University of Alberta

Mild, Green and Catalytic: *Ortho*-Iodoarylboronic Acids for Direct Amide Bond Formation at Room Temperature

By

Raed M. Al-Zoubi

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

Doctor of Philosophy

Department of Chemistry

©Raed M. Al-Zoubi
Spring 2011
Edmonton, Alberta

Permission is hereby granted to the University of Alberta Libraries to reproduce single copies of this thesis and to lend or sell such copies for private, scholarly or scientific research purposes only. Where the thesis is converted to, or otherwise made available in digital form, the University of Alberta will advise potential users of the thesis of these terms.

The author reserves all other publication and other rights in association with the copyright in the thesis and, except as herein before provided, neither the thesis nor any substantial portion thereof may be printed or otherwise reproduced in any material form whatsoever without the author's prior written permission.

Examining Committee

Dr. Dennis G. Hall, Department of Chemistry

Dr. Todd L. Lowary, Department of Chemistry

Dr. Frederick G. West, Department of Chemistry

Dr. Gabriel Hanna, Department of Chemistry

Dr. Kamaljit Kaur, Faculty of Pharmacy and Pharmaceutical Sciences

Dr. J. Michael Chong, Department of Chemistry, University of Waterloo

I dedicate this work in memory of my father

Mohammed A. Al-Zoubi

Abstract

Although the thermal direct formation of amide bonds has been known since 1858, the mechanism of the reaction remains poorly understood and is still a major scientific issue. The direct reaction between amines and carboxylic acids generates a thermodynamically stable ammonium carboxylate salt. In order to generate amide bonds from these salts, harsh reaction conditions with temperatures as high as 250 ^{o}C are required. The majority of the methods in the literature use stoichiometric reagents, which have very poor atom economy and are associated with many limitations such as poor reactivity, low conversions, toxicity, racemizations, and cumbersome purifications.

Recently, boron reagents have provided a prospect for much "greener" alternatives for this long standing problem. The use of catalytic arylboronic acids for direct amide formation offers more environmentally benign reaction conditions. This thesis describes the exceptional reactivity of *ortho*-iodoarylboronic acids as catalysts for mild, green and waste-free direct amide bond formation at ambient temperature. Chapter Two of this thesis discusses my efforts toward the discovery of *ortho*-substituted arylboronic acids, and especially *ortho*-haloarylboronic acids as catalysts for direct amide bond formation at ambient temperature. *Ortho*-iodoarylboronic acid (termed IBA, first generation catalyst) was found to be the best *ortho*-haloarylboronic acid catalyst providing higher yields of the amide product.

Extensive study of the steric and electronic effects on the reactivity of the first generation boronic acid catalyst in order to design a better catalyst for direct amide bond formation is disclosed in Chapter Three. In particular, Chapter Three outlines the development of 5-methoxy-2-iodoarylboronic acid (termed MIBA, second generation catalyst) and 4-iodo-3-furanboronic acid (termed FIBA, third generation catalyst).

Chapter Four will delineate a methodology for regioselective *ortho*-iodination of arylboronic acids. This methodology provided the desired iodoarylboronic acid compounds in only a one step synthesis and directly from cheap and available starting materials.

As a second part of my thesis, Chapter Five will discuss a diversity-oriented synthesis of a 30-member library of thiomarinol analogues via the oxa[4+2] cycloaddition/allylboration methodology developed in the Hall laboratory. This library was designed through a collaboration study between Prof. Hall and Prof. Waldmann in Germany using the protein structure similarity clustering (**PSSC**) computational approach.

Acknowledgements

This PhD project would not have been possible without the support of many people. First, I would like to express my sincere gratitude and appreciation to my supervisor, Dr. Dennis Hall, for his guidance, encouragement, abundant assistance and friendship. My thanks also go to the Department of Chemistry at the University of Alberta for the great and dynamic research environment. I am grateful to my supervisory committee members: Dr. Todd L. Lowary, Dr. Glen R. Loppnow.

I would like to thank my colleagues over the years that I have worked with and that helped to make graduate school an enjoyable adventure. I am particularly thankful to Marlin Penner for all his help improving my English and for proof reading my thesis.

My deepest gratitude is also to the support services here at the University of Alberta. I am thankful to the NMR staff (particularly the Late Glen Bigham and Mark Miskolzie), Wayne Moffat and all the people in the Spectral Services labs, the Mass Spectrometry Lab, the machine shop, the storeroom and the glass shop. My appreciation and thanks are also to my dear friends, Dr. Farooq Al-Shamali and Dr. Sameeh Salameh for their help and friendship.

I am also thankful to the laboratories of Dr. F. G. West, Dr. J. C. Vederas, Dr. J. M. Stryker and Dr. T. Lowary for providing me with chemicals when there was an urgent need for prior.

I am also thankful for all the help of our secretary, Diane Dowhaniuk, who processed various applications and forms for me over the years. The research presented in this thesis would not be possible without the help of funding agencies. I would also like to acknowledge the University of Alberta for a Queen Elizabeth II Scholarship for supporting my research.

I want to thank my Mother, brothers (Eyad, Ahmad and Anas), sisters (Raeda and Dania), father-in-law and mother-in-law for their encouragement, love and never-ending support. I also want to express my love and gratitude to my dear wife Isra'a for her understanding, support and endless love through the duration of my PhD study. Finally and most importantly, all the gratitude and thanks are to Allah Almighty; and may the peace and blessings of Allah be upon his last messenger (Prophet Mohammed) and his family and companions.

List of Abbreviations

Ac	Acetyl
ACS	American Chemical Society
AOP	7-Azabenzotriazol-1-yloxytris(dimethyamino) phosphonium hexafluorophosphate
AMP	Adenosine-5'-monophosphate
APIs	Active Pharmaceutical Ingredients
Ar	Aryl group
ATP	Adenosine-5'-triphosphate
BDDC	Bis[[4-(2,2-dimethyl-1,3-dioxolyl)]-methyl] carbodiimide
BDMP	5-(1*H*-Benzotriazol-1-yloxy)-3,4-dihydro-1-methyl-2H-pyrrolium hexachloroantimonate
BDP	Benzotriazol-1-yl diethylphosphate
BEC	*N*-*tert*-Butyl-*N'*-ethylcarbodiimide
BEMT	2-Bromo-3-ethyl-4-methyl thiazolium tetrafluoro-borate
BEP	2-Bromo-1-ethyl pyridinium tetrafluoroborate
BEPH	2-Bromo-1-ethyl pyridinium hexachloroantimonate
BMC	*N*-*tert*-Butyl-*N'*-methylcarbodiimide
BMP-Cl	*N,N'*-Bismorpholinophosphinic chloride
BMPI	2-Bromo-1-methylpyridinium iodide
BMTB	2-Bromo-3-methyl-4-methyl thiazolium bromide
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BOI	2-(Benzotriazol-1-yl)oxy-1,3-dimethyl imidazolidinium hexafluorophosphate
BOMI	Benzotriazol-1-yloxy-*N,N*-dimethyl-methaniminium

	hexachloroantimonate
BOP	Benzotriazol-1-yloxytris(dimethyl-amino)-phosphonium hexafluorophosphate
BOP-Cl	*N,N'*-Bis(2-oxo-3-oxazolidinyl)-phosphinic chloride
BORSM	Based on recovered starting material
BPMP	1-(1*H*-Benzotriazol-1-yloxy)phenyl-methylene pyrrolidinium hexachloroantimonate
BroP	Bromo tris(dimethylamino phosphonium) hexafluorophosphate
brs	Broad singlet
BTC	Bis(trichloromethyl)carbonate
BTFFH	Bis(tetramethylene)fluoroformamidinium hexafluorophosphate
n-Bu	*n*-Butyl
*t*Bu	*tert*-Butyl
Calcd	Calculated
cat	Catalytic amount
CBMIT	1,1'-Carbonylbis(3-methyl-imidazolium)triflate
Cbz	Carbobenzyloxy
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-Carbonyldiimidazole
CDMT	2-Chloro-4,6-dimethoxy-1,3,5-triazine
CIB	2-Chloro-1,3-dimethylimidazolidinium tetrafluoroborate
CIC	*N*-Cyclohexyl-*N'*-isopropylcarbodiimide
CIP	2-Chloro-1,3-dimethylimidazolidinium hexafluoro-phosphate
CMBI	2-Chloro-1,3-dimethyl 1*H*-benzimidazolium hexafluorophosphate
CMPI	2-Chloro-1-methylpyridinium iodide

DAST	Diethylaminosulfur trifluoride
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
dddd	Doublet of doublets of doublets of doublets
DBDMAP	2,6-Di-*tert*-butyl-4-(dimethylamino)pyridine
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEBP	Diethy2-(3-oxo-2,3-dihydro-1,2-benziso sulfonazol-yl) phosphonate
DEE	Diethylether
DECP	Diethylcyanophosphonate
DEPB	Diethyl phosphorobromidate
DEPBO	*N*-Diethoxyphosphoryl benzoxazolone
DEPBT	3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one
DEPC	Diphenyl phosphorochloridate
DFIH	1,3-Dimethyl-2-fluoro-4,5-dihydro-1*H*-imidazolium hexafluorophosphate
DFT	Electron Functional Theory
DIC	*N,N'*-Diisopropylcarbodiimide
DIEA(DIPEA)	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DOMP	5-(3',4'-Dihydro-4'-oxo-1',2',3'-benzotriazin-3'-yloxy)-3,4-dihydro-1-methyl 2*H* pyrrolium hexachloroantimonate
DOPBO	*N*-(2-Oxo-1,3,2-dioxaphosphorinanyl)-
DOPBT	Benzoxazolone 3-[*O*-(2-oxo-1,3,2-dioxaphosphorin-anyl)-oxy]-1,2,3-benzotriazin-4(3H)-one
DPP-Cl	Diphenylphosphinic chloride

