 127.7, 127.6, 34.5, 27.7, 20.1, 19.4.

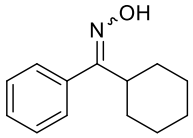


4-7

Cyclopropyl phenyl oxime (4-7)[20]: Prepared from cyclopropyl phenyl ketone (0.69 mL, 4.99 mmol). Isolated as an off-white solid (358 mg, 49%, 2.8:1 mixture of isomers) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.71 (br s, 1H), 7.45-7.34 (m, 5H), 2.33-2.27 (m, 1H, major), 1.80-1.74 (m, 0.5 H, minor), 0.97-0.93 (m, 2H), 0.84-0.79 (m, 1H, minor), 0.65 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.8, 134.2, 128.7, 128.3, 128.1, 9.0, 5.5.

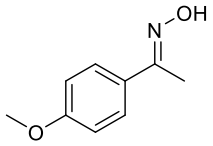


4-9

Cyclohexyl phenyl oxime (4-9)[20]: Prepared from cyclohexyl phenyl ketone (941 mg, 5.00 mmol). Isolated as a white solid (998 mg, 98%, 1.2:1 mixture of isomers) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.42 (br s, 1H), 8.23 (br s, 1H), 7.35-7.35 (m, 2H), 7.30-7.27 (m, 1H), 7.19-7.17 (m, 2H), 3.27-3.20 (m, 1H), 2.41-2.36 (m, 1H), 1.79-1.67 (m, 6H), 1.63-1.56 (m, 2H), 1.50 (br s, 1H), 1.44-1.36 (m, 1H), 1.32-1.05 (m, 7H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.7, 163.2, 136.1, 133.9, 128.4, 128.2, 128.04, 127.95, 127.5, 44.3, 38.1, 30.5, 29.3, 26.3, 26.2, 26.0 (two carbon signals missing); **^{13}C NMR** (125 MHz; CD_3OD): δ 165.3, 163.6, 137.8, 136.0, 129.3, 129.2, 128.99, 128.98, 128.94, 128.8, 45.5, 39.3, 31.9, 30.5, 27.5, 27.3, 27.22, 27.19.

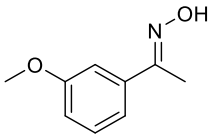


4-11

4'-Methoxyacetophenone oxime (4-11)[17]: Prepared from 4-methoxyacetophenone (750 mg, 4.99 mmol). Isolated as a white solid (722 mg, 88%) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.54 (s, 1H), 7.58 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 3.83 (s, 3H), 2.28 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.6, 155.7, 129.2, 127.5, 114.0, 55.5, 12.2.

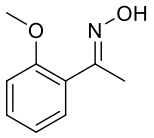


4-13

3'-Methoxyacetophenone oxime (4-13)[20]: Prepared from 3-methoxyacetophenone (0.70 mL, 5.10 mmol). Isolated as a pale yellow oil (805 mg, 96%) and used without further further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.83 (br s, 1H), 7.30 (app t, *J* = 8.0 Hz, 1H), 7.21-7.19 (m, 2H), 6.93 (dd, *J* = 8.0, 2.4 Hz, 1H), 3.84 (s, 3H), 2.29 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.7, 156.0, 137.9, 129.5, 118.6, 115.1, 111.4, 55.3, 12.3.



4-15

2'-Methoxyacetophenone oxime (4-15)[17]: Prepared from 2-methoxyacetophenone (0.69 mL, 5.00 mmol). Isolated as a white solid (711 mg, 86%, 7:1 mixture of *E*/*Z* isomers) and used without further purification.

Major isomer:

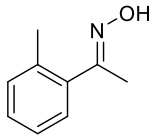
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.97 (s, 1H), 7.35-7.30 (m, 2H), 6.95 (td, *J* = 7.5, 1.0 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 3.84 (s, 3H), 2.24 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.4, 157.0, 130.1, 129.4, 126.8, 120.6, 111.1, 55.4, 15.2.

Apparent signals for Minor isomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.05 (s, 1H), 7.16 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.00 (td, *J* = 7.5, 1.0 Hz, 1H), 3.84 (s, 3H), 2.18 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.6, 154.8, 129.9, 128.4, 124.2, 120.5, 111.2, 55.6, 21.3.



4-17

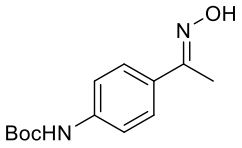
2'-Methylacetophenone oxime (4-17): Prepared from 2-methylacetophenone (0.44 mL, 5.02 mmol). Isolated as a pale yellow oil (431 mg, 58%, 2.4:1 mixture of *E*/*Z* isomers) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.88 (s, 1H), 8.24 (s, 1H), 7.30-7.20 (m, 5H), 7.10 (d, *J* = 7.4 Hz, 1H), 2.38 (s, 3H), 2.29 (s, 1H), 2.25 (s, 3H), 2.18 (s, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.1, 156.7, 137.4, 135.7, 135.5, 134.6, 130.6, 130.0, 128.53, 128.49, 128.1, 125.9, 125.80, 125.79, 21.9, 20.0, 19.4, 15.9;

IR (microscope, cm^{-1}): 3228, 3063, 2921, 1625;

HRMS (EI): for $C_9H_{11}ON$: calcd. 149.0841; found 149.0840.



4-19

***tert*-Butyl-4-acetylphenylcarbamate oxime (4-19)**: Prepared from *tert*-butyl (4-acetylphenyl) carbamate (1.18 g, 5.00 mmol). Isolated as an off-white solid (1.26 g, 99%) and used without further purification.

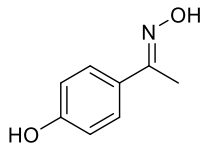
M.p. 144-147 °C;

^{1}H NMR (CD_3OD, 500 MHz): δ 7.56 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 6.60 (s, 1H), 2.26 (s, 3H), 1.53 (s, 9H);

^{13}C NMR (CD_3OD, 125 MHz): δ 155.8, 155.1, 141.4, 132.7, 127.5, 119.3, 81.0, 28.7, 12.0;

IR (Microscope, cm^{-1}): 3366, 3248, 3069, 2993, 2973, 1911, 1703, 1642, 1588;

HRMS (ESI): for $C_{13}H_{19}N_2O_3$: calcd. 251.1390; found 251.1386.

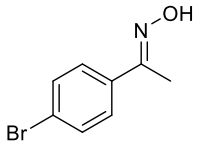


4-21

4'-Hydroxyacetophenone oxime (4-21)[32]: Prepared from 4-hydroxyacetophenone (683 mg, 5.02 mmol). Isolated as a pale brown solid (604 mg, 80%) and used without further purification.

^{1}H NMR (CD_3OD, 500 MHz): δ 7.47 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 2.18 (s, 3H);

^{13}C NMR (CD_3OD, 125 MHz): δ 159.5, 156.2, 129.8, 128.5, 116.1, 12.1.

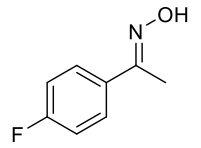


4-23

4′-Bromoacetophenone oxime (4-23)[20]: Prepared from 4-bromoacetophenone (1.00 g, 5.00 mmol). Isolated as a pale yellow solid (957 mg, 89%) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.44 (s, 1H), 7.53-7.49 (m, 4H), 2.27 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.2, 135.4, 131.7, 127.6, 123.6, 12.0.



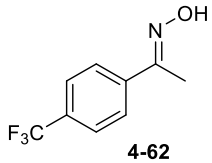
4-25

4′-Fluoroacetophenone oxime (4-25)[14]: Prepared from 4-fluoroacetophenone (0.60 mL, 4.90 mmol). Isolated as an off-white solid (738 mg, 98%) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.50 (s, 1H), 7.61 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.07 (t, *J* = 8.8 Hz, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.6 (d, *J* = 249.0 Hz), 155.3, 132.8 (d, *J* = 3.3 Hz), 128.0 (d, *J* = 8.2 Hz), 115.6 (d, *J* = 21.8 Hz), 12.3;

^{19}F NMR ($CDCl_3$, 469 MHz): δ –112.2 (m, 1F).



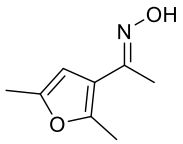
4-62

4'-(Trifluoromethyl)benzophenone oxime (4-62): Prepared from 4'-(trifluoromethyl) benzophenone (939 mg, 4.99 mmol). Isolated as an off-white solid (949 mg, 93%) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.34 (s, 1H), 7.75 (m, 2H), 7.64 (m, 2H), 2.31 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.2, 140.0, 131.2, 126.5, 125.6, 124.1, 12.2.

^{19}F NMR ($CDCl_3$, 376 MHz): δ –62.8 (s, 3F).



4-27

3-Acetyl-2,5-dimethylfuran oxime (4-27)[33]: Prepared from 3-acetyl-2,5-dimethylfuran (0.47 mL, 5.10 mmol). Isolated as a pale yellow solid (401 mg, 51%) and used without further purification.

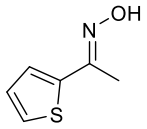
M.p. 67-68 °C;

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.31 (s, 1H), 6.03 (s, 1H), 2.40 (s, 3H), 2.24 (s, 3H), 2.15 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.0, 149.8, 148.5, 117.9, 105.5, 13.9, 13.5, 13.3;

IR (microscope, cm^{-1}): 3280, 2926, 1905, 1645, 1620, 1585;

HRMS (EI): for $C_8H_{11}O_2N$: calcd. 153.0790; found 153.0790.



4-29

2-Acetylthiophene oxime (4-29)[14]: Prepared from 2-acetylthiophene (0.54 mL, 5.00 mmol). Isolated as a white solid (672 mg, 95%, 2.2:1 mixture of *E*/*Z* isomers) and used without further purification. Isomers separated for characterization:

Major isomer: White solid.

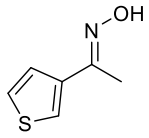
^{1}H NMR (CD_3OD, 500 MHz): δ 7.31 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.27 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.01 (dd, *J* = 5.1, 3.7 Hz, 1H), 2.23 (s, 3H);

^{13}C NMR (CD_3OD, 125 MHz): δ 151.8, 142.3, 127.9, 127.3, 126.9, 12.1.

Minor isomer: White solid.

^{1}H NMR (CD_3OD, 500 MHz): δ 7.61 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.53 (dd, *J* = 3.8, 0.8 Hz, 1H), 7.11 (dd, *J* = 5.1, 3.9 Hz, 1H), 2.30 (s, 3H);

^{13}C NMR (CD_3OD, 125 MHz): δ 147.5, 133.6, 131.5, 130.3, 126.4, 19.5.

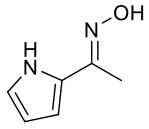


4-31

3-Acetylthiophene oxime (4-31)[34]: Prepared from 3-acetylthiophene (644 mg, 5.10 mmol). Isolated as an off-white solid (644 mg, 92%, 10:1 mixture of *E*/*Z* isomers) and used without further purification. Data for major isomer only shown:

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.50 (s, 1H), 7.48 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.42 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.31 (dd, *J* = 5.1, 2.9 Hz, 1H), 2.28 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.3, 138.6, 126.2, 125.0, 123.8, 12.4.



4-60

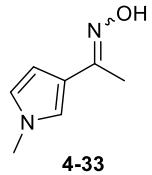
2-Acetylpyrrole oxime (4-60)[35]: Prepared from 2-acetylpyrrole (546 mg, 5.00 mmol). Isolated as a white solid (607 mg, 98%, 2:1 mixture of *E*/*Z* isomers) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.98 (s, 1H, major), 6.82 (s, 0.6H, minor), 6.58-6.57 (m, 1H, major), 6.49-6.47 (m, 0.6H, minor), 6.28-6.27 (m, 1H, major), 6.24-6.22 (m, 0.6H, minor), 2.22 (s, 4H, overlapping);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.1, 145.2, 128.1, 125.8, 121.3, 120.6, 113.8, 110.8, 109.4, 108.8, 18.3, 11.7;

IR (Microsoft, cm^{-1}): 3411, 3131, 2990, 2761, 1631, 1424, 1379;

HRMS (EI): for $C_6H_8ON_2$: calcd. 124.0637; found 124.0635.



4-33

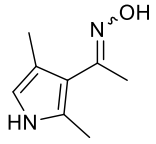
3-Acetyl-1-methylpyrrole oxime (4-33): Prepared from 3-acetyl-1-methylpyrrole (1.00 g, 8.12 mmol) using general procedure. Purified by flash column chromatography (1:1 hexane:EtOAc) and isolated as a light yellow solid (936 mg, 84%, 1:1 mixture of *E*/*Z* isomers).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.79 (br s, 2H), 7.63 (t, *J* = 1.9 Hz, 1H), 6.88 (t, *J* = 1.9 Hz, 1H), 6.61 (t, *J* = 2.5 Hz, 1H), 6.59 (t, *J* = 2.5 Hz, 1H), 6.51-6.49 (m, 1H), 6.43-6.41 (m, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.2, 148.5, 126.7, 122.9, 121.5, 121.2, 121.0, 116.1, 109.9, 106.3, 36.4, 36.4, 19.5, 12.4;

IR (Microscope, cm^{-1}): 3166, 3121, 3065, 2913, 2828, 1631, 1524, 1421, 1374, 1234, 1029;

HRMS (EI) for $C_7H_{10}N_2O$: calcd. 138.0793; found 138.0793.



4-35

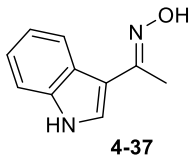
3-Acetyl-2,4-dimethylpyrrole oxime (4-35): Prepared from 3-acetyl-2,4-dimethylpyrrole (500 mg, 3.64 mmol) using general procedure. Purified by flash column chromatography (20:1 DCM:MeOH) and isolated as a light yellow solid (300 mg, 54%, 5:1 mixture of *E*/*Z* isomers).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.65 (br s, 1.2 H), 7.83 (br s, 0.2 H, minor), 7.73 (br s, 1H, major), 6.47 (s, 0.2 H, minor), 6.41 (s, 1H, major), 2.31 (s, 3H, major), 2.22 (s, 3H, major), 2.20 (s, 0.6H, minor), 2.16 (s, 0.6H, minor), 2.12 (s, 3H, major), 2.05 (s, 0.6H, minor);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 154.3 (major), 152.9 (minor), 126.8 (major), 125.9 (minor), 118.1 (major), 117.7 (minor), 117.2 (major), 114.6 (minor), 114.2 (major), 113.4 (minor), 21.8 (minor), 15.6 (major), 12.8 (major), 11.8 (major), 11.3 (minor);

IR (Microscope, cm^{-1}): 3353, 3215, 3061, 2966, 2923, 1651, 1584, 1486, 1427, 1265, 893;

HRMS (EI) for $C_8H_{12}N_2O$: calcd. 152.0950; found 152.0952.

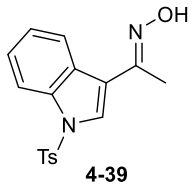


4-37

3-Acetylindole oxime (4-37): Prepared from 3-acetylindole (1.59 g, 10.0 mmol) using general procedure. Purified by flash column chromatography (2:1 hexane:EtOAc) and isolated as a light yellow solid (1.01 g, 58%).

^{1}H NMR (CD_3COCD_3, 500 MHz): δ 10.37 (s, 1H), 9.67 (s, 1H), 8.31-8.18 (m, 1H), 7.62 (d, *J* = 2.7 Hz, 1H), 7.40 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 7.13 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.05 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 2.25 (s, 3H);

^{13}C NMR (CD_3COCD_3, 125 MHz): δ 152.5, 138.3, 126.5, 125.9, 124.1, 123.1, 120.8, 115.2, 112.1, 12.2.



4-39

3-Acetyl-N-tosylindole (4-39): Prepared from 3-acetyl-N-tosylindole (313 mg, 1.00 mmol) using general procedure. Isolated as off white solid (200 mg, 61%) and used without further purification.

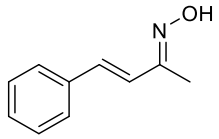
M.p. 146-148 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.21 (d, *J* = 7.9 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 7.81-7.79 (m, 2H), 7.78 (s, 1H), 7.36 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H), 7.29 (ddd, *J* = 8.4, 7.7, 1.1 Hz, 1H), 7.26-7.23 (m, 3H), 2.37 (s, 3H), 2.32 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.2, 145.3, 135.5, 135.0, 130.0, 127.6, 126.9, 126.1, 125.3, 124.0, 123.8, 119.8, 113.3, 21.6, 12.2;

IR (Microscope, cm^{-1}): 3515, 3314, 3140, 3100, 2922, 1597, 1446, 1371, 1171;

HRMS (EI) for $C_{17}H_{16}N_2O_3S$: calcd. 328.0882; found 328.0878.

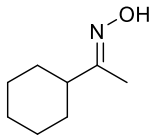


4-41

Benzylideneacetone oxime (4-41): Prepared from benzylideneacetone (1.46 g, 10.0 mmol) using general procedure. Purified by flash column chromatography (2:1 hexane:EtOAc) and isolated as a light yellow solid (672 mg, 42%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.57 (br s, 1H), 7.53-7.48 (m, 2H), 7.40-7.37 (m, 2H), 7.34-7.29 (m, 1H), 6.95 (d, *J* = 16.5 Hz, 1H), 6.90 (d, *J* = 16.4 Hz, 1H), 2.20 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.8, 136.3, 133.4, 128.8, 128.5, 126.9, 125.8, 9.8.

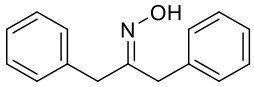


4-43

Cyclohexylethanone oxime (4-43)[36]: Prepared from cyclohexylmethyl ketone (0.70 mL, 5.10 mmol). Isolated as a white solid (649 mg, 90%, 4:1 mixture of *E*/*Z* isomers) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.84 (br s, 1H, major), 3.16 (tt, *J* = 12.0, 3.3 Hz, 0.25H, minor), 2.16-2.11 (m, 1H, major), 1.85 (s, 3H), 1.81-1.77 (m, 4H), 1.72-1.67 (m, 2H), 1.37-1.15 (m, 5H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.5, 162.1, 44.6, 36.2, 30.0, 28.9, 26.11, 26.09, 26.05, 25.95, 16.5, 11.9.

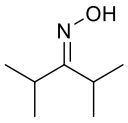


4-45

1,3-Diphenyl-2-propanone oxime (4-45)[20]: Prepared from 1,3-diphenyl-2-propanone (1.05 g, 5.00 mmol). Isolated as a white solid (1.09 g, 96%) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.20 (s, 1H), 7.34-7.30 (m, 4H), 7.28-7.24 (m, 2H), 7.22-7.19 (m, 4H), 3.69 (s, 2H), 3.47 (s, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.1, 136.6, 136.4, 129.25, 129.19, 128.58, 128.57, 126.8, 126.5, 39.6, 32.5.

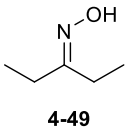


4-47

2,4-Dimethyl-3-pentanone oxime (4-47)[17]: Prepared from 2,4-dimethyl-3-pentanone (0.70 mL, 4.90 mmol). Isolated as a colourless solid (552 mg, 87%) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.76 (s, 1H), 3.19 (septet, J = 7.1 Hz, 1H), 2.55 (septet, J = 6.9 Hz, 1H), 1.16 (d, J = 7.1 Hz, 6H), 1.12 (d, J = 6.9 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.8, 30.7, 27.5, 21.3, 18.8.

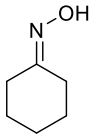


4-49

3-Pentanone oxime (4-49)[35]: Prepared from 3-pentanone (861 mg, 10.0 mmol) using general procedure. Isolated as a colorless oil (950 mg, 94%) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.79 (br s, 1H), 2.40 (q, J = 7.7 Hz, 2H), 2.25 (q, J = 7.4 Hz, 2H), 1.11 (t, J = 7.6 Hz, 3H), 1.11 (t, J = 7.6 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.6, 27.0, 20.9, 10.6, 10.1.

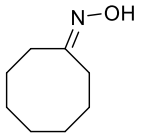


4-51

Cyclohexanone oxime (4-51)[20]: Prepared from cyclohexanone (982 mg, 10.0 mmol) using general procedure. Isolated as a white solid (950 mg, 94%) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67 (br s, 1H), 2.61-2.38 (m, 2H), 2.29-2.11 (m, 2H), 1.90-1.29 (m, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.8, 32.2, 26.9, 25.8, 25.6, 24.4.

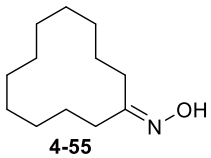


4-53

Cyclooctanone oxime (4-53)[17]: Prepared from cyclooctanone (676 mg, 5.36 mmol). Isolated as a white solid (682 mg, 90%) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.61 (br s, 1H), 2.47-2.44 (m, 2H), 2.29 (app t, *J* = 6.2 Hz, 2H), 1.80-1.72 (m, 4H), 1.55-1.45 (m, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.2, 33.2, 27.2, 26.76, 26.57, 25.4, 24.63, 24.46.

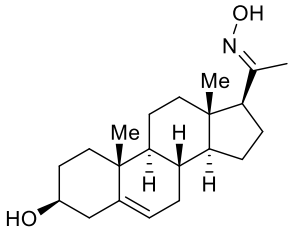


4-55

Cyclododecanone oxime (4-55)[20]: Prepared from cyclododecanone (912 mg, 5.00 mmol). Isolated as a white solid (977 mg, 99%) and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.21 (s, 1H), 2.42 (t, *J* = 6.7 Hz, 2H), 2.26 (t, *J* = 6.6 Hz, 2H), 1.67-1.56 (m, 4H), 1.40-1.33 (m, 13H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.8, 30.3, 26.2, 25.5, 25.1, 24.8, 24.0, 23.5, 23.3, 23.21, 23.15, 22.7.



4-57

Pregnenolone oxime (4-57): Prepared from pregnenolone (948 mg, 3.00 mmol) following the procedure reported by Lambert and co-workers.[1] Purified by recrystallization from methanol and isolated as a white solid (620 mg, 62%).

M.p. 186-188 °C;

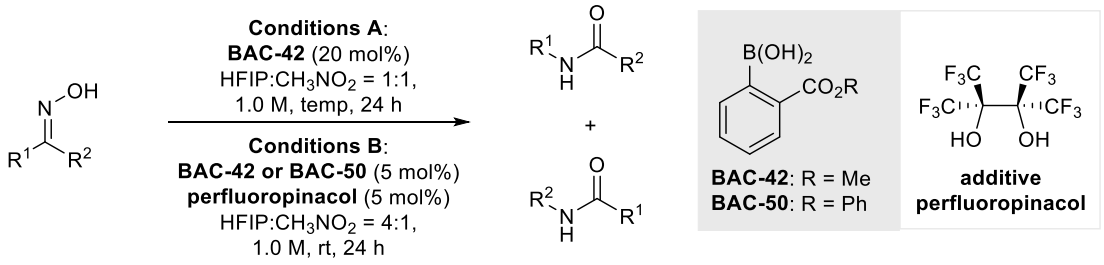
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.62 (br s, 1H), 5.46-5.25 (m, 1H), 3.55 (dddd, *J* = 11.1, 11.1, 4.6, 4.6 Hz, 1H), 2.35-2.00 (m, 6H), 1.96-1.84 (m, 3H), 1.90 (s, 3H), 1.73-1.71 (m, 2H), 1.63-1.44 (m, 7H), 1.35-1.08 (m, 5H), 1.03 (s, 3H), 1.02-0.98 (m, 1H), 0.67 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.0, 140.8, 121.5, 71.8, 56.8, 56.2, 50.2, 43.8, 42.3, 38.7, 37.3, 36.6, 32.1, 31.8, 31.7, 24.2, 23.1, 21.1, 19.4, 15.1, 13.1;

IR (Microscope, cm^{-1}): 3454, 3256, 3030, 2959, 2938, 2913, 2889, 2870, 2852, 1665, 1461, 1435, 1373, 1246;

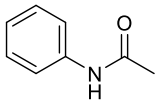
HRMS (EI) for $C_{21}H_{33}NO_2$: calcd. 331.2511; found 331.2513.

4.11.4 General procedure for boronic acid catalyzed direct Beckmann rearrangement



Conditions A: To a 5 mL reaction vial charged with a stir bar, was added the oxime substrate (0.50 mmol) and boronic acid **BAC-42** (18 mg, 0.10 mmol) and perfluoropinacol if needed. A solvent mixture of hexafluoroisopropanol and nitromethane (v:v = 1:1, 0.5 mL) was injected. The reaction vial was then capped, sealed and subjected at the indicated temperature for 24 hours. The crude product was obtained after removal of solvent. The pure amide product was isolated after flash column chromatography using the indicated solvent mixtures.

Conditions B: To a 5 mL reaction vial charged with a stir bar, was added the oxime substrate (0.50 mmol), boronic acid **BAC-42** or **BAC-50** (0.025 mmol) and perfluoropinacol (8 mg, 0.025 mmol). A solvent mixture of hexafluoroisopropanol and nitromethane (v:v = 4:1, 0.5 mL) was injected. The reaction vial was then capped, sealed and subjected at the room temperature for 24 hours. The crude product was obtained after removal of solvent. The pure amide product was isolated after flash column chromatography using the indicated solvent mixtures.

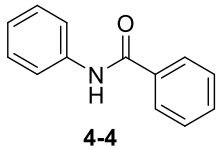


4-2

***N*-Phenylacetamide (4-2)**[20]: Prepared from acetophenone oxime **4-1** (68 mg, 0.50 mmol) and **BAC-42** using the general procedure. Purified by flash column chromatography (1:1 hexane:EtOAc) and isolated as a white solid (56.7 mg, 84% with conditions A; 62.8 mg, 93% with conditions B).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.52 (d, *J* = 7.9 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.12 (t, *J* = 7.3 Hz, 1H), 2.19 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.3, 137.9, 129.0, 124.3, 119.9, 24.6.

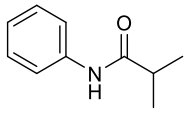


4-4

***N*-Phenylbenzamide (4-4)**[20]: Prepared from benzophenone oxime **4-3** (98 mg, 0.50 mmol) and **BAC-42** using the general procedure. Purified by flash chromatography (1:1 hexane/EtOAc) and isolated as a white solid (85 mg, 87% with conditions A; 92 mg, 94% with conditions B).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (d, *J* = 7.2 Hz, 2H), 7.85 (br s, 1H), 7.65 (d, *J* = 7.8 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.9, 138.1, 135.2, 132.0, 129.2, 128.9, 127.1, 124.7, 120.3.



4-6

***N*-Phenylisobutyramide (4-6)**[17]: Prepared from isobutyrophenone oxime **4-5** (82 mg, 0.50 mmol) and **BAC-42** using the general procedure. Purified by flash chromatography (5:1 hexane/EtOAc) and isolated as an off-white solid (75 mg, 92% with conditions A; 73 mg, 90% with conditions B).

Major compound:

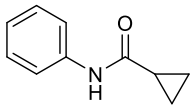
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 (d, *J* = 7.8 Hz, 2H), 7.34-7.30 (m, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 2.52 (septet, *J* = 6.9 Hz, 1H), 1.27 (d, *J* = 7.0 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.2, 138.1, 129.0, 124.1, 119.8, 36.7, 19.6.

Apparent signals for the minor compound:

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.76-7.74 (m, 2H), 7.49-7.47 (m, 1H), 7.44-7.40 (m, 2H), 4.29 (app sextet, *J* = 6.6 Hz, 1H), 1.27 (s, 3H, overlapping);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.7, 135.0, 131.3, 128.5, 126.8, 41.9, 22.9.

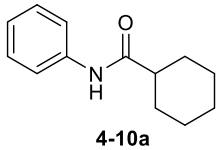


4-8

***N*-Phenylcyclopropanecarboxamide (4-8)**[20]: Prepared from cyclopropyl phenyl oxime **4-7** (82 mg, 0.51 mmol) and **BAC-42** using the general procedure. Purified by flash chromatography (5:1 hexane/EtOAc) and isolated as a white solid (65 mg, 80% with conditions A; 74 mg, 90% with conditions B).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.51-7.50 (m, 2H), 7.45 (s, 1H), 7.30 (app t, *J* = 7.7 Hz, 2H), 7.10-7.07 (m, 1H), 1.55-1.46 (m, 1H), 1.12-1.06 (m, 2H), 0.87-0.81 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.8, 138.1, 129.0, 124.0, 119.7, 15.8, 7.9.

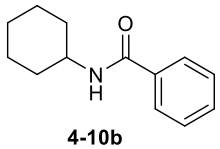


4-10a

***N*-Cyclohexyl-benzamide (4-10a, major)**[20]: Prepared from cyclohexyl phenyl oxime **4-9** (102 mg, 0.50 mmol) and **BAC-42** using the general procedure. Purified by flash column chromatography (5:1 to 1:1 hexane:EtOAc) and isolated as a white solid (99 mg, 97%, 3:1 mixture of isomers with conditions A; 96 mg, 94%, 3:1 mixture of isomers with conditions B).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55 (d, *J* = 7.8 Hz, 2H), 7.35-7.29 (m, 2H), 7.27 (br s, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 2.25 (tt, *J* = 11.7, 3.5 Hz, 1H), 1.98 (d, *J* = 15.0 Hz, 2H), 1.85 (d, *J* = 12.5 Hz, 2H), 1.73-1.72 (m, 1H), 1.61-1.53 (m, 2H), 1.38-1.22 (m, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.4, 138.1, 129.0, 124.1, 119.8, 46.6, 29.7, 25.7.

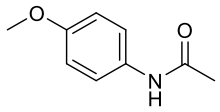


4-10b

***N*-Phenyl-cyclohexanecarboxamide (4-10b, minor)**[20]:

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77 (d, *J* = 7.2 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 5.97 (br s, 1H), 4.01 (dtt, *J* = 14.6, 8.0, 3.9 Hz, 1H), 2.06 (dd, *J* = 12.5, 3.4 Hz, 2H), 1.78 (dt, *J* = 13.4, 3.7 Hz, 2H), 1.68 (dt, *J* = 12.9, 3.8 Hz, 1H), 1.51-1.40 (m, 2H), 1.31-1.18 (m, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.6, 135.2, 131.2, 128.5, 126.8, 48.7, 33.3, 25.6, 24.9.

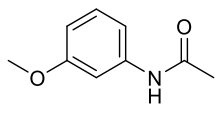


4-12

***N*-(4-Methoxyphenyl)acetamide (4-12)**[17]: Prepared from 4'-methoxyacetphenone oxime **4-11** (84 mg, 0.51 mmol) and **BAC-42** using the general procedure. Purified by flash chromatography (1:1 hexane/EtOAc) and isolated as an off-white solid (81 mg, 96% with conditions A; 81 mg, 96% with conditions B).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.38 (m, 2H), 6.87-6.84 (m, 2H), 3.79 (s, 3H), 2.15 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.2, 156.5, 131.0, 121.9, 114.1, 55.5, 24.3.

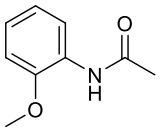


4-14

***N*-(3-Methoxyphenyl)acetamide (4-14)**[20]: Prepared from 3'-methoxyacetophenone oxime **4-13** (85 mg, 0.52 mmol) and **BAC-42** using the general procedure. Purified by flash chromatography (1:1 hexane/EtOAc) and isolated as a pale brown solid (72 mg, 84% with conditions A; 73 mg, 86% with conditions B).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35 (br s, 1H), 7.27 (s, 1H), 7.20 (app t, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 3.79 (s, 3H), 2.16 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.4, 160.1, 139.1, 129.6, 111.9, 110.1, 105.7, 55.3, 24.7.



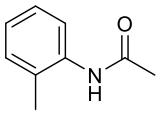
4-16

***N*-(2-Methoxyphenyl)acetamide (4-16)**[17]: Prepared from 2'-methoxyacetphenone oxime **4-15** (84 mg, 0.51 mmol) and **BAC-42** (5 mg, 0.025 mmol) using the general procedure. Purified by flash chromatography (1:1 hexane/EtOAc) and isolated as a white solid (59 mg, 72% with conditions B).

Prepared from 2'-methoxyacetphenone oxime **4-15** (84.2 mg, 0.51 mmol) and **BAC-50** (5.4 mg, 0.022 mmol) using the general procedure. Purified by flash chromatography (1:1 hexane/EtOAc) and isolated as a white solid (76.8 mg, 92%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.35 (d, *J* = 7.8 Hz, 1H), 7.75 (br s, 1H), 7.03 (app t, *J* = 7.7 Hz, 1H), 6.96 (app t, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 3.88 (s, 3H), 2.20 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.1, 147.6, 127.7, 123.6, 121.1, 119.8, 109.9, 55.6, 24.9.

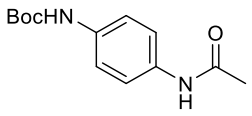


4-18

***N*-(*o*-Tolyl)acetamide (4-18)**[37]: Prepared from 2'-methylacetophenone oxime **4-17** (74 mg, 0.50 mmol) and **BAC-42** using the general procedure. Purified by flash chromatography (1:1 hexane/EtOAc) and isolated as a white solid (53 mg, 71% with conditions A; 52 mg, 70% with conditions B).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.75 (d, *J* = 7.9 Hz, 1H), 7.22-7.18 (m, 2H), 7.08 (app t, *J* = 7.3 Hz, 1H), 6.99 (br s, 1H), 2.26 (s, 3H), 2.20 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.3, 135.65, 135.64, 130.5, 129.3, 126.8, 125.3, 123.4, 24.3, 17.8.



4-20

***tert*-Butyl (4-acetamidophenyl)carbamate (4-20)**: Prepared from *tert*-butyl-4-acetylphenyl carbamate oxime **4-19** (126 mg, 0.50 mmol) and **BAC-42** using the general procedure. Purified by flash chromatography (1:1 hexane/EtOAc) and isolated as a white solid (88 mg, 70% with conditions A; 112 mg, 88% with conditions B).

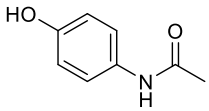
M.p. 160-163 °C;

^{1}H NMR (CD_3OD, 500 MHz): δ 7.42 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 2.09 (s, 3H), 1.51 (s, 9H);

^{13}C NMR (CD_3OD, 125 MHz): δ 171.4, 155.4, 136.8, 134.8, 121.8, 120.2, 80.8, 28.7, 23.6;

IR (Microscope, cm^{-1}): 3331, 2982, 2970, 1865, 1693, 1660;

HRMS (ESI) for $C_{13}H_{18}N_2NaO_3$: calcd. 273.1210; found 273.1214.

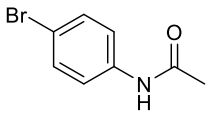


4-22

***N*-(4-Hydroxyphenyl)acetamide (4-22)**[38]: Prepared from 4'-hydroxyacetophenone oxime **4-21** (76 mg, 0.50 mmol) and **BAC-42** using the general procedure. Purified by flash chromatography (EtOAc) and isolated as a red-orange solid (75 mg, 99% with conditions A; 71 mg, 93% with conditions B).

^{1}H NMR (CD_3OD, 500 MHz): δ 7.30 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 4.86 (s, 1H), 2.08 (s, 3H);

^{13}C NMR (CD_3OD, 125 MHz): δ 171.3, 155.4, 131.7, 123.3, 116.2, 23.5.

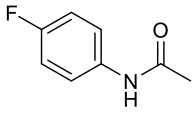


4-24

***N*-(4-Bromophenyl)acetamide (4-24)**[20]: Prepared from 4'-bromoacetophenone oxime **4-23** (108 mg, 0.50 mmol) and **BAC-50** (6 mg, 0.026 mmol) using the general procedure. Purified by flash chromatography (1:1 hexane/EtOAc) and isolated as an off-white solid (92 mg, 85% with conditions B)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43-7.39 (m, 4H), 2.17 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.3, 136.9, 132.0, 121.4, 116.9, 24.6.



4-26

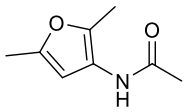
***N*-(4-Fluorophenyl)acetamide (4-26)**[17]: Prepared from 4'-fluoroacetophenone oxime **4-25** (75 mg, 0.49 mmol) and **BAC-42** using the general procedure. Purified by flash chromatography (1:1 hexane/EtOAc) and isolated as a pale brown solid (45 mg, with conditions A; 61 mg, 81% with conditions B).

Prepared from **4-25** (78 mg, 0.51 mmol) and **BAC-50** (6 mg, 0.026 mmol) using the general procedure. Purified by flash chromatography (1:1 hexane/EtOAc) and isolated as a pale brown solid (72 mg, 92%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46-7.43 (m, 2H), 7.31 (br s, 1H), 7.00 (app t, *J* = 8.6 Hz, 2H), 2.16 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.5, 159.6 (d, *J* = 243.5 Hz), 134.0 (d, *J* = 2.8 Hz), 121.9 (d, *J* = 7.9 Hz), 115.7 (d, *J* = 22.5 Hz), 24.5;

^{19}F NMR ($CDCl_3$, 469 MHz): δ –118.0 (m, 1F).

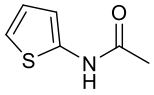


4-28

***N*-(2,5-Dimethylfuran-3-yl)acetamide (4-28)**[39]: Prepared from 3-acetyl-2,5-dimethylfuran oxime **4-27** (77 mg, 0.50 mmol) and **BAC-42** (18 mg, 0.10 mmol) using a modified general procedure at 50 ºC in 1:1 $MeNO_2$:HFIP. Purified by flash chromatography (1:1 hexane/EtOAc) and isolated as a white solid (77 mg, 99%, 2.5:1 mixture of isomers with conditions A).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.64 (br s, 1H), 6.42 (br s, 0.4H) (minor) 6.11 (s, 1H), 5.82 (s, 0.4H) (minor) 2.20 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.6, 149.1, 141.1, 118.7, 104.8, 23.5, 13.6, 11.3.

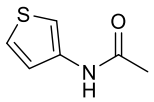


4-30

***N*-(Thiophen-2-yl)acetamide (4-30)**[40]: Prepared from 2-acetylthiophene oxime **4-29** (75 mg, 0.53 mmol) and **BAC-50** (6 mg, 0.026 mmol) using the general procedure. Purified by flash chromatography (1:1 hexane/EtOAc) and isolated as a pale brown solid (56 mg, 74% with conditions B).

^{1}H NMR (CD_3OD, 500 MHz): δ 6.84 (s, 1H), 6.80 (s, 1H), 6.65 (s, 1H), 2.10 (s, 3H);

^{13}C NMR (CD_3OD, 125 MHz): δ 169.3, 140.8, 124.8, 118.3, 112.7, 22.5.



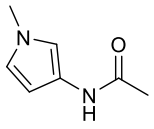
4-32

***N*-(Thiophen-3-yl)acetamide (4-32)**[41]: Prepared from 3-acetyl-1-methylpyrrole oxime **4-31** (72 mg, 0.51 mmol) and **BAC-42** using the general procedure. Purified by flash chromatography

(1:1 hexane/EtOAc) and isolated as a pale brown solid (60 mg, 86% with conditions A; 67 mg, 94% with conditions B).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.57 (br s, 1H), 7.54-7.54 (m, 1H), 7.22-7.21 (m, 1H), 6.98 (d, *J* = 4.9 Hz, 1H), 2.16 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.5, 135.5, 124.5, 120.9, 110.3, 23.9.



4-34

***N*-(1-Methyl-1H-pyrrol-3-yl)acetamide (4-34)**[42]: Prepared from 3-acetyl-1-methylpyrrole oxime **4-33** (69 mg, 0.50 mmol) and **BAC-42** using a modified general procedure at 50 °C. Purified by flash column chromatography (1:1 to 1:2 hexane:EtOAc) and isolated as an off white solid (68 mg, 99% with conditions A; 60 mg, 87% with conditions B).

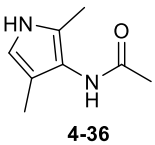
M.p. 83-85 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.16 (br s, 1H), 7.16-6.98 (m, 1H), 6.44 (t, *J* = 2.6 Hz, 1H), 5.92 (dd, *J* = 2.7, 1.8 Hz, 1H), 3.62 (s, 3H), 2.12 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.0, 122.4, 119.6, 113.1, 100.4, 36.5, 23.6;

IR (Microscope, cm^{-1}): 3260, 3128, 2990, 2943, 2881, 2818, 1714, 1637, 1563, 1499, 1340, 1293, 1165;

HRMS (EI) for $C_7H_{10}N_2O$: calcd. 138.0793; found 138.0793.



4-36

***N*-(2,4-Dimethyl-1H-pyrrol-3-yl)acetamide (4-36)**: Prepared from 3-acetyl-2,4-dimethylpyrrole oxime **4-35** (76 mg, 0.50 mmol) and **BAC-42** (18, 0.10 mmol) using a modified general

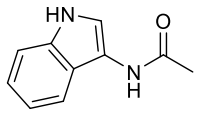
procedure in HFIP:CH_3NO_2 (v:v = 1:1) at 50 °C. Purified by flash column chromatography (20:1 DCM:MeOH) and isolated as a light brown solid (33 mg, 43% with conditions A).

^{1}H NMR (CD_3OD, 500 MHz): δ 9.62 (br s, 1H), 6.26 (s, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.87 (s, 3H);

^{13}C NMR (CD_3OD, 125 MHz): δ 173.2, 123.4, 117.3, 115.8, 113.3, 22.4, 10.7, 9.8;

IR (Microscope, cm^{-1}): 3251, 3090, 2972, 2934, 2861, 1622, 1546, 1475, 1416, 730;

HRMS (ESI) for $C_8H_{13}N_2O$ $[M+H]^+$: calcd. 153.1022; found 153.1023.

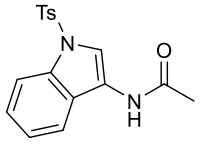


4-38

***N*-(1*H*-Indol-3-yl)acetamide (4-38)**[43]: Prepared from 3-acetylindole oxime **4-37** (88 mg, 0.50 mmol) and **BAC-42** using the general procedure. Purified by flash column chromatography (1:1 hexane:EtOAc) and isolated as a light yellow solid (82 mg, 93% with conditions A; 70 mg, 80% with conditions B).

^{1}H NMR (DMSO-*d6*, 500 MHz): δ 10.70 (br s, 1H), 9.76 (br s, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 2.4 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.06 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 6.96 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 2.06 (s, 3H);

^{13}C NMR (DMSO-*d6*, 125 MHz): δ 166.8, 133.4, 121.3, 120.3, 117.9, 117.8, 115.2, 115.0, 111.2, 22.9.



4-40

***N*-(1-Tosyl-1*H*-indol-3-yl)acetamide (4-40)**: Prepared from 3-acetyl-N-tosylindole oxime **4-39** (164 mg, 0.50 mmol), **BAC-42** using a modified general procedure at 50 °C. Purified by flash

column chromatography (1:1 hexane:EtOAc) and isolated as a light yellow solid (148 mg, 90% with conditions A; 163 mg, 99% with conditions B).

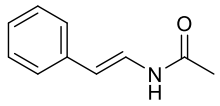
M.p. 192-194 °C;

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.22 (s, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.81-7.74 (m, 2H), 7.42-7.34 (m, 2H), 7.27-7.24 (m, 1H), 7.21-7.19 (m, *J* = 8.0 Hz, 2H), 2.33 (s, 3H), 2.26 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.5, 144.8, 135.0, 133.2, 129.8, 126.9, 125.4, 124.2, 123.1, 120.0, 116.6, 115.6, 114.3, 23.8, 21.6;

IR (Microscope, cm-1): 3302, 3210, 3086, 1915, 1799, 1653, 1553, 1449, 1367, 1168;

HRMS (ESI) for $C_{17}H_{17}N_2O_3S$ $[M+H]^+$: calcd. 329.0954; found 329.0961.



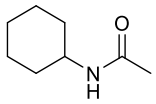
4-42

(E)-*N*-Styrylacetamide (4-42)[44]: Prepared from benzylideneacetone oxime **4-41** (81 mg, 0.50 mmol) and **BAC-42** using the general procedure. Purified by flash chromatography (1:1 hexane/EtOAc) and isolated as a pale brown solid (39 mg, 48% with conditions A; 40 mg, 49% with conditions B).

Prepared from **4-41** (84.0 mg, 0.52 mmol) and **BAC-50** (5.7 mg, 0.024 mmol) using the general procedure. Purified by flash chromatography (1:1 hexane/EtOAc) and isolated as a pale brown solid (62.0 mg, 74%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.56-7.50 (m, 1H), 7.39 (br s, 1H), 7.34-7.28 (m, 4H), 7.21-7.18 (m, 1H), 6.10 (d, *J* = 14.6 Hz, 1H), 2.13 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.4, 136.0, 128.7, 126.7, 125.6, 122.7, 112.5, 23.4.

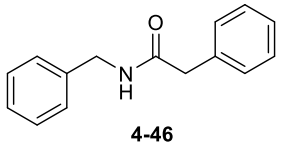


4-44

***N*-Cyclohexylacetamide (4-44)**[45]: Prepared from cyclohexylethanone oxime **4-43** (73 mg, 0.52 mmol) and **BAC-42** using the general procedure. Purified by flash chromatography (1:1 hexane/EtOAc) and isolated as a white solid (60 mg, 83% with conditions A; 61 mg, 85% with conditions B).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.35 (br s, 1H), 3.78-3.71 (m, 1H), 1.94 (s, 3H), 1.92-1.89 (m, 2H), 1.72-1.67 (m, 2H), 1.63-1.59 (m, 1H), 1.39-1.31 (m, 2H), 1.18-1.06 (m, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.0, 48.2, 33.2, 25.5, 24.9, 23.6.

