Design and Synthesis of New Functionalized Boronic Acids for Direct Dehydrative Amidation of Poorly Nucleophilic Amines

by

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Abstract

Amide synthesis has been of great interest to chemists as the amide moiety occrus widely in agrochemicals, pharmaceutical agents, and biologically active molecules. Traditionally, amide bond formation requires the use of activated carboxylic acid derivatives or stochiometric amounts of coupling agents, which are generally toxic, expensive, and result in a large amount of undesired by-products that complicate product purification. To develop more environmentally friendly methodologies and to enhance atom-economy, in the past few decades, chemists have been exploring organoboron-catalyzed dehydrative amidation reactions. A series of bifunctional boronic acid catalysts proposed by Whiting and co-workers exhibited good catalytic activity in direct amide condensation, however they require elevated temperature to afford good yields. Our laboratory reported 5-methoxy-2-iodophenylboronic acid (MIBA) as an efficient catalyst giving high yields at temperatures ranging from ambient to 50 °C. Unfortunately, the substrate scope of MIBA and other catalysts remains limited, especially with aniline derivatives, acyclic secondary amines, and heteroaromatic acids. Attempting to overcome the challenge of amidation of poorly nucleophilic amines, we designed a functionalized boronic acid model aimed at activating the carboxylic acid with the B-O-B motif previously implicated in catalysis, and direct the amine with a proper coordinating group. With balanced structural flexibility and rigidity, boronic acid **A7**, (2'-(methylthio)-[1,1'-biphenyl]-2-yl)boronic acid, was identified as the most efficient promoter to aid in the formation of anilides. An expanded substrate scope with various aniline derivatives was demonstrated with good reaction efficiency. The scalability of the amidation reaction with **A7** along with its reusability exhibited this method's potential usefulness in large-scale reactions. Although work is required in order to further characterize the putative

intermediate and explore the potential interaction between the heteroatom of **A7** and the amine, the preliminary NMR experiments support the formation of a diacyloxy B–O–B bridged intermediate. Partial racemization was observed in (*R*)-2-phenylpropanoic acid synthesis with **A7**, though it gave a higher *ee* than MIBA. The loss of enantiomeric purity may be suppressed by lowering the reaction temperature, which would require a more reactive boronic acid.

Preface

This thesis is an original work by Jingning Zhou under the supervision of Dr. Dennis G. Hall. No part of this thesis has been previously published.

Dedication

To my parents who provided me with invaluable supports throughout this journey.

Acknowledgement

I would like to express my greatest gratitude to Dr. Dennis G. Hall for all his guidance, support, and patience throughout my graduate studies.

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List of Abbreviations

Å	Angstrom
°C	Celsius degree
Ac	Acetyl
ACS	American chemical society
AOP	7-(Azabenzotriazol-1-yl)oxy tris(dimethylamino) phosphonium hexafluorophosphate
aug-cc-pVDZ	Augmented correlation consistent-polarized valence double zeta
B3LYP	3-Parameter hybrid Becke exchange/Lee–Yang–Parr correlation functional
BEMT	2-Bromo-3-ethyl-4-methyl thiazolium tetrafluoroborate
BMTB	2-Bromo-3-methyl-4-methyl thiazolium bromide
Bn	Benzyl
BOP	((1H-Benzo[*d*][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)phosphonium hexafluorophosphate
br s	Broad singlet
Bu	Butyl
CBMIT	1,1'-Carbonylbis(3-methyl-1H-imidazol-3-ium) bis(trifluoromethanesulfonate)
CDI	Carbonyl diimidazole
ChCl	Choline chloride
CIP	2-Chloro-1,3-dimethylimidazolidinium hexafluorophosphate
CMBI	2-Chloro-1,3-dimethyl 1H-benzimidazolium hexafluorophosphate
Cp	Cyclopropane
d	Doublet
DATB	1,3-Dioxa-5-aza-2,4,6-triborinane
DCC	1,3-Diisopropylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane

dd	Doublet of doublets
ddd	Doublet of doublet of doublets
DES	Deep eutectic solvent
DFIH	2-Fluoro-1,3-dimethylimidazolidinium hexafluorophosphate
DIC	Dicyclohexylcarbodiimide
DMAP	*N,N*-Dimethylpyridin-4-amine
DMAPO	4-(*N,N*-dimethylamino)pyridine *N*-oxide
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPF	1,1′-Ferrocenediyl-bis(diphenylphosphine)
EDC	*N*-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
EI	Electron impact
equiv	Equivalence
ESI	Electrospray ionization
Et	Ethyl
g	Gram
GCI	Green Chemistry Institute
h	Hour
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HBTU	3-[Bis(dimethylamino)methyliumyl]-3*H*-benzotriazol-1-oxide hexafluorophosphate
HMPA	Hexamethylphosphoramide
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	Hydroxybenzotriazole
HPLC	High-performance liquid chromatography
i-Pr	Isopropyl
IR	Infrared spectroscopy
LCMS	Liquid chromatography mass spectrometry
m	Multiplet

M	Molar
m/z	Mass-to-charge ratio
Me	Methyl
mg	Milligram
MHz	Megahertz
MIBA	5-Methoxy-2-iodophenylboronic acid
MIDA	*N*-Methyliminodiacetic acid
min	Minute
mL	Milliliter
mm	Millimeter
mmol	Millimole
mol	Mole
MP	Møller–Plesset perturbation theory
MPO	4-Methylpyridine N-oxide
MS	Molecular sieves
NBP	*N*-Butyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance spectroscopy
o	Ortho
p	Para
PFP	Pentafluorophenol
Ph	Phenyl
PMI	Process mass intensity
PNP	4-Nitrophenol
POM	Polyoxometalates
ppm	Parts per million
PPYO	*P*-Pyrrolidinopyridine N-oxide
PyAOP	(7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
PyBOP	Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
q	Quartet

s	Singlet
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
t	Triplet
TAME	*Tert*-amyl methyl ether
TFFH	Tetramethylfluoroformamidinium hexafluorophosphate
THF	Tetrahydrofuran
TOF	Time of flight
Ts	Toluenesulfonyl
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
μL	Microliter

Chapter One: Introduction: Direct Dehydrative Amidation between Carboxylic Acids and Anilines

1.1 Introduction

Amide bond formation plays a critical and ubiquitous role in modern organic synthesis. Among the total syntheses reported in 2014, over 50% contained amidation reactions.[1] Amide bond moieties are also generally present as common building blocks within peptides, proteins, and bioactive molecules.[2] A common derivative of amides are anilides, which can be formed from the condensation between anilines and carboxylic acids. Anilides are a typical moiety found in many herbicides, fungicides, and pharmaceutical molecules.[3] In this chapter, different approaches towards anilides are presented and discussed.

1.2 Anilide Moieties in Natural Products and Bioactive Molecules

To improve agricultural productivity, herbicides are generally utilized as weed control agents. Chemical weed control has been used for over a century, including numerous anilide compounds.[3] Selected examples of anilide herbicides are shown in Figure 1-1. These anilide species work as carotenoid biosynthesis inhibitors, resulting in membrane leaking and the desiccation of tissues.[4] Anilide moieties are also commonly found in fungicides, such as salicylanilide, carboxin, and a novel succinate dehydrogenase inhibitor (SDHI) pyraziflumid.[5] Derivatives of salicylanilide are commonly utilized in pharmacological research. Chlorinated derivatives, such as niclosamide and oxyclozanide, can be used as anthelmintics. Brominated derivatives including dibromsalan and metabromsalan can be used as antibacterial disinfectants.[6] More recently, 23 anilide-containing compounds, including Aubagio, Kalydeco, Doliprane, and Lipitor, were among the top 200 small molecule pharmaceuticals by retail sales in 2020.[7]

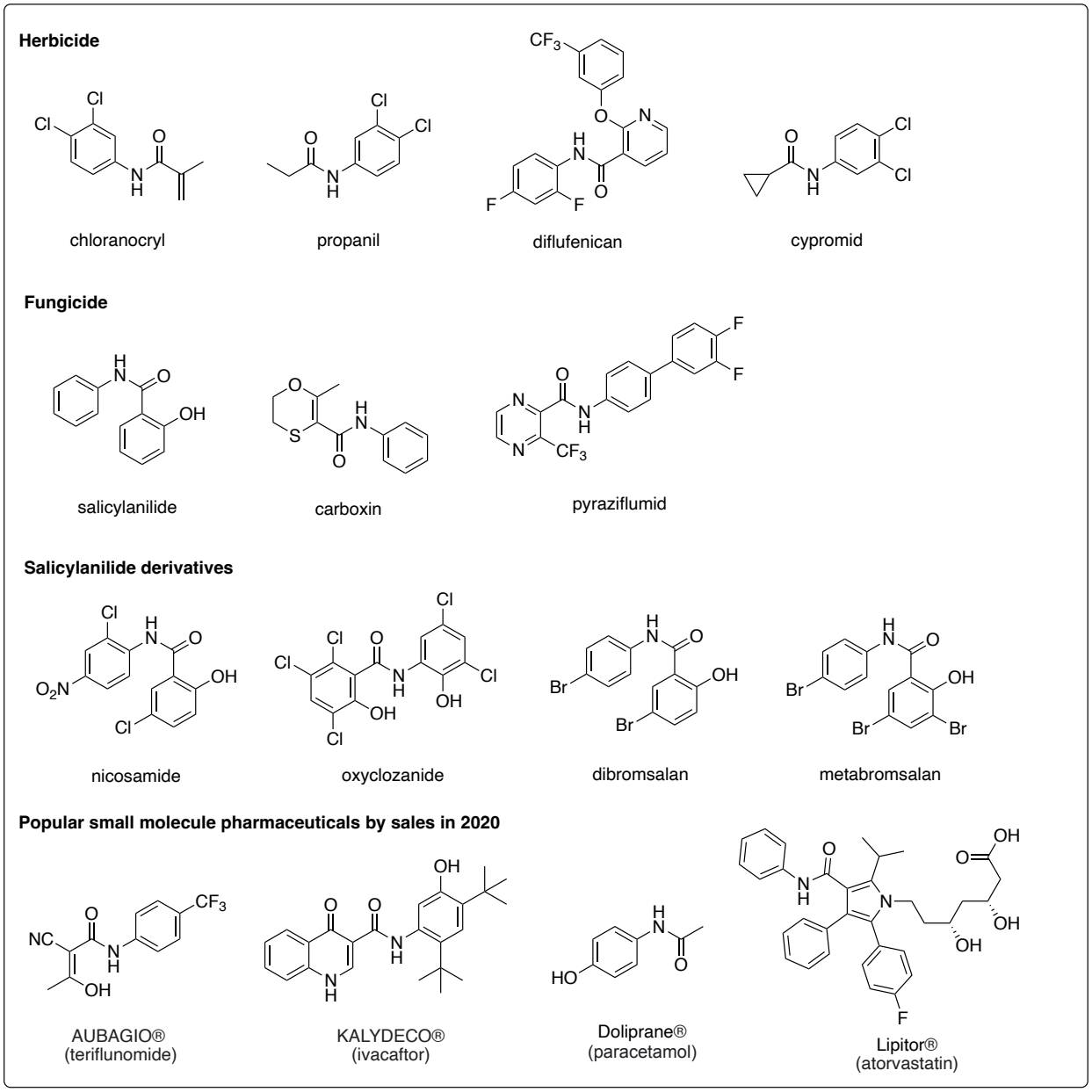


Figure 1-1: Examples of anilide molecules with bioactivity.

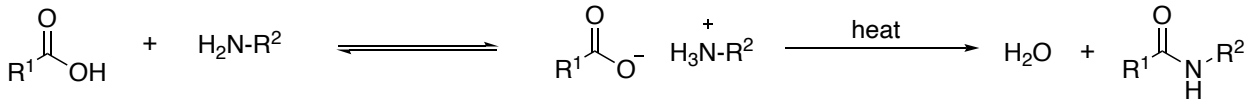
According to the statistical study of synthesis building blocks published by Wang in 2021,[8] among approximately 7000 unique amine species used in syntheses from 2007–2016, over one third of amine building blocks are aniline derivatives. However, the direct amide condensation with anilines remains challenging due to their electron deficiency and reduced nucleophilicity, especially considering atom-economy, energy cost, and ease of purification.

1.3 Established Methods for the Synthesis of Anilides

A 2007 survey by the American Chemical Society (ACS) Green Chemistry Institute (GCI) declared the development of "greener" amidation reactions a high priority research area for global pharmaceutical manufacturing.[2] Correspondingly, the pursuit of novel amidation methods with high atom economy has been of interest to chemists for decades. In this section, various established protocols for direct amide condensation of anilines will be reviewed, and their individual advantages and disadvantages will be discussed.

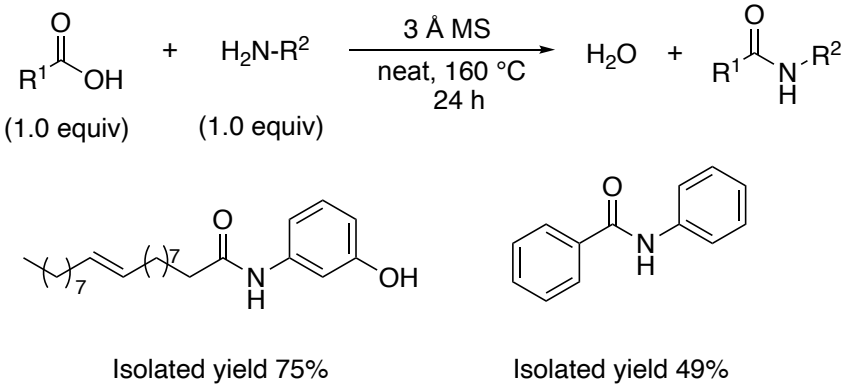
1.3.1 Thermal Dehydrative Amidation

To develop an amidation method that is green, clean, and efficient, the direct dehydrative process is an attractive solution where a carboxylic acid and amine are coupled together without a stochiometric activator. Upon mixing acid and amine at ambient temperature, an acid-base reaction was observed (Scheme 1-1).[9] The equilibrium between neutral reagents and the ammonium carboxylate salt is influenced by the acidity/basicity of the substrates as well as the reaction conditions. The formation of the ammonium carboxylic salt is preferred in polar protic solvents and the ion pairs remain associated instead of diffusing apart in non-polar solvents.[9] To dehydrate the ammonium carboxylate, significant heating is required, which strictly limits the functional group tolerance of this method.



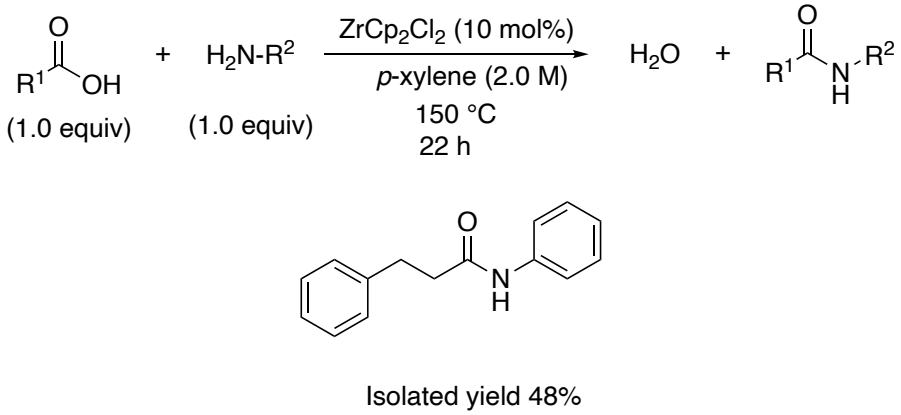
Scheme 1-1: Direct dehydrative amidation reaction.

Direct amidation was observed as a background reaction in catalytic amide studies. Gooβen and co-workers reported the direct thermal amidation under neat conditions in 2009.[10] The reactions required heating at 160 ℃ for 24 h in the presence of 3 Å molecular sieves. Among 14 reported substrates, only two anilide examples were reported as shown in Scheme 1-2.



Scheme 1-2: Anilide examples reported by Gooβen and co-workers in 2009.

The thermal amidation reaction can also be conducted without the removal of water. According to a report by Williams and co-workers in 2012, the amidation reaction between unactivated carboxylic acids and amines can be performed at 110–150 ℃ in the presence of a zirconium catalyst.[11] The only successful anilide example is shown in Scheme 1-3.

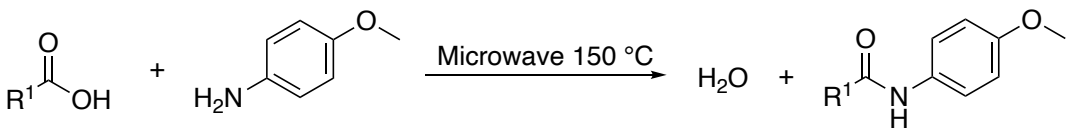


Scheme 1-3: Anilide example reported by Williams and co-workers in 2012.

1.3.2 Microwave Irradiation

Microwave irradiation is famous for rapidly and uniformly heating reaction mixtures with high frequency electric fields.[12] It has been decades since microwave irradiation was utilized for amidation reactions. As the heat source, microwave irradiation promotes the pyrolysis of the ammonium carboxylate salt under solvent-free conditions.[13] Although it provides a simplified and efficient method for amidation reactions, microwave conditions are still limited to simple achiral substrates due to potential decomposition and racemization. In 2002, Volatron demonstrated that under microwave conditions the excess of one reagent was beneficial to the

nucleophilic attack of the amine's nitrogen to the carbonyl group of carboxylic acid (Table 1-1).[14]



R^1	Reagent Ratio (Acid: Amine)	Isolated Yield (%)
Bn	1:1	62
Bn	1:1.5	68
Bn	1.5:1	69
n-C_9H_{19}	1:1	23
n-C_9H_{19}	1:1.5	58
n-C_9H_{19}	1.5:1	34

Table 1-1**:** The effect of reagent ratio under microwave conditions reported by Volatron in 2002.

The potential hydrogen bonding interactions enhanced the electrophilicity of the carbonyl as depicted in Figure 1-2. A similar enhancing effect was also observed upon the addition of imidazole into the reaction between benzoic acid and benzylamine and the yield improved from 13 to 61%.[15]

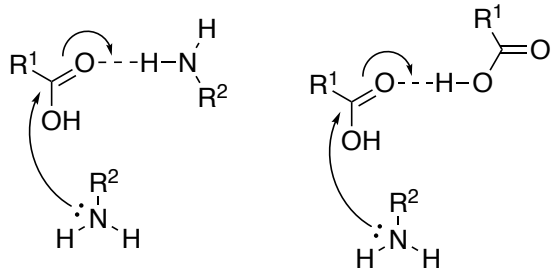
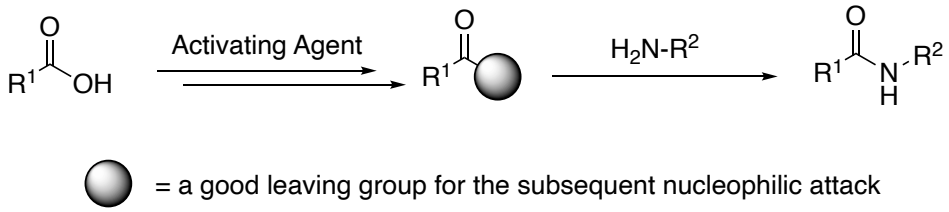


Figure 1-2: The hydrogen bonding interactions proposed to enhance the electrophilicity of the carbonyl group.

1.3.3 Non-Boron Reagents for Anilide Condensation

1.3.3.1 Stoichiometric Activation of Carboxylic Acids

To enhance the efficiency of amide formation, methods have been developed to activate a carboxylic acid ahead of the nucleophilic attack from amine. An array of methods has been developed to transform unactivated carboxylic acids into acyl halides, anhydride, or ester. Various carbodiimide, imidazolium, ammonium, phosphonium, and uronium reagents were utilized in carboxylic acid activation. The activated acylating agents are formed either independently or *in situ*, and the common idea shared by those activation reagents is to create a good leaving group onto the carboxylic acid (Scheme 1-4).



Scheme 1-4: Activation of the carboxylic acid.

Acyl halide reagents are the most common activating agents for hindered substrates. In 1903, the first chlorinating method with thionyl chloride, $SOCl_2$, was introduced by Fisher.[16] Since then, numerous halogenating reagents have been developed (Figure 1-3), such as $(COCl)_2$,[17] PCl_5,[18] cyanuric chloride,[19] tetramethylfluoroformamidinium hexafluorophosphate (TFFH), and 2-Fluoro-1,3-dimethylimidazolidinium hexafluorophosphate (DFIH).[20]

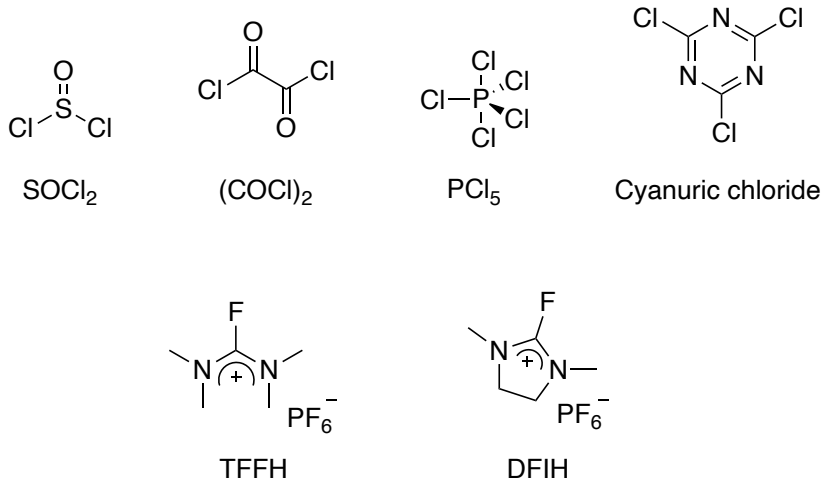
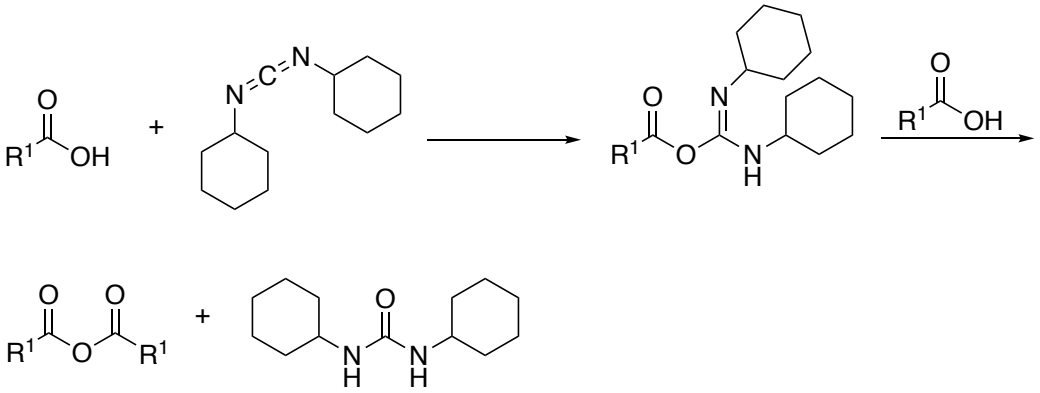


Figure 1-3: Select halogenating reagents.

Those reagents can effectively convert carboxylic acids into reactive acid halide species. However, the biggest concern of those methods is the production of a stochiometric amount of side product. When a chlorinating reagent is used, a stochiometric amount of base is needed to balance the potential pH change caused by the acidic by-product, HCl. Furthermore, the use of oxalyl chloride, $(COCl)_2$, produces stoichiometric amounts of HCl, CO_2, and CO. The highly toxic carbon monoxide may cause severe safety hazards, which limits the application of this method in large-scale production.[21] The chlorinating agent proposed by Ghosez, cyanuric chloride, avoids the formation of acid by-product. However, the formation of the neutral side-product, 4,6-dichloro-1,3,5-triazin-2-ol, is still not ideal in terms of the atom economy of the reaction.[19] An acid fluoride is formed *in situ* under reaction conditions using TFFH or DFIH. However, the short shelf lives of these reagents and their toxic by-products restrict the applications of those fluorinating reagents.[20]

The applications of anhydride and ester reagents have similar limitations in terms of atom economy. After the activation of the carboxylic acid, only part of the acid precursor will remain in the final amide product. The preparation of symmetrical anhydrides requires either azeotropic distillation of the carboxylic acid or a stochiometric amount of dicyclohexylcarbodiimide (DCC), resulting in extra energy cost and reduced atom economy (Scheme 1-5).[22] The cost can be reduced by using mixed anhydrides, however the regioselectivity of the subsequent nucleophilic attack by the amine needs to be carefully controlled through steric or electronic effects within the anhydride.[23]



Scheme 1-5: Preparation of symmetric anhydride with DCC.

As shown in Figure 1-4, the most common choices of ester reagents are hydroxybenzotriazole (HOBt),[24] 4-nitrophenol (PNP),[25] and pentafluorophenol (PFP).[26] After reacting with the carboxylic acid, the active esters can react with amines under mild conditions. The electron withdrawing effect of the substituent within the alcohol reagent enhances the electrophilicity of the resulting ester and promotes the nucleophilic attack of the amine. According to Carpino in 1993, 1-hydroxy-7-azabenzotriazole (HOAt) exhibited higher reactivity than HOBt, which might be explained by the additional coordinating effect between nitrogen of the amine and the pyridine nitrogen (Figure 1-5).[27]

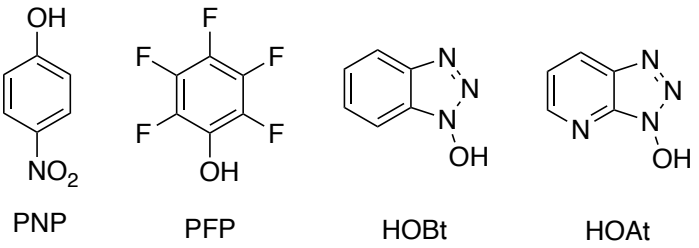


Figure 1-4: Selected alcohols for active ester formations.

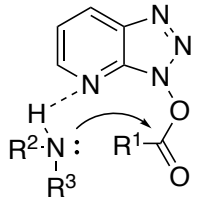


Figure 1-5: The coordinating effect between HOAt and amine.

Popular carbodiimide reagents, such as dicyclohexylcarbodiimide (DCC), 1,3-diisopropylcarbodiimide (DIC), and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide (EDC), exhibit a balance between moderate reactivity and a fair commercial cost (Figure 1-6).[28]

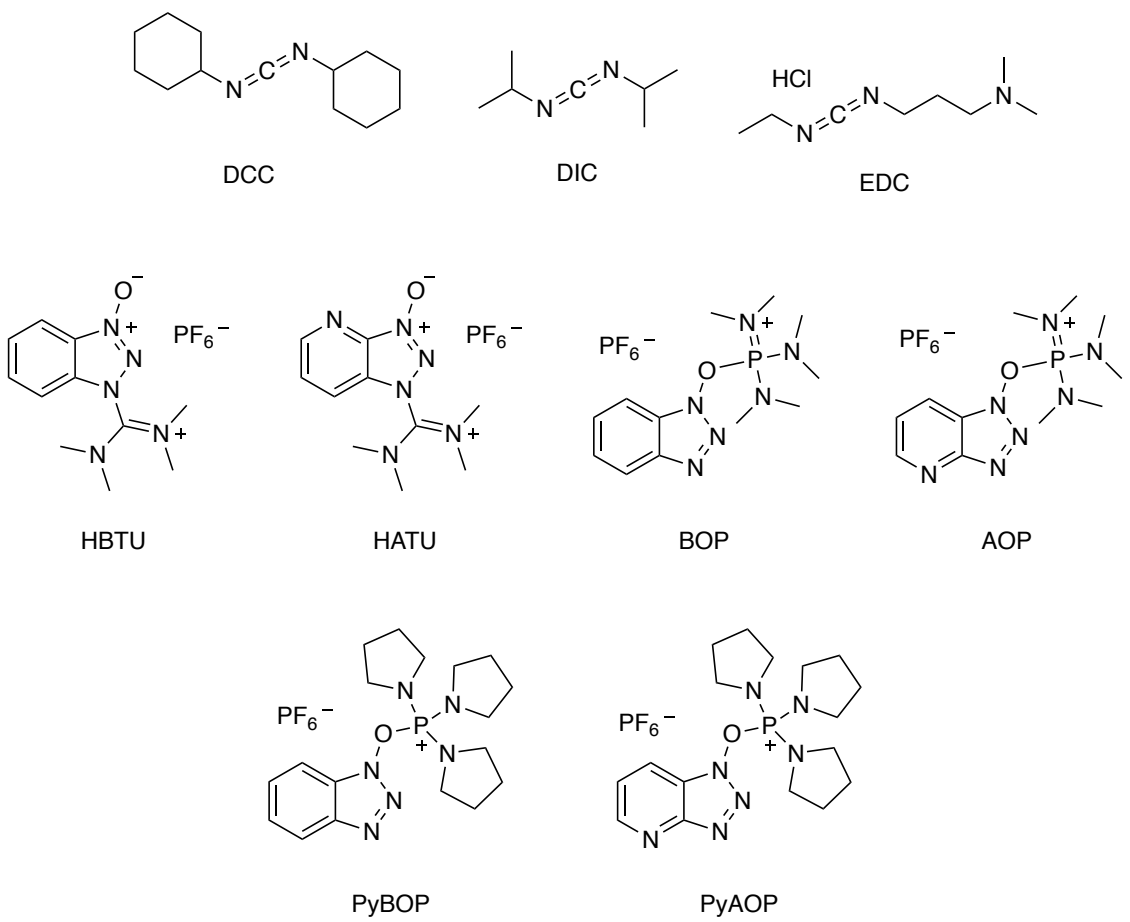
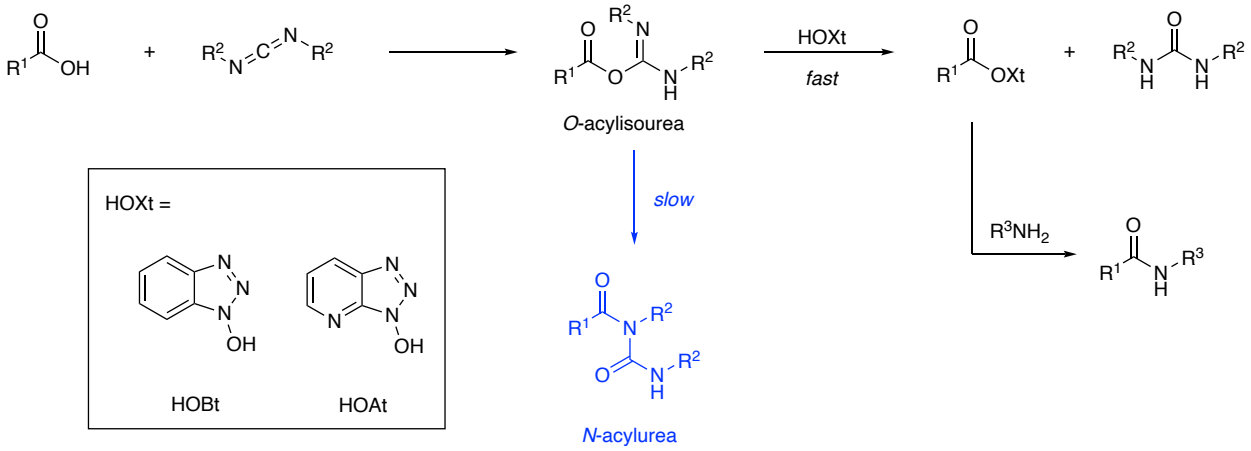


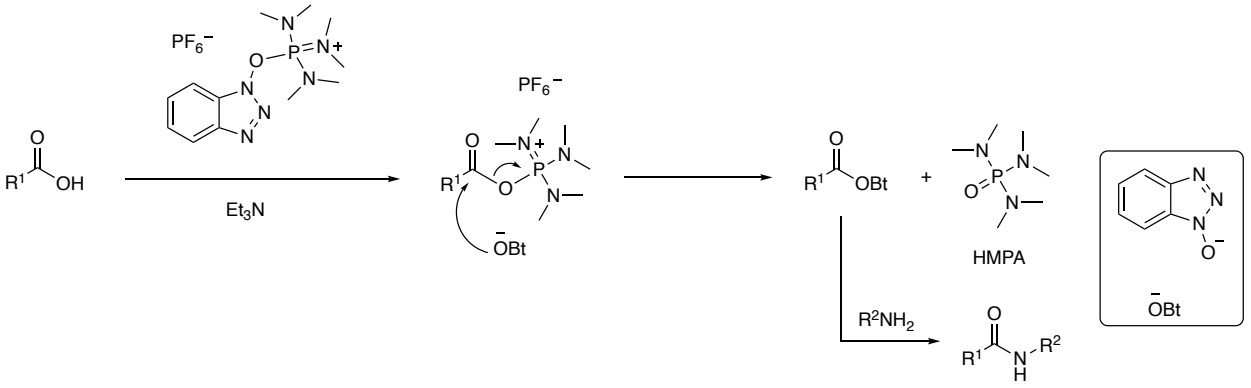
Figure 1-6: Selected amide coupling reagents.

To enhance the efficiency of those carbodiimide-mediated reactions, HOBt or HOAt can be added to prevent the formation of undesired *N*-acylurea. Due to the acidity of HOXt, the *O*-acylisourea intermediate remains protonated, suppressing the intramolecular shifting that forms an unreactive side-product (Scheme 1-6).[28] Based on the development of carbodiimide reagents, HOBt- and HOAt-based uronium, phosphonium, and immonium salts are recognized as efficient techniques for direct, stoichiometric amidation reactions (Figure 1-6), such as 3-[bis(dimethylamino)methyliumyl]-3*H*-benzotriazol-1-oxide hexafluorophosphate (HBTU), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU),[29] ((1H-benzo[*d*][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP),[30] 7-(azabenzotriazol-1-yl)oxy tris(dimethylamino) phosphonium hexafluorophosphate (AOP),[31] benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), and (7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyAOP).[32]



Scheme 1-6: HOXt acts as an additive in the carbodiimide-mediated amidation reaction.

HBTU and HATU provide quick coupling reactions where the formation of the urea by-product drives the reaction to completion. In those reactions, HOBt can also be used as an additive to further accelerate the reaction rate during the amidation reaction.[33] With the assistance from a base such as triethylamine or Hünig's base, BOP, also known as Castro's reagent, was the first reported phosphorous-based reagent. The mechanism is shown in Scheme 1-7. Despite the high reactivity of Castro's reagent, the formation of a toxic side-product, hexamethylphosphoramide (HMPA), raises concerns of using this method in industrial production.[34] To overcome this problem, different variations like AOP, PyBOP, and PyAOP were generated. In PyBOP and PyAOP, the dimethylamine attached to the phosphorus was replaced by pyrrolidine, which avoids the formation of HMPA.



Scheme 1-7: Mechanism of BOP mediated amidation reaction.

The most famous imidazolium reagent, carbonyl diimidazole (CDI), provides base-free, one-pot conditions for amide bond formation.[35,36] In the mechanism shown in 1-7, the carbonyl

carbon of CDI is attacked by the carboxylate, affording the active imidazolide intermediate. Upon the addition of amine, the desired amide product is formed along with the side product imidazole. Other efficient imidazolium reagents are shown in Figure 1-7. In 1998, Rapoport and co-workers disclosed a new imidazolium reagent 1,1'-carbonylbis(3-methyl-1H-imidazol-3-ium) bis(trifluoromethanesulfonate) (CBMIT), with a methylated nitrogen on the imidazole rings.[37] The triflate salt exhibited high reactivity with hindered substrates and little racemization was observed with the assistance from copper additives. However, CBMIT is sensitive to moisture and the reaction solvent was limited to nitromethane due to its high polarity.[37] Recently, Xu's group has reported the imidazolium reagents 2-chloro-1,3-dimethyl 1H-benzimidazolium hexafluorophosphate (CMBI) and 2-bromo-3-ethyl-4-methyl thiazolium tetrafluoroborate (BEMT). CMBI was developed based on the molecular structure of 2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate (CIP)[38] and exhibited good reactivity towards hindered peptide bond formation during the synthesis of Actinomycin D.[39] In the reactions of *N*-alkylated amino acids, BEMT showed good reactivity whereas racemization hampered the usage of this reagent.[40] As an improved alternative, 2-bromo-3-methyl-4-methyl thiazolium bromide (BMTB) was published by Wischnat in 2003.[41] This crystalline and non-hygroscopic reagent is easy to handle and can be stored at room temperature for months.

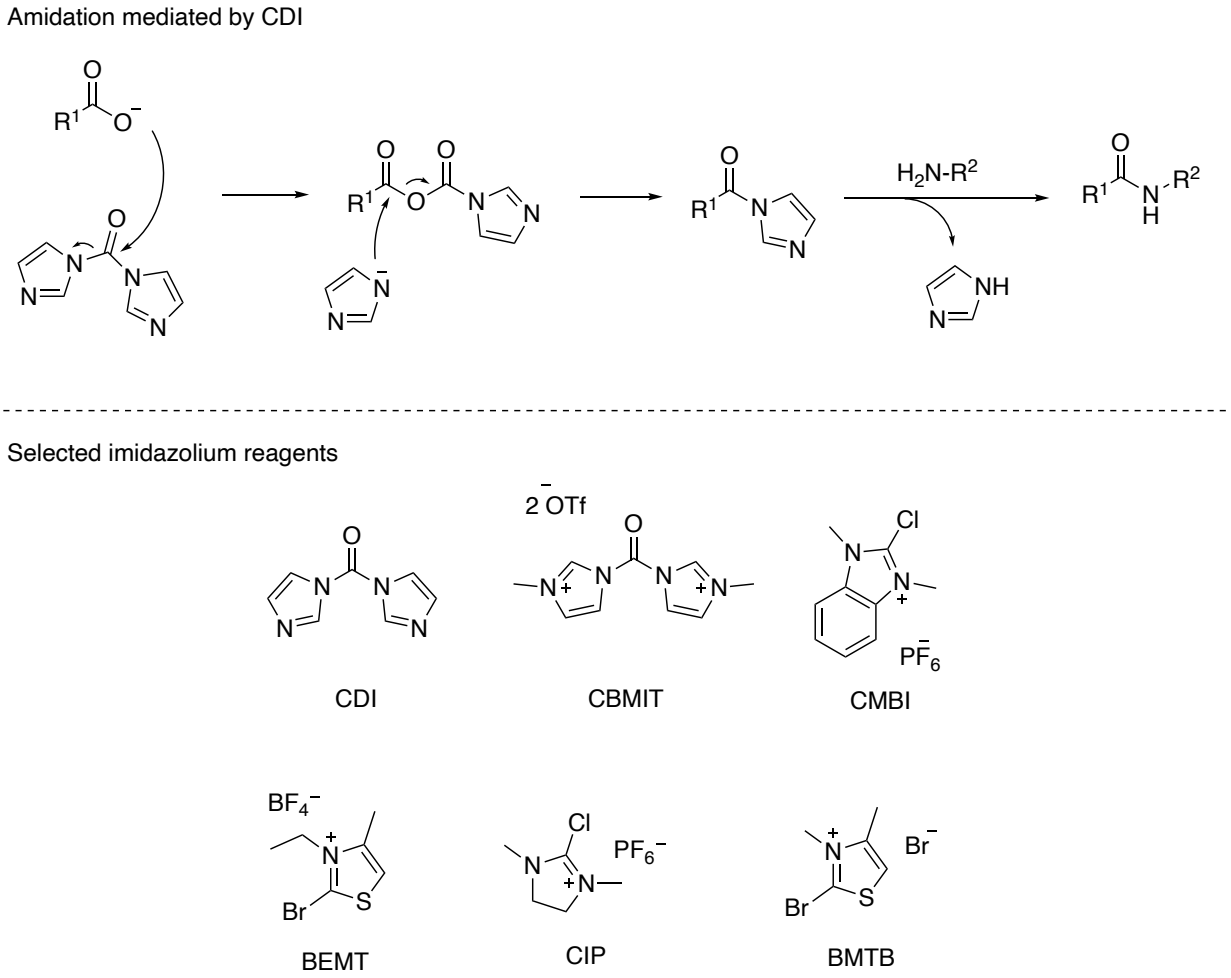


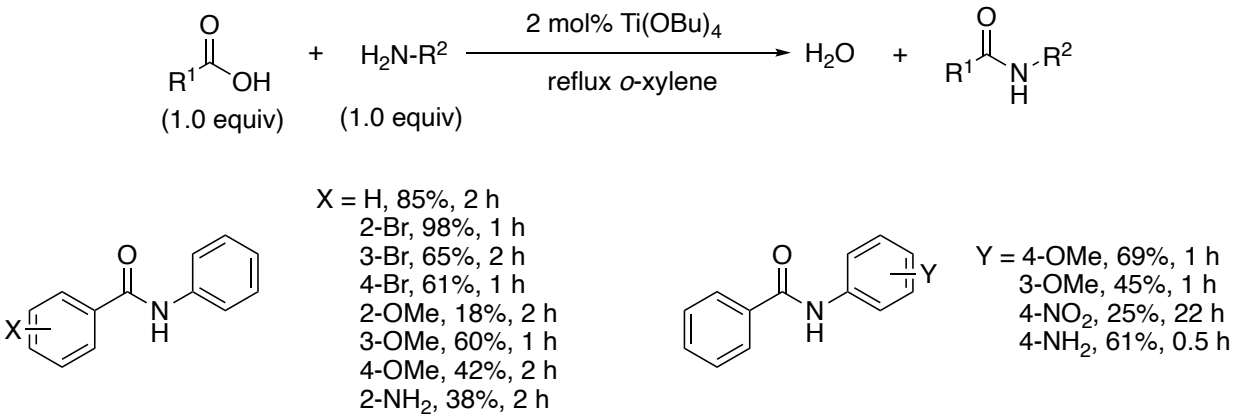
Figure 1-7: Amidation mediated by CDI and selected imidazolium reagents.

The development of methods for stochiometric activation of carboxylic acids for amide bond synthesis mainly focuses on reagent reactivity, potential racemization, and the effect of side products. This also reflects the common drawbacks shared by many of the techniques discussed in this section, such as hazardous by-products, instability of the reagents, high cost of the reaction, and poor atom economy. Combining activating reagents enhances the reaction efficiency but causes difficulty in purification and reduced atom economy. In pursuit of greener methods that can activate the carboxylic acid with a lower E-factor (total mass of waste divided by total mass of product) and PMI (total mass in a process step divided by mass of product) factor, chemists have been exploring catalytic strategies in the past decades.

1.3.3.2 Metal Catalysis

Multivalent metal salts have exhibited excellent reactivities in direct amidation of unactivated carboxylic acids. Based on a literature review from Sheppard in 2019,[42] group IV metal catalysts are the dominant class of metal-based catalysts for challenging amidation reactions with anilines. These salts, except hafnium species, are generally commercially available or easy to prepare. Since they are produced from naturally abundant metals, they have the advantage of low commercial cost. However, methods with those metal catalysts generally require high reaction temperatures which is disadvantageous and largely limited the substrate scope. Sugi and co-workers compared the reactivities of various metal reagents with a model reaction between palmitic acid and decylamine in refluxing mesitylene.[43] The relative catalytic reactivities are as follows: $FeCl_3 \cdot 6H_2O$ > $ZnCl_2$ > $NiCl_2 \cdot 6H_2O$ > $MnCl_2 \cdot 6H_2O$ > $CoCl_2 \cdot 6H_2O$ > $CrCl_3 \cdot 6H_2O$ > $ZrOCl_2 \cdot 8H_2O$ > $CuCl_2 \cdot 4H_2O$ > $InCl_3$ > $AlCl_3 \cdot 6H_2O$.

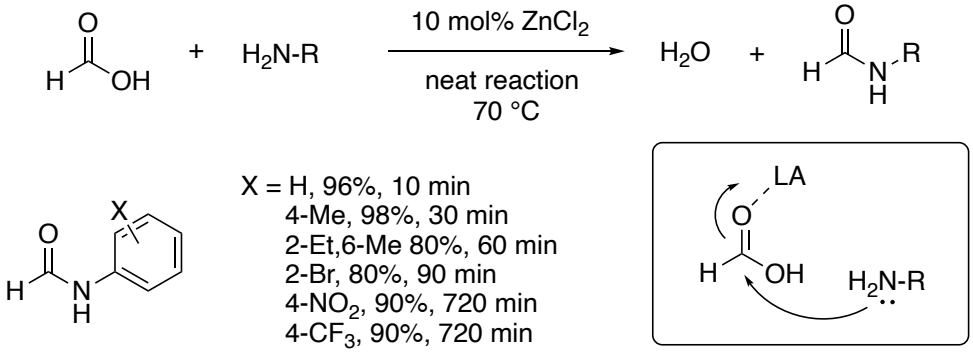
The first reported metal catalyst for the *N*-acylation of aniline was $Ti(OBu)_4$, disclosed by Shteinberg in 1988.[44] The amide coupling between benzoic acid and aniline derivatives was catalyzed by 2 mol% $Ti(OBu)_4$ in refluxing *o*-xylene at 145 ℃.[41] The reaction was completed in 1–2 hours with yields ranging from 38% to 98%. Selected examples are depicted in Scheme 1-8. Relatively lower reactivities were observed with electron-rich benzoic acids or electron deficient anilines. Additionally, in refluxing aniline, the reaction between aniline and 3-hydroxy-2-naphthoic acid afforded amide product in 80% yield when the titanium salt-catalyzed reaction was heated at 180 ℃ for 2 hours. A similar Ti(IV) alkoxide, $Ti(O^iPr)_4$, has demonstrated catalytic reactivity in reactions of functionalized substrates including amino acids, but no anilide examples has been reported.[43]



Scheme 1-8: Selected examples of amidation reactions catalyzed by $Ti(OBu)_4$.

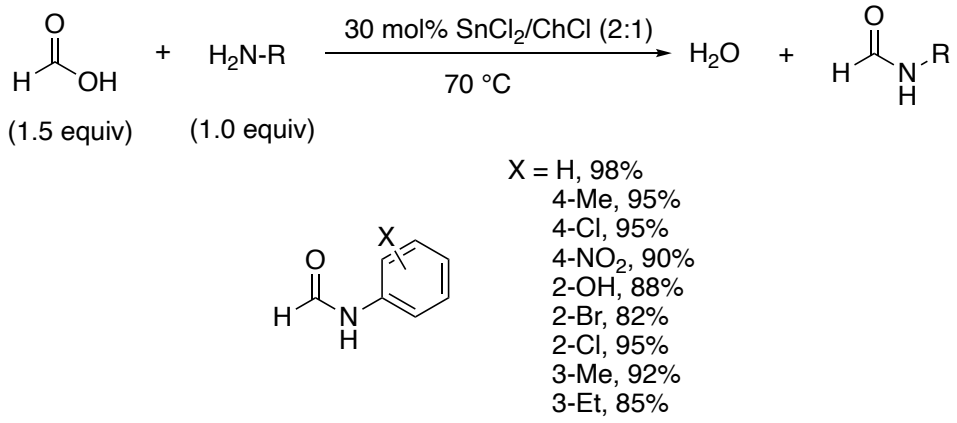
There are also reported protocols with another group IV metal catalyst, Zr. According to the data published by Williams,[45] with 5 mol% Cp_2ZrCl_2, *N*,3-diphenylpropanamide was afforded in 45% yield when heated in toluene at 110 ℃ for 24 hours. When $ZrCl_4$ was used instead, a yield of 37% was observed. Under the same conditions, *N*-(4-hydroxyphenyl)acetamide was obtained using Cp_2ZrCl_2 with a yield of 88% after 24 hours. Zr(IV)- and Hf(IV)-substituted polyoxometalates (POM) also exhibited catalytic reactivity in intramolecular amide bond formation with amino acids and dipeptides. The reactions were conducted open to air in DMSO at 70 ℃, whereas no anilide substate has been reported in intermolecular amidation reactions.[46]

In 2009, Shekhar reported the *N*-acylation of aniline with 10 mol% zinc chloride in neat formic acid.[47] At 70 ℃, electron rich aniline derivatives afforded formamide products in 80–98% yields in 10–90 min as shown in Scheme 1-9. In the proposed mechanism, zinc acts as a Lewis acid, activating the carboxylic acid towards nucleophilic attack by interacting with the carbonyl oxygen.



Scheme 1-9: Selected examples of formamides obtained with $ZnCl_2$ and proposed intermediate.

Tin chloride was reported to be an efficient catalyst when combined with a Deep Eutectic Solvent (DES) [48] by Azizi in 2012.[49] DES is a novel reaction medium made by heating the mixture of quaternary ammonium salt and metal halide. With 30 mol% of $SnCl_2$/ choline chloride (ChCl) DES catalyst, formanilide products with various substituents were obtained at up to quantitative yields at 70 ℃ within 20 min. As the amide coupling reagent, formic acid exhibited higher reactivity than trimethyl orthoformate. Selected formanilide products are shown in Scheme 1-10.



Scheme 1-10: Selected formanilide examples obtained with $SnCl_2$/ChCl DES catalyst.