DPPA	Diphenylphosphoryl azide
dq	Doublet of quartet
dr	Diastereomeric ratio
EDC	1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
EDDQ	*N*-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
ee	Enantiomeric excess
EI	Electron Impact
equiv	Equivalents
er	Enantiomeric ratio
ESI	Electrospray Ionization
Et	Ethyl
FDPP	Pentafluorophenyl diphenyl phosphinate
FEB	2-Fluoro-1-ethyl pyridinium tetrafluoroborate
FEPH	2-Fluoro-1-ethyl pyridinium hexachloroantimonate
FIBA	4-iodo-3-furanboronic acid
Fmoc	9-Fluorenylmethyloxycarbonyl
FOMP	5-(Pentafluorophenyloxy)-3,4-dihydro-1-methyl 2H pyrrolium hexachloroantimonate
GCI	Green Chemistry Institute
HATU	*O*-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBTU	*O*-(Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HDTU	*O*-(3,4-Dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMPA	Hexamethylphosphoramide
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	1-Hydroxybenzotriazole
HOSu	*N*-Hydroxysuccinimide

HONB	*N*-Hydroxy-5-norbornene-endo-2,3-dicarboxyimide
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IR	Infrared spectroscopy
MIBA	5-Methoxy-2-iodophenylboronic acid
MPTO	3-Dimethylphosphinothioyl-2(3*H*)-oxazolone
NCA	*N*-Carboxy Anhydride
NDPP	Norborn-5-ene-2,3-dicarboximidodiphenylphosphate
NMP	*N*-Methylpyrrolidinone
OAc	Acetoxy
OBn	Benzeloxy
OEt	Ethoxy
O*i*-Pr	*iso*-Propoxy
O*t*-Bu	*tert*-Butoxy
OMe	Methoxy
Ph	Phenyl
Pr	*n*-Propyl
i-Pr	*iso*-Propyl
PNP	p-Nitrophenol
PFP	Pentafuorophenol
PTF	Benzyltriphenylphosphonium dihydrogen trifluoride
PyAOP	[(7-Azabenzotriazol-1-yl)oxy]tris-(pyrrolidino) phosphonium hexafluorophosphate
PyBOP	Benzotriazol-1-yloxytri(pyrrolidino)-phosphonium hexafluorophosphate
PyBroP	Bromotri(pyrrolidino)phosphonium hexafluorophosphate
PyCloP	Chlorotri(pyrrolidino)phosphonium hexafluorophosphate

q	Quartet
R	Generic alkyl group
rt	Room temperature
t	Triplet
TBTU	*O*-Benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate
TCA	Thiocarbamic acid
TDBTU	2-(3,4-Dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TFFH	Tetramethylfluoroformamidinium hexafluorophosphate
TPP	Triphenylphosphine
TPTU	*O*-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate
TSTU	*O*-(*N*-Succinimidyl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate
UNCA	Urethane *N*-carboxy anhydrides

TABLES OF CONTENTS

CHAPTER ONE

DIRECT AMIDE BOND FORMATION AND PEPTIDE SYNTHESIS [GENERAL BACKGROUND]

1.1 INTRODUCTION 1

1.2 METHODS AND STRATEGIES FOR AMIDE BOND FORMATION 3

1.2.1 NON-BORON REAGENTS FOR DIRECT AMIDE BOND FORMATION 6

1.2.1.1 STOICHIOMETRIC ACTIVATION OF CARBOXYLIC ACIDS 6

1.2.1.1.1 ACYL HALIDE REAGENTS 6

1.2.1.1.2 ANHYDRIDE REAGENTS 10

1.2.1.1.3 ESTER REAGENTS 14

1.2.1.1.4 CARBODIIMIDE REAGENTS 15

1.2.1.1.5 IMIDAZOLIUM REAGENTS 17

1.2.1.1.6 AMMONIUM REAGENTS 19

1.2.1.1.7 PHOSPHOROUS REAGENTS 19

1.2.1.1.8 URONIUM/GUANIDINIUM REAGENTS 21

1.2.1.2 CATALYTIC ACTIVATION OF CARBOXYLIC ACIDS 22

1.2.1.2.1 3 Å OR 4 Å MOLECULAR SIEVES 25

1.2.1.2.2 MULTIVALENT METAL SALTS 26

1.2.1.2.3 ACTIVATED K60 (KIESELGEL 60) SILICA GEL 27

1.2.2 BORON REAGENTS FOR DIRECT AMIDE BOND FORMATION 28

1.2.2.1 STOICHIOMETRIC ACTIVATION OF CARBOXYLIC ACIDS 28

1.2.2.1.1 TRISDIALKYLAMINOBORANE [$B(NR'_2)_3$] 28

1.2.2.1.2 TRIALKYLBORANES [BR_3] & TRIALKOXYBORANES [$B(OR)_3$] 29

1.2.2.1.3 CHLORODIALKOXYBORANES [$ClB(OR')_2$] 29

1.2.2.1.4 BORANE AND CATECHOLBORANE 31

1.2.2.2 CATALYTIC ACTIVATION OF CARBOXYLIC ACIDS 32

1.2.2.2.1 ELECTRON-POOR PHENYLBORONIC ACIDS 32

1.2.2.2.2 BORIC ACID 37

1.2.2.2.3 AMINOPHENYLBORONIC ACIDS 40

1.3 CONCLUSION 45

1.4 Project Objectives 47
1.5 References 47

Chapter two

CATALYTIC AMIDE BOND FORMATION BY *ORTHO*-HALOPHENYLBORONIC ACIDS: FIRST GENERATION CATALYSTS

2.1 Introduction 56
2.2 Results 61
2.2.1 Initial Screening of *Ortho*-Functionalized Phenylboronic acids 61
2.2.2 The Effect of Drying Agents on Catalytic Direct Amide Bond Formation 63
2.2.3 Second Round of Evaluation of Different *Ortho*-Substituted Phenylboronic acids Under Optimized Reaction Conditions 65
2.2.4 The Steric Influence of *Ortho*-Substituted Phenylboronic acid Catalysts on Direct Amide Bond Formation 70
2.2.5 Comparison between our catalytic system (*ortho*-bromo and *ortho*-iodophenylboronic acids) and promising phenylboronic acids found in the literature. 72
2.2.6 Substrate scope of catalytic direct amide bond formation at ambient temperature. 73
2.2.7 Effect of additives on catalytic direct amide bond formation 76
2.3 Organocatalytic Activation of Unsaturated Carboxylic Acids for Diels-Alder Reactions 77
2.4 Synthesis of *Ortho*-Iodophenylboronic acid 81
2.5 Conclusion–First Generation Catalyst System 82
2.6 Experimental 83
2.6.1 General Information 83
2.6.2 Preparation and characterization data for *ortho*-Iodophenylboronic acid **2-24** 84
2.6.3 General Procedure for Organocatalytic Amidations 85