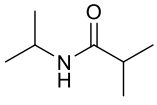


4-46

***N*-Benzyl-2-phenylacetamide (4-46)**[20]: Prepared from oxime **4-45** (110 mg, 0.49 mmol) and **BAC-50** (6 mg, 0.025 mmol) using the general procedure. Purified by flash chromatography (2:1 hexane/EtOAc) and isolated as an off-white solid (108 mg, 98% with conditions B).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37-7.33 (m, 2H), 7.31-7.23 (m, 6H), 7.37-7.17 (m, 11H), 7.19-7.17 (m, 2H), 5.69 (s, 1H), 4.42 (d, J = 5.8 Hz, 2H), 3.64 (s, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.8, 138.1, 134.8, 129.5, 129.1, 128.7, 127.5, 127.44, 127.42, 43.9, 43.6.



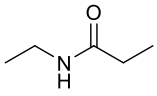
4-48

***N*-Isopropylisobutyramide (4-48)**[17]: Prepared from 2,4-dimethyl-3-pentanone oxime **4-47** (68 mg, 0.52 mmol) and **BAC-42** using the general procedure. Purified by flash chromatography

(1:1 hexane/EtOAc) and isolated as a white solid (55 mg, 81% with conditions A: 57 mg, 84% with conditions B).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.23 (br s, 1H), 4.06 (app sextet, *J* = 6.8 Hz, 1H), 2.27 (septet, *J* = 6.9 Hz, 1H), 1.13 (app d, *J* = 6.3 Hz, 9H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.0, 41.0, 35.7, 22.8, 19.6.

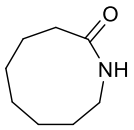


4-50

***N*-Ethylpropionamide (4-50)**[46]: Prepared from 3-pentanone oxime **4-49** (51 mg, 0.50 mmol) **BAC-42** (9 mg, 0.05 mmol) and perfluoropinacol (17 mg, 0.05 mmol) using a modified general procedure at 50 °C. Purified by flash column chromatography (1:1 hexane:EtOAc to 20:1 DCM:MeOH) and isolated as a light yellow oil (37 mg, 74% with conditions B).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.24 (qd, *J* = 7.3, 5.7 Hz, 2H), 2.16 (q, *J* = 7.6 Hz, 2H), 1.10 (t, *J* = 7.5 Hz, 3H), 1.10 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.8, 34.3, 29.7, 14.8, 9.9.

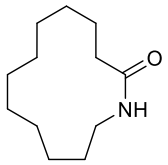


4-54

Azonan-2-one (4-54)[17,47]: Prepared from cyclooctanone oxime **4-53** (71 mg, 0.50 mmol) and **BAC-42** (5 mg, 0.026 mmol) using a modified general procedure at 50 ºC. Purified by flash chromatography (1:1 hexane/EtOAc to 20:1 CH_2Cl_2/MeOH) and isolated as a white solid in forms of cis/trans amide rotamers (68 mg, 96%, 2:1 mixture of isomers with conditions B).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.86 (br s, 1H), 5.32 (br s, 0.5H, minor), 3.36-3.33 (m, 2H), 2.42 (app t, J = 6.4, 2H), 2.16 (br s, 0.5H, minor), 1.85-1.80 (m, 2H), 1.73 (br s, 0.5H, minor), 1.63-1.59 (m, 5H), 1.55-1.51 (m, 2H), 1.47 (br s, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.8, 176.5, 43.3, 40.4, 38.7, 33.1, 30.1, 29.35, 29.22, 27.8, 25.9, 25.50, 25.44, 24.5, 23.7, 23.0.

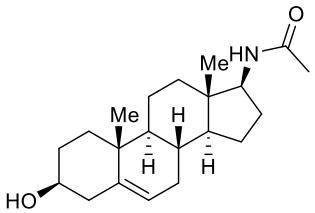


4-56

Azacyclotridecan-2-one (4-56)[20]: Prepared from cyclododecanone oxime **4-55** (100 mg, 0.50 mmol) and **BAC-42** (4.6 mg, 0.026 mmol) using a modified general procedure at 50 ºC. Purified by flash chromatography (2:1 hexane/EtOAc to EtOAc) and isolated as a white solid (99 mg, 99% with conditions A; 96 mg, 96% with conditions B).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.52 (s, 1H), 3.31-3.28 (m, 2H), 2.20-2.18 (m, 2H), 1.70-1.65 (m, 2H), 1.53-1.48 (m, 2H), 1.39-1.29 (m, 14H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.6, 39.2, 37.1, 28.5, 26.9, 26.5, 26.4, 25.9, 25.4, 25.1, 24.8, 24.1.



4-58

***N*-((3S,8R,9S,10R,13S,14S,17S)-3-Hydroxy-10,13-dimethyl 2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)acetamide (4-58)**: Prepared from pregnenolone oxime **4-57** (85 mg, 0.25 mmol), **BAC-42** (5 mg, 0.025 mmol) and perfluoropinacol (8 mg, 0.25 mmol) using a modified general procedure in pure HFIP at 50 °C. Purified by flash column chromatography (4:1 to 2:1 DCM:acetone) and isolated as a white solid (84 mg, 98% with conditions B).

M.p. 231-233 °C;

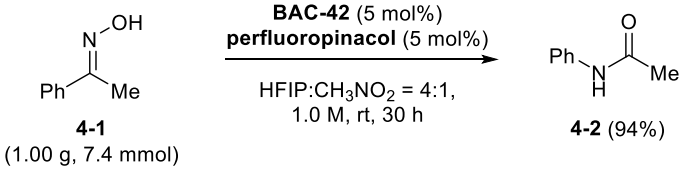
^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.36-5.33 (m, 1H), 5.26 (d, *J* = 8.4 Hz, 1H), 3.97-3.83 (m, 1H), 3.57-3.48 (m, 1H), 2.35-2.07 (m, 3H), 2.04-1.96 (m, 1H), 1.98 (s, 3H), 1.90-1.82 (m, 2H), 1.77-1.62 (m, 2H), 1.61-1.17 (m, 9H), 1.16-1.04 (m, 2H), 1.05-0.92 (m, 1H), 1.01 (s, 3H), 0.70 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.9, 140.9, 121.3, 71.7, 58.9, 52.9, 50.1, 42.7, 42.3, 37.3, 36.8, 36.6, 32.1, 31.6, 31.5, 28.7, 23.7, 23.6, 20.6, 19.4, 12.0;

IR (Microscope, cm^{-1}): 3273, 3195, 3082, 2962, 2899, 2846, 1646, 1556, 1436, 1372, 1058;

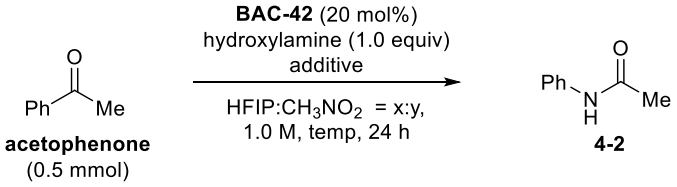
HRMS (ESI) for $C_{21}H_{34}NO_2$ $[M+H]^+$: calcd. 332.2584; found 332.2589.

4.11.5 Procedure for gram-scale Beckmann rearrangement *via* BAC-42



To a 15 mL round bottom flask charged with a stir bar, was added the oxime **4-1** (1.00 g, 7.40 mmol), boronic acid **BAC-42** (67 mg, 0.37 mmol) and perfluoropinacol (124 mg, 0.37 mmol). A solvent mixture of hexafluoroisopropanol and nitromethane (v:v = 4:1, 7.4 mL) was injected. The reaction vial was then capped, sealed and subjected at the room temperature for 30 hours. The crude product was obtained after removal of solvent. The product amide **4-2** was purified by flash column chromatography (1:1 hexane:EtOAc) and isolated as a white solid (940 mg, 94%).

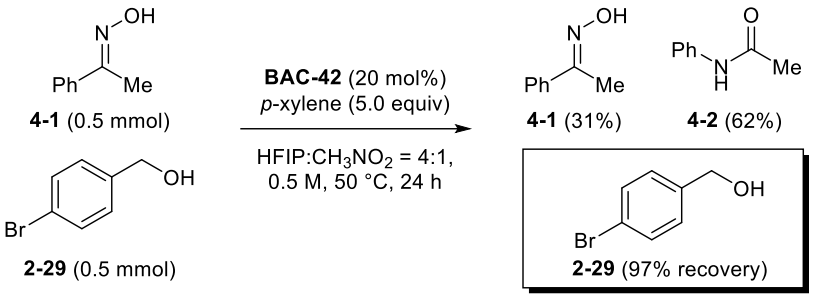
4.11.6 General procedure for the one-pot Beckmann rearrangement from ketone



To a 5 mL reaction vial charged with a stir bar, was added acetophenone (60 mg, 0.50 mmol), hydroxylamine (0.50 mmol), boronic acid **BAC-42** (18 mg, 0.10 mmol) and additives as indicated. A solvent mixture of hexafluoroisopropanol and nitromethane (v:v = 1:1 or 4:1, 0.5 mL) was injected. The reaction vial was then capped, sealed and subjected at the indicated

temperature for 24 hours. The crude product was obtained after removal of solvent and subjected to ^{1}H NMR analysis.

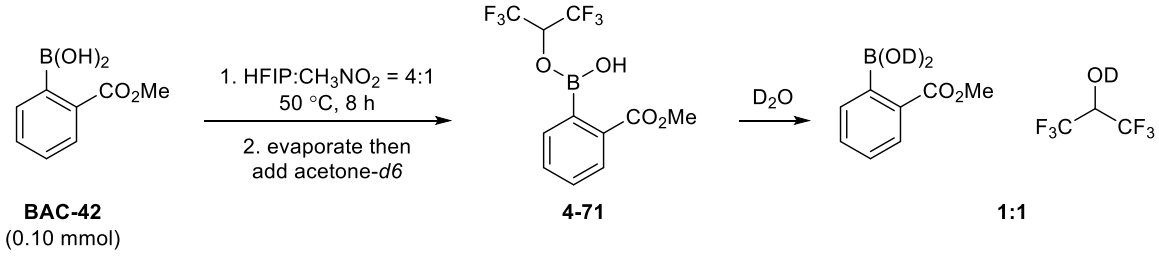
4.11.7 Procedure for the orthogonal catalysis *via* BAC-42



To a 5 mL reaction vial charged with a stir bar, was added the oxime **4-1** (68 mg, 0.50 mmol), 4-bromobenzyl alcohol (94 mg, 0.50 mmol), *p*-xylene (265 mg, 2.50 mmol) and boronic acid **BAC-42** (18 mg, 0.10 mmol). A solvent mixture of hexafluoroisopropanol and nitromethane (v:v = 4:1, 1.0 mL) was injected. The reaction vial was then capped, sealed and subjected at 50 °C for 24 hours. The crude product was obtained after removal of solvent. The remaining oxime **4-1** (31%), amide product **4-2** (62%) and 4-bromobenzyl alcohol (97%) were isolated by flash column chromatography (1:1 hexane:EtOAc).

4.11.8 Mechanistic studies

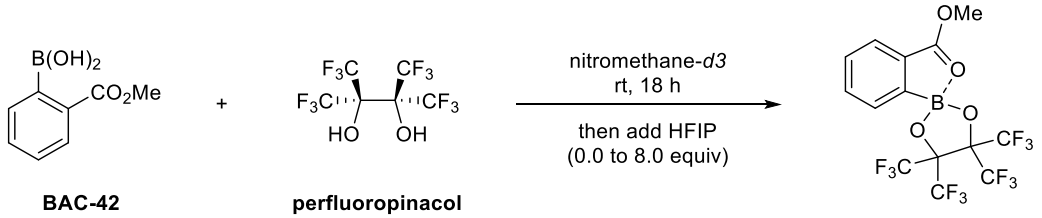
4.11.8.1 Procedure for the evaporation experiments to examine the role of HFIP



To a 5 mL round bottom flask charged with a stir bar, was added boronic acid **BAC-42** (18 mg, 0.10 mmol) followed by a solvent mixture of nitromethane and hexafluoropropanol (v:v = 1:4, 2 mL). The round bottom flask was then capped and allowed to stir at 50 °C for 8 hours. After the

indicated time, the reaction mixture was cooled to room temperature. Product was obtained and placed under vacuum for 1 hour after the removal of solvent. Initial ^{1}H NMR and ^{11}B NMR studies of the product were performed in anhydrous acetone-*d6*. A complicated mixture of compound **4-71** was observed for both ^{1}H NMR and ^{11}B NMR as shown in **Figure 4-1** and **Figure 4-3**. The same set of NMR experiments was run in acetone-d6 with 1 drop of D_2O. A 1:1 ratio of boronic acid **BAC-42** and HFIP was observed as shown in **Figure 4-2** and **Figure 4-4**.

4.11.8.2 Procedure for the experiments to explore the role of perfluoropinacol



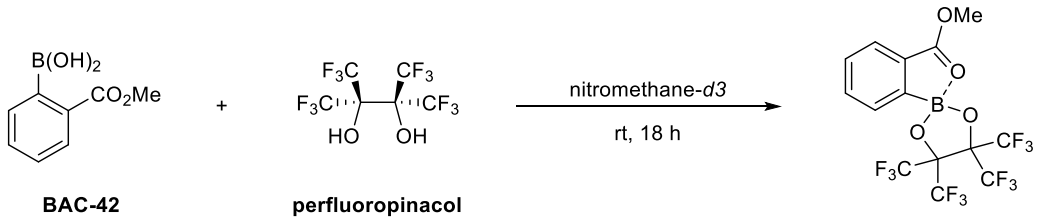
BAC-42
0.025 mmol

perfluoropinacol
(1.0 equiv)

4-72

To a vial charged with a stir bar, was added boronic acid **BAC-42** (5 mg, 0.025 mmol) and perfluoropinacol (8 mg, 0.025 mmol) in nitromethane-*d3* (0.7 mL). The reaction mixture was allowed to stir at room temperature for 18 h before subjected to ^{1}H NMR, ^{11}B NMR and ^{19}F NMR spectroscopic studies. The corresponding spectrums are shown as **Figure 4-6**, **Figure 4-8** and **Figure 4-10**.

Afterwards, the previous mixture of boronic acid **BAC-42** and perfluoropinacol was titrated using various amounts of HFIP from 0.0 to 8.0 equivalents. As a result, the corresponding ^{1}H NMR, ^{19}F NMR and ^{11}B NMR spectra were recorded as **Figure 4-11** and **Figure 4-12**. At the end point, ^{13}C NMR, HSQC, HMBC spectrums of reaction mixture with 8.0 equivalents of HFIP were also recorded as **Figure 13** to **Figure 15**.



BAC-42
0.025 mmol

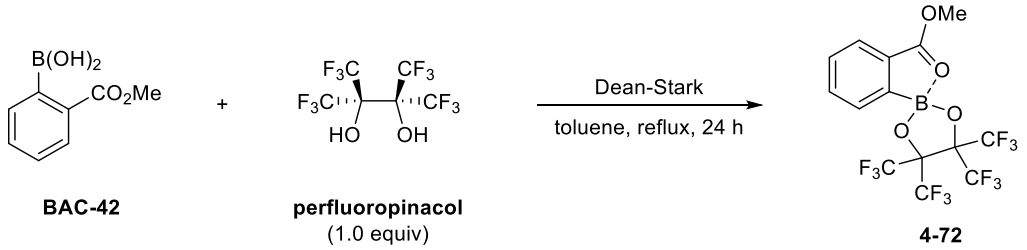
perfluoropinacol
(2.0 or 3.0 equiv)

4-72

To a vial charged with a stir bar, was added boronic acid **BAC-42** (5 mg, 0.025 mmol) and perfluoropinacol (17 mg, 0.05 mmol or 25 mg, 0.075 mmol) in d3-nitromethane (0.7 mL). The

reaction mixture was allowed to stir at room temperature for 18 h before subjected to ^{11}B NMR spectroscopic studies. The corresponding spectrums are shown as **Figure 4-16**.

4.11.8.3 Synthesis and mechanistic investigation of compound 4-72



Methyl 2-(4,4,5,5-tetrakis(trifluoromethyl)-1,3,2-dioxaborolan-2-yl)benzoate (4-72): To a 25 mL round bottom flask charged with a stir bar, was added boronic acid **BAC-42** (180 mg, 1.00 mmol) and perfluoropinacol (334 mg, 1.0 mmol) in 10 mL of toluene. The reaction mixture was heated up to reflux using a Dean-Stark apparatus for 24 hours. After the indicated time, the reaction mixture was cooled down to room temperature. Compound **4-72** was obtained as a light yellow solid (454 mg, 95%, decomposed upon heating) after the removal of excess toluene.

^{1}H NMR (CD_3NO_2, 500 MHz): δ 7.98-7.96 (m, 1H), 7.87-7.84 (m, 1H), 7.76-7.74 (m, 1H), 7.67-7.64 (m, 1H), 4.53 (s, 3H);

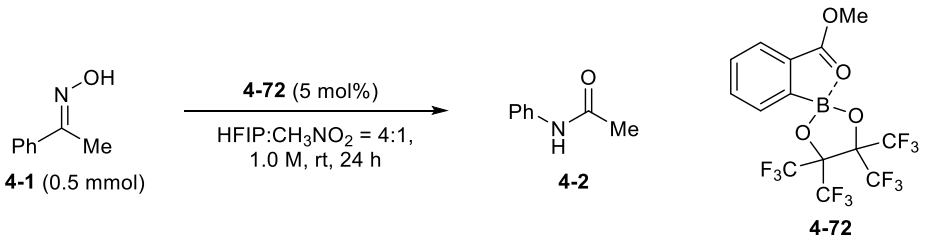
^{13}C NMR (CD_3NO_2, 125 MHz): δ 182.8, 137.1, 130.7, 130.5, 130.1, 125.6, 121.5 (q, J = 293.9 Hz), 87.6, 59.4 (The boron-bound carbon was not detected due to quadrupolar relaxation of boron);

^{19}F NMR (CD_3NO_2, 469 MHz): δ –69.9 (s, 12 F);

^{11}B NMR (CD_3NO_2, 160 MHz): δ 14.9;

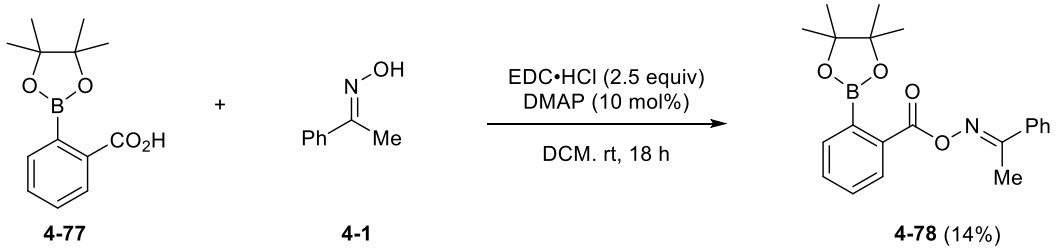
IR (Microscope, cm^{-1}): 1620, 1591, 1566, 1485, 1444, 1244, 1209, 1119;

HRMS (EI) for $C_{14}H_7BF_{12}O_4$: calcd. 478.0246; found 478.0237.



To a 5 mL reaction vial charged with a stir bar, was added the oxime **4-1** (68 mg, 0.50 mmol) and the boronic ester **7-72** (12 mg, 0.025 mmol). A solvent mixture of hexafluoroisopropanol and nitromethane (v:v = 4:1, 0.5 mL) was injected. The reaction vial was then capped, sealed and subjected at the room temperature for 24 hours. The crude product was obtained after removal of solvent. The product amide **4-2** was purified by flash column chromatography (1:1 hexane:EtOAc) and isolated as a white solid (62.8 mg, 93%).

4.11.8.4 Synthesis and characterization of the oxime ester intermediates



(*E*)-1-Phenylethan-1-one *O*-(2-(4,4,5,5,-tetrmethyl-1,3,2-dioxaborolan-2-yl)benzoyl oxime (4-78): To flame-dried 50 mL round bottom flask charged with a stir bar, was added a solution of 2-carboxyphenyl pinacol boronate **4-77** (496 mg, 2.00 mmol) in 20 mL of DCM followed by EDC·HCl (959 mg, 5.00 mmol), DMAP (24 mg, 0.20 mmol). The reaction was allowed to stir under nitrogen atmosphere for 15 minutes before the addition of oxime **4-1** (270 mg, 2.00 mmol). After continuous stirring for 24 hours at room temperature, the reaction mixture was quenched with 20 mL of water. The resulting mixture was extracted with DCM (3 × 10 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. The oxime ester was purified by flash column chromatography (10:1 to 4:1 hexane:MTBE) and isolated as a white solid (100 mg, 14%).

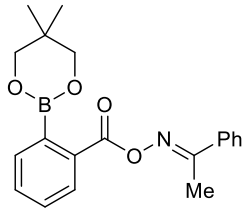
M.p. 120-122 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.00 (d, *J* = 7.8 Hz, 1H), 7.84-7.77 (m, 2H), 7.61-7.52 (m, 2H), 7.49-7.34 (m, 4H), 2.50 (s, 3H), 1.42 (s, 12H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.2, 163.8, 135.0, 132.8, 132.8, 132.0, 130.6, 129.1, 128.6, 128.5, 127.3, 84.2, 24.9, 15.0;

IR (Microscope, cm^{-1}): 3028, 2980, 2932, 1734, 1599, 1570, 1347, 1310, 1249, 757;

HRMS (ESI) for $C_{21}H_{25}BNO_4$ $[M+H]^+$: calcd. 366.1871; found 366.1881;



4-80

(*E*)-1-Phenylethan-1-one *O*-(2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoyl) oxime (4-80): Prepared from 2-bromo benzoic acid (804 mg, 4.00 mmol) and oxime **4-1** (405 mg, 3.00 mmol) using the general procedure from Section 4.11.2, step 1 and 2. Purified by flash column chromatography (10:1 to 3:1 hexane:EtOAc) and isolated as an off-white solid (282 mg, 40% for step 2).

M.p. 78-79 °C;

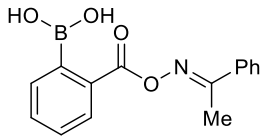
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.99 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 6.9 Hz, 2H), 7.57 (app dt, *J* = 14.6, 7.1 Hz, 2H), 7.49-7.38 (m, 4H), 3.81 (s, 4H), 2.51 (s, 3H), 1.09 (s, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.0, 163.8, 134.9, 132.3, 132.1, 131.8, 130.6, 128.6, 128.5, 128.4, 127.3, 72.5, 31.8, 22.1, 14.9 (The boron-bound carbon was not detected due to quadrupolar relaxation of boron);

^{11}B NMR ($CDCl_3$, 160 MHz): δ 28.3;

IR (Microscope, cm^{-1}): 3012, 2963, 2929, 2885, 1725, 1689, 1565, 1472, 1314, 1253, 1130, 1065;

HRMS (ESI) for $C_{20}H_{22}BNO_4Na$ $[M+Na]^+$: calcd. 374.1534; found 374.1532.



BAC-51

(*E*)-(2-((((1-Phenylethylidene)amino)oxy)carbonyl)phenyl)boronic acid (BAC-51): Prepared from neopentyl boronic ester **4-80** (282 mg, 0.80 mmol) using the general procedure from Section 4.11.2, step 3. Purified by recrystallization (3:1 hexane:DCM) and isolated as a white solid (45 mg, 20%, decomposed upon heating).

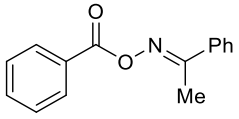
^{1}H NMR (CD_3COCD_3 + 1 drop D_2O, 500 MHz): δ 8.03 (d, *J* = 7.7 Hz, 1H), 7.87 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.65-7.54 (m, 2H), 7.52-7.41 (m, 4H), 2.54 (s, 3H);

^{13}C NMR (CD_3COCD_3 + 1 drop D_2O, 125 MHz): δ 165.9, 164.1, 136.1, 133.2, 132.9, 132.8, 131.4, 129.8, 129.5, 129.1, 127.9, 14.7 (The boron-bound carbon was not detected due to quadrupolar relaxation of boron);

^{11}B NMR (CD_3COCD_3 + 1 drop D_2O, 160 MHz): δ 30.1;

IR (Microscope, cm^{-1}): 3423, 3064, 3023, 2930, 2856, 1718, 1596, 1444, 1314, 1268, 1124, 1045, 912;

HRMS (ESI) for $C_{15}H_{13}BNO_4$ $[M-H]^-$: calcd. 282.0943; found 282.0943.



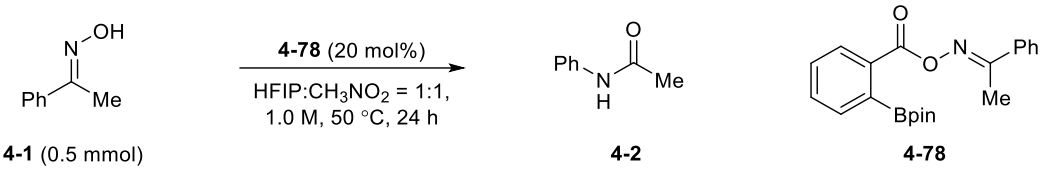
4-81

(*E*)-1-Phenylethan-1-one *O*-benzoyl oxime (4-81): Oxime ester was prepared according to the reported procedure by Guan and co-workers[48] and isolated as a white solid (560 mg, 78%).

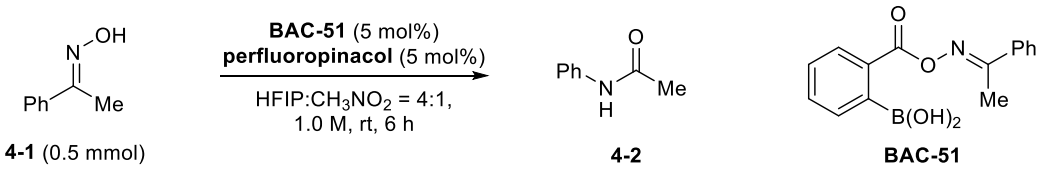
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.16-8.10 (m, 2H), 7.85-7.78 (m, 2H), 7.64-7.59 (m, 1H), 7.53-7.48 (m, 2H), 7.48-7.36 (m, 3H), 2.53 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.8, 163.6, 134.9, 133.3, 130.7, 129.7, 129.3, 128.6, 128.6, 127.2, 77.3, 14.7.

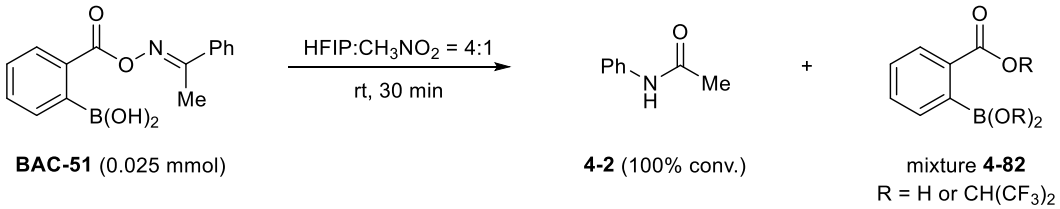
4.11.8.5 Mechanistic investigation with the oxime ester intermediates



To a 5 mL reaction vial charged with a stir bar, was added the oxime **4-1** (68 mg, 0.50 mmol) and the oxime ester **7-78** (37 mg, 0.10 mmol). A solvent mixture of hexafluoroisopropanol and nitromethane (v:v = 1:1, 0.5 mL) was injected. The reaction vial was then capped, sealed and subjected at the 50 °C for 24 hours. The crude product was obtained after removal of solvent and subjected to ^{1}H NMR spectroscopic study. Amide **4-2** was obtained in 72% yield using 1,4-dinitrobenzene as an internal standard.



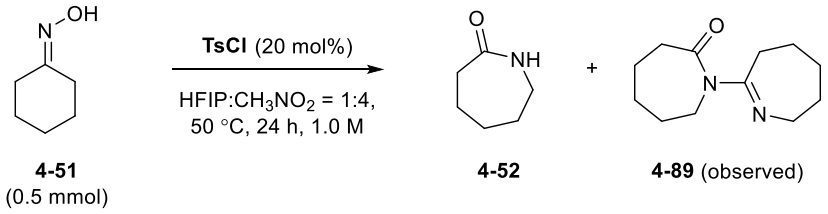
To a 5 mL reaction vial charged with a stir bar, was added the oxime **4-1** (68 mg, 0.50 mmol), boronic acid **BAC-51** (7 mg, 0.025 mmol) and perfluoropinacol (8 mg, 0.025 mmol). A solvent mixture of hexafluoroisopropanol and nitromethane (v:v = 4:1, 0.5 mL) was injected. The reaction vial was then capped, sealed and subjected at the room temperature for 6 hours. The crude product was obtained after removal of solvent and subjected to ^{1}H NMR spectroscopic study. Amide **4-2** was obtained in 101% yield using 1,4-dinitrobenzene as an internal standard.



To a vial with a stir bar was added oxime ester **BAC-51** (7 mg, 0.025 mmol) in a solvent mixture of hexafluoroisopropanol and nitromethane (v:v = 4:1, 0.5 mL). The reaction mixture was allowed to stir at room temperature and monitored by TLC. After 30 min, full conversion of

boronic acid **BAC-51** was observed. The crude mixture was subjected to NMR spectroscopic studies after the removal of solvent. ^{1}H NMR analysis shows formation of the product **4-2** along with mixture of the HFIP carboxyl ester and HFIP boronic ester **4-82 (Figure 4-19)**. The identification of the mixture **4-82** was further elucidated in the following ^{13}C NMR (**Figure 4-20**) and HMBC (**Figure 4-21**) analysis.

4.11.8.6 Comparative experiments to observe the dimer 4-89 using TsCl and BAC-42

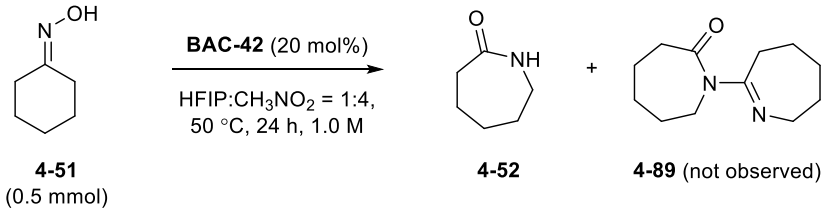


4-51
(0.5 mmol)

4-52

4-89 (observed)

To a 5 mL reaction vial charged with a stir bar, was added the oxime **4-51** (57 mg, 0.50 mmol) and 4-toluenesulfonyl chloride (19 mg, 0.10 mmol). A solvent mixture of hexafluoroisopropanol and nitromethane (v:v = 4:1, 0.5 mL) was injected. The reaction vial was then capped, sealed and subjected at 50 °C for 24 hours. The crude product was obtained after removal of solvent and subjected to ^{1}H NMR spectroscopic study and HRMS analysis. As shown in **Scheme 4-29**, the product **4-52** was observed along with the dimer **4-89**.



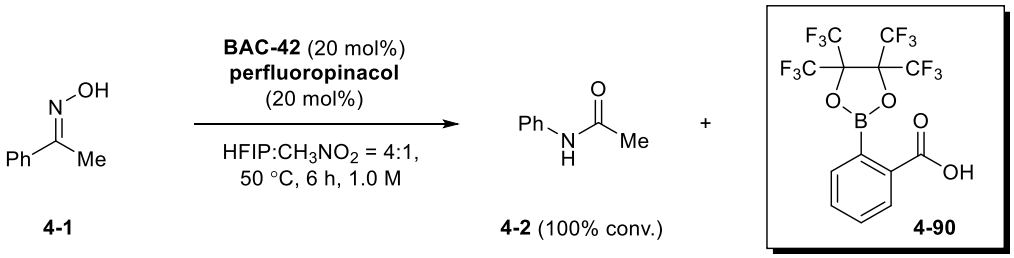
4-51
(0.5 mmol)

4-52

4-89 (not observed)

To a 5 mL reaction vial charged with a stir bar, was added the oxime **4-51** (57 mg, 0.50 mmol) and **BAC-42** (18 mg, 0.10 mmol). A solvent mixture of hexafluoroisopropanol and nitromethane (v:v = 4:1, 0.5 mL) was injected. The reaction vial was then capped, sealed and subjected at 50 °C for 24 hours. The crude product was obtained after removal of solvent and subjected to ^{1}H NMR spectroscopic study and HRMS analysis. As shown in **Scheme 4-30**, the product **4-52** was observed, but not the dimer **4-89**.

4.11.8.7 Analysis of the degradation of BAC-42 in the reaction conditions



To a 5 mL reaction vial charged with a stir bar, was added the oxime **4-1** (68 mg, 0.50 mmol), boronic acid **BAC-42** (18 mg, 0.10 mmol) and perfluoropinacol (33 mg, 0.10 mmol). A solvent mixture of nitromethane and hexafluoroisopropanol (v:v = 1:4, 0.5 mL) was injected. The reaction vial was then capped, sealed and subjected at the 50 °C for 6 hours. The crude product was obtained after removal of solvent and subjected to UPLC-MS study (**Scheme 4-31**).

4.12 References

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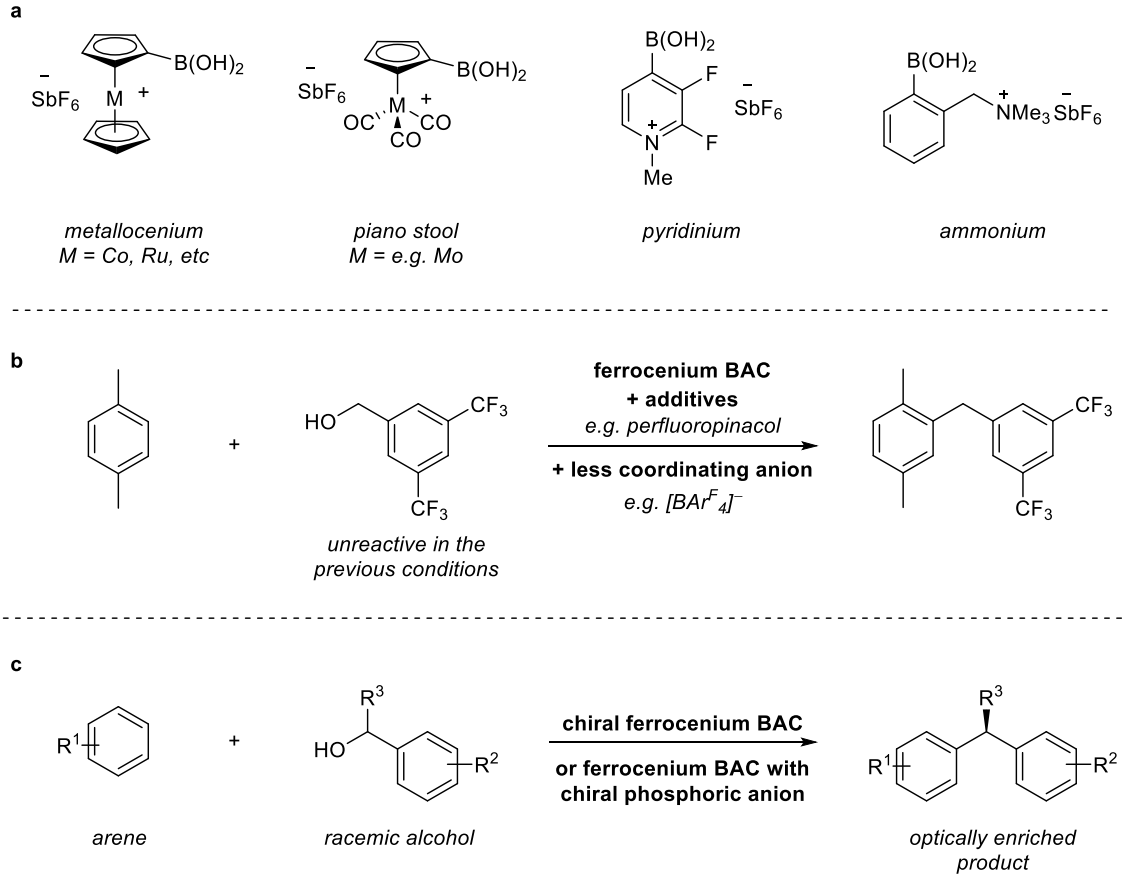
Chapter 5 Conclusions and Future Perspectives

Catalysis is the key to the production of numerous chemical commodities. By reducing the activation energy, direct transformations of previously inert starting materials become accessible. In this context, boronic acid catalysis (BAC) can be developed into a general and versatile strategy for the direct functionalization of hydroxyl groups, since it bypasses the need for wasteful stoichiometric activation processes. While the last decade has seen great advances in the direct activation of carboxylic acids and ketones *via* BAC (Chapter 1), very few reports illustrate its potential in the direct transformation of alcohols. The research described in this thesis describes the efforts towards the direct activation of alcoholic C–O bonds *via* BAC as a mean to render synthetic chemistry more efficient. The concept of BAC is also extended to other substrates, such as oximes.

Chapter 2 describes the successful Friedel-Crafts alkylation of arenes with π–activated alcohols by BAC. A rationale for the unexpectedly higher reactivity of tetrafluorophenylboronic acid compared to pentafluorophenylboronic acid is provided. Through the design of a novel ion redistribution process, the cationic ferrocenium boronic acid hexafluoroantimonate salt was developed into a highly reactive catalyst for direct Friedel-Crafts benzylation with deactivated benzylic alcohols and electron-neutral arenes. In this way, a library of valuable diarylmethane compounds was prepared. Despite these advances, there are still some limitations that can be improved: (a) Due to its electrophilic 17-electron configuration, the ferrocenium boronic acid salt displays a lack of stability in the presence of strong nucleophiles. Decomposition of the ferrocenium scaffold was observed in some cases. A potential solution to this problem includes replacing the iron cation with other metal centers, such as cobalt. As an 18-electron complex, the cobaltocenium boronic acid hexafluoroantimonate salt could be a stable and highly reactive catalyst for the direct Friedel-Crafts alkylation. Of course, other arylboronic acids with cationic structures, such as the pyridinium salts, should also be considered (**Scheme 5-1a**). (b) There are certain substrates that do not perform well in the optimal conditions, such as highly electron-poor benzylic alcohols and tertiary aliphatic alcohols. To overcome the difficulties with these substrates, different fluorinated diol additives, such as perfluoropinacol (Chapter 4) could be tested as part of a highly electrophilic two-component BAC system. Alternatively, a less coordinating anion, such as tetrakis[3,5-bis(trifluoromethyl)phenyl]borate $[BAr^{F}_{4}]^{-}$, may be worthwhile to explore (**Scheme 5-1b**). (c) There has been no example of direct asymmetric

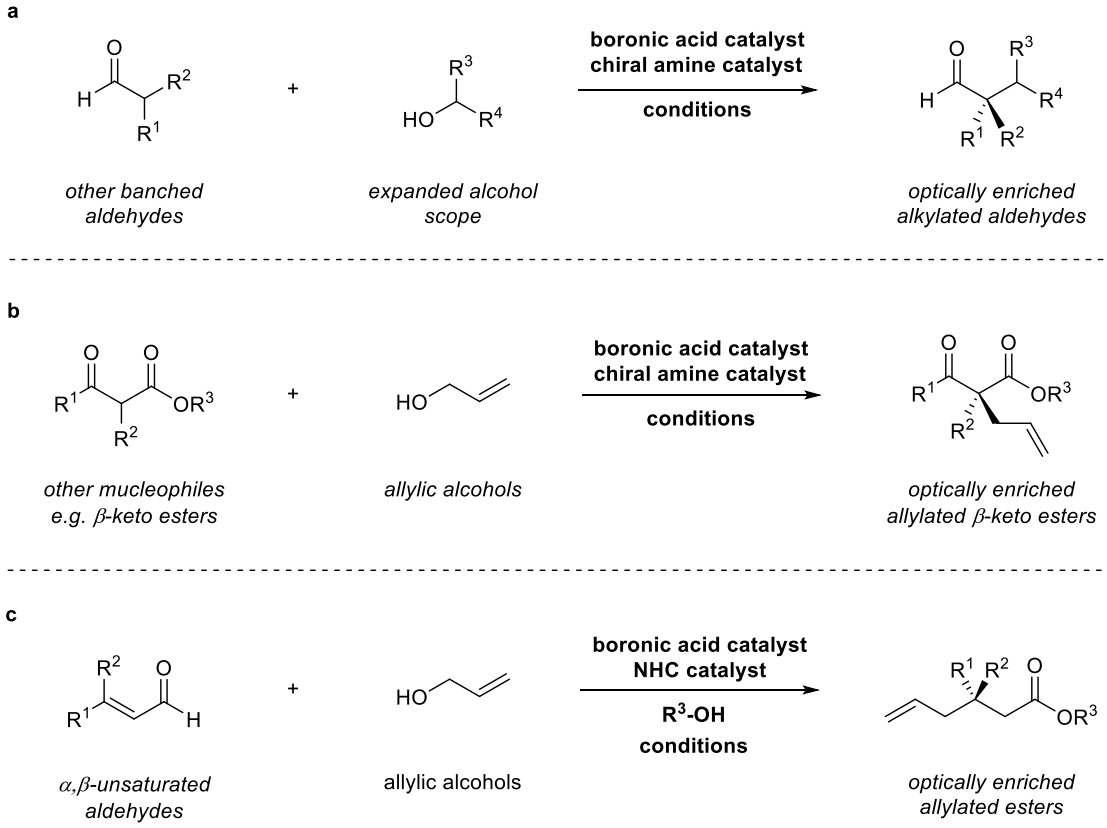
Friedel-Crafts alkylation of prochiral secondary alcohols with BAC. The formation of carbocation intermediates in the Friedel-Crafts reaction renders the asymmetric variant of this process highly challenging. In this regard, the design of a chiral ferrocenium boronic acid or a two-component system combining ferrocenium boronic acid with a chiral diol could be beneficial, since a chiral ion pair would be generated with the carbocation in the C–O bond breaking event. In another design, ferrocenium boronic acids with chiral anions, such as chiral phosphoric anion, could be introduced. Exchange of the boronate anion with a chiral anion may lead to ion-pairing of the carbocation and the chiral anion, which could provide stereoselective functionalization of alcohols (**Scheme 5-2c**).



Scheme 5-1. (a) Design of new cationic boronic acid salts; (b) Strategies to activate highly electron-poor alcohols; (c) Proposals to achieve asymmetric Friedel-Craft alkylation *via* BAC.

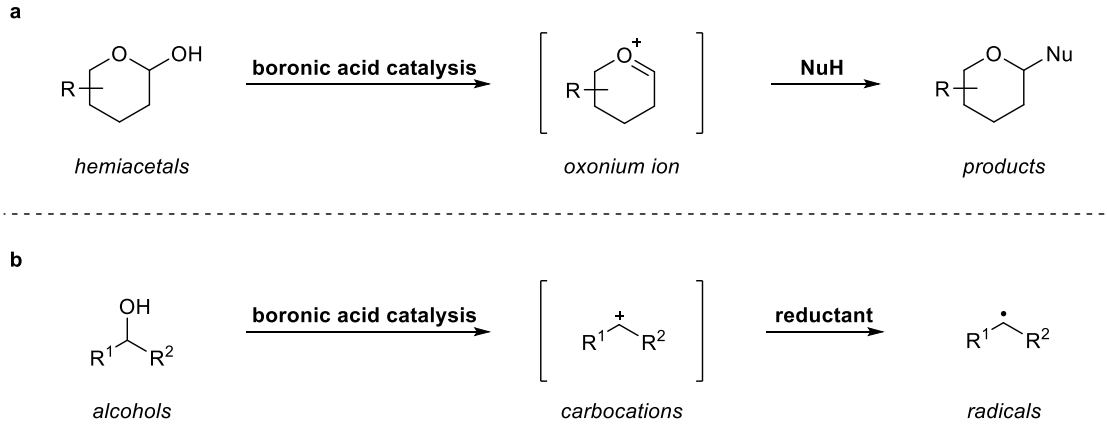
In Chapter 3, the first dual catalysis strategy merging boronic acid catalysis and chiral amine catalysis is described. Catalytic enantioselective allylation of branched aldehydes with allylic

alcohols was achieved, providing valuable methyl-aryl all-carbon quaternary centers in good yield and high enantioselectivity. Although this is the first demonstration of dual catalysis using BAC, dual catalysis is a largely unexplored area of this chemistry. There are a number of areas for improvement and new opportunities. (a) For example, the reaction suffers from a limited substrate scope. Only the diphenyl allylic alcohol is applicable in the protocol. Reaction conditions for a broader scope of allylic alcohols require further development. Similarly, more efforts are required to expand the scope of the nucleophiles to alkyl-alkyl branched aldehydes, since only methyl-aryl branched aldehydes served as efficient coupling partners in the current protocol (**Scheme 5-2a**). (b) As an extension, other nucleophiles that employ chiral amine catalysis should also be considered, such as ketones and β-keto esters (**Scheme 5-2b**). (c) It is envisioned that BAC could also be used in parallel with other modes of catalysis, such as NHC system (**Scheme 5-2c**).



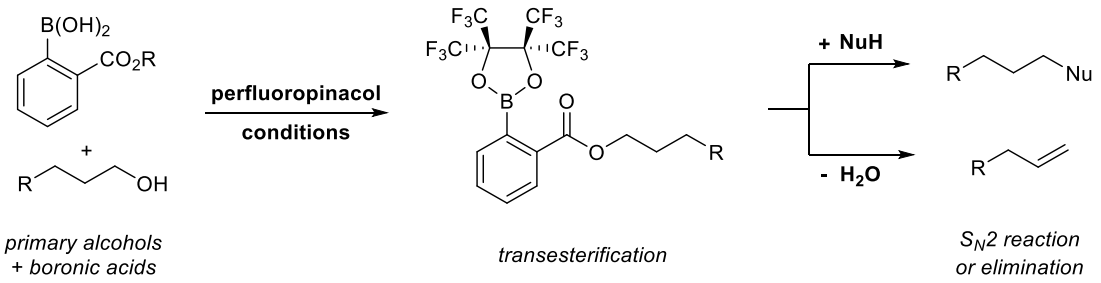
Scheme 5-2. (a) Extension of the dual catalytic asymmetric allylation to a broader substrate scope; (b) The use of β-keto esters as nucleophiles in dual catalysis with BAC; (c) Dual catalysis uniting BAC and NHC catalysis.