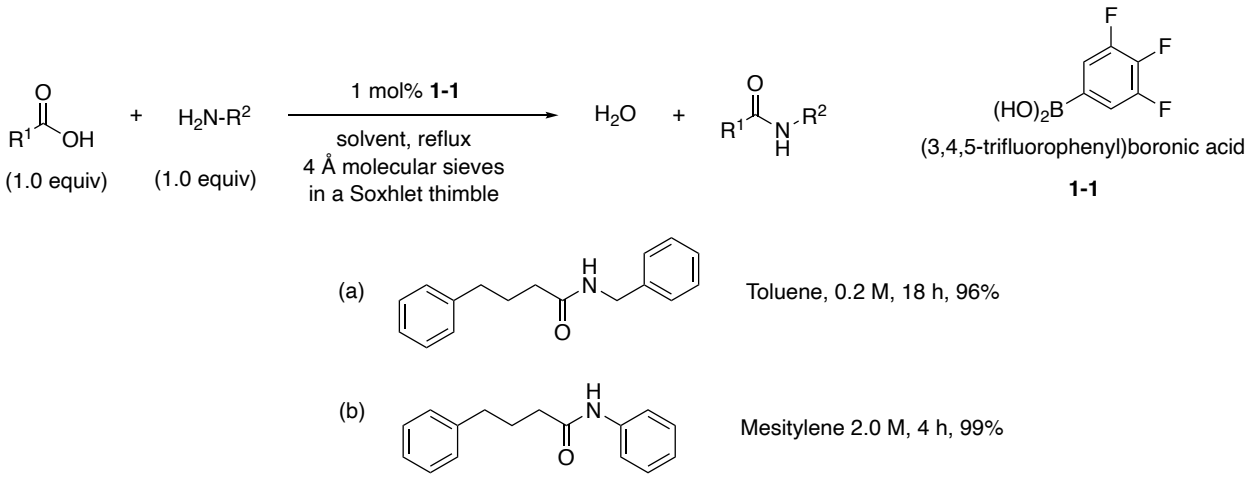
Anilides have also been prepared using heterogenous metal-containing catalysts. For example, the recyclable Zeolite-HY catalyst reported by Kulkarni in 2000,[50] nano-MgO proposed by Reddy in 2010,[51] nano sulfated-TiO_2 published by Hosseini-Savari in 2011,[52] and sulfated tungstate.[53] These protocols generally offer good catalyst recyclability but require elevated temperatures ranging from 115 to 120 ℃. The substrate scopes are always limited to a few carboxylic acids, like formic acid or acetic acid. The developments of more universally applicable methods are still ongoing.

1.3.4 Boron Reagents for Direct Anilide Condensation

1.3.4.1 Boron Reagents Effective at Temperatures Above 100 °C

1.3.4.1.1 Electron Poor Arylboronic Acid: 3,4,5-Trifluorophenylboronic Acid

The first catalytic boron reagents for amidation reactions were reported by Yamamoto and co-workers in 1996.[54] Using 5 mol% arylboronic acid **1-1**, the reagents were heated in refluxing toluene with 4 Å molecular sieves in a Soxhlet thimble to remove water. The boronic acid catalyst is thermally stable and is stable to exposure to acid, base, and air.

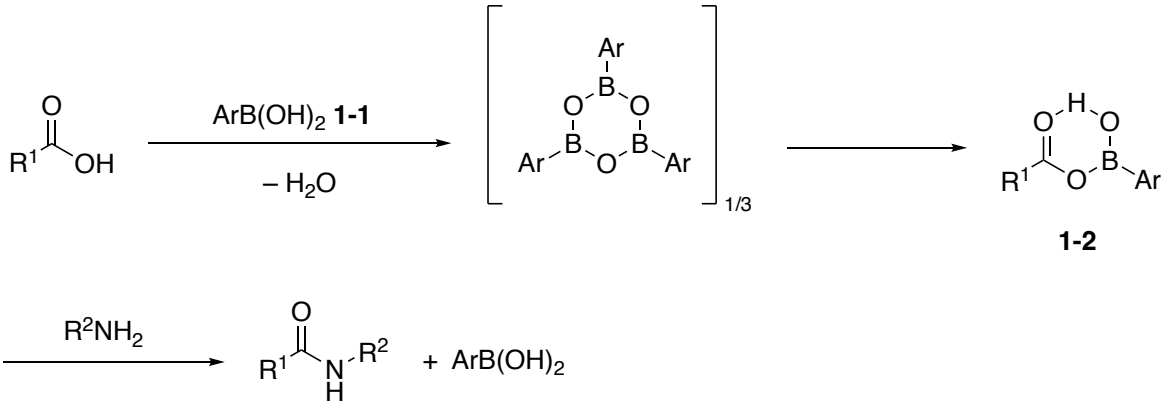


Scheme 1-11: Amidation catalyzed by Yamamoto's reagent **1-1**.

With favored substrates, such as the reaction (a) between 4-phenylbutyric acid and benzylamine, 18-hour heating at 110 °C was required to afford the amide product in a yield of 96%. With more challenging substrates, such as the reaction (b) between 4-phenylbutyric acid and aniline, the reaction required heating in refluxing mesitylene at 165 °C for 4 hours to afford the amide product in a yield of 99%. The conditions are also applicable to sterically hindered carboxylic acids and amino acids. Minimal racemization was observed in reactions between optically active aliphatic α-hydroxycarboxylic acids and benzylamine. In 2000, the same group reported applications of Yamamoto's catalyst in the synthesis of polyamides, such as aramids semi-aromatic nylons.[55] The polycondensation was conducted in refluxing *o*-xylene or 10:1

(w/w) *m*-terphenyl and *N*-butyl-2-pyrrolidinone (NBP) with the reaction temperature cycling between 200 and 300 ℃.

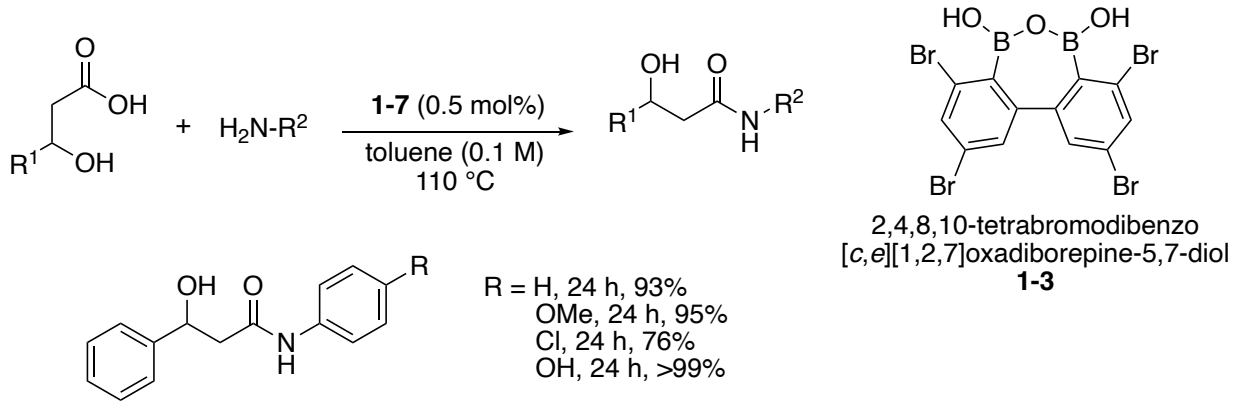
The authors also proposed the mechanism of their reported arylboronic acid-mediated amidation reactions (Scheme 1-12). The formation of (acyloxy)boron compound **1-2**, which the authors demonstrated to be the rate-determining step, was confirmed when **1-2** was isolated and characterized with IR and proton NMR in their control experiments. The authors theorized that the electron-withdrawing effect from the three fluoride substituents on the aromatic ring promoted the formation of the active (acyloxy)boron species, which was subsequently attacked by the nucleophilic amine.



Scheme 1-12: The proposed mechanism of boronic acid **1-1** catalyzed amidation reaction.

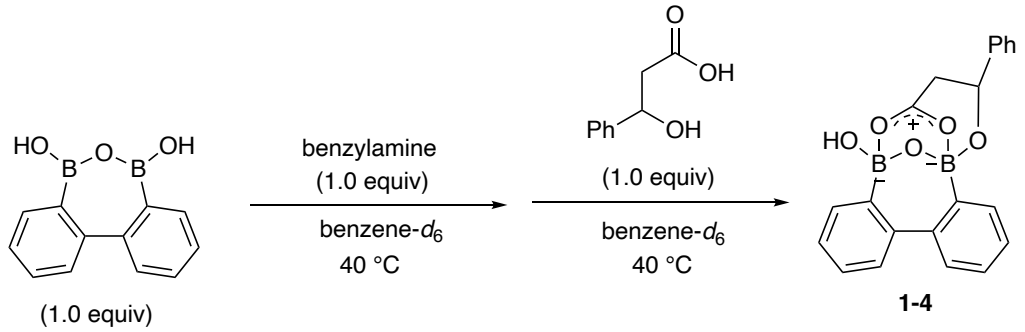
1.3.4.1.2 Biphenyl-based Diboronic Acid Anhydride

In 2019, Shimada and co-workers reported a novel diboronic acid anhydride species **1-3** with a pre-organized B–O–B structure as the catalyst for direct amidation reactions with hydroxycarboxylic acids.[56,57] The reactions proceeded in toluene at 110 ℃ for several hours without any dehydration protocols. Various *β*-hydroxycarboxylic acids were coupled with amines under these conditions catalyzed by 0.5 mol % **1-3**. Excellent yields ranging from 76% to >99% were obtained with *β*-aryl carboxylic acid substrates with electron-donating or electron-withdrawing groups. The amidation method was also applicable with *α*-branched and *α*-tertiary amines. Functionalities like alkyl chloride, silyl ether, amide, alkyne, and ester groups within the amines were also tolerated. A few aniline derivatives with electron-donating groups were also included in the substrate scope (Scheme 1-13).



Scheme 1-13: Structure of **1-3** and selected anilide substrates.

To investigate the mechanism, the authors conducted a control experiment with benzylamine and 3-methoxy-3-phenylpropanoic acid under standard conditions. With the *β*-hydroxyl group within the carboxylic acid methylated, no reaction was observed, which indicated the necessity of the OH on the *β* position. Under standard conditions, the mixture of diboronic acid anhydride, benzylamine, and β-hydroxycarboxylic acid was detected with negative ESI-MS. An *m/z* peak at 371.1259 was observed in accordance with intermediate **1-4** in Scheme 1-14. In the NMR experiments, a boron signal at 5.46 ppm was observed and corresponded to the tetrahedral boron atom.



Scheme 1-14: The NMR detection of hypothesized intermediate **1-4**.

The proposed mechanism is shown in Figure 1-8. Upon condensation of the *β*-hydroxyl group, a covalent B–O bond was formed, directing the formation of the bidentate reactive intermediate, which then undergoes nucleophilic attack by the amine to afford the amide product.

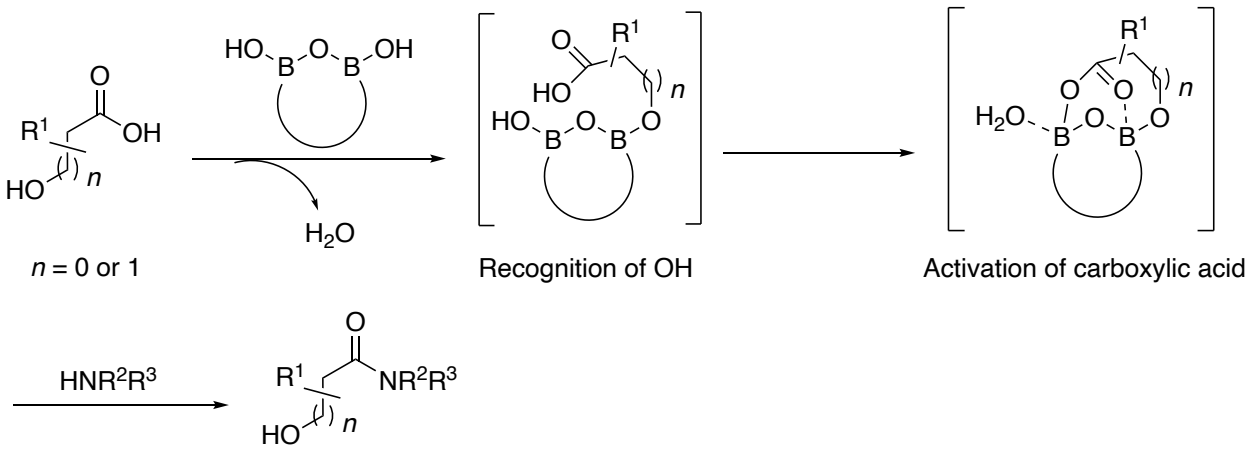
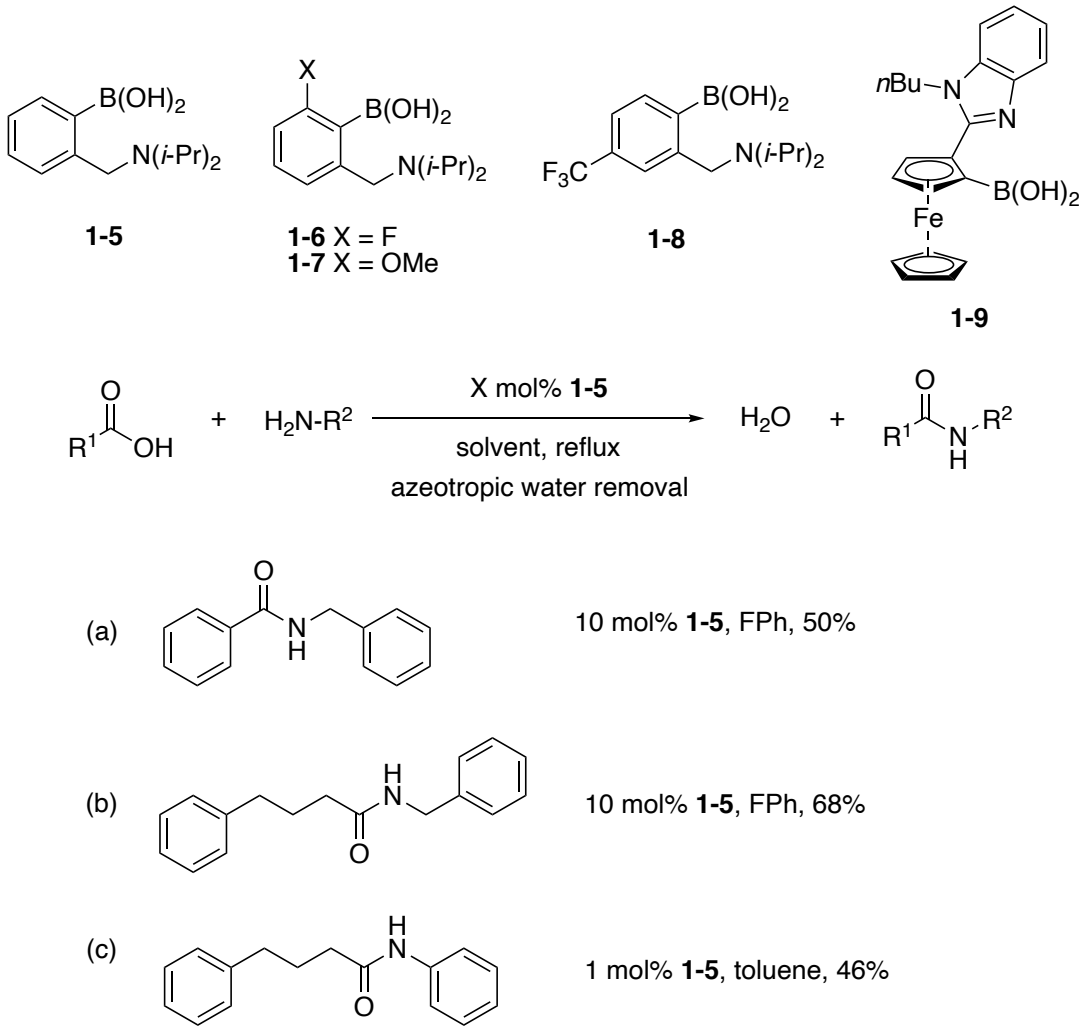


Figure 1-8: The proposed mechanism of amidation reactions mediated by the diboronic acid anhydride **1-4**.

1.3.4.1.3 Bifunctional (Aminomethyl)arylboronic Acids

In 2006, the first aminoarylboronic acid catalyst for amidation reactions was proposed by Whiting and co-workers.[58] Compared with boric acid, phenylboronic acid, and Yamamoto's catalyst, the bifunctional catalyst **1-5** can efficiently promote amide condensation at lower temperatures. The reaction (a) between benzoic acid and benzylamine can proceed in refluxing fluorobenzene at 85 ℃ in a yield of 50%. The amide condensation (b) between 4-phenylbutanoic acid and benzylamine afforded amide product with the yield of 68% in fluorobenzene. In contrast, with poorly nucleophilic amines, such as aniline, the reaction with 1 mol% **1-5** (c) afforded the anilide product with a yield of 46% but it required heating in refluxing benzene at 120 ℃.



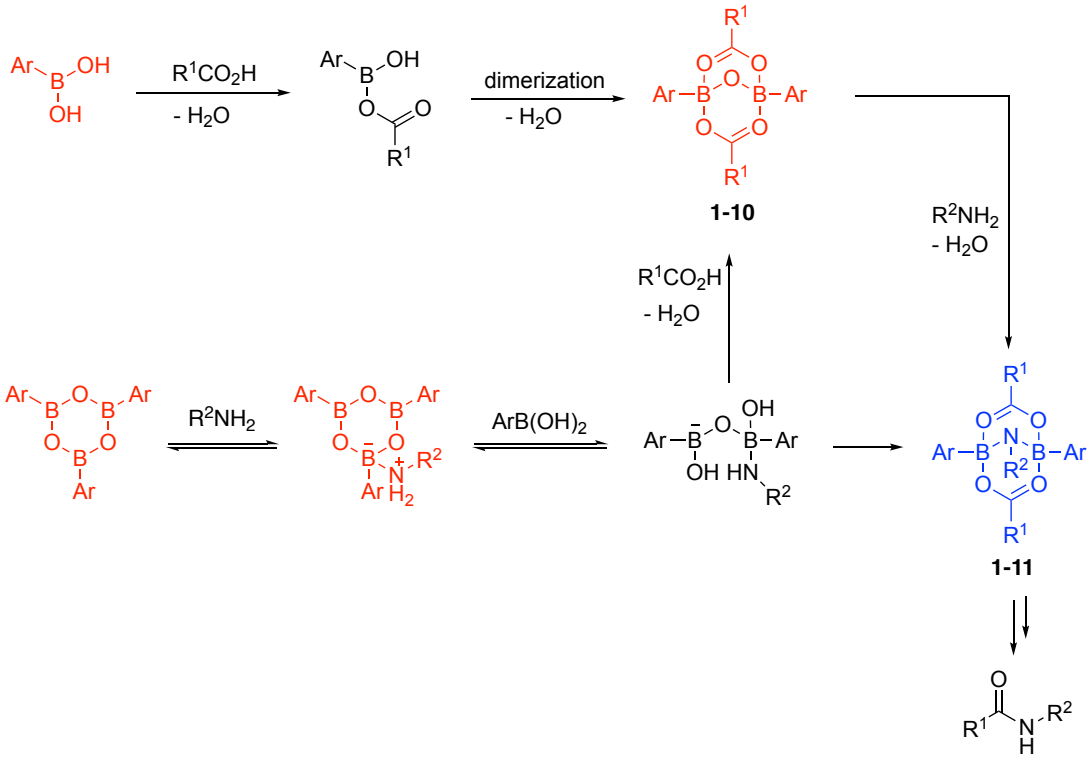
Scheme 1-15: Selected bifunctional (aminomethyl)boronic acids and substrates published by the Whiting Group.

In 2008, Whiting reported the related *ortho*-substituted aminoarylboronic acid catalysts **1-6** and **1-7**. Based on kinetic studies, arylboronic acids with electron-donating groups, like *o*-methoxy in **1-7**, led to a decrease in reaction rate compared to **1-5** and **1-6** under the same conditions. This difference may result from the increased steric hindrance around the boron center which suppressed the interaction between boronic acid and carboxylic acid. Whereas the *p*-trifluoromethyl substituted boronic acid **1-8** considerably enhanced the reaction rate of amidation over **1-5**, especially in fluorobenzene at 85 °C.[59]

In 2008, the same group published the first boronic acid catalyst **1-9** for asymmetric amidation, which selectively promoted the amidation between racemic branched benzylamines and achiral carboxylic acids *via* kinetic resolution. The ferrocene-based bifunctional

aminoboronic acid allowed the amide coupling to happen at a relatively lower temperature in fluorobenzene, which improved the method's functional group tolerance and % *ee*.[60]

The mechanism proposed by Whiting and co-workers in 2018 provided an insight into the crucial intermediates.[61] The combined observations of NMR, IR, X-ray crystallography, reactivity experiments, and computational calculations indicated that it is a dimeric B–X–B motif (X = O, NR) that is capable of intramolecular carbonyl activation as well as directed amine delivery through B-N interactions. The proposed mechanism is summarized in Figure 1-13. From control experiments, it is noteworthy that pre-stirring the reaction before addition of the amine was essential for efficient boronic acid catalyzed amidation reactions. It was observed that during the 15-min pre-stirring, in the presence of molecular sieves, the boronic acid formed the diacyloxy B–O–B bridged complex **1-10** with the carboxylic acid. The other potential reaction pathway through the formation of boroxine might be disfavored due to steric congestion around the *ortho*-functionalized boronic acid, which is supported by computational calculations.[61] In the control reaction between **1-10** and the amine under dehydrative conditions, **1-15** was formed and observed by boron NMR. The resonance of **1-11** was similar to the boron signal detected in the standard reaction under catalytic conditions. Hence, the authors tentatively proposed the formation of the amine-bridged dimeric species **1-11** as shown in Figure 1-9.



Compounds which have been fully characterized in this study by X-ray crystallography are shown in red
Compounds which have been observed by NMR and/or mass spectrometry are shown in blue

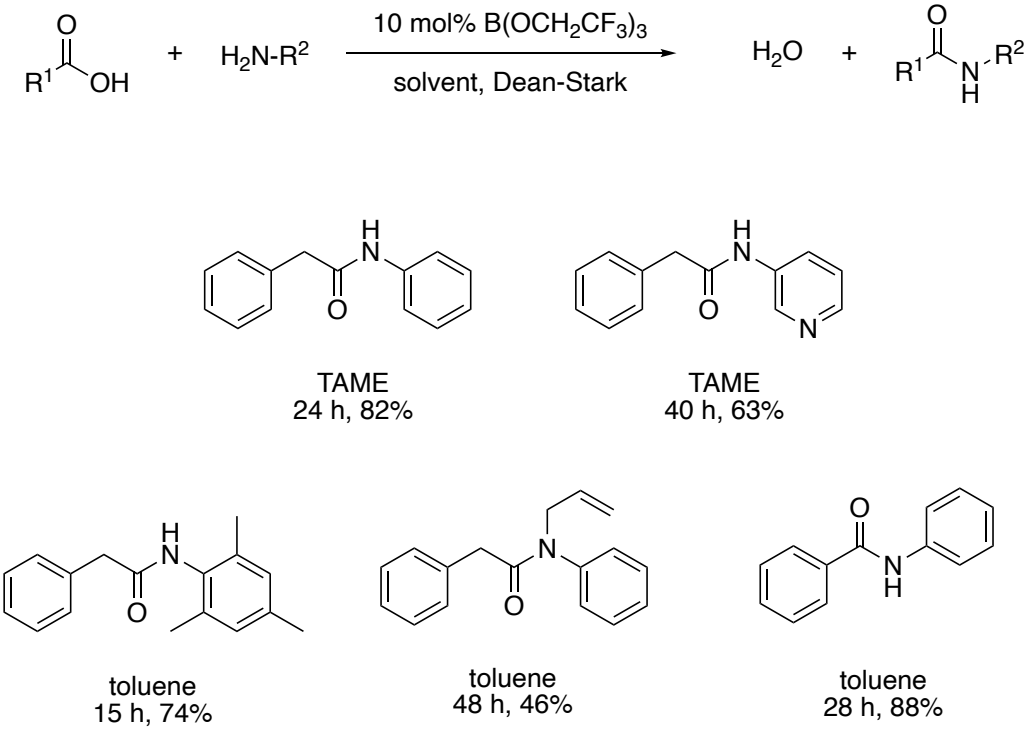
Figure 1-9: The amidation reaction mechanism proposed by Whiting and co-workers in 2018.

1.3.4.2 Boron Reagents Effective at Temperatures Below 100 ℃

1.3.4.2.1 Borate Ester Catalysis

In 2017, Sheppard and co-workers proposed a simple borate catalyst for direct dehydrative amidation reactions (Scheme 1-16).[62] By using a Dean-Stark apparatus, the conditions avoided the addition of molecular sieves to remove water, which reduced waste production and lowered the process mass intensity (PMI). The protocol exhibited a wide substrate scope, including sterically hindered tertiary amides, dipeptides, and optically active amides. The reactions of most substrates were conducted in refluxing *tert*-amyl methyl ether (TAME) at 86 ℃. However, the stronger conditions with refluxing toluene were required in reactions with challenging substrates. Selected anilide products were shown in Scheme 1-16. Additionally, in their previous study in

2013,[63] amidation reactions with electron-rich anilines can be achieved in acetonitrile at 80 ℃, though two equivalents of $B(OCH_2CF_3)_3$ were required.



Scheme 1-16: The $B(OCH_2CF_3)_3$ mediated amidation reaction and selected anilide examples

The proposed catalytic cycle for this reaction is shown in Figure 1-10. Kinetic studies of this reaction suggested a potential off-cycle equilibrium between the ammonium carboxylate salt and neutral amide coupling reagents. Based on the fluorine NMR data, there was less than one equivalent of trifluoroethanol released during the amidation reaction, which indicated the effective boron species **1-12** has two alkoxy groups. Boron NMR analysis of the reaction crude suggested the existence of the tetrahedral boron, which can be accounted with the Lewis base adduct **1-13**. Since a first-order dependence on catalyst was observed, the authors ruled out di- or multi-boron species in the mechanism. Following the nucleophilic attack of **1-13**, the amide product is released from **1-14**. The condensation between the carboxylic acid and **1-15** regenerates **1-13** and releases water.

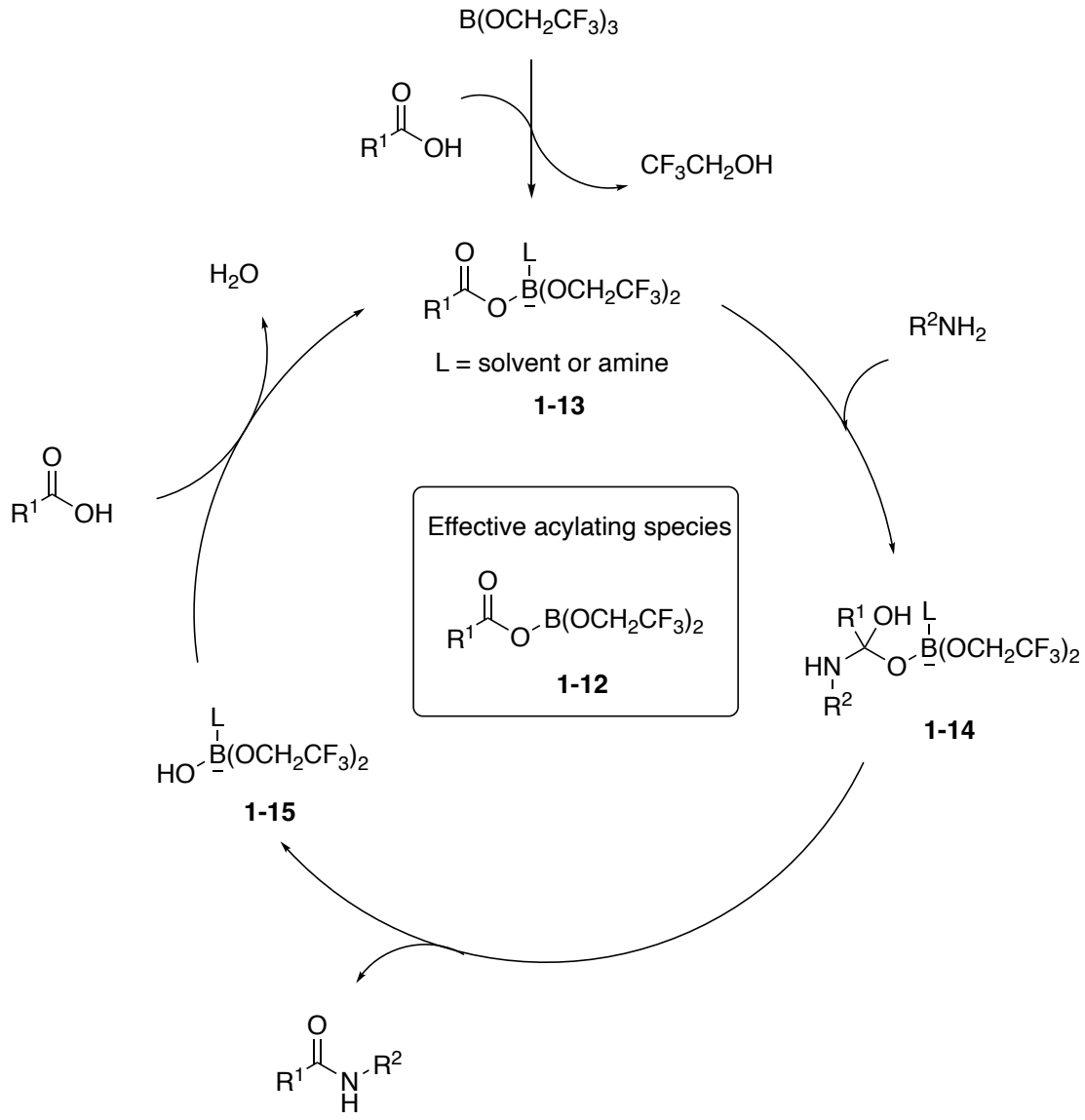
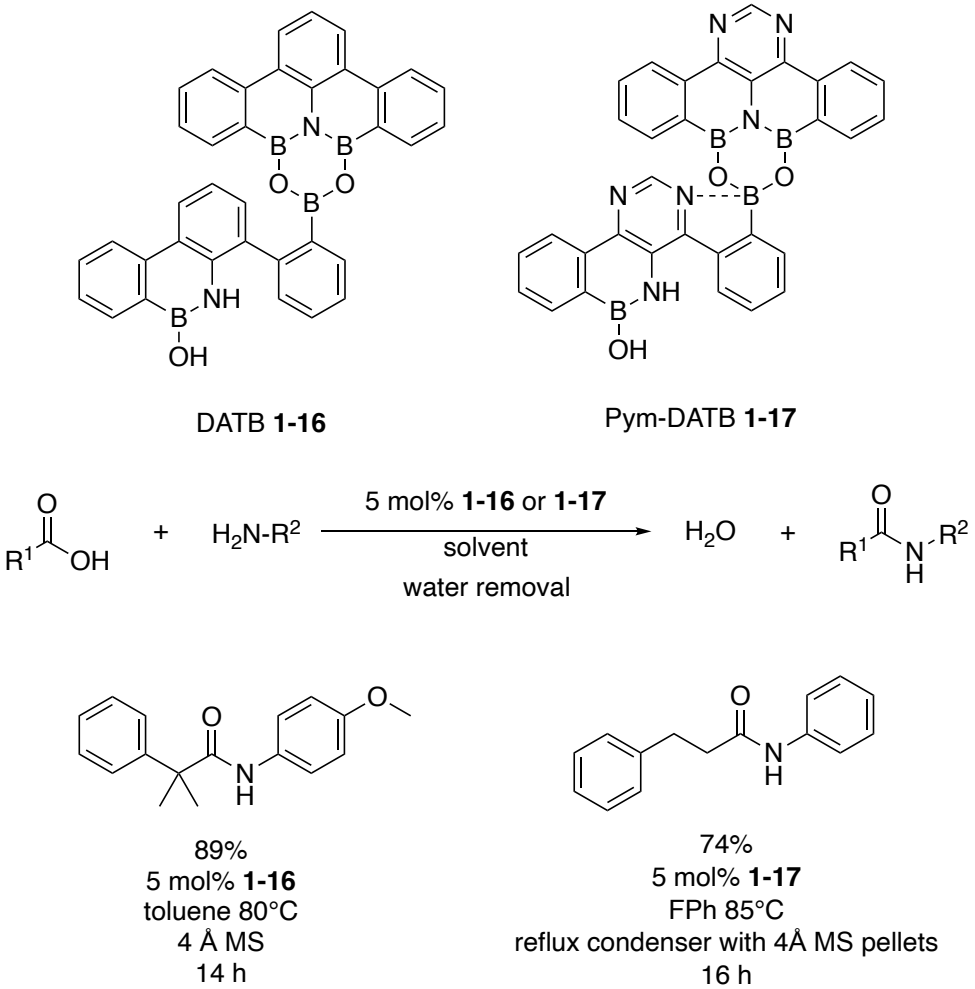


Figure 1-10: The proposed mechanism of the amidation reaction catalyzed by $B(OCH_2CF_3)_3$.

A solid phase work-up of this reaction was developed with three commercially available resins: Amberlyst A-26(OH), Amberlyst 15, and Amberlyst IRA743. Upon treatment with those resins and $MgSO_4$, followed by filtration and evaporation, unreacted acid, amine, and boron-containing impurities were removed with comparable efficiency to traditional aqueous workups.[63]

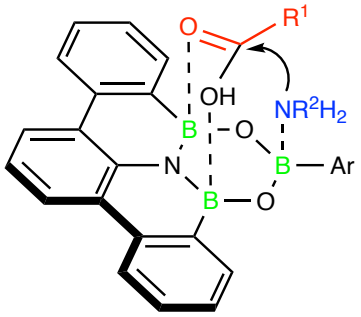
1.3.4.2.2 Oligo-boron Reagents: DATB and Pym-DATB

In 2017, Shibasaki and co-workers proposed a polyboron catalyst, **1-16,** which features a 1,3-dioxa-5-aza-2,4,6-triborinane (DATB) ring system.[64] In the presence of 4 Å molecular sieves, DATB **1-16** was able to promote the direct dehydrative amidation of 4-methoxy aniline in toluene at 80 ℃. A second aniline substrate was reported with the second-generation catalyst, Pym-DATB **1-17**, in refluxing fluorobenzene.[65] Substrates are shown in Scheme 1-17. Although the superiority of **1-17** over **1-16** is not impressive with the aniline examples, the enhanced reactivity of **1-17** with hindered substrates, the tolerance of Lewis-acid or base labile functionalities, and the compatibility of stereogenic α-carbons, as well as a simplified catalyst synthesis and purification, favoured catalyst **1-17** with broad applications.



Scheme 1-17: Anilide substrates with DATB **1-16** and Pym-DATB **1-17**.

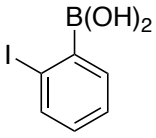
Within the six-membered B_3NO_2 core, the three boron atoms were proposed to direct amide coupling reagents simultaneously as shown by the key intermediate **1-18**. The authors proposed that the multisite activation can efficiently lower the entropy cost of the transition state.[64] However, the proximity effect between boron and nitrogen depicted in this model also suppresses the nucleophilicity of the amine.



1-18

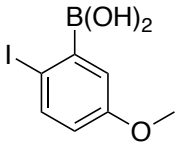
Figure 1-11: Key intermediate **1-18** for amidation reactions catalyzed by DATB **1-16**.

At lower temperatures, apart from Whiting's bifunctional catalysts and Shibasaki's poly-boron species, there are also other novel species that have exhibited excellent reactivities in direct amide couplings (Figure 1-12). However, the substrate scopes of these protocols were generally limited to amidation reactions with electron-deficient arylamines.



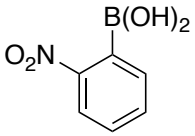
1-19

Hall (2008)



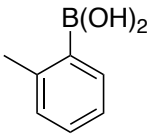
1-20

Hall (2012)



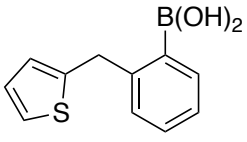
1-21

Whiting, Liu (2013)



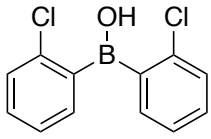
1-22

Whiting, Liu (2013)



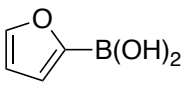
1-23

Blanchet (2015)



1-24

Blanchet (2015)



1-25

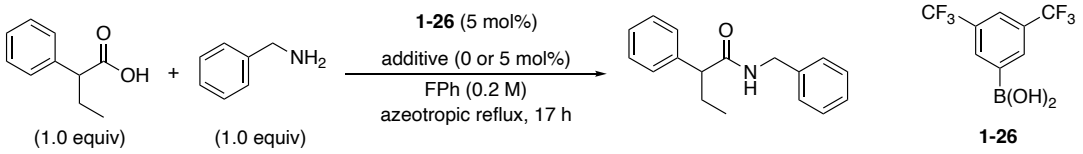
Tam, Chen (2015)

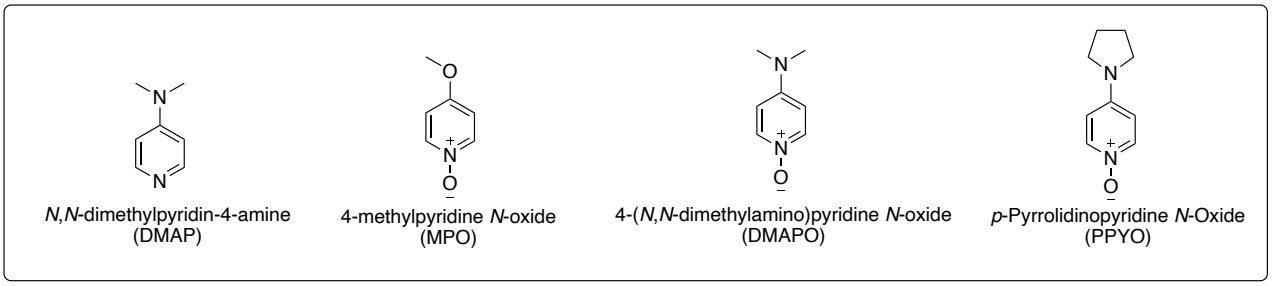
Figure 1-12: Selected organoboron catalysts for amidation reactions at temperatures below 100 °C.

In 2008, the Hall Group reported *ortho*-iodophenylboronic acid, **1-19**, as an efficient amidation catalyst at room temperature.[66] The second-generation catalyst, 5-methoxy-2-iodophenylboronic acid (MIBA, **1-20**), was developed to give higher yields in shorter reaction times at temperatures ranging from ambient to 50 °C.[67,68] A broad range of cyclic amines and amines bearing phenol, pyridine, furan, indole etc. were covered in the substrate scope. In 2013, Whiting and Liu published *o*-nitro- and *o*-tolylphenyl boronic acids, **1-21** and **1-22**. Those two boronic acid species were combined together to promote dipeptide formation from protected amino acids at 65 °C.[69] Later, the Blanchet Group reported a bench-stable boronic acid **1-23** and a novel borinic acid **1-24** for the synthesis of dipeptides in fluorobenzene at 65°C.[70,71] The inexpensive 2-furanylboronic acid **1-25** was identified by Tam and Chen as an efficient catalyst in the amidation condensation between aliphatic carboxylic acids and aliphatic primary amines at room temperature.[72]

1.3.5 Lewis Base Co-catalyst DMAPO

In 2016, 4-(*N*,*N*-dimethylamino)pyridine *N*-oxide (DMAPO) was reported to cooperate with different aryl boronic acid catalysts for amide condensation.[73] Boronic acid **1-26**, which was reported by the Yamamoto Group in 1996, was never applied with anilide substrate.[54] As shown in Table 1-2, in a model reaction between 2-phenylbutyric acid and benzylamine, DMAPO exhibited outstanding reactivity compared with various nucleophilic additives.

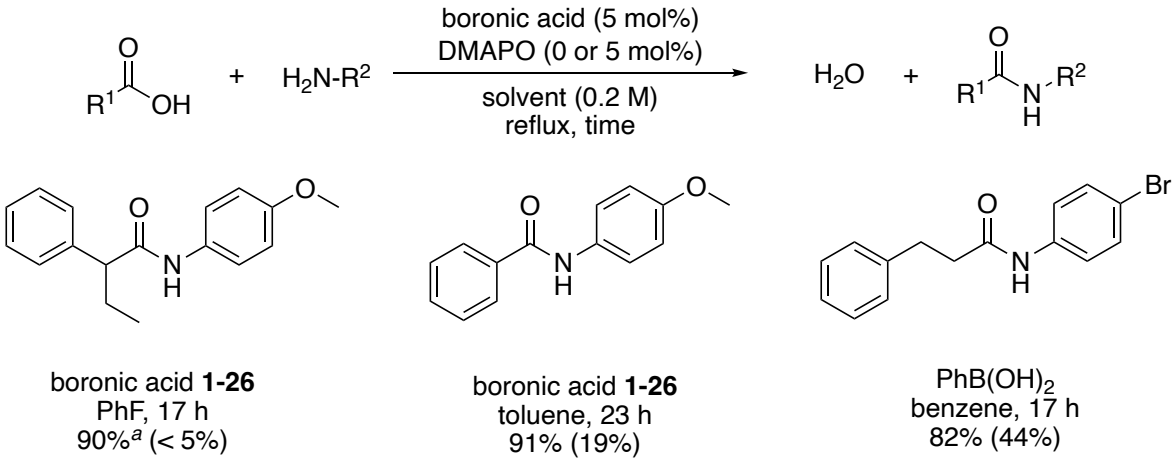




Entry	Additive	Isolated yield (%)
1	None	<5
2	*i*-Pr$_2$EtN	<5
3	DMAP	<5
4	MPO	<5
5	DMAPO	99
6	PPYO	27

Table 1-2: Additive effects on the amidation reaction between 2-phenylbutyric acid and benzylamine.

Anilide substrates were produced under the catalysis of the combined boronic acid-DMAPO as shown in Scheme 1-18. Cooperating with different boronic acids, the addition of DMAPO can drastically promote the reaction efficiency at both low and high temperatures.



Scheme 1-18: Selected anilide products afforded under the catalysis of the combined boronic acid-DMAPO. The yield shown in parenthesis was obtained without DMAPO. [a]: 10 mol% of each of the catalysts was used.

The authors proposed a secondary activation of the carboxylic acid group upon nucleophilic attack from DMAPO on the acyloxyboron intermediate **1-27**. The resulting cationic intermediate **1-28** with enhanced reactivity is subsequently attacked by the amine to afford the final product (Figure 1-13).

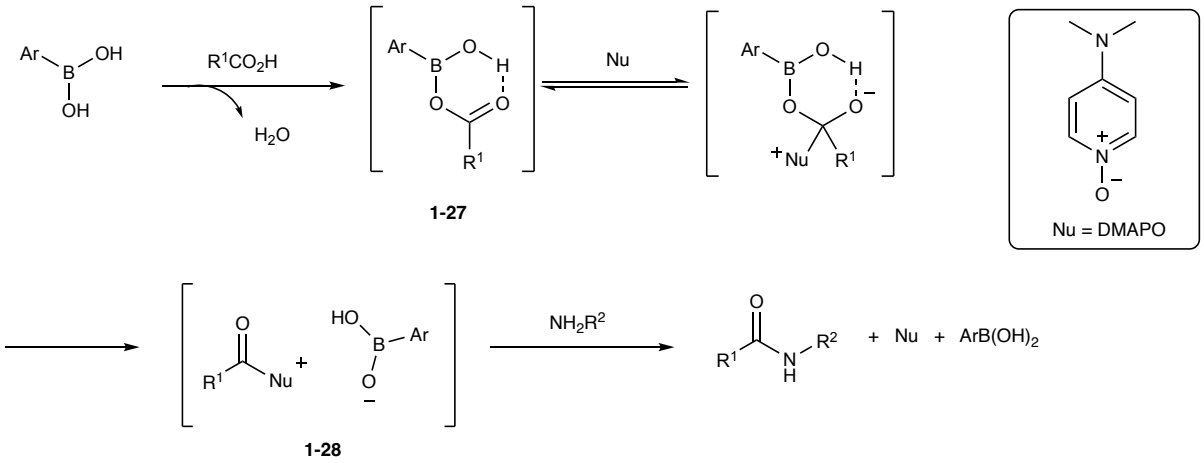


Figure 1-13: The proposed mechanism of secondary activation by the nucleophilic additive DMAPO.

1.4 Conclusion

Though anilide moieties are commonly found in natural products and bioactive molecules, the direct dehydrative amidation of electron-deficient aryl amines remains a challenging transformation in organic synthesis. Traditional thermal conditions and microwave protocols requiring temperatures above 250 °C have a higher energy cost as well as substrate limitations.

To activate the carboxylic acid, stochiometric amounts of activating agents, which are often toxic and/or expensive, are required. These activating agents also result in undesired side-products and poor atom economy. The development of metal catalyzed amidation methods provided alternative options, especially with the multivalent group IV metal salts.

Boron reagents are also an important class of amidation catalysts. They are advantageous due to their affordable cost and low toxicity. The boronic acids and borate esters described in this section exhibit versatile applications in direct dehydrative amidation of aniline derivatives. However, many of those activating reagents, such as the electron-deficient arylboronic acid proposed by Yamamoto, Sheppard's borate ester, the biphenyl-based diboronic acid anhydride reported by Shimada, and Whiting's bifunctional catalysts generally require elevated temperatures above 100 ℃. These harsher thermal conditions raised concerns about energy cost as well as potential decomposition and racemization of the substrates. Anilides were also possible to obtain at lower temperatures by boron-catalyzed amidation Shibasaki's poly-boron species. The nucleophilic additive DMAPO can also assist various arylboronic acid to catalyze

the direct dehydrative amide coupling between challenging substrates. However, the anilide substrate scope of reactions at lower temperatures are still limited, an extensive exploration on organoboron-promoted anilide condensation protocol is needed.

1.5 Project Objectives

The objective of this research project was focused on the development of a new boronic acid which is capable of promoting the amide condensation of anilines, at a temperature that is relatively close to ambient temperature. A functionalized boronic acid model was designed, aiming at activating the carboxylic acid with the B-O-B motif previously implicated in catalysis[74] and direct the amine with a proper coordinating group. With balanced structural flexibility and rigidity, a series of functionalized boronic acids were synthesized and evaluated for amidation of aniline derivatives.

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Chapter Two: Design and Synthesis of New Functionalized Boronic Acids for Direct Dehydrative Amidation of Poorly Nucleophilic Amines

In this chapter, a series of novel boronic acids with biphenyl scaffolds were examined to identify the most efficient derivatives for assisting anilide formation. Various reaction parameters were optimized, and the standard conditions were utilized to expand the substrate scope with anilines. Results of the investigation of possible racemization, a scale-up feasibility study, and the recovery of boronic acid are presented. Attempts were also made to explore the mechanism of the dehydrative amidation.

2.1 Introduction

As described in Chapter One, organoboron reagents are advantageous catalysts for direct dehydrative amidation reactions due to their affordable cost and low toxicity. However, it was observed that acids or amines with aromatic rings required a longer reaction time and higher temperatures than the reaction between aliphatic acids and amines.[66,75] The synthesis of anilides, the amide products obtained with poorly nucleophilic amines, either requires elevated temperature to be efficient[60,69,71] or have limited substrate scope.[65,67,68] This thesis attempts to address this problem, and was inspired by Whiting's mechanistic study showing that a dimeric B–X–B motif (X = O, NR) facilitates intramolecular carbonyl activation as well as directed amine delivery through hydrogen bonding interactions.[61] Thus, the goal of this project is to improve the direct amidation reactions of poorly nucleophilic amines by designing a biphenyl boronic acid that contains a directing group, as illustrated by the speculated intermediate shown

in Figure 2-1. In this design, the distance and linkage between the boron atom and the directing group will be optimized to balance the structural flexibility and rigidity.

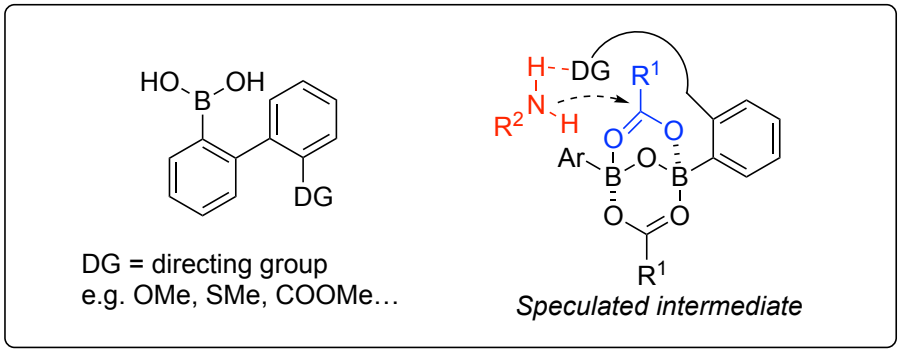
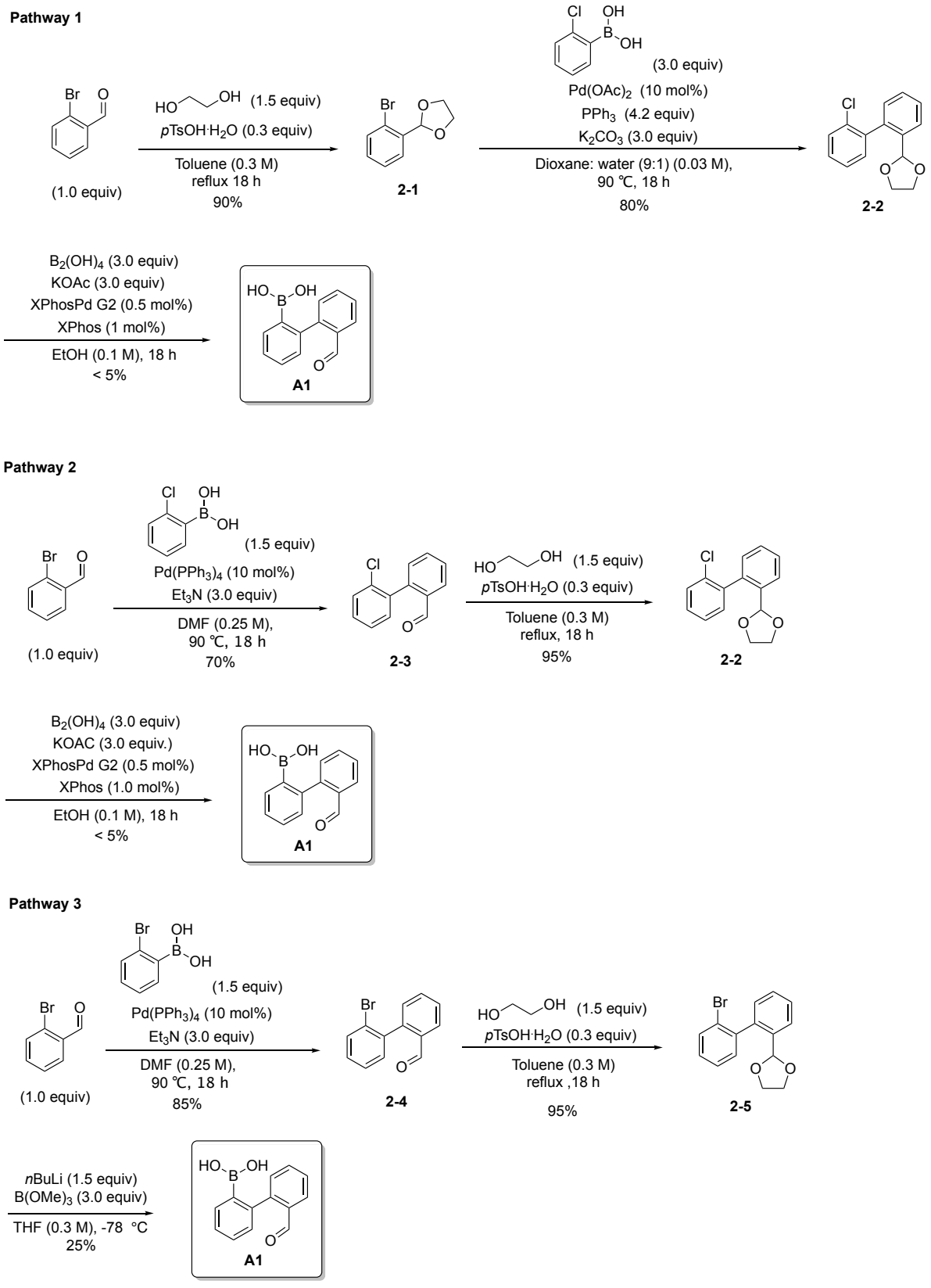


Figure 2-1: New functionalized boronic acids model and speculated intermediate.