2.6.3.1 AMIDES PREPARATION AND CHARACTERIZATION DATA....86
2.6.3.1.1.1 *N*-BENZYL-2-PHENYL-ACETAMIDE (**TABLE 2-5, ENTRY 1**)....86
2.6.3.1.1.2 *N*-BUTYL-2-PHENYL-ACETAMIDE (**TABLE 2-5, ENTRY 3**) 86
2.6.3.1.1.3 PENT-4-ENOIC ACID ISOBUTYLAMIDE (**TABLE 2-5, ENTRY 4**) 86
2.6.3.1.1.4 HEPTANOIC ACID BENZYLAMIDE (**TABLE 2-5, ENTRY 5**) 86
2.6.3.1.1.5 2-PHENYL-1-PYRROLIDIN-1-YL-ETHANONE (**TABLE 2-5, ENTRY 7**) 87
2.6.3.1.1.6 2-PHENYL-1-PIPERDIN-1-YL-ETHANONE (**TABLE 2-5, ENTRY 8**)....87
2.6.3.1.1.7 *N*-BENZYL-4-IODOBENZAMIDE (**TABLE 2-5, ENTRY 6**)....87
2.6.3.1.1.8 PENT-4-ENOIC ACID (7-ISOPROPYL-1,4α-DIMETHYL-1,2,3,4,4α,9,10,10α-OCTAHYDRO PHENANTHREN-1-YLMETHYL)-AMIDE (**TABLE 2-6, ENTRY 1**)....88
2.6.3.1.1.9 {2-[5-(BENZYLCARBOMOYL-METHOXY)-1H-INDOL-3-YL] ETHYL}-CARBAMIC ACID TERT-BUTYL ESTER (**TABLE 2-6, ENTRY 3**) 88
2.6.3.1.1.10 2-[1-(4-CHLORO-BENZOYL)-5-METHOXY-2-METHYL-1*H*-INDOL-3-YL]-*N*-ISO-BUTYL-ACETAMIDE (**TABLE 2-6, ENTRY 2**)....89
2.6.3.1.1.11 *N*-BENZYL-2-[1-(4-CHLORO-BENZOYL)-5-METHOXY-2-METHYL-1*H*-INDOL-3-YL]-ACETAMIDE (**TABLE 2-6, ENTRY 2**)....89
2.6.3.1.1.12 (*S*)-*N*-BENZYL-2-(4-ISOBUTYL-PHENYL)-PROPIONAMIDE (**TABLE 2-6, ENTRY 6**)....90
2.6.3.1.1.13 (*S,R*)-2-(4-ISOBUTYL-PHENYL)-*N*-(1-PHENYL-ETHYL)-PROPIONAMIDE (**TABLE 2-6, ENTRY 6**)....91
2.6.3.1.1.14 *N*-BENZYL-*N*-METHYL-BUTYRAMIDE 92
2.6.3.2 GENERAL PROCEDURE FOR THE DIELS-ALDER REACTION. 92
2.6.3.2.1 CYLOADDUCT PREPARATION AND CHARACTERIZATION DATA 92
2.6.3.2.1.1 3,4-DIMETHYL-CYCLOHEX-3-ENECARBOXYLIC ACID (**TABLE 2-7, ENTRY 1**) 92
2.6.3.2.1.2 BICYCLO[2.2.1]HEPT-5-ENE-2-CARBOXYLIC ACID (**TABLE 2-7, ENTRY 2**)....93

2.6.3.2.1.3 7-Oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**Table 2-7, entry 3**)....93
2.6.3.2.1.4 1-Bromo-3,4-dimethyl-cyclohex-3-enecarboxylic acid (**Table 2-7, entry 4**)....93
2.6.3.3 Procedure for Competition Reaction Between Carboxylic Acid and Ester Toward Diels-Alder Cycloaddition....94
2.6.3.3.1 3,4-Dimethyl-cyclohex-3-enecarboxylic acid and methyl 3,4-dimethyl cyclohex-3-enecarboxylate (**Equation 2-2 (A)**)....94
2.6.3.4 Procedure for the Sequential One-pot Diels-Alder/Amidation Reaction....94
2.6.3.4.1 3,4-Dimethyl-cyclohex-3-enecarboxylic acid benzyl amide (**Equation 2-2 (B)**)....94
2.7 References....95

Chapter three

A SECOND GENERATION CATALYST SYSTEM FOR DIRECT AMIDE BOND: IMPLICATION OF STERIC AND ELECTRONIC EFFECTS

3.1 Introduction....97
3.2 The Design of an Improved Catalyst for Direct Amide Bond Formation....99
3.2.1 Implication of the Steric Effects on Reactivity of 3-Substituted-2-Iodophenylboronic acids....101
3.2.1.1 Synthesis of 3,5-Dimethyl-2-Iodophenylboronic acid (**3-8**)....104
3.2.1.2 Attempts Toward the Synthesis of 3-Tert-Butyl-2-Iodophenylboronic acid (**3-10**) and 3-Phenyl-2-Iodophenylboronic acid (**3-11**)....104
3.2.2 Implication of the Electronic Effects on the Reactivity Of 2-Iodophenylboronic acids....107

3.2.2.1 Electron-poor *Ortho*-Iodophenylboronic acid 107
3.2.2.1.1 Synthesis of 5-Fluoro-2-Iodophenylboronic acid **3-21** and 3,4,5-Trifluoro-2-Bromophenylboronic acid **3-23** 110
3.2.2.2 Electron-rich *Ortho*-Iodophenylboronic acids 111
3.2.2.2.1 Synthesis of **3-26** and **3-27** 117
3.2.2.2.2 Attempts toward the synthesis of **3-28** and **3-29** 118
3.2.2.2.3 Synthesis of **3-42** to **3-51** 126
3.2.2.2.4 Synthesis of **3-52** 128
3.2.3 Optimization of Reaction Parameters 129
3.2.3.1 Optimization of Reaction Solvent 129
3.2.3.2 Optimization of Amine Stoichiometry 130
3.2.3.3 Optimization of Reaction Concentration 131
3.2.4 Substrate Scope for Catalytic Direct Amide Bond Formation 133
3.2.5 Mechanistic Aspects of the Direct Amidation Catalyzed With *Ortho*-Iodophenylboronic acids 134
3.3 Rational Design of an Improved Catalytic System for the Direct Amide-Bond Formation: Third Generation Catalyst 139
3.3.1 Efficiency of FIBA (**3-75**) In Direct Amide Bond Formation at Ambient Temperature 142
3.4 Recent Quantum Chemical Studies From Tommaso Marcelli 144
3.5 Conclusion 147
3.6 Experimental 148
3.6.1 General Information 148
3.6.1.1 Preparation and Analytical Data of 3,5-Dimethyl-2-Iodophenylboronic acid (**3-10**) 148
3.6.1.2 Preparation and Data Analytical of Tert-Butyl-2-Tert-Butylphenyl carbamate (**3-14**) 148
3.6.1.3 Preparation and Analytical Data of Tert-Butyl-2-Tert-Butyl-4-Iodophenyl Carbamate (**Scheme 3-4, Step 1**) 149
3.6.1.4 Preparation and Analytical Data of Tert-Butyl-2-Tert-Butyl-4-Methylphenyl Carbamate (**3-15**) 150
3.6.1.5 Preparation and Analytical Data of 2-Tert-Butyl-4-Methylaniline (**Scheme 3-4, Step 3**) 150

3.6.1.6 Preparation and Analytical Data of 2-Tert-Butyl-6-Iodo-4-Methylaniline (**Scheme 3-4, Step 45**)....151
3.6.1.7 Preparation and Analytical Data of Tert-Butyl 2-Tert-Butylphenyl carbamate (**3-16**)....151
3.6.1.8 Preparation and Analytical Data of Tert-Butyl 2-Biphenylcarbamate (**3-17**)....152
3.6.1.9 Preparation and Analytical Data of Tert-Butyl 6-Iodo-2-Biphenylcarbamate (**3-18**)....152
3.6.1.10 Preparation and Analytical Data of Tert-Butyl 6-Iodo-2-Biphenylamine (**Scheme 3-5, Step1**)....153
3.6.1.11 Preparation and Analytical Data of 1,2-Diiodo-3-Biphenyl (**3-19**)....154
3.6.1.12 Preparation and Analytical Data of 2-Bromo-3,4,5-Trifluorophenyl boronic Acid (**3-21**)....154
3.6.1.13 Preparation and Analytical Data of 5-Fluoro-2-Iodophenylboronic Acid (**3-22**)....155
3.6.1.14 Preparation and Analytical Data of 2-Iodo-4,5-Dimethoxyphenyl boronic Acid (**3-26**)....156
3.6.1.15 Preparation and Analytical Data of 2-Iodo-4,5-Dimethoxy-3-Methylphenylboronic Acid (**3-27**)....156
3.6.1.16 Preparation and Analytical Data of 2-Iodo-6-Methoxyphenylboronic Acid (**3-32**)....157
3.6.1.17 Preparation and Analytical Data of 6-Iodo-2,3-Dimethoxyphenyl boronic Acid (**3-33**)....157
3.6.1.18 Preparation and Analytical Data of 1,2-Dimethoxybenzene (**3-34**)....158
3.6.1.19 Preparation and Analytical Data of 1,2-Diiodo-4,5-Dimethoxybenzene (**3-35**)....158
3.6.1.20 Preparation and Analytical Data of 1,2-Dimethoxy-3-Methylbenzene (**3-36**)....159
3.6.1.21 Preparation and Analytical Data of 1,2-Diiodo-4,5-Dimethoxy-3-Methylbenzene (**3-37**)....159