The research described in Chapter 2 and Chapter 3 focuses on the direct activation of alcohols *via* carbocation intermediates. As an extension of the BAC concept, the direct activation and transformation of hemiacetals *via* oxonium ions could be considered. Research in this field could potentially be applied to the direct functionalization of carbohydrates (**Scheme 5-3a**). Furthermore, an interesting question to ask is that, can the carbocation intermediates be reduced into radicals for further transformation (**Scheme 5-3b**)?



Scheme 5-3. (a) Activation of hemiacetals *via* BAC; (b) The possibility of reducing the carbocation intermediate into radicals in catalysis design.

Chapter 4 demonstrates that the concept of BAC can be further extended to the direct activation of oxime N–OH bonds. An operationally simple protocol has been developed for the Beckmann rearrangement of oximes using arylboronic acids substituted with *ortho*-carboxyester groups. In addition to the broad functional group tolerance, the BAC Beckmann rearrangement features a unique two-step reaction mechanism: boron induced oxime transesterification and boron assisted Beckmann rearrangement. Although the Beckmann rearrangement was discovered over 100 years ago, the development of the BAC Beckmann rearrangement sheds light on potential solutions to other long lasting challenges of direct hydroxyl group activation, such as the direct S_N2 reaction and E2 elimination from primary alcohols. Activation of primary alcohols could possibly be achieved if the similar boron induced alcohol transesterification or transsulfonylation could occur. A potential design for the direct S_N2 reaction and E2 elimination using arylboronic acids with *ortho*-carboxyester groups is shown in **Scheme 5-4**.



Scheme 5-4. Potential reaction designs of the S_N2 reaction and elimination using boronic acids with *ortho*-carboxyester groups.

Although it has been over 50 years since the first report of catalytic reactions with BAC, this area of research is still in its infancy. The research and proposals described in this thesis constitute only a small fraction of the potential of BAC in organic synthesis. The author believes that with increasing attention from the community, boronic acid catalysis can be developed into a general platform for direct functionalization of hydroxyl groups.

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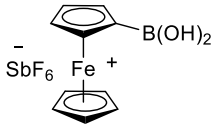
Appendices

Appendix 1: Selected copies of NMR spectra

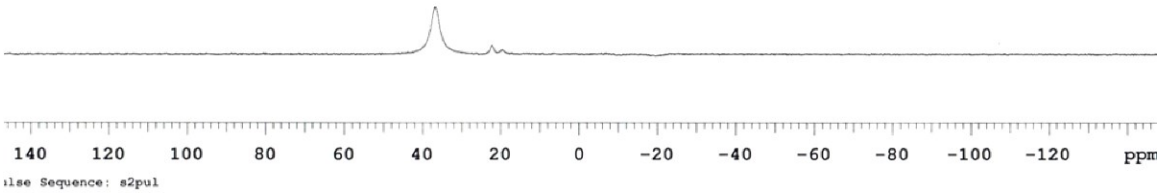
NMR spectra of **BAC-26**. Top: ^{11}B NMR (acetone-*d6*, 128 MHz);

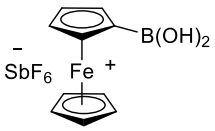
Bottom: ^{19}F NMR acetone-*d6*, 376 MHz);

^{1}H NMR and ^{13}C NMR were not obtained in high quality due to the paramagnetism of iron (III);

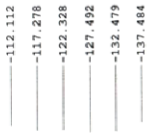


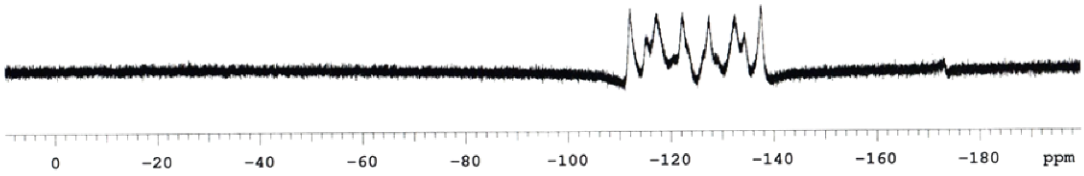
BAC-26



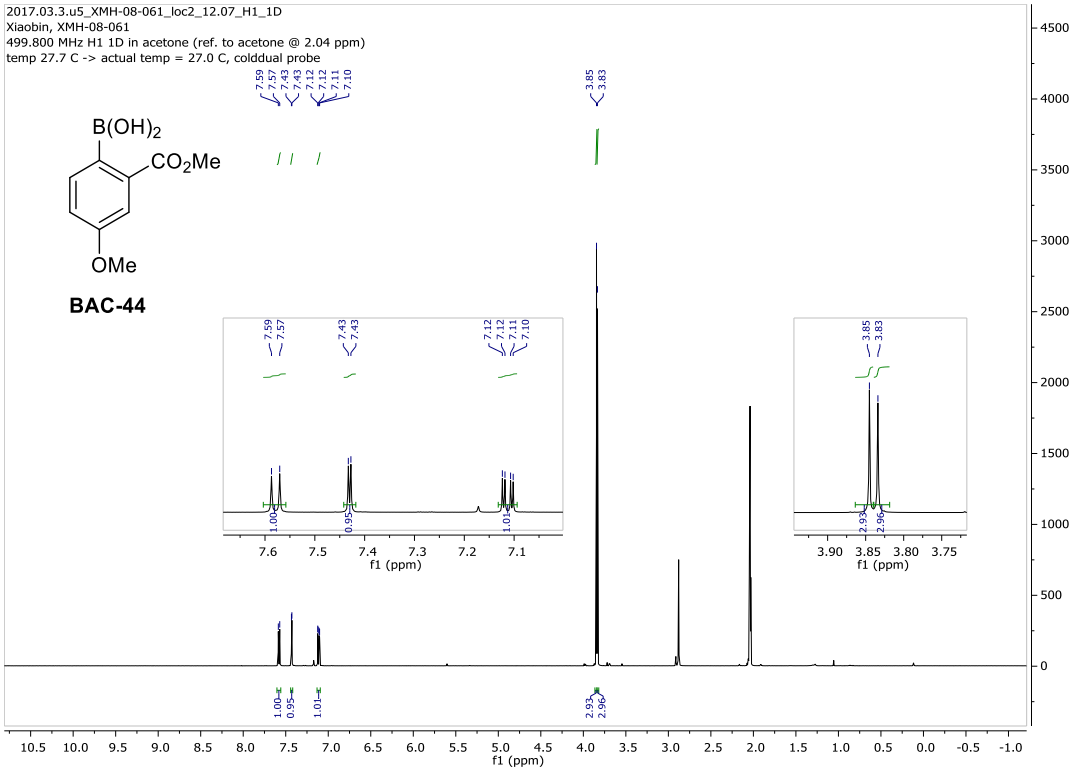


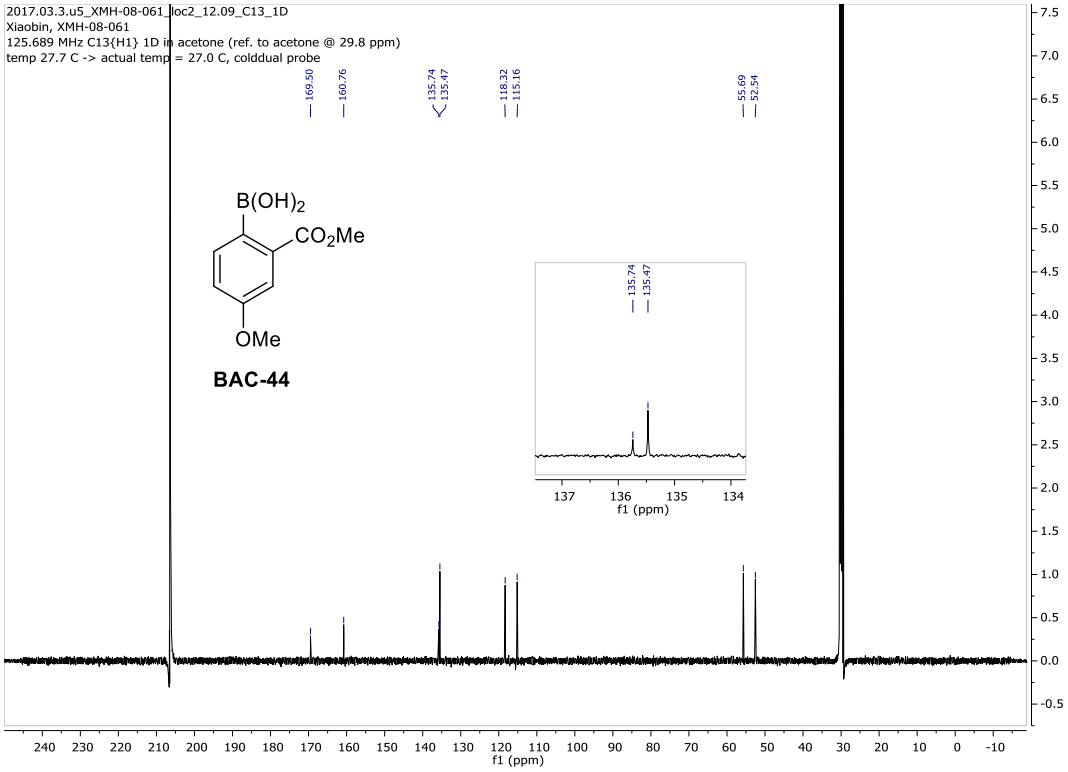
BAC-26



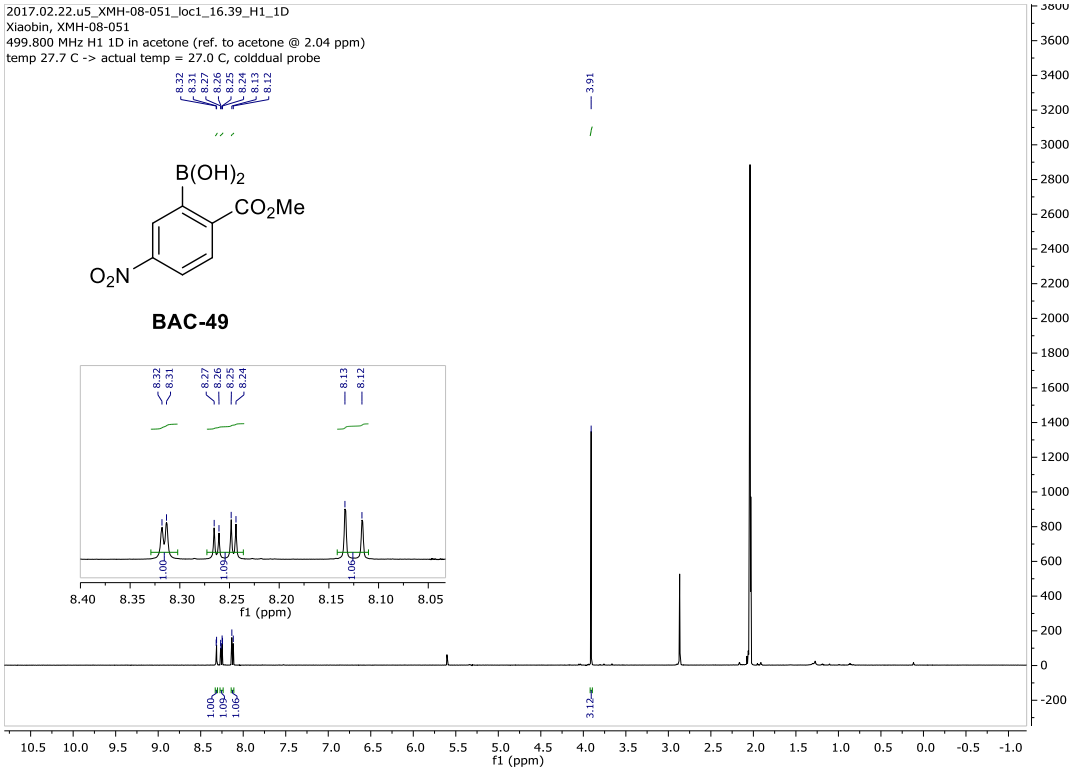


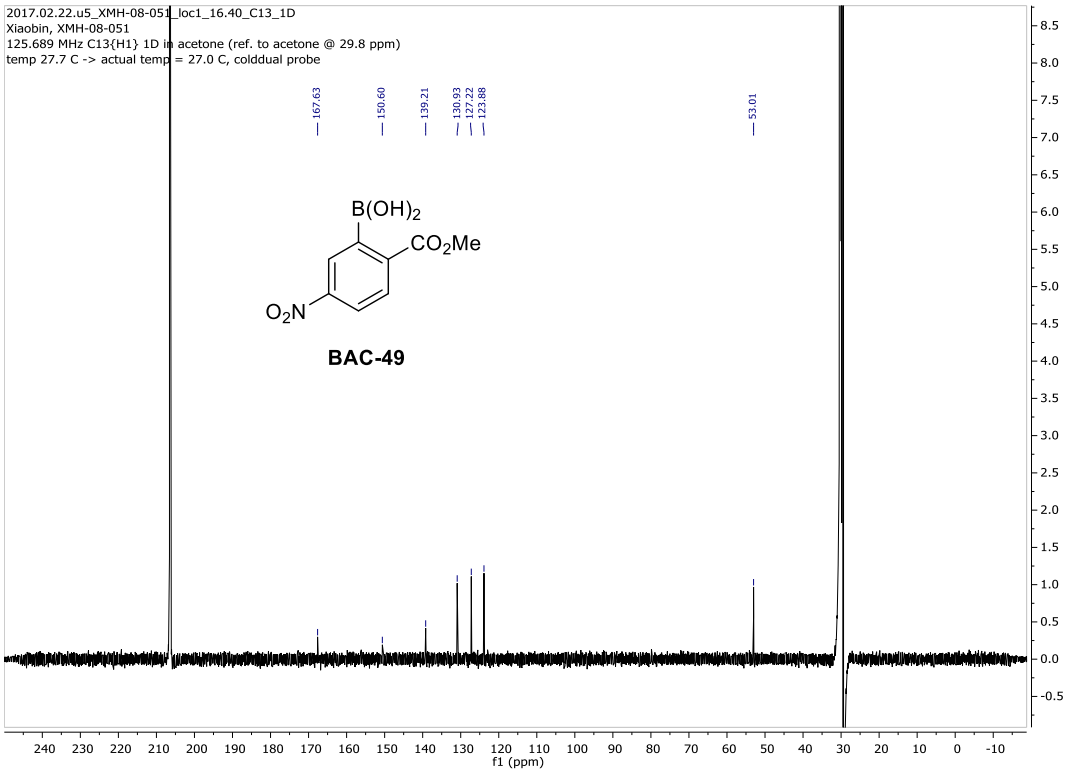
NMR spectra of **BAC-44**. Top: ^{1}H NMR (acetone-*d6* + 1 drop of D_2O, 500 MHz). Bottom: ^{13}C NMR acetone-*d6* + 1 drop of D_2O, 125 MHz)



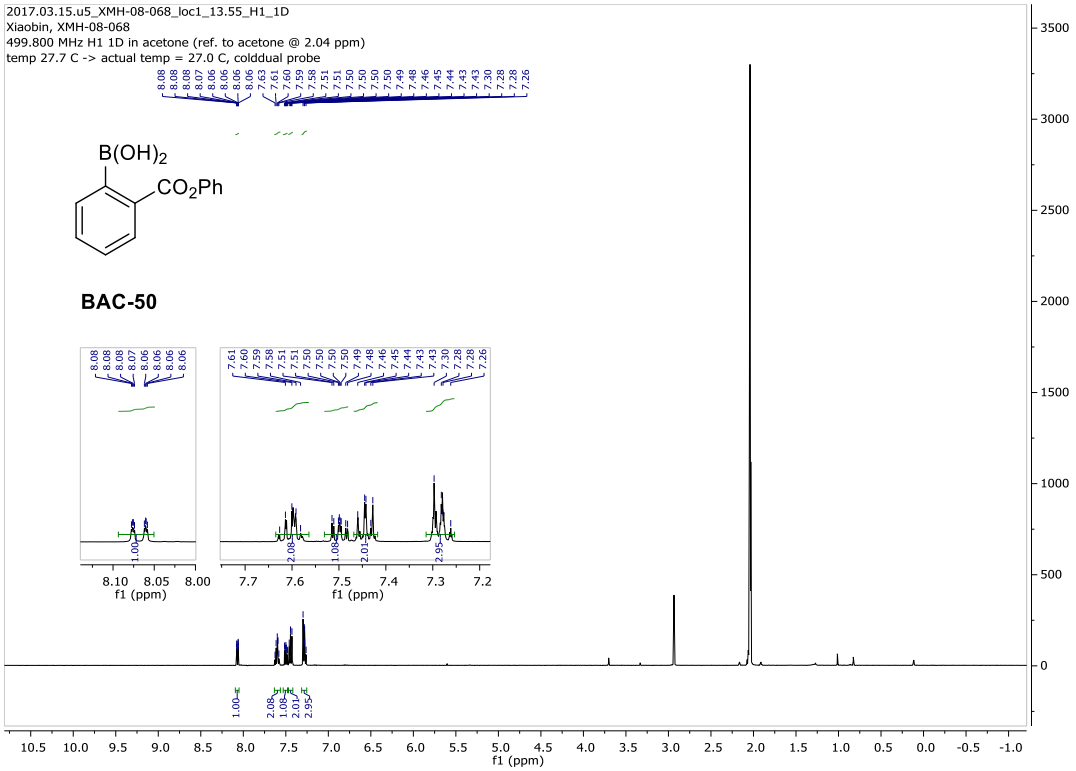


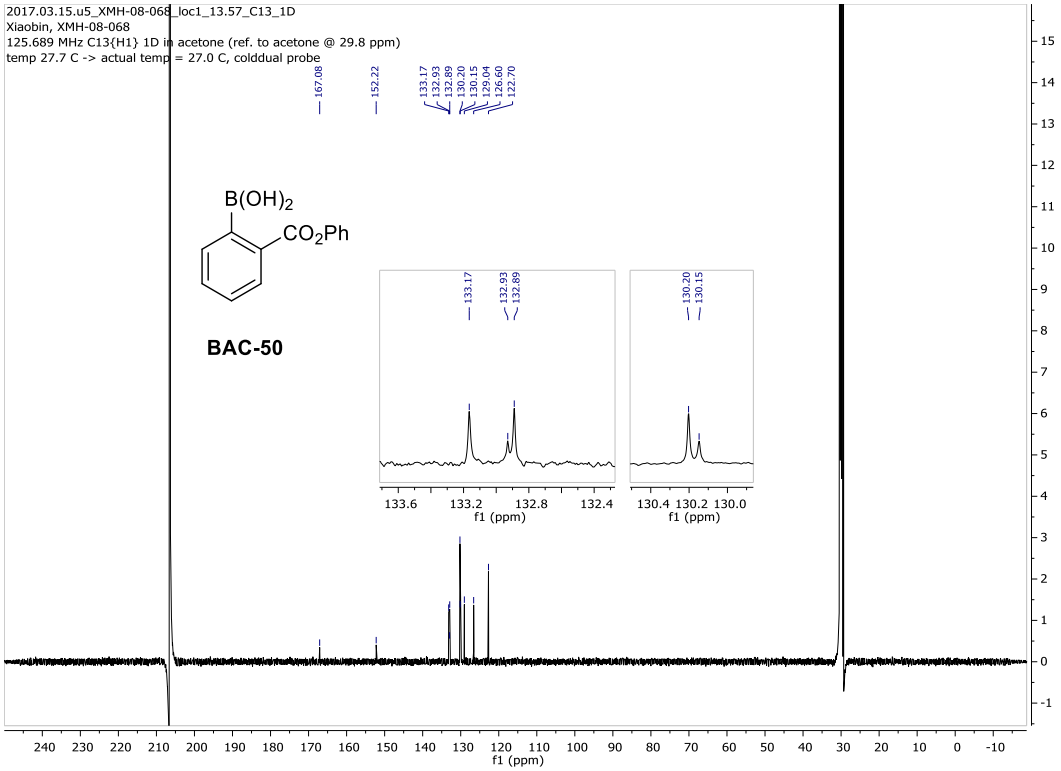
NMR spectra of **BAC-49**. Top: ^{1}H NMR (acetone-*d6* + 1 drop of D_2O, 500 MHz). Bottom: ^{13}C NMR (acetone-*d6* + 1 drop of D_2O, 125 MHz)



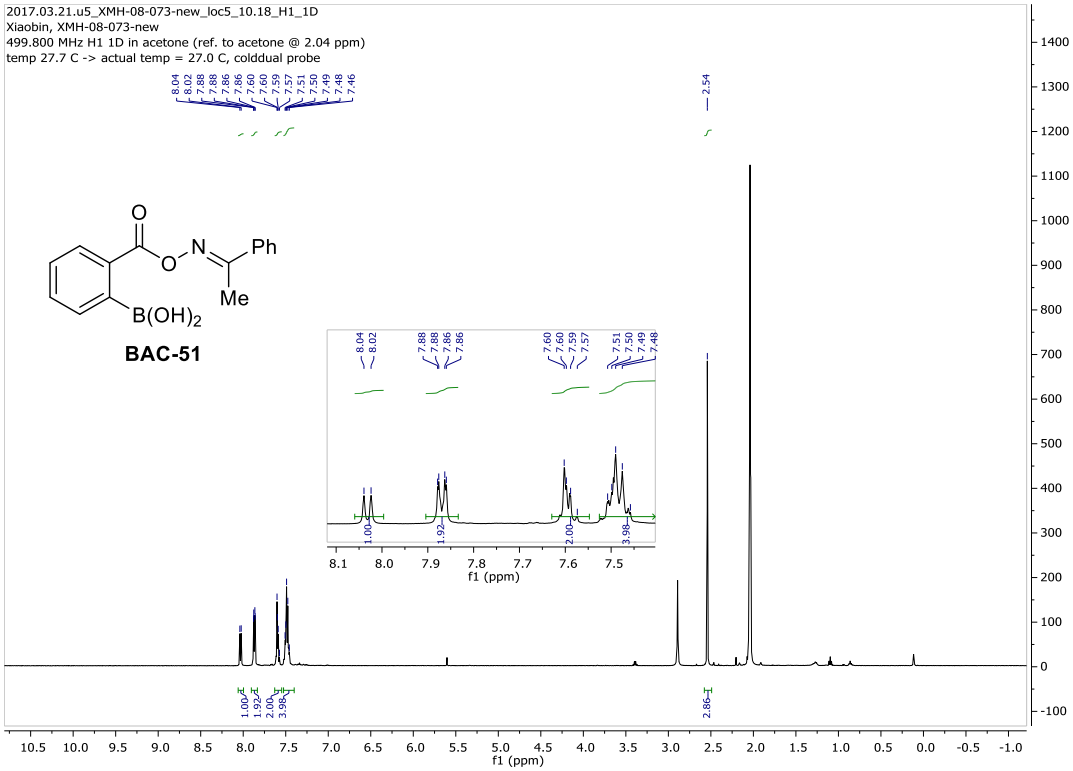


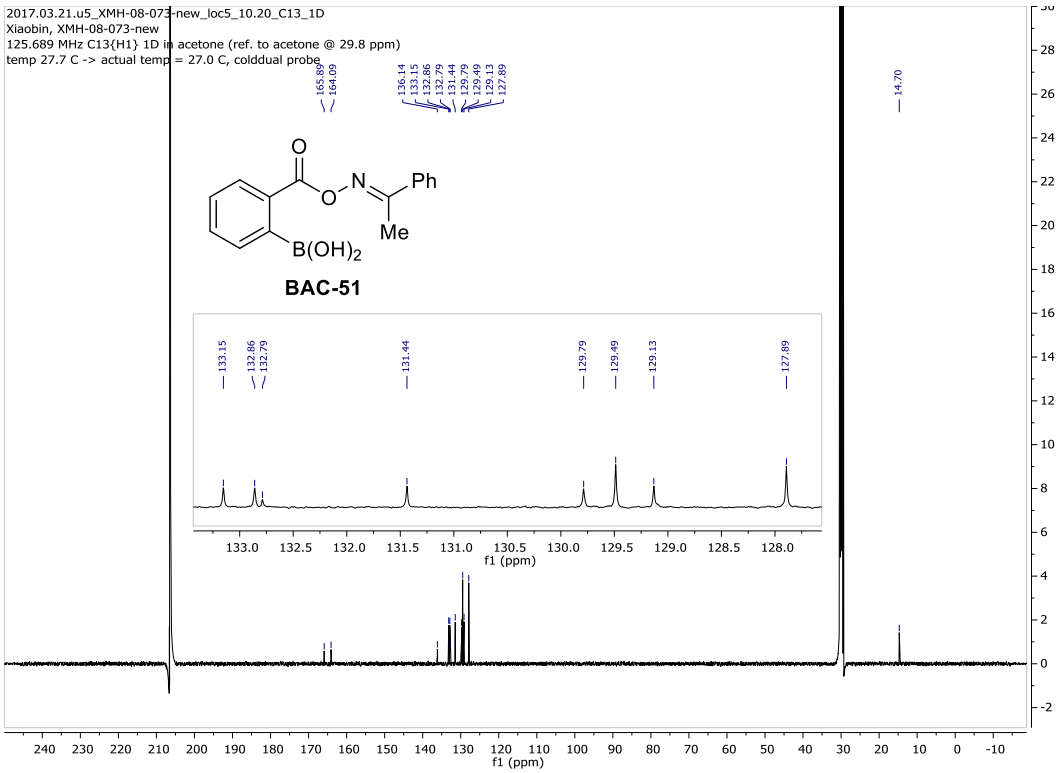
NMR spectra of **BAC-50**. Top: ^{1}H NMR (acetone-*d6* + 1 drop of D_2O, 500 MHz). Bottom: ^{13}C NMR (acetone-*d6* + 1 drop of D_2O, 125 MHz)



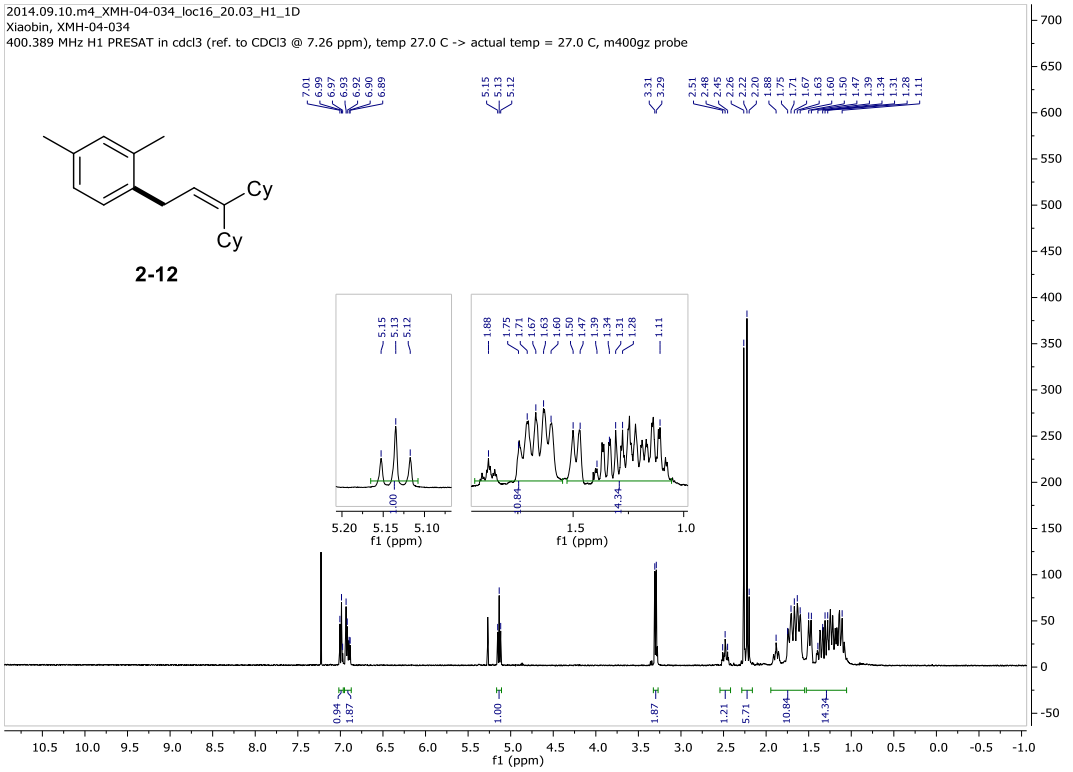


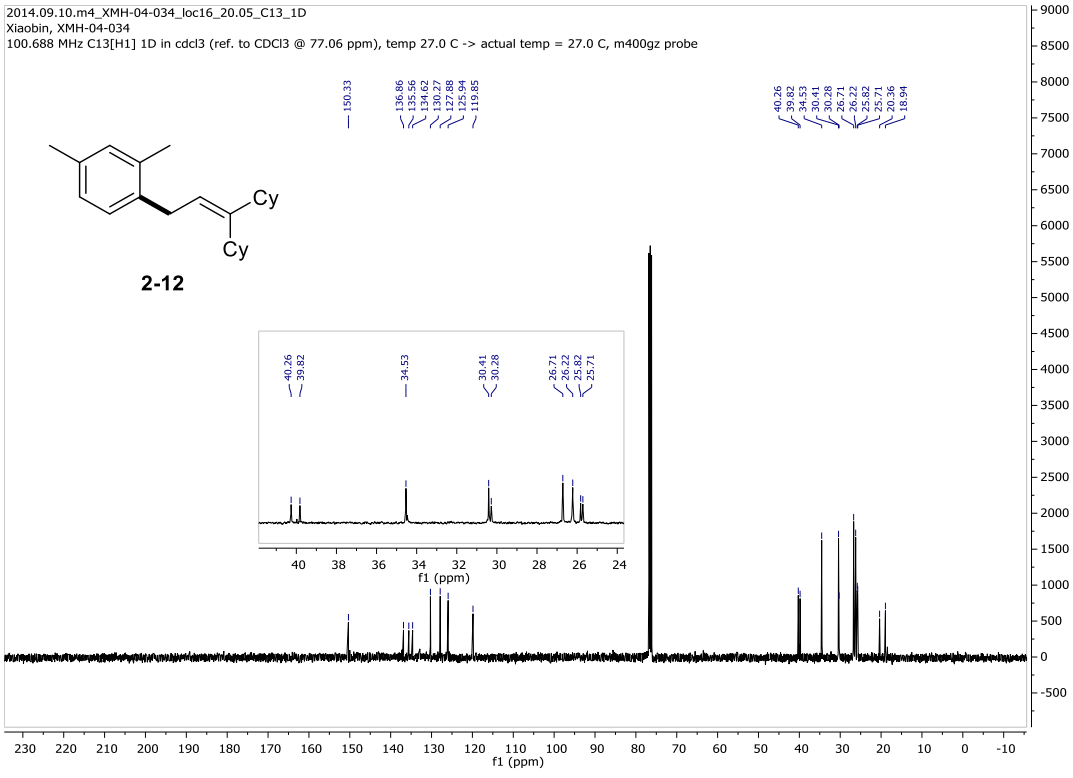
NMR spectra of **BAC-51**. Top: ^{1}H NMR (acetone-*d6* + 1 drop of D_2O, 500 MHz). Bottom: ^{13}C NMR (acetone-*d6* + 1 drop of D_2O, 125 MHz)



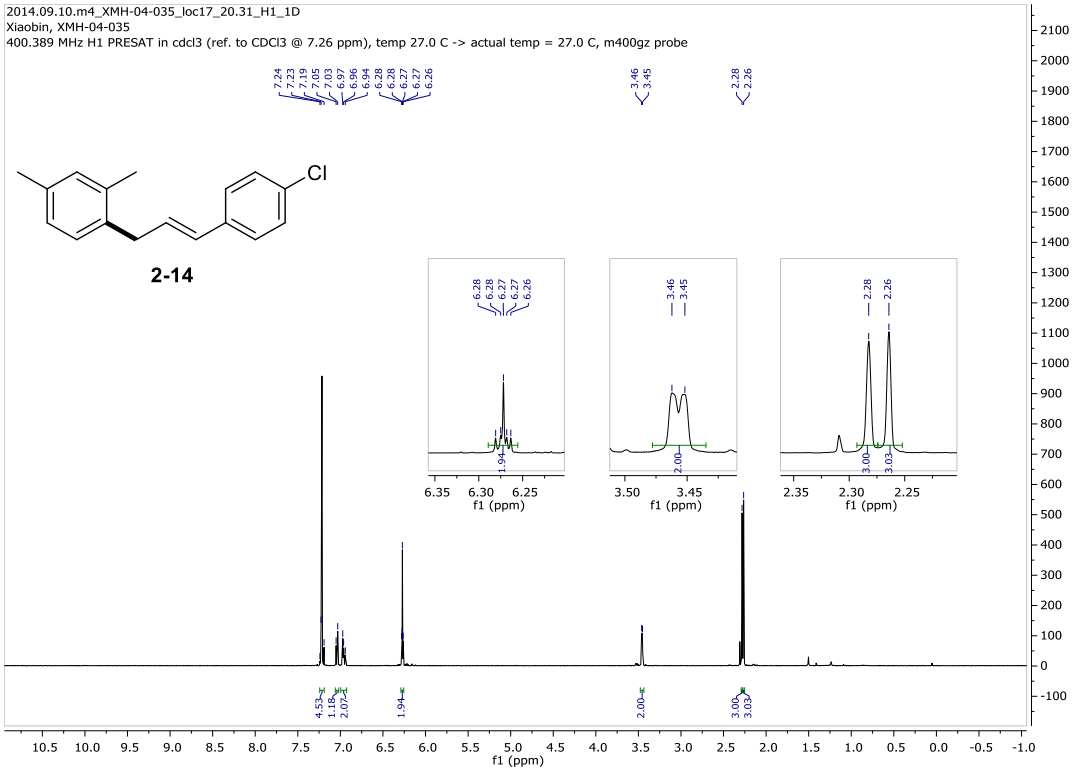


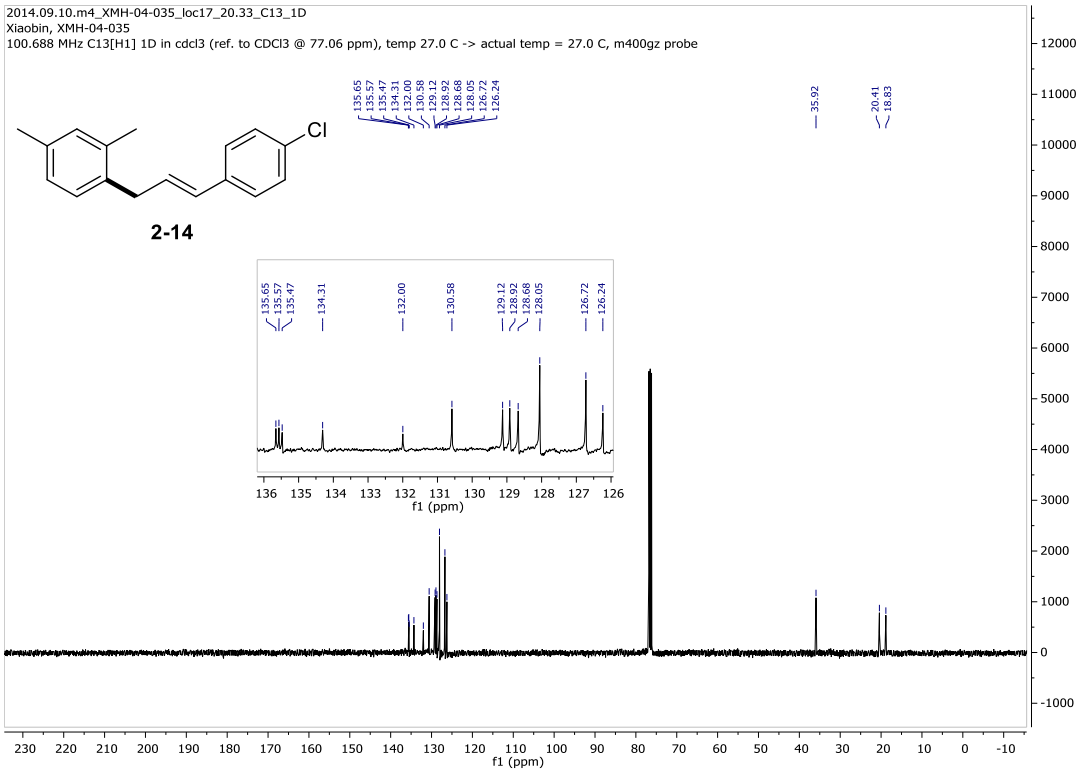
NMR spectra of **2-12**. Top: ^{1}H NMR ($CDCl_3$, 400 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 100 MHz)



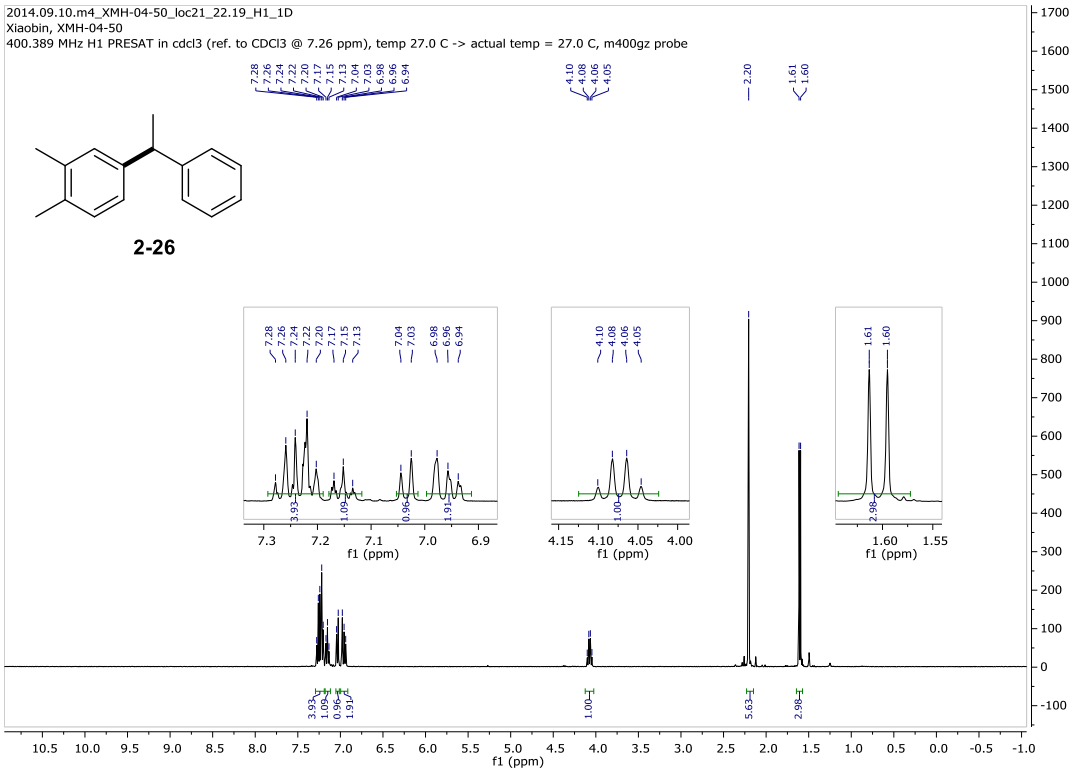


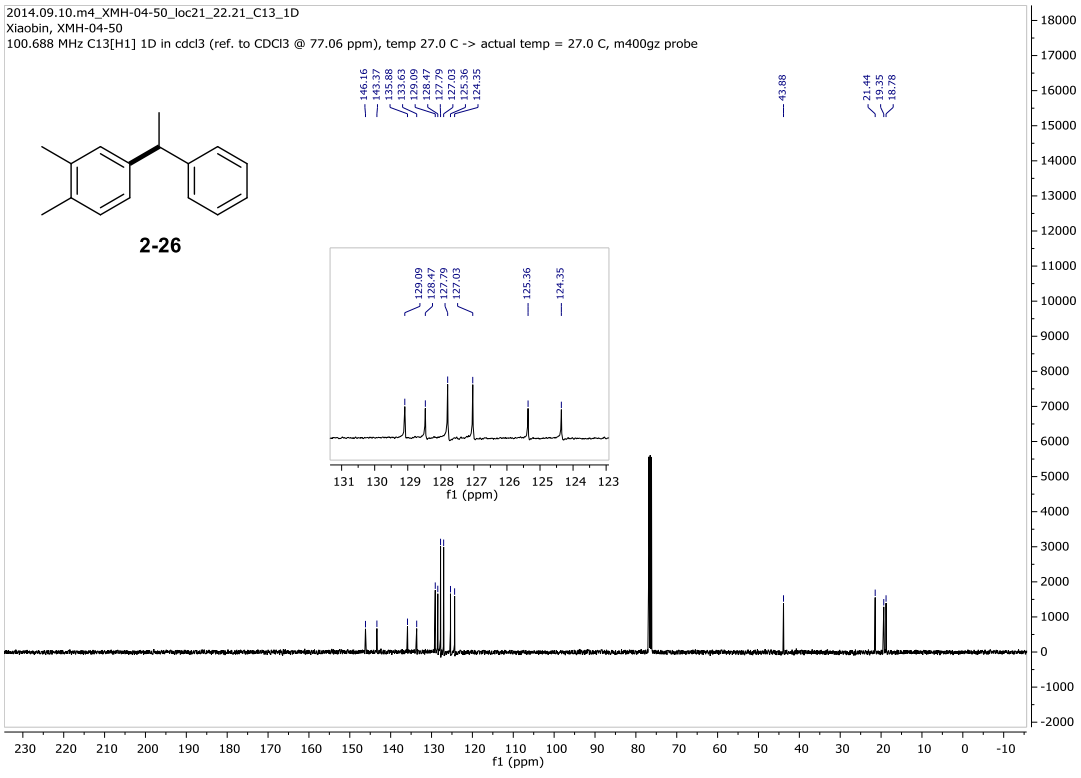
NMR spectra of **2-14**. Top: ^{1}H NMR ($CDCl_3$, 400 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 100 MHz)



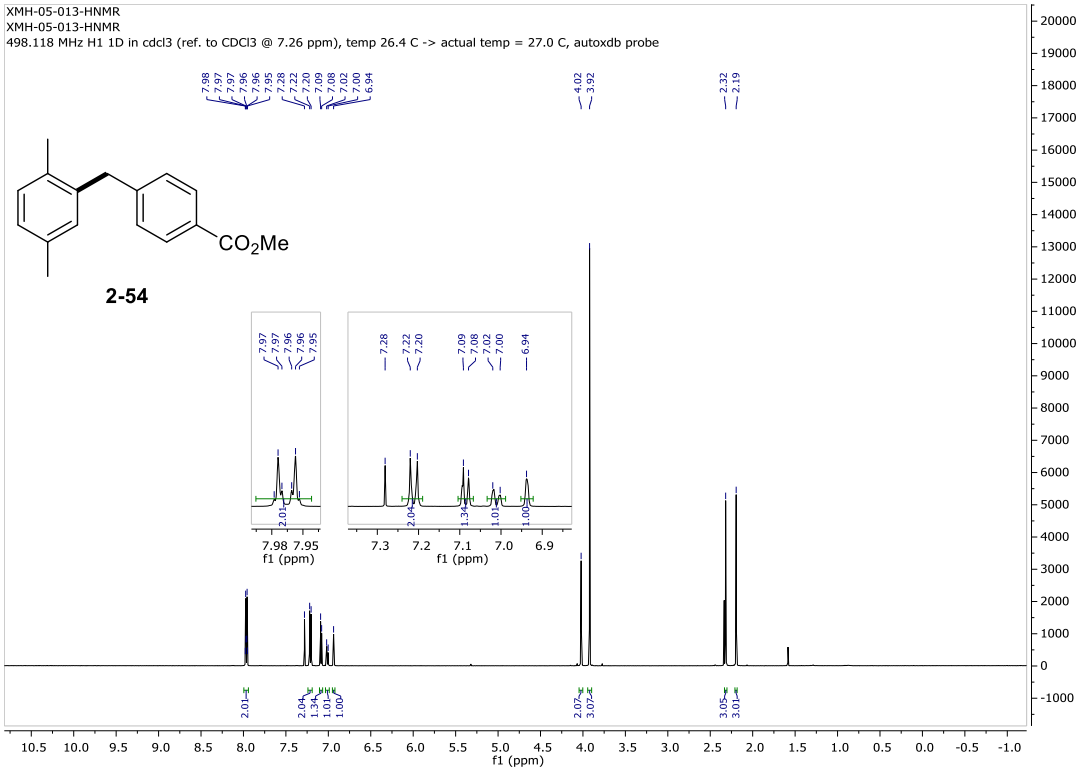


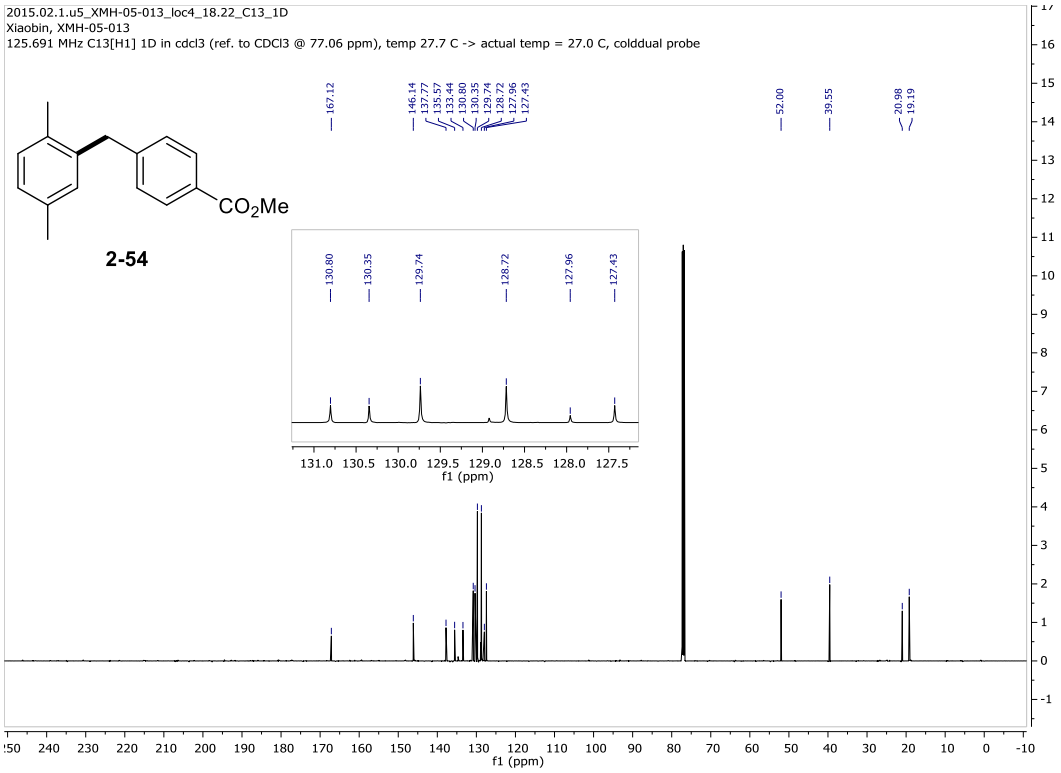
NMR spectra of **2-26**. Top: ^{1}H NMR ($CDCl_3$, 400 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 100 MHz)