2.2 Synthesis and Screening of New Functionalized Boronic Acids

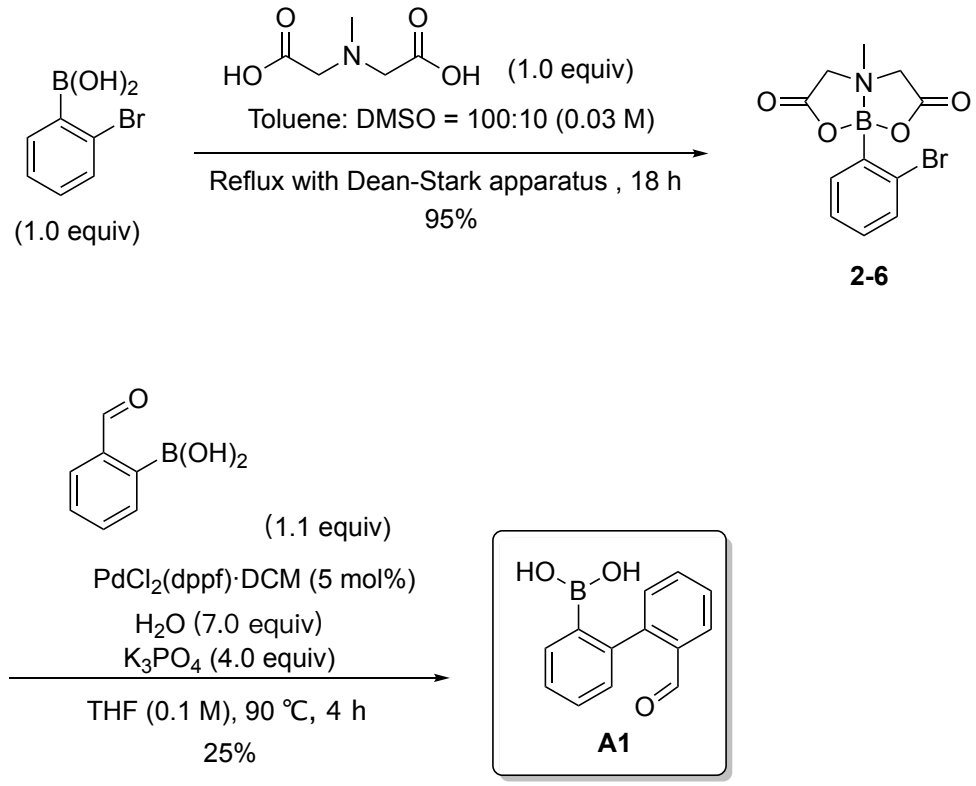
Dr. Marco Paladino, a postdoctoral researcher from the Hall Group, found that boronic acid **A1** can promote the amidation reaction between phenylacetic acid and aniline. Based on his findings, different approaches were taken to optimize the synthesis of **A1** as shown in Scheme 2-1. In pathway 1 and 2, aldehyde protection and cross-coupling were conducted in different sequences to afford chloro-substituted intermediate **2-2**, which is reported to be more reactive than its bromo-substituted analog under the borylation conditions published by Molander et al. in 2012.[76] However, the poor efficiency of the borylation of intermediate **2-2** under these conditions disfavored either route. As an alternative, lithiation-borylation was conducted with intermediate **2-5** (pathway 3) giving a yield of 20% over 3 steps.



Scheme 2-1: Initial synthesis of boronic acid **A1**.

The one-pot homologation of boronic acids published by Watson in 2015 provided another approach towards boronic acid **A1**.[77] In pathway 4 (Scheme 2-2), the *N*-methyliminodiacetic acid (MIDA) protected boronic ester (BMIDA **2-6**) was isolated by recrystallization, which largely simplified the purification process. Under the optimized basic conditions, the cross-coupling between BMIDA **2-6** and (2-formylphenyl)boronic acid afforded **A1** in 25% yield. To control the amount of water within the reaction, anhydrous THF was used as the solvent and 7.0 equivalents of degassed water were added. Using K_3PO_4 as the base allowed a slow release of the desired boronic acid product, while suppressing the formation of oligomers. Considering the overall yield (which is similar to that of pathway 3), the ease of operation and purification made pathway 4 the favored route for the synthesis of boronic acid **A1**.

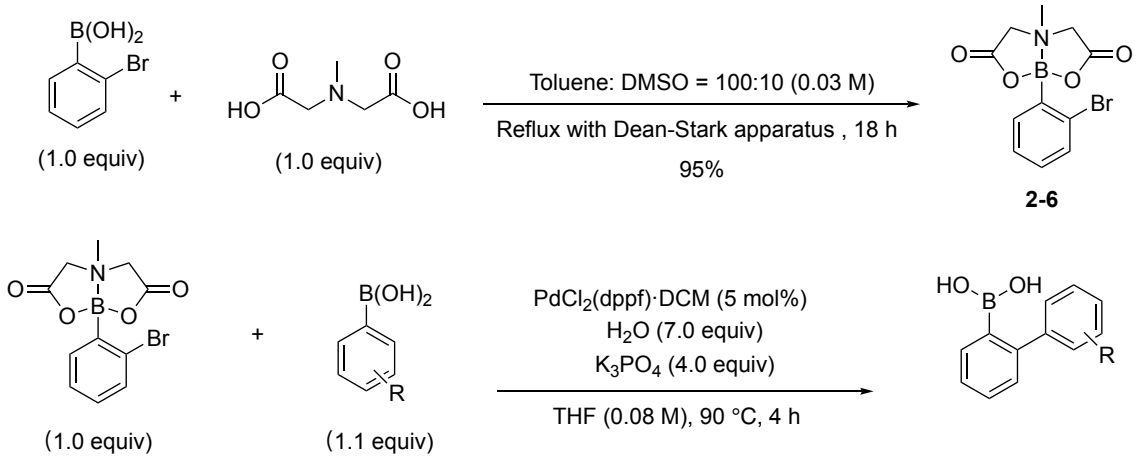
Pathway 4

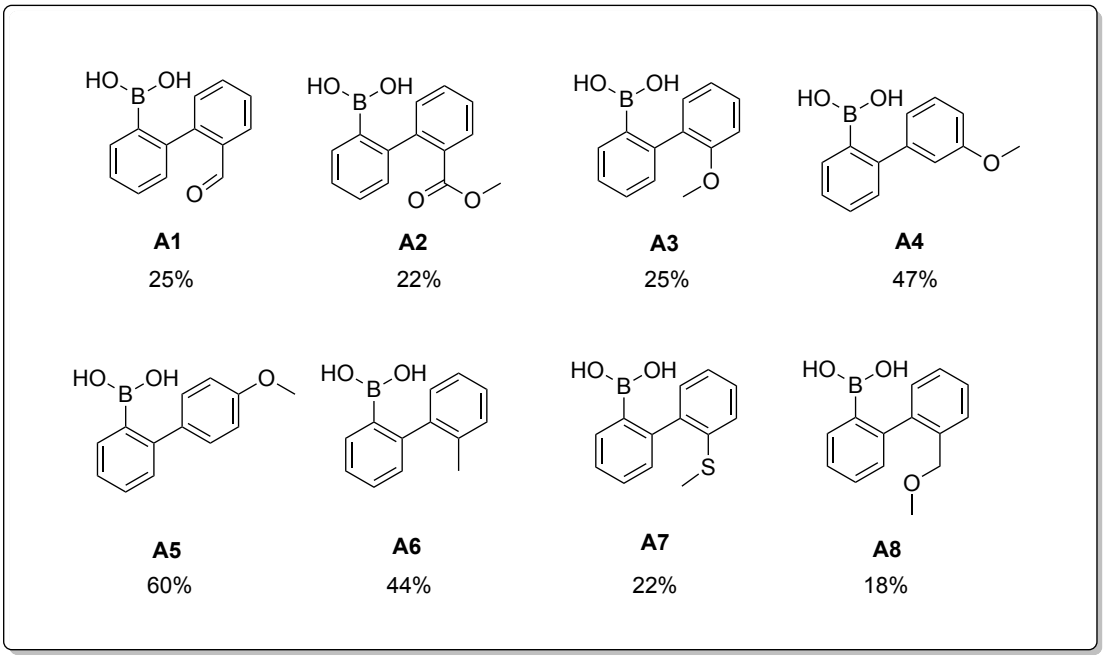


Scheme 2-2: Synthesis of boronic acid A1 from BMIDA **2-6**.

A panel of boronic acids with substituted biphenyl scaffolds was synthesized following pathway 4. In order to identify the optimal boronic acid, different functionalized boronic acids were reacted with BMIDA **2-6**, affording compounds **A1**–**A8** as shown in Scheme 2-3. Limited yields of the biaryl boronic acids were obtained in the synthesis of **A1**, **A2**, **A3 A7**, and **A8**. The

steric hindrance of the *ortho*-substituents in functionalized boronic acids largely suppressed the C–C bond formation. Further optimization of the synthetic route was conducted after identifying the optimal boronic acid for amidation reaction and will be discussed later (Table 2-2).

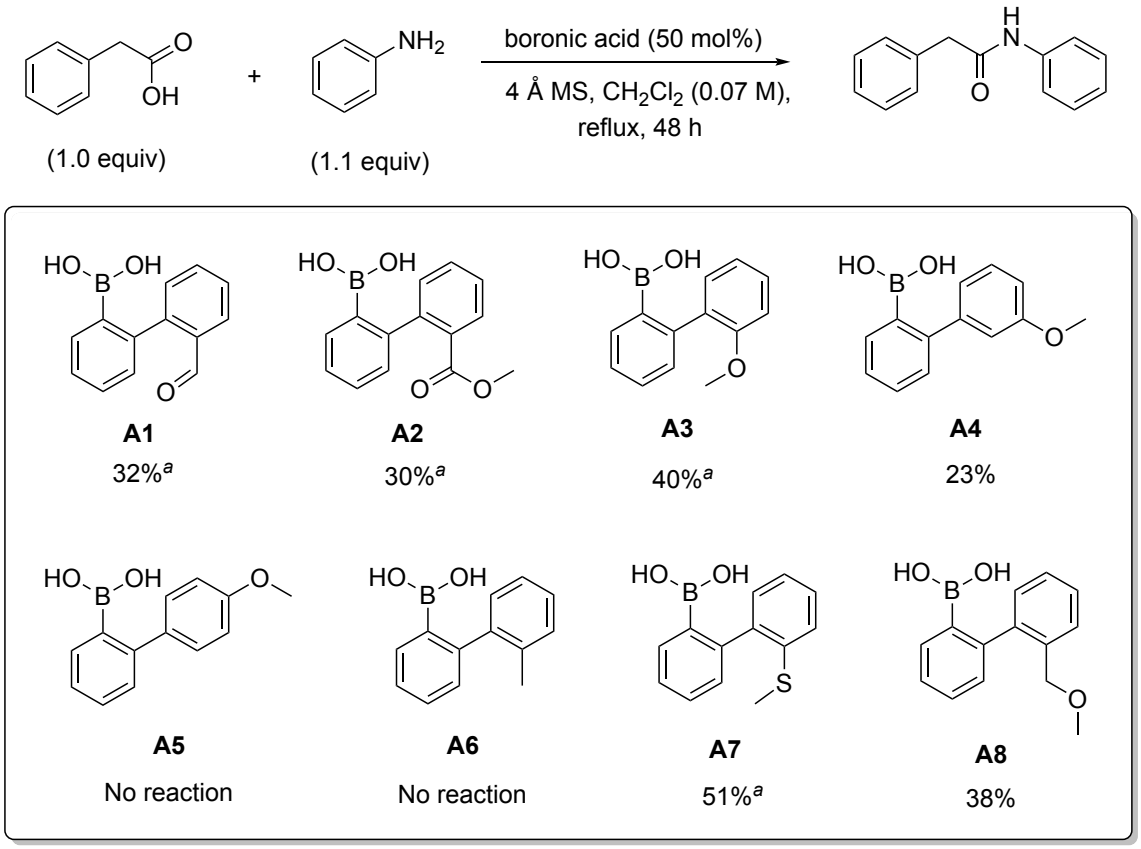




Scheme 2-3: Synthesis of new functionalized boronic acids.

The amidation reaction between phenylacetic acid and aniline was tested with each boronic acid (Scheme 2-4). The reaction was conducted in a sealed pressure tube in refluxing dichloromethane at 50 °C. To make a consistent comparison among boronic acids, 0.5 equivalents of boronic acids **A1**–**A8** was utilized in the model reaction. The amidation reactions with boronic acids **A1**, **A2**, **A3**, and **A7** were performed in duplicate, and the average yields were

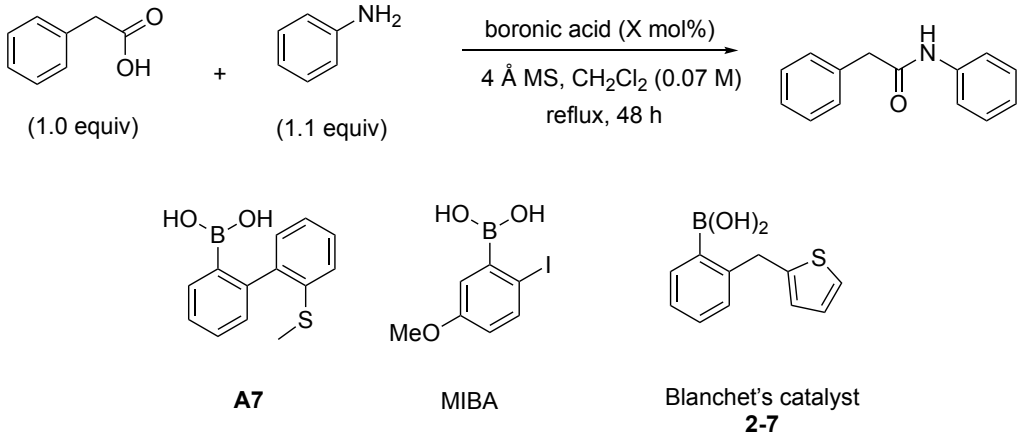
reported. Compounds **A1** and **A2** exhibited similar reactivities with yields of 32% and 30% respectively. The yields afforded by boronic acids **A3**, **A4**, and **A5** illustrate the necessity of a proper distance between the boron atom and the directing group. When the methoxy group is *ortho* to the phenyl ring and the oxygen atom is five bonds away from the boron atom (boronic acid **A3**), the reaction provided 40% of the desired anilide product. As the directing group is moved further to the *meta* position, the yield of the reaction with boronic acid **A4** dropped to 23%. No product was observed in the reaction with **A5** when the methoxy group is *para* to the phenyl ring. Interestingly, when using boronic acid **A8** with a methoxymethyl group ortho to the phenyl ring and the oxygen atom six bonds away from the boron atom, 38% of anilide product was obtained. Compared to the methoxy group in boronic acid **A4** where the oxygen atom is also six bonds away from the boron atom, the relatively higher flexibility of the directing group in **A8** potentially enhanced the reactivity of the boronic acid during the amidation reactions. Without a directing group with a heteroatom, no product was observed in the reaction with **A6** whereas 51% of anilide product was afforded in the reaction with **A7**. Based on the speculated intermediate, it was hypothesized that the interaction between the directing group and the amine enhances the reaction efficiency. Among all the boronic acids examined in this study, the use of (2'-(methylthio)-[1,1'-biphenyl]-2-yl)boronic acid **A7** provided the optimal yield of anilide product.



Scheme 2-4: Screening of new functionalized boronic acids using a model amidation reaction between phenylacetic acid and aniline. [a]: the reaction was performed in duplicate, and the average yield was reported.

For comparison between the previously reported boron catalysts and boronic acid **A7**, a model reaction was examined between phenylacetic acid and aniline in the presence of MIBA, compound **2-7,** or boronic acid **A7** in dichloromethane at 50 ºC (Table 2-1). In the model reaction, one gram of pre-activated molecular sieves was used per 0.5 mmol carboxylic acid, based on the previous optimization work in our group.[67] In 2015, Blanchet reported boronic acid **2-7** as an effective catalyst for peptide synthesis.[78] With the sulfur atom five bonds away from the boron atom, the authors proposed that the interaction between the sulfur (as a hydrogen bond acceptor) and the carboxylic acid accounts for the effectiveness of the directing group. Both boronic acid **2-7** and MIBA[66–68] are effective catalysts for amidation at room temperature, though no anilide examples have ever been reported with either catalyst. The model reaction for preparing *N*,2-diphenylacetamide was conducted with 0.2 equivalents and 0.5 equivalents of each boronic acid. Using 0.2 equivalents of boronic acid, the reactions with **A7** or MIBA afforded anilide product in similar yields (entries 1 and 3). By increasing the equivalents of boronic acid, anilide was obtained with a yield of 51% in the reaction promoted by **A7** (entry 2).

A negligible increase in yield, from 18% to 22%, was observed in the reaction with MIBA (entries 3–4). With either 0.2 or 0.5 equivalents of boronic acid **2-7**, the reaction afforded *N*,2-diphenylacetamide in yields below 10% (entries 5–6). Overall, the model reaction demonstrated that boronic acid **A7** exhibits superior reactivity over the other two catalysts.

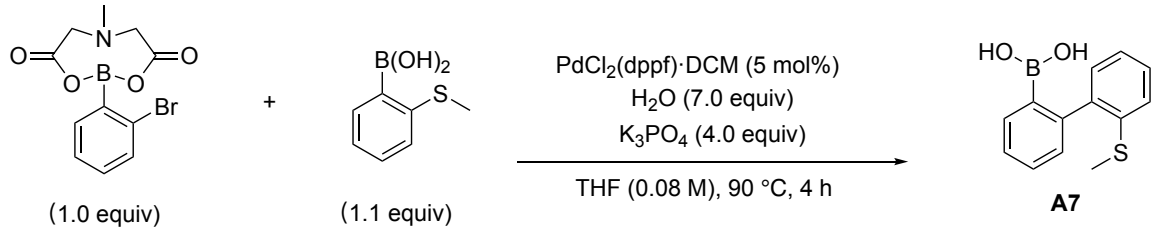


Entry	Boronic acid	Boronic acid equiv	Yield
1	**A7**	0.2	17%
2	**A7**	0.5	51%
3	MIBA	0.2	18%
4	MIBA	0.5	22%
5	**2-7**	0.2	5%
6	**2-7**	0.5	8%

Table 2-1: Comparison between boronic acid A7 and previously reported catalysts. For the amidation reactions above, 1.0 g 4 Å MS was used per 0.5 mmol carboxylic acid.

With compound **A7** determined as the optimal boronic acid for anilide formation, further optimization of the **A7** synthesis was conducted (Table 2-2). By switching the palladium catalyst, decreased yields were observed (entries 2–3). Longer reaction times resulted in a higher yield of undesired oligomers along with a decreased yield of the target boronic acid **A7** (entry 4). Addition of the ligand 1,1′-ferrocenediyl-bis(diphenylphosphine) (DPPF) did not improve the reaction efficiency (entry 5). A higher yield of boronic acid product **A7** was obtained when the quantity of $PdCl_2(dppf)\cdot DCM$ was increased from 5 mol% to 10 mol% (entry 6). The optimal yield for **A7** synthesis was obtained when 2.0 equivalents of (2-(methylthio)phenyl)boronic acid

and 0.1 equivalents of $PdCl_2$(dppf)·DCM were employed in the cross-coupling conditions (entry 7).



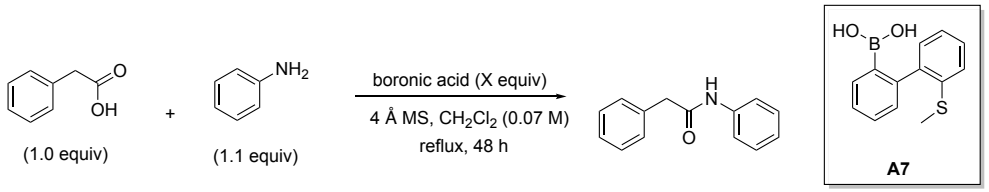
Entry	Variation from the standard conditions	Yield
1	-	22%
2	$Pd(OAc)_2$ (10 mol%), SPhos (20 mol%), K_3PO_4 (3.0 equiv), 1,4-dioxane (0.24 M), 75 ºC, 4 h	10%
3	PEPPSI-IPr (5 mol%)	8%
4	Reaction time 18 h	10%
5	Additional DPPF (10 mol%)	10%
6	$PdCl_2$(dppf)·DCM (10 mol%)	24%
7	$PdCl_2$(dppf)·DCM (10 mol%), 2.0 equiv of (2-(methylthio)phenyl)boronic acid	35%

Table 2-2: The optimization of the synthesis of boronic acid **A7**.

2.3 Optimization of Reaction Parameters

With the optimal boronic acid in hand, an optimization of the amidation reaction conditions was conducted as shown in Table 2-3. As a comparison, a parallel reaction was also conducted with MIBA. The model reaction between phenylacetic acid and aniline was conducted with 0.2 equivalents of boronic acid **A7** and MIBA respectively, affording the amide product with a limited isolated yield of 17% and 18% (entries 1–2). For the reaction with **A7** at 50 °C, switching the solvent to THF or toluene did not improve the yield (entries 3–4). An increase in yield was observed when 0.5 equivalents of boronic acid was employed in the reaction with **A7** and MIBA

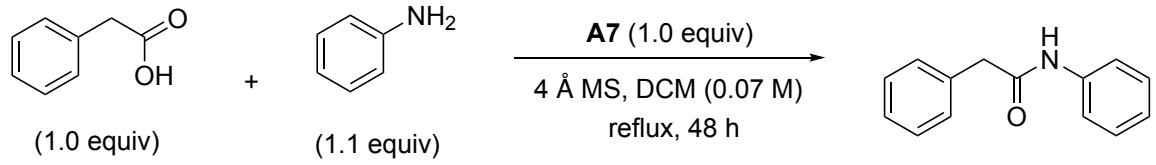
(entries 5–6). However, no further improvement in yield was obtained when the amount of boronic acid was increased to 1.0 equivalents (entries 7–8).



Entry	Boronic acid (BA)	BA equiv	Yield
1	**A7**	0.2	17%
2	MIBA	0.2	18%
3[a]	**A7**	0.2	10%
4[b]	**A7**	0.2	<5%
5	**A7**	0.5	51%
6	MIBA	0.5	22%
7	**A7**	1.0	52%
8	MIBA	1.0	23%

Table 2-3: Optimization of boronic acid A7 equivalents. For the amidation reactions above, 1.0 g 4 Å MS was used per 0.5 mmol carboxylic acid. [a]: THF was used as the solvent and the reaction was heated at 50 °C. [b]: Toluene was used as the solvent and the reaction was heated at 50 °C.

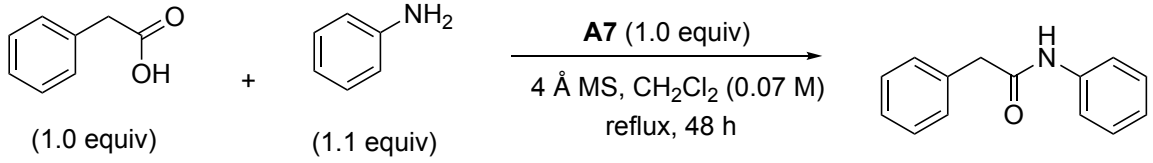
To explore the potential factors that limited the turn-over rate of the boronic acid, a model reaction with 1.0 equivalent of boronic acid **A7** was conducted with 1.0 equivalent of pre-made *N*,2-diphenylacetamide (Table 2-4). With the addition of the pre-made amide product, no product-inhibition effect was observed (entry 2). To minimize the potential interaction between amine and boronic acid that may interfere with the reaction efficiency, attempts were also made to promote the turn-over rate of the boronic acid by using a syringe pump to provide a slow-addition of the aniline. However, no obvious improvement was observed in the parallel reactions (entries 3–4).



Entry	Variation from the standard conditions	Yield
1	-	52%
2	1.0 equiv of pre-made amide was added	64%
3	Reaction was worked up in 5 h	18%
4	Aniline was slowly added with a syringe pump over 5 h	18%

Table 2-4: Investigation into potential factors that may limit the turn-over rate of the boronic acid.

Aniline stoichiometry was then optimized, and it was found that excess of carboxylic acid or aniline decreased the reaction yield (Table 2-5, entries 2–4). Molecular sieves are necessary for the success of the dehydrative amidation but doubled usage of molecular sieves was not beneficial to the yield (entries 5–6). At temperatures from 50–60 °C, DCM was the optimal solvent compared with toluene, acetonitrile, diethyl ether, and fluorobenzene (entries 7–10). When the reaction was conducted in fluorobenzene, which has a boiling point of 85 °C, the reaction yield was improved from 25% to 70% when the reaction temperature was increased from 50 °C to 85 °C (entries 10–11).



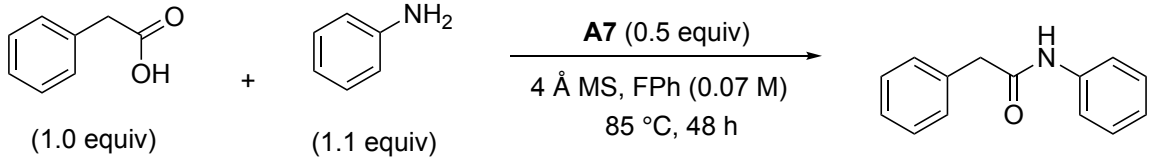
Entry	Variation from the standard conditions	Yield
1	-	51%
2	Carboxylic Acid: Aniline = 1.0: 1.5	33%
3	Carboxylic Acid: Aniline = 1.0: 1.0	50%
4	Carboxylic Acid: Aniline = 1.5: 1.0	38%
5	1.0 g 4 Å molecular sieves was used per 0.25 mmol carboxylic acid	52%
6	No molecular sieves	0%
7	Reaction in toluene at 50 °C	15%
8	Reaction in MeCN at 50 °C	25%
9	Reaction in DCE at 60 °C	16%
10	Reaction in FPh at 50 °C	25%

11	Reaction in FPh at 85 °C	70%

Table 2-5: Optimization of aniline stoichiometry, molecular sieves usage, solvent, and temperature. Unless otherwise specified, 1.0 g 4 Å MS was used per 0.5 mmol of carboxylic acid.

To further optimize the reaction conditions in FPh at 85 °C, the amount of boronic acid, reaction temperature, and additive equivalents were adjusted and compared (Table 2-6). At 85 °C, when the boronic acid amount was decreased from 0.5 to 0.2 equivalents, the reaction yield dropped from 70% to 35% (entry 2). Using 1.0 equiv of **A7** provided a limited improvement to the yield (entry 3). For both **A7** and MIBA, lowering the reaction temperature resulted in decreased yields (entries 4–5).

According to a report by Ishihara and co-workers in 2016, 4-(*N*,*N*-dimethylamino)pyridine *N*-oxide (DMAPO) can cooperate with arylboronic acids to promote amidation reactions.[73] As introduced in Chapter One, electrophilic activation of the carbonyl by interaction with the boronic acid promotes formation of a reactive pyridinium salt intermediate species for which the energy barrier of the subsequent nucleophilic attack by amine is lowered. Using the model reaction between phenylacetic acid and aniline, the addition of DMAPO improved the reaction efficiency with both **A7** and MIBA (entries 6–8). The optimal amount of DMAPO was determined to be 0.05 equivalents (entries 6 and 9). When the reaction concentration was raised from 0.07 M to 0.2 M, the yield dropped from 83% to 74% (entries 6 and 10). This result is consistent with the trend previously reported by our group.[68]



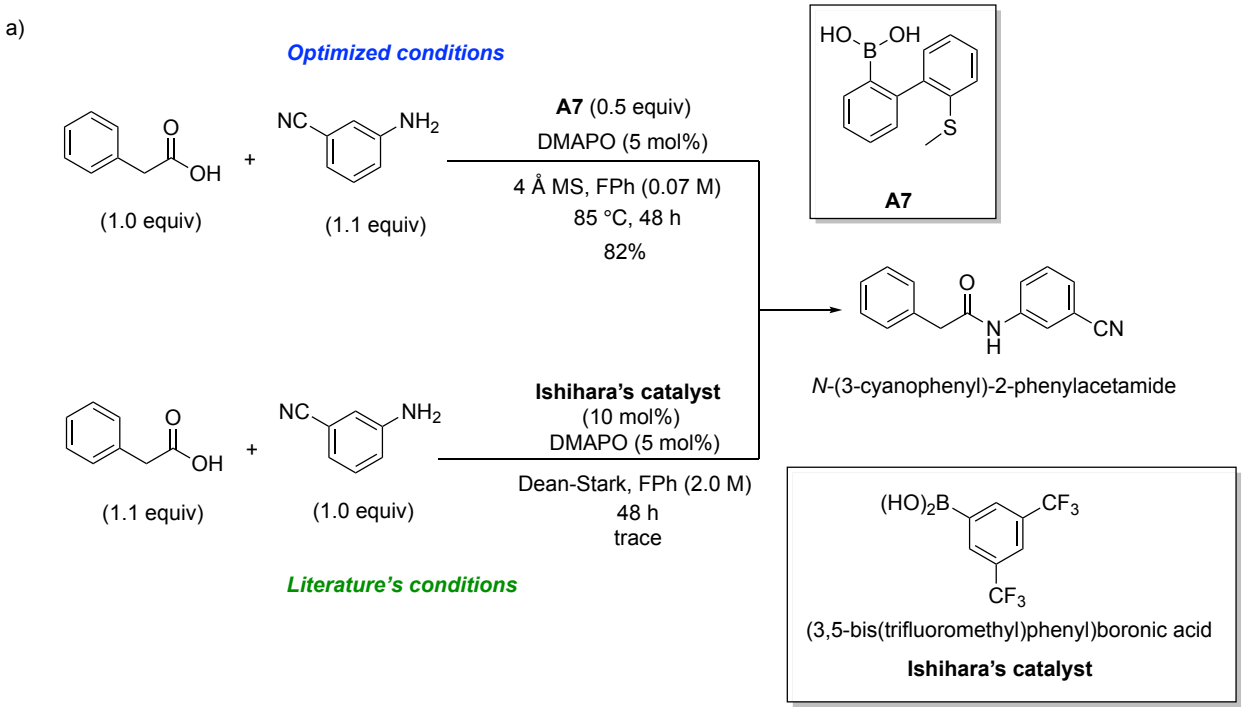
Entry	Variation from the standard conditions	Yield
1	-	70%
2	0.2 equiv **A7**	35%
3	1.0 equiv **A7**	73%
4	65 °C	25%
5	0.5 equiv MIBA; 65 °C	22%
6	5 mol% DMAPO was added	83%
7	0.5 equiv MIBA	35%

8	0.5 equiv MIBA, 5 mol% DMAPO was added	65%
9	10 mol% DMAPO was added	82%
10	5 mol% DMAPO was added, 0.2 M	74%

Table 2-6: A further optimization of the reaction conditions in FPh at 85 °C. Unless otherwise specified, 1.0 g 4 Å MS was used per 0.5 mmol of carboxylic acid.

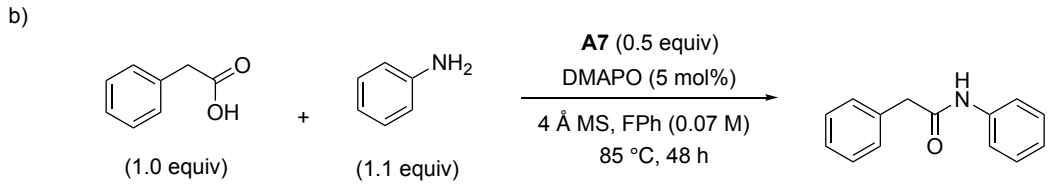
To compare our optimized amidation conditions with the protocol described by Ishihara and co-workers, [73] a pair of condensation reactions between phenylacetic acid and 3-aminobenzonitrile were set up in parallel (Scheme 2–5). Under the previously reported conditions, which were only demonstrated for electron-rich anilines, the reaction was catalyzed by 10 mol% of bis(trifuoromethyl)phenylboronic acid (Ishihara's catalyst) and 5 mol% DMAPO was added as the additive. The reaction in fluorobenzene was heated to reflux with a Dean-Stark apparatus. In 48 hours, trace amount of *N*-(3-cyanophenyl)-2-phenylacetamide was obtained following the literature's protocol. In contrast, 82% yield of amide product was prepared under our optimized conditions with 0.5 equivalents of **A7**. An additional control experiment was conducted with 0.5 equivalents of Ishihara's boronic acid. Under our optimized conditions, 34% yield of amide product was obtained with bis(trifuoromethyl)phenylboronic acid. However, following the reported protocol, the yield of the reaction with Ishihara's boronic acid dropped to 15%. Switching from our optimized conditions to the reported ones, the yield of the reaction with boronic acid **A7** decreased from 82% to 64%.

In the amidation reaction of an electron deficient aniline, our conditions exhibited higher efficiency than the reported protocol [73] and boronic acid **A7** exhibited a higher reactivity over bis(trifuoromethyl)phenylboronic acid. Thus, overall boronic acid **A7** outperforms previously reported procedures with different boronic acids such as MIBA and bis(trifuoromethyl)phenylboronic acid. In conclusion, the optimal conditions for the dehydrative condensation between phenylacetic acid and aniline were systematically identified and are depicted in Scheme 2-5. As described in the next section, these conditions will be applied to a study of substrate scope.



When 0.5 equivalents of boronic acid were used in the amidation reaction:

	A7	**Ishihara's catalyst**
Optimized conditions	82%	34%
Literature's conditions	64%	15%



Scheme 2-5: a) Comparison of our optimized conditions and literature's conditions. b) The optimized conditions for anilide preparation.

2.4 Substrate Scope

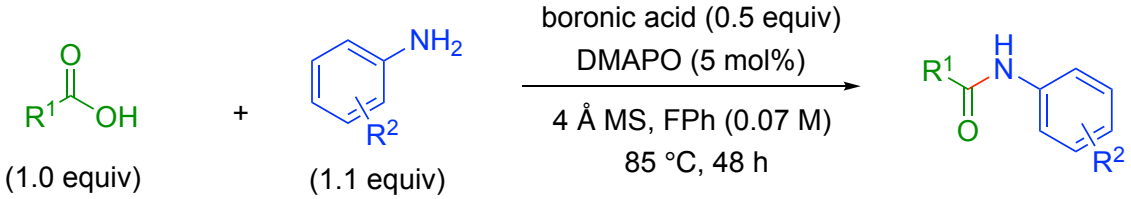
With the optimized boronic acid-assisted amidation reaction conditions in hand, the scope of the amidation reaction between phenylacetic acid and aniline derivatives was explored further. Since the advantage of DMAPO as an additive varied case by case, both boronic acid **A7** and MIBA

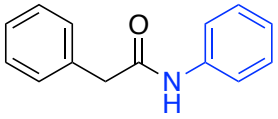
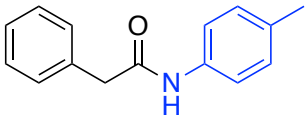
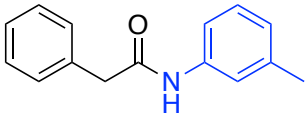
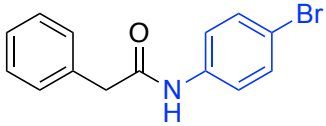
were employed with and without DMAPO. The isolated yields for all variations of the conditions are listed below (Table 2-7).

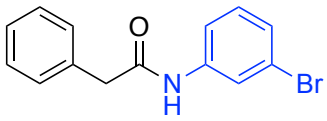
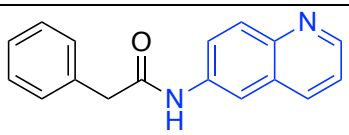
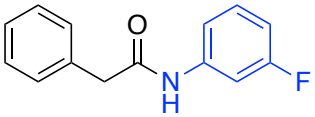
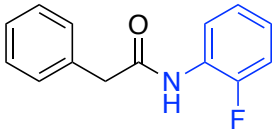
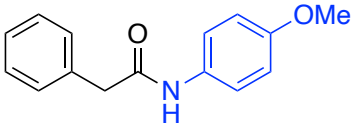
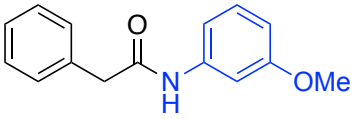
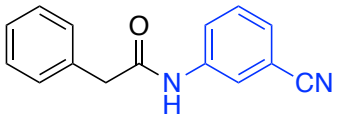
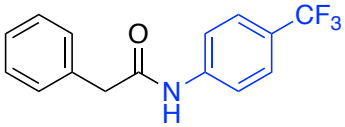
The use of DMAPO in the condensation between phenylacetic acid and *p*-tolylaniline improved the yield from 10% to 47% with **A7** and from 38% to 50% with MIBA (entry 2). With the addition of DMAPO, an enhancement in yield was also observed with 2-phenyl-*N*-(*m*-tolyl)acetamide, which was obtained with **A7** in 88% yield and MIBA in 80% yield (entry 3). With the addition of DMAPO, **A7** exhibited higher reactivity over MIBA in the formation of *N*-(4-bromophenyl)-2-phenylacetamide (entry 4) and *N*-(3-bromophenyl)-2-phenylacetamide (entry 5). With the potential acid-base reaction between the nitrogen of quinoline and the carboxylic acid, when the amount of carboxylic acid was increased to 2.0 equivalents, the yield of 2-phenyl-*N*-(quinolin-6-yl)acetamide increased from 34% to 85% in the reaction mediated by boronic acid **A7** (entry 6). Good yields were obtained with **A7** and MIBA in the synthesis of *N*-(3-fluorophenyl)-2-phenylacetamide (entry 7) and *N*-(2-fluorophenyl)-2-phenylacetamide (entry 8). For the amidation reaction between phenylacetic acid and 4-methoxyaniline, the use of boronic acid **A7** along with DMAPO afforded the anilide product in 80% yield (entry 9). *N*-(3-Methoxyphenyl)-2-phenylacetamide was afforded in 82% yield with boronic acid **A7** and 80% yield with MIBA (entry 10). The amidation reaction between phenylacetic acid and an aniline bearing an electron withdrawing group can also proceed with **A7** or MIBA cooperating with DMAPO, for example *N*-(3-cyanophenyl)-2-phenylacetamide was afforded using **A7** with a yield of 82% (entry 11). However, only 27% of 2-phenyl-*N*-(4-(trifluoromethyl)phenyl)acetamide was obtained with **A7** using DMAPO (entry 12). The reaction between phenylacetic acid and hindered 2,4,6-trimethylaniline with MIBA and DMAPO afforded 60% yield of the anilide product. However, only trace amount of *N*-mesityl-2-phenylacetamide was obtained when **A7** was used instead (entry 13). This sterically demanding aniline substrate might have a poor interaction with boronic acid **A7**, significantly lowering the reaction efficiency. The reaction between phenylacetic acid and 4-aminophenol was not successful with either **A7** or MIBA (entry 14). In this case, the interaction between the unprotected hydroxy group and the boronic acid may potentially interfere with the amidation reaction.

Variations of carboxylic acids were also included in the substrate scope (entries 15–18). With the addition of DMAPO, N-phenyl-α-methyl-benzeneacetamide was afforded in 44% yield with

boronic acid **A7** and 35% yield with MIBA (entry 15). The congestion around the alpha-methylated carbonyl might disfavor the formation of the diacyloxy B–O–B intermediate, suppressing the activation of the carboxylic acid. The amidation between 3-phenylpropanoic acid and aniline afforded 85% yield of *N,3*-diphenylpropanamide with **A7** and 70% yield of anilide product was obtained when MIBA was used instead (entry 16). The amidation conditions are also applicable with heptanoic acid. *N*-phenylheptanamide was afforded in 80% yield with **A7** and 77% yield with MIBA (entry 17). However, the reaction between aniline and benzoic acid remains challenging under current conditions. Trace amount of *N*-(3-bromophenyl)benzamide was observed in the amidation reaction with either boronic acid **A7** or MIBA.



Entry	Product	Yield with **A7**		Yield with MIBA	
		Without DMAPO	With DMAPO	Without DMAPO	With DMAPO
1	 **2-8**	70%	83%	35%	65%
2	 **2-9**	10%	47%	38%	50%
3	 **2-10**	32%	88%	33%	80%
4	 **2-11**	35%	66%	31%	37%

5	 **2-12**	31%	80%	42%	61%
6	 **2-13**	24%	34% 85%[a]	40%	41%
7	 **2-14**	47%	71%	38%	53%
8	 **2-15**	40%	69%	42%	70%
9	 **2-16**	83%	80%	94%	90%
10	 **2-17**	78%	82%	72%	80%
11	 **2-18**	45%	82%	30%	65%
12	 **2-19**	15%	27%	22%	38%

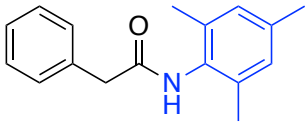
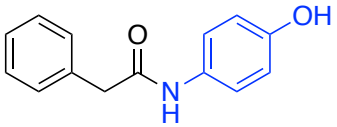
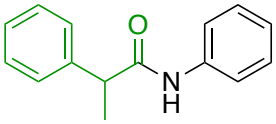
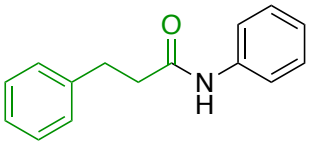
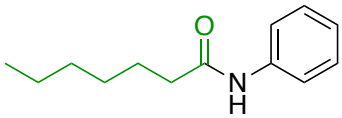
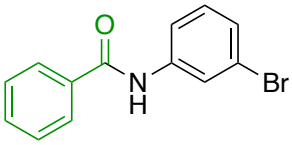
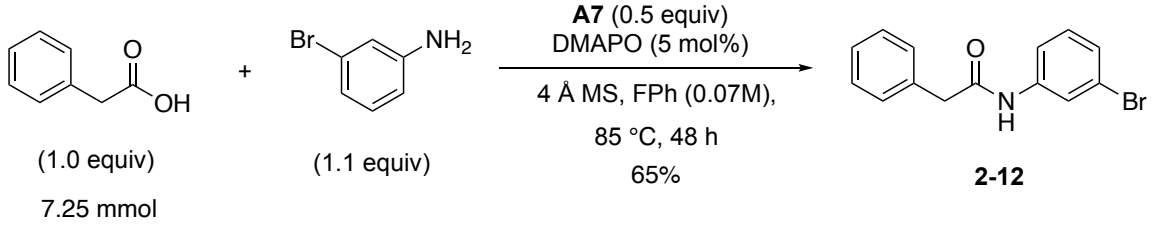
13	 **2-20**	-	trace	-	60%
14	 **2-21**	-	trace	-	trace
15	 **2-22**	-	44%	-	35%
16	 **2-23**	-	85%	-	70%
17	 **2-24**	-	80%	-	77%
18	 **2-25**	-	trace	-	trace

Table 2-7: Substrate scope with **A7** and MIBA under the optimized amidation conditions. 1.0 g 4 Å MS was used per 0.5 mmol carboxylic acid. [a]: 2.0 equiv of phenylacetic acid, 1.0 equiv of aniline, and 1.0 g 4 Å MS per 0.5 mmol aniline were used instead.

2.5 Gram-Scale Reaction and Recovery of the Boronic Acid

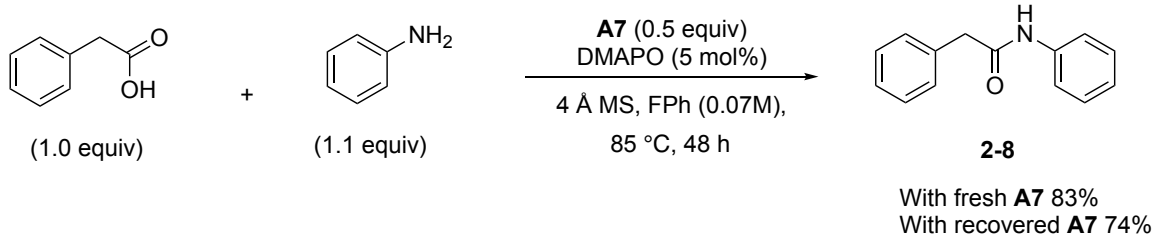
A gram-scale reaction between phenylacetic acid and 4-bromoaniline was conducted using **A7**, affording 1.37 g of the amide product **2-12** with a yield of 65%. Some unreacted aniline was

detected by liquid chromatography mass spectrometry (LCMS). Flash column chromatography was used to isolate the desired anilide as well as boronic acid **A7** with a recovery rate of 76%. Considering the biggest drawback of our conditions is the requirement of 0.5 equivalents of the boronic acid, recovery of boronic acid **A7** directly from column chromatography is advantageous.



Scheme 2-6: Gram scale amidation reaction with boronic acid **A7**.

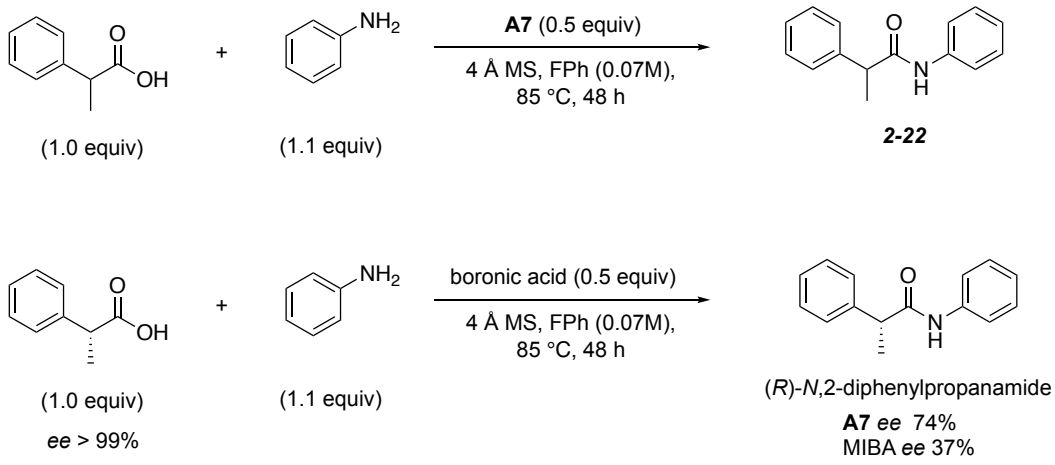
Using the recovered boronic acid **A7**, 74% of *N*,2-diphenylacetamide was obtained from a 0.12 mmol scale reaction. The recovered boronic acid **A7** was able to promote the amidation reaction with comparable efficiency to the original batch.



Scheme 2-7: Reusability of boronic acid **A7**.

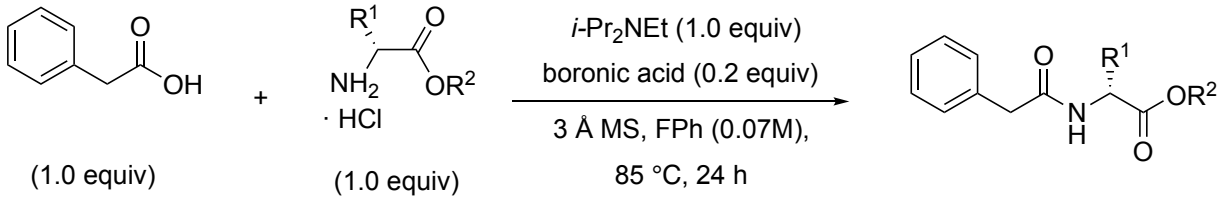
2.6 Investigation of Possible Racemization

Chiral carboxylic acids with a stereogenic α carbon are readily epimerizable due to the acidity of the α proton. Under amidation conditions, activation of the carbonyl through interaction with the boronic acid further stabilizes the negative charge developed upon deprotonation of the α proton. Consequently, the enantiomeric purity can be partially eroded through keto-enol tautomerization. An investigation of possible racemization was conducted using aniline and (*R*)-2-phenylpropanoic acid. The reactions were heated at 85°C for 48 hours and the amide product was isolated by column chromatography. The enantiomeric excesses were determined by chiral high-performance liquid chromatography (HPLC).