3.6.1.22 Preparation and Analytical Data of Tert-Butyl 2-Methoxyphenylcarbamate (**3-38**) 160
3.6.1.23 Preparation and Analytical Data of Tert-Butyl 2-Iodo-6-Methoxyphenylcarbamate (**Scheme 3-12, Step 1**) 160
3.6.1.24 Preparation and Analytical Data of 2-Iodo-6-Methoxybenzenamine (**3-39**) 161
3.6.1.25 Preparation and Analytical Data of 1,2-Diiodo-3-Methoxybenzene (**3-30**) 161
3.6.1.26 Preparation and Analytical Data of 1,2-Diiodo-3,4-Dimethoxybenzene (**3-40**) 162
3.6.1.27 Preparation and Analytical Data of 8-Iodonaphthalen-1-Yl-1-Boronic Acid (**3-52**) 162
3.6.1.28 Preparation and Analytical Data of 1,8-Diiodonaphthalene (**3-56**) 163
3.6.1.29 Preparation and Analytical Data of Diisopropyl 8-Iodonaphthalen-1-Yl-1-Boronate (**3-57**) 163
3.6.1.30 Preparation and Analytical Data of 4-Iodofuran-3-Yl-3-Boronic Acid (**3-75**) 164
3.6.1.31 Preparation and Analytical Data of 3,4-Diiodofuran (3-76) 165
3.6.1.32 Preparation and Analytical Data of (*E*)-2,3-Diiodobut-2-Ene-1,4-Diol (**3-80**) 165
3.6.2 General Procedure for direct Amidation 165
3.6.2.1 Amide Preparation and Characterization Data 166
3.6.2.1.1 Tert-Butyl 7-Oxo-7-(Pyrrolidin-1-Yl)Heptyl carbamate 3-65 (**Table 3-8, Entry 6**) 166
3.6.2.1.2 Tert-Butyl 3-(Hexylcarbamoyl)Propylcarbamate 3-66 (**Table 3-8, Entry 7**) 166
3.6.2.1.3 Tert-Butyl 2-(Hexylcarbamoyl)Ethylcarbamate 3-67 (**Table 3-8, Entry 8**) 167
3.6.2.1.4 (*S*)-2-(4-Isobutylphenyl)-1-(Pyrrolidin-1-Yl)Propan-1-One 3-69 (**Table 3-8, Entry 10**) 167
3.6.2.1.5 (2*S*)-2-(4-Isobutylphenyl)-*N*-((*R*)-1-Phenylethyl) Propanamide 3-70 (**Table 3-8, Entry 11**) 168

3.6.2.1.6 TERT-BUTYL 3-(BENZYLCARBAMOYL)PROPYLCARBAMATE (**SCHEME 3-8, EQ.1**) 168
3.6.2.1.7 TERT-BUTYL 2-(BENZYLCARBAMOYL)ETHYLCARBAMATE (**SCHEME 3-8, EQ.2**) 168
3.7 REFERENCES 169

CHAPTER FOUR

MILD SILVER(I)-MEDIATED REGIOSELECTIVE IODINATION AND BROMINATION OF PHENYLBORONIC ACIDS AND THEIR APPLICATION TOWARD CHEMOSELECTIVE SUZUKI-MIYAURA COUPLING

4.1 INTRODUCTION 171
4.2 RESULTS 179
4.2.1 INITIAL SCREENING FOR A MILD AND CONVENIENT IODINATION METHOD OF PHENYLBORONIC ACIDS 179
4.3 CHEMOSELECTIVE SUZUKI-MIYAURA COUPLING FOR *ORTHO*-IODOPHENYLBORONIC ACIDS 184
4.4 CONCLUSION 185
4.5 EXPERIMENTAL 186
4.4.1 GENERAL INFORMATION 186
4.4.2 GENERAL PROCEDURE FOR HALOGENATION OF PHENYLBORONIC ACIDS 187
4.4.2.1 SYNTHESIS OF 2-IODO-5-METHOXYPHENYLBORONIC ACID (**4-9**) 187
4.4.2.2 SYNTHESIS OF 2-IODO-5-METHOXYPHENYLBORONIC ACID (**4-10**) 187
4.4.2.3 SYNTHESIS OF 4-FLUORO-2-IODO-5-METHOXYPHENYLBORONIC ACID (**4-11**) 188
4.4.2.4 SYNTHESIS OF 3-FLUORO-2-IODO-5-METHOXYPHENYLBORONIC ACID (**4-12**) 188
4.4.2.5 SYNTHESIS OF 5-AMINO-2-IODOPHENYLBORONIC ACID (**4-13**) 188
4.4.2.6 SYNTHESIS OF 5-(BENZYLOXY)-2-IODOPHENYLBORONIC ACID (**4-14**) 189
4.4.2.7 SYNTHESIS OF 2-IODO-3,5-DIMETHOXYPHENYLBORONIC ACID (**4-15**) 189

4.4.2.8 Synthesis of 5-(dimethylamino)-2-iodophenylboronic acid (**4-16**) 189
4.4.2.9 Synthesis of 5-(dimethylamino)-2-bromophenylboronic acid (**4-17**) 190
4.4.2.10 Synthesis of 5-acetamido-2-iodophenylboronic acid (**4-18**) 190
4.4.2.11 Synthesis of 5-acetamido-2-bromophenylboronic acid (**4-19**) 190
4.4.2.12 Synthesis of 2-iodo-3,4,5-trimethoxyphenylboronic acid (**4-20**) 191
4.4.2.13 Synthesis of 2-bromo-3,4,5-trimethoxyphenylboronic acid (**4-21**) 191
4.4.2.14 Synthesis of 5-amino-2,6-dibromophenylboronic acid (**4-22**) 191
4.4.2.15 Synthesis of 4-(methoxycarbonyl)-2-iodo-5-methoxyphenylboronic acid (**4-23**) 191
4.4.2.16 Synthesis of 3,5-dimethyl-2-iodophenylboronic acid (**4-24**) 192
4.4.3 General Procedure for Chemoselective Suzuki-Miyaura Cross-Couplings 192
4.4.3.1 Synthesis of 2-(4-methoxyphenyl)-4-methoxyiodobenzene (**4-29**) 192
4.4.3.2 Synthesis of 2-(4-nitrophenyl)-4-methoxyiodobenzene (**4-30**) 193
4.4.3.3 Synthesis of 2-(4-biphenyl)-4-methoxyiodobenzene (**4-31**) 193
4.4.3.4 Synthesis of 2-(3,5-bis(trifluoromethyl)phenyl)-4-methoxyiodobenzene (**4-32**) 193
4.4.3.5 Synthesis of tert-butyl 2-tert-butyl-4-(2-iodo-5-methoxyphenyl) phenylcarbamate (**4-33**) 194
4.4.4 General Procedure for One-pot Chemoselective Double Suzuki-Miyaura Couplings 194
4.4.4.1 Synthesis of 1-(4-tolyl)-2-(3-tert-butyl-4-tert-butylcarbamate)-4-methoxybenzene (**4-34**) 195
4.4.4.2 Synthesis of 1-(2,4-difluorophenyl)-2-(4-nitrophenyl)-4-methoxy benzene (**4-35**) 195

4.4.4.3 Synthesis of 2-(4-methoxyphenyl)-4-methoxy-1-phenylbenzene (**4-36**) 196
4.4.4.4 Synthesis of 1-(4-tolyl)-2-(4-biphenyl)-4-methoxybenzene (**4-37**) 196
4.6 References 196

Chapter Five

DIVERSITY-ORIENTED SYNTHESIS OF A 30 MEMBER LIBRARY OF THIOMARINAL ANALOGS VIA OXA[4+2]CYCLOADDITION/ALLYLBORATION METHODOLOGY

5.1 Introduction 200
5.2 Library of thiomarinol analogues through diversity-oriented synthesis 207
5.2.1 Synthesis of α-hydroxyalkyl dihydropyran analogues (**5-55**) 207
5.2.2 Acetal reduction of α-hydroxyalkyl dihydropyrans 212
5.2.3 Dihydroxylation of α-hydroxyalkyl 2H–pyran derivatives into "thiomarinol analogues" 216
5.3 Conclusion 221
5.4 Experimental Details and Characterization Data 221
5.4.1 General Information 221
5.4.1.1 Preparation of (*Z*)-1-ethoxyoct-1-ene (**5-2c**) 222
5.4.1.2 Preparation of (*E*)-3-boronoacrolein (**5-6**) 223
5.4.2 Synthesis of (*E*)-3-boronoacrolein pinacol ester (**5-1**) 223
5.4.2.1 Synthesis of 2-((2*S*,4*S*)-2-ethoxy-3,4-dihydro-2*H*-pyran-4-yl)-4,4,5,5-tetramethyl -1,3,2-dioxaborolane (**5-5a**) 224
5.4.2.2 Synthesis of 2-((2*S*,3*R*,4*R*)-2-ethoxy-3,4-dihydro-3-methyl-2*H*-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**5-5b**) 224
5.4.2.3 Synthesis of 2-((2*S*,3*R*,4*R*)-2-ethoxy-3,4-dihydro-3-methyl-2*H*-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**5-5c**) 225

5.4.3 General Procedure for Cr (III)-Catalyzed Three-Component [4+2] Cycloaddition/ Allylboration Using Ethyl Vinyl Ether 225
5.4.3.1 Synthesis of (*R*)-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)(phenyl)methanol (**5-7**) 226
5.4.3.2 Synthesis of 4-((*R*)-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)(hydroxy) methyl) benzonitrile (**5-8**) 226
5.4.3.3 Synthesis of (*R*)-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)(p-tolyl)methanol (**5-9**) 227
5.4.3.4 Synthesis of (*R*)-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)(4-nitrophenyl) methanol (**5-10**) 227
5.4.3.5 Synthesis of (*R*)-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)(4-(trifluoro methyl) phenyl)methanol (**5-11**) 228
5.4.3.6 Synthesis of (*R*)-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)(4-fluorophenyl) methanol (**5-12**) 228
5.4.3.7 Synthesis of (*R*)-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)(o-tolyl)methanol (**5-13**) 229
5.4.3.8 Synthesis of (*R*)-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)(2-fluorophenyl) methanol (**5-14**) 229
5.4.3.9 Synthesis of (*R*)-1-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)-3-phenyl propan-1-ol (**5-15**) 230
5.4.3.10 Synthesis of (*R*)-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl) (naphthalen-2-yl) methanol (**5-16**) 230
5.4.3.11 Synthesis of (*R*)-(2-bromo-5-fluorophenyl)((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)methanol (**5-17**) 231
5.4.3.12 Synthesis of (*R*)-1-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl) pentan-1-ol (**5-18**) 231
5.4.3.13 Synthesis of (*R*)-cyclohexyl((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)methanol (**5-19**) 231
5.4.3.14 Synthesis of *N*-(4-((*R*)-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)(hydroxy)methyl) phenyl)acetamide (**5-20**) 232
5.4.3.15 Synthesis of 1-(3-((*R*)-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)(hydroxy)methyl)-1*H*-indol-1-yl)ethanone (**5-21**) 232