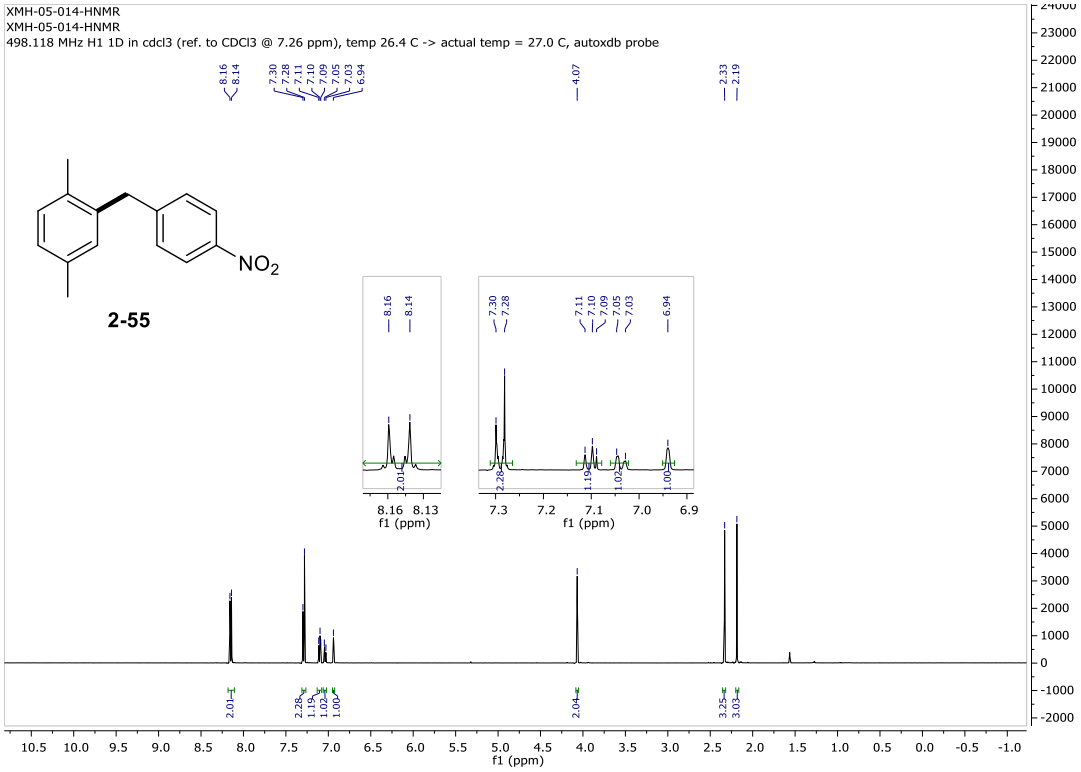


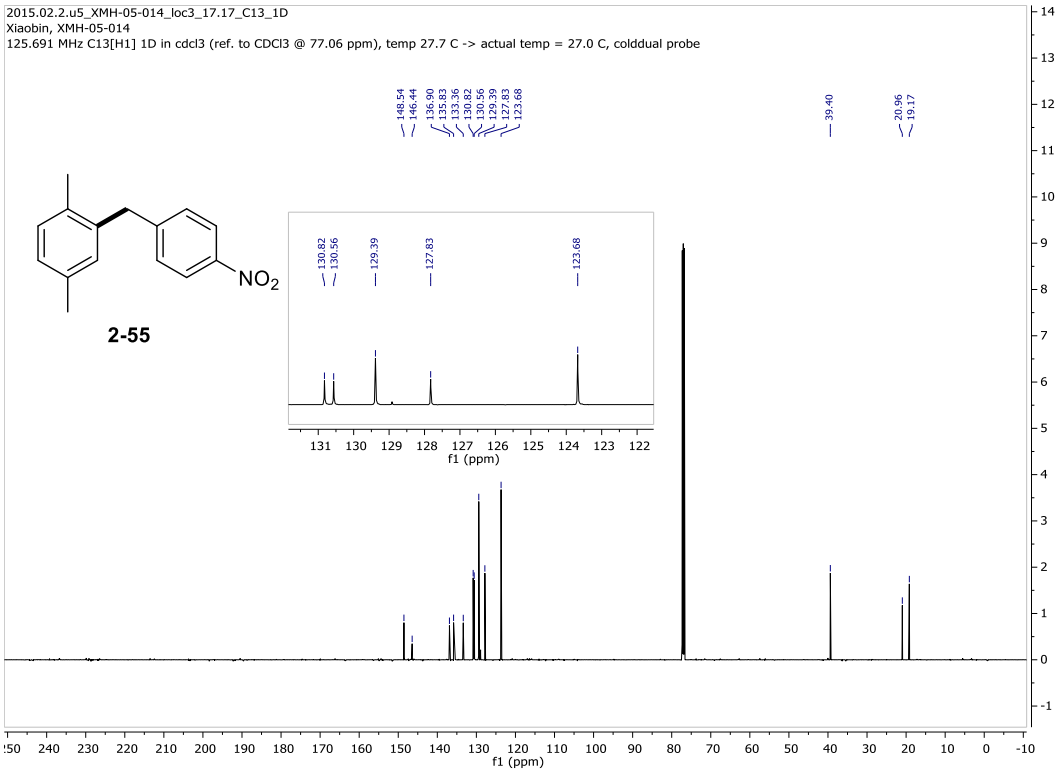
NMR spectra of **2-54**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



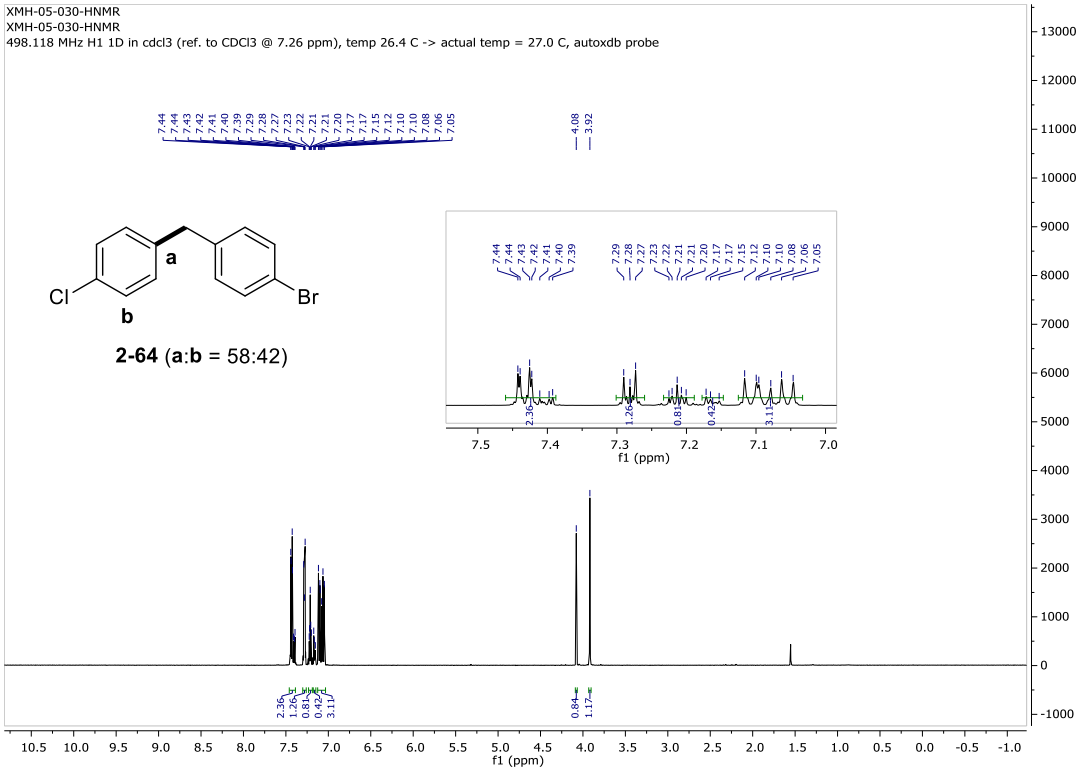


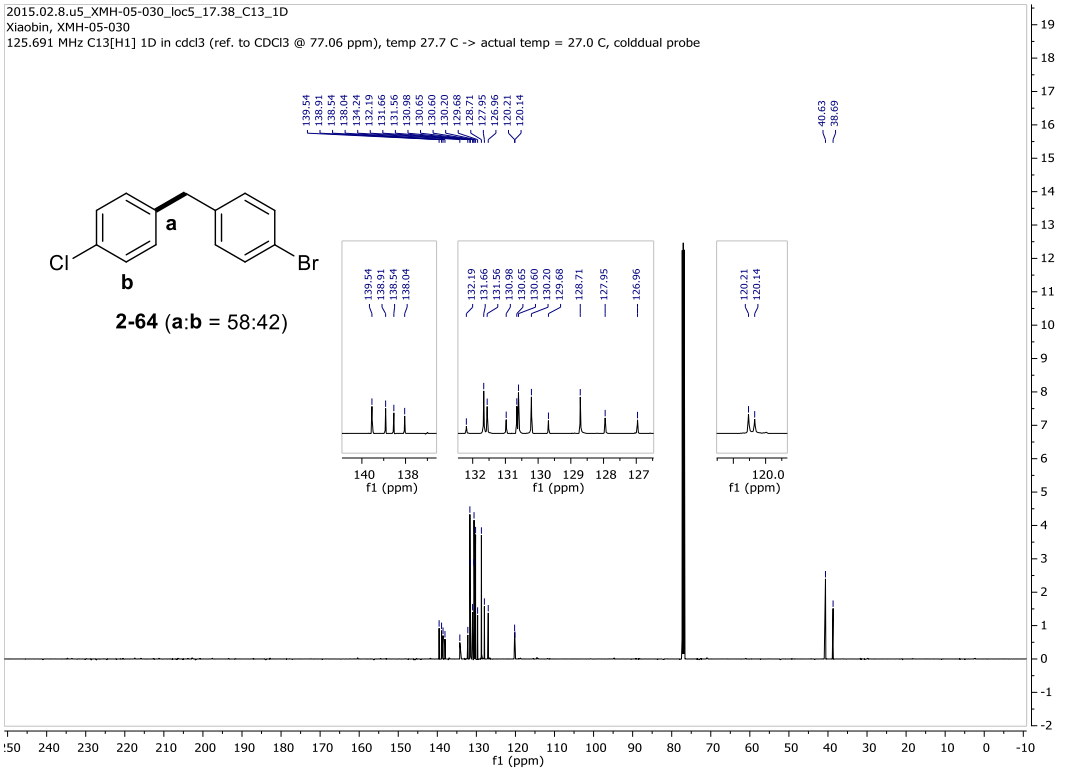
NMR spectra of **2-55**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



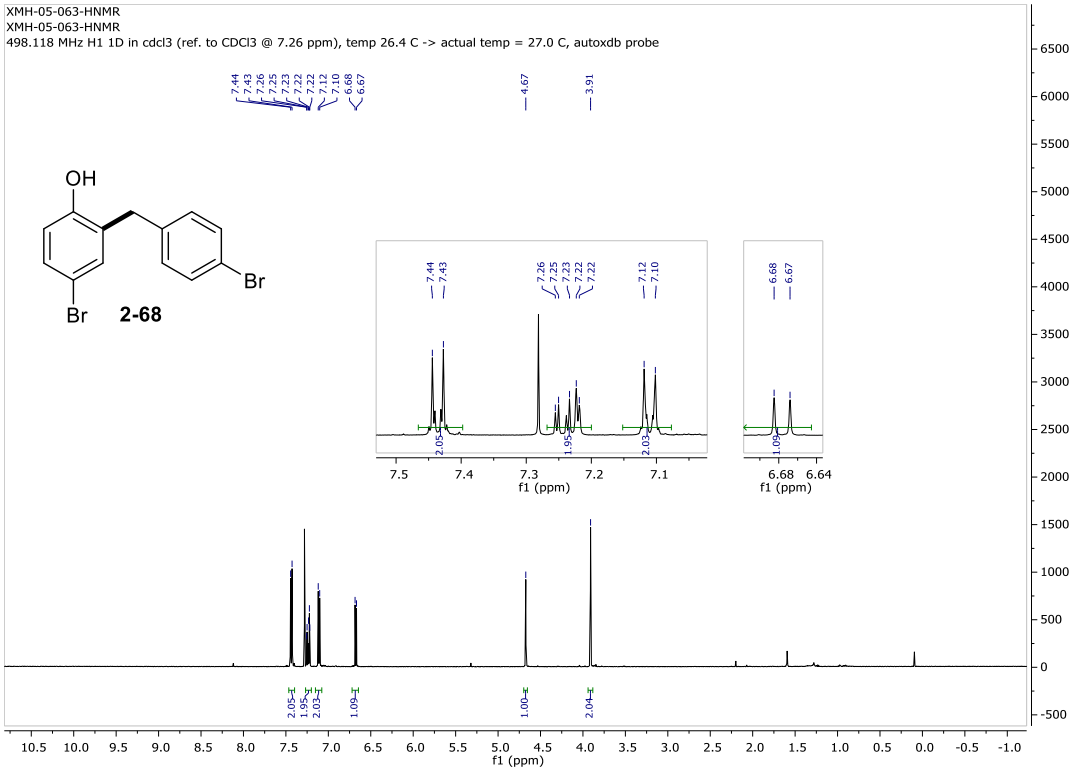


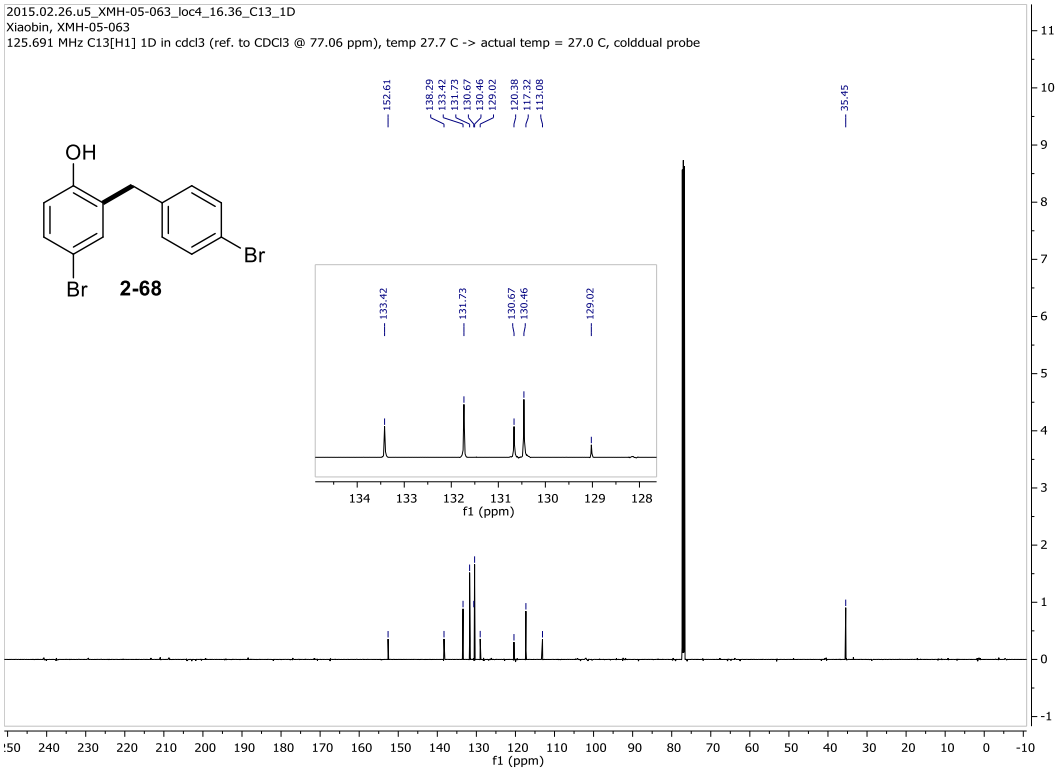
NMR spectra of **2-64**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



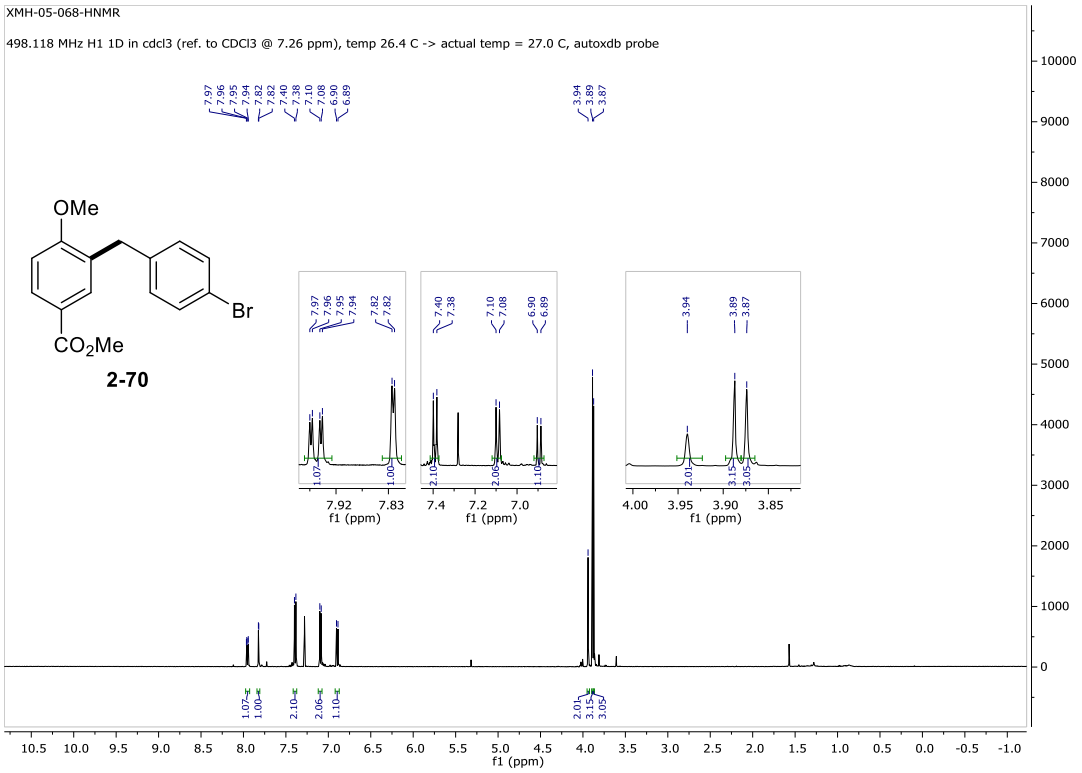


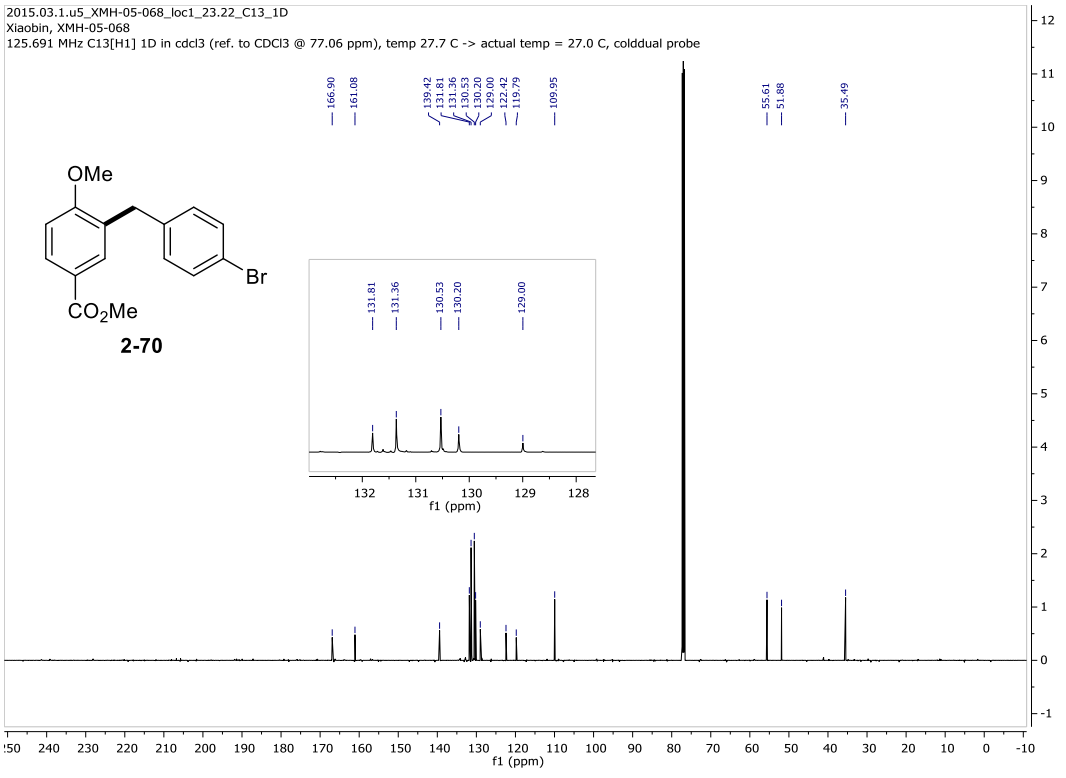
NMR spectra of **2-68**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



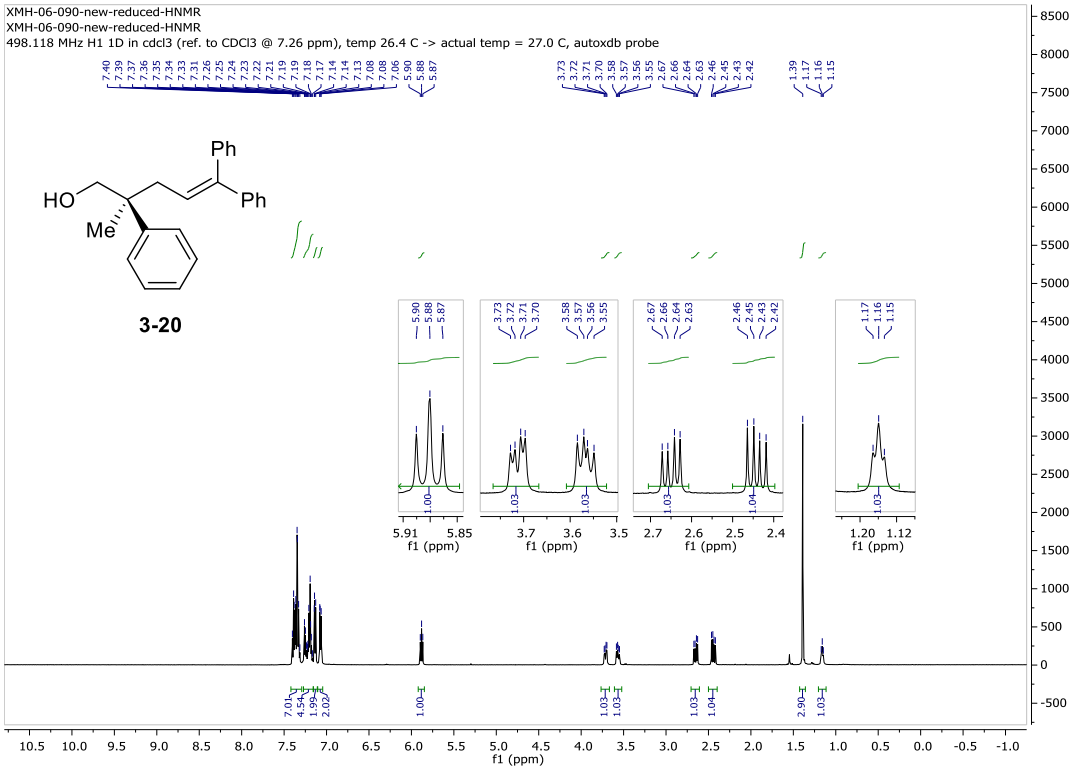


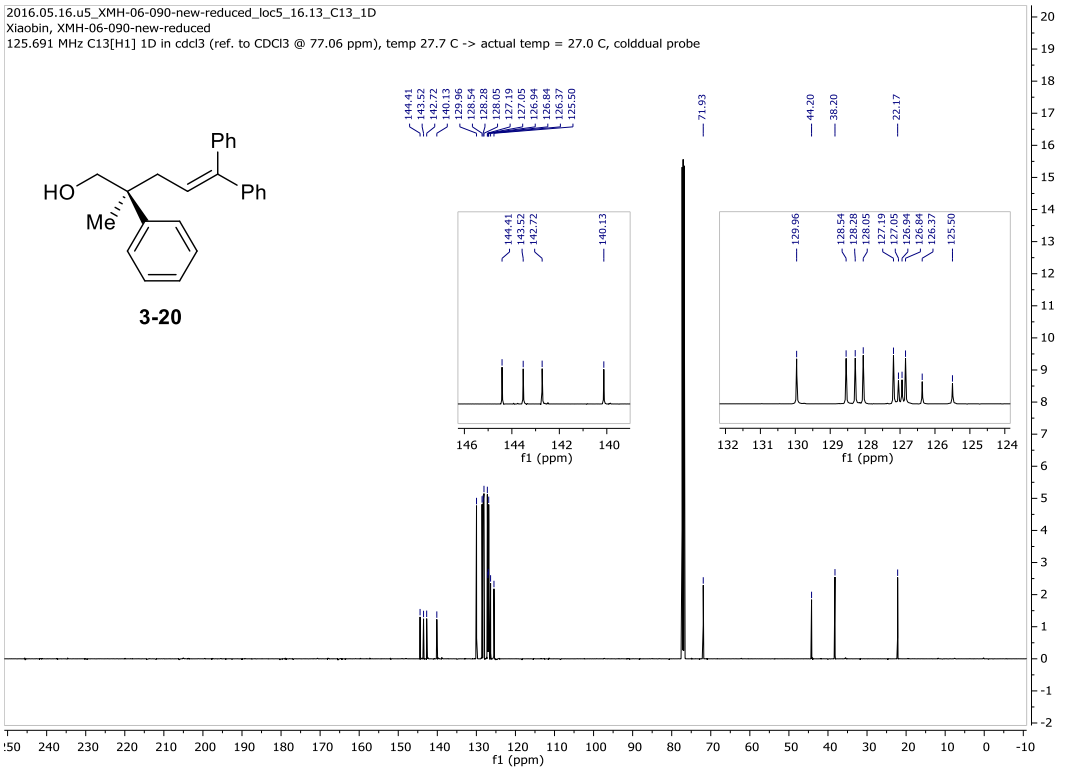
NMR spectra of **2-70**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



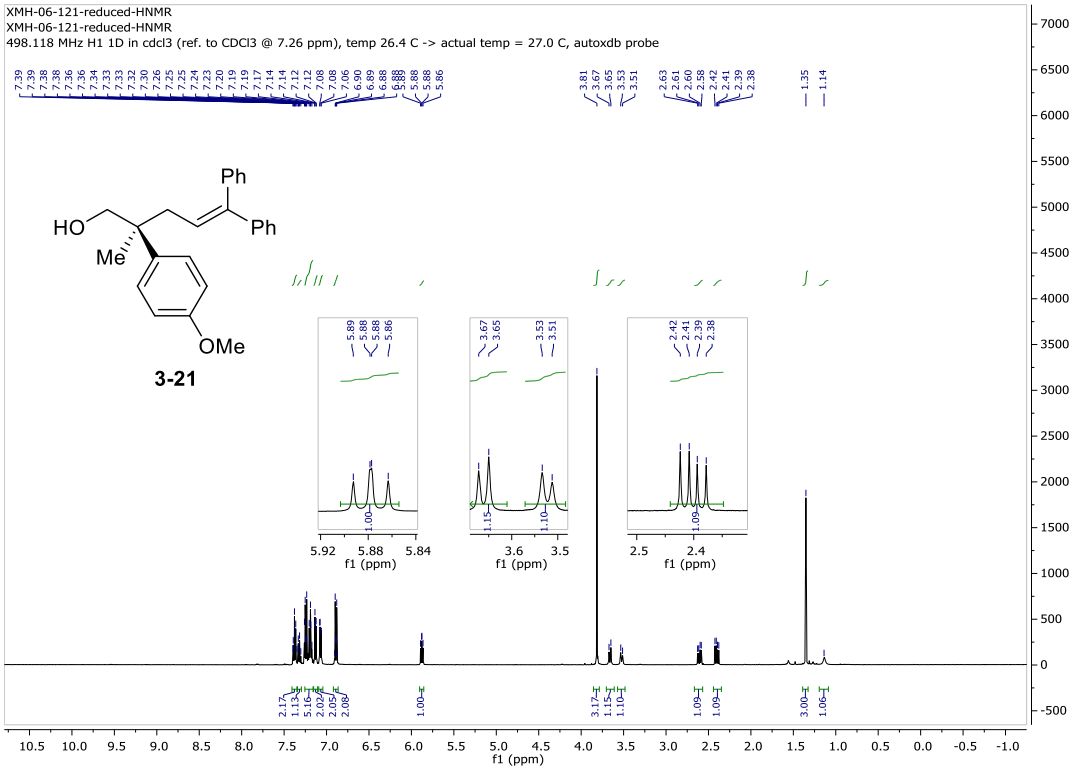


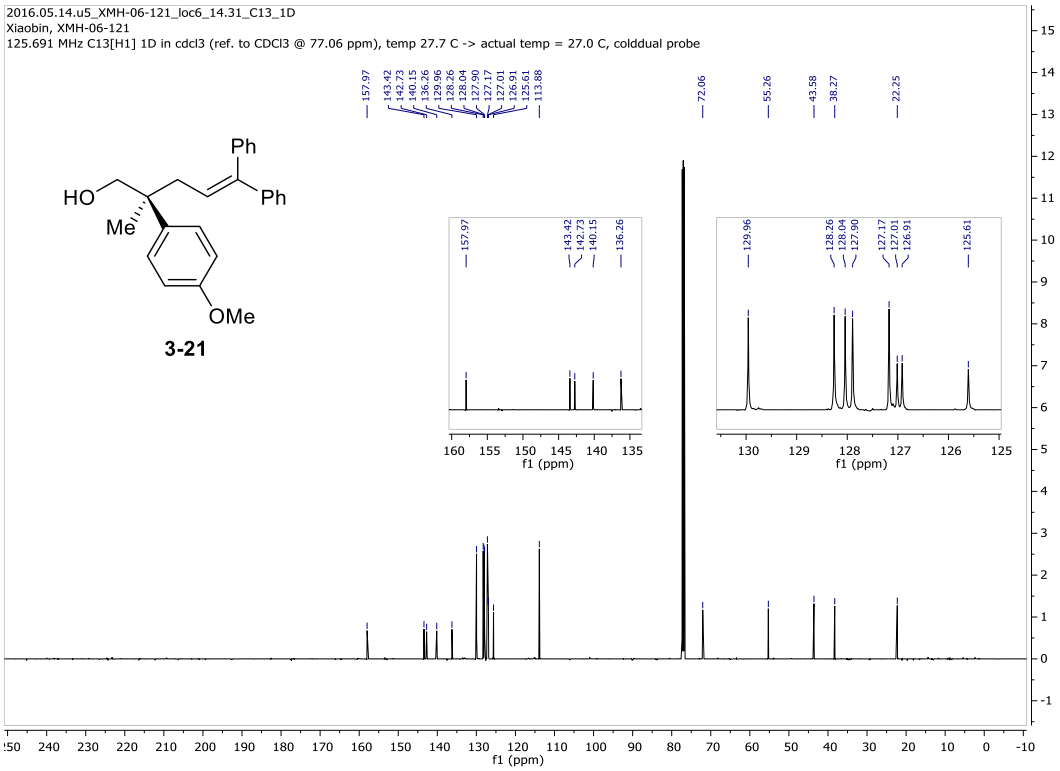
NMR spectra of **3-20**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



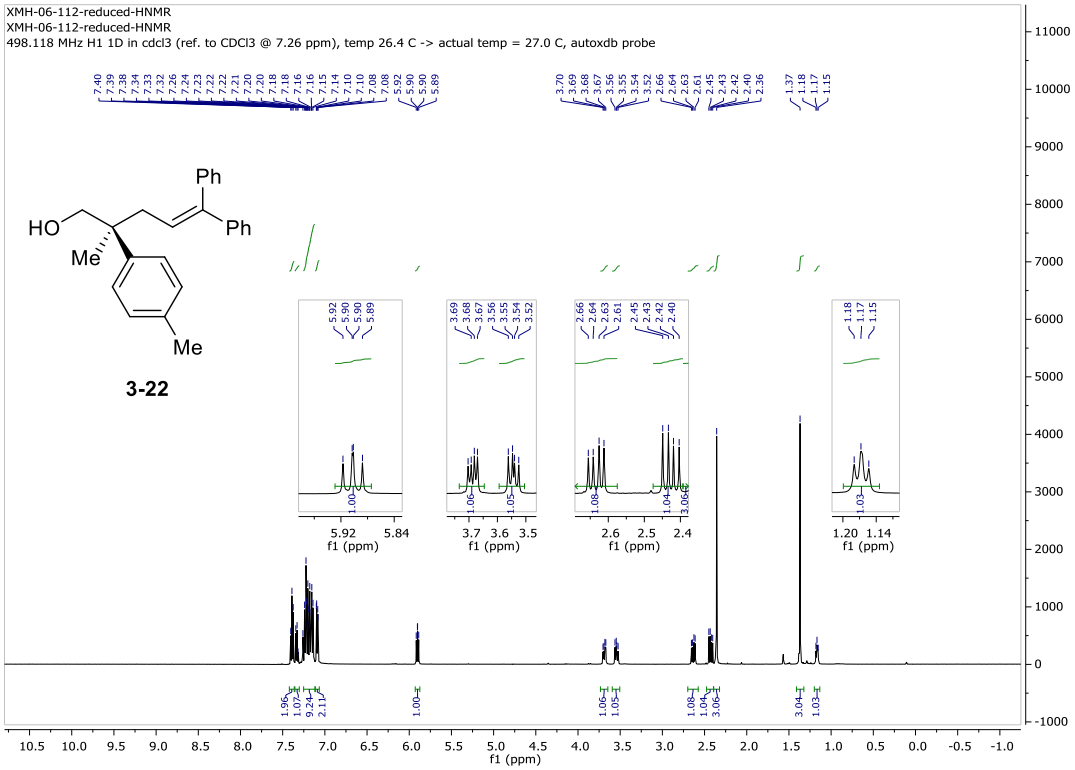


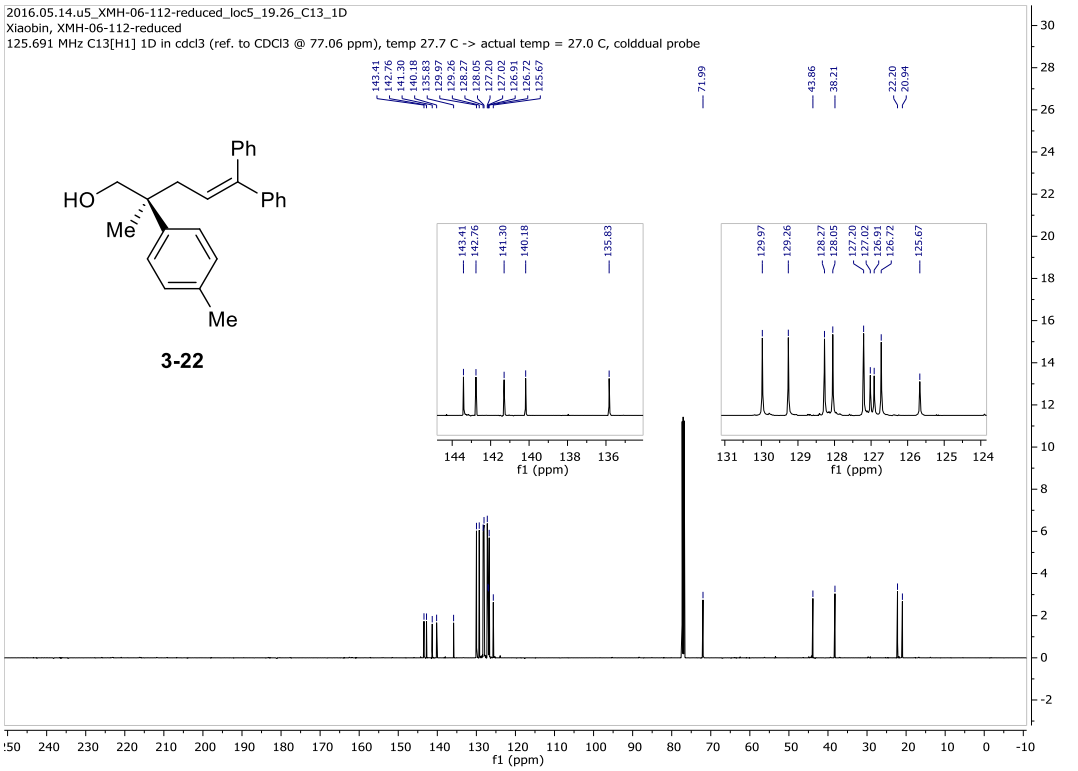
NMR spectra of **3-21**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



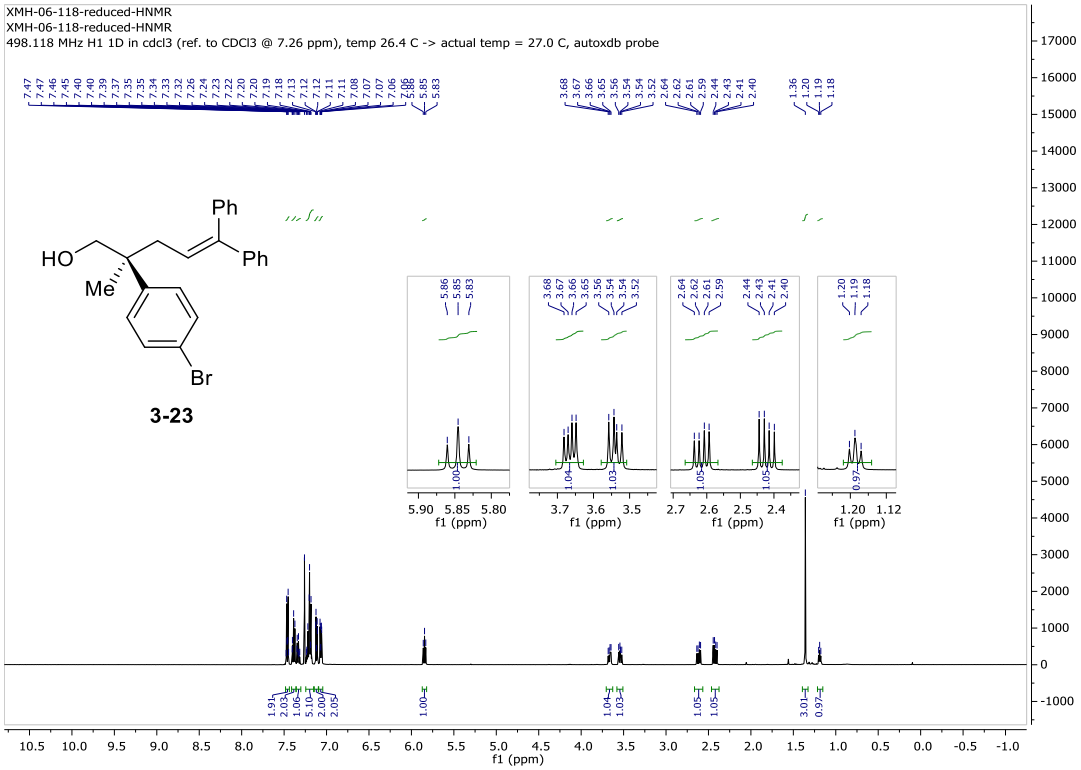


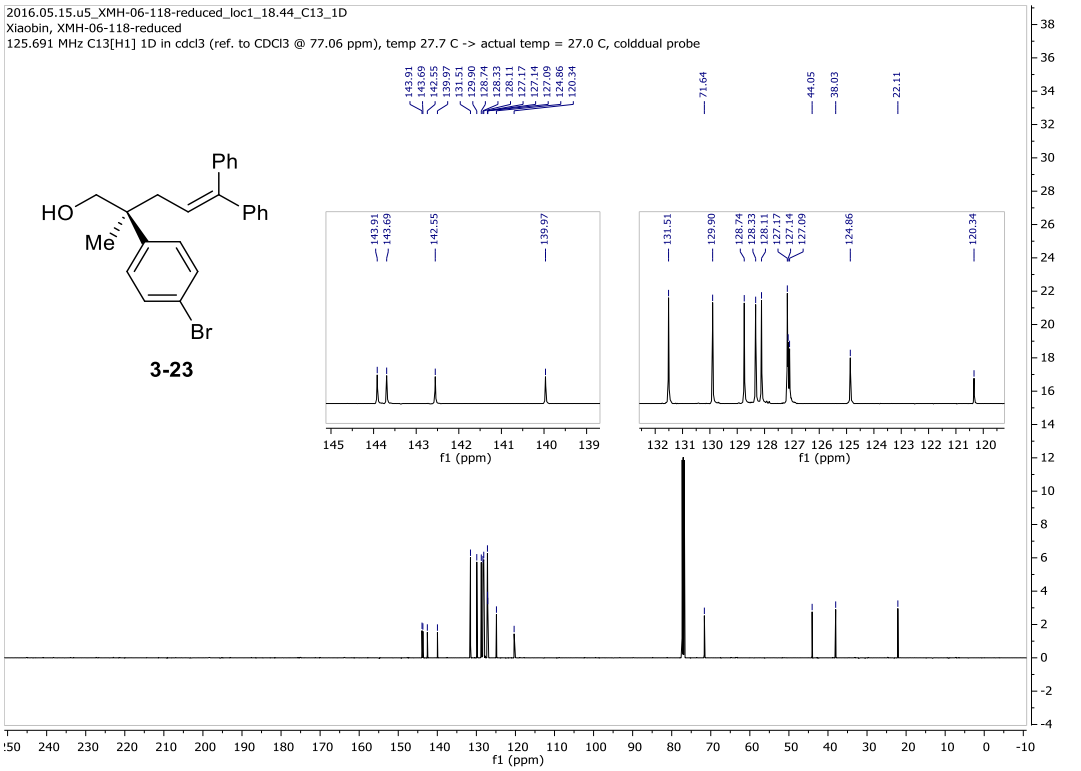
NMR spectra of **3-22**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