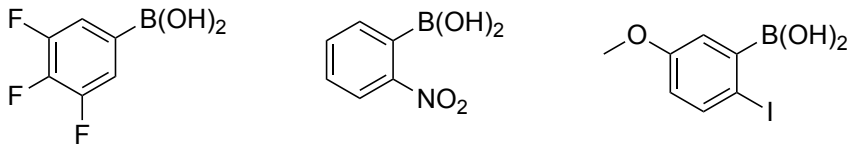


Scheme 2-8: Determination of enantiomeric excesses for the amidation reaction with a chiral acid obtained with chiral HPLC.

As depicted in Scheme 2-8, partial racemization, with 74% *ee*, was observed in the reaction between (*R*)-2-phenylpropanoic acid and aniline with boronic acid **A7**. In contrast, anilide product with a poorer enantiomeric purity, 37% *ee*, was obtained when MIBA was used instead. When the reaction temperatures were lowered from 85 °C to 65 °C, trace amount of product was observed with either **A7** or MIBA. The possible factors causing the loss of enantiomeric purity are the reaction temperature, the nature of the catalyst, and the nature of the substrates. As previously reported by the Hall Group and Whiting Group, [68,79] MIBA and Whiting's catalysts (**2-26** and **2-27**) were compared as shown below (Scheme 2-9). Although little epimerization was observed in the synthesis of amide **2-28** promoted by boronic acid **2-26** (entry 4), partial racemization cases (entries 1, 2, and 5) were reported in Whiting's epimerization study where the reactions were heated in FPh at 85 °C. In contrast, when the temperature was lowered to 50 °C, the reactions catalyzed by MIBA afforded amide products **2-28** and **2-29** with 99% *ee*.[68,79] Comparing the syntheses of chiral amides **2-28** and **2-29** with different boronic acids at different temperatures, a lower reaction temperature may suppress undesired racemization.

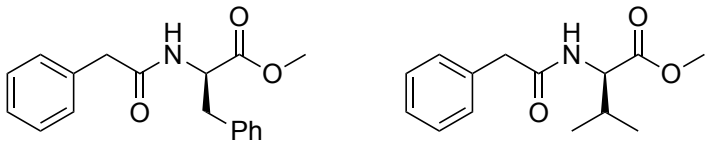


Boronic Acid:



2-26 **2-27** MIBA

Amide products:



2-28 **2-29**

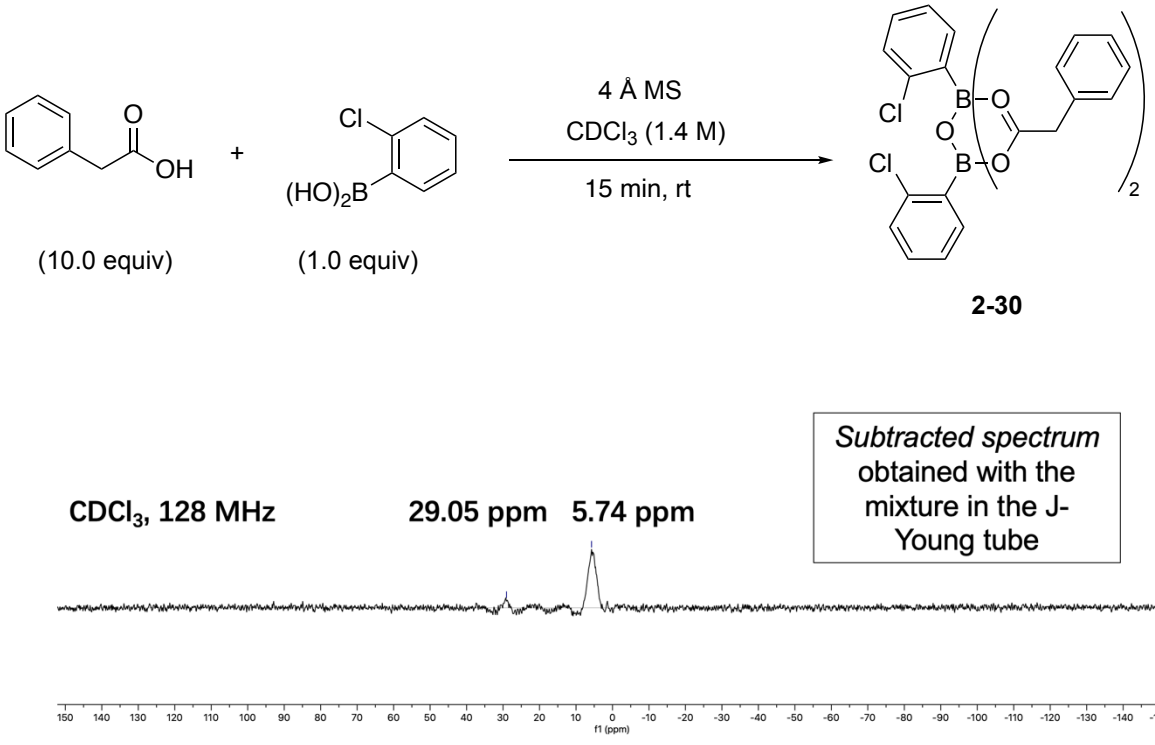
Entry	Amide product	BA	*ee* (%)
1	**2-28**	**2-26**	64
2	**2-28**	**2-27**	67
3[a]	**2-28**	MIBA	99
4	**2-29**	**2-26**	99
5	**2-29**	**2-27**	71
6[a]	**2-29**	MIBA	99

Scheme 2-9: Examples in previously reported epimerization studies. [a]: The reaction was conducted in toluene at 50 °C instead.

2.7 Investigation of the Reaction Mechanism

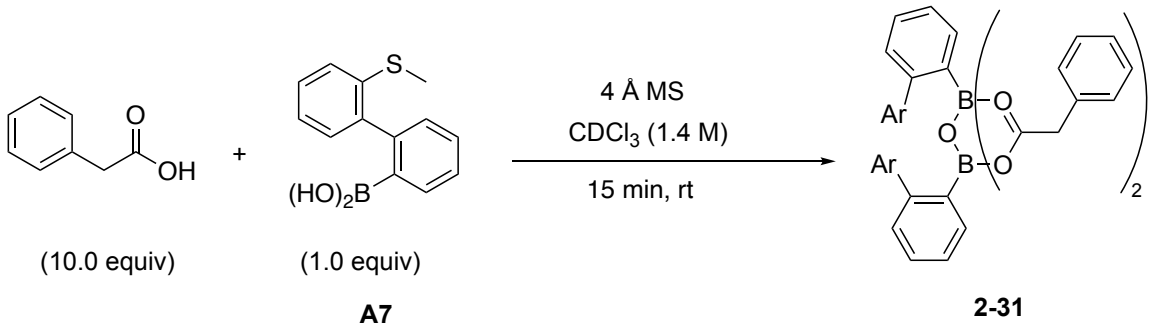
To gain insight into the amidation reaction mechanism, NMR experiments were conducted with phenylacetic acid and boronic acid **A7**. Solvent $CDCl_3$ was dried with 4Å beaded molecular sieves overnight. Under nitrogen atmosphere, phenylacetic acid (1.0 mmol) and arylboronic acid (0.1 mmol) were added to a J-Young tube and dissolved in dry $CDCl_3$ (0.7 mL). After the addition of activated molecular sieves (the height of sieves was 6 mm from the bottom of the NMR tube after settling), the tube was sealed, and the sample was submitted to the spectrometer.

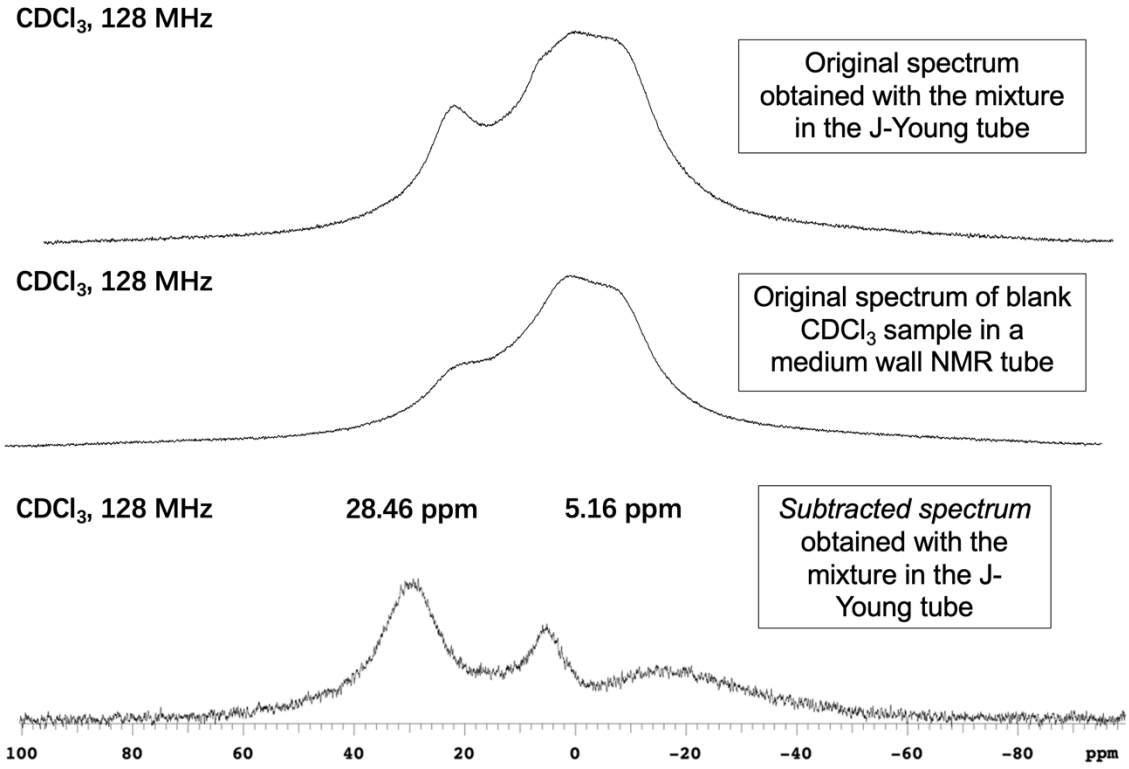
As described in Whiting's mechanistic study,[61] intermediate **2-30** was reproduced with phenylacetic acid and 2-chlorophenylboronic acid. The signal was obtained by artificially subtracting the interfering background signal from the NMR tube. Apart from 2-chlorophenylboronic acid's boron signal at 29.05 ppm, the signal at 5.74 ppm matches the reported data.



Scheme 2-10: ^{11}BNMR experiment with phenylacetic acid and 2-chlorophenylboronic acid.

The NMR experiment was repeated with boronic acid **A7** instead of 2-chlorophenylboronic acid. Again, the interference from the boron-containing NMR tube was eliminated with an artificial subtraction. On the subtracted ^{11}B NMR spectrum, a new signal at 5.16 ppm was observed as shown in Scheme 2-11, along with the boron signal of the arylboronic acid **A7** at 28.46 ppm. The signal at 5.16 ppm is consistent with formation of a diacyloxy B–O–B bridged intermediate **2-31**.





Scheme 2-11: ^{11}B NMR experiment with phenylacetic acid and boronic acid **A7**.

The observation of the signals of intermediates **2-30** and **2-31** emphasized the importance of the "pre-stirring" step in the amidation protocol where the carboxylic acid was stirred with boronic acid in the presence of molecular sieves prior to the addition of the amine. In the

diacyloxy B–O–B bridged intermediate **2-30** and **2-31**, the carboxylic acid is activated intramolecularly by the dimeric B–O–B motif, which effectively lowers the energy barrier of the subsequent nucleophilic attack from the amine.

Although its beneficial effect was confirmed from the comparison with other substituents (Table 2-4), the role of the sulfide substituent in boronic acid **A7** still remains vague. A computational study of the hydrogen bonding of O-H···O and O-H···S units was conducted by Wategaonkar and co-workers using a calculation at the MP2 level for the B3LYP/aug-cc-pVDZ-optimized structures.[80] The binding energy of *p*-cresol-MeOH complex was calculated to be 8.7 kcal/mol, which is higher than that of *p*-cresol-MeSH complex (6.9 kcal/mol). Although sulfur is generally considered to be a weaker hydrogen bond acceptor compared to oxygen when the donor is OH, calculations reported by Khanna and Singh in 2014 suggest that the $(CH_3)_2S\cdots NH_2CH_3$ adduct is more stable by 0.49 kcal/mol relative to its oxygen analog.[81] Additionally, the stabilizing energy of $(CH_3)_2S$ with other selected hydrogen bond donors is lower than the oxygen analog by only 0.03–1.7 kcal/mol. When the donor is an amine, the difference of hydrogen bonding ability between sulfur and oxygen is minimal. Accordingly, it is unclear how the directing effect between amine and the heteroatom (S of **A7** and O of **A3**) can account for the reactivity difference between boronic acid **A7** and **A3**. It is also possible that the sulfide substituent promotes the formation of the dimeric B–O–B motif with balanced steric and electronic effects.

2.8 Conclusion

Anilide moieties are commonly found in natural products and bioactive molecules but are barely covered in the substrate scopes of current boron-based amidation reagents and catalysts. To overcome the challenge of direct dehydrative anilide synthesis, a series of novel boronic acids with biphenyl scaffolds were developed to catalyze these amidation reactions. The design of the organoboron species was based on a speculated amidation intermediate where the carboxylic acid was activated intramolecularly and the amine was activated and directed via hydrogen bonding interactions by the heteroatom substituent towards nucleophilic attack onto the acyl unit.

The optimal boronic acid (2'-(methylthio)-[1,1'-biphenyl]-2-yl)boronic acid, **A7**, exhibited good reactivity in promoting the amidation reaction between phenylacetic acid and aniline at 85

°C in fluorobenzene. The versatility and scope of this methodology was demonstrated with various aniline derivatives such as toluidines, halogenated anilines, electron-rich anilines, electron-deficient anilines, and the heterocyclic quinolin-6-amine. However, the reaction with a sterically demanding aniline, 2,4,6-trimethylaniline, was not successful with boronic acid **A7**, probably due to the congestion around the activated carbonyl preventing the bulky amine from approaching the activated carbonyl. Due to a potential undesired interaction between the hydroxy group and the boronic acid, the reaction of 4-aminophenol was unsuccessful with both **A7** and MIBA. Variations of the carboxylic acid were also included, and the corresponding anilides, *N,2*-diphenylpropanamide, *N,3*-diphenylpropanamide, and *N*-phenylheptanamide were obtained. However, trace amount of *N*-(3-bromophenyl)benzamide was observed in the amidation reaction with either boronic acid **A7** or MIBA. The reaction between aniline and benzoic acid remains challenging under current conditions.

To demonstrate the scalability of this procedure, a gram-scale synthesis of N-(3-bromophenyl)-2-phenylacetamide was conducted to afford 65% yield of the desired product and 76% of boronic acid **A7** was recovered by column chromatography. To investigate potential racemization of the amidation reaction with chiral carboxylic acid, the synthesis of (*R*)-*N*,2-diphenylpropanamide was conducted with 75% *ee*. The partial loss of enantiomeric purity might be suppressed by using a more reactive boronic acid that can promote the amidation reaction at a lower temperature. Attempts were also made to explore the mechanism of the dehydrative amidation. When phenylacetic acid was mixed with **A7** at a 10:1 ratio, in the presence of activated molecular sieves, a boron signal was observed at 5.17 ppm that supports the existence of the diacyloxy B–O–B bridged intermediate proposed by Whiting and co-workers.[74]

2.9 Experimental

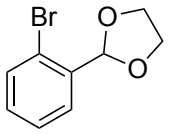
2.9.1 General Information

Unless otherwise stated, all reactions were performed under nitrogen atmosphere using flame-dried glassware. Toluene, THF and dichloromethane were dried from a double cartridge solvent

purification system. Dioxane was distilled from CaH_2. Anhydrous DMF, and absolute EtOH were commercially available. Analytical thin layer chromatography was performed on silica gel 60 F254 plates. NMR spectra were recorded on 400, 500, or 700 MHz instruments. The chemical shifts given in ppm were referenced to the residual proton signal of the deuterated solvent. Proton and boron NMR experiments of boronic acids were performed in deuterated solvent with an added drop of deuterated water to minimize formation of the corresponding boronic anhydrides. The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet. Because of their low intensity (resulting from quadrupolar coupling), ^{13}C signals arising from the quaternary carbon bearing the boronic acid group were not always observed and therefore were not always listed. High-resolution mass spectra (TOF analyzer) were recorded using either electron impact (EI) or electrospray ionization (ESI) techniques, obtained by the mass spec lab. Infrared spectra were obtained with frequencies expressed in cm^{-1}. Powdered 4Å molecular sieves (<5 μm) were dried overnight under high vacuum (< 2 mbar) at 300 °C using sand bath and heating mantle. All the different catalysts were stored in a fridge, under inert atmosphere. Chiral HPLC was conducted with IB column with an eluent of isopropanol: hexanes (5: 95) and the flow rate was 0.5 mL/min.

2.9.2 Synthesis of Compound 2-1, 2-2, 2-3, 2-4, and 2-5.

2.9.2.1 Synthesis of 2-(2-Bromophenyl)-1,3-dioxolane (2-1)



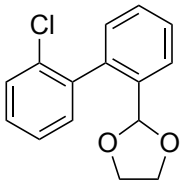
Following the literature's procedure,[82] bromobenzaldehyde (2.0 g, 11 mmol) was dissolved in toluene instead of benzene. The title compound was isolated as a yellow oil (2.3 g, 90% yield). Characterization data for the product matched the data found in the literature. [82]

^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, J = 7.6, 1.8 Hz, 1 H), 7.55 (dd, J = 7.9, 1.2 Hz, 1 H), 7.34 (dt, J = 7.6, 1.2 Hz, 1 H), 7.21 (dt, J = 7.9, 1.8 Hz, 1 H), 6.08 (s, 1 H), 4.16–4.08 (comp m,

AA’ part of AA’BB’, 2 H), 4.07–4.01 (comp m, BB’ part of AA’BB’, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.5, 132.9, 130.7, 127.8, 127.4, 122.6, 102.6, 65.3.

2.9.2.2 Synthesis of 2-(2-Bromophenyl)-1,3-dioxolane (2-2)

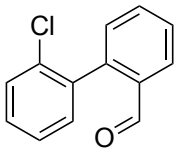


Following the literature’s procedure,[82] toluene instead of benzene was used as the solvent. Compound **2-3** (0.63 g, 3.0 mmol) was used instead of 2-bromobenzaldehyde. The title compound was isolated as a yellow oil (0.74 g, 95% yield). Characterization data for the product matched the data found in the literature. [83]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77–7.63 (m, 1 H), 7.52–7.38 (m, 3 H), 7.36–7.27 (m, 3 H), 7.23–7.16 (m, 1 H), 5.54 (s, 1 H), 4.10–4.06 (comp m, A part of AA’BB’, 1 H), 4.01–3.97 (comp m, A’ part of AA’BB’, 1 H), 3.92–3.88 (comp m, B part of AA’BB’, 1 H), 3.85–3.81 (comp m, B’ part of AA’BB’, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2, 138.8, 135.6, 133.4, 131.9, 130.1, 130.0, 129.3, 128.8, 128.2, 126.6, 126.2, 123.9, 101.2, 65.5, 65.3.

2.9.2.3 Synthesis of 2'-Chloro-[1,1'-biphenyl]-2-carbaldehyde (2-3)



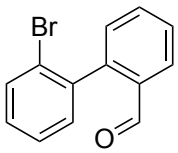
Following the literature’s procedure,[84] 2-bromobenzaldehyde (0.95 g, 5.2 mmol) was reacted with 2-chlorophenylboronic acid (1.2 g, 7.8 mmol). The title compound was isolated as a yellow

oil (0.79 g, 70% yield). Characterization data for the product matched the data found in the literature.[85]

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.18–8.03 (m, 1 H), 7.71 (td, J = 7.5, 1.5 Hz, 1 H), 7.63–7.51 (m, 2 H), 7.45–7.33 (m, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.7, 142.8, 137.0, 134.0, 133.8, 133.7, 131.9, 131.1, 129.8, 129.8, 128.7, 127.6, 127.0.

2.9.2.4 Synthesis of 2'-Bromo-[1,1'-biphenyl]-2-carbaldehyde (2-4)

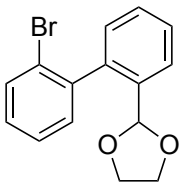


Following the literature's procedure,[84] 2-bromobenzaldehyde (0.95 g, 5.2 mmol) was reacted with 2-bromophenylboronic acid (1.6 g, 7.8 mmol). The title compound was isolated as a yellow oil (1.1 g, 85% yield). Characterization data for the product matched the data found in the literature. [82]

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1 H), 8.04 (ddd, J = 7.8, 1.5, 0.6 Hz, 1H), 7.74–7.62 (m, 2 H), 7.55 (tt, J = 7.8, 1.5 Hz, 1H), 7.44–7.38 (m, 1 H), 7.35–7.29 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.4, 143.8, 138.9, 134.0, 133.8, 133.7, 132.2, 131.1, 130.8, 129.8, 128.7, 127.6, 123.6.

2.9.2.5 Synthesis of 2-(2'-Bromo-[1,1'-biphenyl]-2-yl)-1,3-dioxolane (2-5)

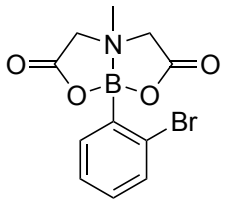


Following the literature's procedure,[82] toluene instead of benzene was used as the solvent. Compound **2-4** (1.1 g, 4.4 mmol) was used instead of bromobenzaldehyde. The title compound was isolated as a yellow oil (0.72 g, 95%). Characterization data for the product matched the data found in the literature.[83]

^{1}H (400 MHz, $CDCl_3$) δ 7.74–7.62 (m, 2 H), 7.44 (dtd, J = 16.2, 7.4, 1.6 Hz, 2 H), 7.38–7.30 (dt, m, 2 H), 7.30–7.21 (m, 2 H), 7.20–7.11 (m, 1 H), 5.52 (s, 1 H), 4.10–4.05 (comp m, A part of AA'BB', 1 H), 3.99–3.92 (comp m, A' part of AA'BB', 1 H), 3.91–3.83 (comp m, BB' part of AA'BB', 2 H).

^{13}C (176 MHz, $CDCl_3$) δ 140.9, 140.8, 140.7, 135.1, 132.2, 131.9, 130.0, 129.1, 128.2, 128.0, 126.8, 126.2, 123.9, 101.2, 65.4, 65.1.

2.9.3 Synthesis of 2-Bromophenylboronic acid MIDA ester (2-6)



A 500 mL round-bottomed flask with magnetic stirrer bar was charged with 2-biphenylboronic acid (1.0 g, 5.0 mmol, 1.0 equiv), *N*-methyliminodiacetic acid (0.74 g, 5.0 mmol, 1.0 equiv), and 10:1 mixture of toluene and DMSO (0.030 M, 150:15 mL). The reaction was heated to reflux with Dean-Stark apparatus open to the air for 20 hours. Upon completion, the reaction was allowed to cool to room temperature and the solvent was removed under reduced pressure to give a yellow solution. Et_2O (50 mL) was added, and the mixture was left sitting at room temperature for an hour. The resulting white precipitate was removed by filtration and the solid was washed with Et_2O (2 x 50 mL). The solid was collected to give the title compound as a white amorphous solid (1.4 g, 95%). Characterization data for the product matched the data found in the literature.[86]

^{1}H NMR (500 MHz, CD_3CN) δ 7.67 (dd, J = 7.5, 1.9 Hz, 1 H), 7.62 (dd, J = 7.9, 1.2 Hz, 1 H), 7.39 (ddd, J = 7.5, 7.4, 1.2 Hz, 1 H), 7.30 (ddd, J = 7.9, 7.4, 1.9 Hz, 1 H), 4.08 (AB q, 4 H), 2.73 (s, 3 H).

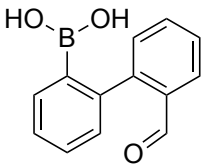
^{13}C NMR (126 MHz, CD_3CN) δ 169.4, 137.4, 134.6, 132.3, 128.7, 127.9, 65.2, 49.5.

^{11}B NMR (160 MHz, CD_3CN) δ 11.4.

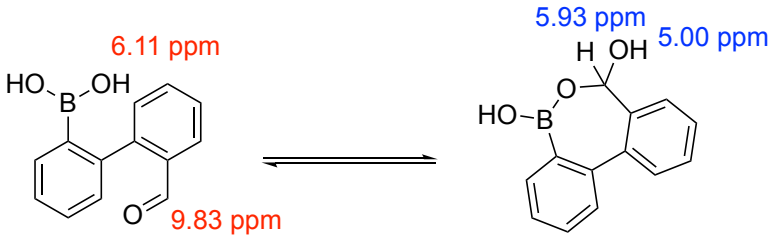
2.9.4 Synthesis of Biphenyl Boronic Acid

General Procedure A for Preparation of Boronic Acid Catalyst A1, A2, A3, A4, A5, A6, A7, and **A8**: An oven-dried microwave vial equipped with magnetic stirrer bar was charged with 2-bromophenylboronic acid MIDA ester **2-6** (1.0 equiv), arylboronic acid (1.1 equiv), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5.0 mol %), and anhydrous K_3PO_4 (4.0 equiv). The vial was purged with N_2 before addition of THF (0.080 M) and H_2O (7.0 equiv). The reaction was heated to 90 °C for 4 hours then allowed to cool to room temperature. The reaction mixture was filtered through a short pad of Celite and eluted through silica with a 1:1 mixture of ethyl acetate and hexanes. Fractions containing product were collected in acetonitrile evaporated under vacuum to afford the title compound.

2.9.4.1 Synthesis of (2'-Formyl-[1,1'-biphenyl]-2-yl)boronic acid (A1)



The title compound was prepared following the general procedure A, with 2-bromophenylboronic acid MIDA ester **2-6** (0.25 g, 1.6 mmol, 1.0 equiv) and 2-formyl phenyl boronic acid (0.26 g, 1.8 mmol, 1.1 equiv). The product was isolated as a white solid (0.091 g, 25% yield). An equilibrium between the “open” form with free boronic acid and the “closed” form was reflected on ^{1}H NMR spectrum. HSQC and ^{1}H NMR with D_2O addition have confirmed the peaks at 6.11 ppm, 5.69 ppm, and 4.99 ppm are OH protons.



^{1}H NMR (500 MHz, CD_3CN) δ 9.83 (s, 0.5 H), 7.94 (d, J = 7.8 Hz, 0.6 H), 7.78 (d, J = 7.4 Hz, 0.8 H), 7.71 (d, J = 6.6 Hz, 0.8 H), 7.67–7.52 (m, 3 H), 7.49–7.43 (m, 3 H),7.37 (d, J = 7.4 Hz, 0.6 H), 7.27 (d, J = 7.4 Hz, 0.6 H), 6.11(s, 0.5 H), 5.93 (br s, 0.4 H), 5.68 (s, 1 H), 4.99 (br s, 0.4 H).

^{13}C NMR (126 MHz, CD_3CN) δ 193.0, 148.2, 142.6, 139.7, 134.1, 134.1, 132.1, 131.3, 129.7, 128.6, 128.2, 128.0, 127.5.

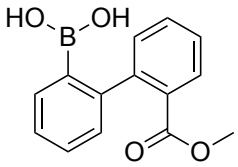
^{11}B NMR (160 MHz, CD_3CN) δ 29.6.

IR (Cast film, cm^{-1}): 3436, 3059, 2849, 2752, 1690, 1596, 1439.

HRMS (ESI) *m/z* for $C_{13}H_{10}BO_3^-$ $[M–H]^-$: calcd. 225.0801; found 225.0814.

Melting point (°C): 138–139.

2.9.4.2 Synthesis of (2'-(Methoxycarbonyl)-[1,1'-biphenyl]-2-yl)boronic acid (A2)



The title compound was prepared following the general procedure A, with 2-bromophenylboronic acid MIDA ester **2-6** (0.25 g, 1.6 mmol) and 2-methoxylcarbonylphenyl boronic acid (0.32 g, 1.8 mmol). The product was isolated as a white solid (0.090 g, 22% yield).

^{1}H NMR (500 MHz, CD_3CN) δ 8.06 (s, 1 H), 7.79 (dd, J = 7.8, 1.4 Hz, 1 H), 7.63 (dd, J = 7.3, 1.7 Hz, 1 H), 7.56 (td, J = 7.5, 1.4 Hz, 1 H), 7.47 (td, J = 7.6, 1.4 Hz, 1 H), 7.41–7.30 (m, 2 H), 7.25 (dd, J = 7.8, 1.4 Hz, 1 H), 7.08–7.06 (m, 1 H), 3.63 (s, 3 H).

^{13}C NMR (125 MHz, CD_3CN) δ 170.1, 145.9, 144.7, 133.5, 132.0, 131.9, 131.8, 129.9, 129.6,

129.4, 128.2, 127.3, 52.7.

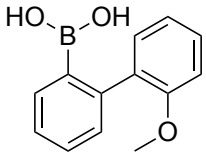
^{11}B NMR (128 MHz, CD_3CN) δ 28.8 ppm.

IR (Cast film, cm^{-1}): 3057, 2950, 2924, 1727, 1539, 1436, 1351.

HRMS (ESI) *m/z* for $C_{14}H_{12}BO_4^-$ $[M–H]^-$: calcd. 255.0834; found 255.0830.

Melting point (°C): 142–143.

2.9.4.3 Synthesis of (2'-Methoxy-[1,1'-biphenyl]-2-yl)boronic acid (A3)



The title compound was prepared following the general procedure A, with 2-bromophenylboronic acid MIDA ester **2-6** (0.25 g, 1.6 mmol) and 2-methoxy boronic acid (0.27 g, 1.8 mmol). The product was isolated as a white solid (0.091 g, 25% yield).

^{1}H NMR (400 MHz, CD_3CN) δ 7.59 (d, J = 6.8 Hz, 1 H), 7.44–7.40 (m, 1 H), 7.37–7.26 (m, 4 H), 7.05–7.00 (m, 2 H), 3.72 (s, 3 H).

^{13}C NMR (176 MHz, CD_3CN) δ 156.3, 141.9, 132.5, 131.4, 130.7, 129.5, 129.3, 128.9, 126.2, 120.8, 110.9, 54.4.

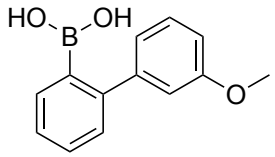
^{11}B NMR (128 MHz, CD_3CN) δ 28.8.

IR (Cast film, cm^{-1}): 3053, 2935, 2833, 1594, 1482, 1349.

HRMS (ESI) *m/z* for $C_{13}H_{12}BO_3^-$ $[M–H]^-$: calcd. 227.0885; found 227.0895.

Melting point (°C): 131–132.

2.9.4.4 Synthesis of (3'-Methoxy-[1,1'-biphenyl]-2-yl)boronic acid (A4)



The title compound was prepared following the general procedure A, with 2-bromophenylboronic acid MIDA ester **2-6** (0.25 g, 1.6 mmol) and 3-methoxy boronic acid (0.27 g, 1.8 mmol). The product was isolated as a colorless oil (0.17 g, 47% yield).

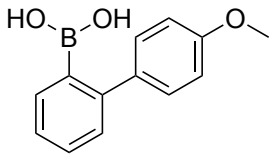
^{1}H NMR (700 MHz, CD_3CN) δ 7.59 (d, J = 6.6 Hz, 1 H), 7.44–7.39 (m, 2 H), 7.36–7.33 (m, 2 H), 6.94 (dd, J = 8.3, 2.6 Hz, 1 H), 5.70 (s, 2 H), 3.83 (s, 3 H).

^{13}C NMR (176 MHz, CD_3CN) δ 160.6, 146.3, 145.7, 133.9, 130.4, 130.1, 129.5, 127.4, 121.9, 115.3, 113.5, 55.9.

^{11}B NMR (128 MHz, CD_3CN) δ 30.5.

IR (Cast film, cm^{-1}): 3451, 3056, 2938, 2833, 1592, 1438, 1349. HRMS (ESI) *m/z* for $C_{13}H_{12}BO_3^-$ $[M–H]^-$: calcd. 227.0885; found 227.0895.

2.9.4.5 Synthesis of (4'-Methoxy-[1,1'-biphenyl]-2-yl)boronic acid (A5)



The title compound was prepared following the general procedure A, with 2-bromophenylboronic acid MIDA ester **2-6** (0.25 g, 1.6 mmol) and 4-methoxy boronic acid (0.27 g, 1.8 mmol). The product was isolated as a white solid (0.22 g, 60% yield).

^{1}H NMR (400 MHz, CD_3CN) δ 7.57 (dd, J = 7.3, 1.5 Hz, 1 H), 7.43–7.28 (m, 5 H), 7.00–6.96 (m, 2 H), 3.82 (s, 3 H).

^{13}C NMR (126 MHz, CD_3CN) δ 160.2, 146.2, 136.5, 134.9, 134.1, 130.7, 130.2, 129.5, 126.9,

114.7, 55.9.

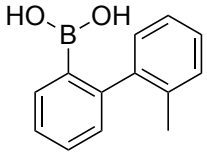
^{11}B NMR (128 MHz, CD_3CN) δ 30.4.

IR (Cast film, cm^{-1}): 3052, 3032, 3012, 2957, 1592, 1460, 1345.

HRMS (ESI) *m/z* for $C_{13}H_{12}BO_3^-$ $[M–H]^-$: calcd. 227.0885; found 227.0895.

Melting point (°C): 130–131.

2.9.4.6 Synthesis of (2'-Methyl-[1,1'-biphenyl]-2-yl)boronic acid (A6)



The title compound was prepared following the general procedure A, with 2-bromophenylboronic acid MIDA ester **2-6** (0.25 g, 1.6 mmol) and 2-methyl boronic acid (0.27 g, 1.8 mmol). The product was isolated as a white solid (0.15 g, 44% yield).

^{1}H NMR (700 MHz, CD_3CN) δ 7.76 (d, J = 7.4 Hz, 1 H), 7.45 (td, J = 7.5, 1.4 Hz, 1 H), 7.37 (td, J = 7.5, 1.4 Hz, 2 H), 7.31 (d, J = 4.9 Hz, 2 H), 7.27–7.23 (m, 1 H), 7.16 (dd, J = 7.4, 3.0 Hz, 2 H), 5.24 (s, 2 H), 2.10 (s, 3 H).

^{13}C NMR (176 MHz, CD_3CN) δ 147.1, 143.7, 136.7, 134.9, 131.2, 130.5, 130.3, 130.1, 128.7, 127.4, 126.7, 20.4.

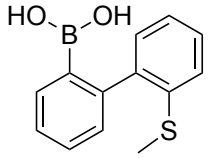
^{11}B NMR (128 MHz, CD_3CN) δ 29.2.

IR (Cast film, cm^{-1}): 3055, 3014, 2923, 2854, 1592, 1475, 1344.

HRMS (ESI) *m/z* for $C_{13}H_{12}BO_2^-$ $[M–H]^-$: calcd. 211.0936; found 211.0945.

Melting point (°C): 135–136.

2.9.4.7 Synthesis of (2'-(Methylthio)-[1,1'-biphenyl]-2-yl)boronic acid (A7)



The title compound was prepared following the general procedure A, with 2-bromophenylboronic acid MIDA ester **2-6** (0.25 g, 1.6 mmol) and (2-(methylthio)phenyl)boronic acid (0.54 g, 3.2 mmol). The product was isolated as a white solid (0.14 g, 35% yield).

^{1}H NMR (400 MHz, CD_3CN) δ 7.73 (dd, J = 7.7, 1.4 Hz, 1 H), 7. 47–7.32 (m, 4 H), 7.23 (td, J = 7.4, 1.4 Hz, 1 H) 7.18–7.13 (m, 2 H), 2.35 (s, 3 H).

^{13}C NMR (126 MHz, CD_3CN) δ 145.6, 142.2, 138.5, 134.7, 130.5, 130.5, 129.3, 127.9, 125.6, 125.5, 15.5.

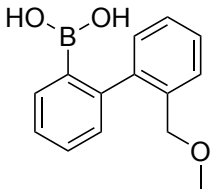
^{11}B NMR (128 MHz, CD_3CN) δ 29.3.

IR (Cast film, cm^{-1}): 3054, 2936, 2833, 1594, 1482, 1349.

HRMS (ESI) *m/z* for $C_{13}H_{12}BO_2S^-$ $[M–H]^-$: calcd. 243.0657; found 243.0661.

Melting point (°C): 170–172.

2.9.4.8 Synthesis of (2'-(Methoxymethyl)-[1,1'-biphenyl]-2-yl)boronic acid (A8)



The title compound was prepared following the general procedure A, with 2-bromophenylboronic acid MIDA ester **2-6** (0.25 g, 1.6 mmol) and (2-(methoxymethyl)phenyl)boronic acid (0.29 g, 1.8 mmol), The product was isolated as a white solid (0.069 g, 18% yield).

^{1}H NMR (500 MHz, CD_3CN) δ 7.63 (dd, J = 7.4, 1.3 Hz, 1 H), 7.45–7.35 (m, 5 H), 7.16–7.14 (m, 1 H), 7.13–7.10 (m, 1 H), 4.28–4.24 (d, J = 20 Hz, 2 H) 3.07 (s, 3 H).

^{13}C NMR (126 MHz, CD_3CN) δ 145.1, 145.1, 135.9, 133.6, 130.7, 130.5, 129.4, 129.2, 129.1, 128.5, 127.3, 73.8, 58.6.

^{11}B NMR (126 MHz, CD_3CN) δ 29.8.

IR (Cast film, cm^{-1}): 3055, 2924, 2893, 1592, 1436, 1353.

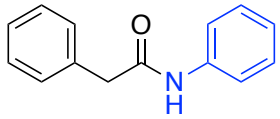
HRMS (ESI) *m/z* for $C_{14}H_{14}BO_3^-$ $[M–H]^-$: calcd. 241.1041; found 241.1050.

Melting point (°C): 80–80.5.

2.9.5 Synthesis of Anilide

General Procedure B for Preparation of Anilide: To a flame-dried 5 mL pressure tube with a stirring bar was added phenylacetic acid (0.13 mmol, 1.0 equiv), pre-activated 4Å molecular sieves (1.0 g per 0.5 mmol carboxylic acid), and boronic acid **A7** (0.50 equiv). The distilled fluorobenzene (1.9 mL, 0.070 M) was added to the mixture and the mixture was stirred at room temperature for 15 min before the addition of aniline (0.15 mmol, 1.1 equiv) and DMAPO (0.0060 mmol, 0.050 equiv). The reaction mixture was sealed and heated for 48 h at 85 °C. The reaction mixture was filtered through a pad of Celite 545 with 10 mL of dichloromethane. The filtrate was concentrated and loaded onto column. The title anilide was isolated with column chromatography (ethyl acetate: hexanes = 1:5) and dried under vacuum. Characterization data for the product matched the data found in the literature.

2.9.5.1 Synthesis of N,2-Diphenylacetamide (2-8)[87]

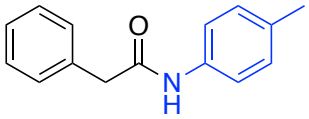


The title compound was prepared following the general procedure B and was isolated as a white solid (0.023 g, 83% yield).

^{1}H NMR (500 MHz, CD_3CN) δ 8.40 (br s, 1 H), 7.54 (dd, J = 8.6, 1.2 Hz, 2 H), 7.35–7.26 (m, 7 H), 7.08 (t, J = 7.4 Hz, 1 H), 3.66 (s, 2 H).

^{13}C NMR (126 MHz, CD_3CN) δ 170.3, 139.9, 136.8, 130.2, 129.7, 129.4, 127.7, 124.7, 120.4, 44.6.

2.9.5.2 Synthesis of 2-Phenyl-N-(p-tolyl)acetamide (2-9)[88]

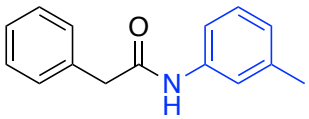


The title compound was prepared following the general procedure B and was isolated as a white solid (0.014 g, 18% yield).

^{1}H NMR (700 MHz, CD_3CN) δ 8.33 (br s, 1 H), 7.41 (d, J = 8.4 Hz, 2 H), 7.35–7.34 (m, 4 H), 7.27 (ddd, J = 8.4, 5.2, 3.5 Hz, 1 H), 7.11 (d, J = 8.4 Hz, 2 H), 3.62 (s, 2 H), 2.28 (s, 3 H).

^{13}C NMR (176 MHz, CD_3CN) δ 170.1, 137.4, 136.9, 134.3, 130.2, 130.1, 129.4, 127.7, 120.6, 44.5, 20.8.

2.9.5.3 Synthesis of 2-Phenyl-N-(m-tolyl)acetamide (2-10)[88]

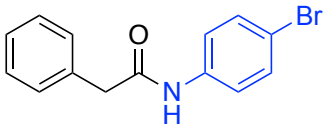


The title compound was prepared following the general procedure B and was isolated as a white solid (0.027 g, 88% yield).

^{1}H NMR (700 MHz, CD_3CN) δ 8.34 (br s, 1 H), 7.37–7.33 (m, 6 H), 7.27 (ddd, J = 8.6, 5.3, 3.4 Hz, 1 H), 7.18 (t, J = 7.8 Hz, 1 H), 6.90 (d, J = 7.3 Hz, 1 H), 3.63 (s, 2 H), 2.30 (s, 3 H).

^{13}C NMR (176 MHz, CD_3CN) δ 170.3, 139.9, 139.7, 136.9, 130.2, 129.6, 129.4, 127.7, 125.4, 121.0, 117.6, 44.6, 21.5.

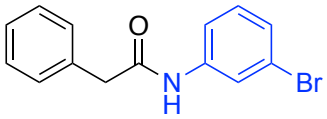
2.9.5.4 Synthesis of N-(4-Bromophenyl)-2-phenylacetamide (2-11) [88]



The title compound was prepared following the general procedure B and was isolated as a white solid (0.026 g, 66% yield).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.42–7.31 (m, 9 H), 7.09 (s, 1 H), 3.73 (s, 2 H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.2, 136.8, 134.3, 132.0, 129.7, 129.5, 127.9, 121.5, 117.2, 44.9.

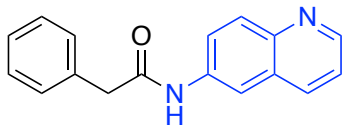
2.9.5.5 Synthesis of N-(3-Bromophenyl)-2-phenylacetamide (2-12) [88]



The title compound was prepared following the general procedure B and was isolated as a white solid (0.031 g, 80% yield).

^{1}H NMR (500 MHz, CD_3CN) δ 8.52 (br s, 1 H), 7.87 (t, J = 2.1 Hz, 1 H), 7.46–7.44 (dt, J = 6.8, 2.1 Hz, 1 H), 7.37–7.33 (m, 4 H), 7.30–7.26 (m, 1 H), 7.24–7.21 (m, 2 H), 3.66 (s, 2 H). ^{13}C NMR (126 MHz, CD_3CN) δ 170.6, 141.4, 136.5, 131.5, 130.3, 129.5, 127.8, 127.4, 122.9, 122.8, 44.5.

2.9.5.6 Synthesis of 2-Phenyl-N-(quinolin-6-yl)acetamide (2-13) [89]

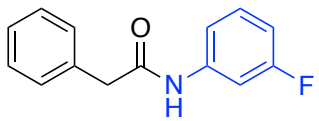


To a flame-dried 5 mL pressure tube with a stirring bar was added phenylacetic acid (0.27 mmol, 2.0 equiv), pre-activated 4Å molecular sieves (1.0 g per 0.50 mmol carboxylic acid), and boronic acid **A7** (0.068 mmol, 0.50 equiv). The distilled fluorobenzene (1.9 mL, 0.070 M) was added to the mixture and the mixture was stirred at room temperature for 15 min before the addition of aniline (0.13 mmol, 1.0 equiv) and DMAPO (0.0060 mmol, 0.050 equiv). The reaction mixture was sealed and heated for 48 h at 85 °C. The reaction mixture was filtered through a pad of Celite 545 with 10 mL of dichloromethane. The filtrate was concentrated and loaded onto column. The title anilide was isolated with column chromatography (ethyl acetate: hexanes = 1:5) and dried under vacuum. The title compound was isolated as a white solid (0.030 g, 85% yield).

^{1}H NMR (400 MHz, CD_3CN) δ 8.77 (d, J = 4.2, 1.7 Hz, 1 H), 8.72 (br s, 1 H), 8.32 (d, J = 2.4 Hz, 1 H), 8.18 (d, J = 8.4 Hz, 1 H), 7.97 (d, J = 9.1 Hz, 1 H), 7.73 (dd, J = 9.1, 2.4 Hz, 1 H), 7.42–7.34 (m, 5 H), 7.31–7.27 (m, 1 H), 3.72 (s, 2 H).

^{13}C NMR (126 MHz, CD_3CN) δ 170.8, 150.3, 146.3, 137.9, 136.7, 136.4, 130.8, 130.3, 129.6, 129.5, 127.8, 124.1, 122.6, 116.4, 44.6.

2.9.5.7 Synthesis of N-(3-Fluorophenyl)-2-phenylacetamide (2-14) [90]

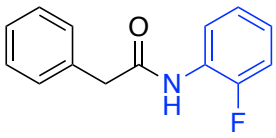


The title compound was prepared following the general procedure B and was isolated as a white solid (0.022 g, 71% yield).

^{1}H NMR (700 MHz, CD_3CN) δ 8.61 (br s, 1 H), 7.56 (dt, J = 11.6, 2.3 Hz, 1 H), 7.35 (d, J = 4.7 Hz, 4 H), 7.31–7.27 (m, 2 H), 7.24 (d, J = 8.2 Hz, 1 H), 6.82 (td, J = 9.4, 2.3 Hz, 1 H), 3.65 (s, 2 H).

^{13}C NMR (176 MHz, CD_3CN) δ 170.7, 164.4 (d, J = 242.5 Hz), 141.6 (d, J = 10.7 Hz), 136.5, 131.2 (d, J = 10.0 Hz), 130.3, 129.5, 127.9, 115.9 (d, J = 2.8 Hz), 111.0 (d, J = 19.0 Hz), 107.4 (d, J = 26 Hz), 44.5.

2.9.5.8 Synthesis of N-(2-Fluorophenyl)-2-phenylacetamide (2-15) [91]

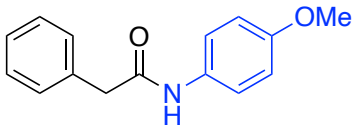


The title compound was prepared following the general procedure B and was isolated as a white solid (0.021 g, 69% yield).

^{1}H NMR (700 MHz, CD_3CN) δ 8.18 (br s, 1 H), 8.04–8.01 (m, 1 H), 7.36 (d, J = 4.5 Hz, 4 H), 7.31–7.28 (m, 1 H), 7.16–7.10 (m, 3 H), 3.73 (s, 2 H).

^{13}C NMR (176 MHz, CD_3CN) δ 170.6, 154.4 (d, J = 242.5 Hz), 136.6, 130.3, 129.5, 127.9, 127.3 (d, J = 10.4 Hz), 126.0 (d, J = 7.2 Hz), 125.3 (d, J = 3.8 Hz), 124.2, 116.0 (d, J = 16.9 Hz), 44.3.

2.9.5.9 Synthesis of N-(4-Methoxyphenyl)-2-phenylacetamide (2-16) [92]

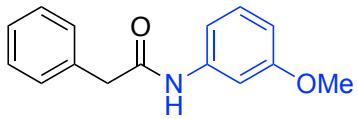


The title compound was prepared following the general procedure B and was isolated as a white solid (0.026 g, 80% yield).

^{1}H NMR (700 MHz, CD_3Cl_3) δ 7.41–7.39 (m, 2 H), 7.34–7.30 (m, 5 H), 6.59 (br s, 1 H), 6.82–6.80 (m, 2 H), 3.77 (s, 3 H), 3.72 (s, 2 H).

^{13}C NMR (176 MHz, CD_3Cl_3) δ 169.1, 156.7, 134.7, 130.8, 129.7, 129.4, 127.8, 121.9, 114.2, 55.6, 44.8.

2.9.5.10 Synthesis of N-(3-Methoxyphenyl)-2-phenylacetamide (2-17) [90]

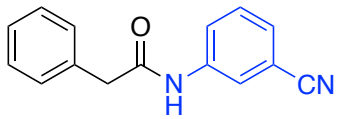


The title compound was prepared following the general procedure B and was isolated as a white solid (0.026 g, 82% yield).

^{1}H NMR (500 MHz, CD_3CN) δ 8.41 (br s, 1 H), 7.35 (d, J = 4.4 Hz, 4 H), 7.30–7.26 (m, 2 H), 7.20 (t, J = 8.2 Hz, 1 H), 7.06–7.05 (m, 1 H), 6.64 (dd, J = 8.2, 2.6 Hz, 1 H), 3.75 (s, 3 H), 3.63 (s, 2 H).

^{13}C NMR (126 MHz, CD_3CN) δ 170.4, 161.0, 141.2, 136.8, 130.5, 130.3, 129.4, 127.8, 118.2, 112.6, 110.1, 106.1, 55.8, 44.6.

2.9.5.11 Synthesis of N-(3-Cyanophenyl)-2-phenylacetamide (2-18)[93]

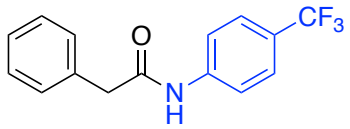


The title compound was prepared following the general procedure B and was isolated as a white solid (0.026 g, 82% yield).