5.4.3.16 Synthesis of (*R*)-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)(1-methyl-1*H*-pyrrol-2-yl)methanol (**5-22**) 233
5.4.3.17 Synthesis of (*S*)-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)(furan-2-yl)methanol (**5-23**) 233
5.4.3.18 Synthesis of (*S*)-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)(thiophen-2-yl)methanol (**5-24**) 234
5.4.4 General Procedure for Cr (III)-Catalyzed Three-Component [4+2] Cycloaddition/ Allylboration Using Ethyl 1-Propenyl Ether 234
5.4.4.1 Synthesis of (*R*)-((2*R*,5*R*,6*S*)-6-ethoxy-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)(phenyl) methanol (**5-25**) 235
5.4.4.2 Synthesis of 4-((*R*)-((2*R*,5*R*,6*S*)-6-ethoxy-5,6-dihydro-5-methyl-2*H*-pyran-2-yl) (hydroxy)methyl)benzonitrile (**5-26**) 235
5.4.4.3 Synthesis of (*R*)-1-((2*R*,5*R*,6*S*)-6-ethoxy-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)-3-phenylpropan-1-ol (**5-27**) 236
5.4.4.4 Synthesis of (*R*)-((2*R*,6*S*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)(1-methyl-1*H*-pyrrol-2-yl)methanol (**5-28**) 236
5.4.4.5 Synthesis of (*R*)-((2*R*,5*R*,6*S*)-6-ethoxy-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)(o-tolyl) methanol (**5-29**) 237
5.4.4.6 Synthesis of (*R*)-((2*R*,5*R*,6*S*)-6-ethoxy-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)(4-(trifluoromethyl)phenyl) methanol (**5-30**) 237
5.4.4.7 Synthesis of (*R*)-((2*R*,5*R*,6*S*)-6-ethoxy-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)(naphthalen-2-yl)methanol (**5-31**) 238
5.4.4.8 Synthesis of (*R*)-((2*R*,5*R*,6*S*)-6-ethoxy-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)(4-fluorophenyl)methanol (**5-32**) 238
5.4.4.9 Synthesis of (*R*)-((2*R*,5*R*,6*S*)-6-ethoxy-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)(2-fluorophenyl)methanol (**5-33**) 239
5.4.4.10 Synthesis of (*R*)-(2-bromo-5-fluorophenyl)((2*R*,5*R*,6*S*)-6-ethoxy-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)methanol (**5-34**) 239
5.4.4.11 Synthesis of (*R*)-1-((2*R*,5*R*,6*S*)-6-ethoxy-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)pentan-1-ol (**5-35**) 240

5.4.4.12 Synthesis of (*R*)-cyclohexyl((2*R*,5*R*,6*S*)-6-ethoxy-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)methanol (**5-36**) 240
5.4.4.13 Synthesis of (*S*)-((2*R*,5*R*,6*S*)-6-ethoxy-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)(furan-2-yl)methanol (**5-37**) 241
5.4.4.14 Synthesis of (*R*,2*E*)-1-((2*R*,5*R*,6*S*)-6-ethoxy-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)-3-phenyl prop-2-en-1-ol (**5-38**) 241
5.4.4.15 Synthesis of (*R*,2*E*)-1-((2*R*,5*R*,6*S*)-6-ethoxy-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)hex-2-en-1-ol (**5-39**) 242
5.4.4.16 Synthesis of (1*R*)-1-((2*R*,5*R*,6*S*)-6-ethoxy-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)-3-(5-methyl furan-2-yl)butan-1-ol (**5-40**) 242
5.4.5 General Procedure for Cr (III)-Catalyzed Three-Component [4+2] Cycloaddition/ Allylboration Using (*Z*)-1-Ethoxyoct-1-ene 243
5.4.5.1 Synthesis of (*R*)-((2*R*,5*R*,6*S*)-6-ethoxy-5-hexyl-5,6-dihydro-2*H*-pyran-2-yl) (phenyl) methanol (**5-41**) 243
5.4.5.2 Synthesis of 4-((*R*)-((2*R*,5*R*,6*S*)-6-ethoxy-5-hexyl-5,6-dihydro-2*H*-pyran-2-yl) (hydroxy)methyl)benzonitrile (**5-42**) 244
5.4.5.3 Synthesis of (*R*)-1-((2*R*,5*R*,6*S*)-6-ethoxy-5-hexyl-5,6-dihydro-2*H*-pyran-2-yl)-3-phenylpropan-1-ol (**5-43**) 244
5.4.5.4 Synthesis of (*R*)-((2*R*,5*R*,6*S*)-6-ethoxy-5-hexyl-5,6-dihydro-2*H*-pyran-2-yl)(4-(trifluoromethyl)phenyl)methanol (**5-44**) 245
5.4.5.5 Synthesis of (*R*)-((2*R*,5*R*,6*S*)-6-ethoxy-5-hexyl-5,6-dihydro-2*H*-pyran-2-yl)(4-fluorophenyl)methanol (**5-45**) 245
5.4.5.6 Synthesis of (*R*)-1-((2*R*,5*R*,6*S*)-6-ethoxy-5-hexyl-5,6-dihydro-2*H*-pyran-2-yl) pentan-1-ol (**5-46**) 246
5.4.5.7 Synthesis of (*R*)-cyclohexyl((2*R*,5*R*,6*S*)-6-ethoxy-5-hexyl-5,6-dihydro-2*H*-pyran-2-yl)methanol (**5-47**) 246
5.4.5.8 Synthesis of (*S*)-((2R,5R,6S)-6-ethoxy-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)(furan-2-yl)methanol (**5-48**) 247
5.4.5.9 Synthesis of (*R*,2*E*)-1-((2*R*,5*R*,6*S*)-6-ethoxy-5-hexyl-5,6-dihydro-2*H*-pyran-2-yl)hex-2-en-1-ol (**5-49**) 247

5.4.6 Synthesis of (*Z*,1*R*,2*R*)-6-ethoxy-1-phenylhex-3-ene-1,2-diol (**5-51**) 248
5.4.7 General Procedure for the synthesis of bicyclic acetal products 248
5.4.7.1 Synthesis of (1*R*,5*R*,7*R*)-7-phenyl-6,8-dioxa-bicyclo[3.2.1]oct-2-ene (**5-52**) 249
5.4.7.2 Synthesis of 4-((1*R*,5*R*,7*R*)-6,8-dioxa-bicyclo[3.2.1]oct-2-en-7-yl)benzo nitrile (**5-53**) 249
5.4.7.3 Synthesis of *N*-(4-((1*R*,5*R*,7*R*)-6,8-dioxa-bicyclo[3.2.1]oct-2-en-7-yl)phenyl)acetamide (**5-54**) 249
5.4.7.4 Synthesis of (1*R*,4*R*,5*R*,7*R*)-7-(2-fluorophenyl)-4-methyl-6,8-dioxa-bicyclo[3.2.1]oct-2-ene (**5-55**) 250
5.4.7.5 Synthesis of (1*R*,4*R*,5*R*,7*R*)-7-(4-fluorophenyl)-4-hexyl-6,8-dioxa-bicyclo[3.2.1]oct-2-ene (**5-56**) 250
5.4.7.6 Synthesis of 4-((1*R*,4*R*,5*R*,7*R*)-4-hexyl-6,8-dioxa-bicyclo[3.2.1]oct-2-en-7-yl)benzonitrile (**5-57**) 250
5.4.7.7 Synthesis of (1*R*,4*R*,5*R*,7*R*)-7-(4-(trifluoromethyl)phenyl)-4-hexyl-6,8-dioxa-bicyclo[3.2.1]oct-2-ene (**5-58**) 251
5.4.8 General Procedure for Acetal Reduction 251
5.4.8.1 Synthesis of (*R*)-((*R*)-5,6-dihydro-2*H*-pyran-2-yl)(phenyl)methanol (**5-59**) 252
5.4.8.2 Synthesis of 4-((*R)*-((*R*)-5,6-dihydro-2*H*-pyran-2-yl)(hydroxy)methyl) benzonitrile (**5-60**) 252
5.4.8.3 Synthesis of (*R*)-((*R*)-5,6-dihydro-2*H*-pyran-2-yl)(p-tolyl)methanol (**5-61**) 252
5.4.8.4 Synthesis of (*R*)-((*R*)-5,6-dihydro-2*H*-pyran-2-yl)(4-nitrophenyl) methanol (**5-62**) 253
5.4.8.5 Synthesis of (*R*)-(4-(trifluoromethyl) phenyl) ((*R*)-5,6-dihydro-2*H*-pyran-2-yl) methanol (**5-63**) 253
5.4.8.6 Synthesis of (*R*)-(4-fluorophenyl)((*R*)-5,6-dihydro-2*H*-pyran-2-yl) methanol (**5-64**) 253
5.4.8.7 Synthesis of (*R*)-((*R*)-5,6-dihydro-2*H*-pyran-2-yl)(o-tolyl)methanol (**5-65**) 254
5.4.8.8 Synthesis of (*R*)-(2-fluorophenyl)((*R*)-5,6-dihydro-2*H*-pyran-2-yl)methanol (**5-66**) 254