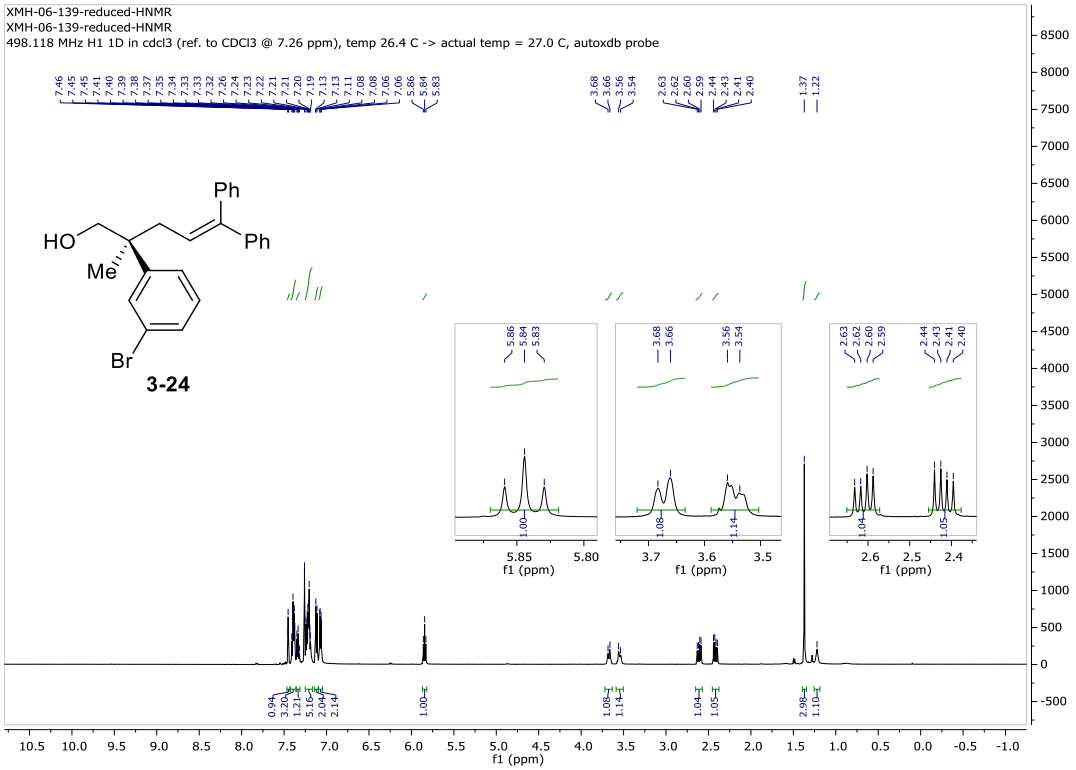


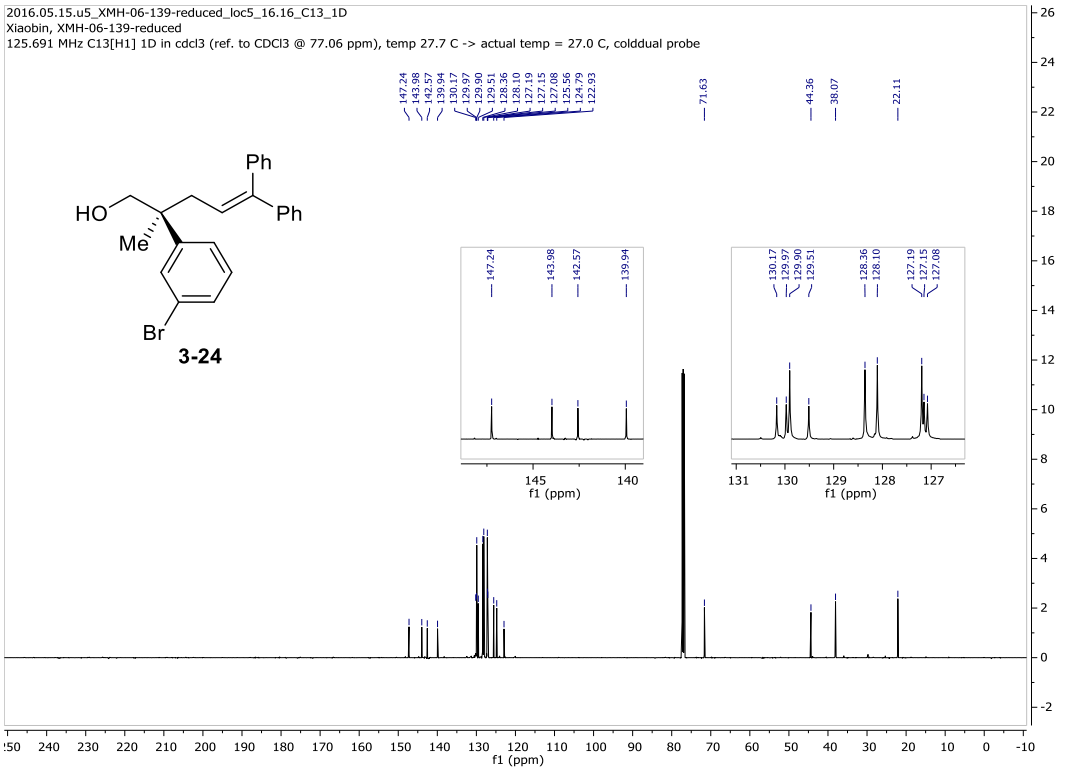
NMR spectra of **3-23**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



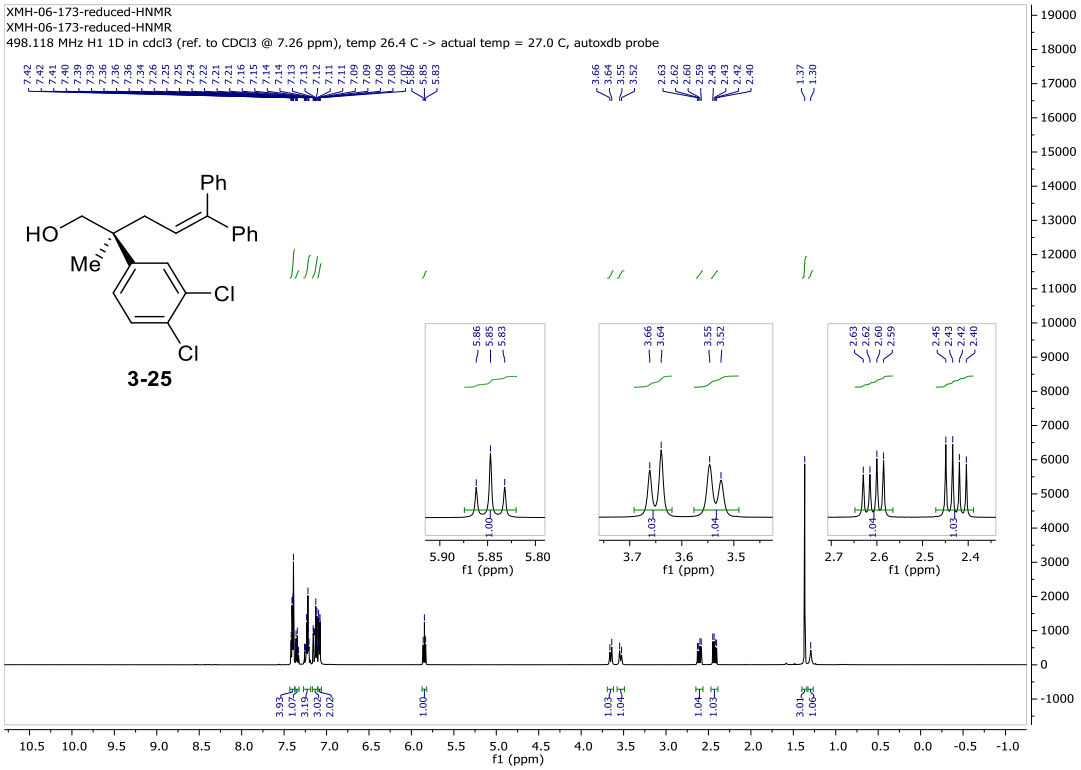


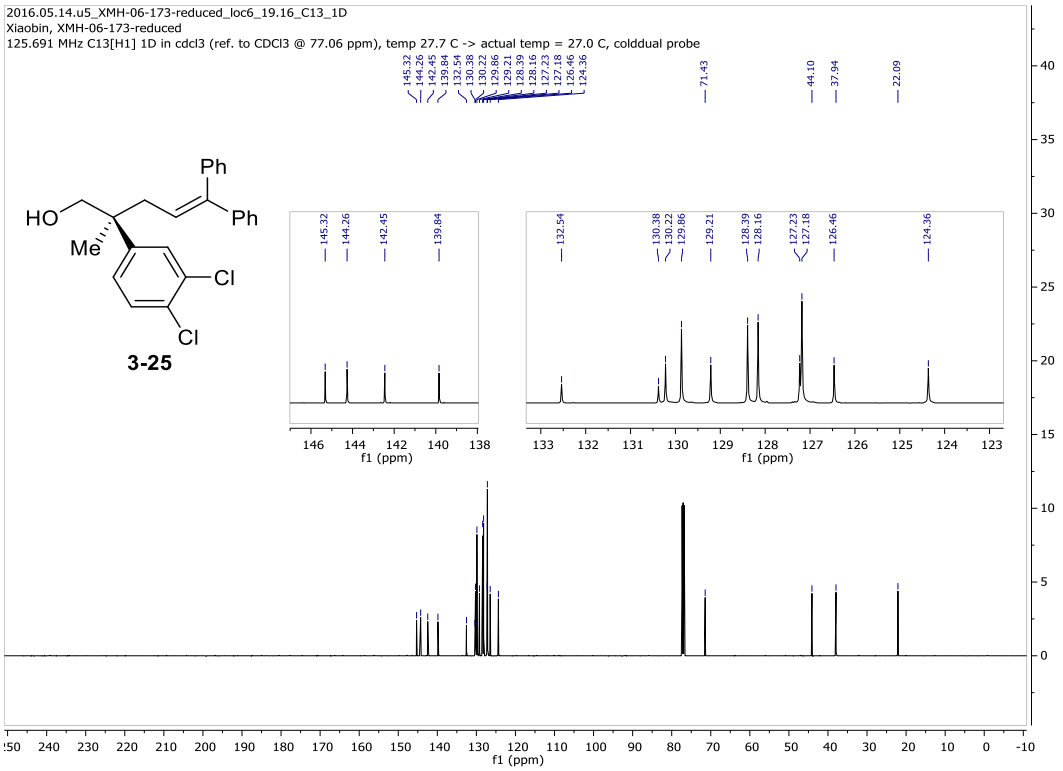
NMR spectra of **3-24**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



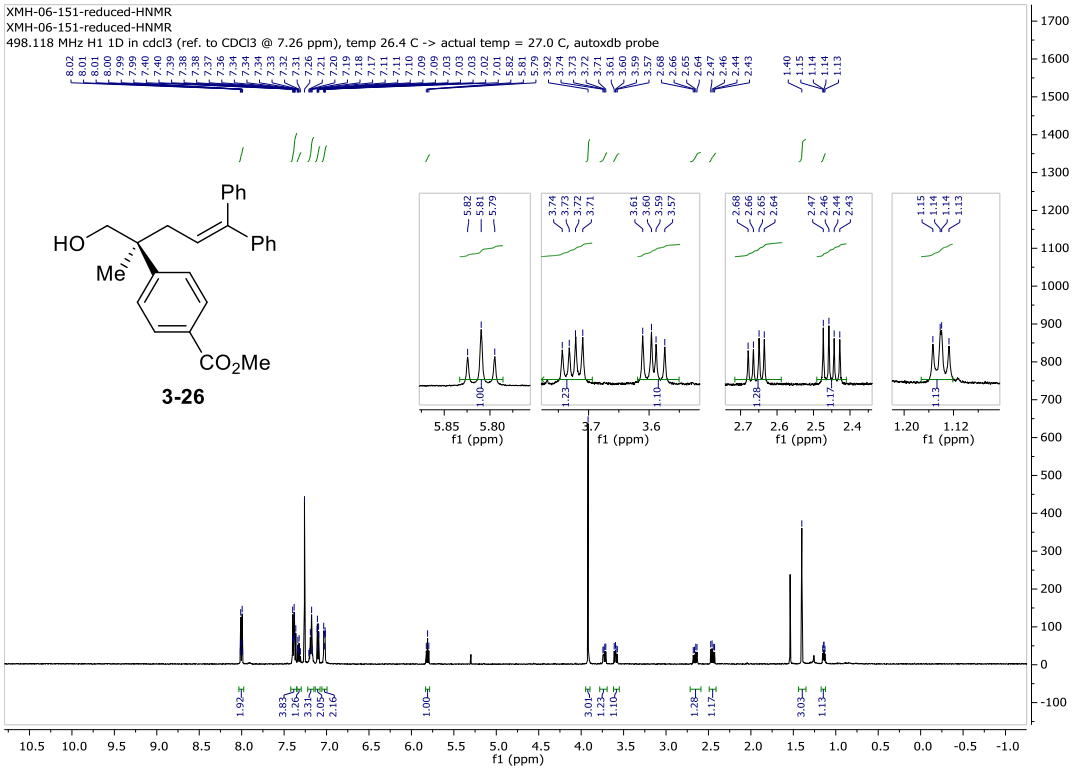


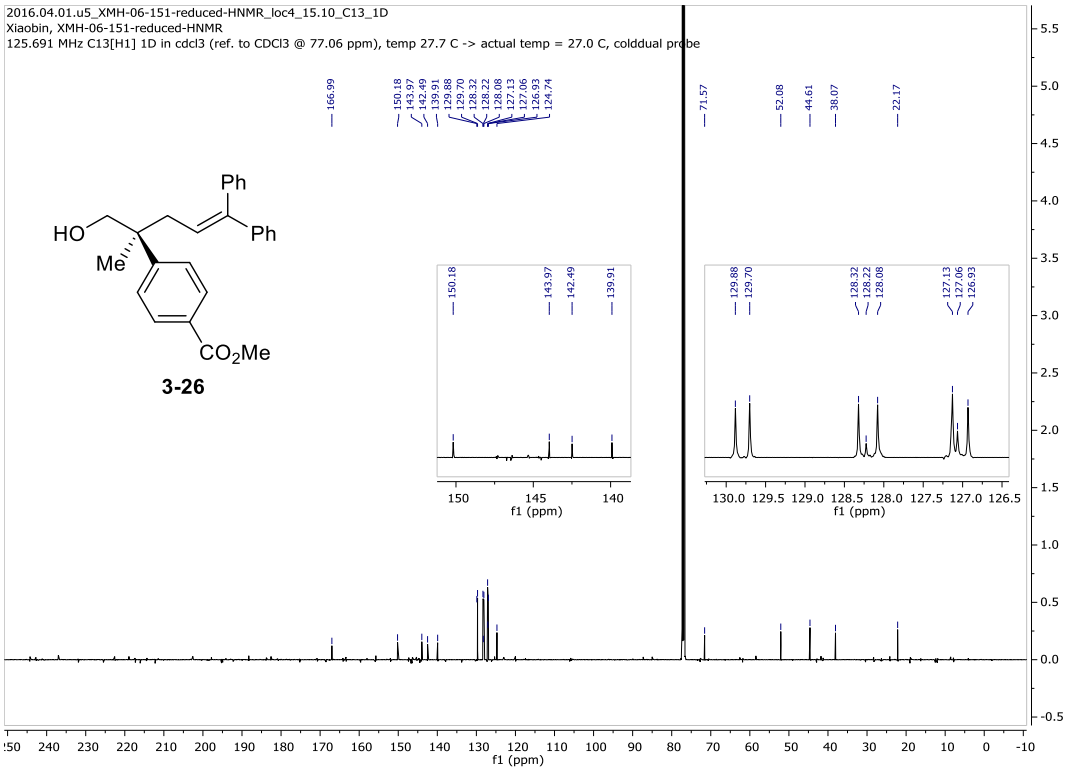
NMR spectra of **3-25**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



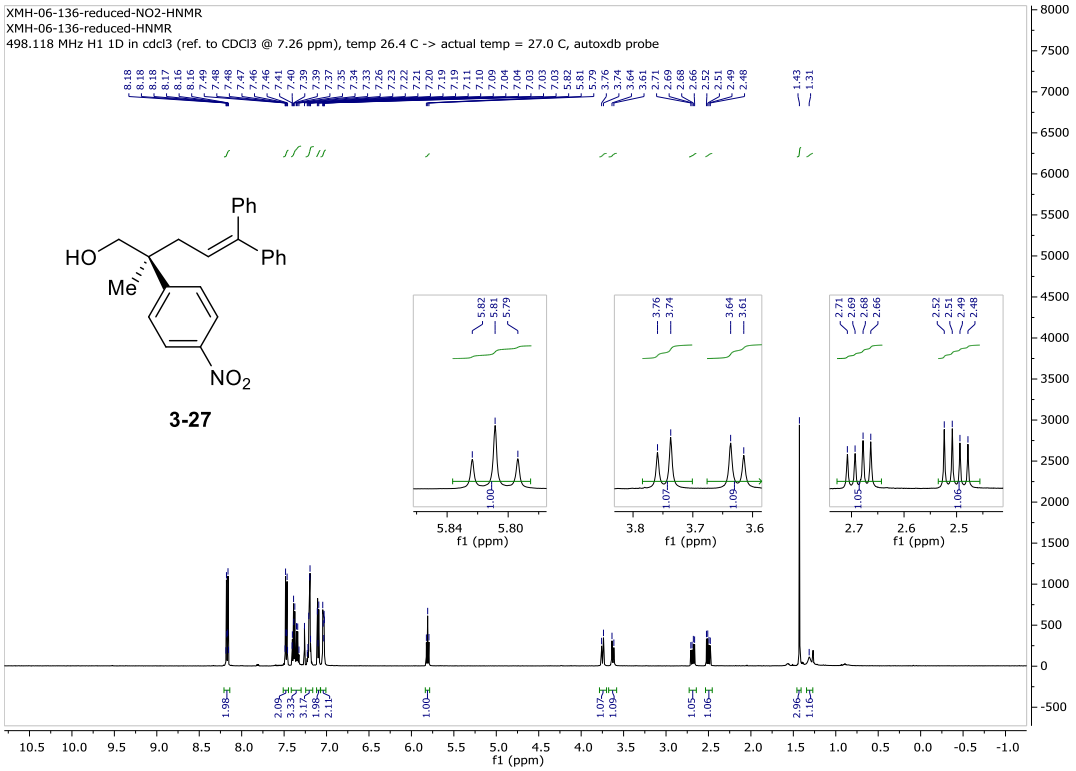


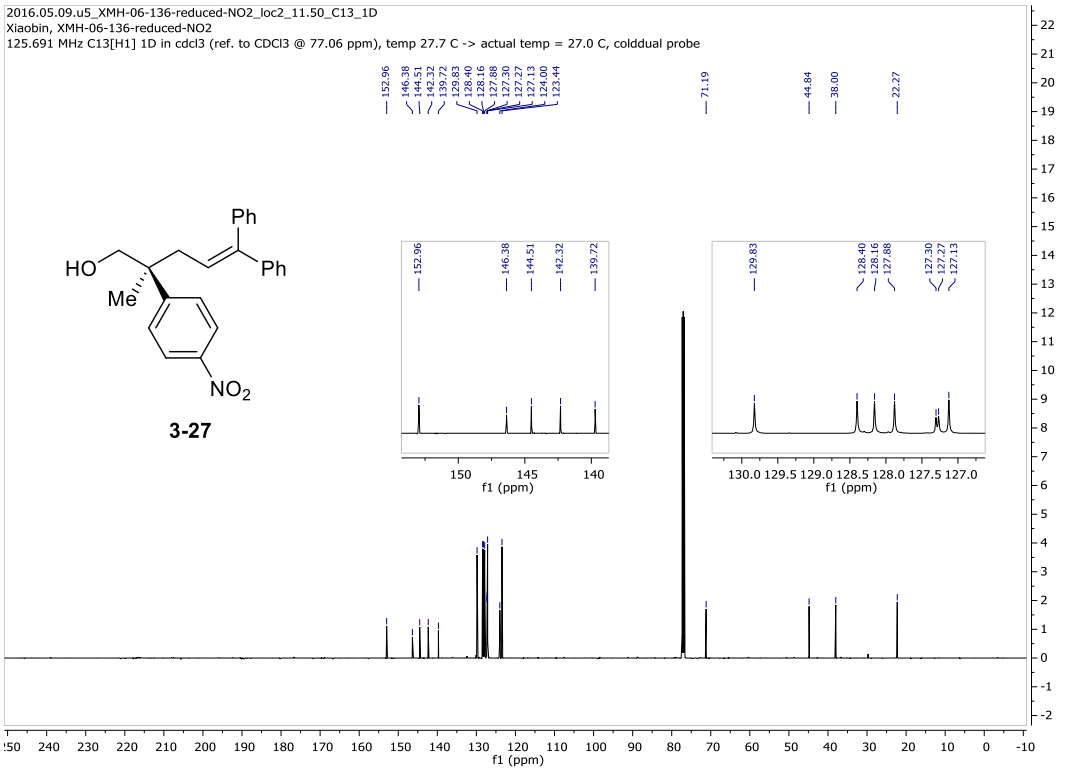
NMR spectra of **3-26**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



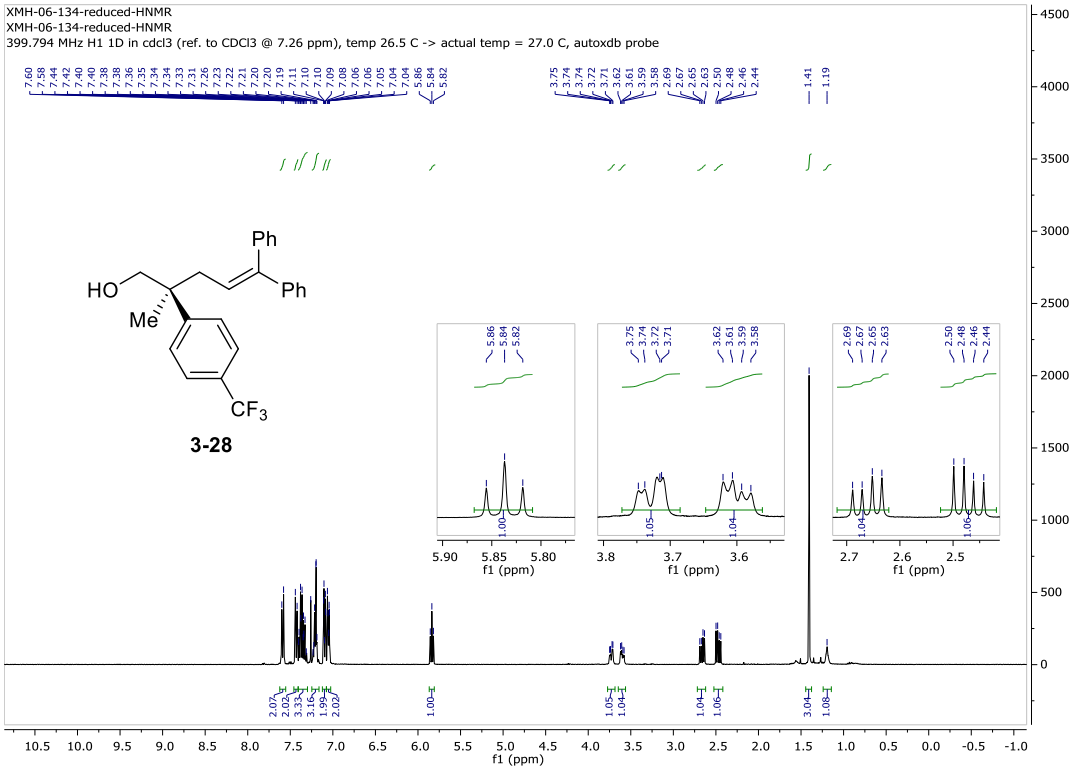


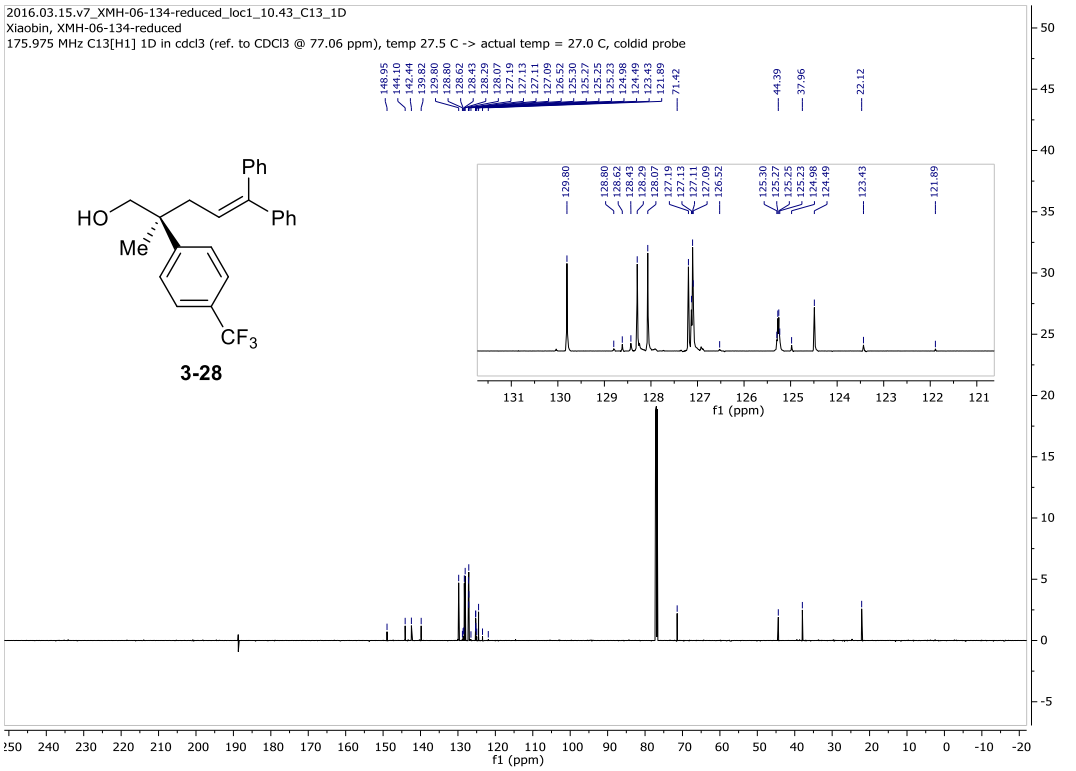
NMR spectra of **4-27**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



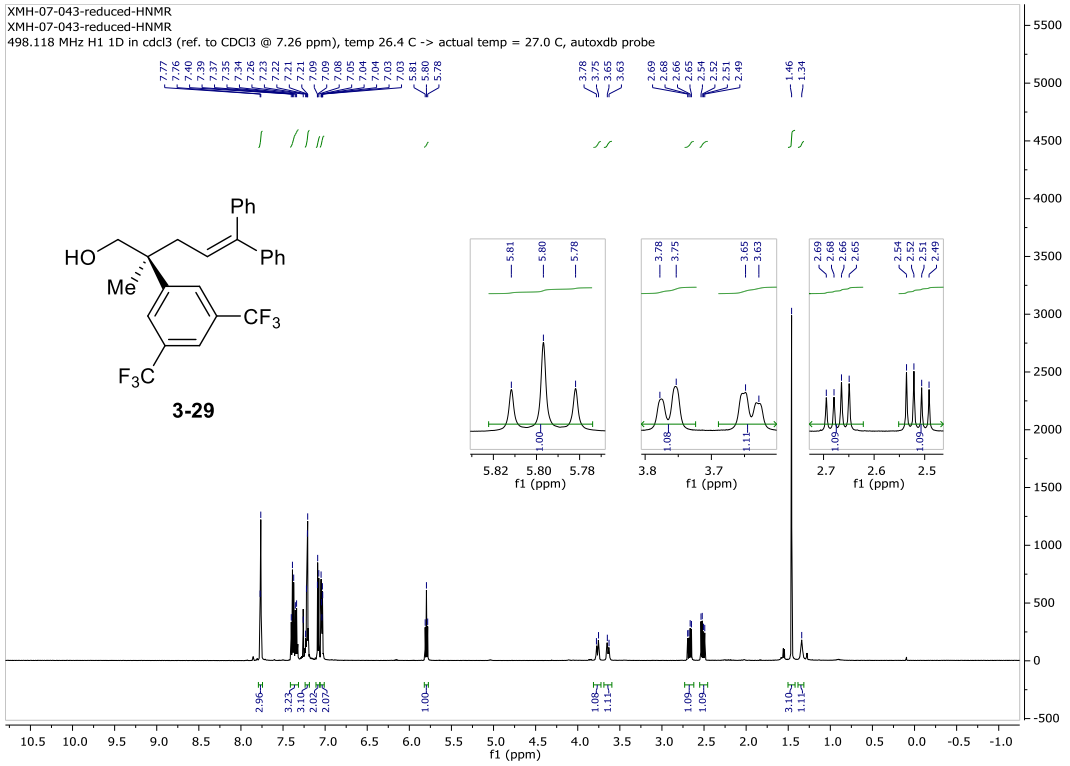


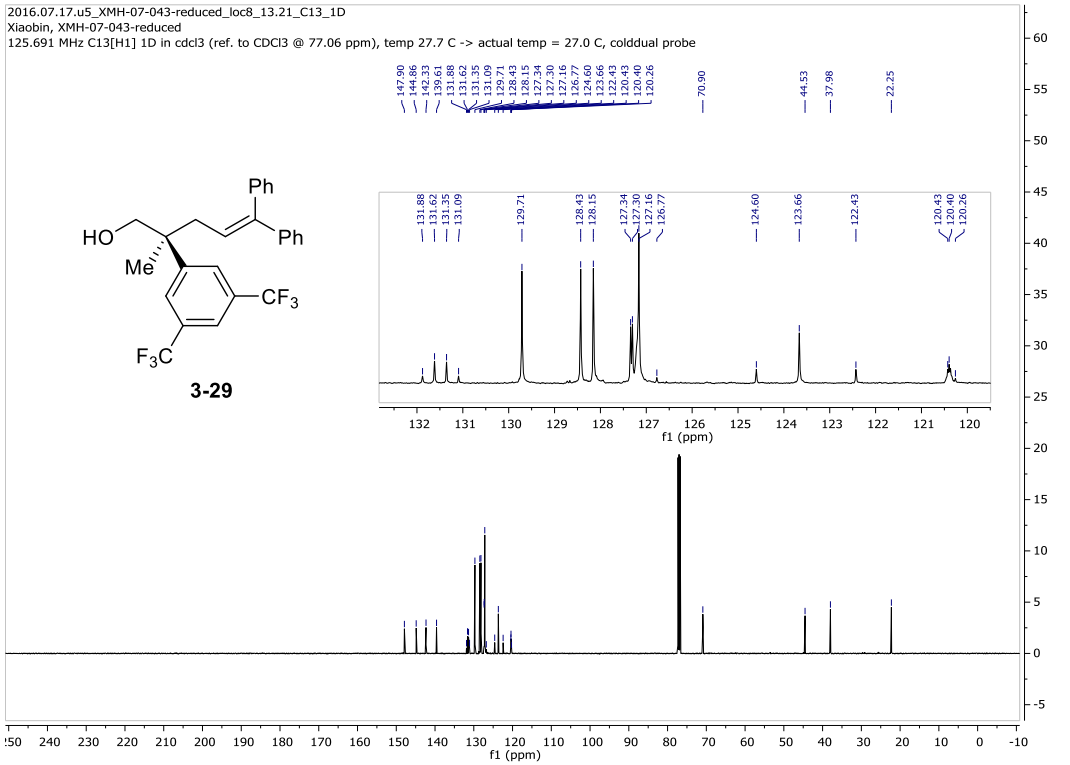
NMR spectra of **4-28**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 175 MHz)



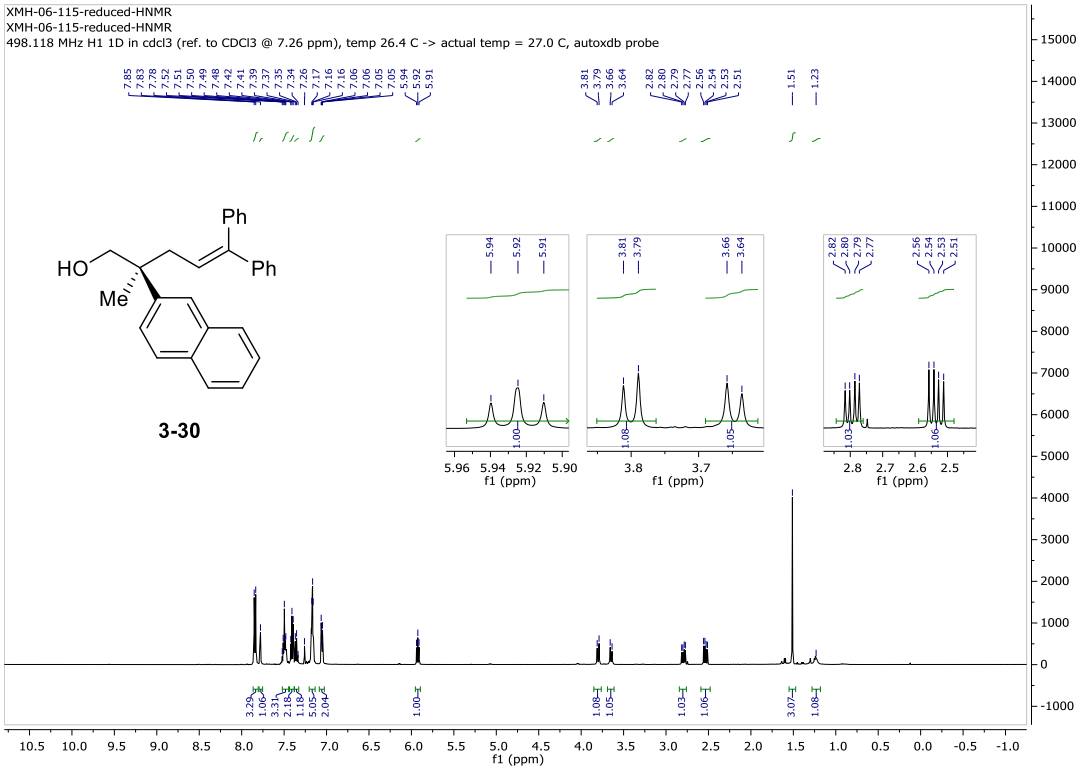


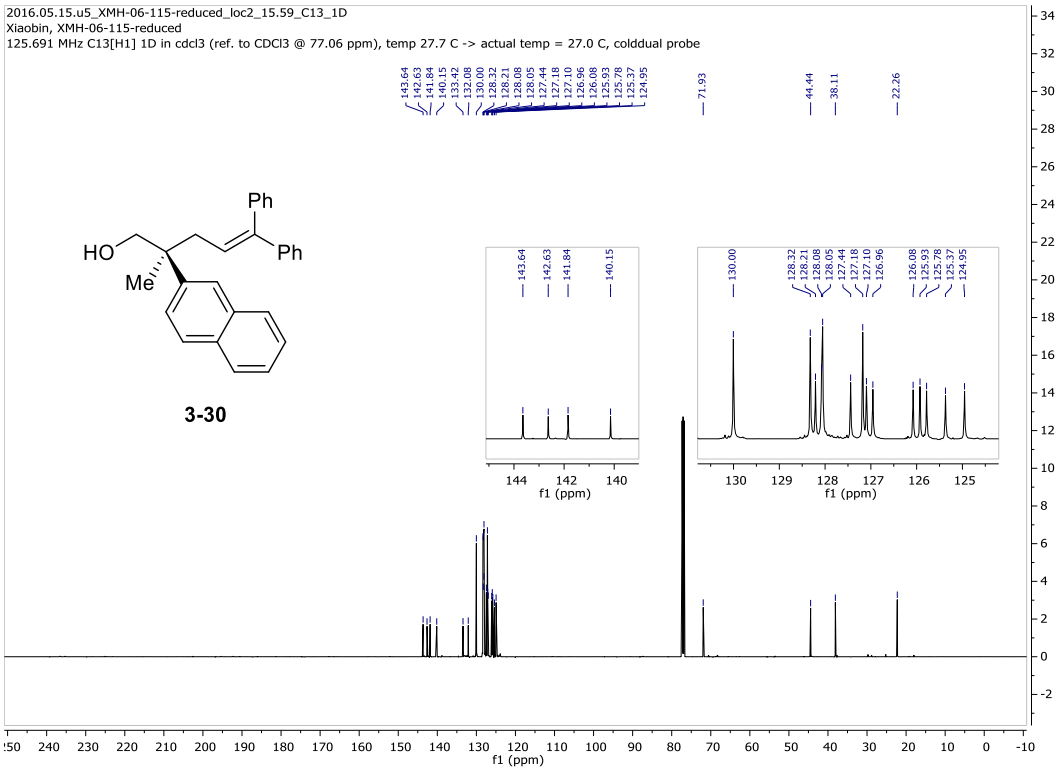
NMR spectra of **3-29**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



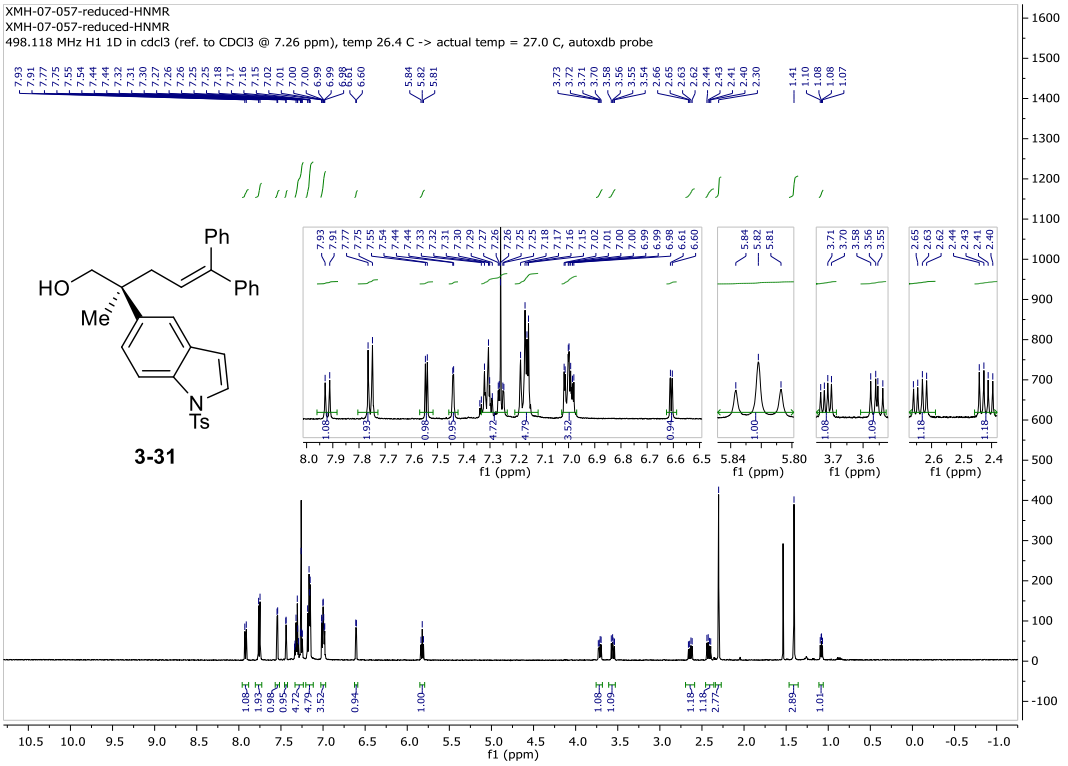


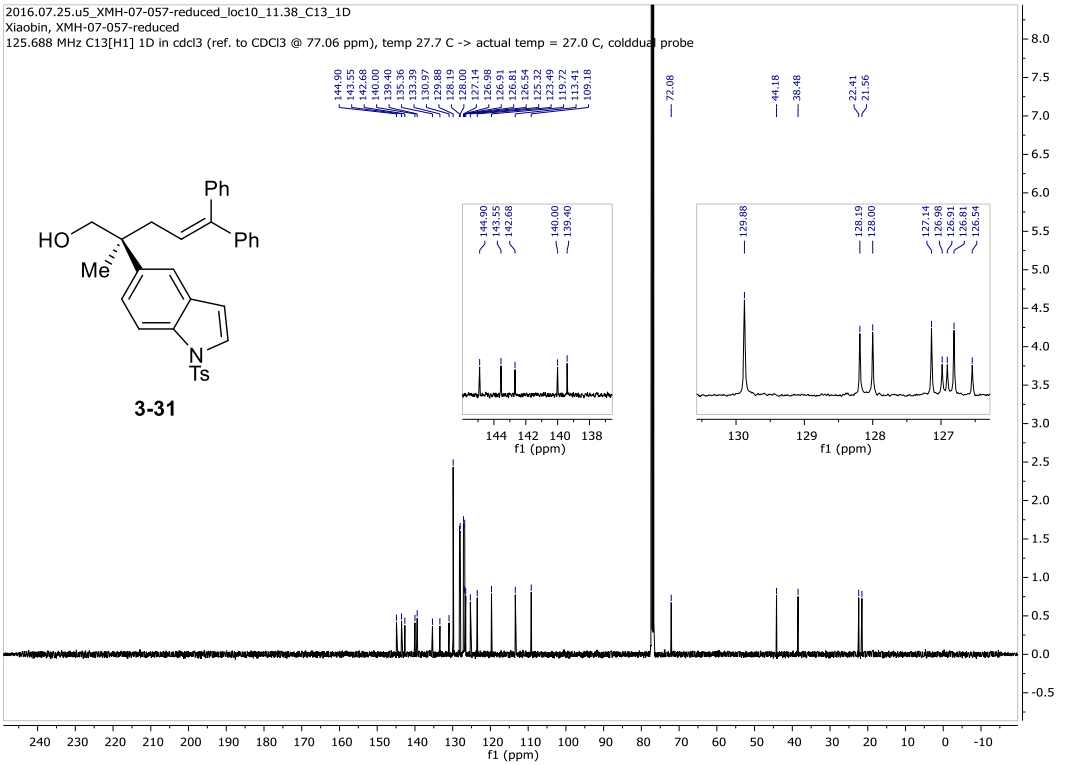
NMR spectra of **3-30**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



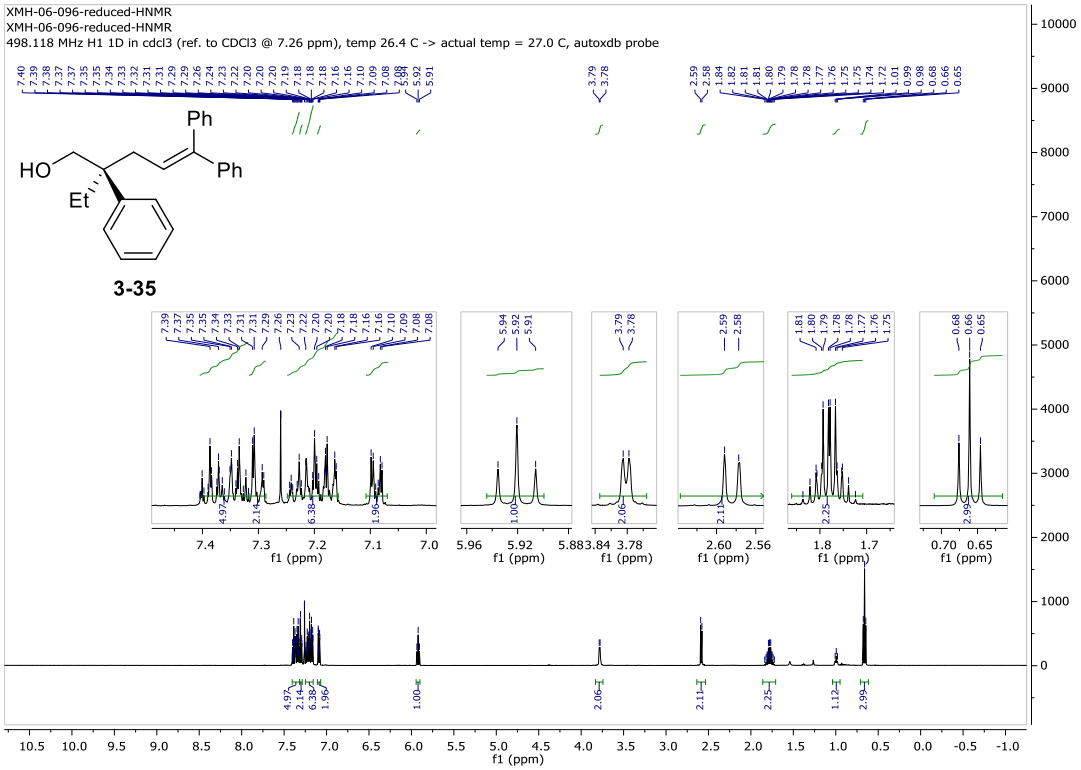


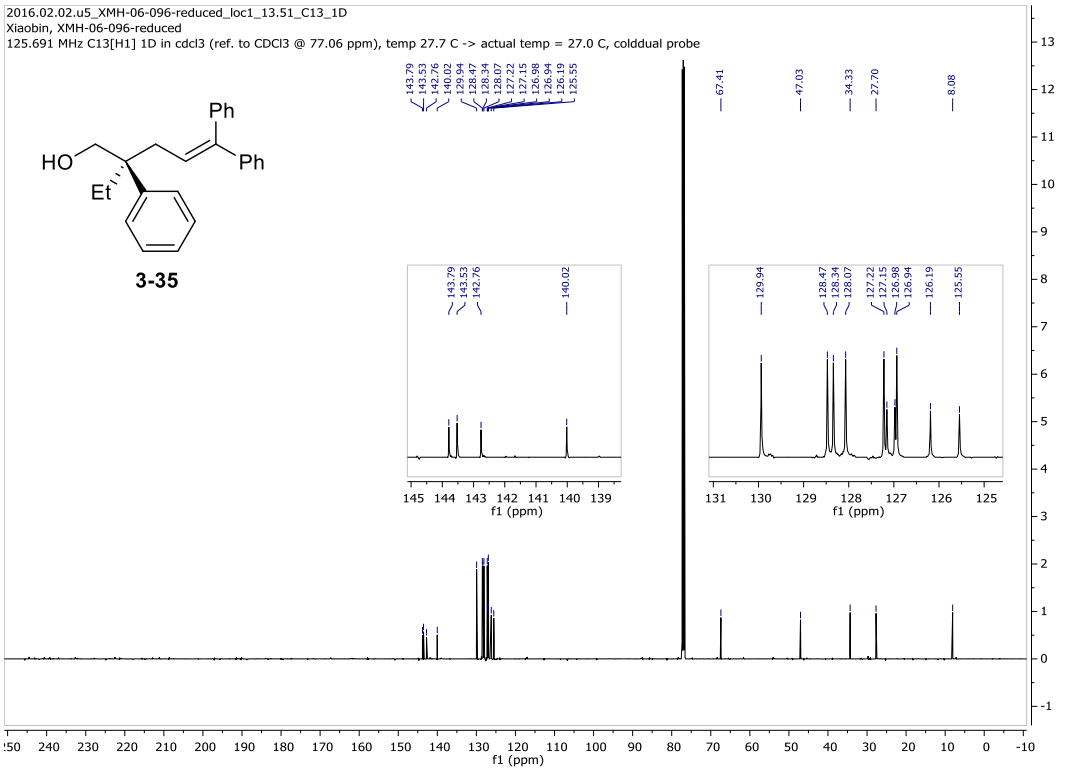
NMR spectra of **3-31**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