^{1}H NMR (500 MHz, CD_3Cl_3) δ 7.83 (br s, 1 H), 7.62 (dt, J = 7.0, 2.4 Hz, 1 H), 7.43–7.32 (m, 7 H), 3.78 (s, 2 H).

^{13}C NMR (126 MHz, CD_3Cl_3) δ 169.5, 138.6, 133.9, 129.9, 129.6, 129.5, 128.1, 128.0, 124.0, 123.0, 118.5, 113.1, 44.9.

2.9.5.12 Synthesis of 2-Phenyl-N-(4-(trifluoromethyl)phenyl) acetamide (2-19) [92]

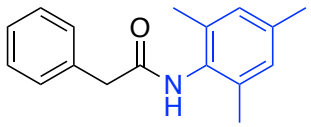


The title compound was prepared following the general procedure B and was isolated as a white solid (0.010 g, 27% yield).

^{1}H NMR (500 MHz, CD_3CN) δ 8.69 (br s, 1 H), 7.75 (d, J = 8.5 Hz, 2 H), 7.61 (d, J = 8.5 Hz, 4 H), 7.35 (d, J = 4.4 Hz, 4 H), 7.36–7.26 (m, 1 H), 3.70 (s, 2 H).

^{13}C NMR (126 MHz, CD_3CN) δ 170.9, 143.4, 136.4, 130.3, 129.5, 127.9, 126.9 (q, J = 3.8 Hz), 125.3, 124.4, 120.1, 44.5.

2.9.5.13 Synthesis of N-Mesityl-2-phenylacetamide (2-20)[94]

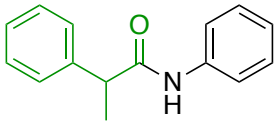


The title compound was prepared following the general procedure B with boronic acid MIBA instead of boronic acid **A7**. The product was isolated as a white solid (0.020 g, 60% yield).

^{1}H NMR (500 MHz, CD_3CN) δ 7.70 (br s, 1 H), 7.40–7.34 (m, 4 H), 7.30–7.26 (m, 1 H), 3.66 (s, 2 H), 2.23 (s, 3 H), 2.05 (s, 6 H).

^{13}C NMR (126 MHz, CD_3CN) δ 170.5, 137.6, 137.2, 136.6, 133.1, 130.8, 129.4, 129.3, 127.7, 118.3, 43.9, 20.9, 18.3.

2.9.5.14 Synthesis of N-Phenyl-α-methyl-benzeneacetamide (2-22)[95]

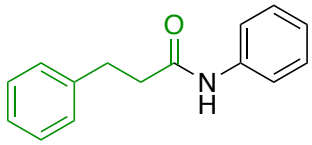


The title compound was prepared following the general procedure B and was isolated as a white solid (0.013 g, 44% yield).

^{1}H NMR (400 MHz, CD_3CN) δ 8.31 (br s, 1 H), 7.53 (d, J = 9.9 Hz, 2 H), 7.42–7.40 (m, 2 H), 7.36–7.24 (m, 5 H), 7.06 (t, J = 7.4 Hz, 1 H), 3.75 (q, J = 7.0 Hz, 1 H), 1.47 (d, J = 7.0 Hz, 3 H).

^{13}C NMR (126 MHz, CD_3CN) δ 173.5, 143.0, 134.0, 129.7, 129.5, 128.4, 127.9, 124.6, 120.4, 48.0, 19.1.

2.9.5.15 Synthesis of N,3-Diphenylpropanamide (2-23)[96]

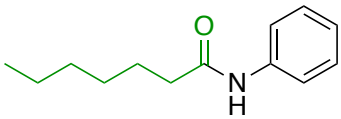


The title compound was prepared following the general procedure B and was isolated as a white solid (0.024 g, 85% yield).

^{1}H NMR (400 MHz, CD_3CN) δ 8.24 (s, 1 H), 7.52 (d, J = 8.2 Hz, 2 H), 7.31–7.26 (m, 6 H), 7.19 (t, J = 6.9 Hz, 1 H), 7.06 (t, J = 7.4 Hz, 1 H), 2.97 (t, J = 7.7 Hz, 2 H), 2.62 (t, J = 7.7 Hz, 2 H).

^{13}C NMR (126 MHz, CD_3CN) δ 171.6, 142.3, 140.0, 129.7, 129.4, 129.3, 127.0, 124.5, 120.3, 118.3, 39.3, 31.2.

2.9.5.16 Synthesis of N-Phenylheptanamide (2-24)[96]



The title compound was prepared following the general procedure B and was isolated as a white solid (0.020 g, 80% yield).

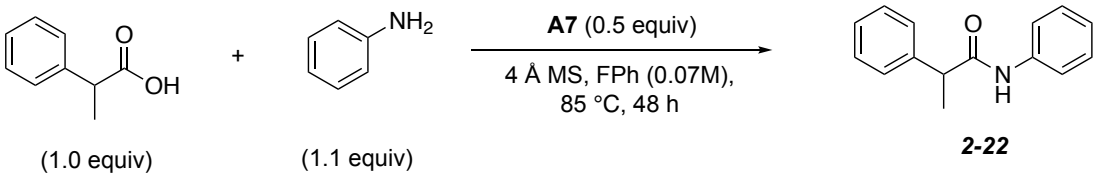
^{1}H NMR (400 MHz, CD_3CN) δ 8.22 (s, 1 H), 7.62–7.53 (m, 2 H), 7.32–7.28 (m, 2 H), 7.06 (tt, J = 7.4, 1.2 Hz, 1 H), 7.06 (t, J = 7.4 Hz, 1 H), 2.30 (t, J = 7.8 Hz, 2 H), 1.67–1.61 (m, 2 H), 1.38–1.30 (m, 6 H), 0.91–0.88 (m, 3 H).

^{13}C NMR (126 MHz, CD_3CN) δ 172.6, 140.2, 129.7, 124.3, 120.3, 37.8, 32.3, 29.6, 26.2, 23.2, 14.3.

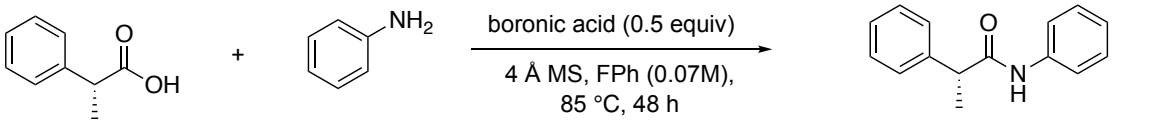
2.9.6 NMR Experiments

Following Whiting's procedure, NMR experiments were conducted. $CDCl_3$ was dried with molecular sieves beads overnight. Under nitrogen protection, phenylacetic acid (1 mmol) and arylboronic acid (0.1 mmol) were added to a J-Young tube and completely dissolved in dry $CDCl_3$ (0.7 mL). After the addition of activated molecular sieves (6 mm from the bottom of the NMR tube after settling down), the tube was sealed, and the sample was submitted to the spectrometer.

2.9.7 Chiral HPLC



(1.0 equiv) (1.1 equiv) ***2-22***

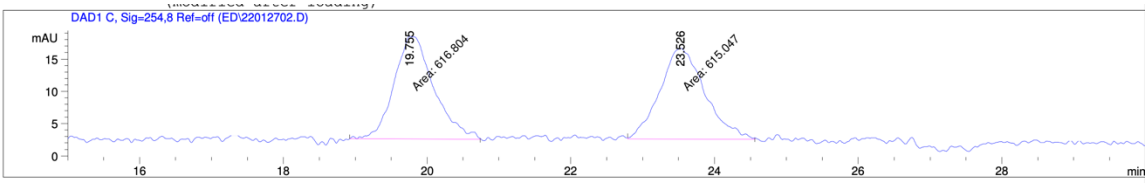


(1.0 equiv) (1.1 equiv) (*R*)-*N*,2-diphenylpropanamide

ee > 99% **A7** *ee* 74%

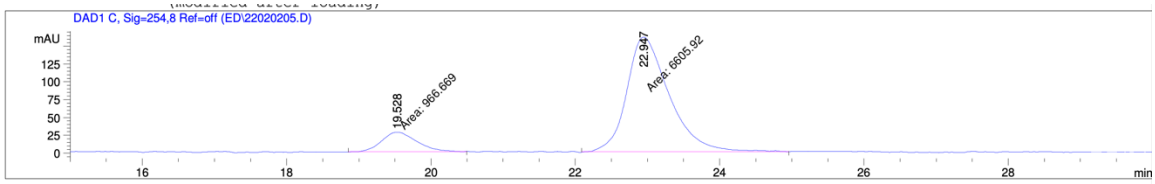
MIBA *ee* 37%

Racemic product:



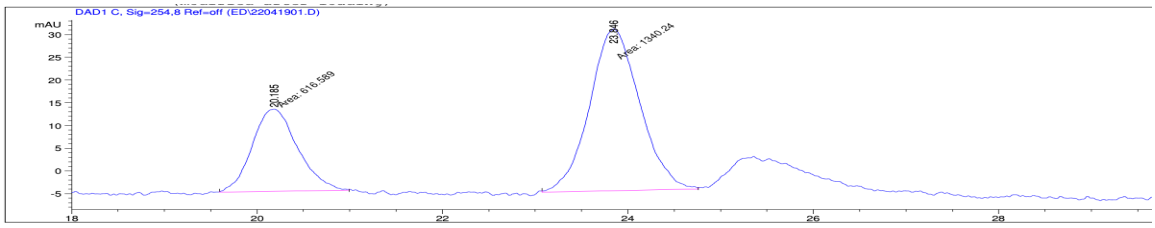

```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=254,8 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  19.755 MM    0.6463  616.80377   15.90568  50.0713
   2  23.526 MM    0.7266  615.04742   14.10817  49.9287

Totals :                  1231.85120   30.01384
```

Product obtained with **A7**:




```
=====================================================================
                    Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=254,8 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  19.528 MM    0.5777  966.66895   27.88725  12.7654
   2  22.947 MM    0.6827 6605.92383  161.27304  87.2346

Totals :                  7572.59277  189.16029
```

Product obtained with MIBA:




```
=====================================================================
                    Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=254,8 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  20.185 MM    0.5668  616.58862   18.13080  31.5095
   2  23.846 MM    0.6267 1340.24243   35.64004  68.4905

Totals :                  1956.83105   53.77084
```

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Chapter Three: Conclusions and Future Directions

As common building blocks within peptides, proteins, and bioactive molecules, amide moieties play critical and ubiquitous roles in modern organic synthesis.[2] A common derivative of amides is anilides, which can be formed from the condensation between anilines and carboxylic acids. The direct dehydrative amidation of electron-deficient aryl amines remains a challenging transformation. Among the existing approaches towards anilides, traditional thermal conditions and microwave protocols requiring temperatures above 250 °C have a higher energy cost as well as limited substrate scope. To activate the carboxylic acid, stochiometric amounts of coupling reagents, which are often toxic and/or expensive, are required.

To catalyze direct dehydrative amidation reactions, the use of boron reagents is advantageous due to their affordable cost and low toxicity. However, many of those activating reagents, such as the electron-deficient arylboronic acid proposed by Yamamoto,[54] the biphenyl-based diboronic acid anhydride reported by Shimada,[56,57] and Whiting's bifunctional catalysts,[60] generally require elevated temperatures above 100 ℃ in anilide synthesis. These harsh thermal conditions result in high energy cost as well as potential decomposition and racemization of the substrates. It is also possible to synthesize anilides at lower temperatures through the boron-catalyzed amidation reaction utilizing Shibasaki's poly-boron species.[64,65] However, the anilide substrate scope of reactions at lower temperatures is still limited.

To extensively explore an organoboron-promoted anilide condensation protocol, a panel of new boronic acids with biphenyl scaffolds were designed based on a speculated amidation intermediate where the carboxylic acid is activated intramolecularly. Then amine is activated and directed via interactions by the heteroatom substituent towards nucleophilic attack onto the acyl unit. A range of functionalized boronic acids were reacted with BMIDA **2-6**, affording compounds **A1**–**A8** (Chapter Two, Scheme 2-3). Boronic acid **A7**, (2'-(methylthio)-[1,1'-biphenyl]-2-yl)boronic acid, was identified as the most efficient boronic acid species to aid in the formation of *N*,2-diphenylacetamide at 50 °C in dichloromethane. Factors including the boronic

acid equivalence, solvent, temperature, reactant stoichiometry, and molecular sieves amount were systematically optimized. The optimal ratio between carboxylic acid and amine was found to be 1:1.1. Fluorobenzene was identified as the best solvent. The reaction temperature was raised up to 85 °C and 0.5 equivalents of **A7** was used to enhance the reaction yield. The addition of 5 mol% of 4-(*N*,*N*-dimethylamino)pyridine *N*-oxide (DMAPO), which was reported to cooperate with arylboronic acids to promote amidation reactions of electron-rich anilines,[73] the amidation reaction efficiency of *N,2*-diphenylacetamide was further improved to 83% yield.

With the optimized conditions in hand, the versatility and scope of this methodology was demonstrated with various aniline derivatives such as toluidines, halogenated anilines, electron-rich anilines, electron-deficient anilines, and the heterocyclic quinolin-6-amine. The reaction with a sterically demanding aniline, 2,4,6-trimethylaniline, was not successful with boronic acid **A7**, hypothetically due to steric congestion around the activated carbonyl blocking the approach of the bulky amine to undergo a nucleophilic attack. Another failed example with 4-aminophenol was believed to be due to a potential undesired interaction between the hydroxyl group and the boronic acid **A7**. Variations of the carboxylic acid were also included, and the corresponding anilides, *N,2*-diphenylpropanamide, *N,3*-diphenylpropanamide, and *N*-phenylheptanamide were obtained. However, trace amounts of *N*-(3-bromophenyl)benzamide were observed in the amidation reaction with either boronic acid **A7** or MIBA. The reaction between aniline and benzoic acid remains challenging under current conditions (Chapter Two, Table 2-7).

To demonstrate the scalability of this protocol, a gram-scale synthesis of *N*-(3-bromophenyl)-2-phenylacetamide was conducted to afford a 65% yield of the desired product. From the crude reaction mixture, 76% of boronic acid **A7** was recovered by column chromatography and the recovered boronic acid **A7** was able to promote the amidation reaction with comparable efficiency to the original batch. Given the fact that chiral carboxylic acids with a stereogenic α carbon are readily epimerizable due to the acidity of the α proton, an investigation of possible racemization was conducted using aniline and (*R*)-2-phenylpropanoic acid. Partial racemization, with 74% *ee*, was observed in the reaction between (*R*)-2-phenylpropanoic acid and aniline with boronic acid **A7**. In contrast, when MIBA was employed, the anilide product had a poorer enantiomeric purity of 37% *ee*. Under amidation conditions, activation of the carbonyl through interaction with the boronic acid decreases the pKa of the alpha hydrogen. The enantiomeric purity can be partially eroded through keto-enol tautomerization, and a lower reaction

temperature may suppress undesired racemization. Unfortunately, when the reaction temperature was lowered from 85 °C to 65 °C, only trace amount of product was observed with either **A7** or MIBA.

According to Whiting's mechanistic study,[74] in the key intermediate, the boronic acid forms a diacyloxy B–O–B bridged dimeric complex **1-14** with the carboxylic acid, which is activated for the subsequent nucleophilic attack from the amine (Chapter One, Figure 1-13). To gain insight into the amidation reaction mechanism under our conditions, following Whiting's procedure, NMR experiments were conducted with a 10:1 mixture of phenylacetic acid and boronic acid **A7** in the presence of activated molecular sieves. A boron signal was observed at 5.16 ppm that supports the formation of the diacyloxy B–O–B bridged intermediate **2-31** (Chapter Two, Scheme 2-11).

Overall, the research presented in this thesis addresses the development of a boronic acid **A7**-based protocol for anilide synthesis. Substrate scope with various aniline derivatives was demonstrated with good reaction efficiency. The scalability of the amidation reaction with **A7** along with its reusability exhibited this method's potential usefulness in large-scale reactions. The preliminary NMR experiments support the formation of a diacyloxy B–O–B bridged intermediate. More work is required in order to further characterize the putative intermediate and explore the potential interaction between the heteroatom of **A7** and the amine. Partial racemization was observed in (*R*)-2-phenylpropanoic acid synthesis with **A7**, though it gave a better *ee* than MIBA. The loss of enantiomeric purity may be suppressed by lowering the reaction temperature, but a more reactive boronic acid would be required. For further catalyst development based on **A7**, the directing group can be oxidized into sulfoxide, which is potentially a stronger H-bond acceptor than the sulfur in the thiomethyl group. Meanwhile, the electron density of the boronic acid can also be tuned by introducing substituents onto the borylated phenyl ring. The distance between boron and heteroatom can be tuned as well. These modifications may further enhance the reactivity of the boronic acids.

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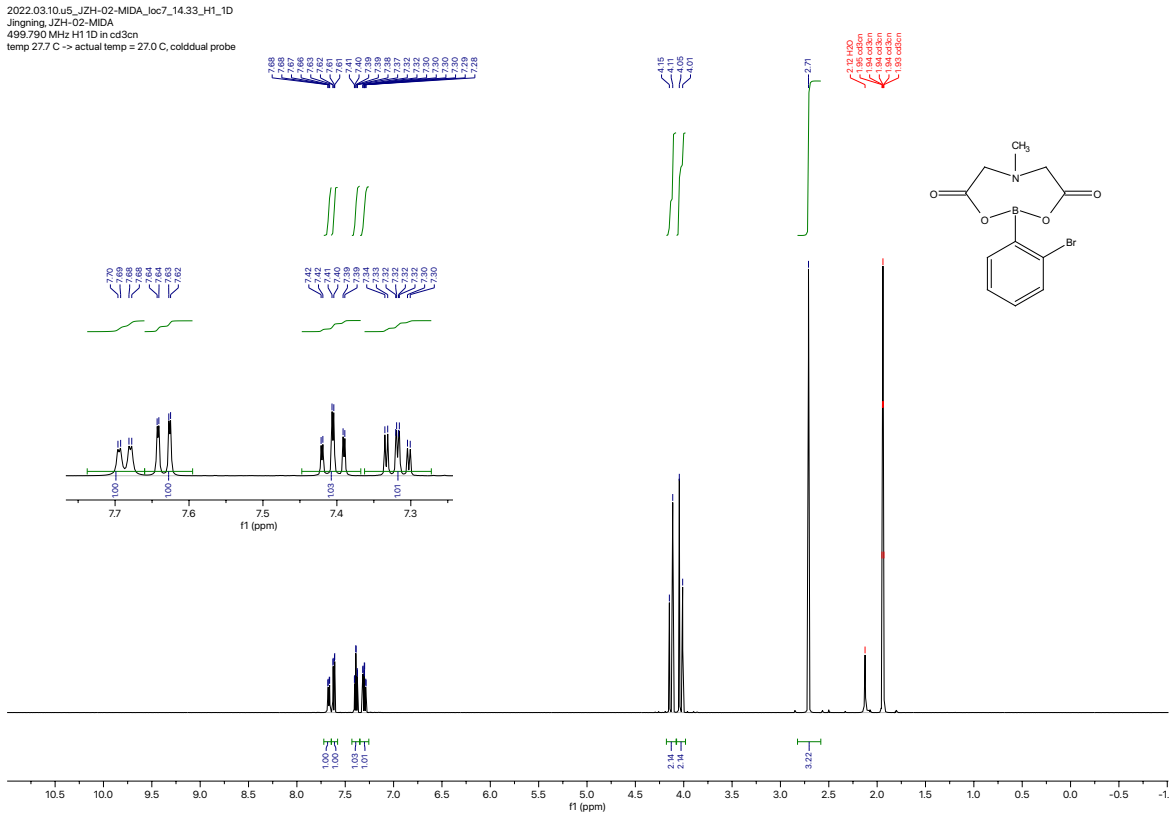
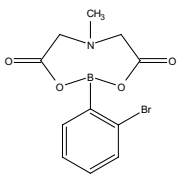
Appendix: Selected copies of NMR spectra

2-Bromophenylboronic acid MIDA ester (2-6)

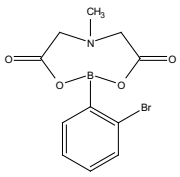


2022.03.10.u5_JZH-02-MIDA_loc7_14.34_C13_1D
Jingning, JZH-02-MIDA
125.685 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

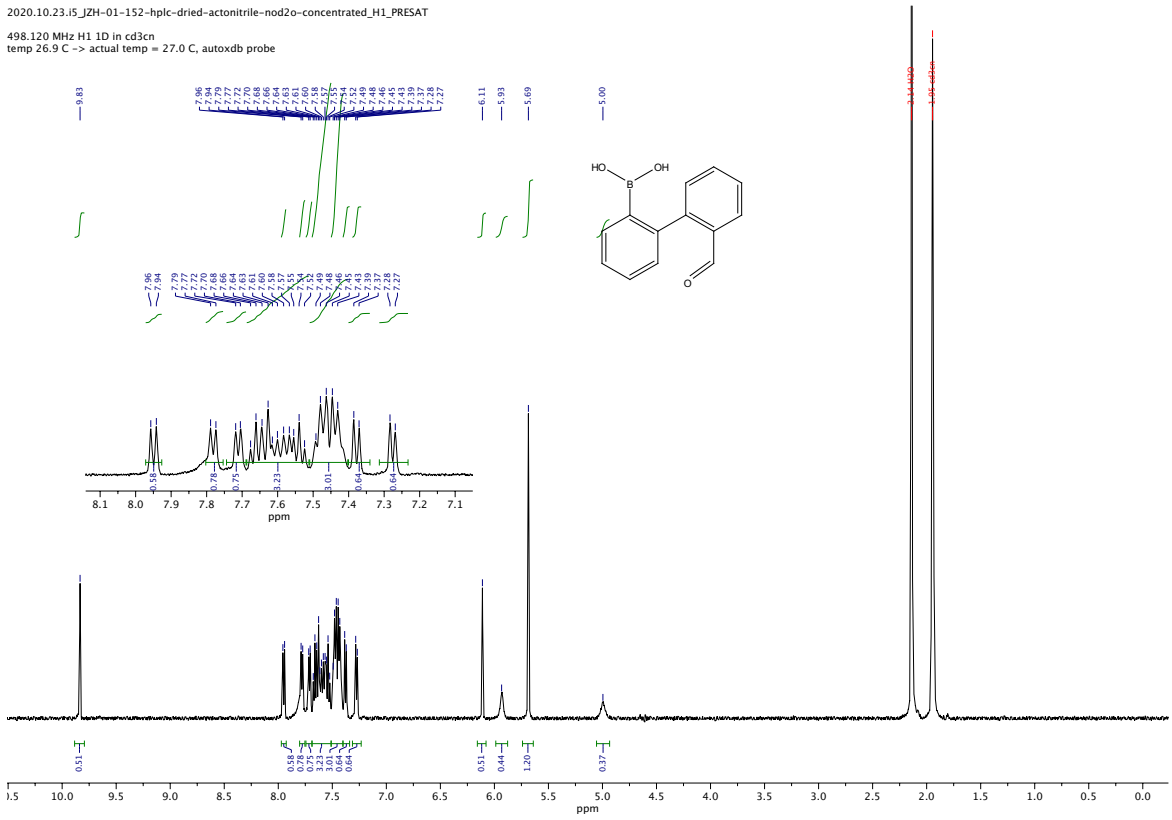


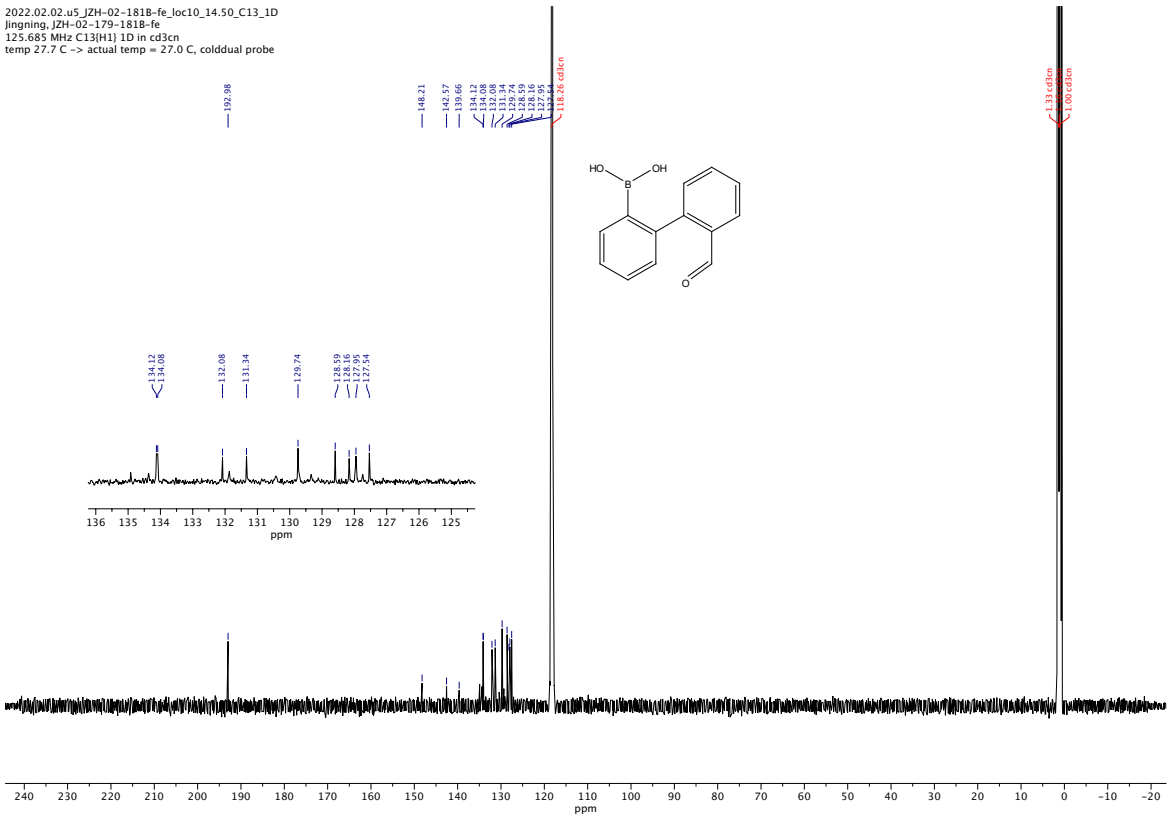
2021.01.12.i5_JZH-01-201-check-ok_B11_1D

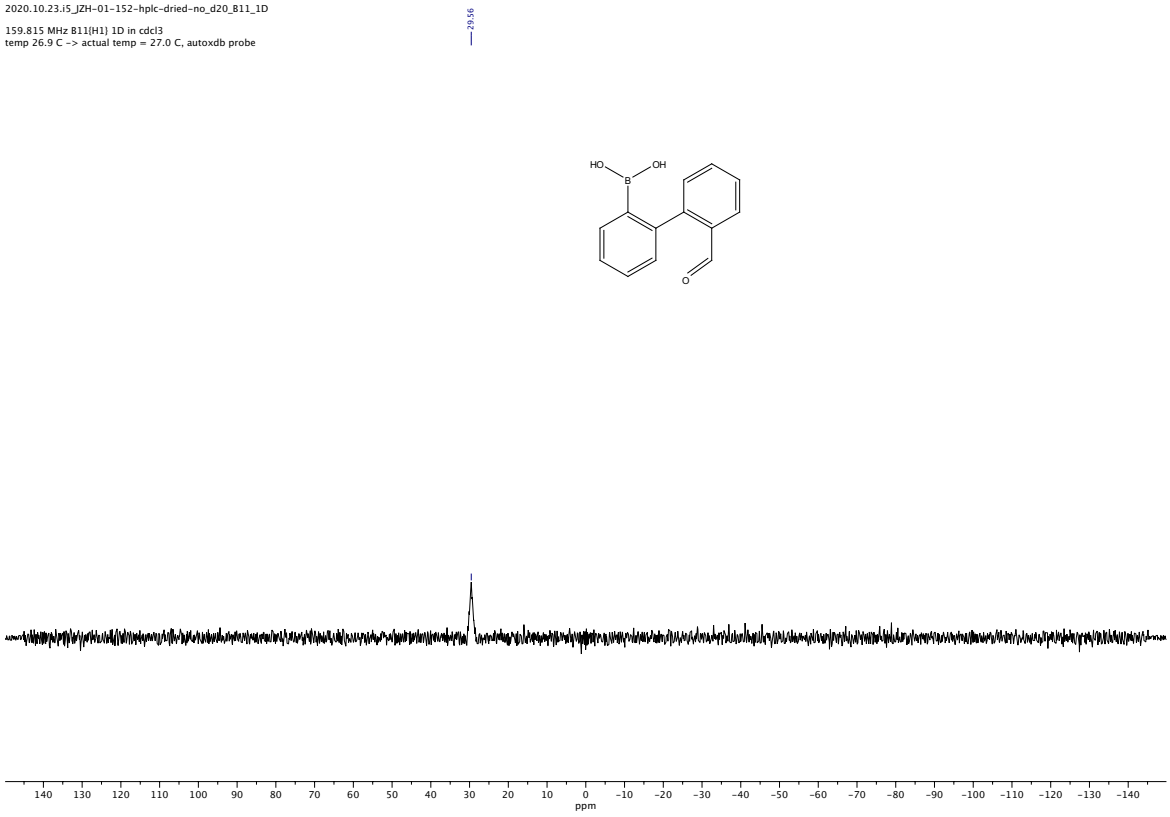
159.816 MHz B11{H1} 1D in cd3cn
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

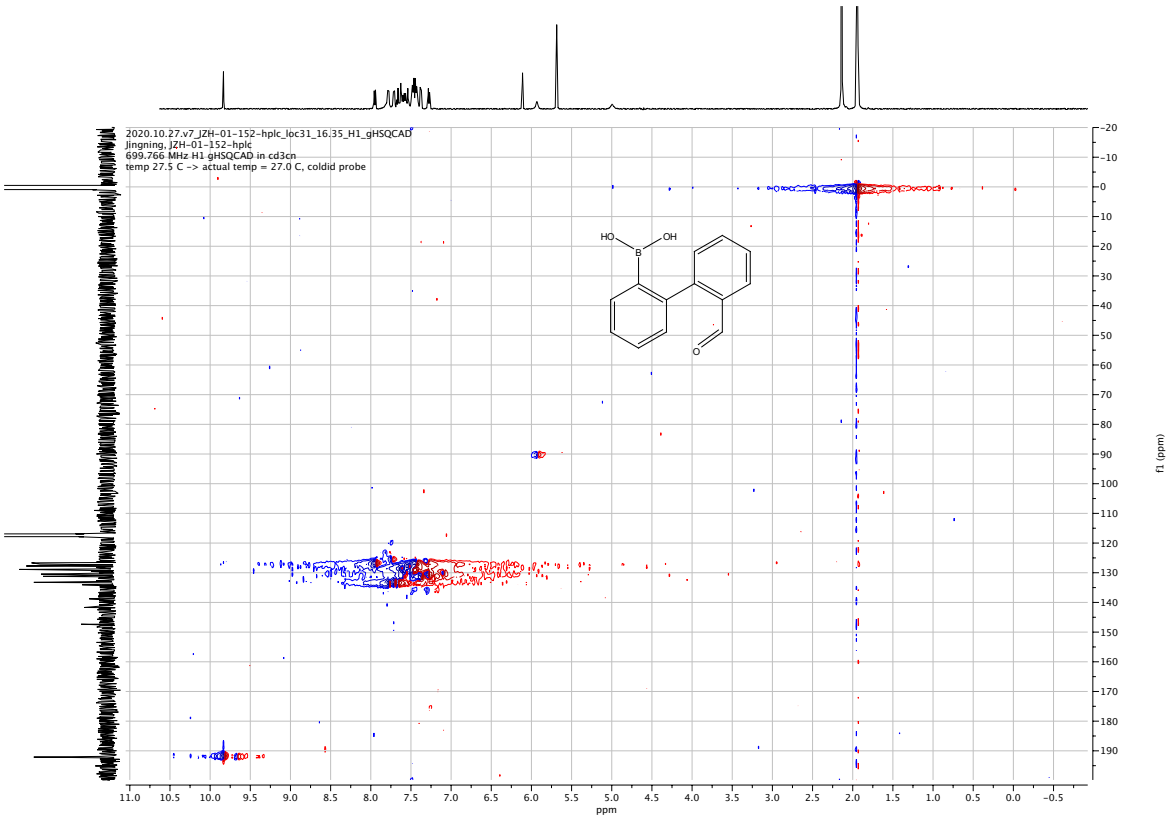


(2'-Formyl-[1,1'-biphenyl]-2-yl)boronic acid (A1)

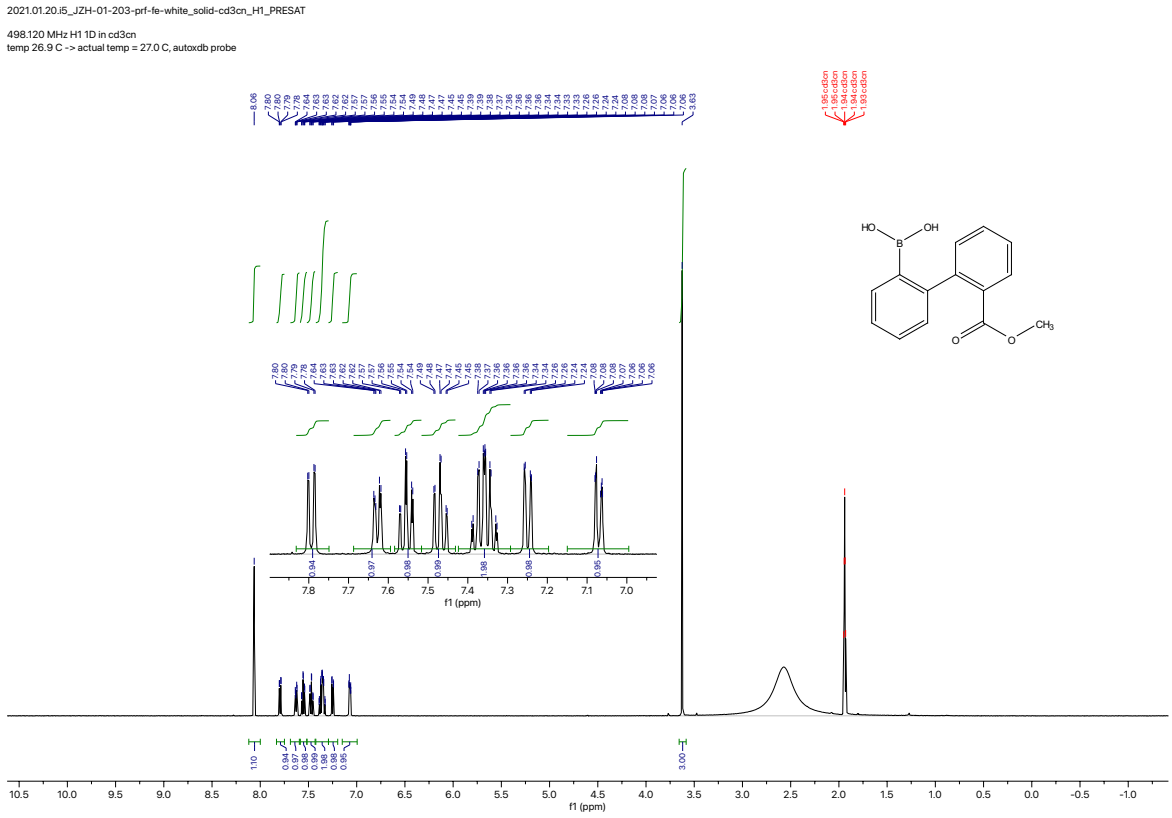


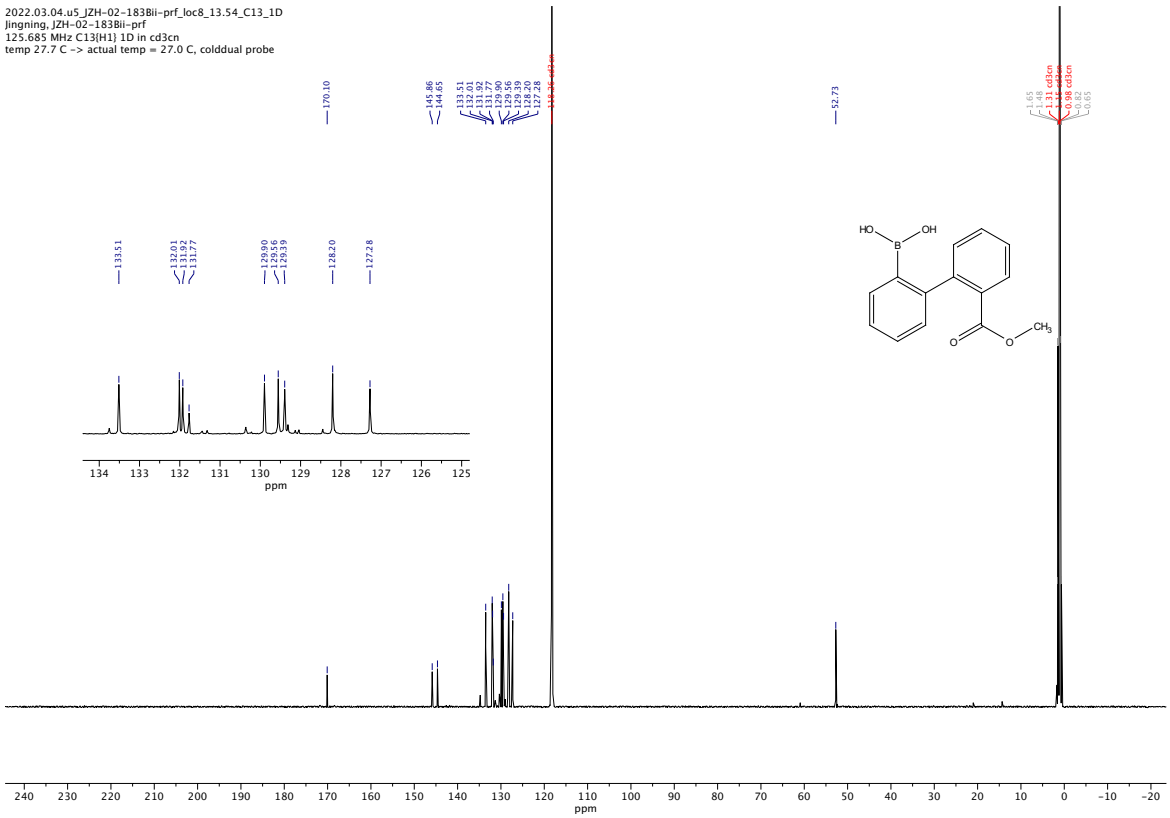

2022.02.02.u5_JZH-02-181B-fe_loc10_14.50_C13_1D
Jingning, JZH-02-179-181B-fe
125.685 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe
192.98
148.21
142.57
139.66
134.12
134.08
132.08
131.34
129.74
128.59
128.16
127.95
127.54
118.26 cd3cn
1.33 cd3cn
1.00 cd3cn
HO
B
OH
O
ppm


2020.10.23.i5_JZH-01-152-hplc-dried-no_d20_B11_1D
159.815 MHz B11{H1} 1D in cdcl3
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe
29.56
HO
B
OH
O
ppm


2020.10.27.v7_JZH-01-152-hplc_loc31_16.35_H1_gHSQCAD
Jingning, JZH-01-152-hplc
699.766 MHz H1 gHSQCAD in cd3cn
temp 27.5 C -> actual temp = 27.0 C, coldid probe
HO
B
OH
O
ppm
f1 (ppm)

(2'-(Methoxycarbonyl)-[1,1'-biphenyl]-2-yl)boronic acid (A2)

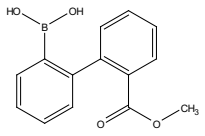


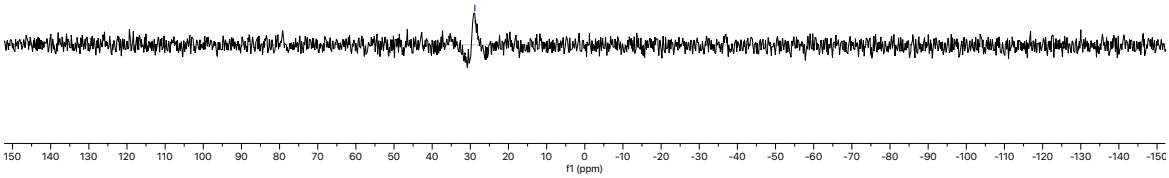

2022.03.04.u5_JZH-02-183Bii-prf_loc8_13.54_C13_1D
Jingning, JZH-02-183Bii-prf
125.685 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe
170.10
145.86
144.65
133.51
132.01
131.92
131.77
129.90
129.56
129.39
128.20
127.28
121.45 cd3cn
52.73
1.65
1.48
1.31 cd3cn
1.15 cd3cn
0.98 cd3cn
0.82
0.65
HO
B
OH
O
O
CH3
ppm
ppm

2021.01.14.mr4_JZH-01-203-prf1-cdcl3_B11_1D

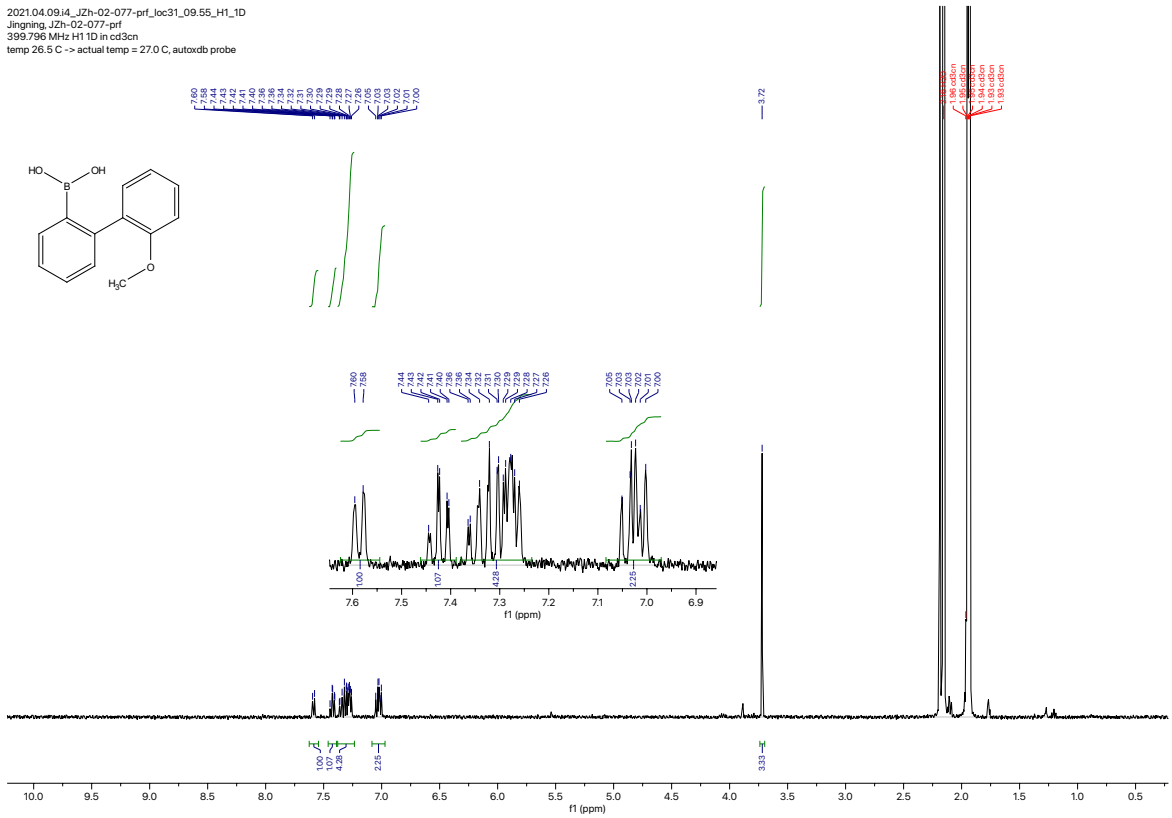
128.328 MHz B11{H1} 1D in cdcl3
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

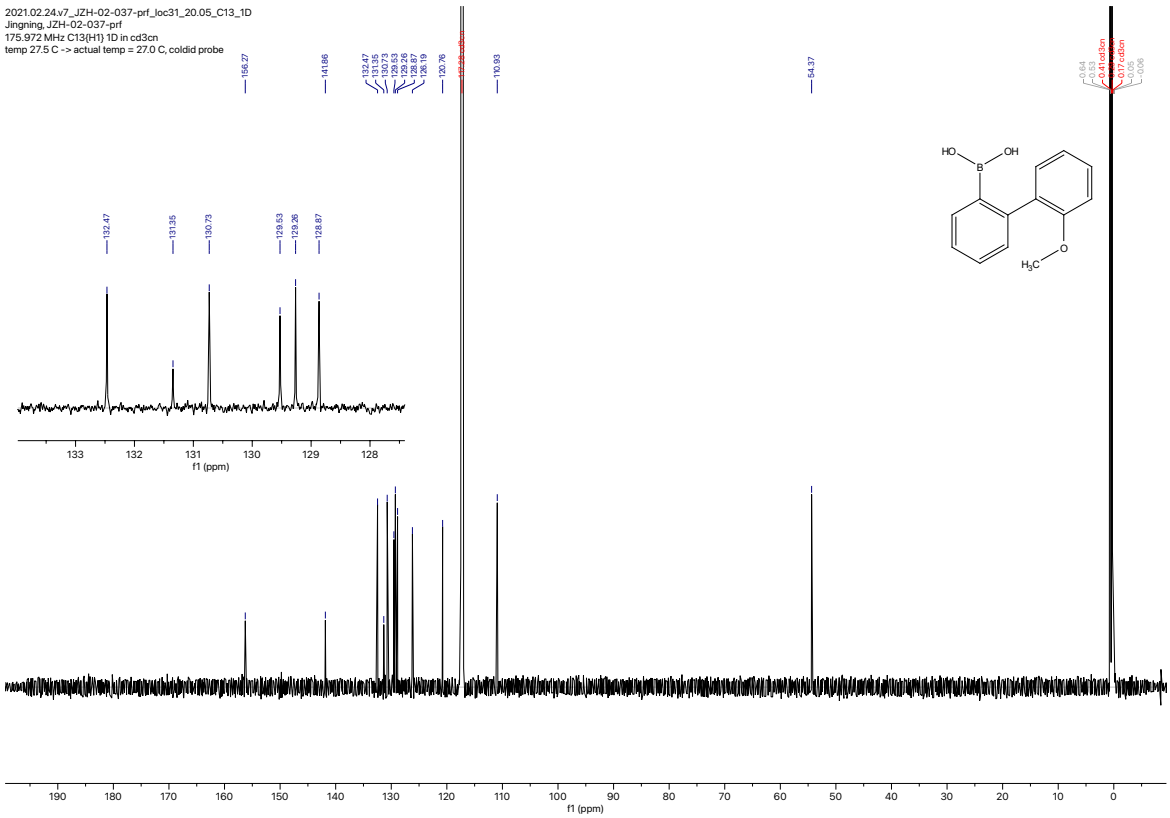
28.82





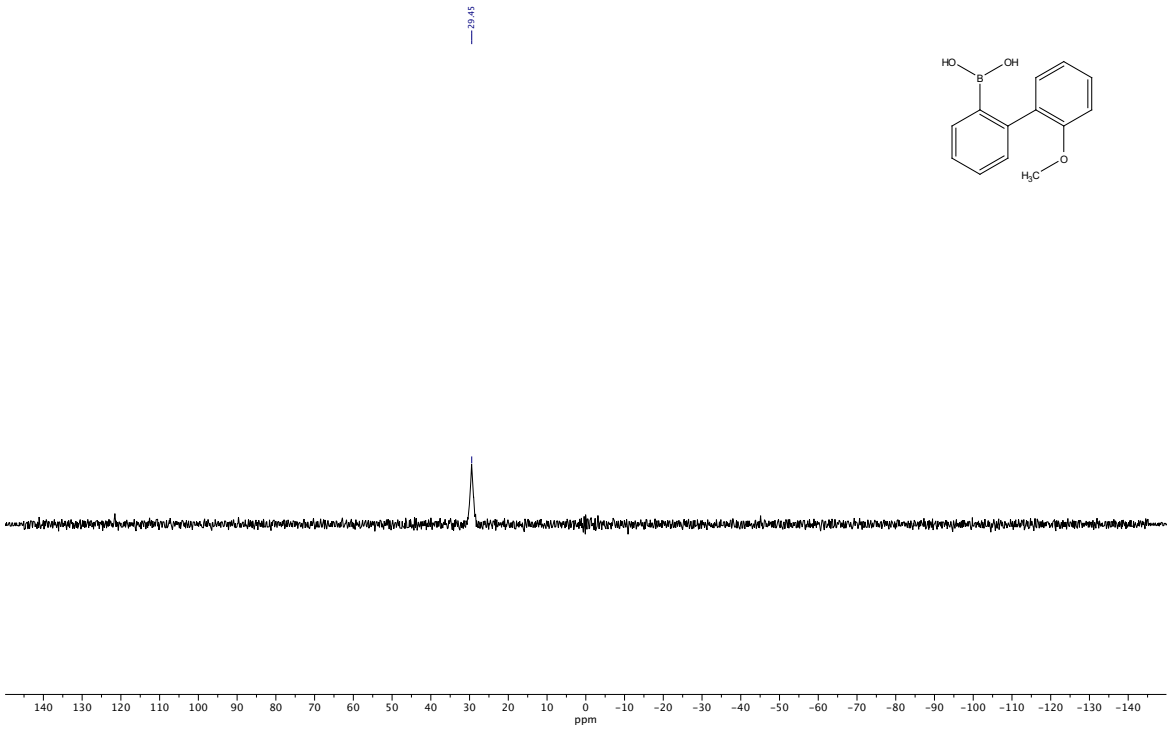
(2'-Methoxy-[1,1'-biphenyl]-2-yl)boronic acid (A3)