5.4.8.9 Synthesis of (*R*)-1-((*R*)-5,6-dihydro-2*H*-pyran-2-yl)-3-phenylpropan-1-ol (**5-67**) 255
5.4.8.10 Synthesis of (*R*)-((*R*)-5,6-dihydro-2*H*-pyran-2-yl)(naphthalen-2-yl)methanol (**5-68**) 255
5.4.8.11 Synthesis of (*R*)-(2-bromo-5-fluorophenyl)((*R*)-5,6-dihydro-2*H*-pyran-2-yl) methanol (**5-69**) 255
5.4.8.12 Synthesis of (*R*)-1-((*R*)-5,6-dihydro-2*H*-pyran-2-yl)pentan-1-ol (**5-70**) 256
5.4.8.13 Synthesis of (*R*)-cyclohexyl((*R*)-5,6-dihydro-2*H*-pyran-2-yl)methanol (**5-71**) 256
5.4.8.14 Synthesis of (*R*)-((2*R*,5*R*)-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)(phenyl) methanol (**5-77**) 256
5.4.8.15 Synthesis of 4-((*R*)-((2*R*,5*R*)-5,6-dihydro-5-methyl-2*H*-pyran-2-yl) (hydroxy)methyl)benzonitrile (**5-78**) 257
5.4.8.16 Synthesis of (*R*)-1-((2*R*,5*R*)-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)-3-phenyl propan-1-ol (**5-79**) 257
5.4.8.17 Synthesis of (*R*)-((2*R*,5*R*)-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)(o-tolyl)methanol (**5-81**) 258
5.4.8.18 Synthesis of (*R*)-(4-(trifluoromethyl)phenyl)((2*R*,5*R*)-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)methanol (**5-82**) 258
5.4.8.19 Synthesis of (*R*)-(4-fluorophenyl)((2*R*,5*R*)-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)methanol (**5-83**) 258
5.4.8.20 Synthesis of (*R*)-(2-fluorophenyl)((2*R*,5*R*)-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)methanol (**5-84**) 259
5.4.8.21 Synthesis of (*R*)-(2-bromo-5-fluorophenyl)((2*R*,5*R*)-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)methanol (**5-86**) 259
5.4.8.22 Synthesis of (*R*)-1-((2*R*,5*R*)-5,6-dihydro-5-methyl-2*H*-pyran-2-yl)pentan-1-ol (**5-87**) 260
5.4.8.23 Synthesis of (*R*)-cyclohexyl((2R,5R)-5,6-dihydro-5-methyl-2*H*-pyran-2-yl) methanol (**5-88**) 260
5.4.8.24 Synthesis of (*R*)-((2*R*,5*R*)-5-hexyl-5,6-dihydro-2*H*-pyran-2-yl)(phenyl) methanol (**5-93**) 261

5.4.8.25 Synthesis of 4-((*R*)-((2*R*,5*R*)-5-hexyl-5,6-dihydro-2*H*-pyran-2-yl)(hydroxy) methyl) benzonitrile (**5-94**) 261
5.4.8.26 Synthesis of (*R*)-1-((2*R*,5*R*)-5-hexyl-5,6-dihydro-2*H*-pyran-2-yl)-3-phenylpropan-1-ol (**5-95**) 262
5.4.8.27 Synthesis of (*R*)-(4-(trifluoromethyl)phenyl)((2*R*,5*R*)-5-hexyl-5,6-dihydro-2*H*-pyran-2-yl)methanol (**5-96**) 262
5.4.8.28 Synthesis of (*R*)-(4-fluorophenyl)((2*R*,5*R*)-5-hexyl-5,6-dihydro-2*H*-pyran-2-yl) methanol (**5-97**) 262
5.4.8.29 Synthesis of (*R*)-1-((2*R*,5*R*)-5-hexyl-5,6-dihydro-2*H*-pyran-2-yl)pentan-1-ol (**5-98**) 263
5.4.8.30 Synthesis of (*R*)-cyclohexyl((2*R*,5*R*)-5-hexyl-5,6-dihydro-2*H*-pyran-2-yl) methanol (**5-99**) 263
5.4.9 General Procedure for Dihydroxylation 264
5.4.9.1 Synthesis of (2*S*,3*R*,4*R*)-tetrahydro-2-((*R*)-hydroxy(phenyl)methyl)-2*H*-pyran-3,4-diol (**5-102**) 264
5.4.9.2 Synthesis of (2*S*,3*R*,4*R*)-tetrahydro-2-((*R*)-hydroxy(p-cyanophenyl) methyl)-2*H*-pyran-3,4-diol (5-**103**) 264
5.4.9.3 Synthesis of (2*S*,3*R*,4*R*)-tetrahydro-2-((*R*)-hydroxy(p-tolyl)methyl)-2*H*-pyran-3,4-diol (**5-104**) 265
5.4.9.4 Synthesis of (2*S*,3*R*,4*R*)-tetrahydro-2-((*R*)-hydroxy(4-nitrophenyl) methyl)-2*H*-pyran-3,4-diol (**5-105**) 265
5.4.9.5 Synthesis of (2*S*,3*R*,4*R*)-2-((*R)*-(4-(trifluoromethyl) phenyl)(hydroxy)methyl)-tetrahydro-2*H*-pyran-3,4-diol (**5-106**) 266
5.4.9.6 Synthesis of (2*S*,3*R*,4*R*)-2-((*R*)-(4-fluorophenyl) (hydroxy) methyl)-tetrahydro-2*H*-pyran-3,4-diol (**5-107**) 266
5.4.9.7 Synthesis of (2*S*,3*R*,4*R*)-tetrahydro-2-((R)-hydroxy(o-tolyl)methyl)-2*H*-pyran-3,4-diol (**5-108**) 267
5.4.9.8 Synthesis of (2*S*,3*R*,4*R*)-2-((*R*)-(2-fluorophenyl)(hydroxy) methyl)-tetrahydro-2*H*-pyran-3,4-diol (**5-109**) 267
5.4.9.9 Synthesis of (2*S*,3*R*,4*R*)-tetrahydro-2-((*R*)-1-hydroxy-3-phenylpropyl)-2*H*-pyran-3,4-diol (**5-110**) 268

5.4.9.10 SYNTHESIS OF (2*S*,3*R*,4*R*)-TETRAHYDRO-2-((*R*)-HYDROXY (NAPHTHALEN-2- YL)METHYL)-2*H*-PYRAN-3,4-DIOL (**5-111**)..... 268
5.4.9.11 SYNTHESIS OF (2*S*,3*R*,4*R*)-2-((*R*)-(2-BROMO-5-FLUOROPHENYL) (HYDROXY METHYL) TETRAHYDRO-2*H*-PYRAN-3,4-DIOL (**5-112**)..... 268
5.4.9.12 SYNTHESIS OF (2*S*,3*R*,4*R*)-TETRAHYDRO-2-((*R*)-1-HYDROXYPENTYL)-2*H*-PYRAN-3,4-DIOL (**5-113**)..... 269
5.4.9.13 SYNTHESIS OF (2*S*,3*R*,4*R*)-2-((*R*)-CYCLOHEXYL(HYDROXY) METHYL)-TETRAHYDRO-2*H*-PYRAN-3,4-DIOL (**5-114**)..... 269
5.4.9.14 SYNTHESIS OF (2*S*,3*R*,4*R*,5*S*)-TETRAHYDRO-2-((*R*)-HYDROXY(PHENYL)METHYL)-5-METHYL-2*H*-PYRAN-3,4-DIOL (**5-115**)..... 270
5.4.9.15 SYNTHESIS OF (2*S*,3*R*,4*R*,5*S*)-2-((*R*)-(4-CYANOPHENYL) (HYDROXY)METHYL)-TETRAHYDRO-5-METHYL-2*H*-PYRAN-3,4-DIOL (**5-116**)..... 270
5.4.9.16 SYNTHESIS OF (2*S*,3*R*,4*R*,5*S*)-TETRAHYDRO-2-((*R*)-1-HYDROXY-3-PHENYL PROPYL)-5-METHYL-2*H*-PYRAN-3,4-DIOL (**5-117**)..... 271
5.4.9.17 SYNTHESIS OF (2*S*,3*R*,4*R*,5*S*)-TETRAHYDRO-2-((*R*)-HYDROXY(O-TOLYL)METHYL)-5-METHYL-2*H*-PYRAN-3,4-DIOL (**5-118**)..... 271
5.4.9.18 SYNTHESIS OF (2*S*,3*R*,4*R*,5*S*)-2-((*R*)-(4-(TRIFLUOROMETHYL) PHENYL) (HYDROXY) METHYL)-TETRAHYDRO-5-METHYL-2*H*-PYRAN-3,4-DIOL (**5-119**)..... 272
5.4.9.19 SYNTHESIS OF (2*S*,3*R*,4*R*,5*S*)-2-((*R*)-(4-FLUOROPHENYL) (HYDROXY)METHYL)-TETRAHYDRO -5-METHYL-2*H*-PYRAN-3,4-DIOL (**5-120**)..... 272
5.4.9.20 SYNTHESIS OF (2*S*,3*R*,4*R*,5*S*)-2-((*R*)-(2-FLUOROPHENYL)(HYDROXY)METHYL)-TETRAHYDRO-5-METHYL-2*H*-PYRAN-3,4-DIOL (**5-121**)..... 273
5.4.9.21 SYNTHESIS OF (2*S*,3*R*,4*R*,5*S*)-2-((*R*)-(2-BROMO-5-FLUOROPHENYL)(HYDROXYL) METHYL)-TETRAHYDRO-5-METHYL-2*H*-PYRAN-3,4-DIOL (**5-122**)..... 273
5.4.9.22 SYNTHESIS OF (2*S*,3*R*,4*R*,5*S*)-TETRAHYDRO-2-((*R*)-1-HYDROXY PENTYL)-5-METHYL-2*H*-PYRAN-3,4-DIOL (**5-123**)..... 274