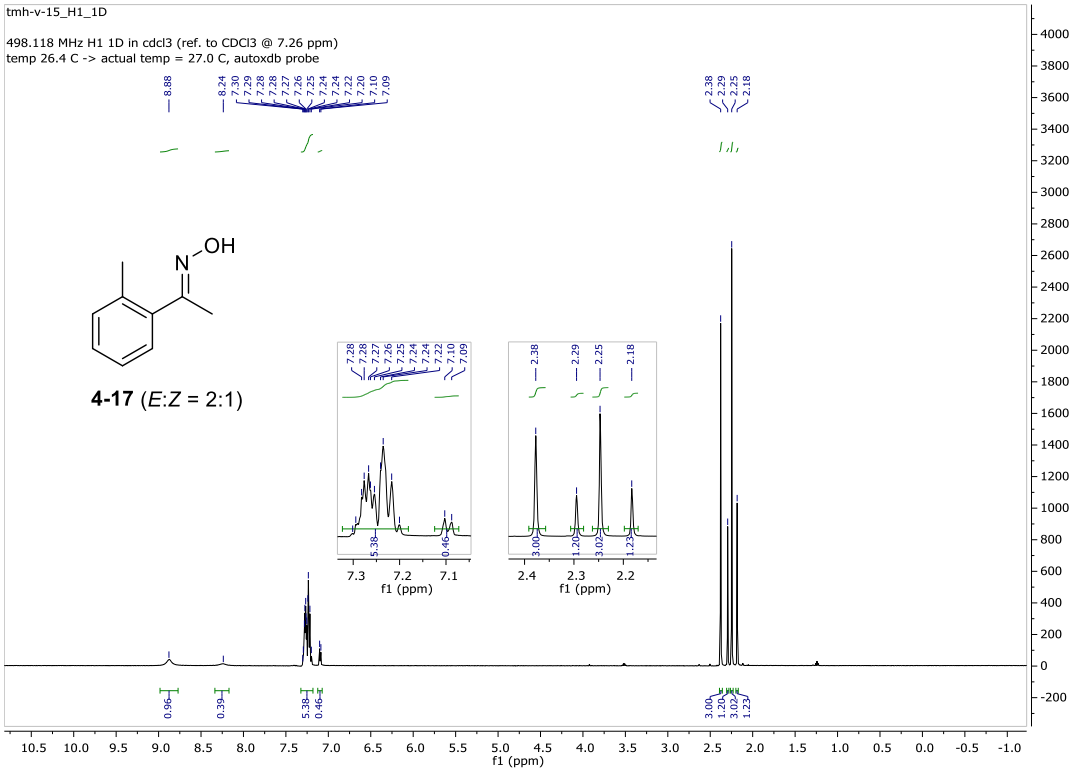


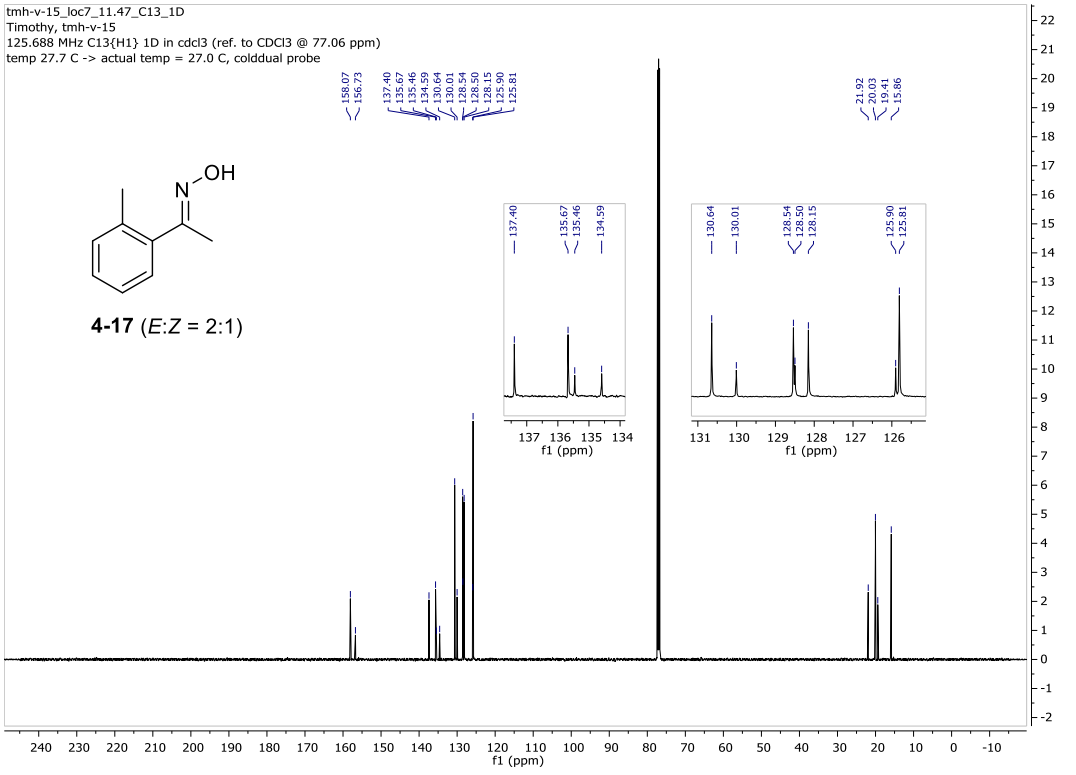
NMR spectra of **3-35**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



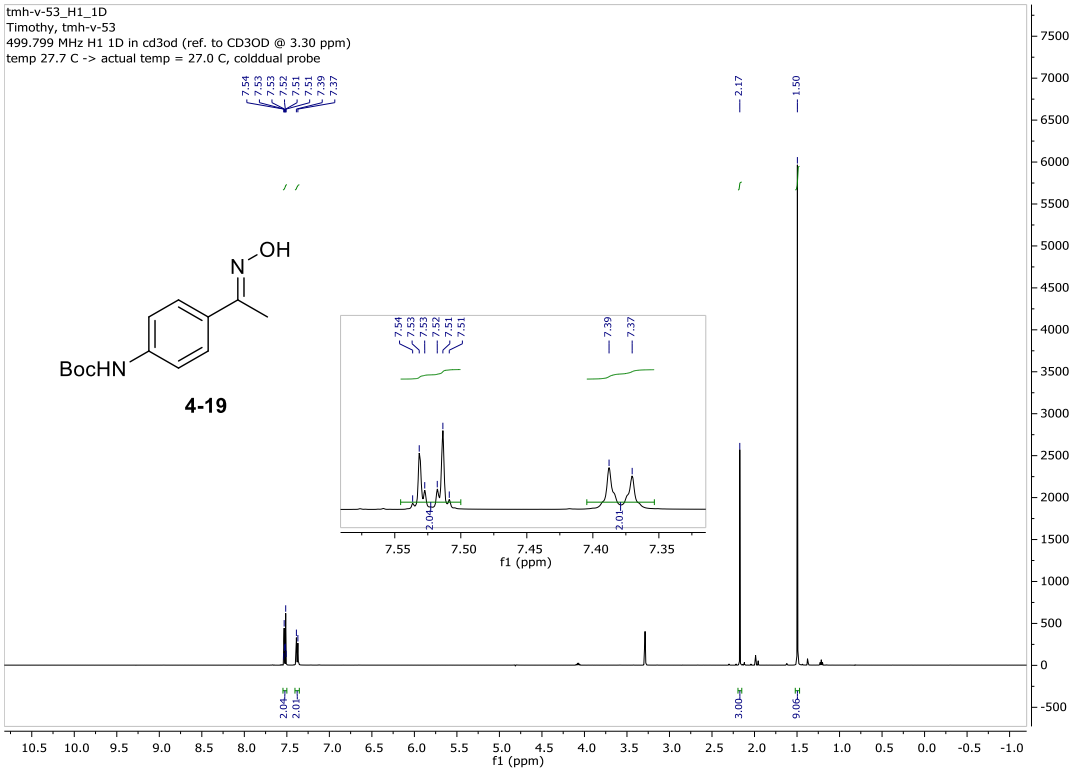


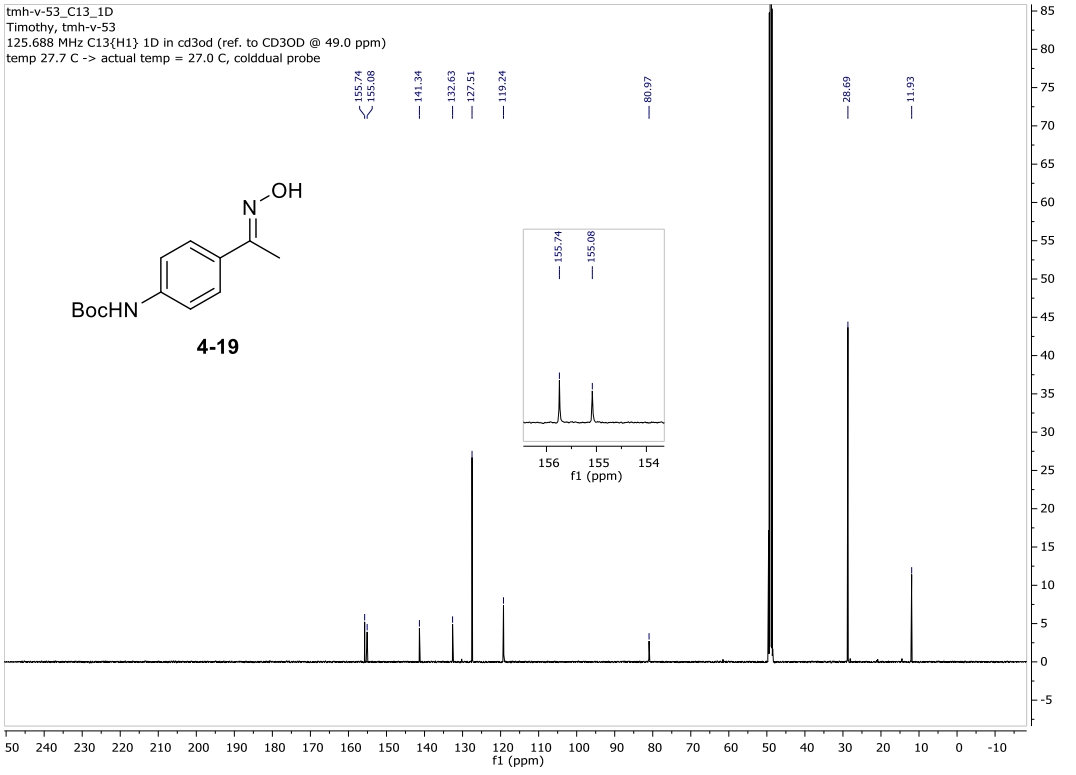
NMR spectra of **4-17**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



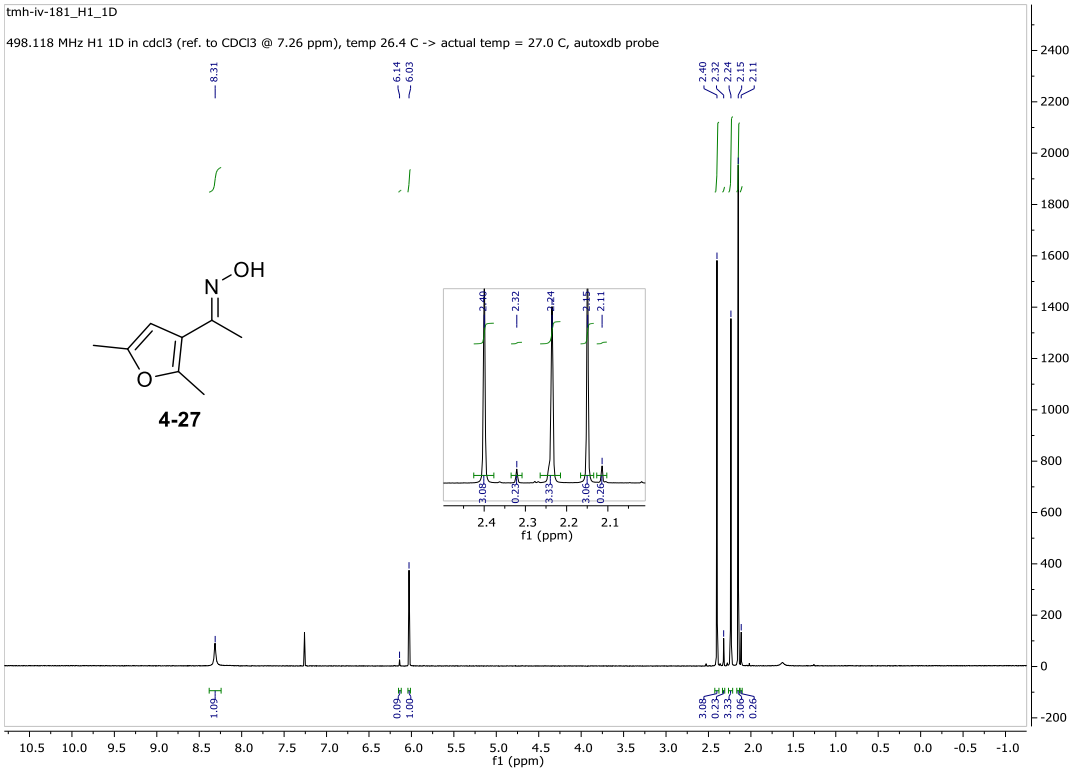


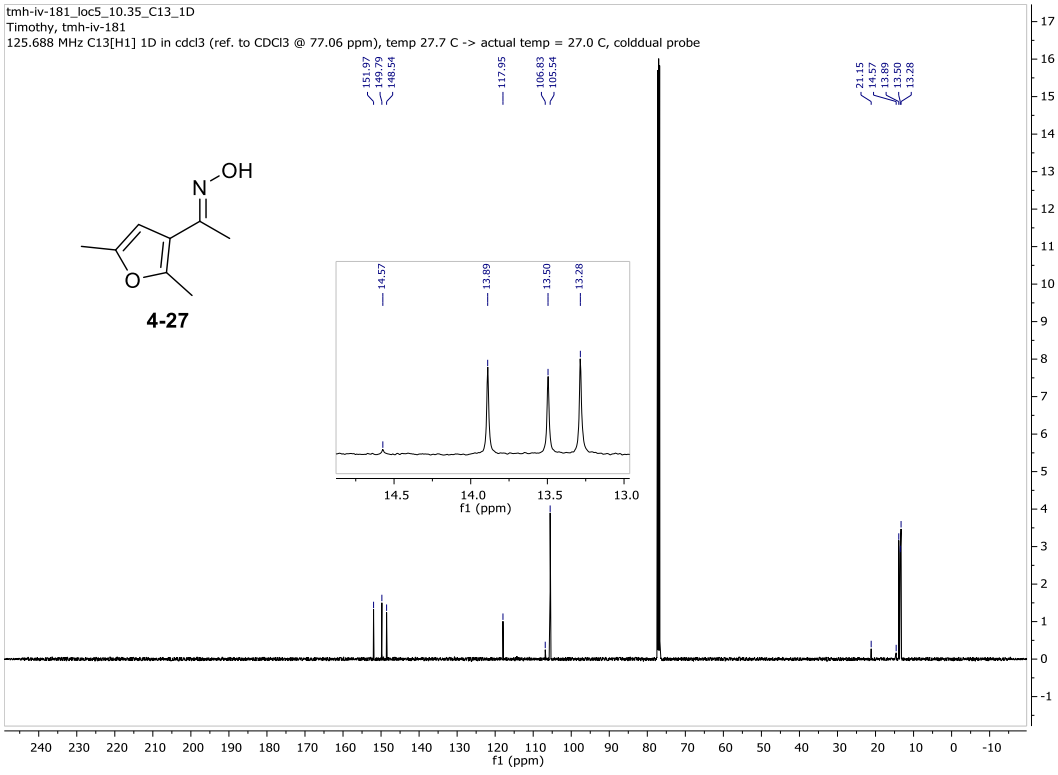
NMR spectra of **4-19**. Top: ^{1}H NMR (CD_3OD, 500 MHz). Bottom: ^{13}C NMR (CD_3OD, 125 MHz)



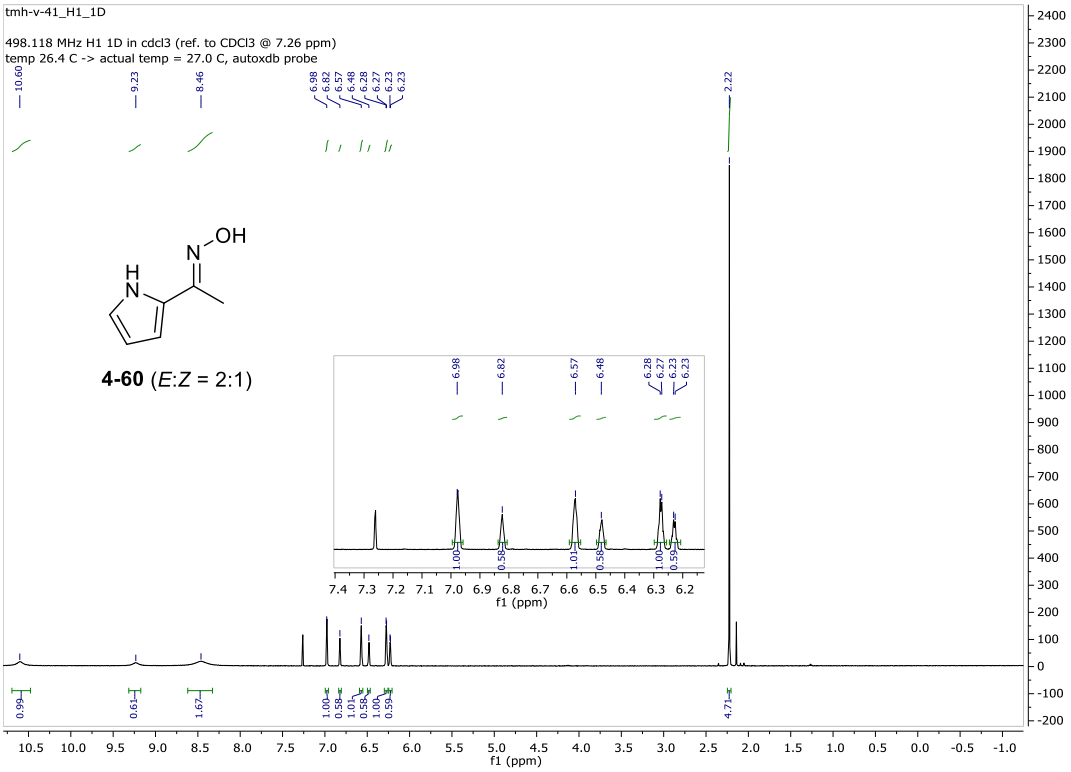


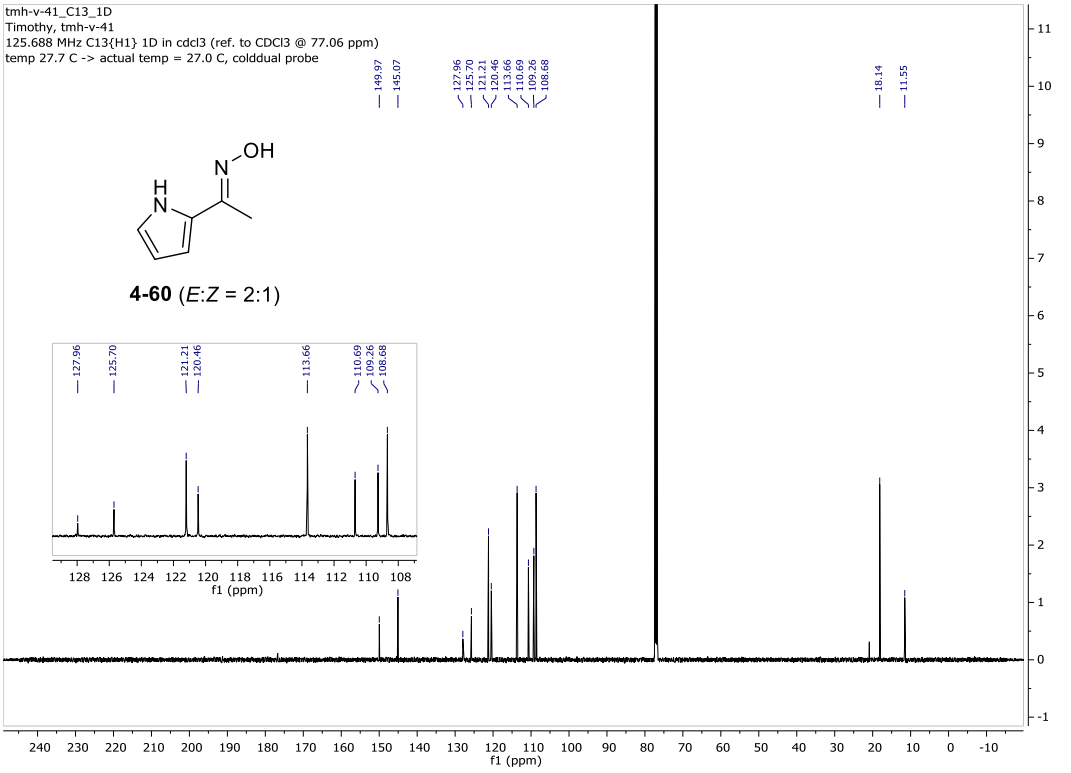
NMR spectra of **4-27**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



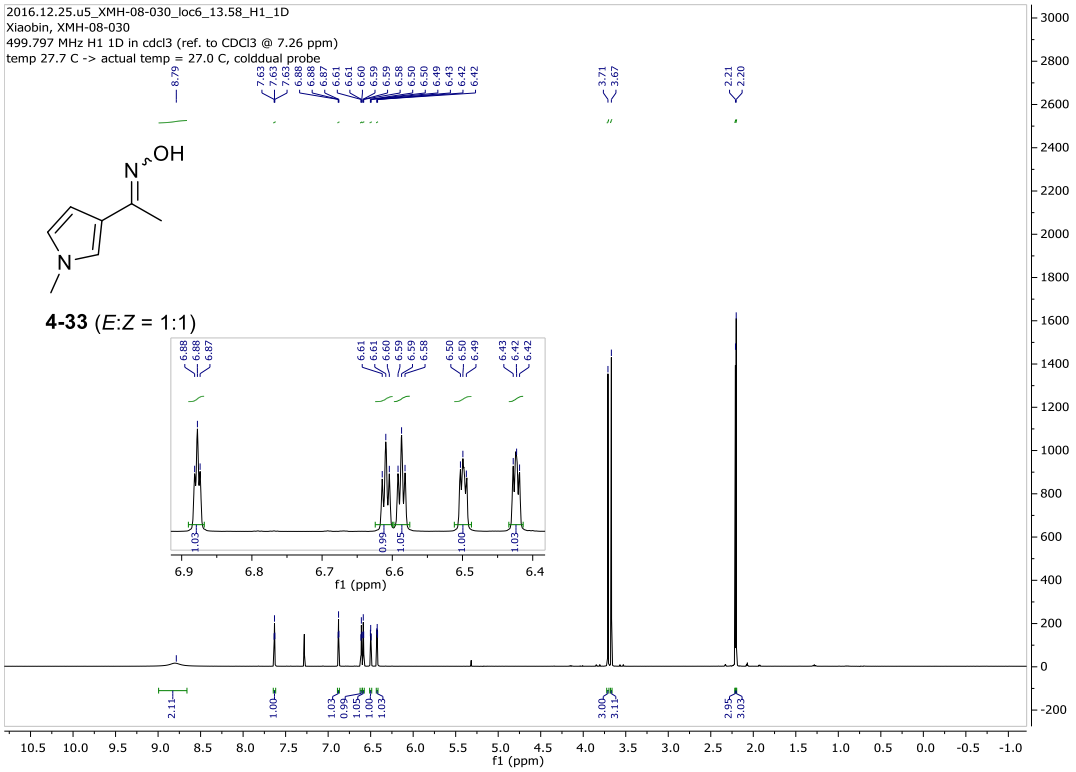


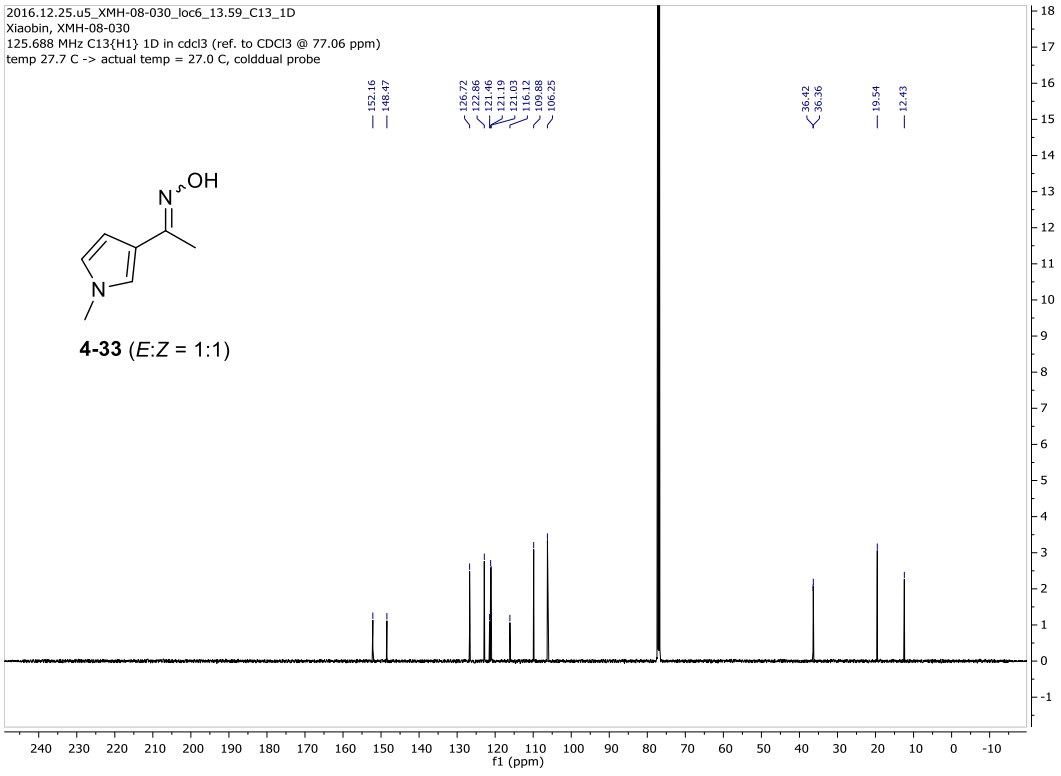
NMR spectra of **4-60**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



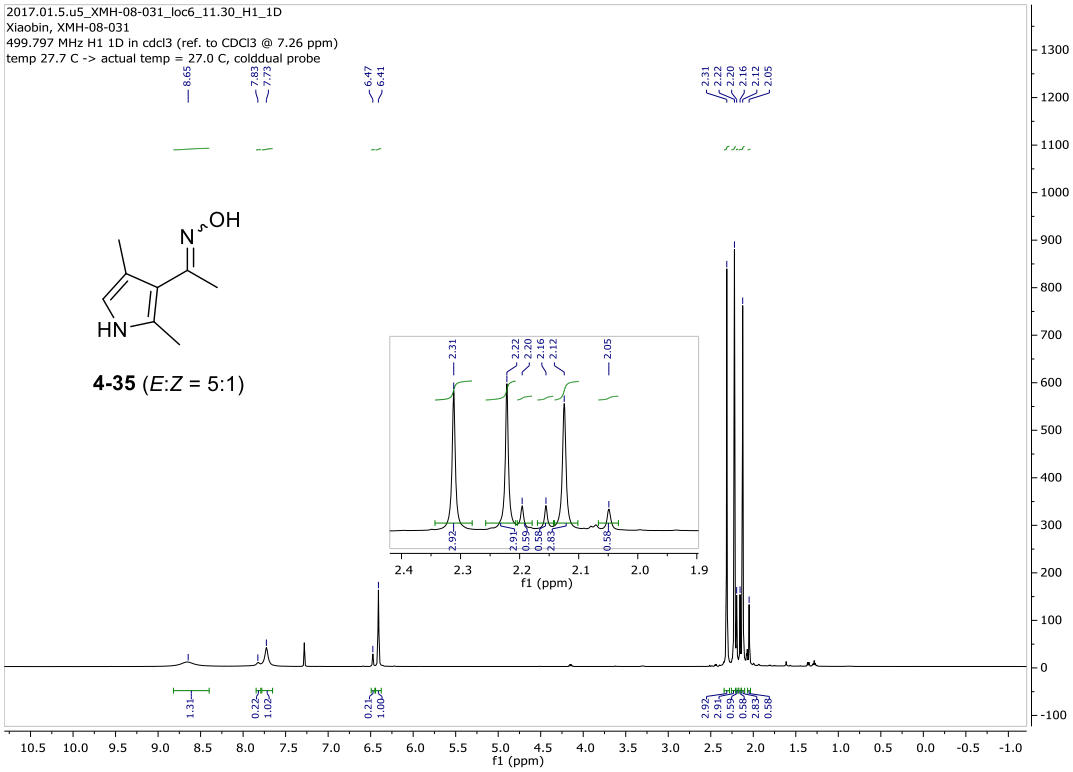


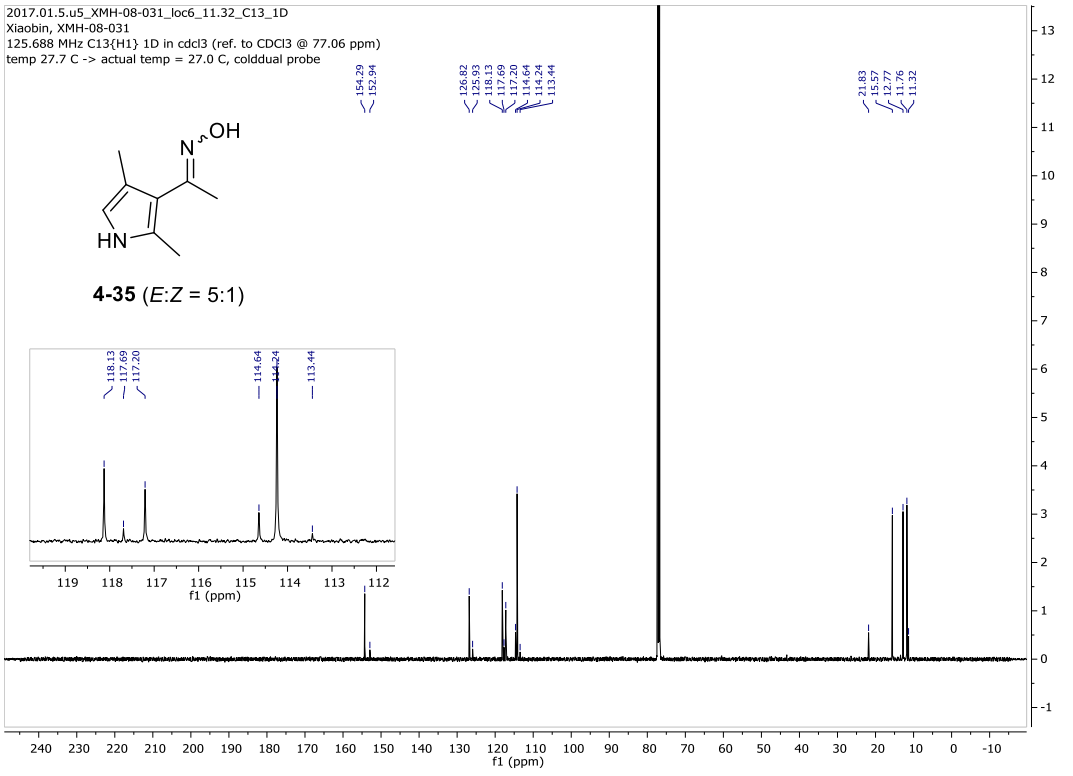
NMR spectra of **4-33**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



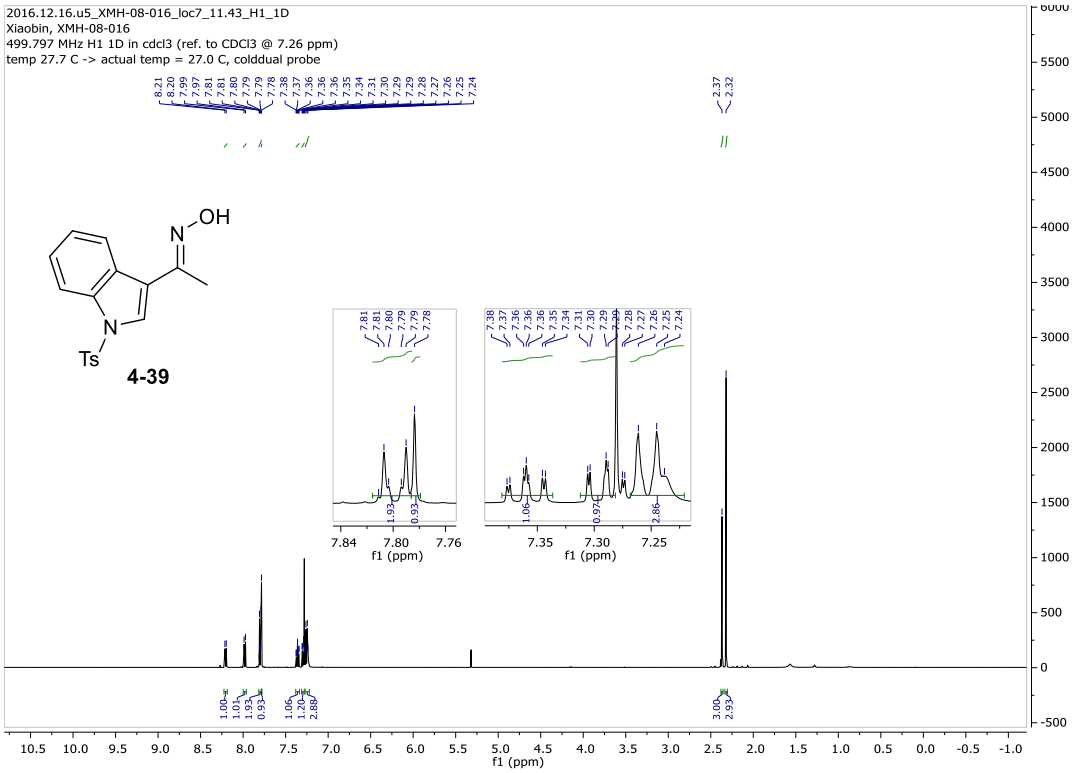


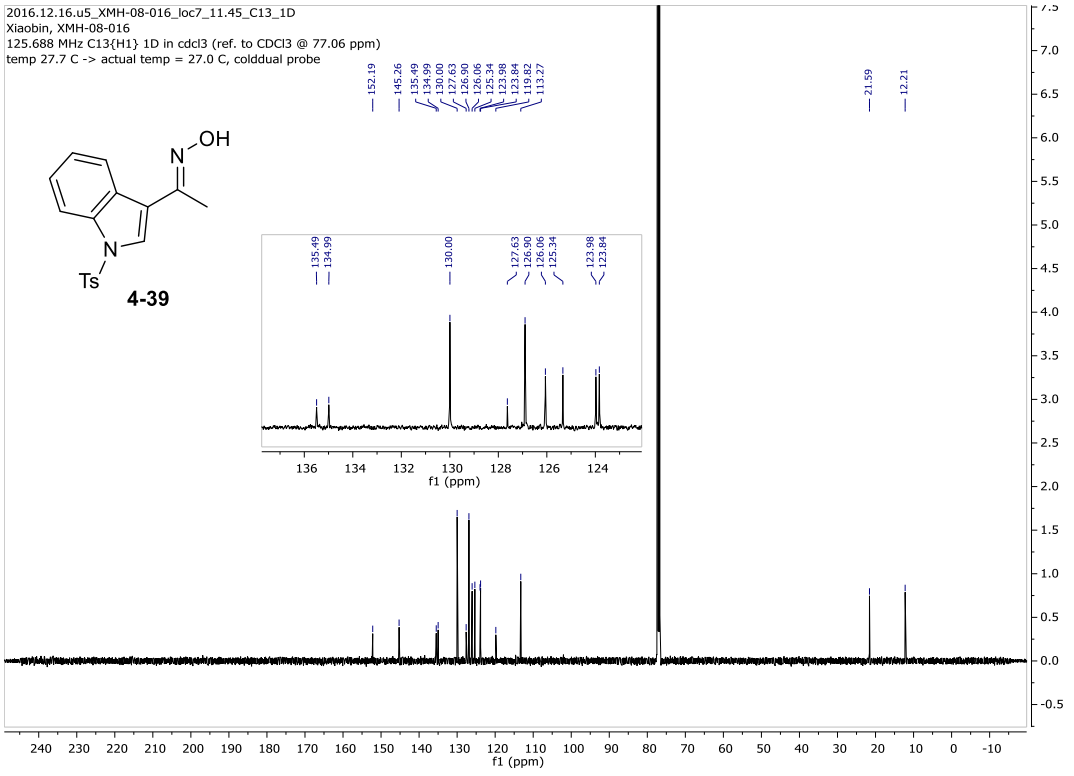
NMR spectra of **4-35**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



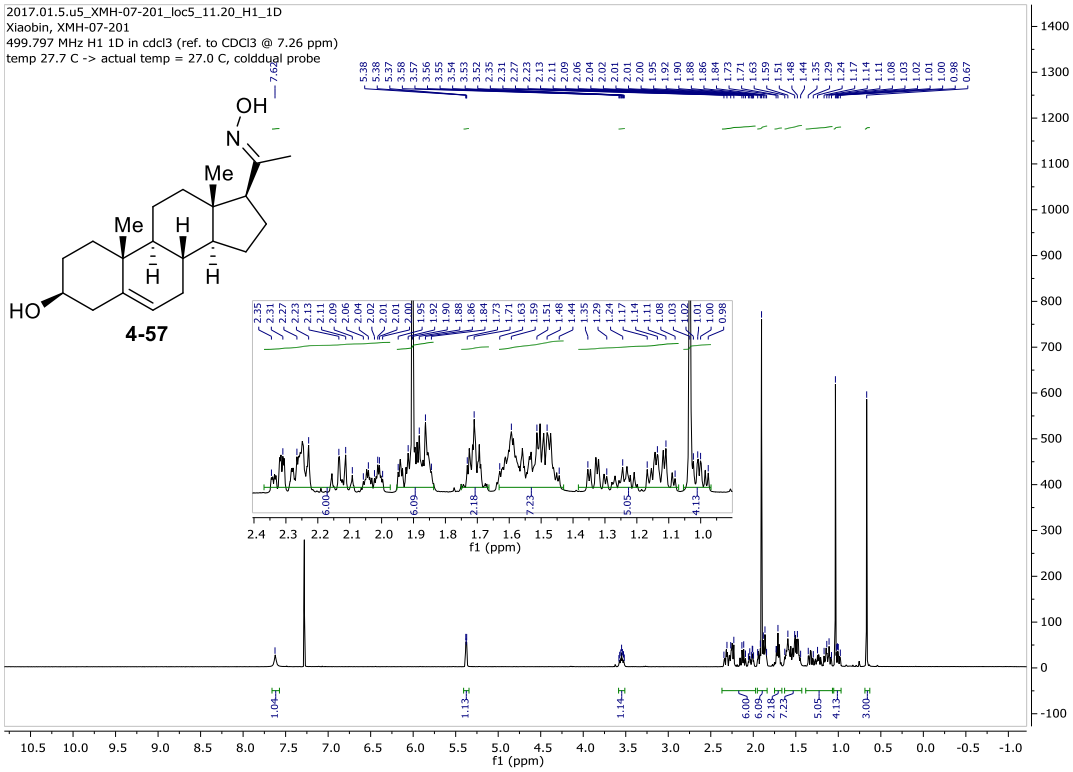


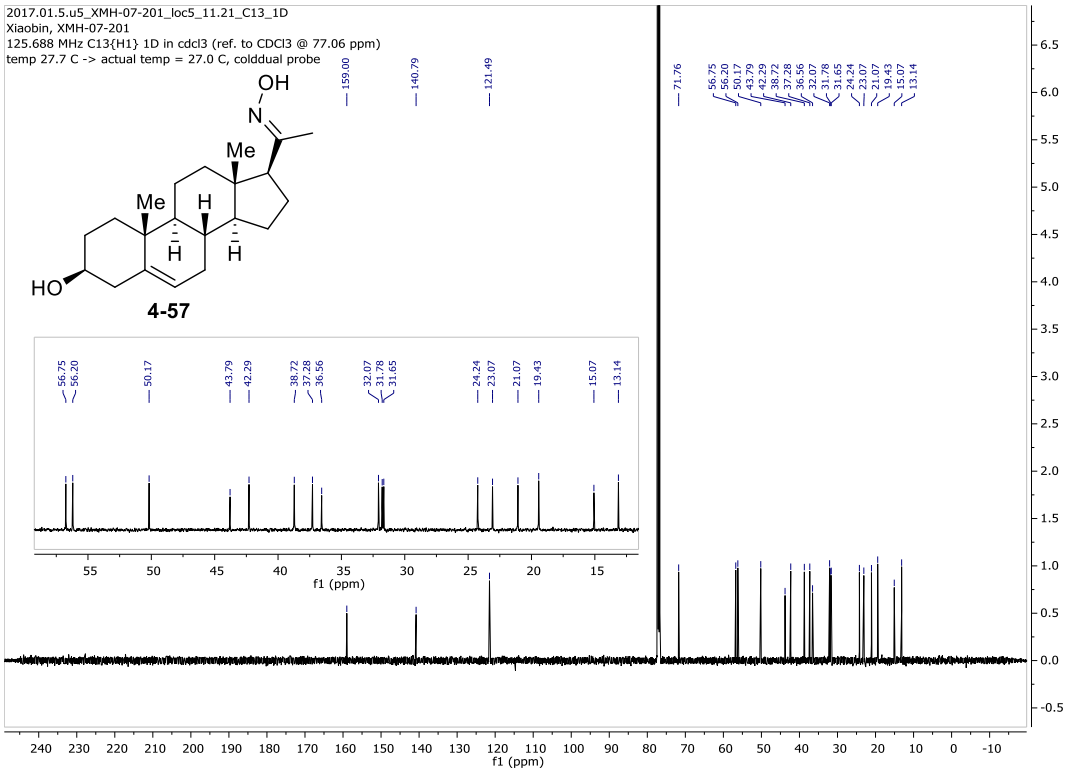
NMR spectra of **4-39**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