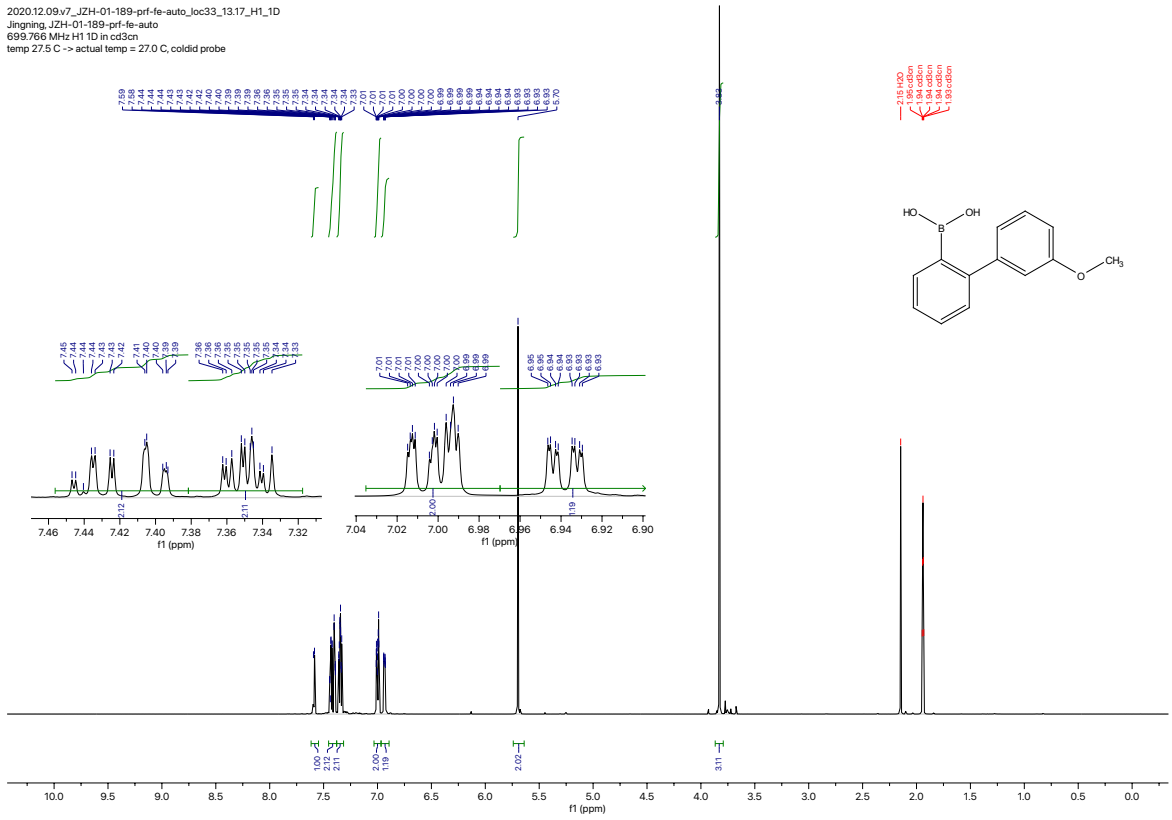

2021.02.24.v7_JZH-02-037-prf_loc31_20.05_C13_1D
Jingning, JZH-02-037-prf
175.972 MHz C13{H1} 1D in cd3cn
temp 27.5 C -> actual temp = 27.0 C, coldid probe
166.27
141.86
132.47
131.35
130.73
129.53
129.26
128.87
128.19
120.76
110.93
54.37
HO
B
OH
O
H3C
f1 (ppm)

2021.02.25.i5_JZH-02-037-prf-confirmed_on_ibd500-cd3cn_B11_1D

159.816 MHz B11{H1} 1D in cd3cn
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe



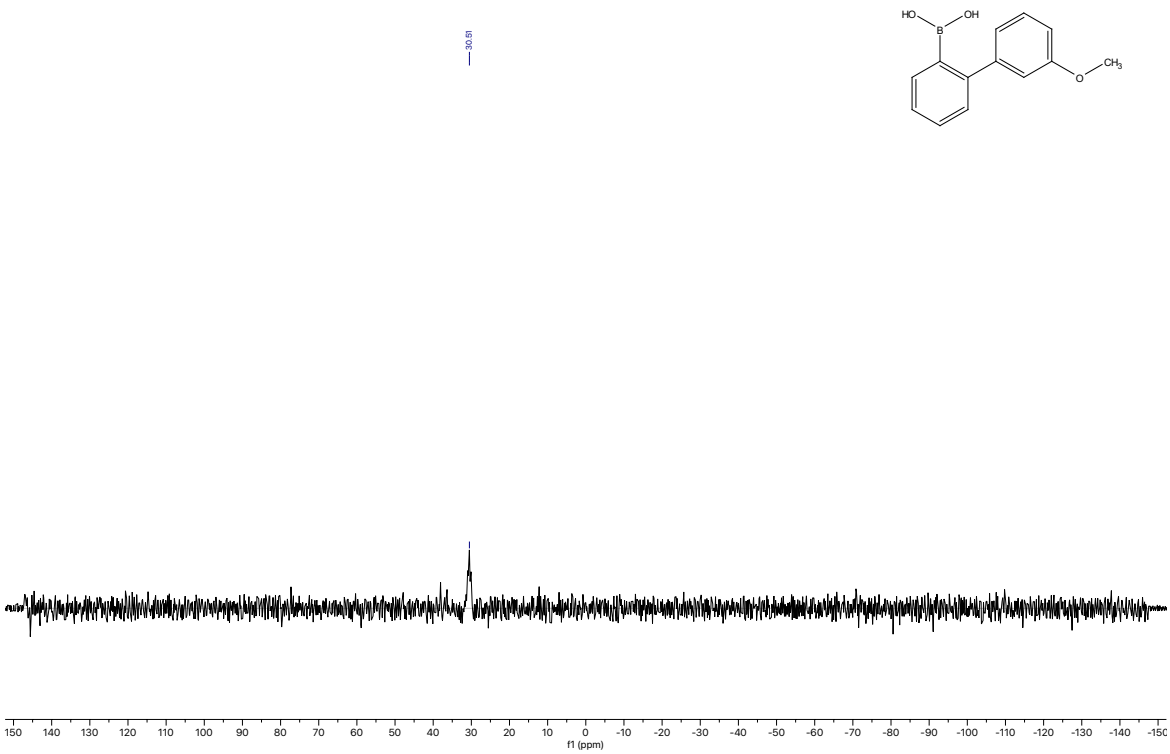
(3'-Methoxy-[1,1'-biphenyl]-2-yl)boronic acid (A4)



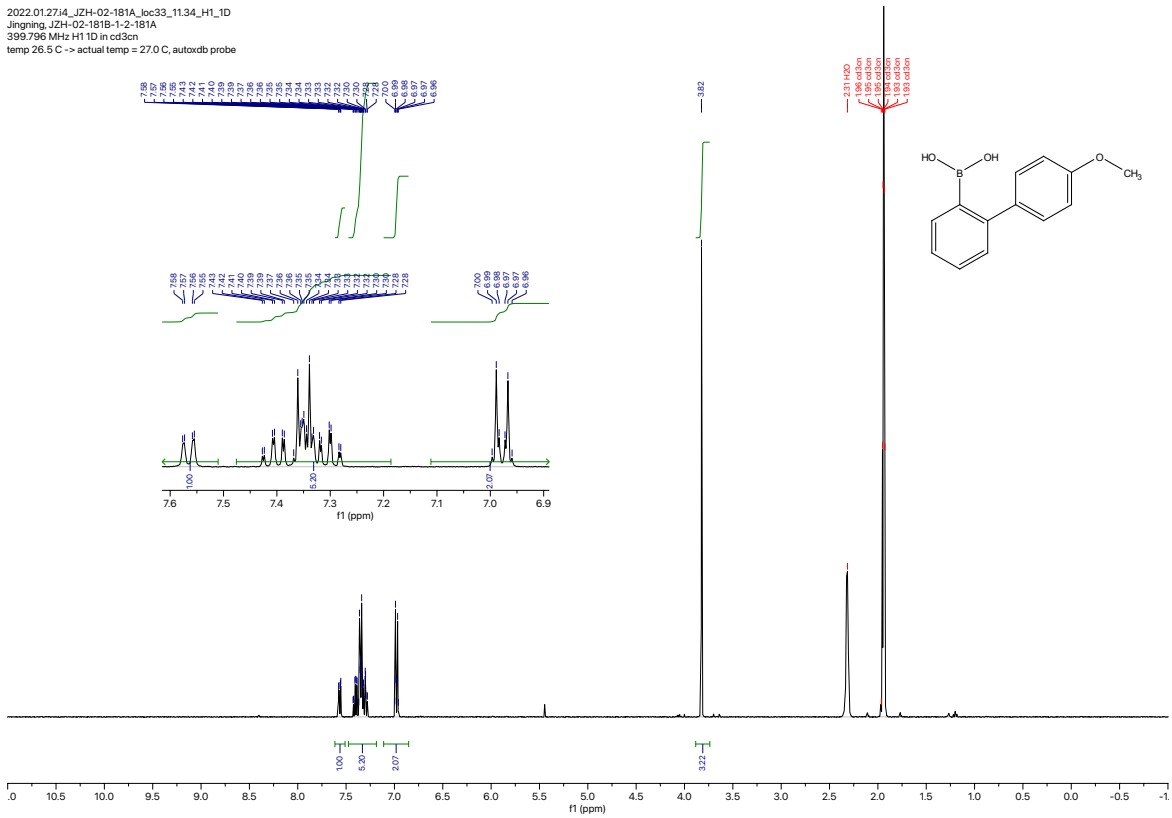

2020.12.09.v7_JZH-01-189-prf-fe-auto_loc33_13.18_C13_1D
Jingning, JZH-01-189-prf-fe-auto
175.972 MHz C13{H1} 1D in cd3cn
temp 27.5 C -> actual temp = 27.0 C, coldid probe
160.61
146.28
145.72
133.88
130.41
130.09
129.50
127.44
121.90
116.26 cd3cn
115.26
113.52
55.86
1.63
1.51
1.39 cd3cn
1.15 cd3cn
1.04
0.92
HO
B
OH
O
CH3
f1 (ppm)

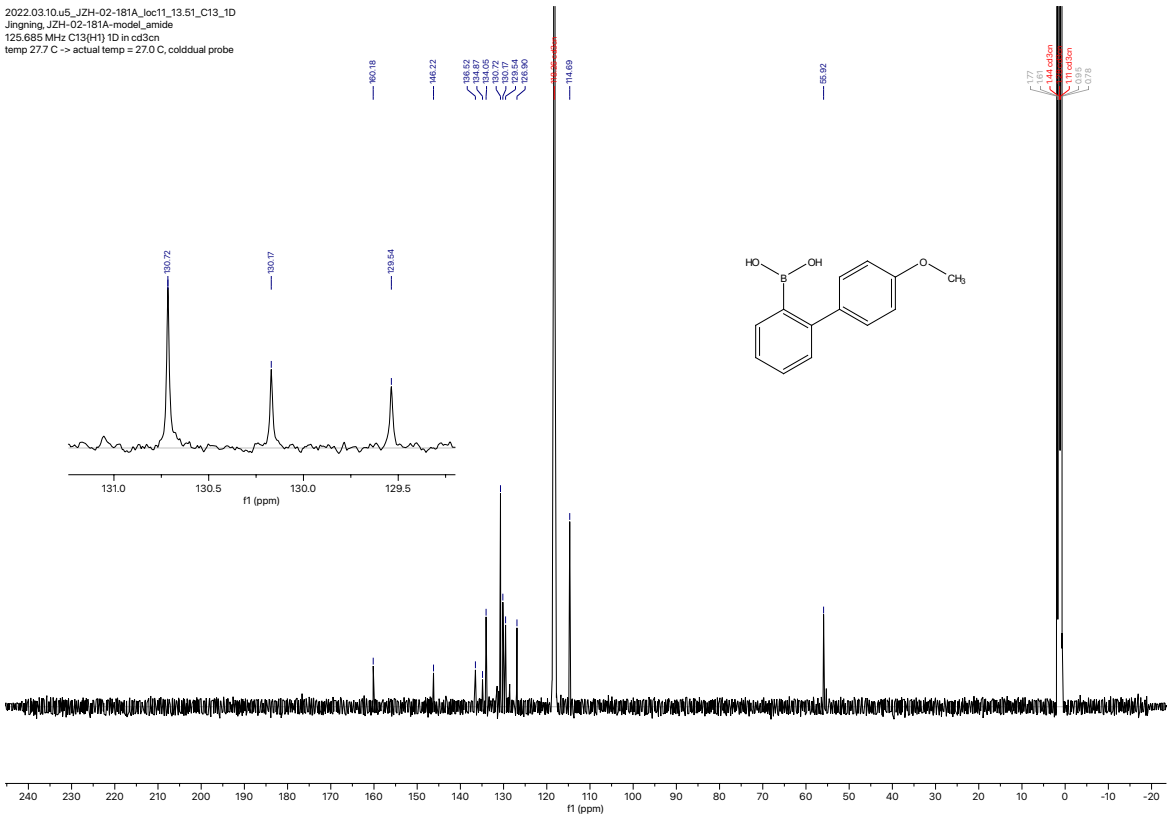
2020.11.20.mr4_JZH-01-189-prf_B11_1D

128.329 MHz B11{H1} 1D in cd3cn
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

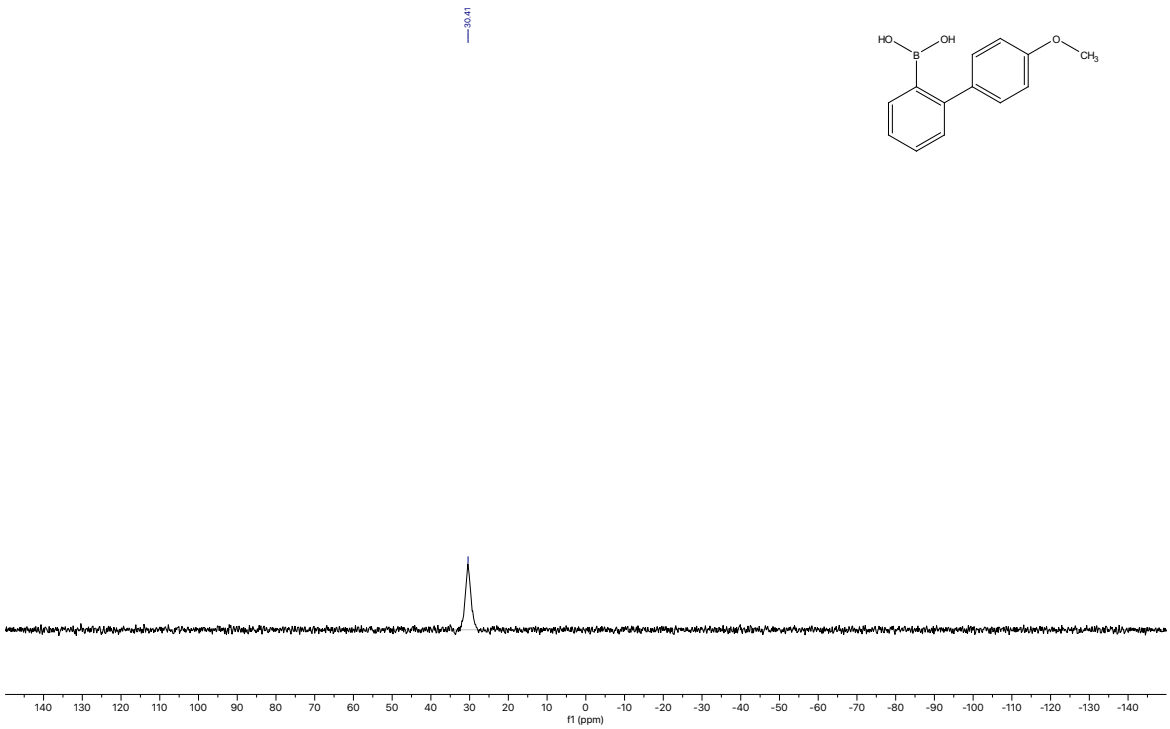


(4'-Methoxy-[1,1'-biphenyl]-2-yl)boronic acid (A5)

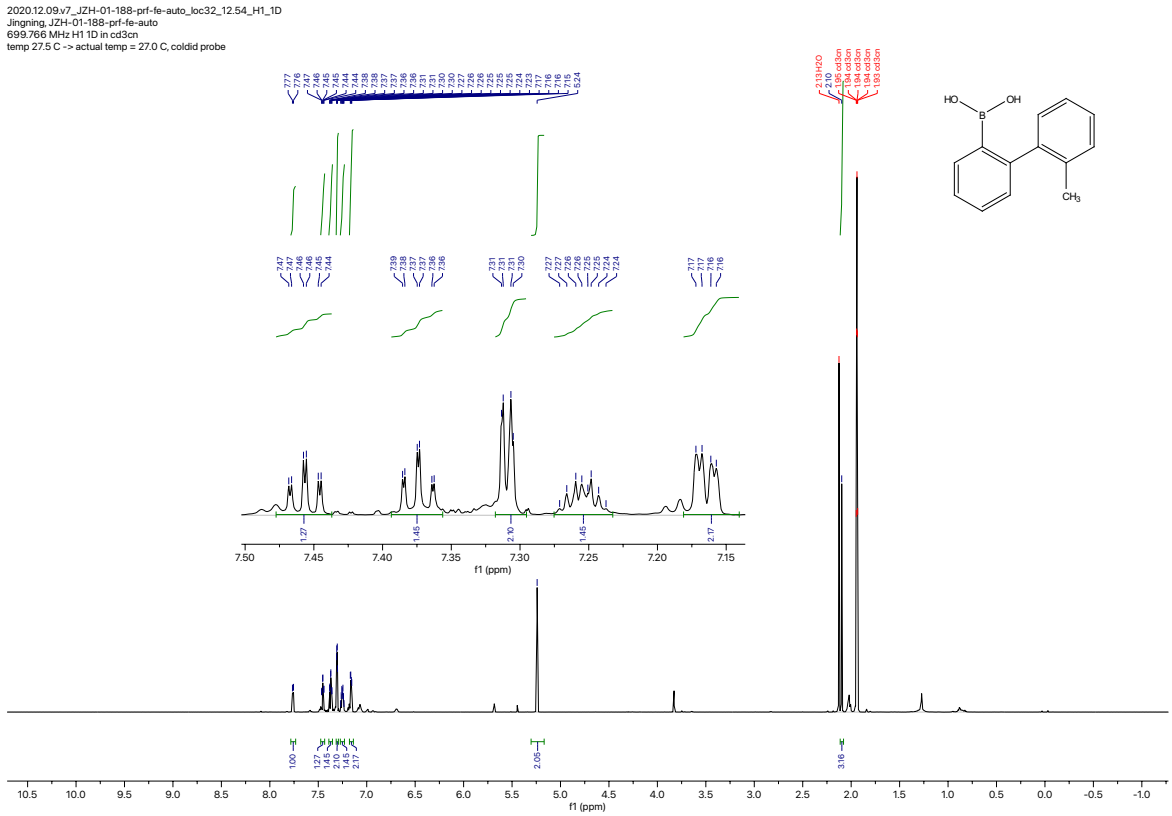


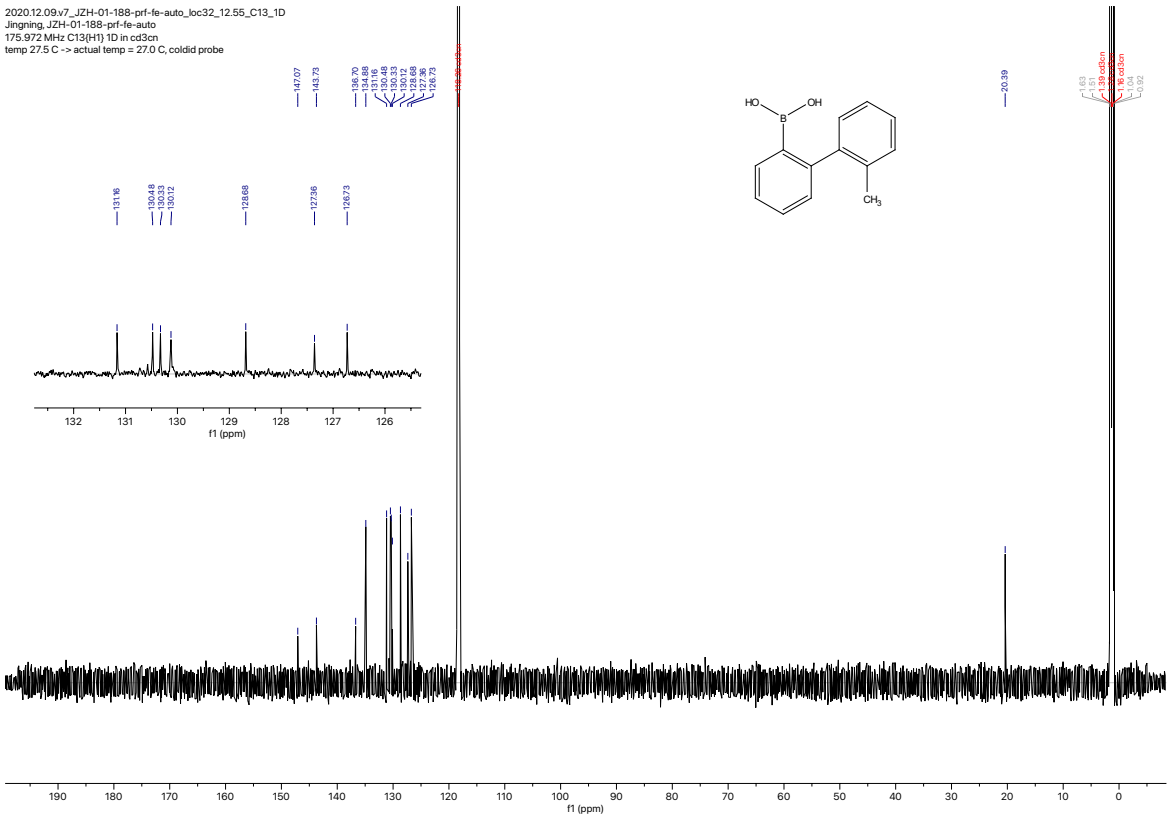

2022.03.10.u5_JZH-02-181A_loc11_13.51_C13_1D
Jingning, JZH-02-181A-model_amide
125.685 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe
160.18
146.22
136.62
134.82
134.05
130.72
130.17
129.54
126.90
114.69
55.92
130.72
130.17
129.54
131.0
130.5
130.0
129.5
f1 (ppm)
HO
B
OH
O
CH3
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

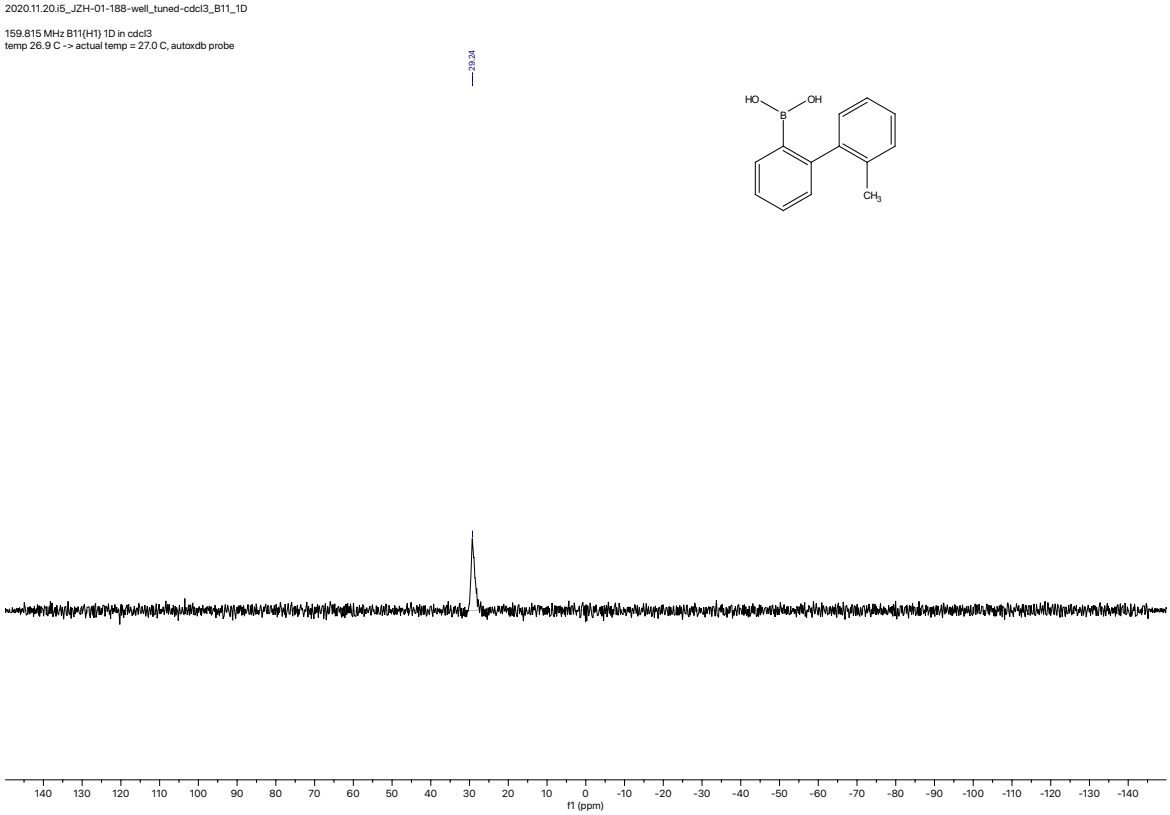
2022.01.27.i4_JZH-02-181A_loc33_11.47_B11_1D
Jingning, JZH-02-181B-1-2-181A
128.270 MHz B11{H1} 1D in cd3cn
temp 26.5 C -> actual temp = 27.0 C, autoxdb probe



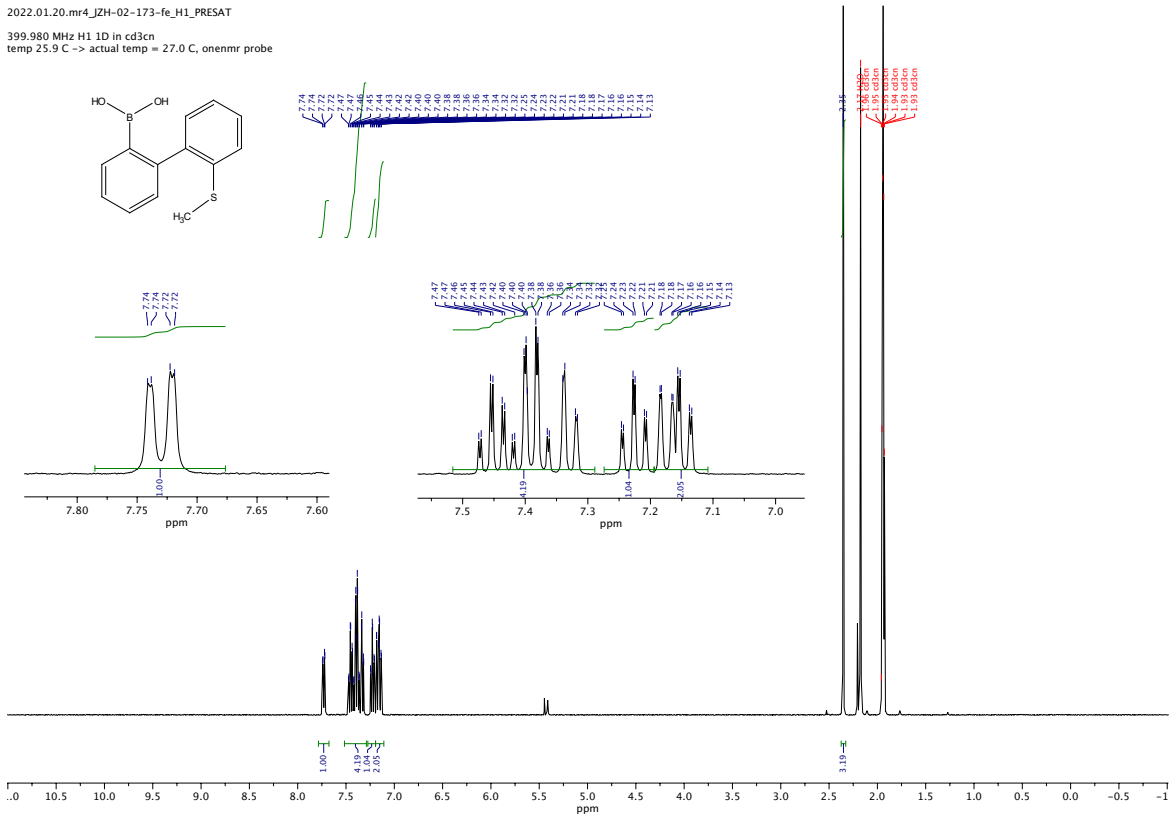
(2'-Methyl-[1,1'-biphenyl]-2-yl)boronic acid (A6)

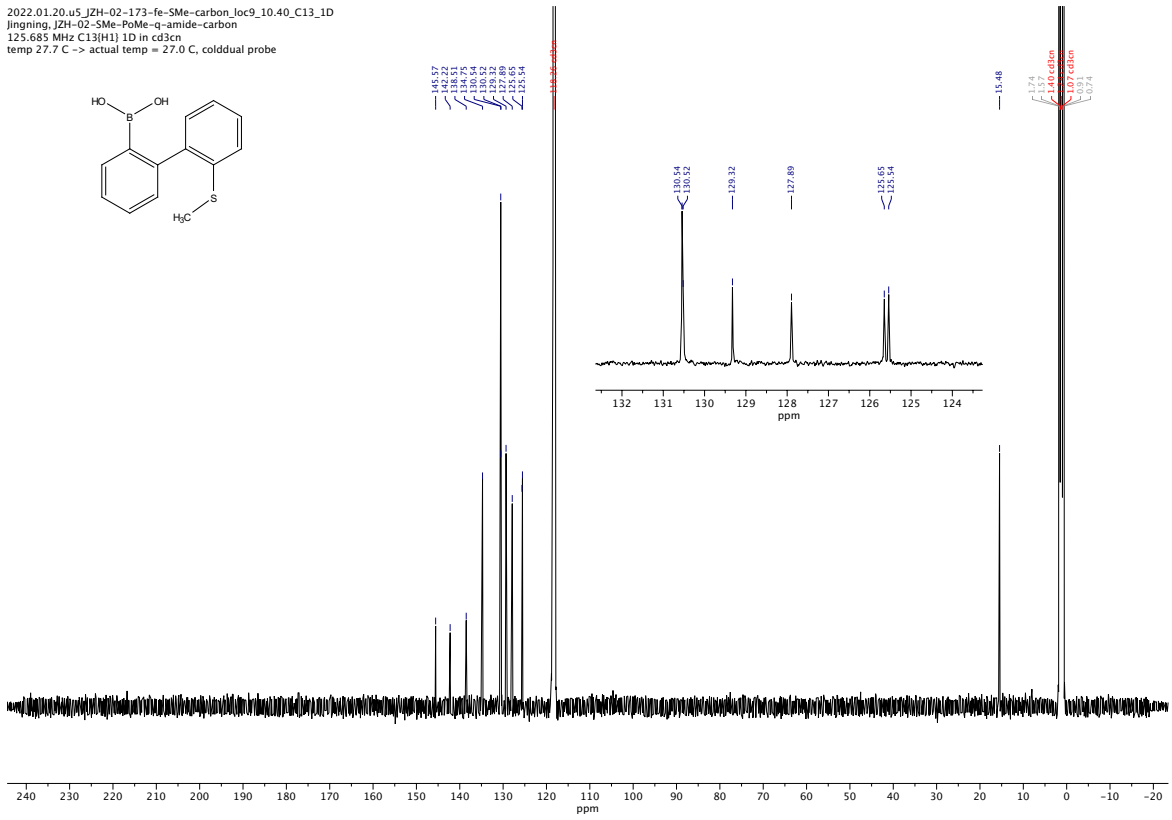



2020.12.09.v7_JZH-01-188-prf-fe-auto_loc32_12.55_C13_1D
Jingning, JZH-01-188-prf-fe-auto
175.972 MHz C13{H1} 1D in cd3cn
temp 27.5 C -> actual temp = 27.0 C, coldid probe
147.07
143.73
136.70
134.88
131.16
130.48
130.33
130.12
128.68
127.36
126.73
131.16
130.48
130.33
130.12
128.68
127.36
126.73
132
131
130
129
128
127
126
f1 (ppm)
HO
B
OH
CH3
20.39
1.93
1.91
1.39 cd3cn
1.04
0.92
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


2020.11.20.i5_JZH-01-188-well_tuned-cdcl3_B11_1D
159.815 MHz B11{H1} 1D in cdcl3
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe
29.24
HO
B
OH
CH3
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)

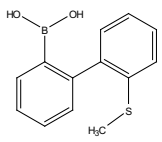
(2'-(Methylthio)-[1,1'-biphenyl]-2-yl)boronic acid (A7)



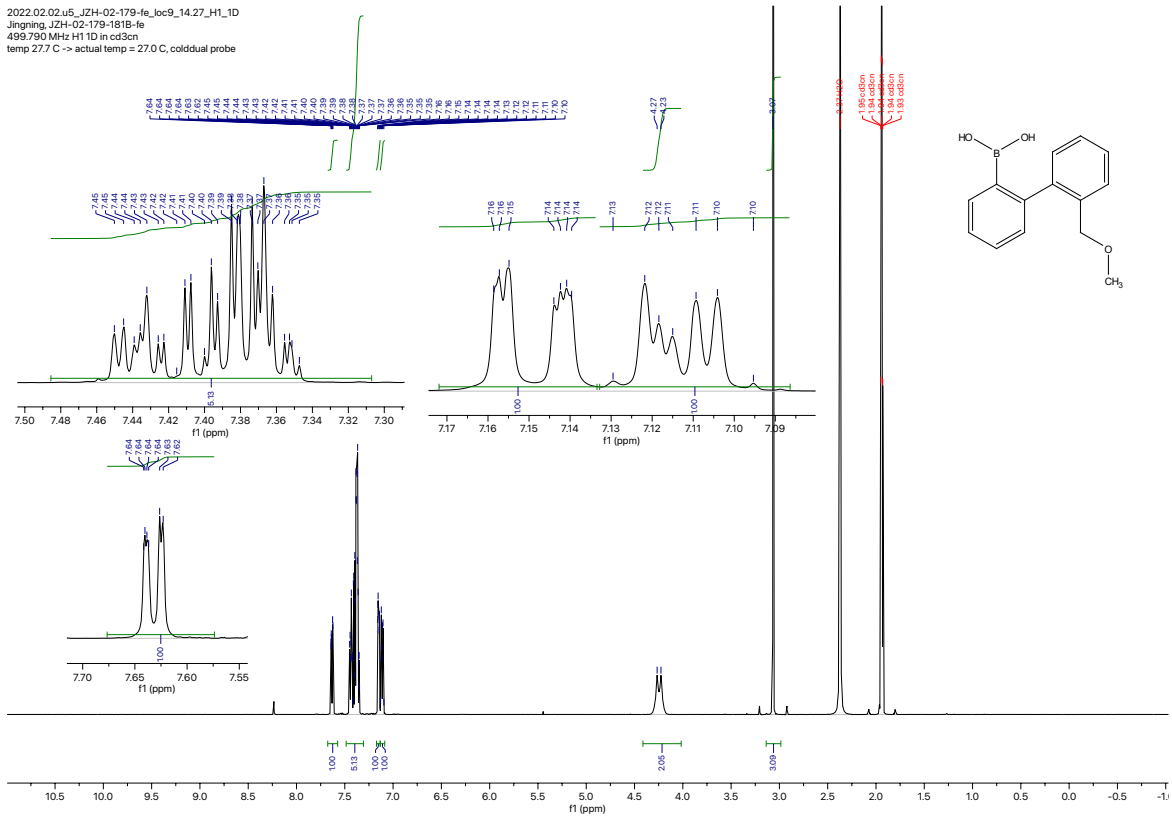

2022.01.20.u5_JZH-02-173-fe-SMe-carbon_loc9_10.40_C13_1D
Jingning, JZH-02-SMe-PoMe-q-amide-carbon
125.685 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe
HO
B
OH
S
H3C
145.57
142.22
138.71
134.75
130.64
130.52
129.32
127.89
125.65
125.54
118.26 cd3cn
15.48
1.74
1.75
1.40 cd3cn
1.07 cd3cn
0.72
0.74
ppm
ppm

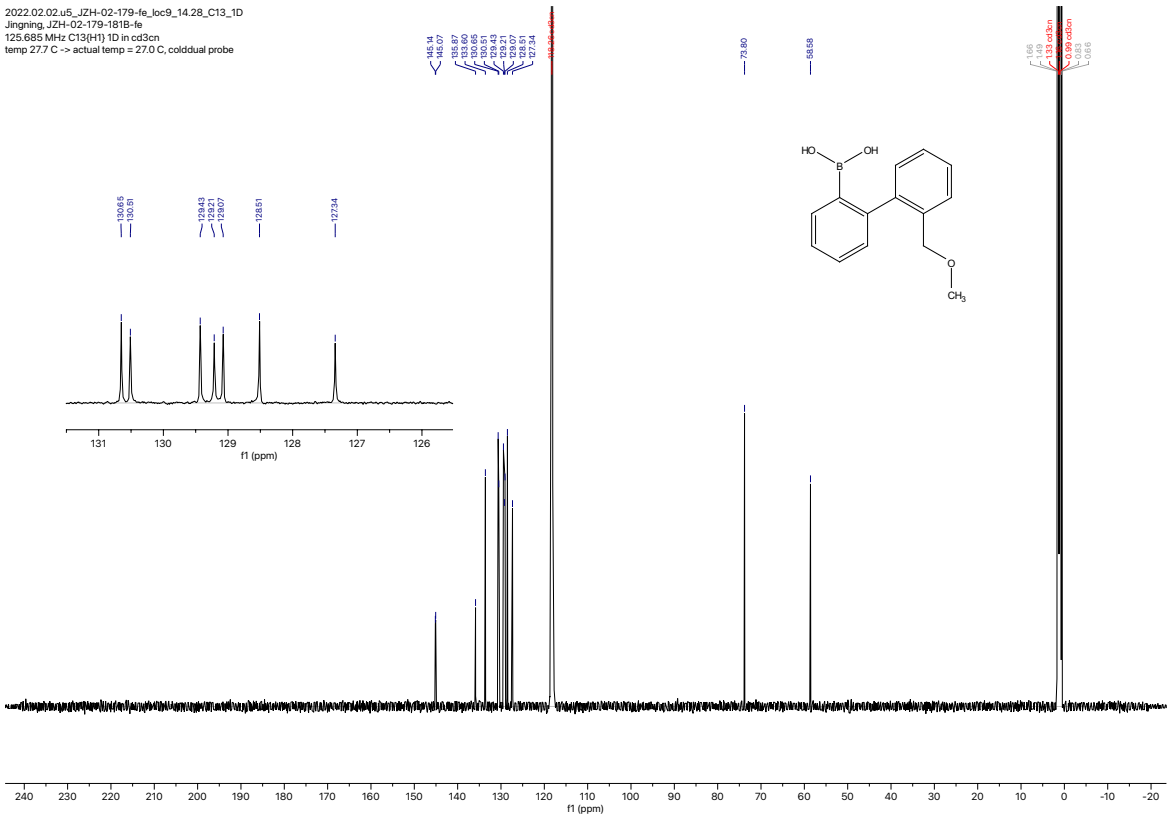
2022.01.20.mr4_JZH-02-173-fe_B11_1D

128.329 MHz B11{H1} 1D in cd3cn
temp 25.9 C -> actual temp = 27.0 C, onenmr probe



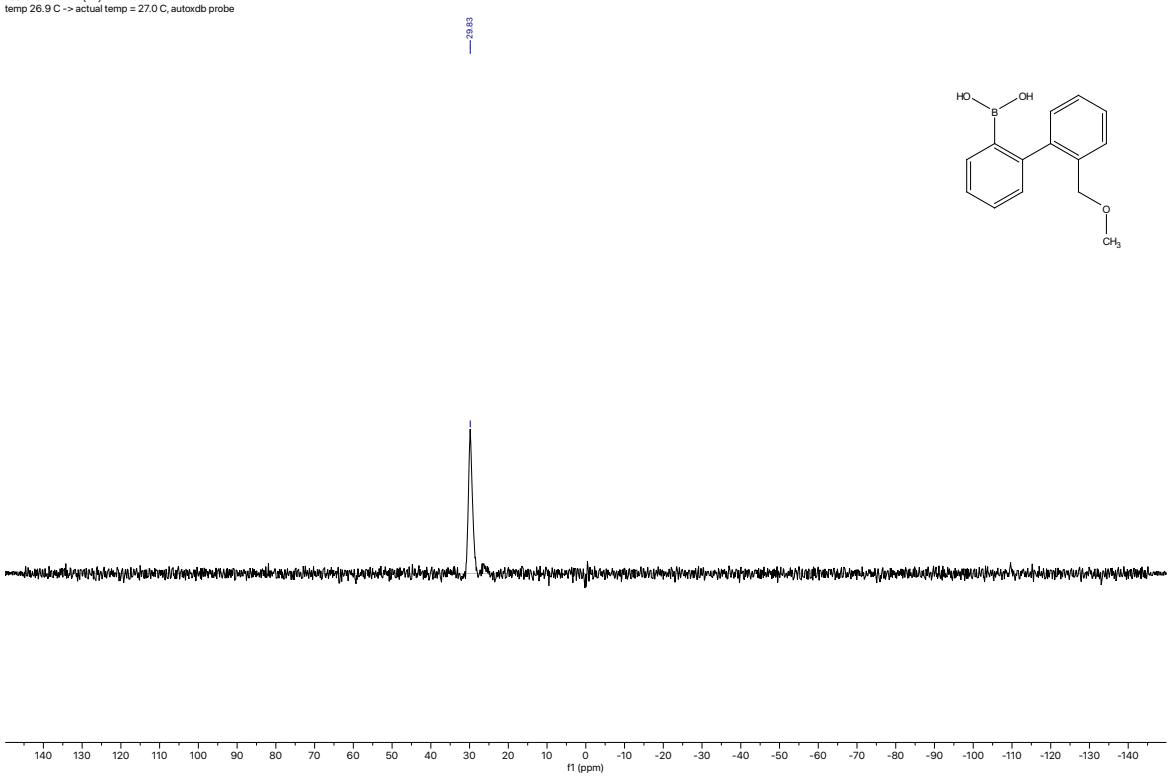
(2'-(Methoxymethyl)-[1,1'-biphenyl]-2-yl)boronic acid (A8)



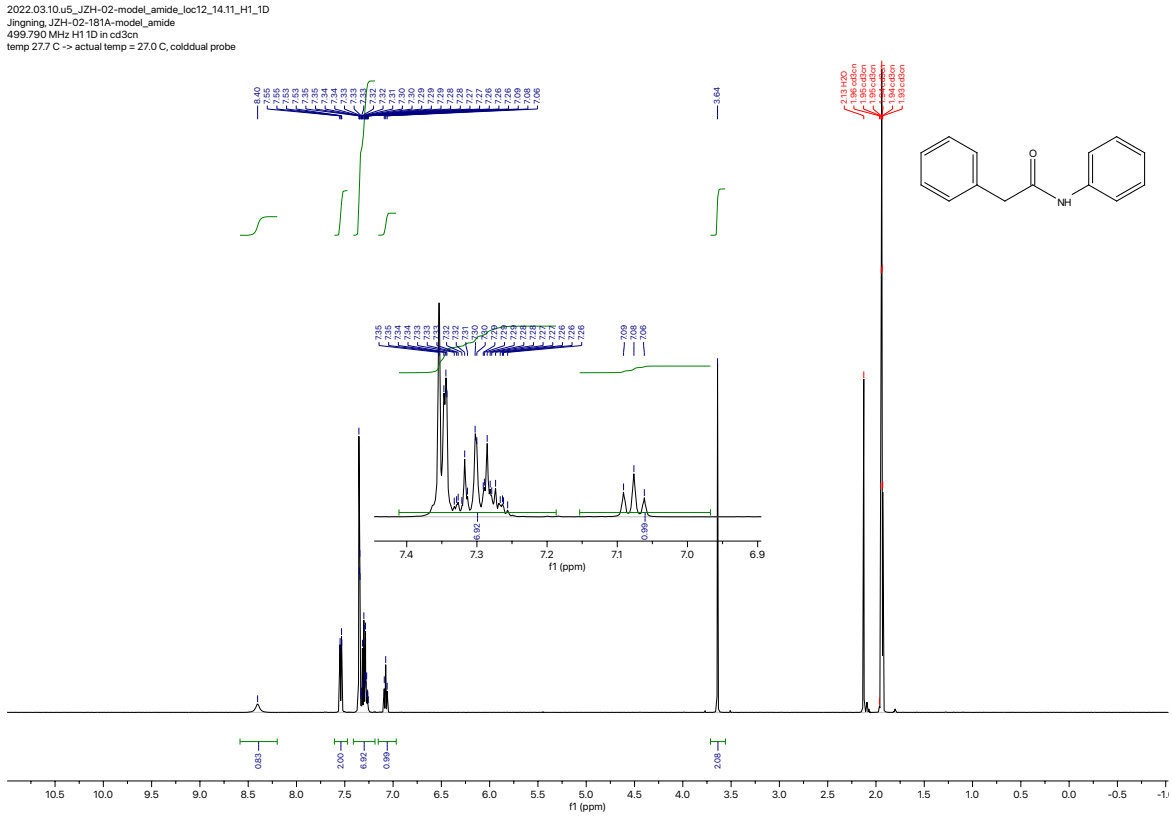

2022.02.02.u5_JZH-02-179-fe_loc9_14.28_C13_1D
Jingning, JZH-02-179-181B-fe
125.685 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe
145.14
145.07
135.87
133.66
130.65
130.51
129.43
129.21
129.07
127.51
127.34
118.26
73.80
58.58
1.66
1.46
1.33 cd3cn
0.19 cdscn
0.07
0.06
130.65
130.51
129.43
129.21
129.07
128.51
127.34
HO
B
OH
O
CH3
131
130
129
128
127
126
f1 (ppm)
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

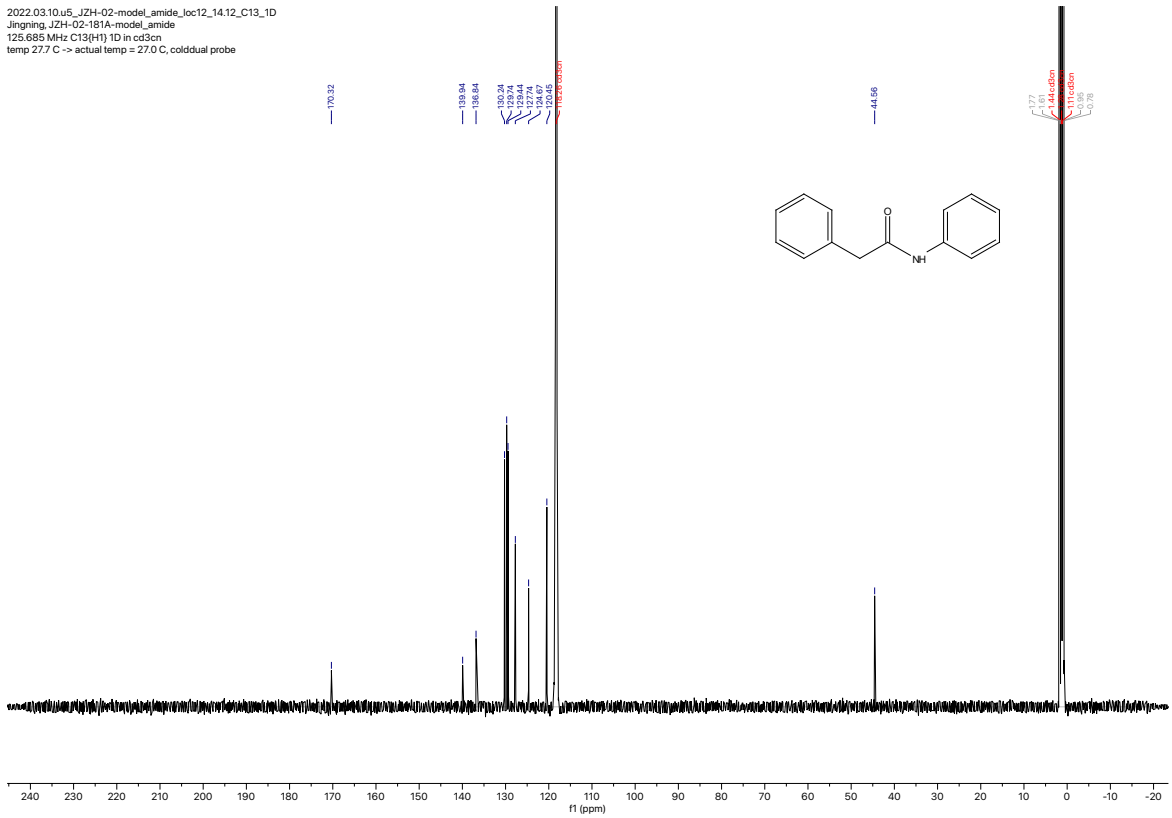
2020.12.02.i5_JZH-01-192-prf-cd3cn_B11_1D