5.4.9.23 Synthesis of (2*S*,3*R*,4*R*,5*S*)-2-((*R*)-cyclohexyl (hydroxy)methyl)-tetrahydro-5-methyl-2*H*-pyran-3,4-diol (**5-124**) 274
5.4.9.24 Synthesis of (2*S*,3*R*,4*R*,5*S*)-5-hexyl-tetrahydro-2-((*R*)-hydroxy(phenyl) methyl)-2*H*-pyran-3,4-diol (**5-125**) 274
5.4.9.25 Synthesis of (2*S*,3*R*,4*R*,5*S*)-2-((*R*)-(4-cyanophenyl) (hydroxy)methyl)-5-hexyl-tetrahydro-2*H*-pyran-3,4-diol (**5-126**) 275
5.4.9.26 Synthesis of (2*S*,3*R*,4*R*,5*S*)-5-hexyl-tetrahydro-2-((*R*)-1-hydroxy-3-phenyl propyl)-2*H*-pyran-3,4-diol (**5-127**) 275
5.4.9.27 Synthesis of (2*S*,3*R*,4*R*,5*S*)-2-((*R*)-(4-(trifluoromethyl) phenyl) (hydroxy)methyl) -5-hexyl-tetrahydro-2*H*-pyran-3,4-diol (**5-128**) 276
5.4.9.28 Synthesis of (2*S*,3*R*,4*R*,5*S*)-2-((*R*)-(4-fluorophenyl) (hydroxy)methyl)-5-hexyl-tetrahydro-2*H*-pyran-3,4-diol (**5-129**) 276
5.4.9.29 Synthesis of (2*S*,3*R*,4*R*,5*S*)-5-hexyl-tetrahydro-2-((*R*)-1-hydroxypentyl)-2*H*-pyran-3,4-diol (**5-130**) 277
5.4.9.30 Synthesis of (2*S*,3*R*,4*R*,5*S*)-2-((*R*)-cyclohexyl(hydroxy) methyl)-5-hexyl-tetrahydro-2*H*-pyran-3,4-diol (**5-131**) 277
5.5 References 277

Chapter Six

CONCLUSIONS AND FUTURE DIRECTIONS

Part I: *Ortho*-Halophenylboronic acids for Direct Amide Bond Formation 280
Part II: Diversity-Oriented Synthesis of a 30 Member Library of Thiomarinol Analogues via oxa[4+2] Cycloaddition/ Allylboration Methodology 281

APPENDIX I

X-RAY CRYSTALLOGRAPHY REPORTS

1. X-RAY CRYSTALLOGRAPHY REPORT OF 2-IODOPHENYLBORONIC ACID 283
2. X-RAY CRYSTALLOGRAPHY REPORT OF 2-BROMO-3,4,5-TRIFLUORO PHENYLBORONIC ACID 284
3. X-RAY CRYSTALLOGRAPHY REPORT OF 5-FLUORO-2-IODOPHENYLBORONIC ACID (85%) / 4-FLUORO-2-IODOPHENYLBORONIC ACID (15%) 285
4. X-RAY CRYSTALLOGRAPHY REPORT OF 1,3,5-TRIS(5-FLUORO-2-IODOPHENYL) BOROXINE 286
5. X-RAY CRYSTALLOGRAPHY REPORT OF 2-IODO-4,5-DIMETHOXY-3-METHYLPHENYLBORONIC ACID 287
6. X-RAY CRYSTALLOGRAPHY REPORT OF 2-IODO-6-METHOXYPHENYLBORONIC ACID 288
7. X-RAY CRYSTALLOGRAPHY REPORT OF 6-IODO-2,3-DIMETHOXY PHENYLBORONIC ACID 289
8. X-RAY CRYSTALLOGRAPHY REPORT OF 1,2-DIIODO-3-METHOXYBENZENE 290
9. X-RAY CRYSTALLOGRAPHY REPORT OF 2-IODO-3,4,5-TRIMETHOXYPHENYL BORONIC ACID 291
10. X-RAY CRYSTALLOGRAPHY REPORT OF 2-IODO-3,5-DIMETHOXYPHENYLBORONIC ACID 292
11. X-RAY CRYSTALLOGRAPHY REPORT OF *t*-BUTYL (2-T-BUTYLPHENYL) CARBAMATE 293
12. X-RAY CRYSTALLOGRAPHY REPORT OF 1-TERT-BUTYL-2,3-DIIODO-5-METHYLBENZENE 294
13. X-RAY CRYSTALLOGRAPHY REPORT OF TERT-BUTYL BIPHENYL-2-YLCARBAMATE 295
14. X-RAY CRYSTALLOGRAPHY REPORT OF 2,6-ANHYDRO-5-DEOXY-1-C-(4-NITROPHENYL) HEXITOL 296

APPENDIX II

^{1}H & ^{13}C NMR SPECTRA OF IMPORTANT COMPOUNDS

1. ^{1}H- ^{13}C & ^{11}B-NMR OF 2-IODOPHENYLBORONIC ACID (**IBA**) IN DMSO-d_6 AND CD_2Cl_2 AT 27 °C 297
2. ^{1}H- & ^{13}C -NMR OF 5-METHOXY-2-IODOPHENYLBORONIC ACID (**MIBA**) IN DMSO-d_6 AT 27 °C 299
3. ^{1}H- & ^{13}C -NMR OF 4-IODO-3-FURANBORONIC ACID (**FIBA**) IN DMSO-d_6 AT 27 °C 300
4. ^{1}H- & ^{13}C -NMR OF 4-FLUORO-2-IODO-5-METHOXYPHENYLBORONIC ACID IN DMSO-d_6 AT 27 °C. 301
5. ^{1}H- & ^{13}C -NMR OF 3-FLUORO-2-IODO-5-METHOXYPHENYLBORONIC ACID IN DMSO-d_6 AT 27 °C. 302
6. ^{1}H- & ^{13}C -NMR OF 5-AMINO-2-IODOPHENYLBORONIC ACID IN DMSO-d_6 AT 27 °C. 303
7. ^{1}H- & ^{13}C -NMR OF 4-FLUORO-5-(BENZYLOXY)-2-IODOPHENYLBORONIC ACID IN DMSO-d_6 304
8. ^{1}H- & ^{13}C -NMR OF 2-IODO-3,5-DIMETHOXYPHENYLBORONIC ACID IN DMSO-d_6 AT 27 °C. 305
9. ^{1}H-& ^{13}C -NMR OF 2-IODO-3,4,5-TRIMETHOXYPHENYLBORONIC ACID IN DMSO-d_6 AT 27 °C. 306
10. ^{1}H- & ^{13}C -NMR OF 5-(DIMETHYLAMINO)-2-IODOPHENYLBORONIC ACID IN DMSO-d_6 AT 27 °C. 307
11. ^{1}H- & ^{13}C -NMR OF 4-(METHOXYCARBONYL)-2-IODO-5-METHOXYPHENYL BORONIC ACID IN DMSO-d_6 AT 27 °C. 308
12. ^{1}H- & ^{13}C -NMR OF 3,5-DIMETHYL-2-IODOPHENYLBORONIC ACID IN DMSO-d_6 AT 27 °C. 309
13. ^{1}H- & ^{13}C -NMR OF TITLE COMPOUND (**5-81**) IN CD_3OD AT 27 °C. 310
14. ^{1}H- & ^{13}C -NMR OF TITLE COMPOUND (**5-69**) IN CD_3OD AT 27 °C. 311
15. ^{1}H- & ^{13}C -NMR OF TITLE COMPOUND (**5-55**) IN CD_3OD AT 27 °C. 312
16. ^{1}H- & ^{13}C -NMR OF TITLE COMPOUND (**5-58**) IN CD_3OD AT 27 °C. 313
17. ^{1}H- & ^{13}C -NMR OF TITLE COMPOUND (**5-103**) IN CD_3OD AT 27 °C. 314