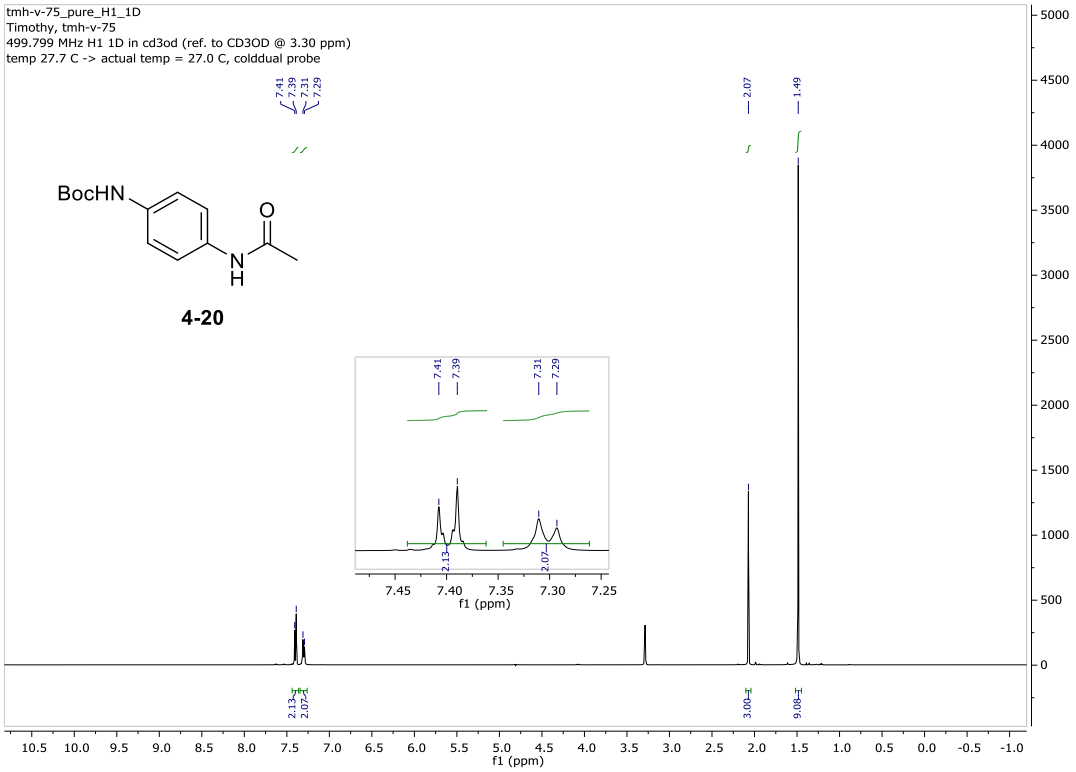


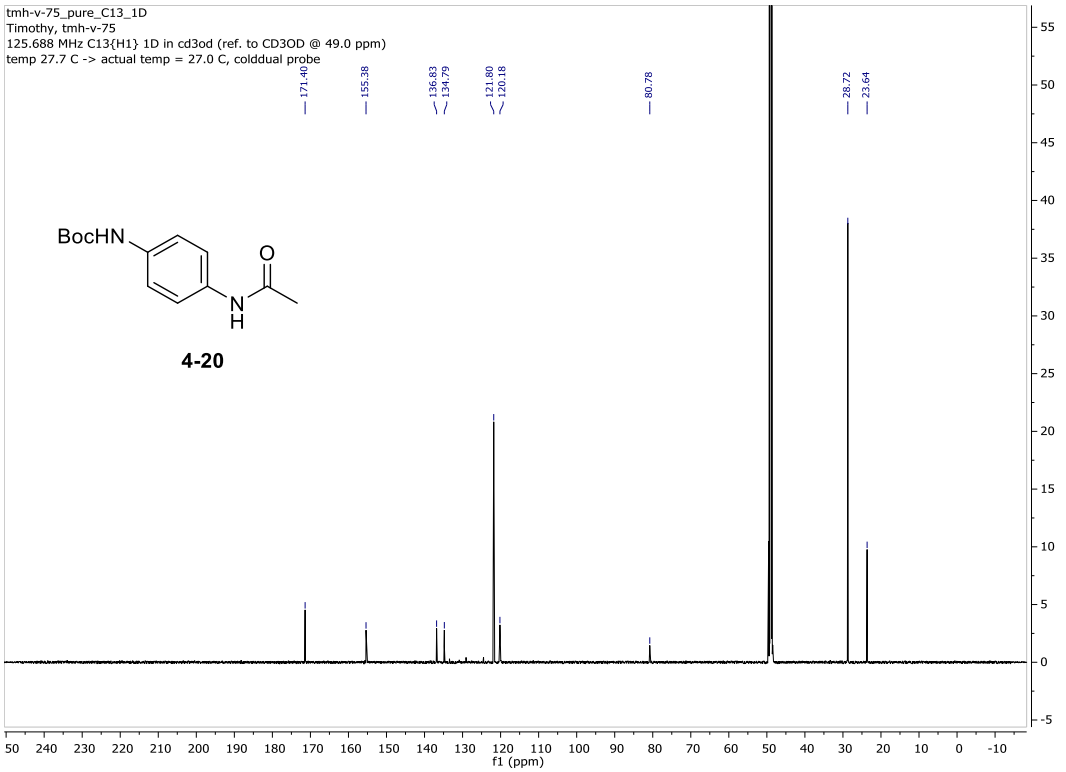
NMR spectra of **4-57**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



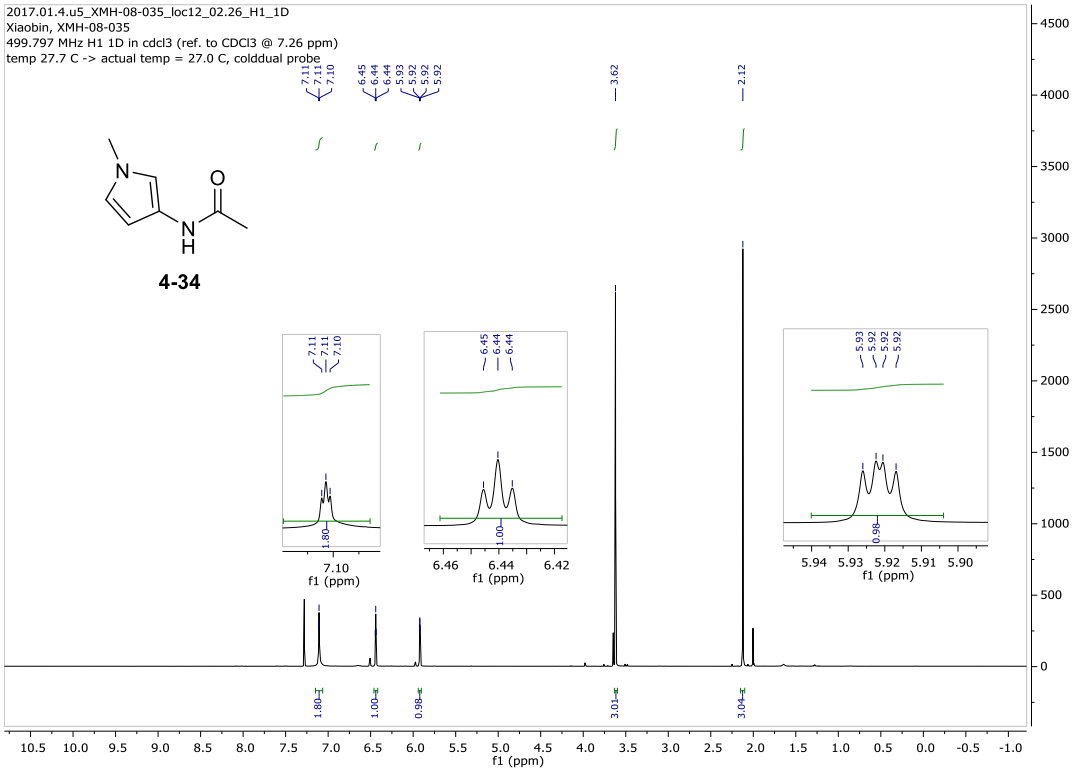


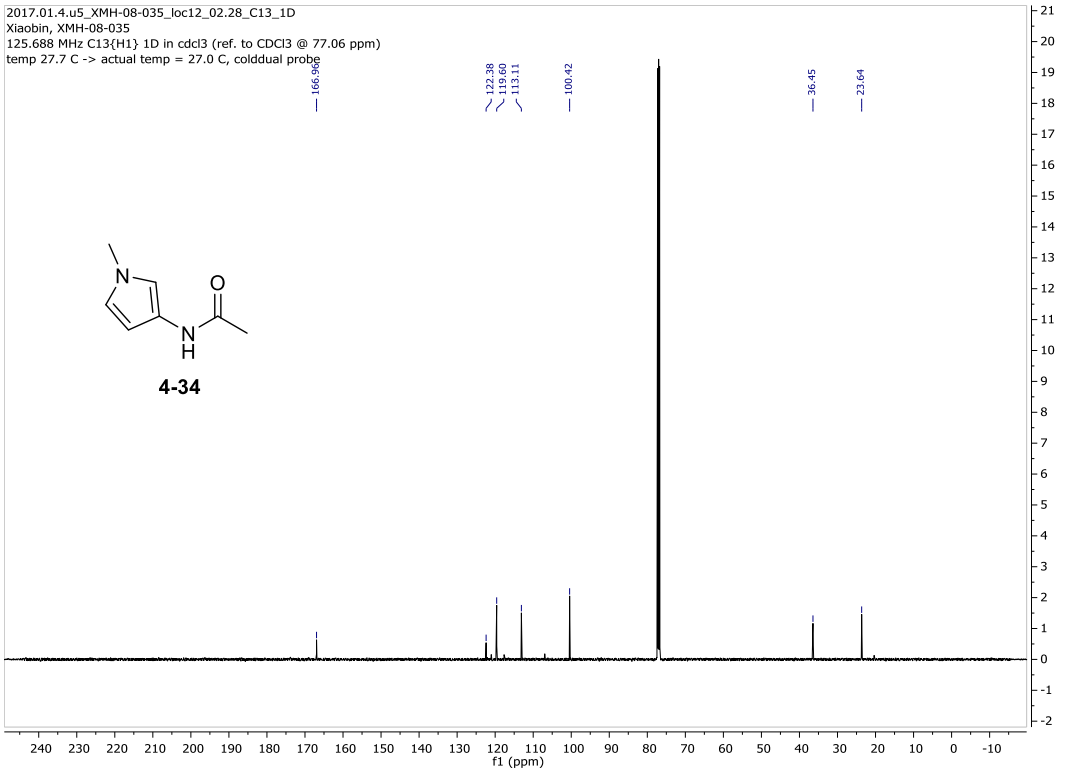
NMR spectra of **4-20**. Top: ^{1}H NMR (CD_3OD, 500 MHz). Bottom: ^{13}C NMR (CD_3OD, 125 MHz)



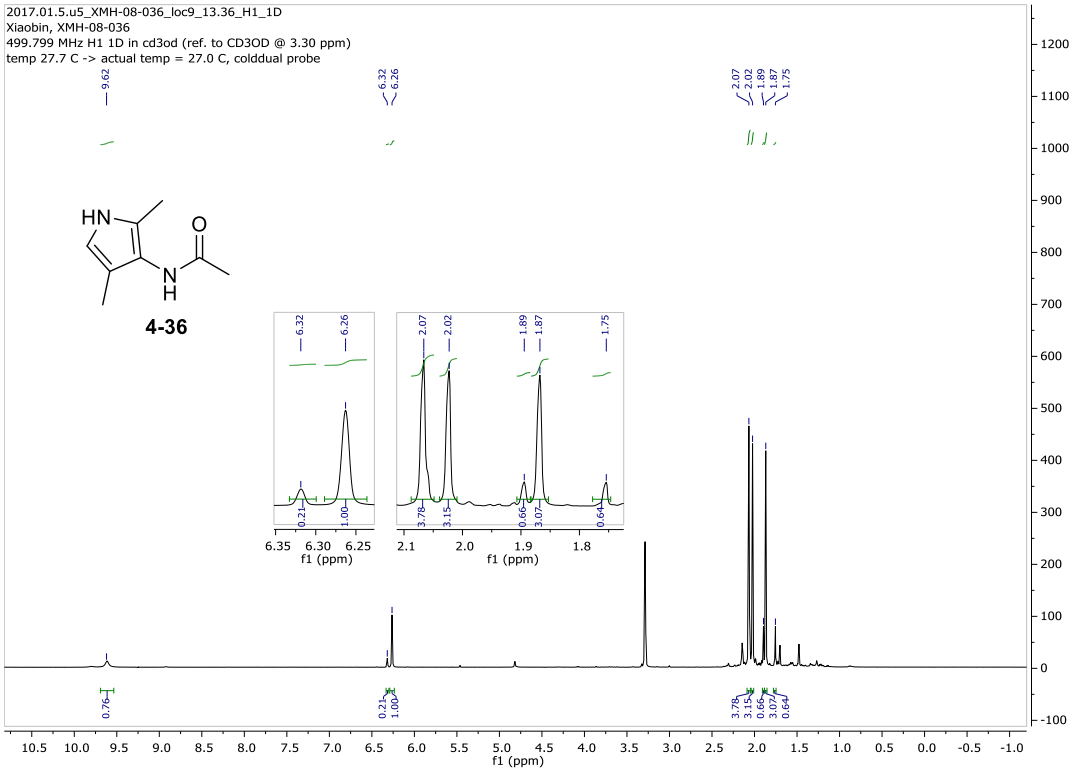


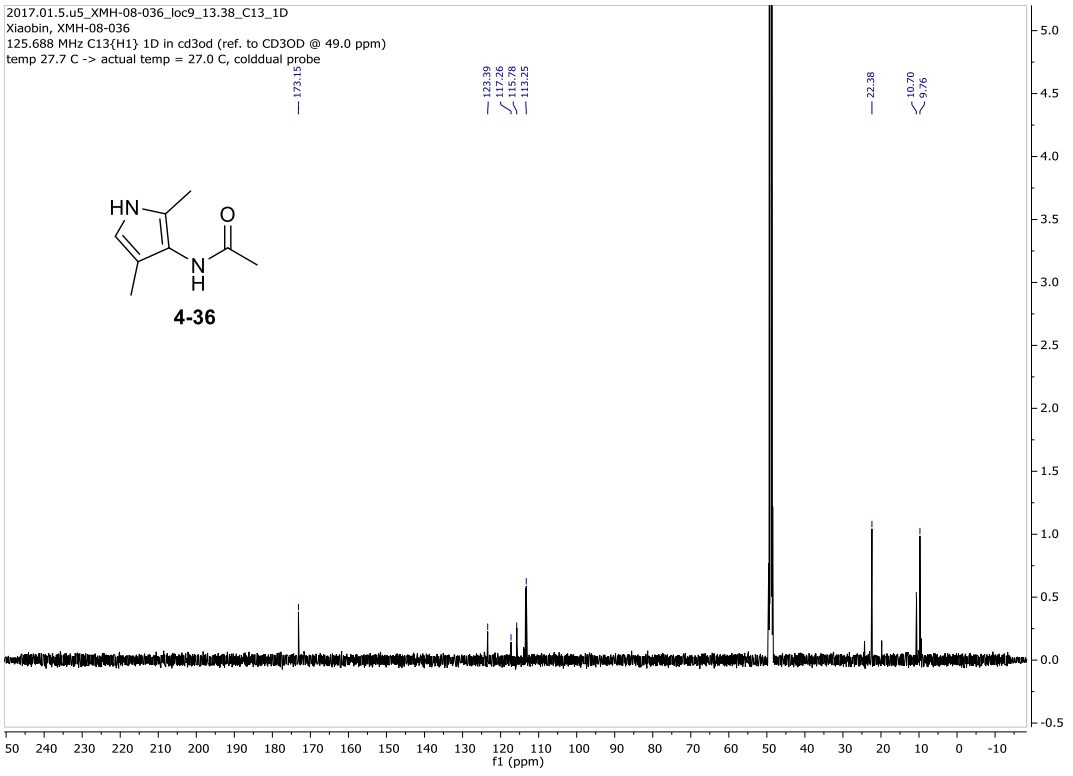
NMR spectra of **4-34**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



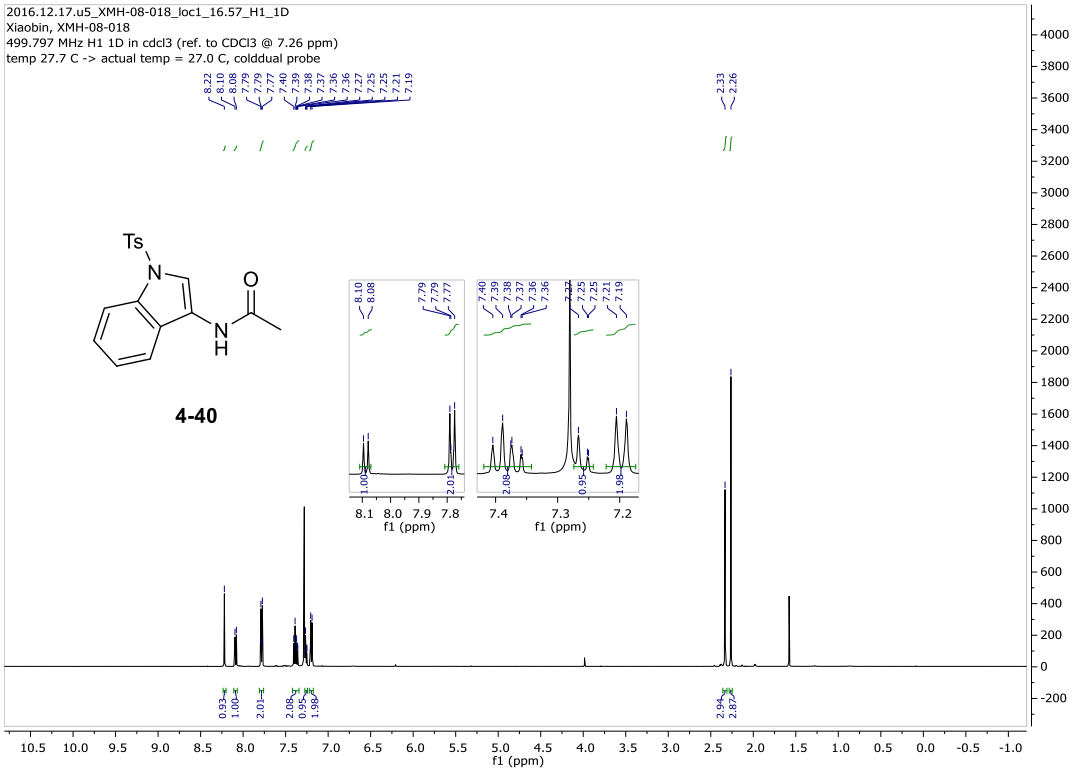


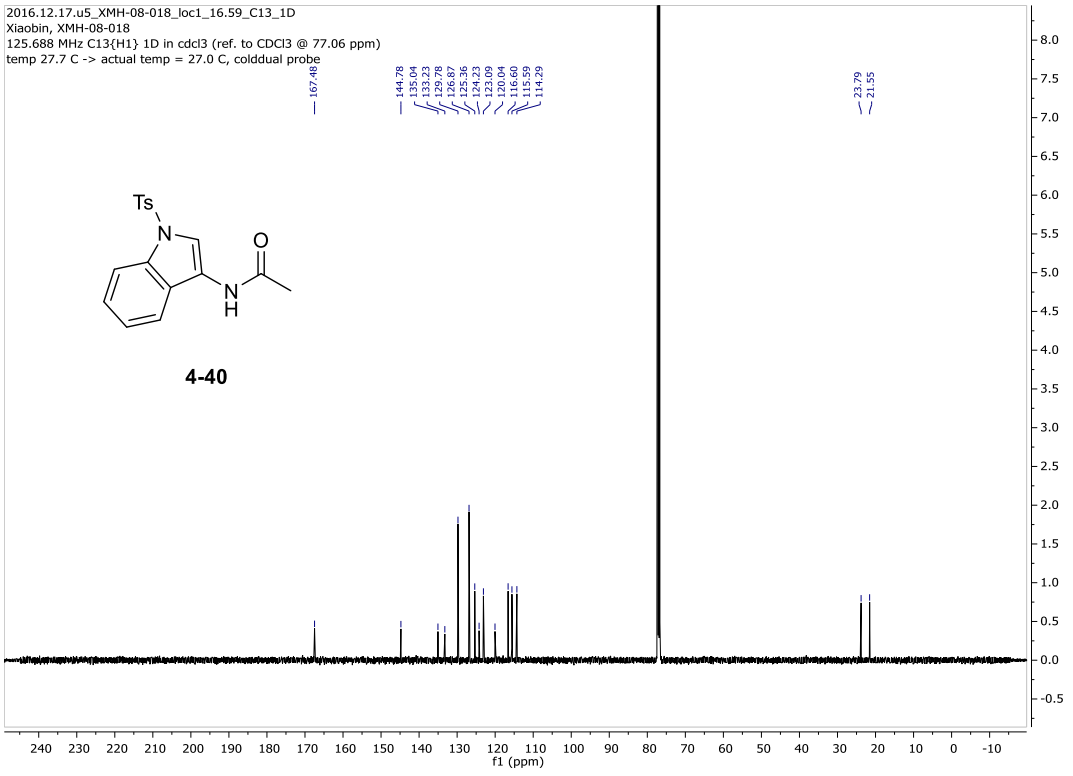
NMR spectra of **4-36**. Top: ^{1}H NMR (CD_3OD, 500 MHz). Bottom: ^{13}C NMR (CD_3OD, 125 MHz)



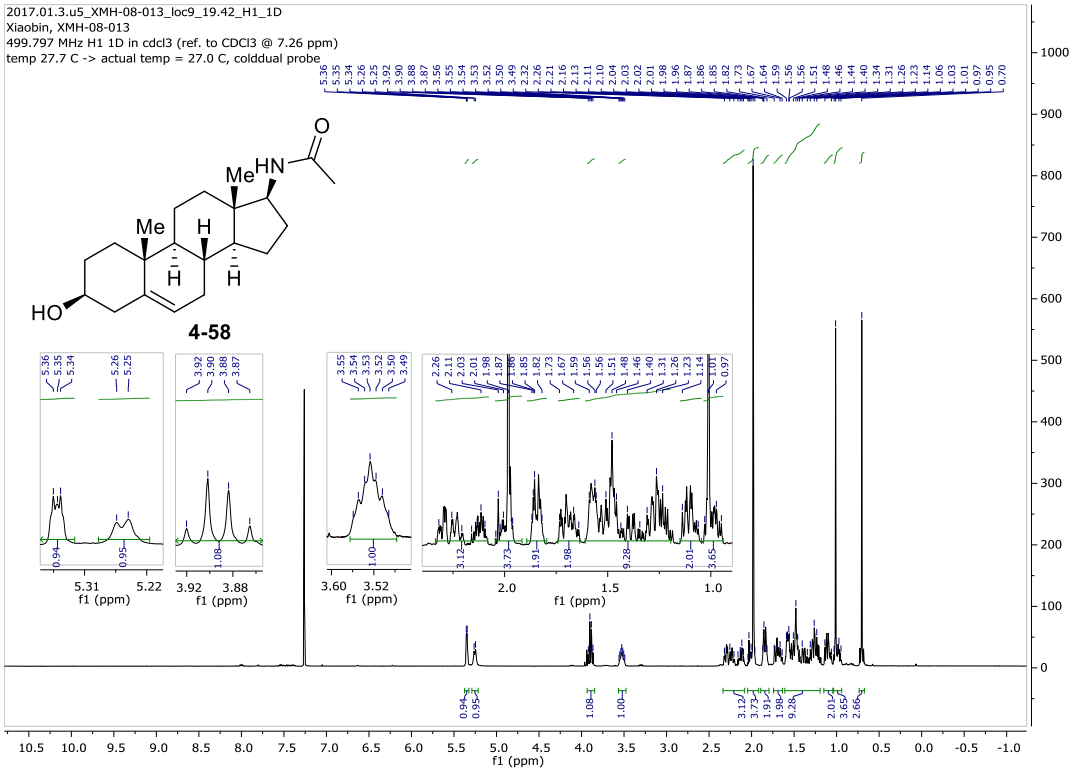


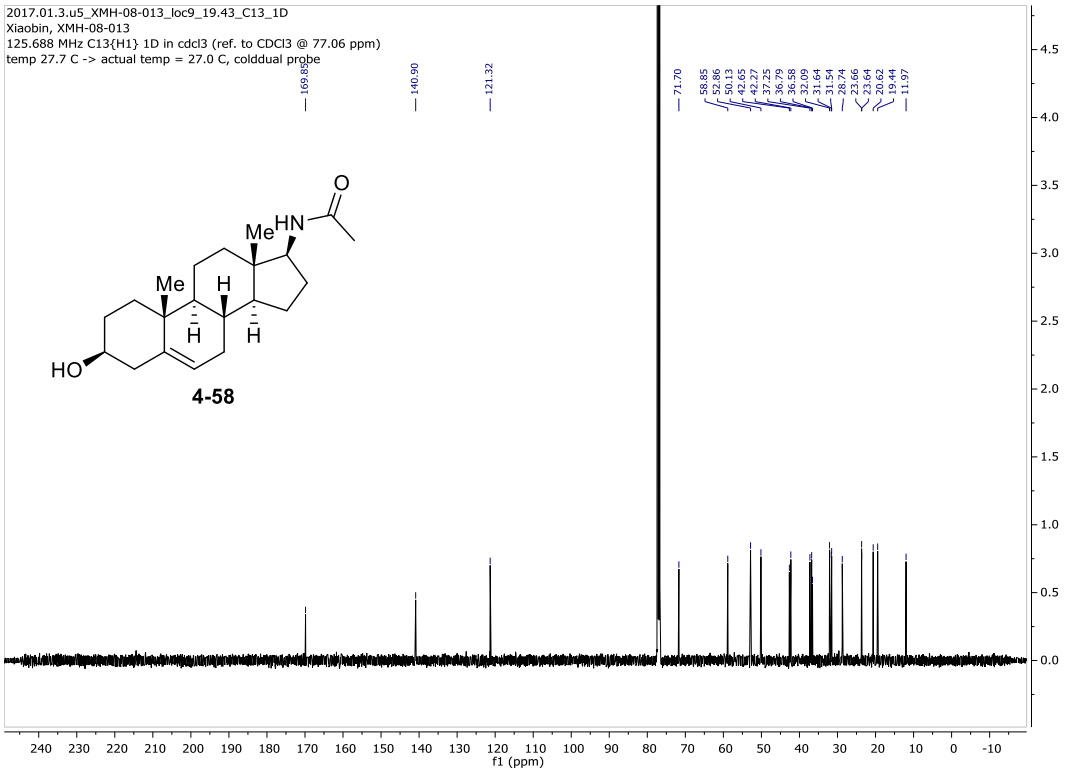
NMR spectra of **4-40**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



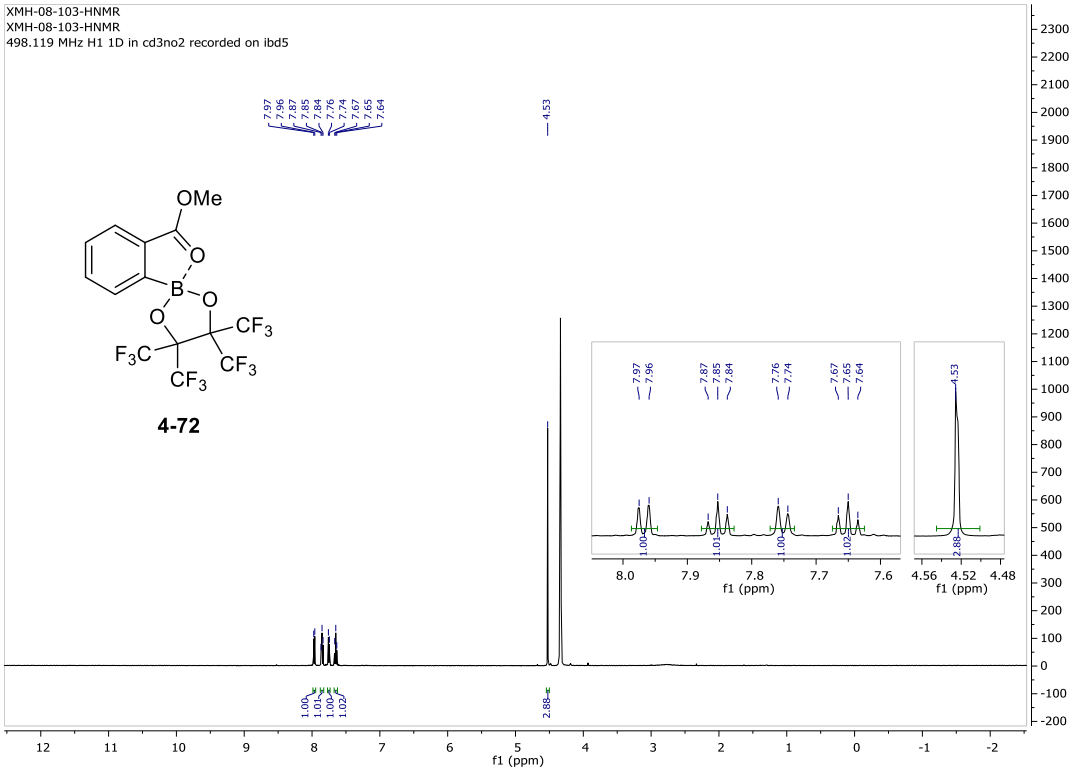


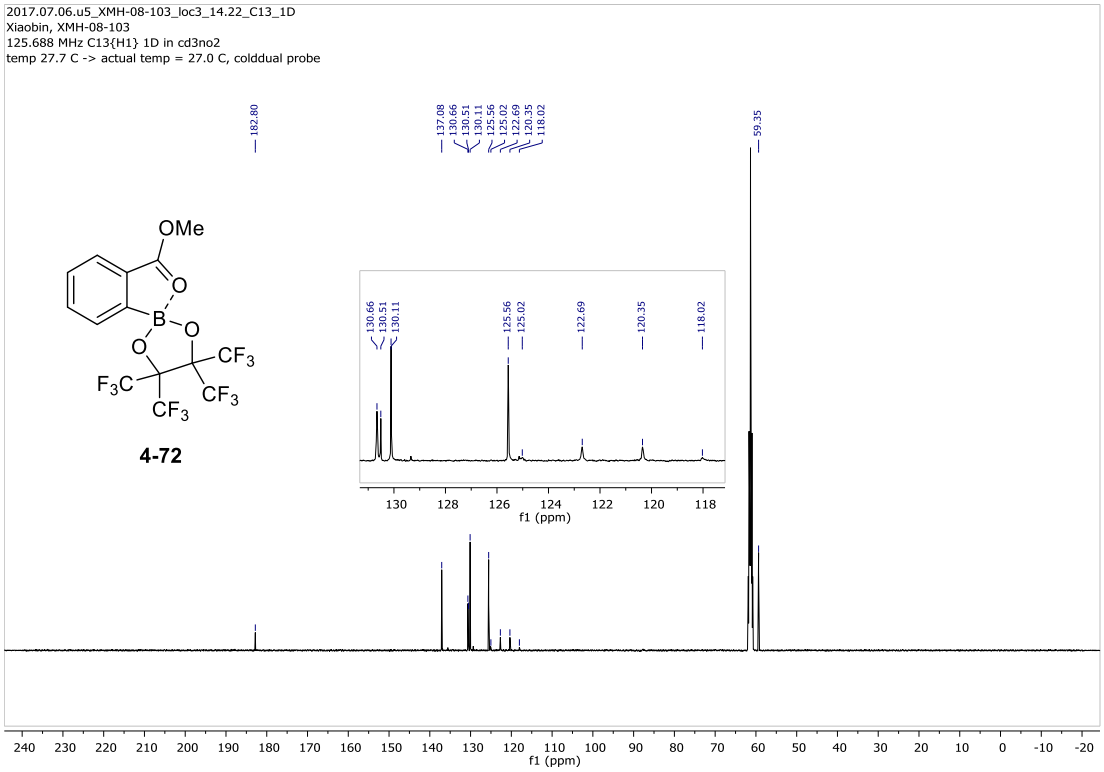
NMR spectra of **4-58**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



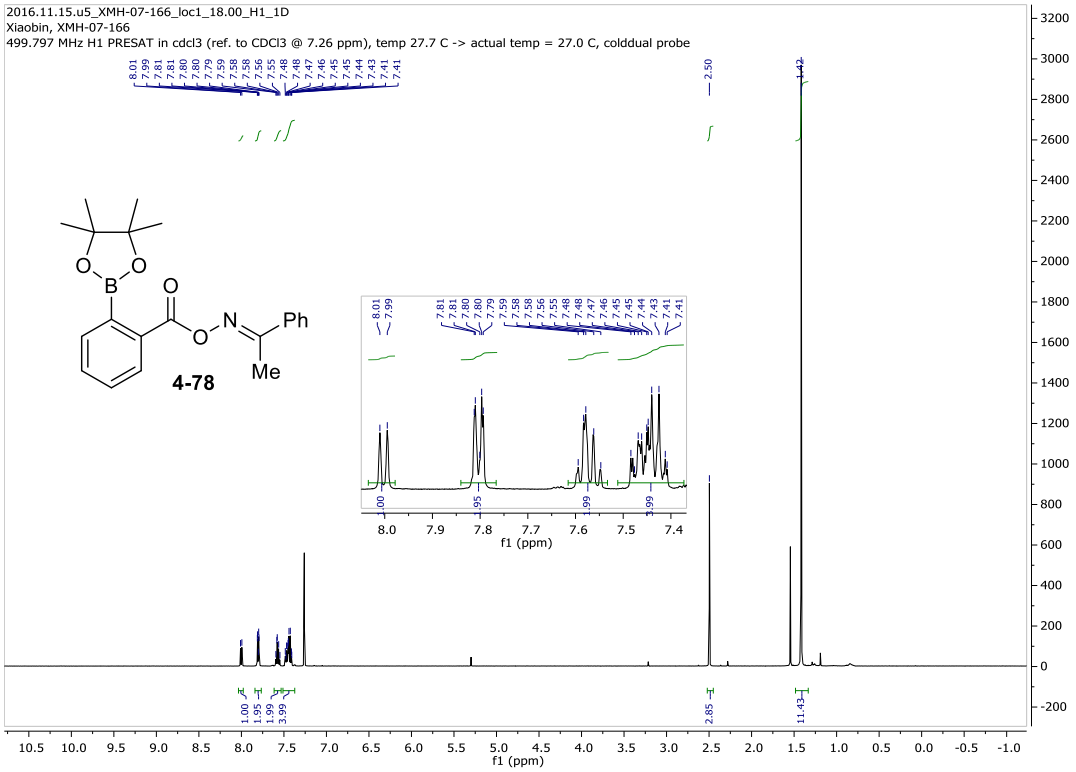


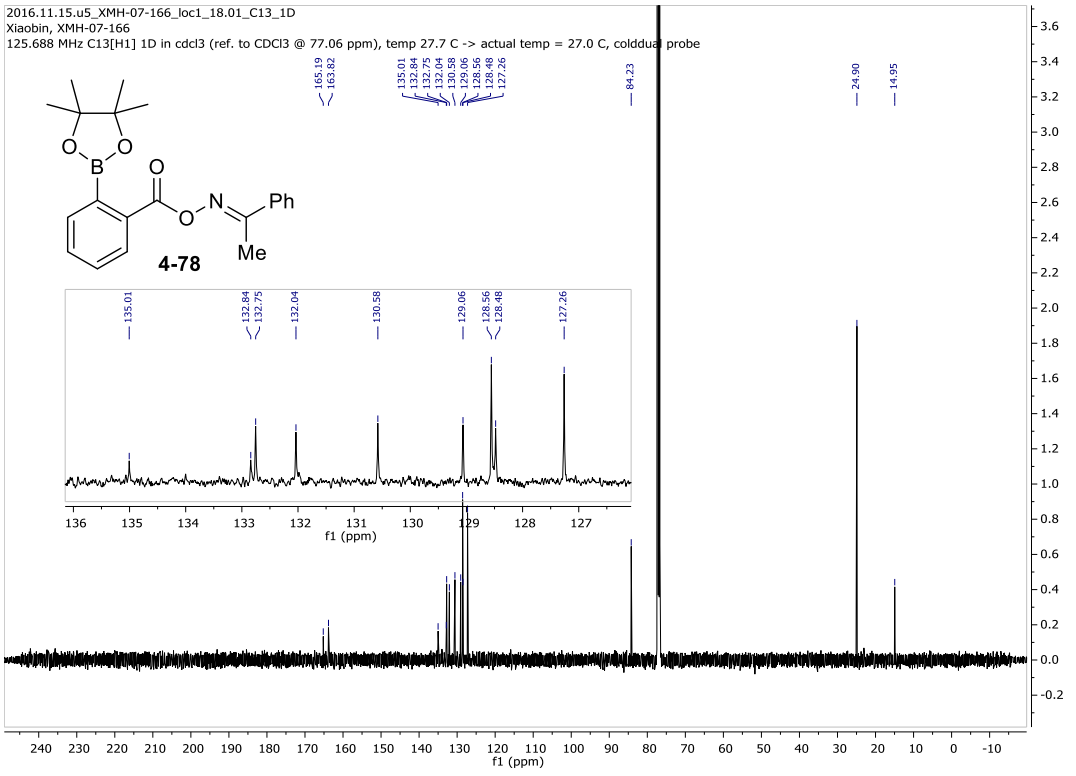
NMR spectra of **4-72**. Top: ^{1}H NMR (CD_3NO_2, 500 MHz). Bottom: ^{13}C NMR (CD_3NO_2, 125 MHz)



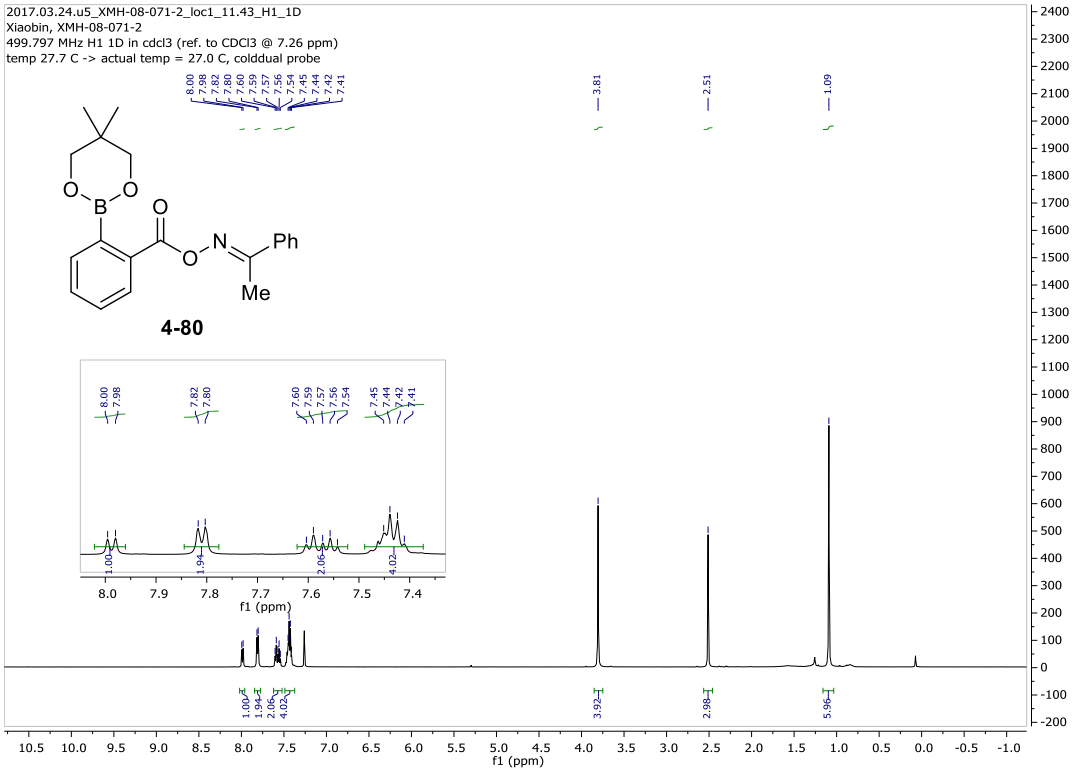


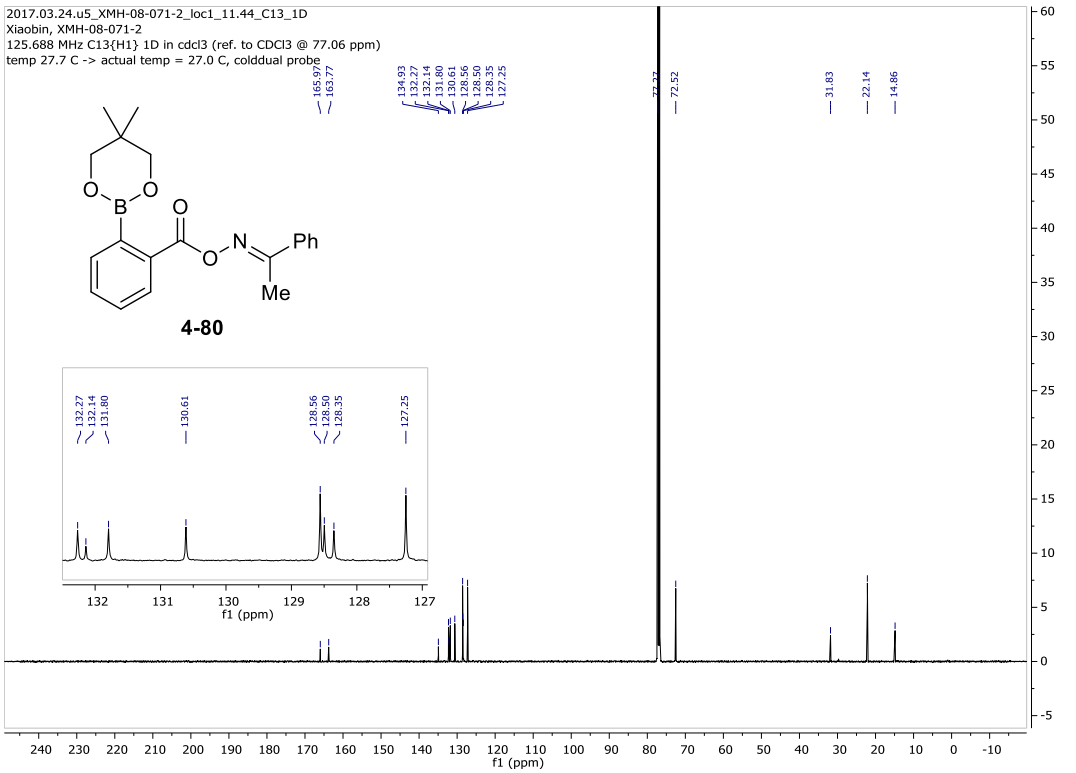
NMR spectra of **4-78**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



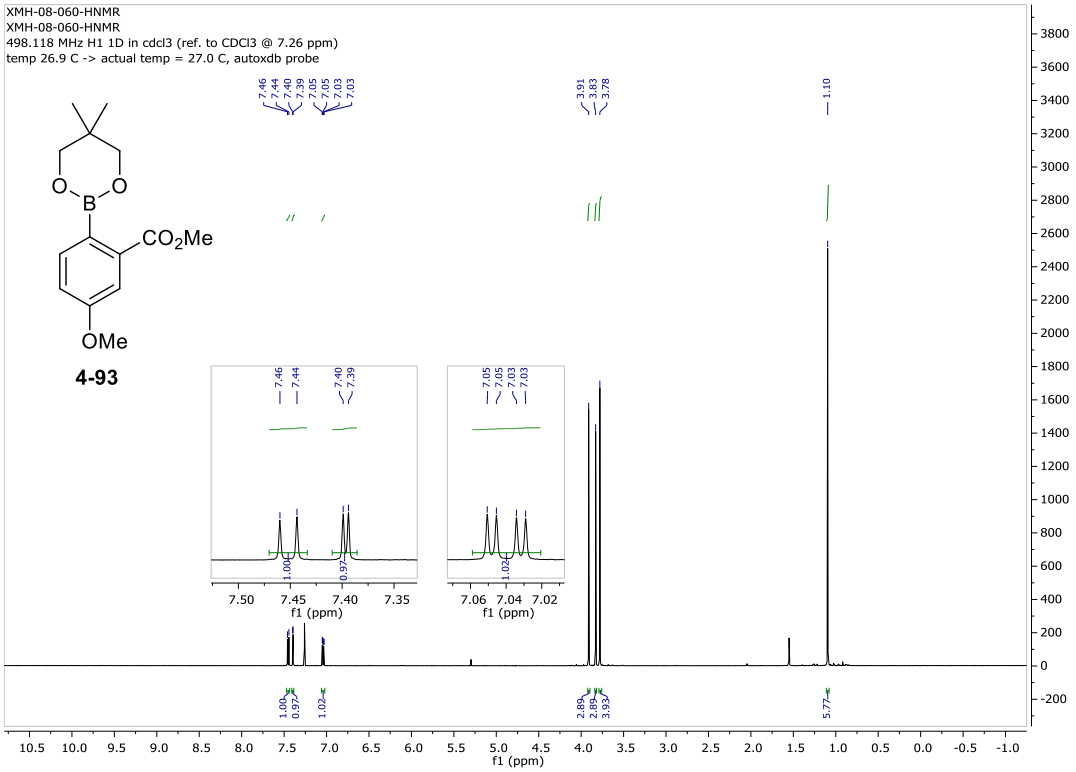


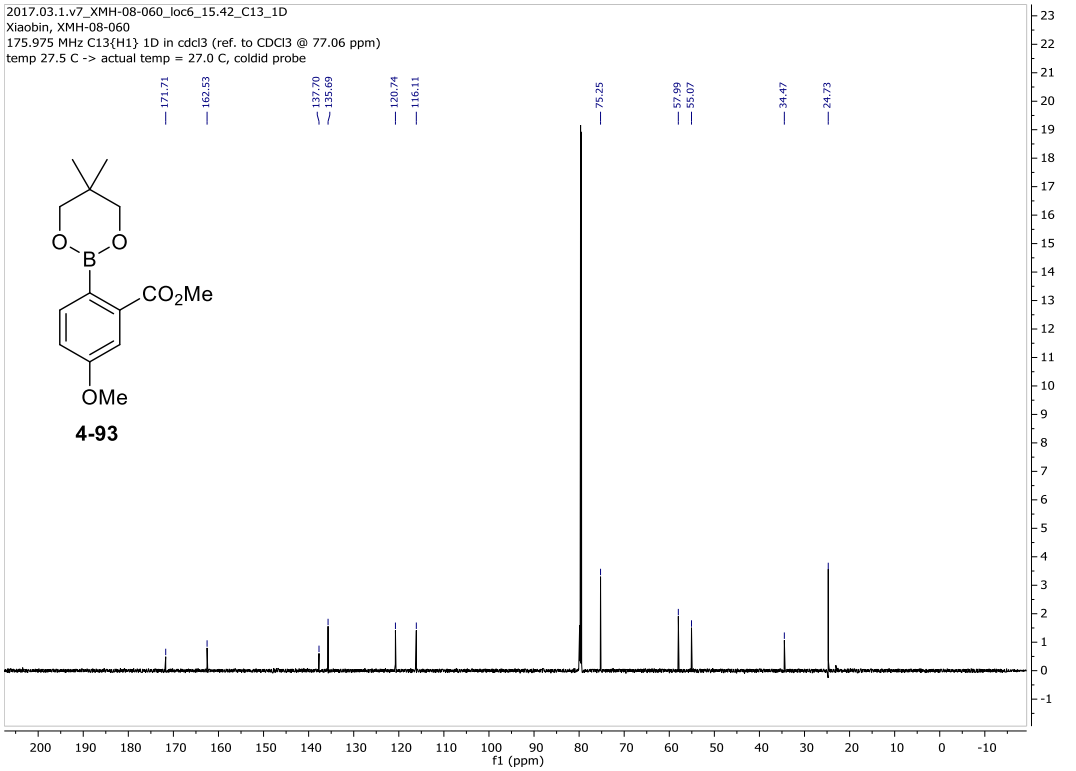
NMR spectra of **4-80**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