159.816 MHz B11{H1} 1D in cd3cn
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

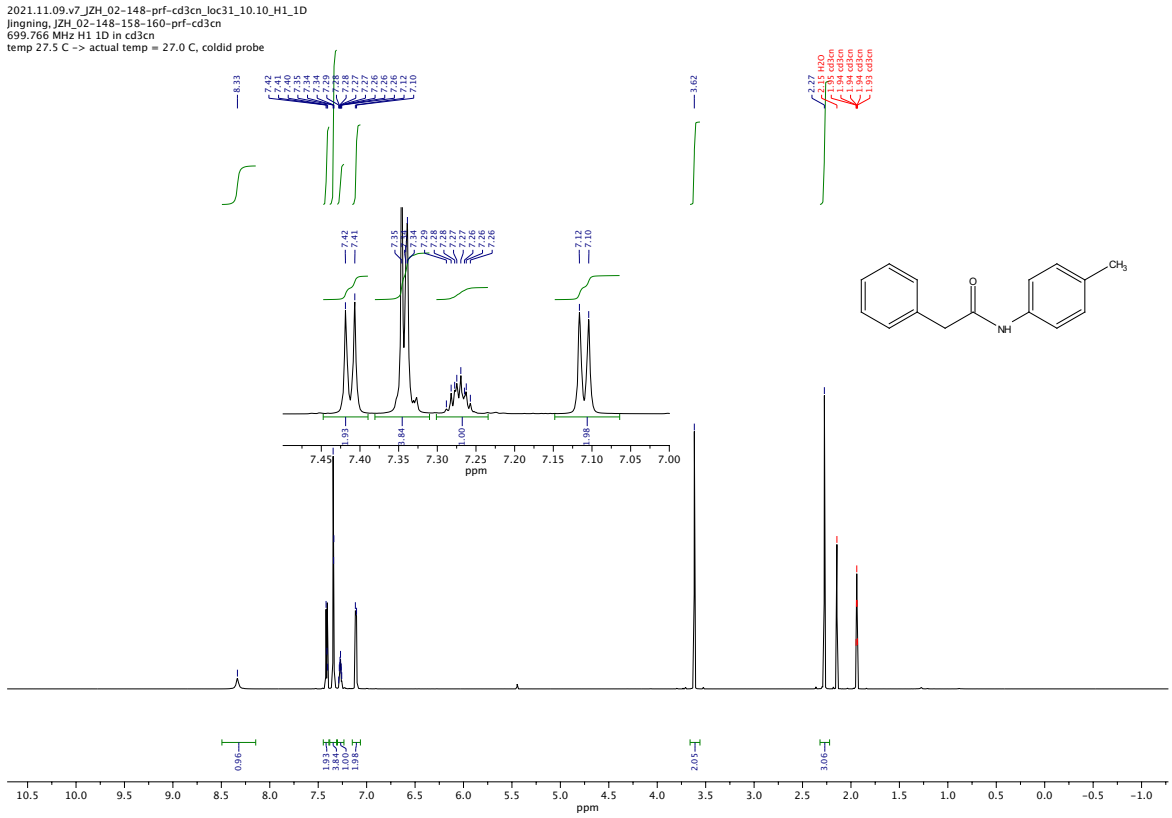


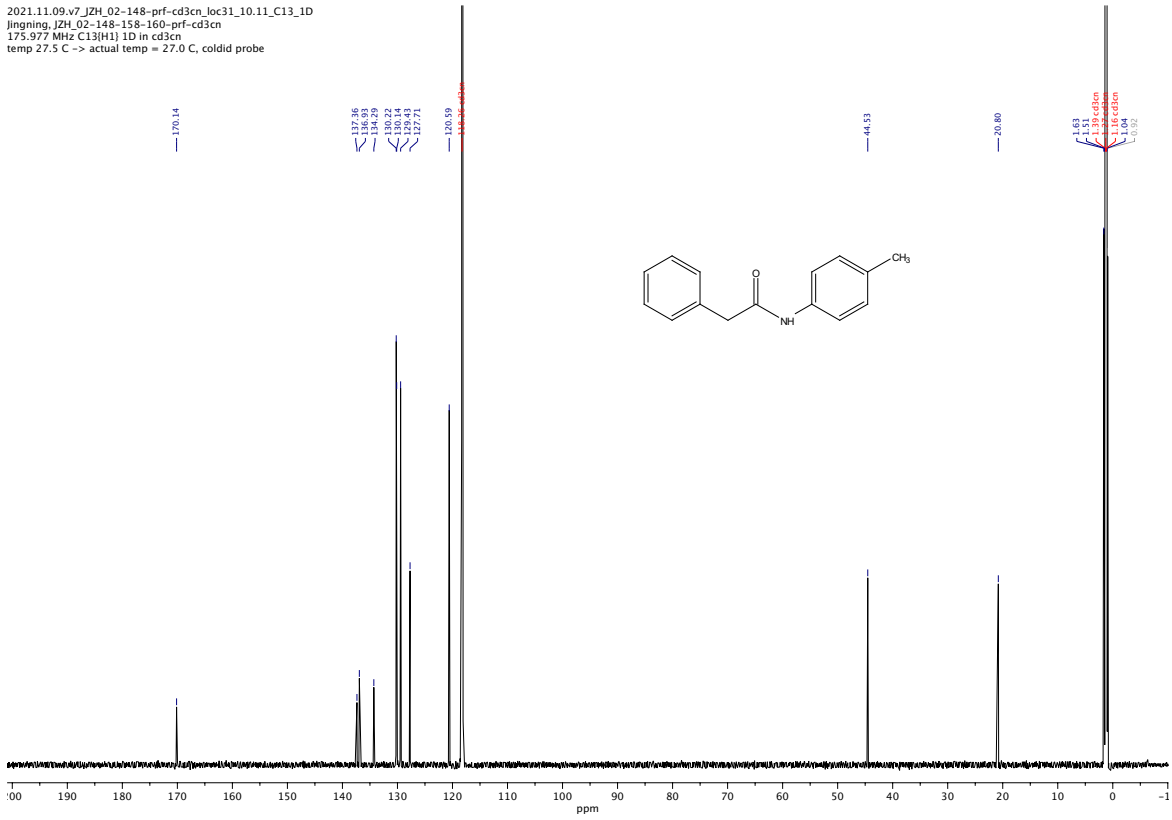
N,2-Diphenylacetamide (2-8)



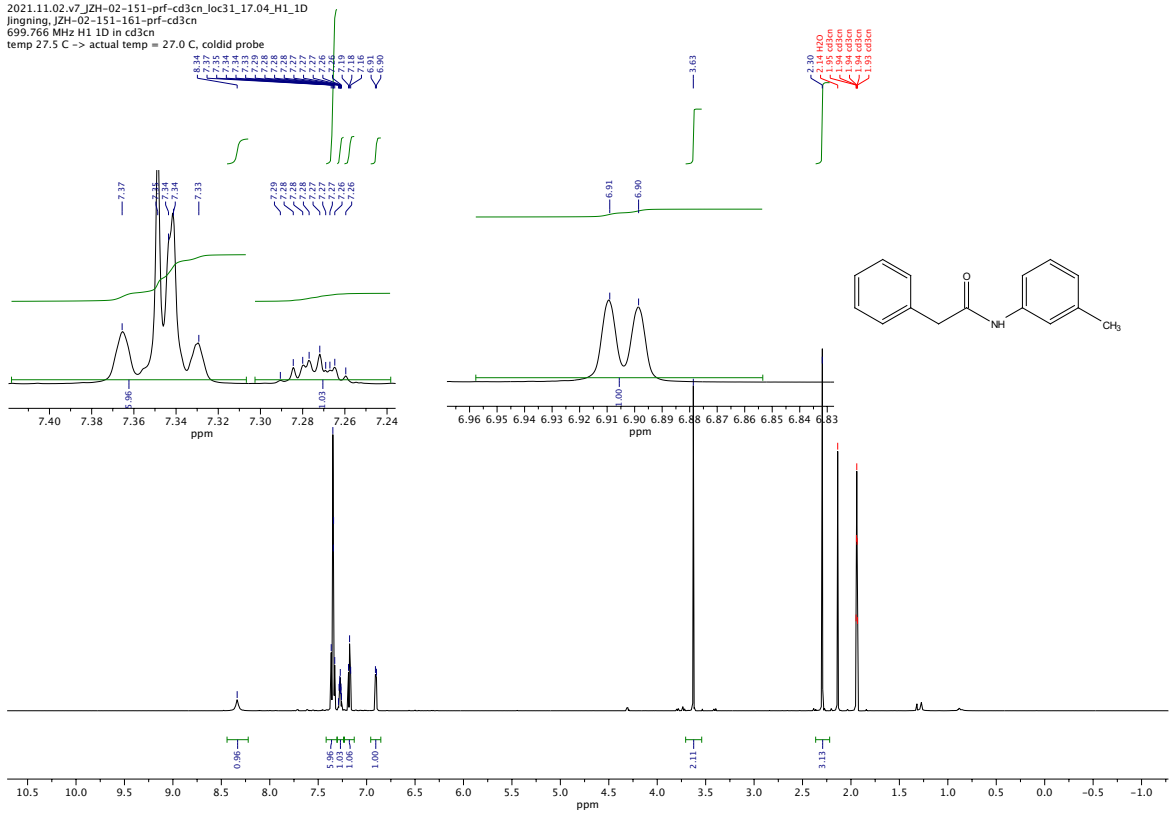

2022.03.10.u5_JZH-02-model_amide_loc12_14.12_C13_1D
Jingning, JZH-02-181A-model_amide
125.685 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe
170.32
139.94
136.84
130.24
129.21
129.04
127.74
124.67
120.65
118.29
44.56
1.77
1.70
1.44
1.11
0.85
0.78
O
NH
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

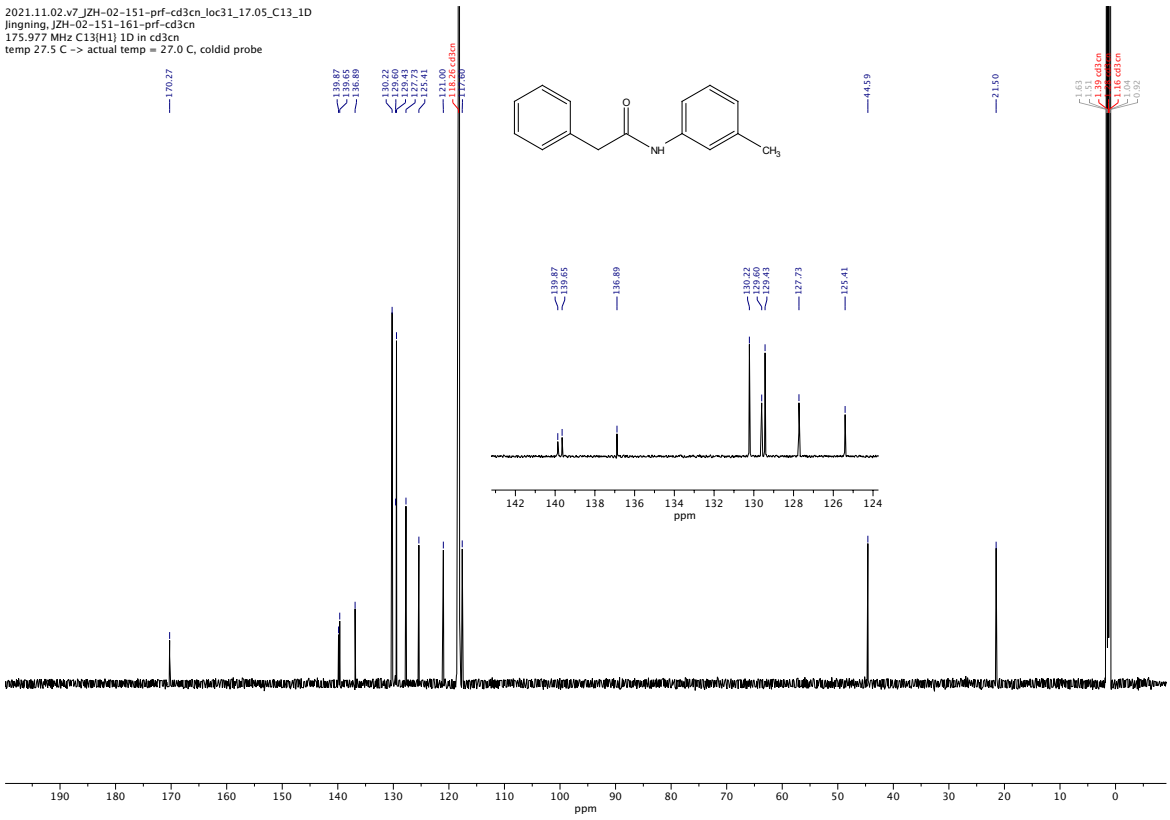
2-Phenyl-*N*-(p-tolyl)acetamide (2-9)



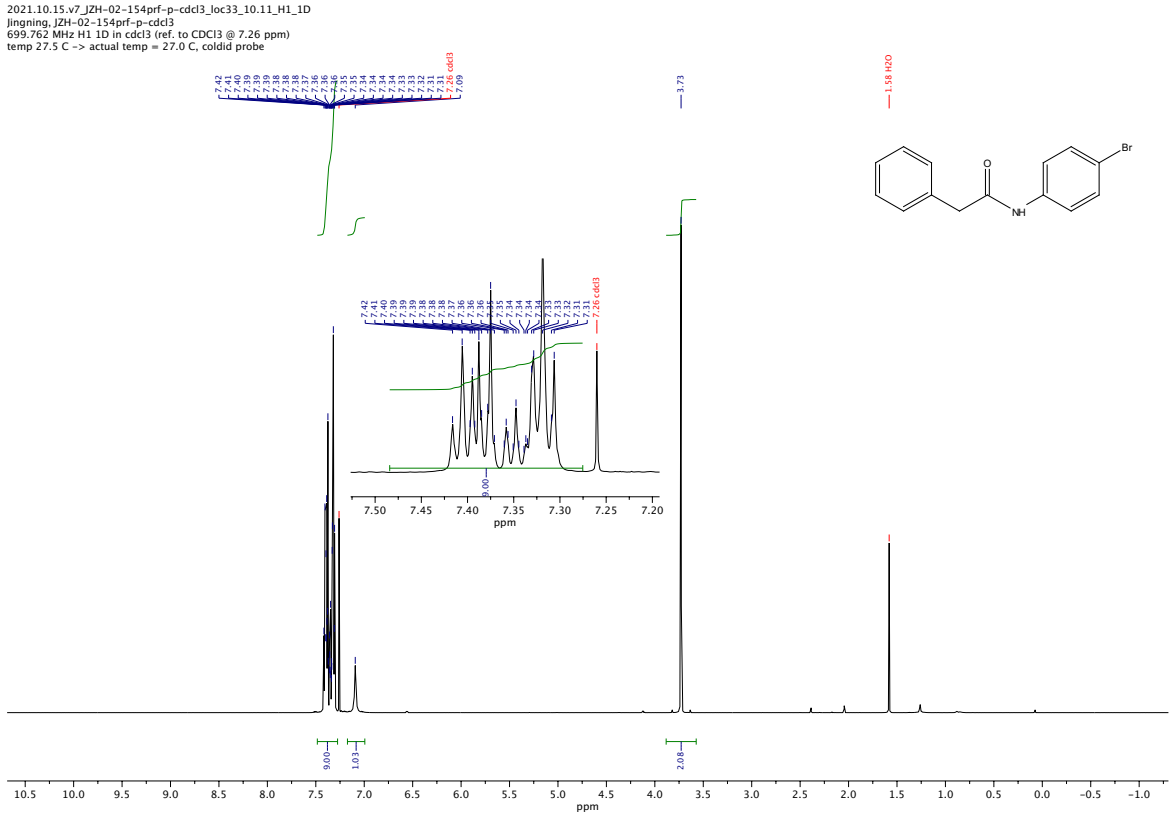

2021.11.09.v7_JZH_02-148-prf-cd3cn_loc31_10.11_C13_1D
Jingning, JZH_02-148-158-160-prf-cd3cn
175.977 MHz C13{H1} 1D in cd3cn
temp 27.5 C -> actual temp = 27.0 C, coldid probe
170.14
137.36
136.93
134.29
130.22
129.54
129.43
127.71
120.59
44.53
20.80
1.63
1.51
1.16
1.04
0.92
O
NH
CH3
ppm

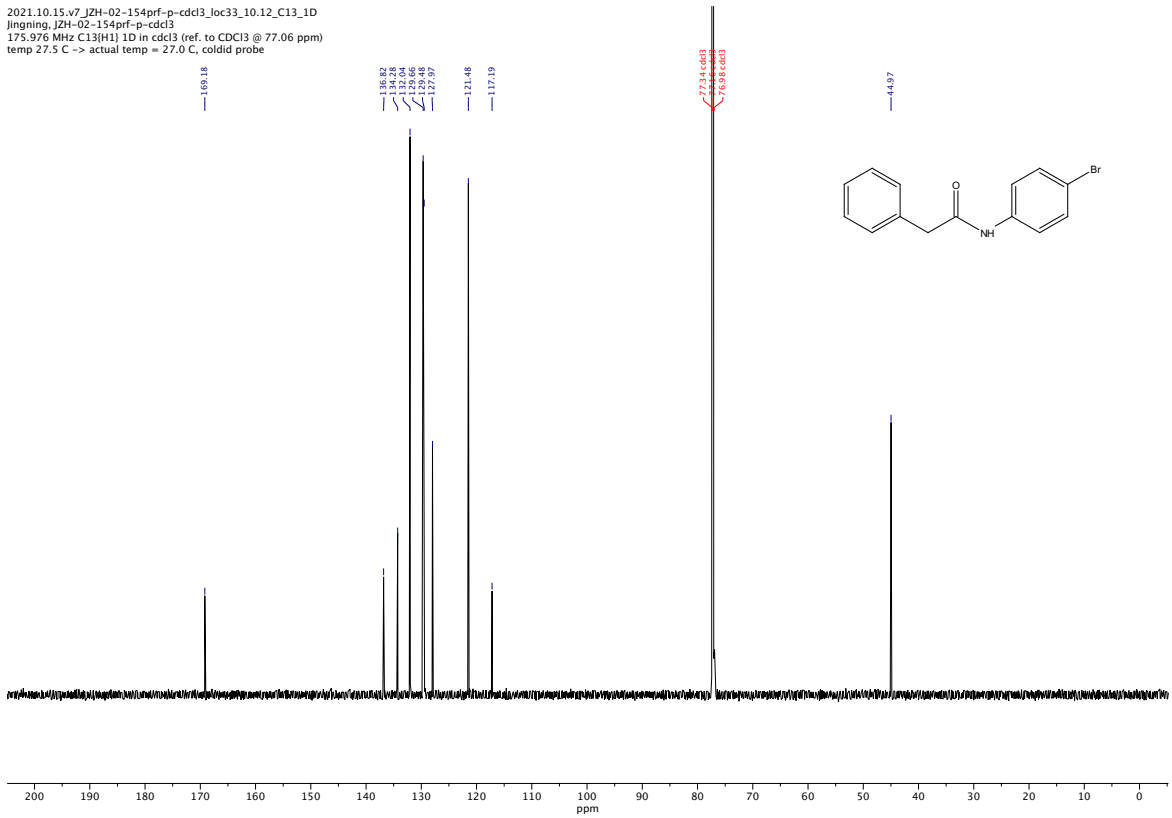
2-Phenyl-*N*-(*m*-tolyl)acetamide (2-10)



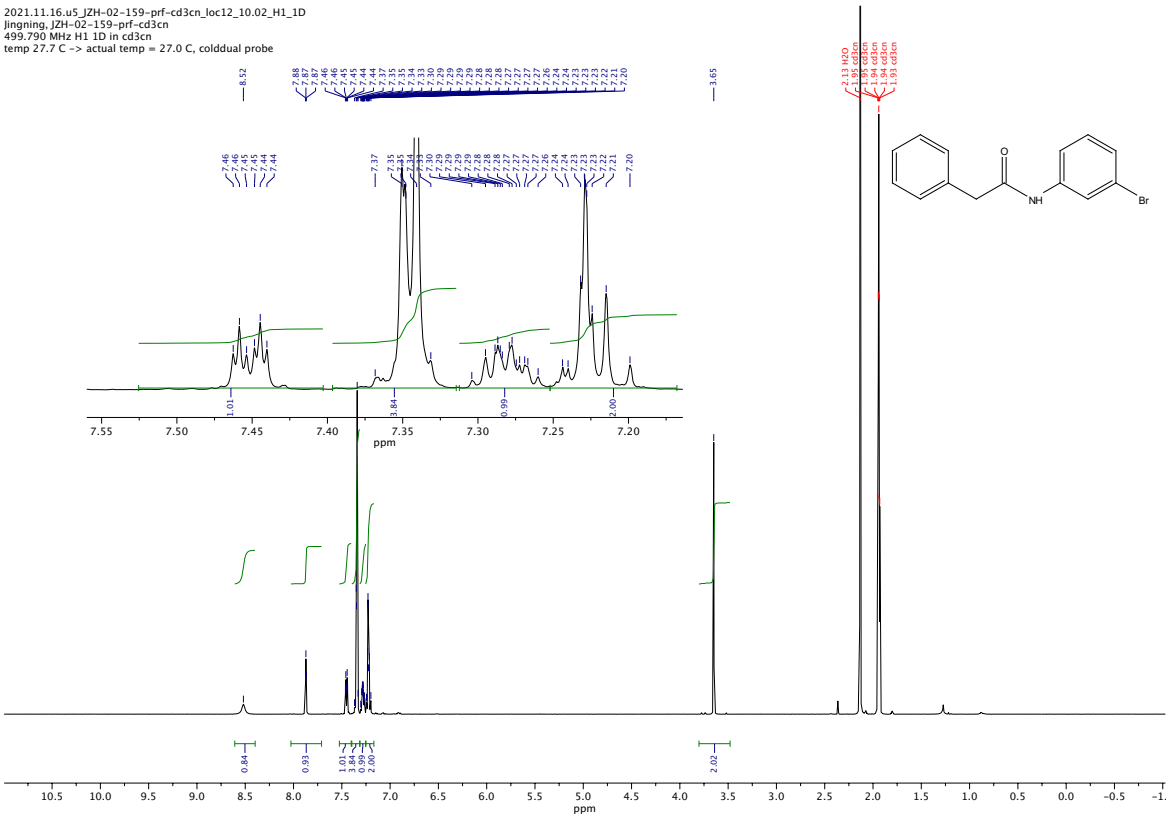

2021.11.02.v7_JZH-02-151-prf-cd3cn_loc31_17.05_C13_1D
Jingning, JZH-02-151-161-prf-cd3cn
175.977 MHz C13{H1} 1D in cd3cn
temp 27.5 C -> actual temp = 27.0 C, coldid probe
170.27
139.87
139.65
136.89
130.22
129.60
129.43
127.73
125.41
121.00
118.26 cd3cn
117.80
44.59
21.50
1.63
1.51
1.39 cd3cn
1.16 cd3cn
1.04
0.92
O
NH
CH3
ppm
ppm

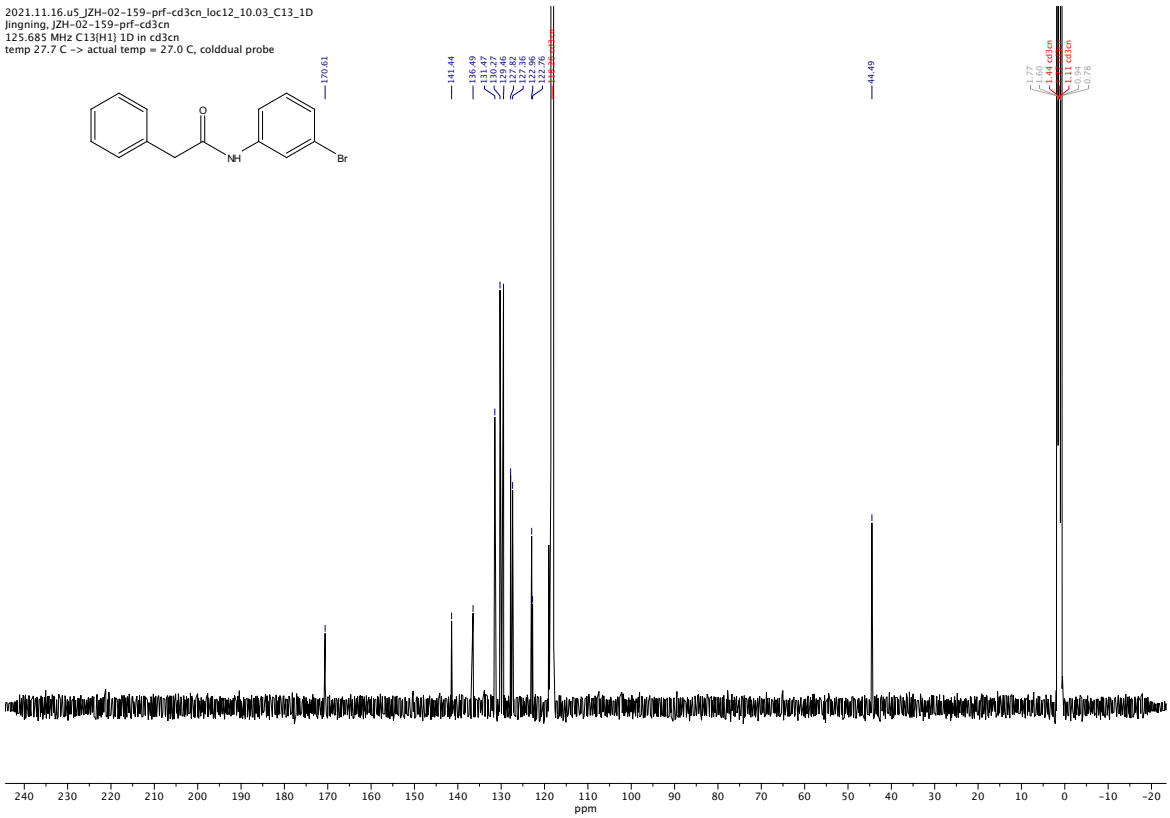
N-(4-Bromophenyl)-2-phenylacetamide (2-11)



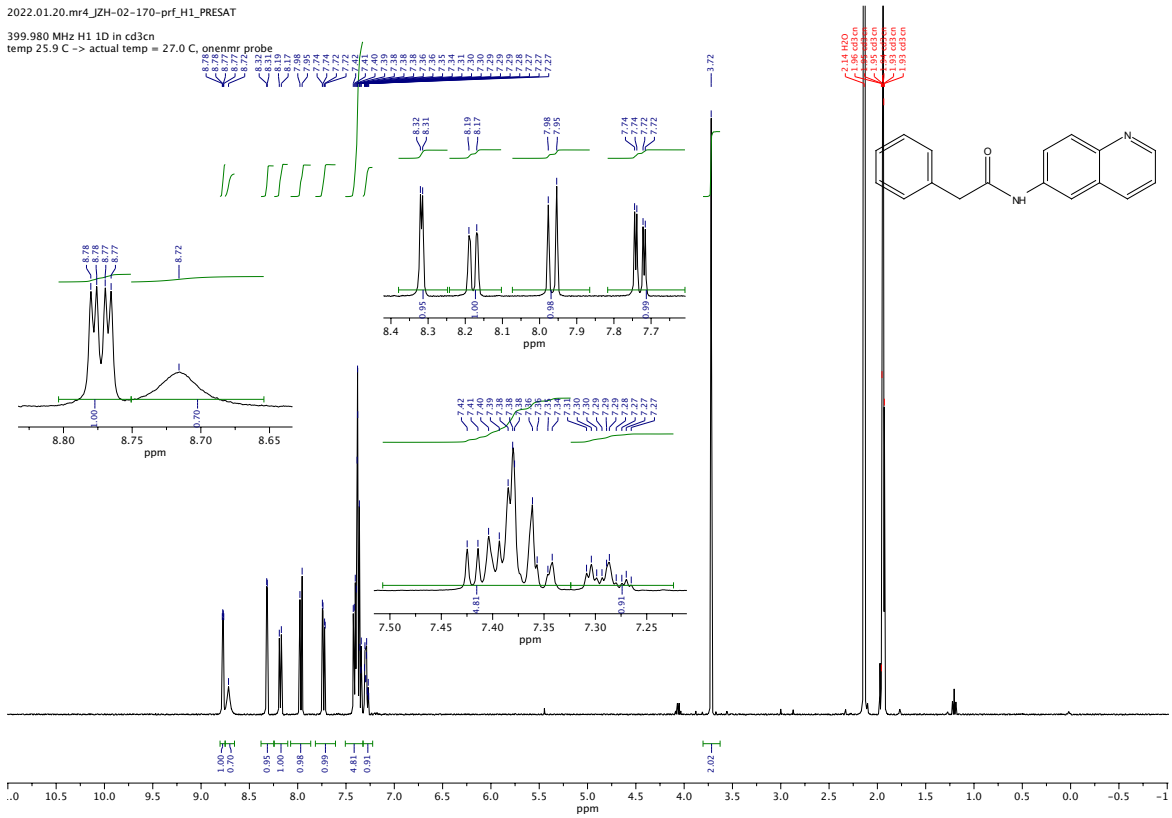

2021.10.15.v7_JZH-02-154prf-p-cdcl3_loc33_10.12_C13_1D
Jingning, JZH-02-154prf-p-cdcl3
175.976 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.5 C -> actual temp = 27.0 C, coldid probe
169.18
136.62
134.28
132.04
129.46
129.40
127.97
121.48
117.19
77.34 cdcl3
77.16 cdcl3
76.98 cdcl3
44.97
Br
O
NH
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

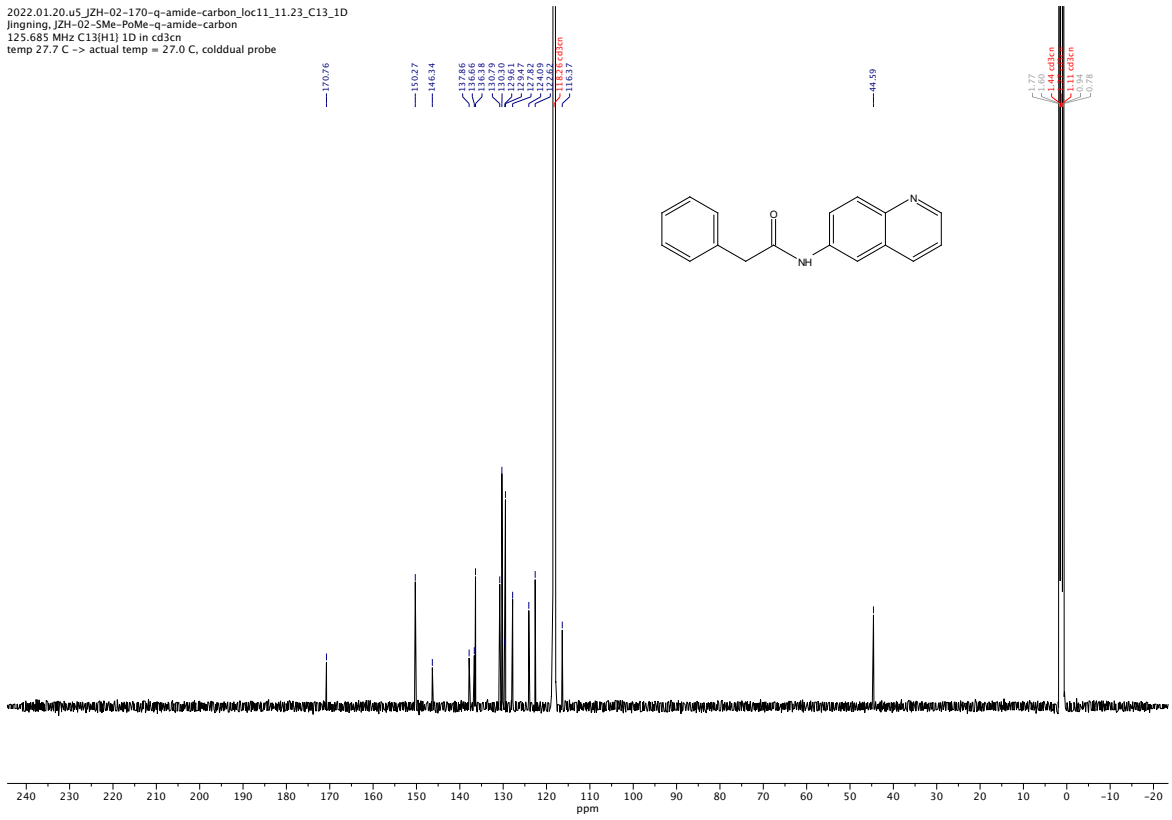
N-(3-Bromophenyl)-2-phenylacetamide (2-12)



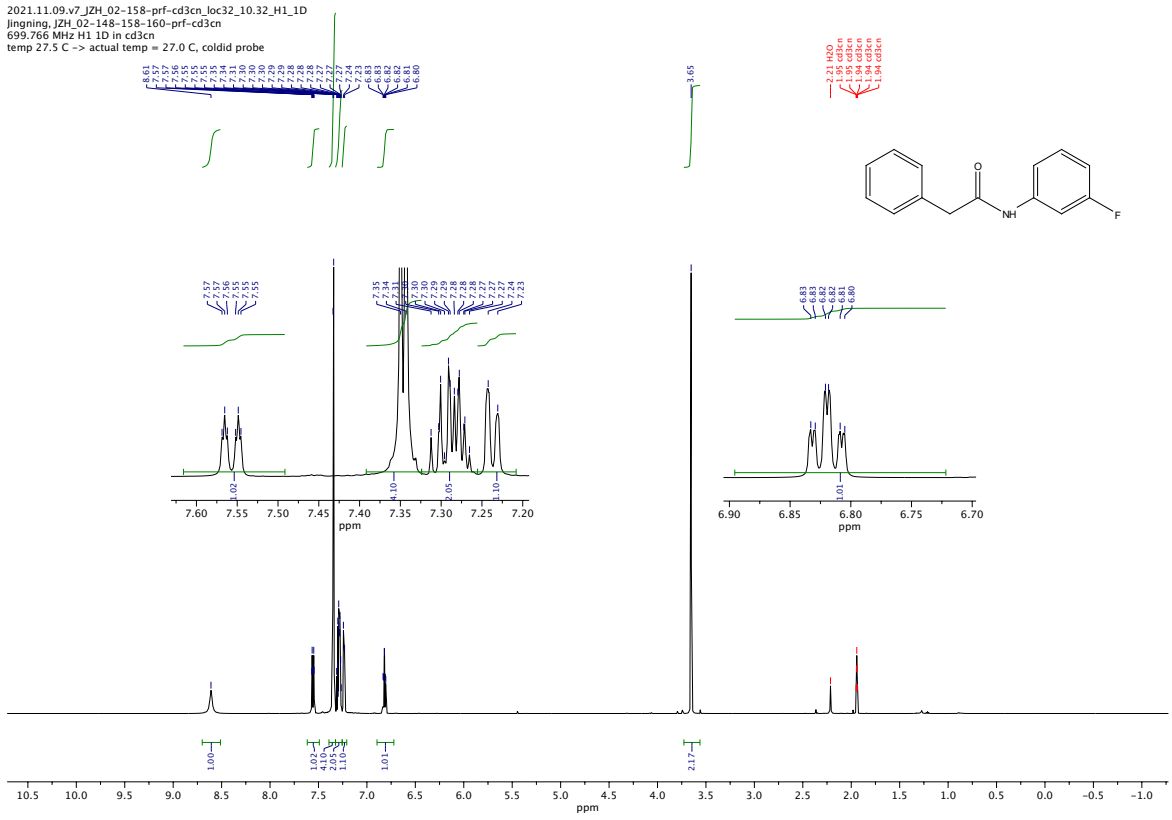

2021.11.16.u5_JZH-02-159-prf-cd3cn_loc12_10.03_C13_1D
Jingning, JZH-02-159-prf-cd3cn
125.685 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe
O
NH
Br
170.61
141.44
136.49
131.47
129.77
129.46
127.82
127.36
122.98
122.76
118.29
44.49
1.44 cd3cn
1.11 cd3cn
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
ppm

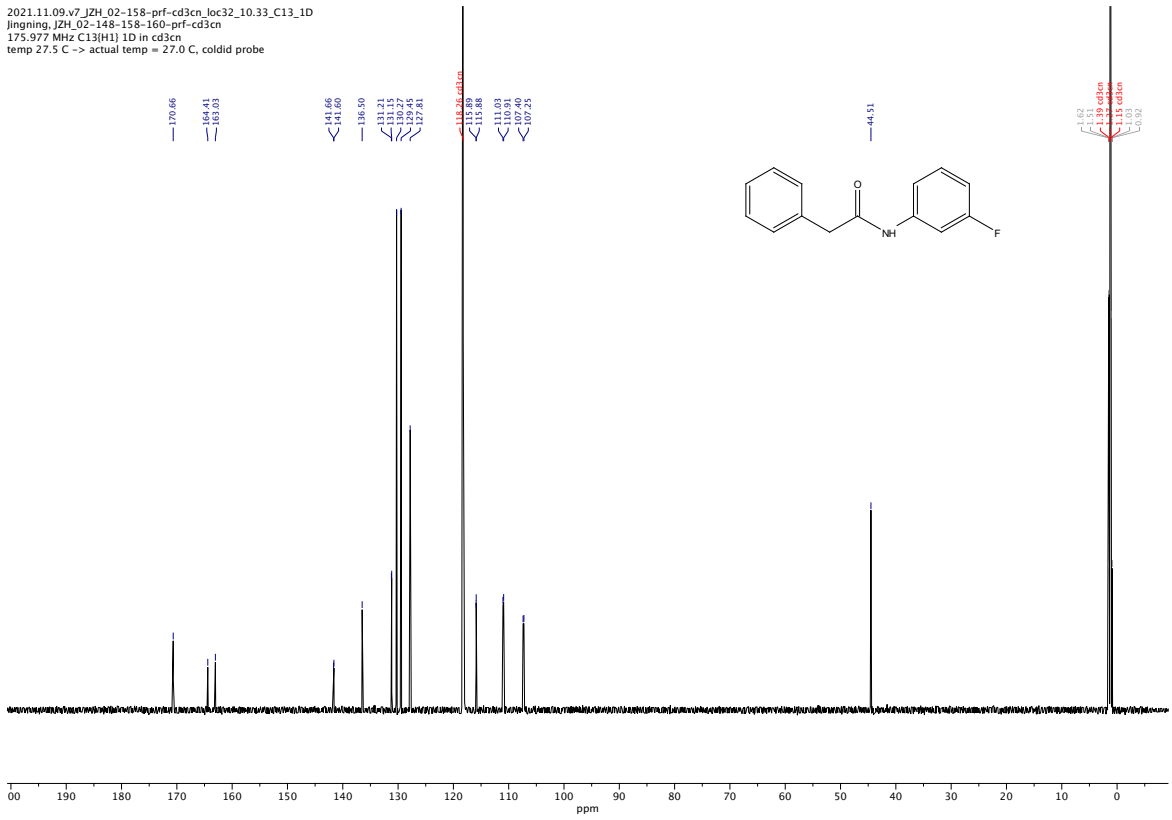
2-Phenyl-*N*-(quinolin-6-yl)acetamide (2-13)



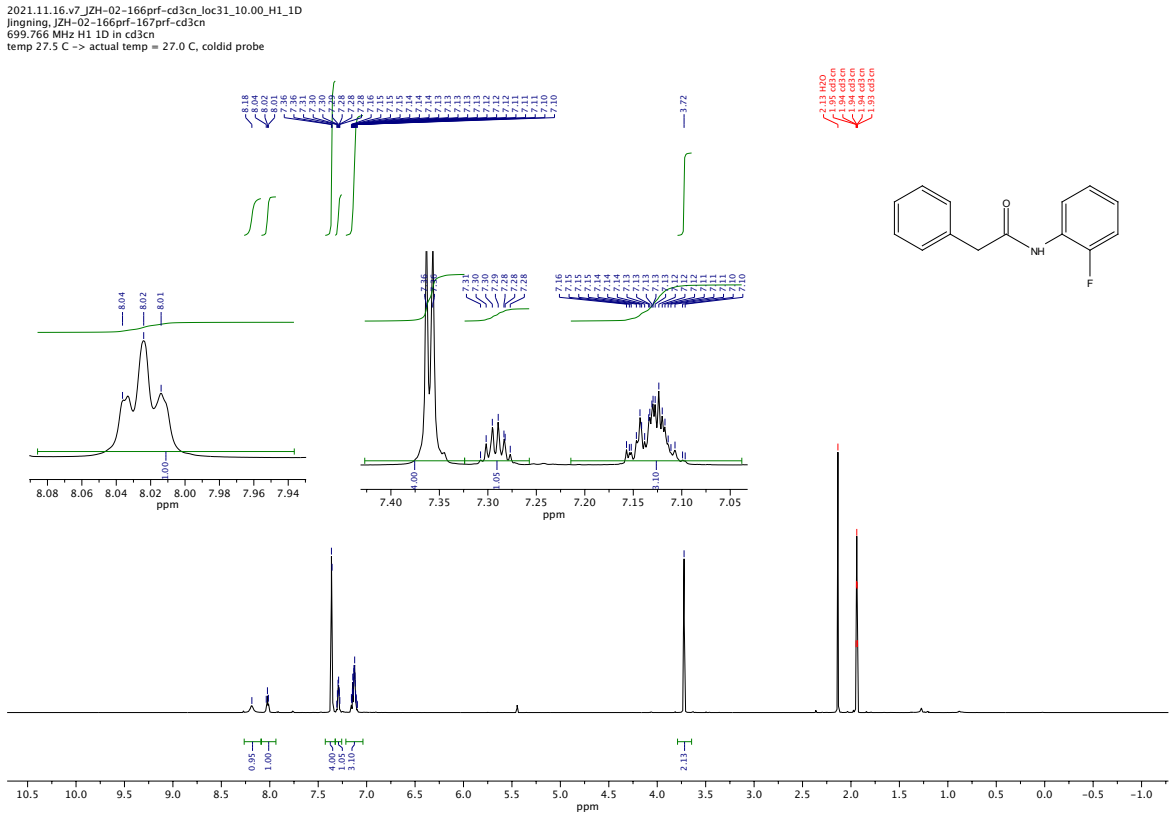

2022.01.20.u5_JZH-02-170-q-amide-carbon_loc11_11.23_C13_1D
Jingning, JZH-02-SMe-PoMe-q-amide-carbon
125.685 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe
170.76
150.27
146.34
137.86
136.66
136.38
130.79
130.30
129.61
129.47
127.82
124.09
122.02
118.26 cd3cn
116.37
44.59
1.77
1.60
1.44 cd3cn
1.31 cd3cn
1.11 cd3cn
0.85
0.78
O
NH
N
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
ppm

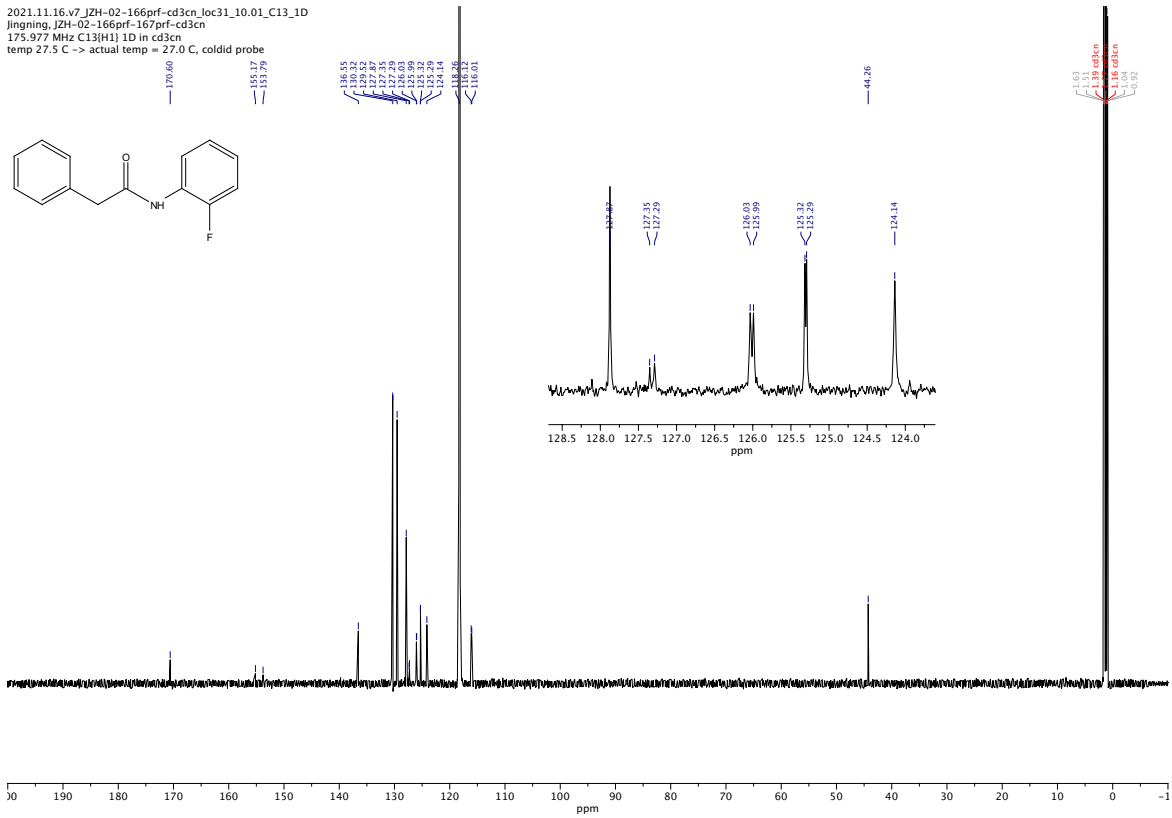
N-(3-Fluorophenyl)-2-phenylacetamide (2-14)



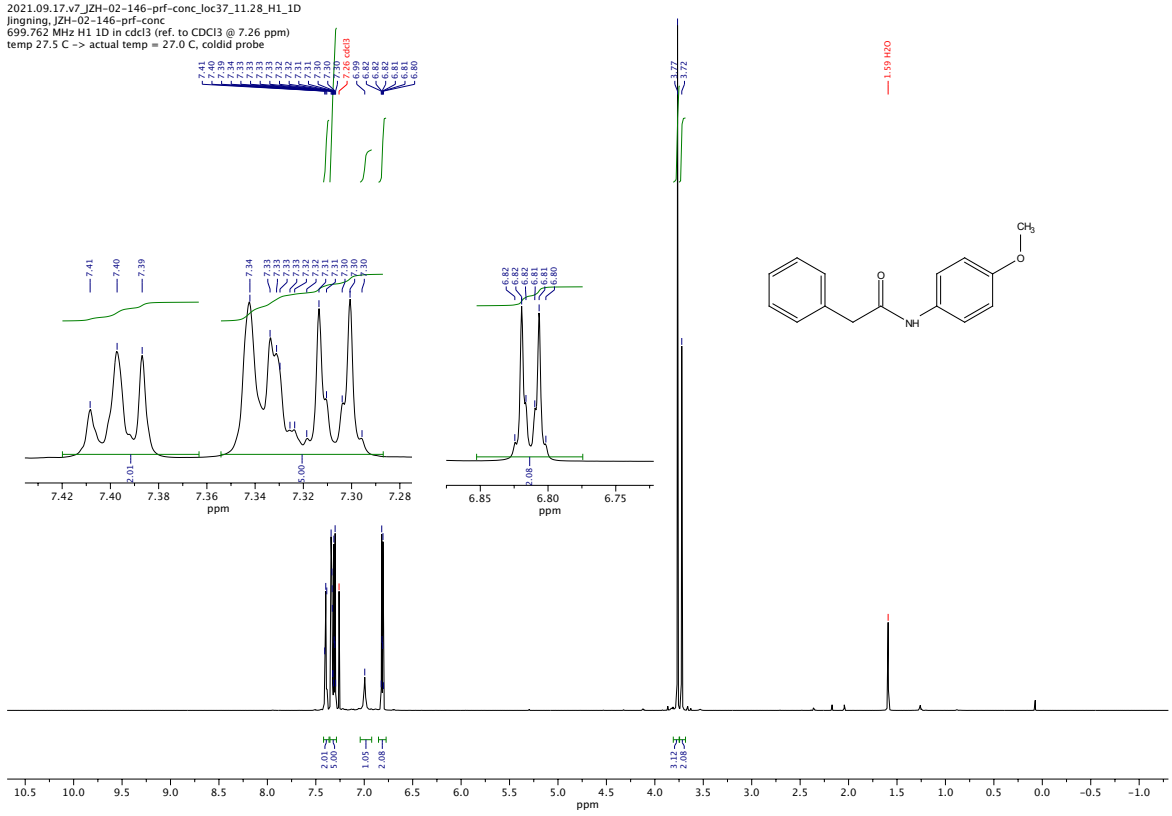

2021.11.09.v7_JZH_02-158-prf-cd3cn_loc32_10.33_C13_1D
Jingning, JZH_02-148-158-160-prf-cd3cn
175.977 MHz C13{H1} 1D in cd3cn
temp 27.5 C -> actual temp = 27.0 C, coldid probe
170.66
164.41
163.03
141.66
141.60
136.50
131.21
131.15
130.27
130.15
127.81
118.26 cd3cn
115.89
115.68
111.03
110.91
107.40
107.25
44.51
1.62
1.51
1.39 cd3cn
1.34 cd3cn
1.15 cd3cn
1.03
0.92
O
NH
F
ppm