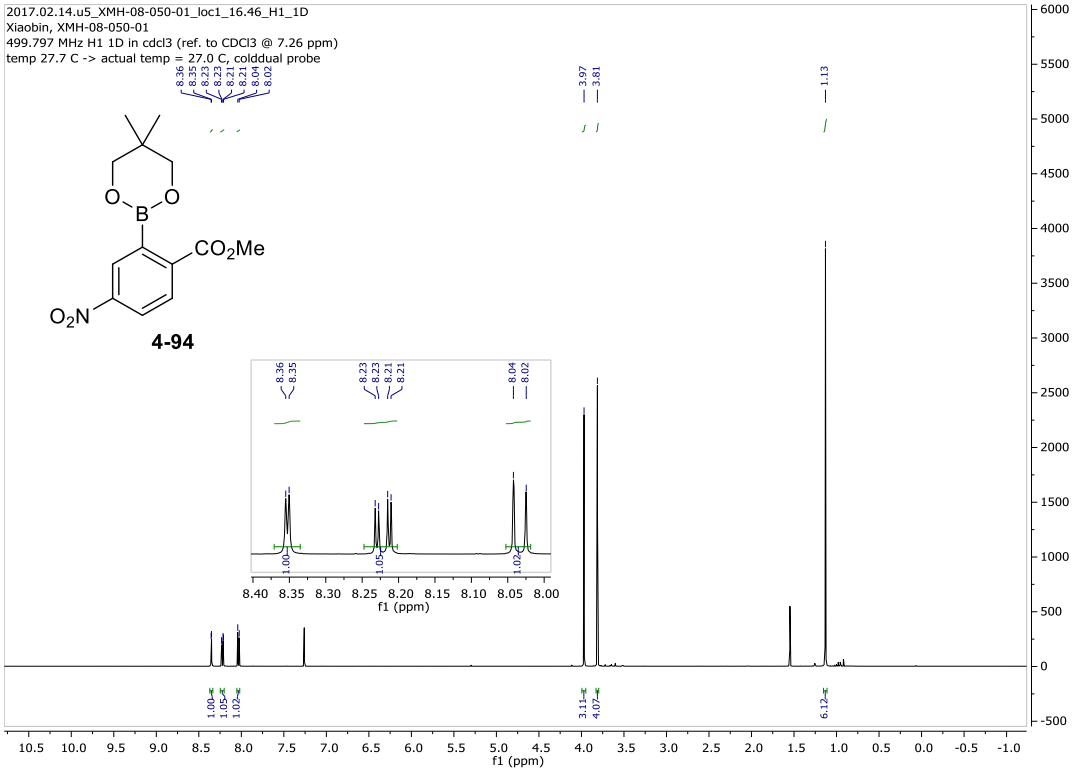


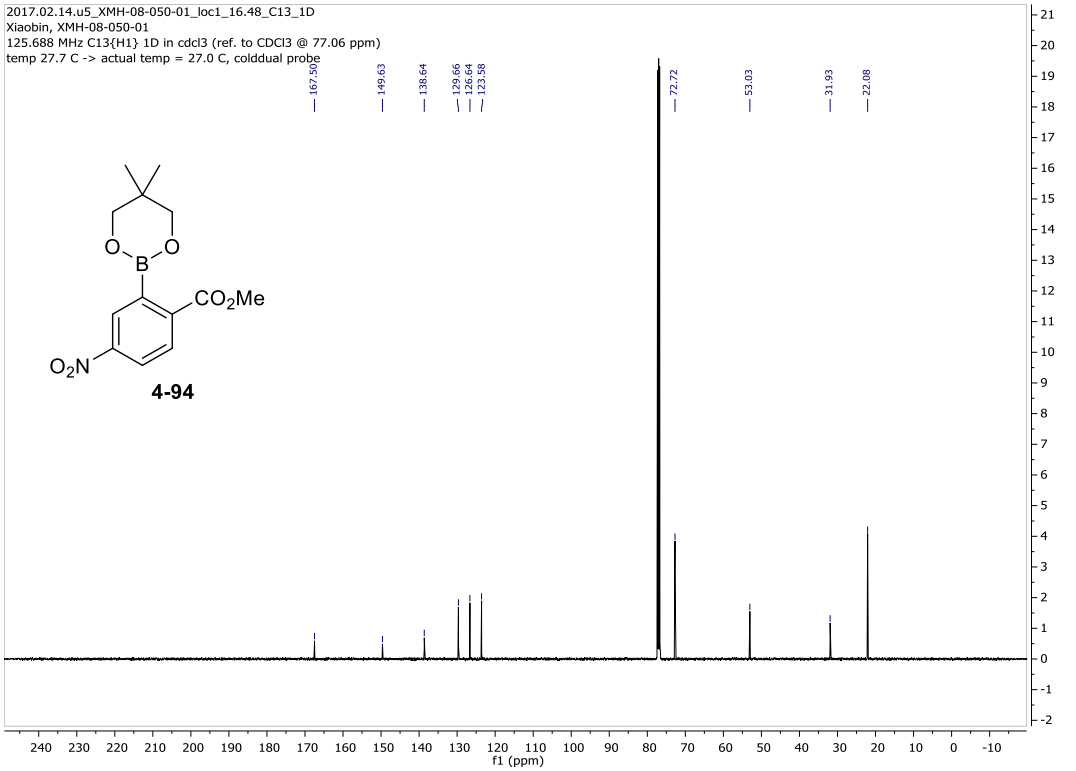
NMR spectra of **4-93**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 175 MHz)



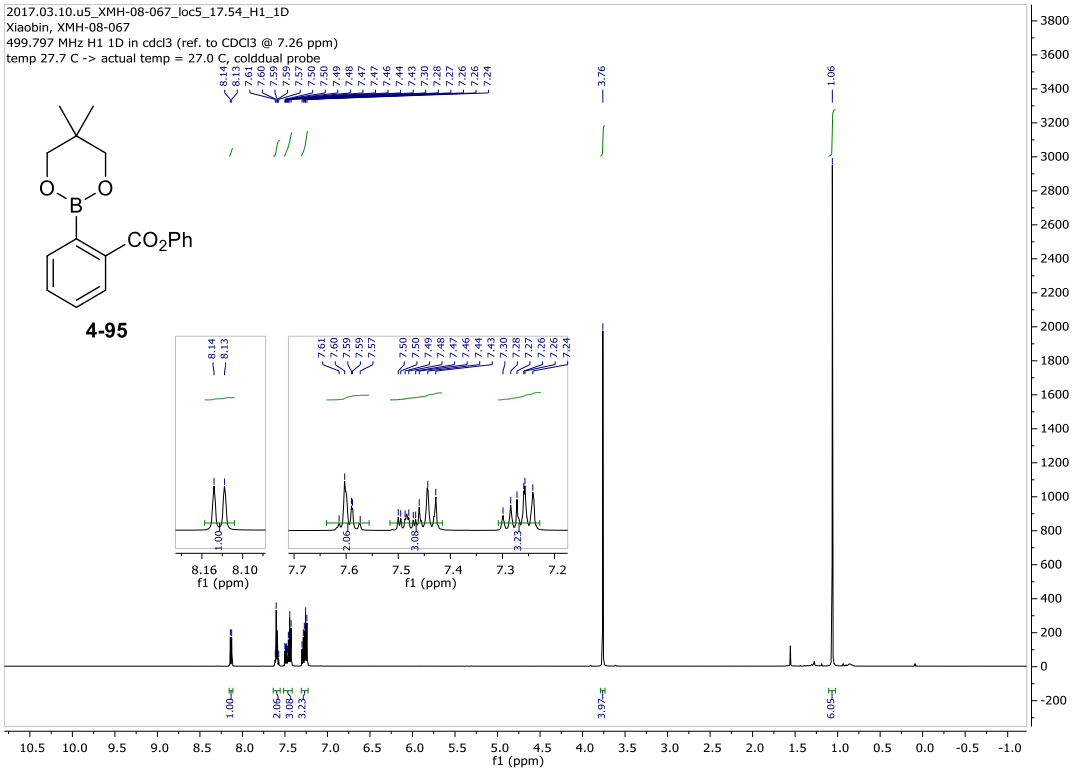


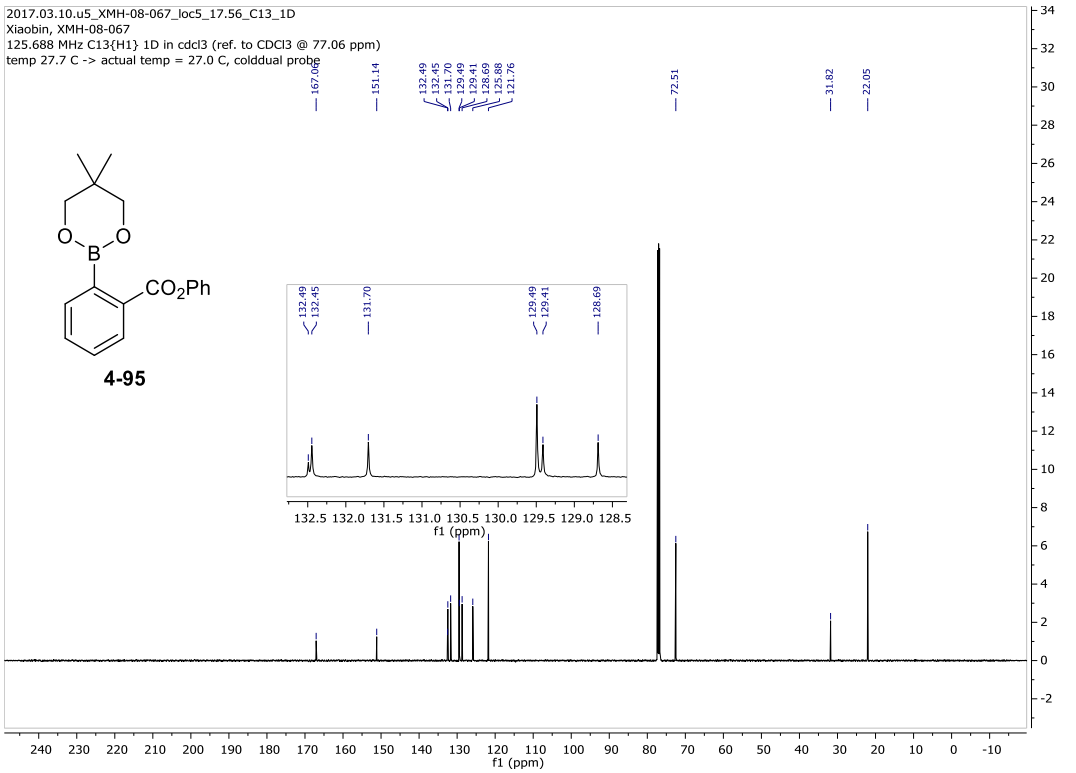
NMR spectra of **4-94**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)





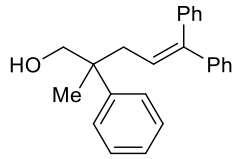
NMR spectra of **4-95**. Top: ^{1}H NMR ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR ($CDCl_3$, 125 MHz)



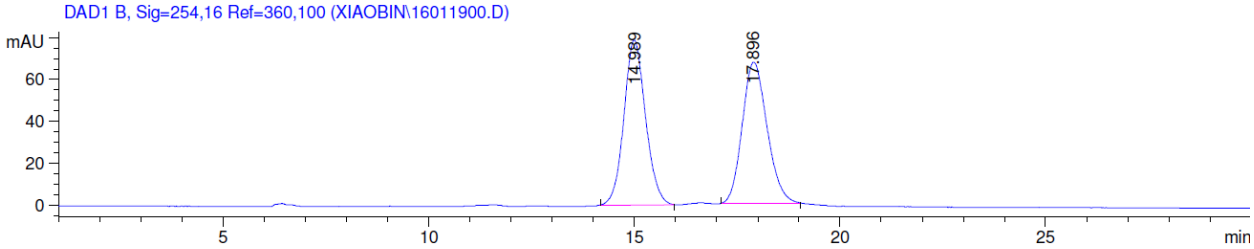


Appendix 2: Selected chromatograms of HPLC measurement

HPLC data for racemic (top) and optically enriched (bottom) **3-20**

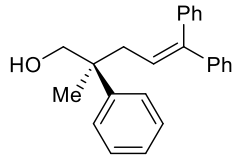


3-20 (racemic)

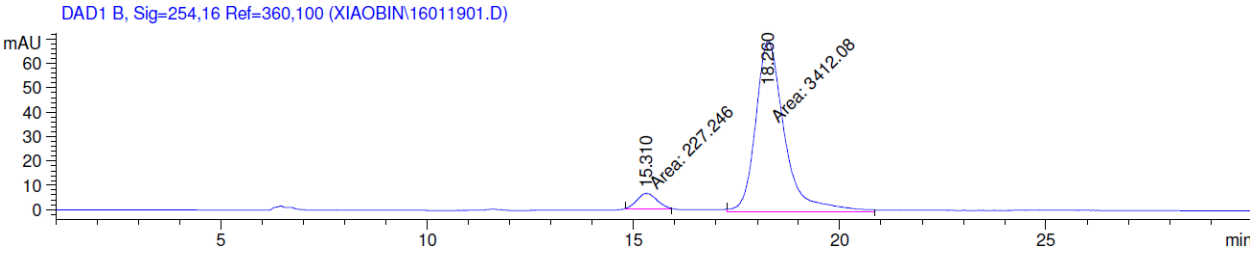


Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.989	BB	0.5624	2890.55542	78.71916	50.3945
2	17.896	BB	0.6497	2845.30127	67.50587	49.6055
Totals :				5735.85669	146.22503	



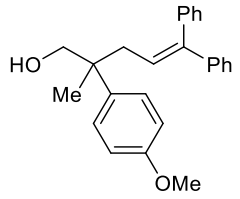
3-20



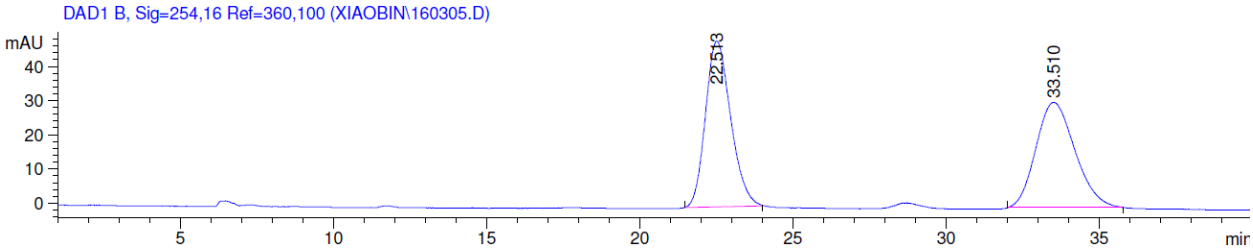
Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.310	MM	0.5778	227.24582	6.55487	6.2442
2	18.260	MM	0.8138	3412.07520	69.88269	93.7558
Totals :				3639.32101	76.43756	

HPLC data for racemic (top) and optically enriched (bottom) **3-21**

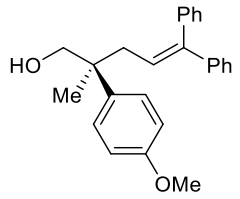


3-21 (racemic)

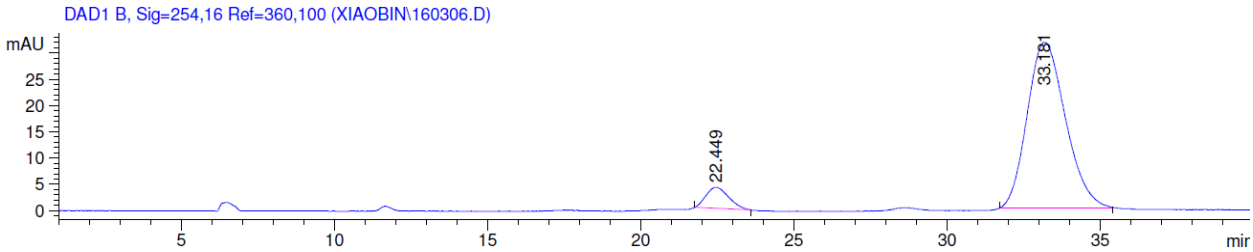


Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.513	BB	0.8638	2786.05811	48.52456	50.4230
2	33.510	BB	1.1438	2739.30908	30.79440	49.5770
Totals :				5525.36719	79.31896	



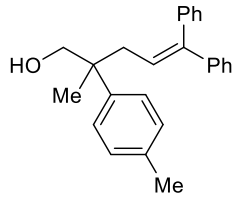
3-21



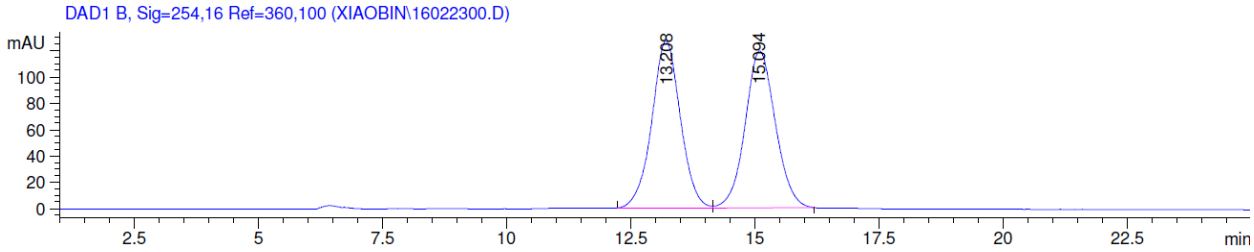
Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.449	BB	0.6242	213.31496	4.06506	7.2200
2	33.181	BB	1.0583	2741.16675	31.59201	92.7800
Totals :				2954.48170	35.65707	

HPLC data for racemic (top) and optically enriched (bottom) **3-22**

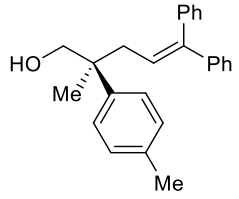


3-22 (racemic)

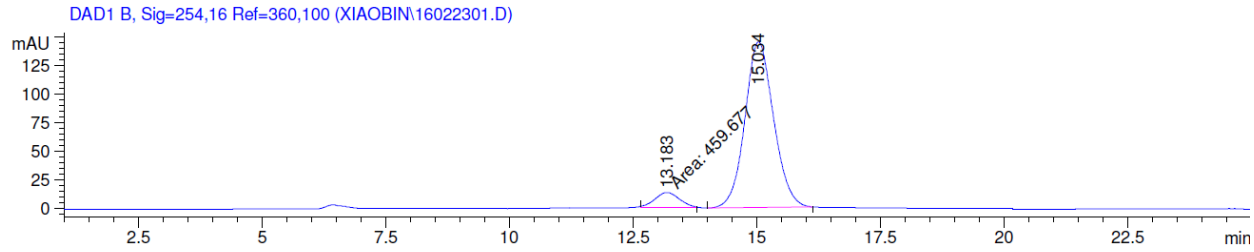


Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.208	BV	0.6120	5092.99951	126.96583	50.0792
2	15.094	VB	0.6423	5076.88770	119.34355	49.9208
Totals :				1.01699e4	246.30938	



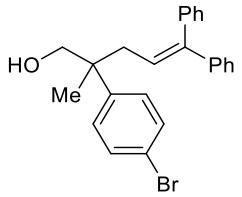
3-22



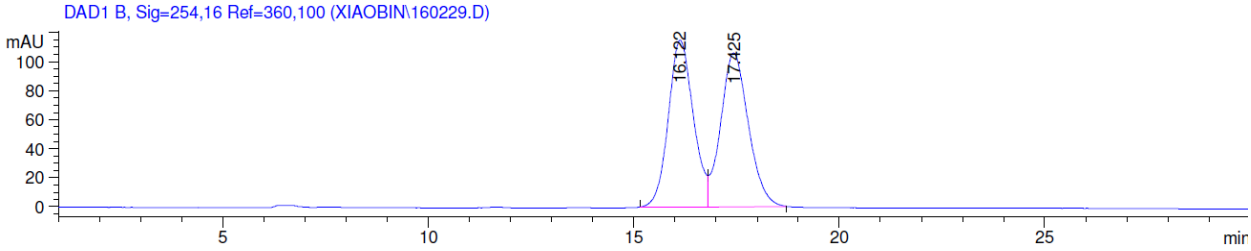
Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.183	MM	0.5785	459.67694	13.24360	7.2871
2	15.034	VB	0.6154	5848.40283	144.74348	92.7129
Totals :				6308.07977	157.98708	

HPLC data for racemic (top) and optically enriched (bottom) **3-23**

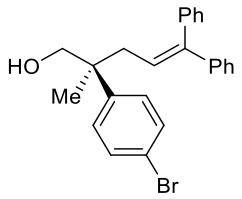


3-23 (racemic)

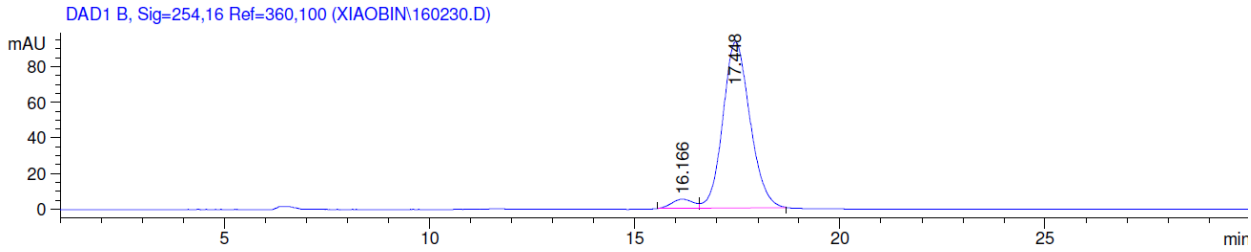


Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.122	BV	0.6456	4890.58008	115.12682	49.5540
2	17.425	VB	0.7137	4978.60693	106.04071	50.4460
Totals :				9869.18701	221.16753	



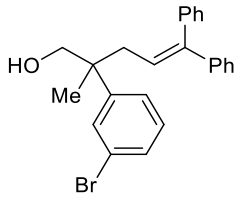
3-23



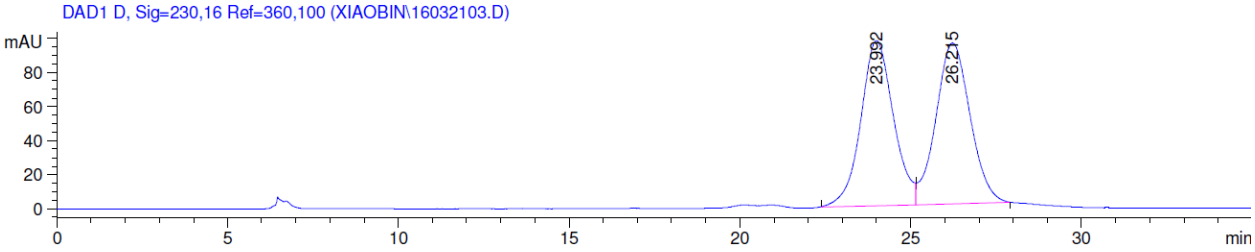
Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.166	BV	0.4684	192.14668	5.20822	4.2881
2	17.448	VB	0.6995	4288.78076	93.09840	95.7119
Totals :				4480.92744	98.30662	

HPLC data for racemic (top) and optically enriched (bottom) **3-24**

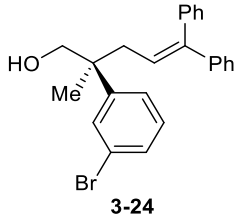


3-24 (racemic)

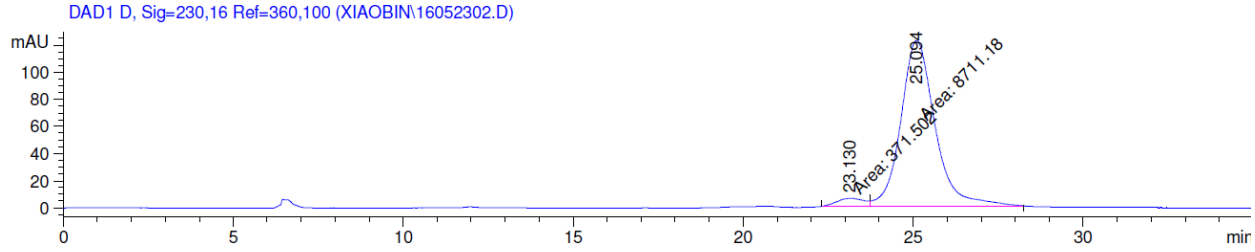


Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.992	BV	0.9819	6464.99756	96.95376	49.4671
2	26.215	VB	1.0573	6604.30322	94.51028	50.5329
Totals :				1.30693e4	191.46404	



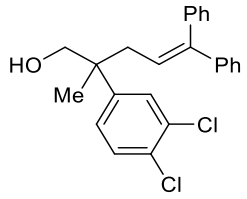
3-24



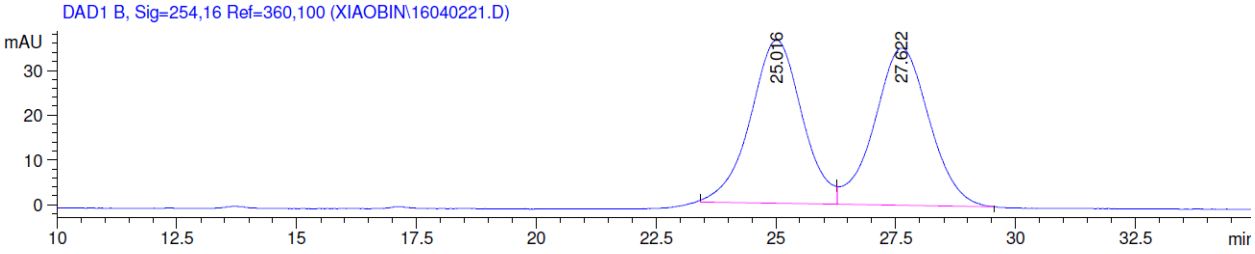
Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.130	MF	0.9636	371.50177	6.42561	4.0902
2	25.094	FM	1.1819	8711.17676	122.83964	95.9098
Totals :				9082.67853	129.26525	

HPLC data for racemic (top) and optically enriched (bottom) **3-25**

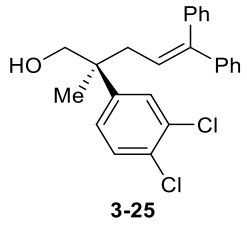


3-25 (racemic)

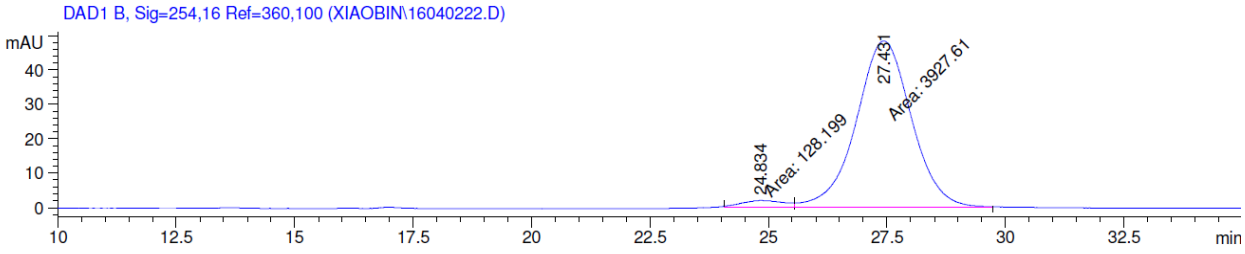


Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.016	BV	1.0473	2741.49609	36.45661	49.4250
2	27.622	VB	1.0808	2805.28223	35.16276	50.5750
Totals :				5546.77832	71.61937	



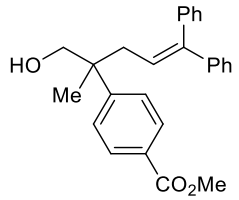
3-25



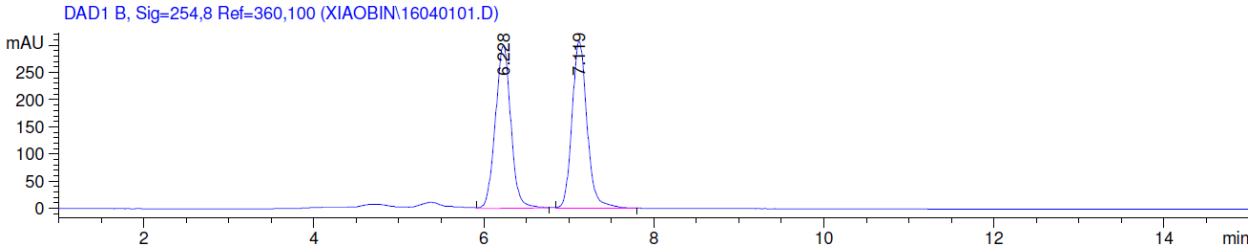
Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.834	MF	1.0602	128.19928	2.01524	3.1609
2	27.431	FM	1.3536	3927.60645	48.36098	96.8391
Totals :				4055.80573	50.37622	

HPLC data for racemic (top) and optically enriched (bottom) **3-26**

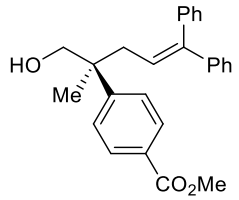


3-26 (racemic)

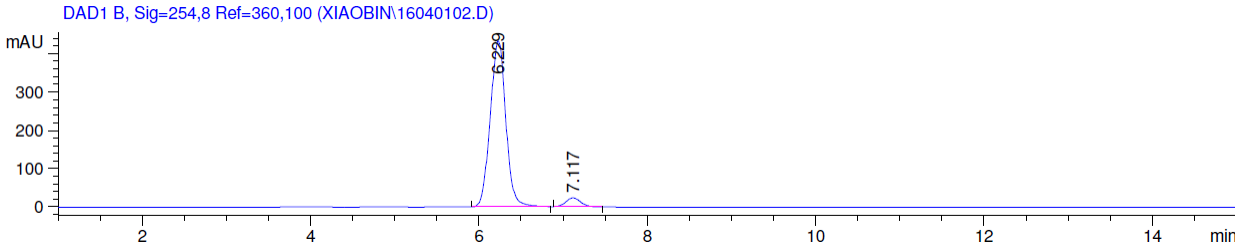


Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.228	VB	0.1967	3812.34888	299.01938	50.1462
2	7.119	BB	0.1876	3790.11304	307.96967	49.8538
Totals :				7602.46191	606.98904	



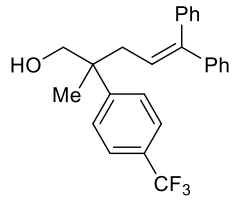
3-26



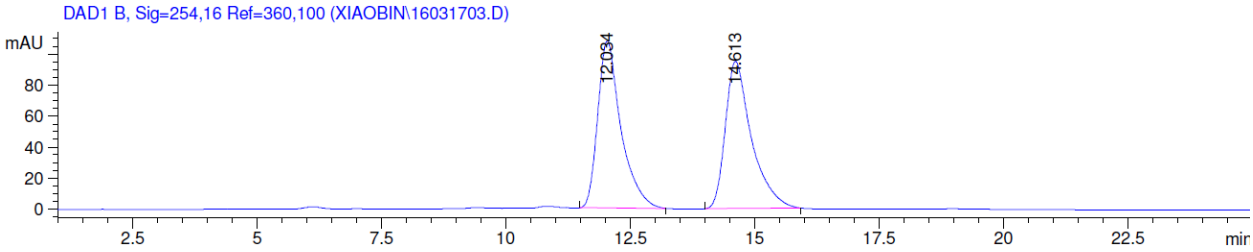
Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.229	BB	0.1982	5588.61719	433.96240	94.9405
2	7.117	BB	0.1909	297.82480	23.66070	5.0595
Totals :				5886.44199	457.62310	

HPLC data for racemic (top) and optically enriched (bottom) **3-28**

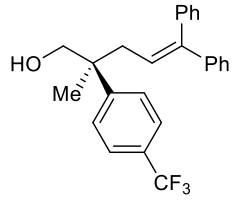


3-28 (racemic)

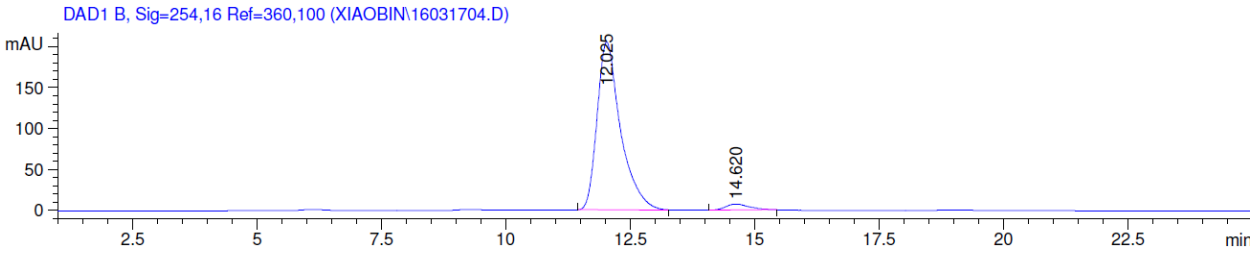


Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.034	BB	0.4815	3510.86914	107.92533	50.0619
2	14.613	BB	0.5429	3502.19312	95.25643	49.9381
Totals :				7013.06226	203.18176	



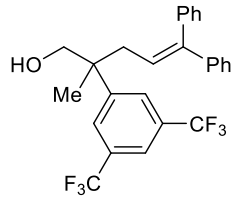
3-28



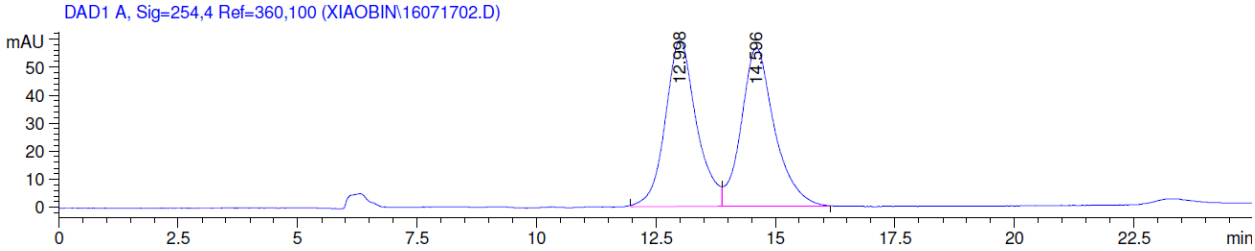
Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.025	BB	0.4850	6729.61084	205.00648	96.3178
2	14.620	PB	0.4834	257.27011	7.47756	3.6822
Totals :				6986.88095	212.48405	

HPLC data for racemic (top) and optically enriched (bottom) **3-29**

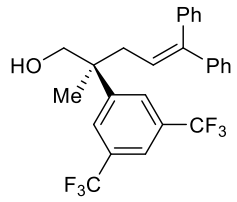


3-29 (racemic)

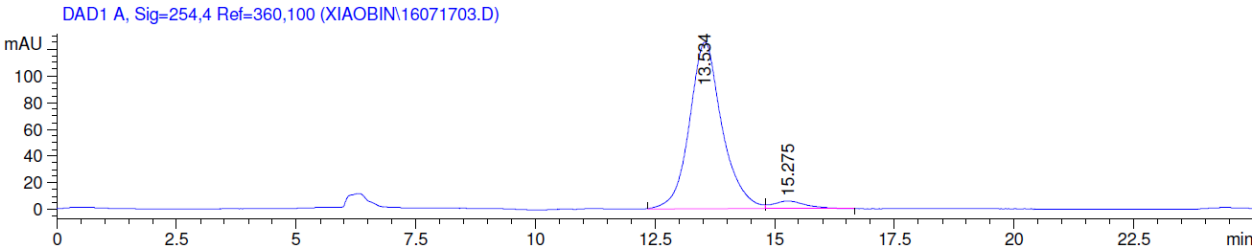


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.998	BV	0.6828	2700.31958	59.35141	49.5277
2	14.596	VB	0.7177	2751.81763	56.74717	50.4723
Totals :				5452.13721	116.09858	



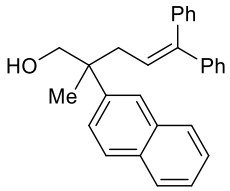
3-29



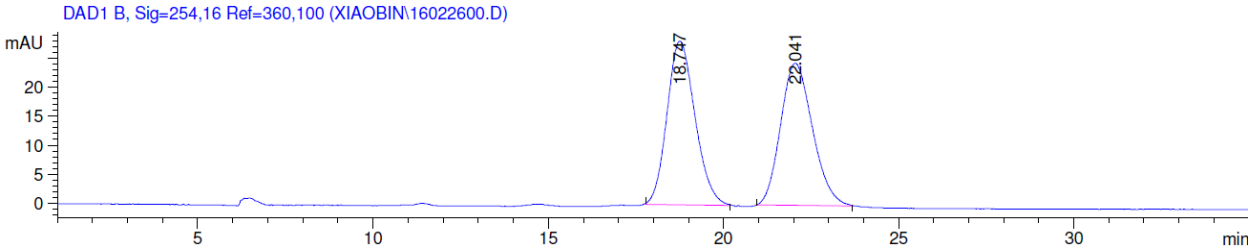
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.534	BV	0.7047	5907.40186	124.69146	95.4082
2	15.275	VB	0.6722	284.31061	5.79667	4.5918
Totals :				6191.71246	130.48813	

HPLC data for racemic (top) and optically enriched (bottom) **3-30**

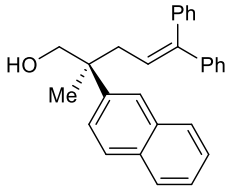


3-30 (racemic)

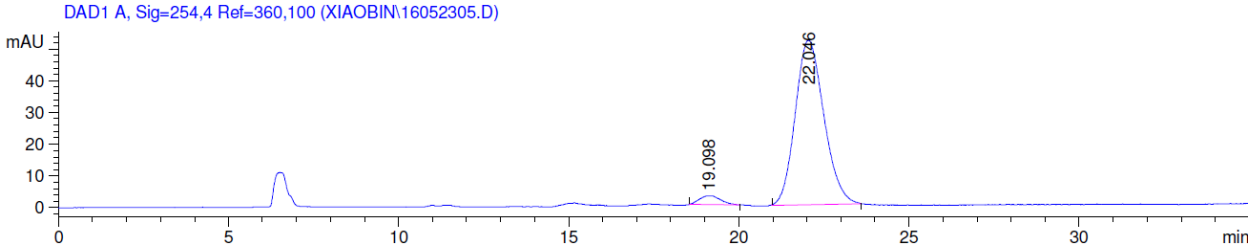


Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.747	BB	0.8049	1570.42920	28.23412	50.1605
2	22.041	BB	0.9141	1560.37695	24.53124	49.8395
Totals :				3130.80615	52.76536	



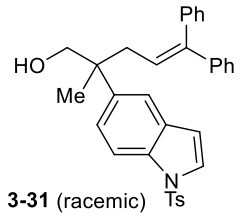
3-30



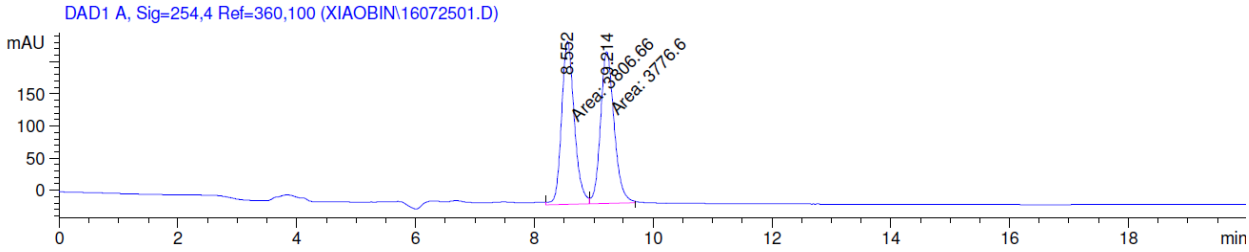
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.098	BB	0.5193	123.67179	2.85537	3.8874
2	22.046	BB	0.6944	3057.67017	52.12016	96.1126
Totals :				3181.34196	54.97553	

HPLC data for racemic (top) and optically enriched (bottom) **3-31**



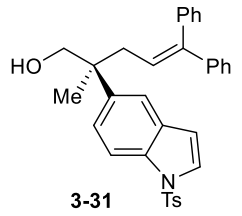
3-31 (racemic)



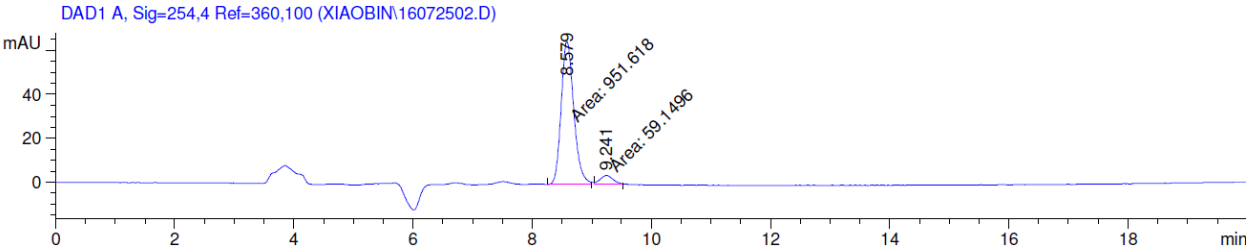
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.552	MF	0.2493	3806.66309	254.48920	50.1982
2	9.214	FM	0.2665	3776.60205	236.21884	49.8018

Totals : 7583.26514 490.70804



3-31

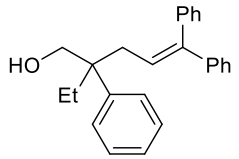


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

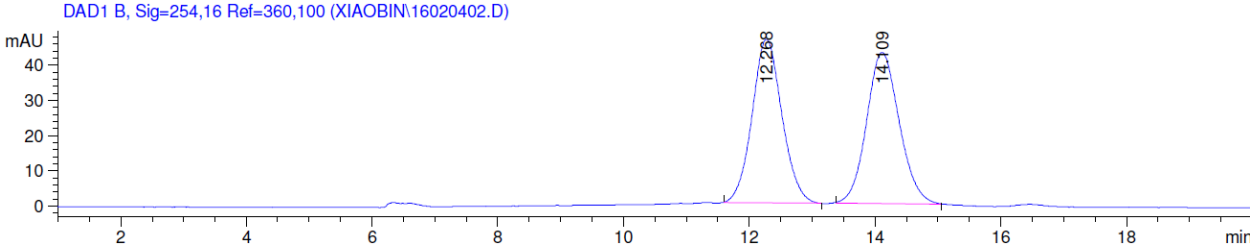
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.579	MM	0.2435	951.61816	65.12590	94.1480
2	9.241	MM	0.2520	59.14965	3.91202	5.8520

Totals : 1010.76781 69.03792

HPLC data for racemic (top) and optically enriched (bottom) **3-35**

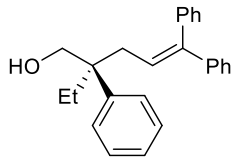


3-35 (racemic)

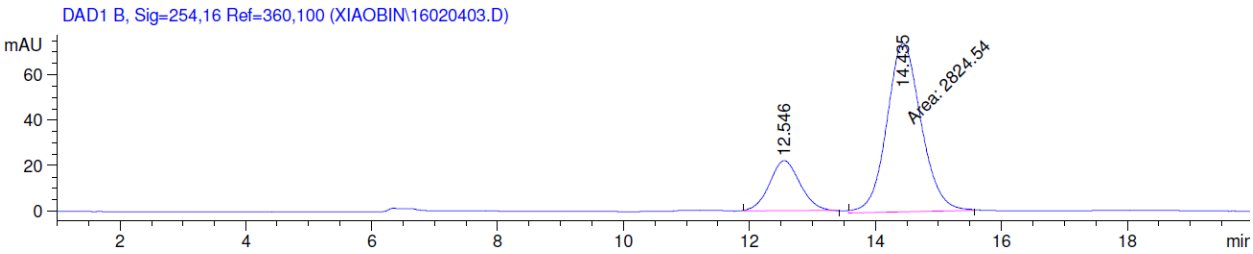


Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.268	BB	0.5078	1533.57788	46.37879	49.6478
2	14.109	BB	0.5589	1555.33923	42.90279	50.3522
Totals :				3088.91711	89.28158	



3-35



Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.546	BP	0.5036	750.12634	22.12191	20.9845
2	14.435	MM	0.6338	2824.53931	74.27210	79.0155
Totals :				3574.66565	96.39401	