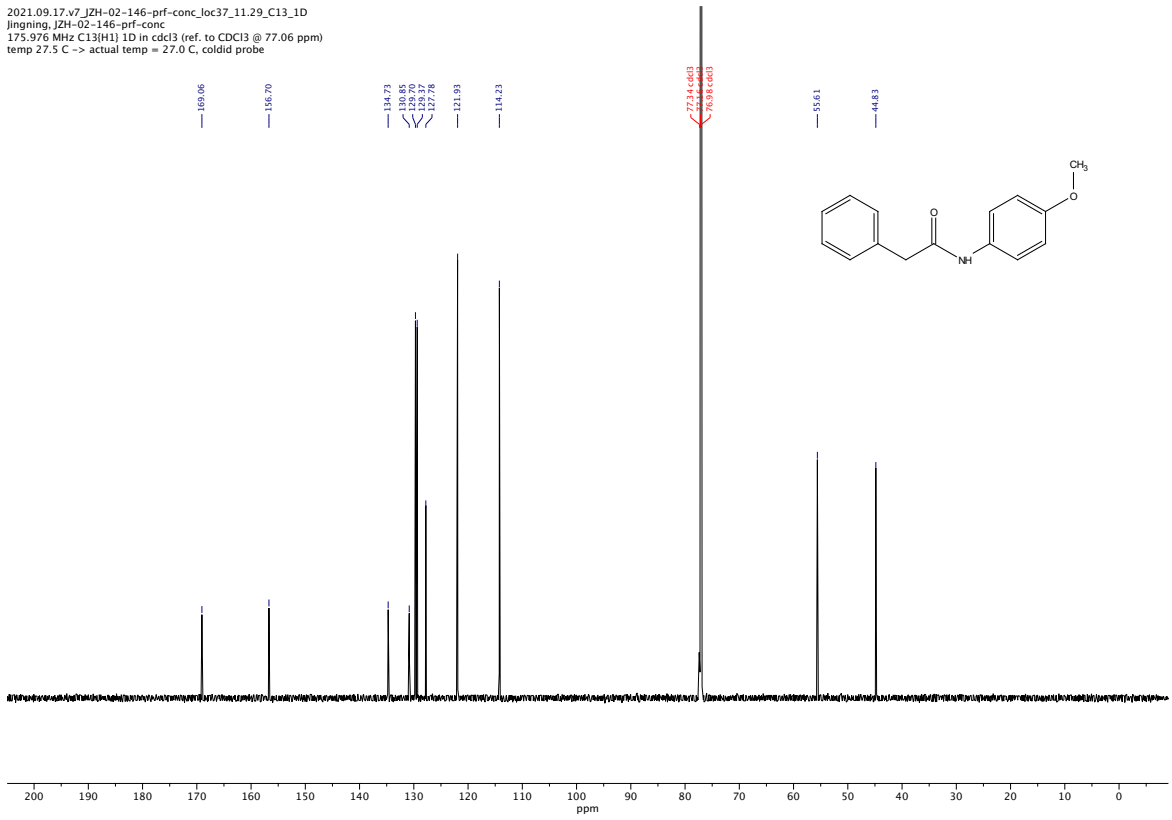
N-(2-Fluorophenyl)-2-phenylacetamide (2-15)



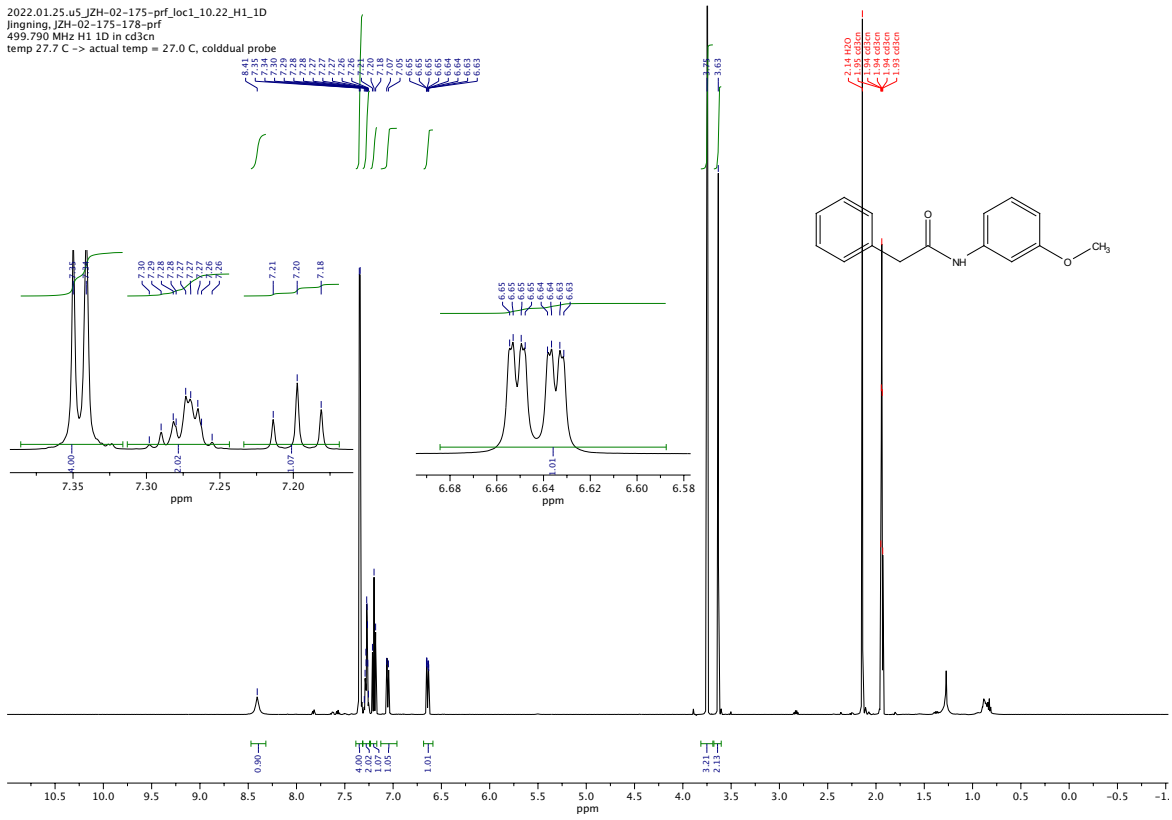

2021.11.16.v7_JZH-02-166prf-cd3cn_loc31_10.01_C13_1D
Jingning, JZH-02-166prf-167prf-cd3cn
175.977 MHz C13{H1} 1D in cd3cn
temp 27.5 C -> actual temp = 27.0 C, coldid probe
170.60
155.17
153.79
136.55
130.32
129.52
127.87
127.35
127.29
126.03
125.99
125.32
125.29
124.14
118.62
118.52
116.01
44.26
1.63
1.53
1.16
O
NH
F
ppm

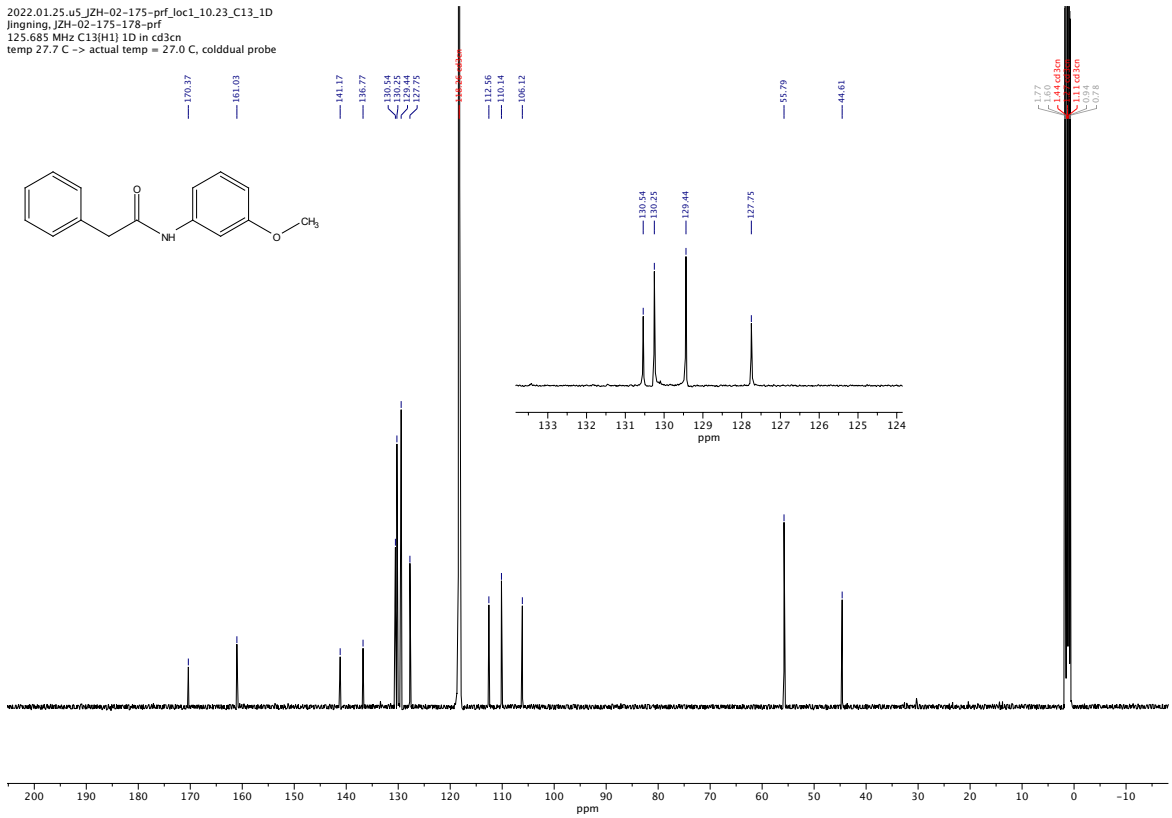
N-(4-methoxyphenyl)-2-phenylacetamide (2-16)



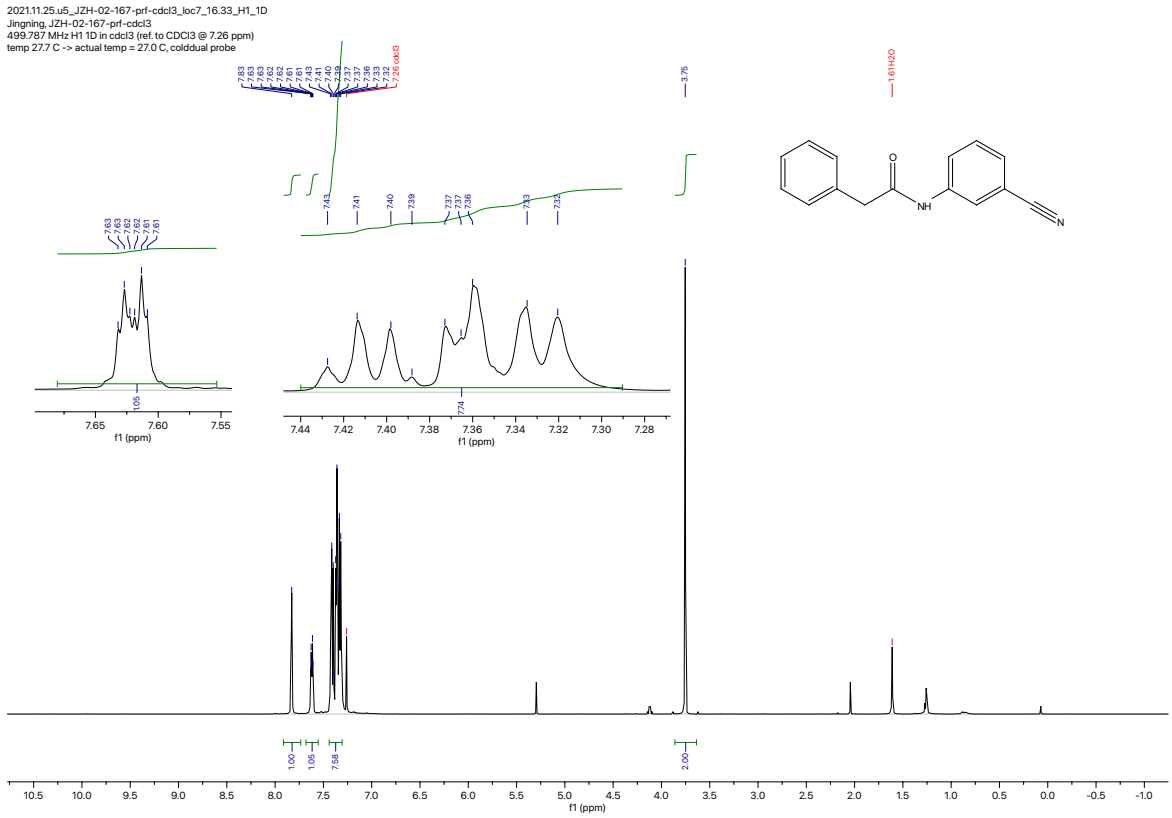

2021.09.17.v7_JZH-02-146-prf-conc_loc37_11.29_C13_1D
Jingning, JZH-02-146-prf-conc
175.976 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.5 C -> actual temp = 27.0 C, coldid probe
169.06
156.70
134.73
130.85
129.70
129.37
127.78
121.93
114.23
77.34 cdcl3
77.14 cdcl3
76.98 cdcl3
55.61
44.83
CH3
O
O
NH
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

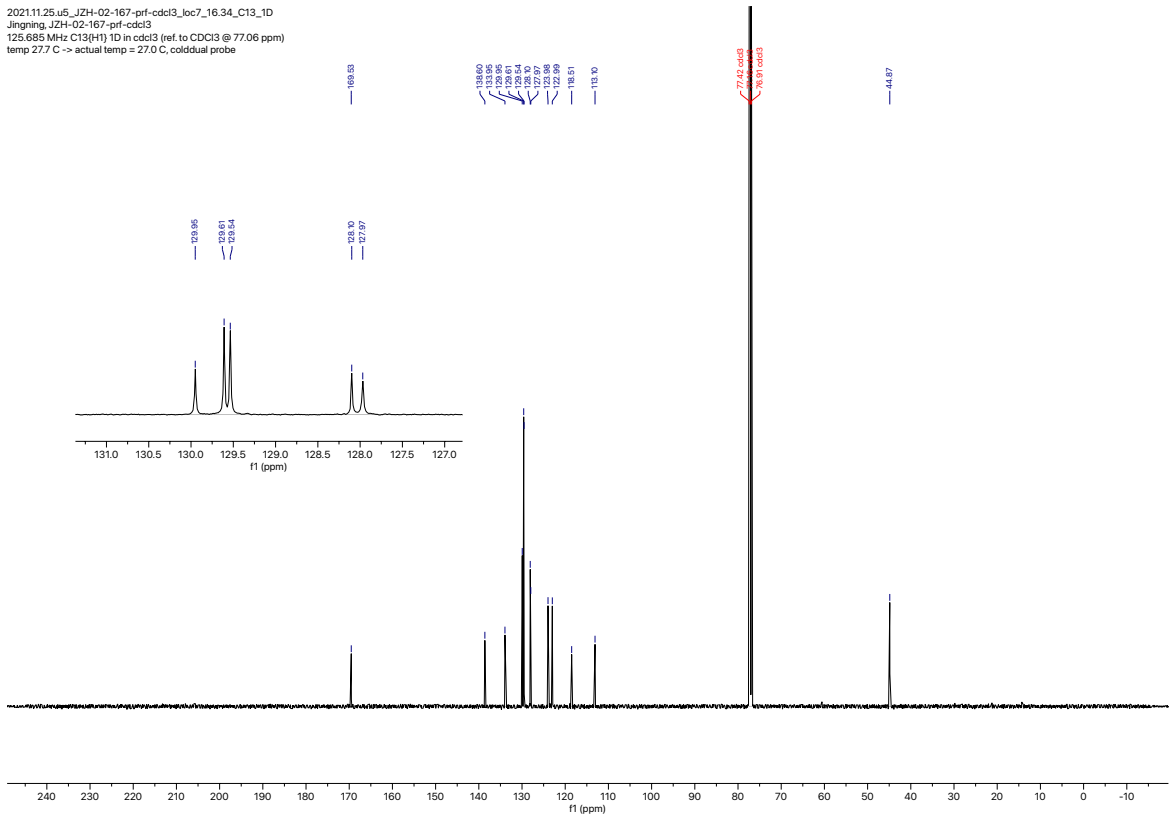
N-(3-methoxyphenyl)-2-phenylacetamide (2-17)



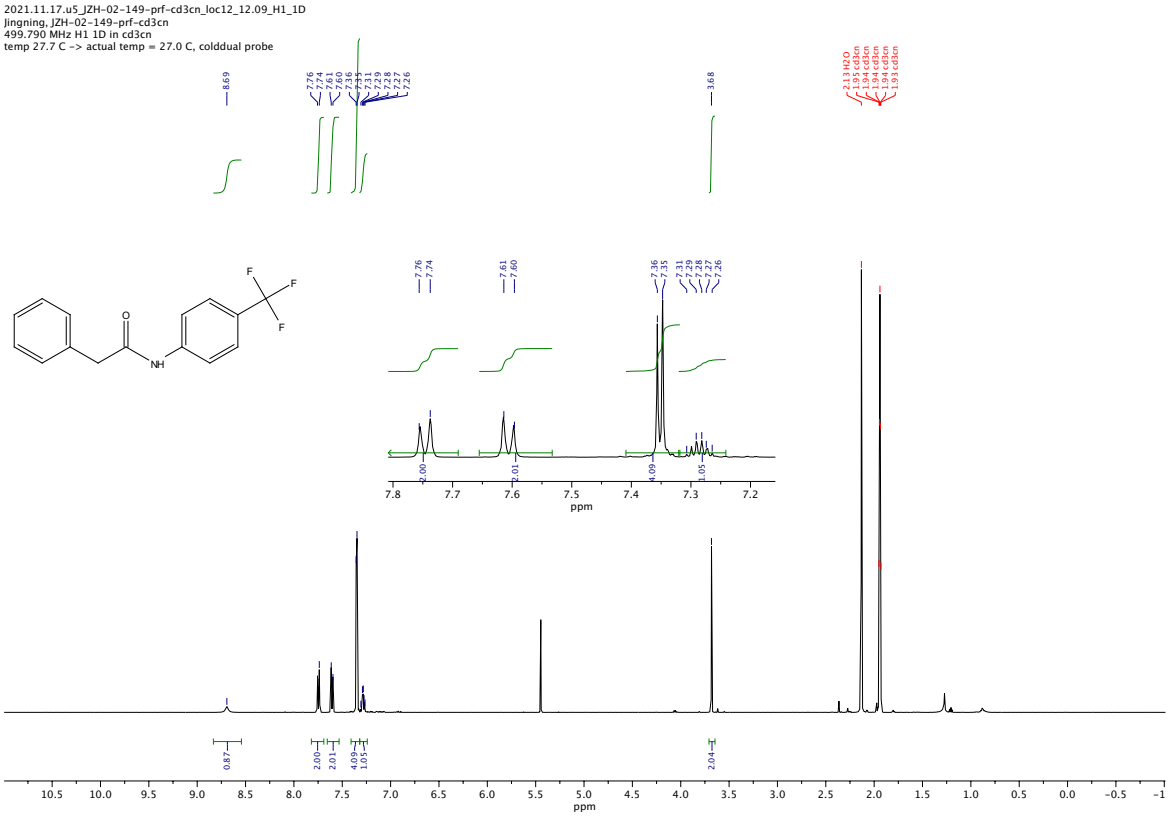

2022.01.25.u5_JZH-02-175-prf_loc1_10.23_C13_1D
Jingning, JZH-02-175-178-prf
125.685 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe
170.37
161.03
141.17
136.77
130.54
130.25
129.44
127.75
118.82 cd3cn
112.56
110.14
106.12
55.79
44.61
1.27
1.60
1.44 cd3cn
1.11 cd3cn
0.94
0.78
O
NH
O
CH3
ppm
ppm

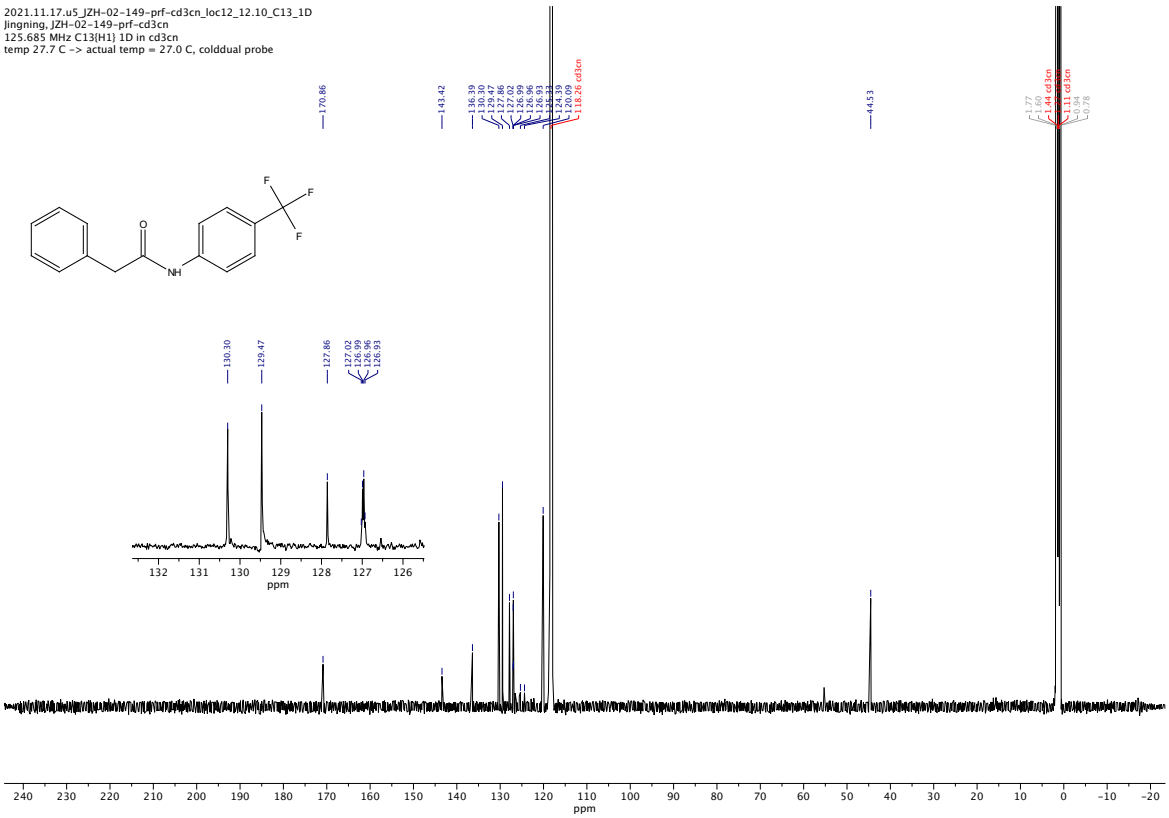
N-(3-cyanophenyl)-2-phenylacetamide (2-18)



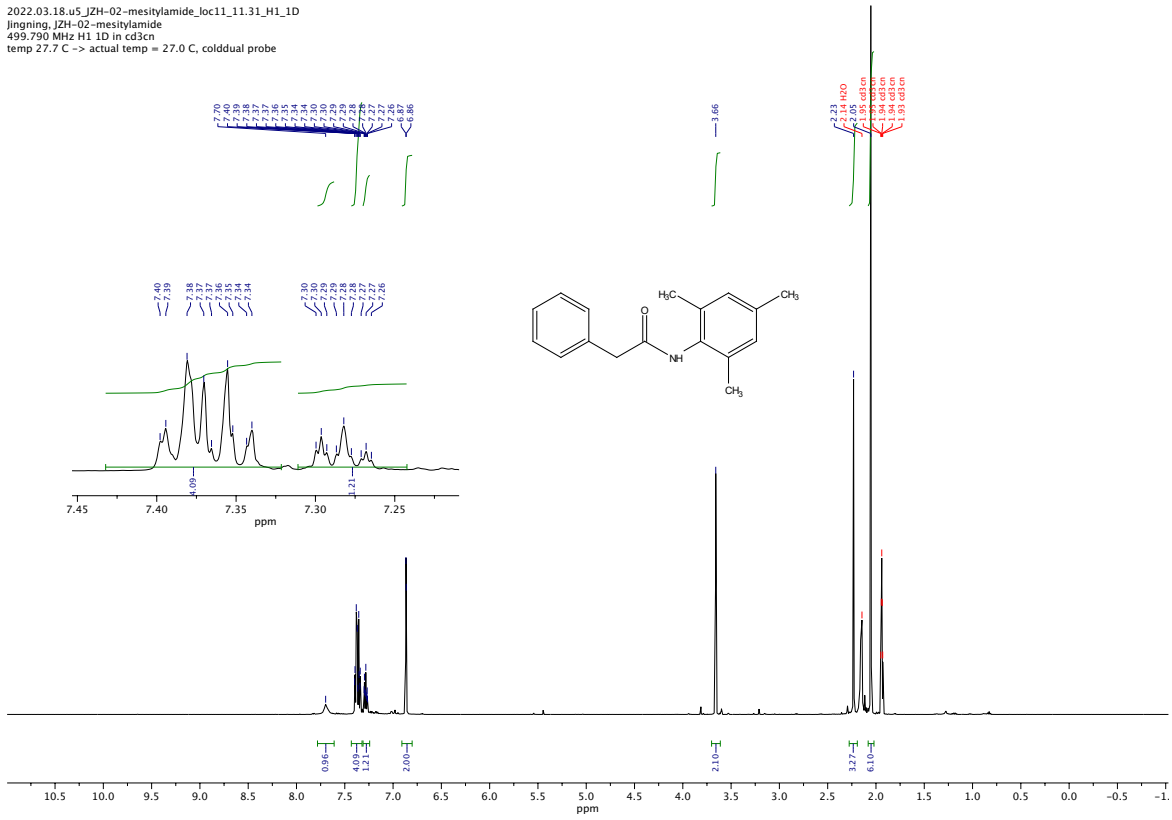

2021.11.25.u5_JZH-02-167-prf-cdcl3_loc7_16.34_C13_1D
Jingning, JZH-02-167-prf-cdcl3
125.685 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
169.53
138.60
133.95
129.95
129.61
129.54
128.10
127.97
123.98
122.99
118.51
113.10
77.42 cdcl3
77.06 cdcl3
76.91 cdcl3
44.87
129.95
129.61
129.54
128.10
127.97
131.0 130.5 130.0 129.5 129.0 128.5 128.0 127.5 127.0
f1 (ppm)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

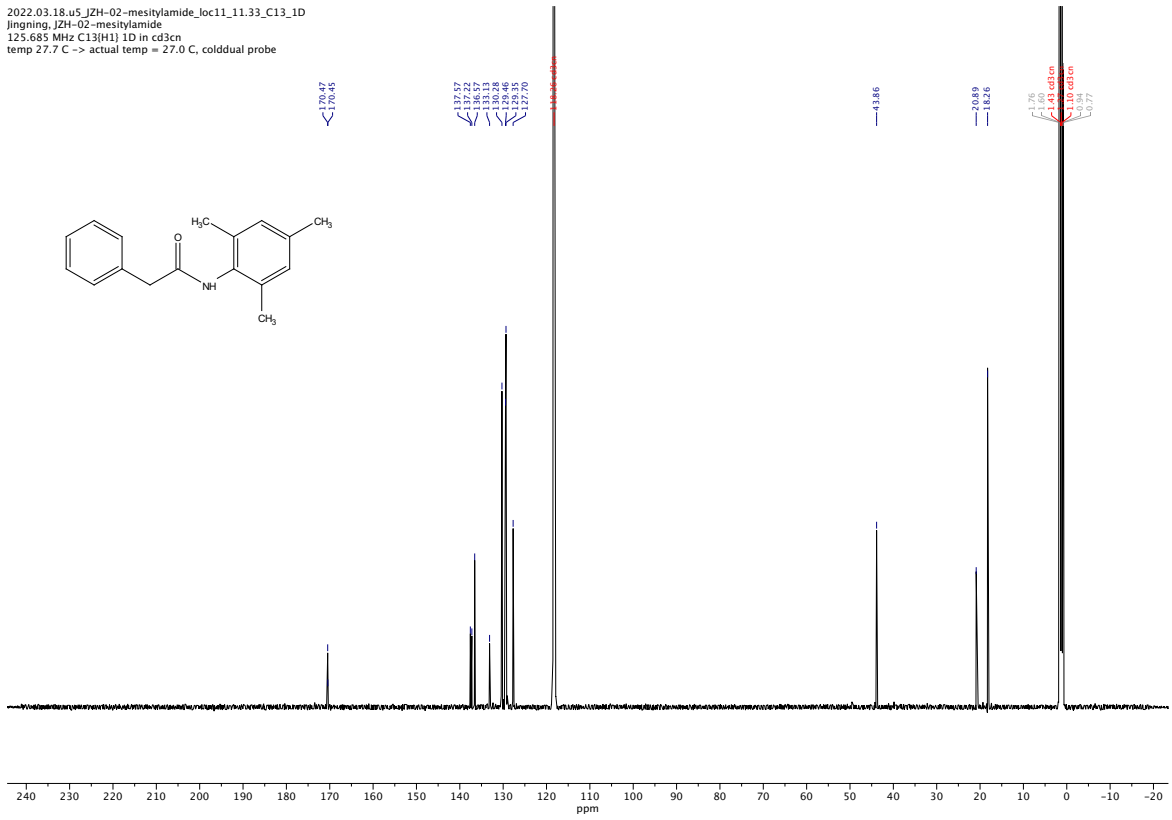
2-phenyl-*N*-(4-(trifluoromethyl)phenyl)acetamide (2-19)



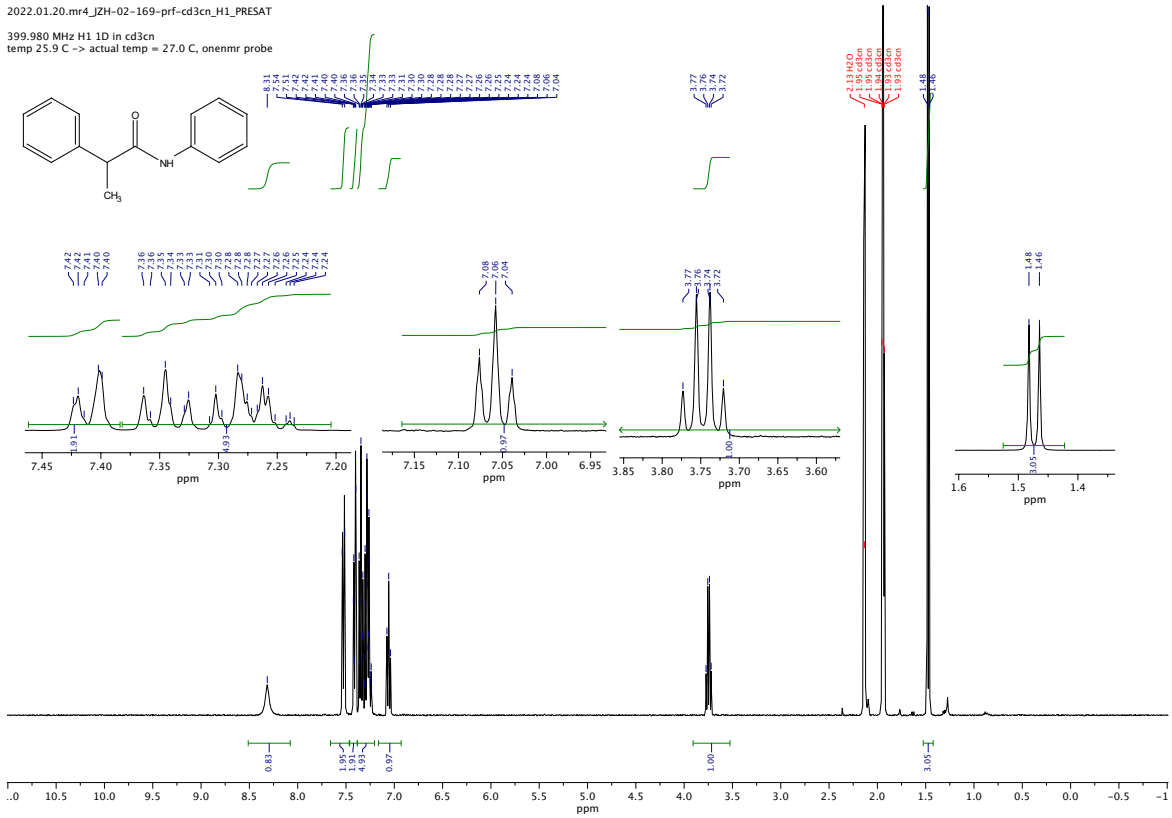

2021.11.17.u5_JZH-02-149-prf-cd3cn_loc12_12.10_C13_1D
Jingning, JZH-02-149-prf-cd3cn
125.685 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe
170.86
143.42
136.39
130.30
129.47
127.86
127.02
126.99
126.96
126.93
124.39
120.09
118.26 cd3cn
44.53
1.27
1.44 cd3cn
1.91 cd3cn
1.94
0.78
F
F
F
O
NH
ppm
ppm

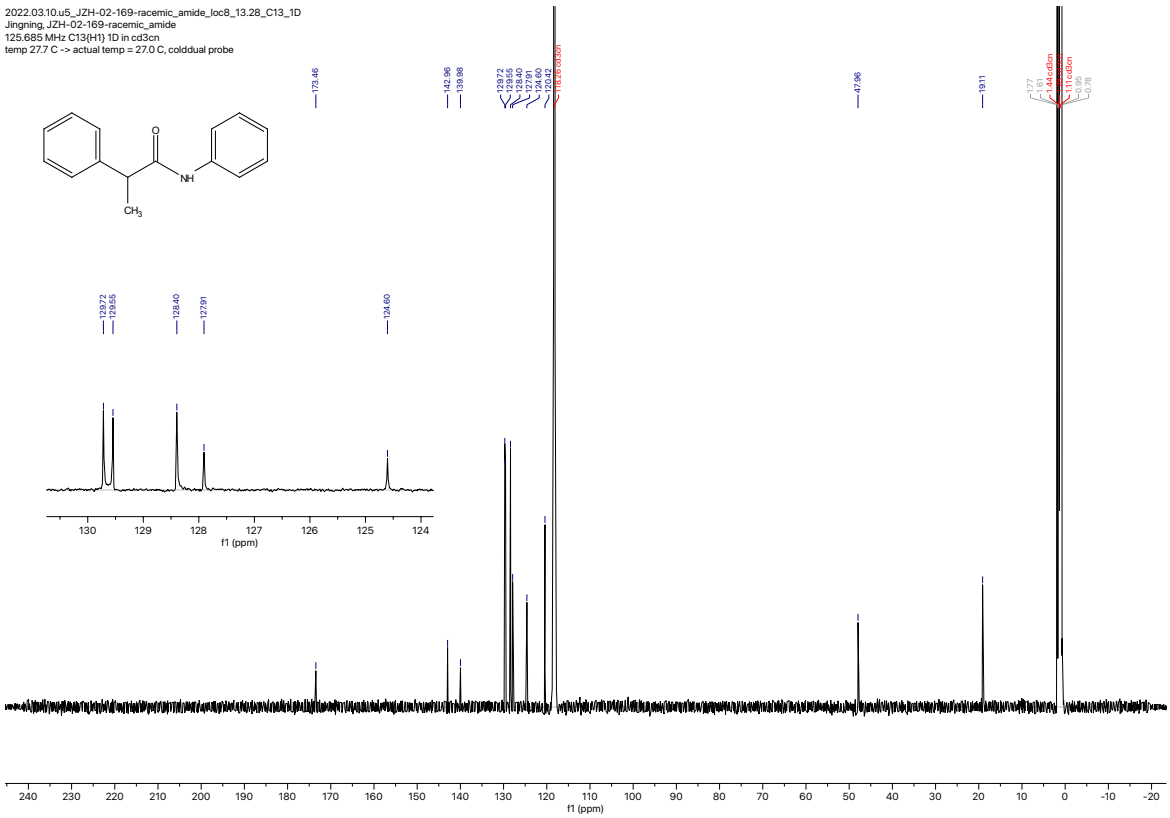
N-mesityl-2-phenylacetamide (2-20)



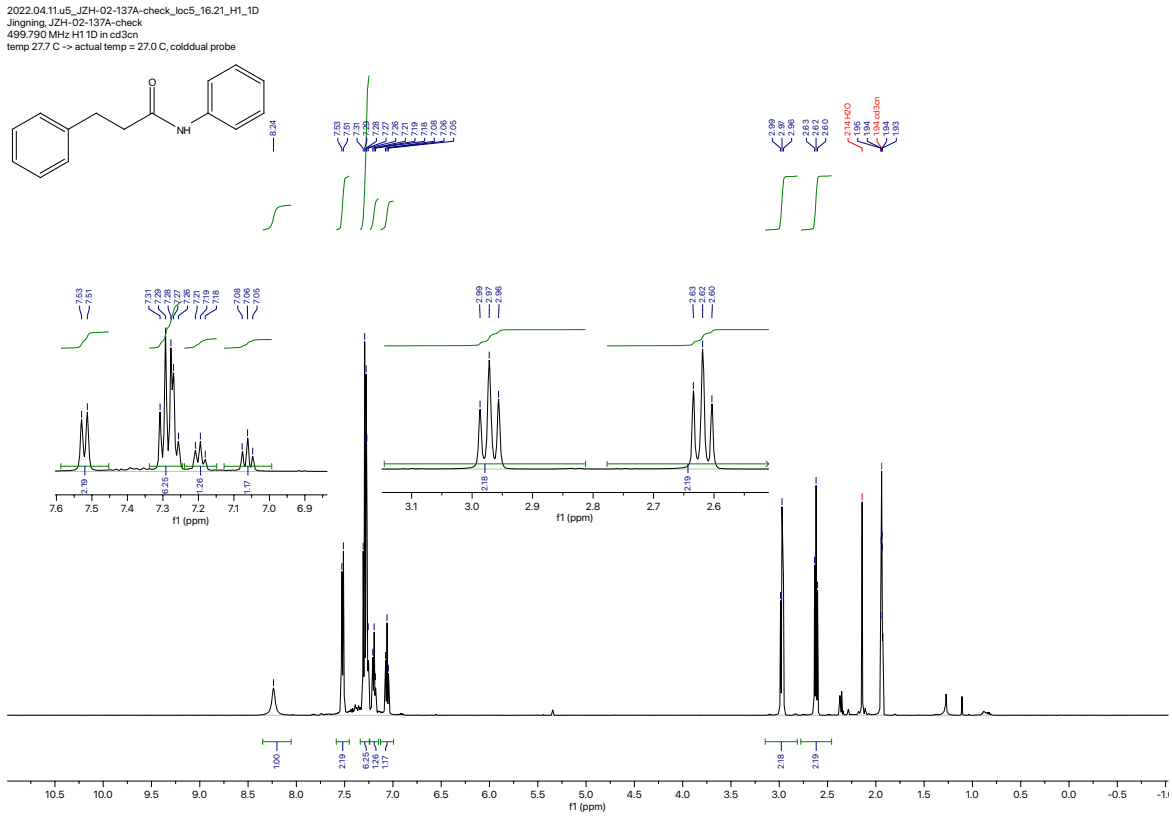

2022.03.18.u5_JZH-02-mesitylamide_loc11_11.33_C13_1D
Jingning, JZH-02-mesitylamide
125.685 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe
170.47
170.45
137.57
137.22
136.57
133.13
131.03
129.46
129.35
127.70
118.26 cd3cn
43.86
20.89
18.26
1.76
1.60
1.43 cd3cn
1.10 cd3cn
0.84
0.77
H3C
CH3
O
NH
CH3
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
ppm

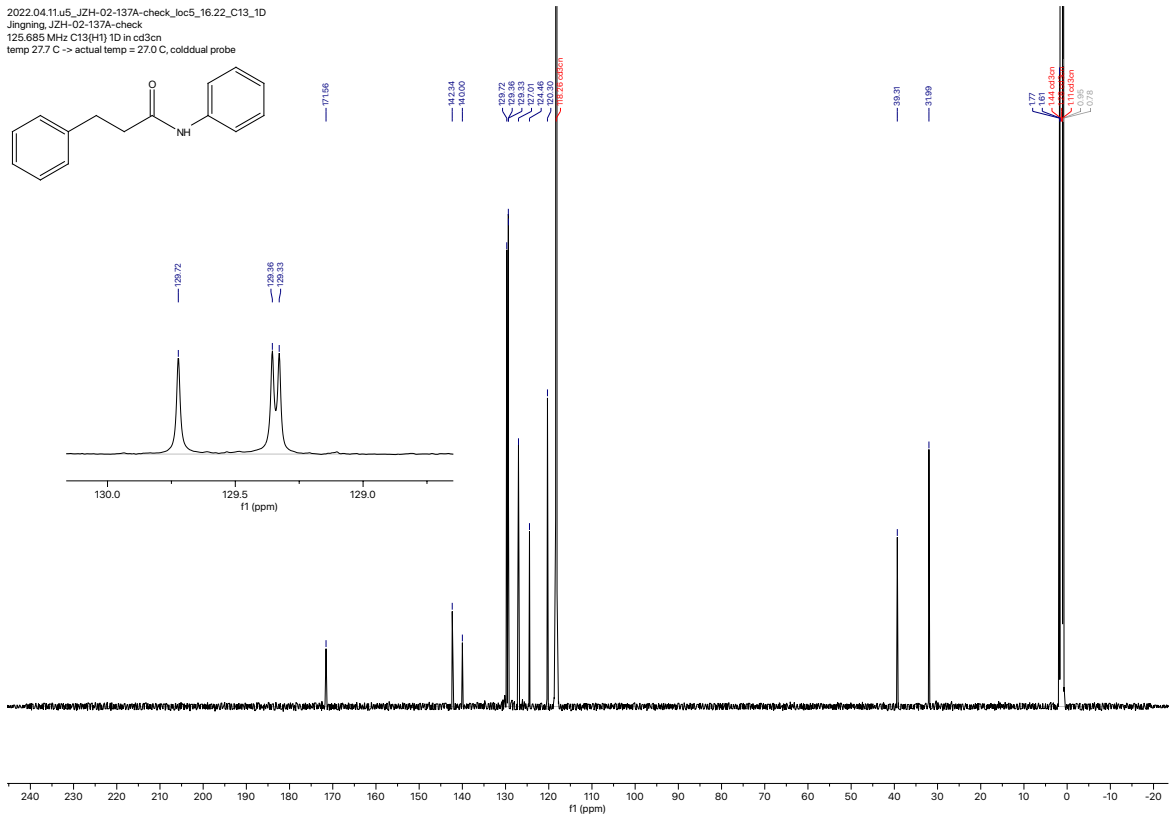
N-Phenyl-α-methyl-benzeneacetamide (2-22)



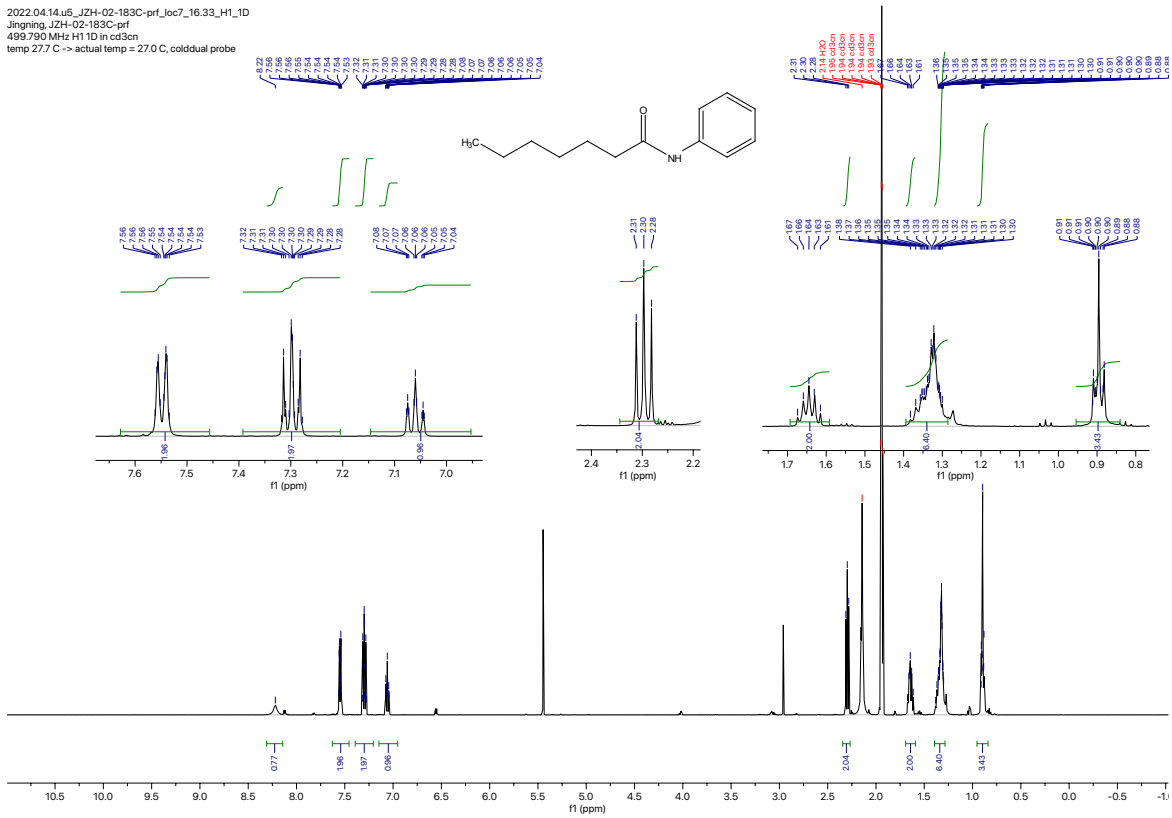

2022.03.10.u5_JZH-02-169-racemic_amide_loc8_13.28_C13_1D
Jingning, JZH-02-169-racemic_amide
125.685 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe
O
NH
CH3
173.46
142.96
139.98
129.72
128.95
128.40
127.91
124.60
47.96
19.11
f1 (ppm)

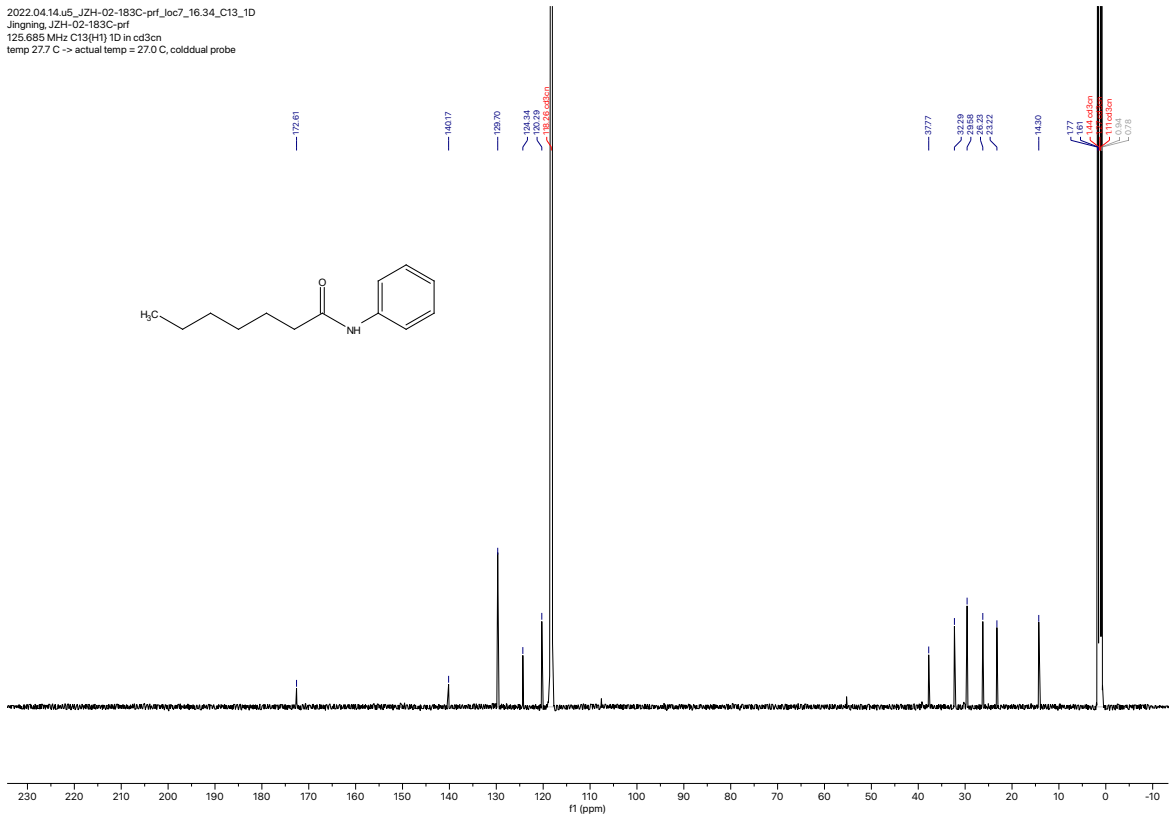
N,3-diphenylpropanamide (2-23)




2022.04.11.u5_JZH-02-137A-check_loc5_16.22_C13_1D
Jingning, JZH-02-137A-check
125.685 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe
O
NH
171.56
142.34
140.00
129.72
129.36
129.33
127.01
124.46
120.03
118.26 cd3cn
39.31
31.99
1.77
1.78
1.44 cd3cn
1.11 cd3cn
1.05
0.78
129.72
129.36
129.33
130.0
129.5
129.0
f1 (ppm)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

N-phenylheptanamide (2-24)




2022.04.14.u5_JZH-02-183C-prf_loc7_16.34_C13_1D
Jingning, JZH-02-183C-prf
125.685 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe
172.61
140.17
129.70
124.34
120.39
118.26 cd3cn
37.77
32.29
29.68
26.23
23.22
14.30
1.77
1.61
1.44 cd3cn
1.11 cd3cn
0.94
0.78
O
NH
H3C
f1 (ppm)