18. ^{1}H- & ^{13}C -NMR OF TITLE COMPOUND (**5-107**) IN CD_3OD AT 27 °C. 315
19. ^{1}H- & ^{13}C -NMR OF TITLE COMPOUND (**5-129**) IN CD_3OD AT 27 °C. 316

LIST OF FIGURES

FIGURE 1-1: AMIDE BONDS, (A) RESONANCE FORMS OF AMIDE BOND, (B) TRANS AND CIS AMIDE BONDS. 2

FIGURE 1-2: STRUCTURES OF PENICILLIN (A MODIFIED TRIPEPTIDE) AND ASPARTAME (DIPEPTIDE). 3

FIGURE 1-3: COMMON CHLORINATING REAGENTS FOR THE AMIDE BOND FORMATION. 7

FIGURE 1-4: STRUCTURES OF OTHER CHLORINATING AGENTS FOR THE DIRECT AMIDE BOND FORMATION. 8

FIGURE 1-5: COMMON FLUORINATING AGENTS FOR AMIDE BOND FORMATION. 10

FIGURE 1-6: STRUCTURES OF FLUORINATING AND BROMINATING AGENTS. 10

FIGURE 1-7: COMMON REAGENTS FOR MAKING MIXED CARBONIC ANHYDRIDE. 12

FIGURE 1-8: STRUCTURES OF SOME *N*-CABYOXY ANHYDRIDES. 13

FIGURE 1-9: COMMON ORGANOPHOSPHORUS REAGENTS FOR AMIDE-BOND FORMATION. 14

FIGURE 1-10: THE ADDITIONAL CHELATION EFFECT OF HOAt WITH AMINE. 15

FIGURE 1-11: COMMONLY USED CARBODIIMIDE REAGENTS EMPLOYED IN AMIDE BOND FORMATIONS. 16

FIGURE 1-12: IMIDAZOLIUM REAGENTS FOR AMIDE BOND FORMATION 18

FIGURE 1-13: AMMONIUM REAGENTS: MUKAIYAMA-TYPE ALTERNATIVES WITH IMPROVED SOLUBILITY. 19

FIGURE 1-14: PHOSPHONIUM REAGENTS EMPLOYED IN AMIDE BOND FORMATION 20

FIGURE 1-15: SOME URONIUM REAGENTS EMPLOYED IN AMIDE-BOND FORMATION. 22

FIGURE 1-16: H-BONDING ASSISTED NUCLEOPHILIC ATTACK OF AMINE IN DIRECT AMIDE FORMATION 25

FIGURE 1-17: STRUCTURES OF 3,4,5-TRIFLUOROPHENYLBORONIC ACID (**1-20**) (YAMAMOTO CATALYST) AND 3,5-TRIFLUOROMETHYLPHENYLBORONIC ACID (**1-21**) 33

FIGURE 1-18: STRUCTURES OF 3,5-BIS(PERFLUORODECYL)PHENYLBORONIC ACID **1-24** AND 4-(PERFLUORODECYL)PHENYLBORONIC ACID (**1-25**). 35

FIGURE 1-19: STRUCTURE OF *N*-ALKYL-4-BORONOPYRIDINIUM IODIDE (**1-26**) AND X-RAY STRUCTURE OF DODECAMER $\mathbf{[1\text{-}26]_{12}}$. 36

FIGURE 1-20: STRUCTURES OF WANG AND ISHIHARA SOLID-SUPPORTED CATALYSTS. 37
FIGURE 1-21: BORIC ACID CATALYZED AMIDE BOND FORMATION OF SOME ACTIVE PHARMACEUTICAL INGREDIENTS (APIS). 38
FIGURE 1-22: YIELD VERSUS TIME/H FOR CATALYSED AND THERMAL DIRECT AMIDE BOND FORMATION BETWEEN BENZOIC ACID AND BENZYLAMINE IN REFLUXING FLUOROBENZENE. 43
FIGURE 1-23: PROPOSED TRANSITION STATE FOR THE ENANTIOSELECTIVITY IN AMIDATION USING CATALYST (**1-39**) 45
FIGURE 2-1: COMPLEXATION OF HEXOPYRANOSIDES USING BENZOBOROXOLE (**2-14**). 60
FIGURE 2-2: PKA MEASUREMENT GRAPH OF *ORTHO*-IODOPHENYLBORONIC ACID (**2-24**) USING ^{11}B-NMR TITRATION. 68
FIGURE 3-1:POSSIBLE POSITIONS IN THE AROMATIC RING FOR CATALYST OPTIMIZATION. 99
FIGURE 3-2: EXPLOITING THE RING SUBSTITUTION AT CARBONS 3-4-5 FOR CATALYST OPTIMIZATION. 101
FIGURE 3-3: PROMISING CATALYSTS WITH LARGER GROUPS AT CARBON 3 AND THEIR DIIODIDE STARTING MATERIALS. 103
FIGURE 3-4: A PLAUSIBLE COMBINATION BETWEEN YAMAMOTO'S CATALYST (**3-20**) AND OUR CATALYST SYSTEM. 107
FIGURE 3-5: THE EFFECT OF ELECTRON DONATING GROUPS ON THE REACTIVITY OF *ORTHO*-IODOPHENYLBORONIC ACID SYSTEM. 137
FIGURE 3-6: PROPOSED IODO-FURANBORONIC ACID (**3-75**). 140
FIGURE 3-7: LOWEST-ENERGY WATER ELIMINATION FOR THE FORMATION OF CIS-AMIDE CATALYZED BY PHENYLBORONIC ACID. 145
FIGURE 3-8: MOST ENERGETICALLY ACCESSIBLE TRANSITION STATES FOR THE USE OF BORONIC ACIDS (**3-1**) AND (**3-83**). 146
FIGURE 4-1: OXYGENATED ORGANOBORON COMPOUNDS. 172
FIGURE 4-2: STRUCTURE OF BORTEZOMIB (VELCADE®, PS-341) (**4-1**) AND AN-2690 (5-FLUORO-1,3-DIHYDRO-1-HYDROXY-2,1-BENZOXA BOROLE) (**4-2**). 173
FIGURE 4-3: ORTEP VIEW OF 2-IODO-3,5-DIMETHOXYPHENYLBORONIC ACID (**4-15**) AND 2-IODO-3,4,5-TRIMETHOXYPHENYLBORONIC ACID (**4-20**). THERMAL GAUSSIAN ELLIPSOIDS AT 20% PROBABILITY LEVEL. 183

FIGURE 5-1: STRUCTURES OF MUPIROCIN (PSEUDOMONIC ACID A) AND MONIC ACID. 201
FIGURE 5-2:MECHANISM OF ACTION FOR $tRNA^{Ile}$ SYNTHETASE, A CLASS I AMINOACYL tRNA SYNTHETASE. 202
FIGURE 5-3: MAP OF MAIN MOLECULAR INTERACTIONS IN THE MUPIROIN-$tRNA^{Ile}$ COMPLEX. 203
FIGURE 5-4: STRUCTURES OF SELECTED MEMBERS OF THE THIOMARINOL FAMILY. 204
FIGURE 5-5: QUALITATIVE PHARMACOPHORE MODEL FOR MUPIROCIN. 205
FIGURE 5-6: AUTOMATED PROTEIN STRUCTURE SIMILARITY CLUSTERING (PSSC).. 206
FIGURE 5-7: ALDEHYDES **5-3(A-U)** AND ENOL ETHERS **5-2(A-C)** AS DIVERSITY RESULT OF ONE OF THE REAGENTS. 210
FIGURE 5-8: STRUCTURES OF THIOMARINOL ANALOGUES..... 218
FIGURE 5-9: nOe RESULT OF ONE OF THE α-HYDROXYALKYL DIHYDROPYRAN PRODUCTS. 219

LIST OF TABLES

TABLE 1-1: ROUNDTABLE LEADING PHARMACEUTICAL COMPANIES VOTING FOR FINDING BETTER REAGENTS FOR PRIORITY AREAS IN RESEARCH.....5

TABLE 1-2: THE EFFECT OF RELATIVE RATIO OF AMINE : ACID IN DIRECT AMIDATION UNDER MICROWAVE CONDITIONS. 25

TABLE 1-3: THE EFFECT OF ADDITIVES ON AMIDATION UNDER AZEOTROPIC-REFLUX CONDITIONS. 28

TABLE 2-1: SELECTED BOND LENGTH (Å) FOR WHITING CATALYSTS (**2-9**, **2-10**) AND (**2-13**). 59

TABLE 2-2: EFFECT OF DRYING AGENTS ON DIRECT AMIDE BOND FORMATION USING CATALYST (**2-19**) 64

TABLE 2-3: LIST OF TESTED ARYLBRORONIC ACIDS UNDER OPTIMIZED REACTION CONDITIONS. 65

TABLE 2-4: SELECTED BOND LENGTHS (Å) AND ANGLES (DEG) FOR *ORTHO*-IODOPHENYLBORONIC ACID (**2-24**) 69

TABLE 2-5: DIRECT AMIDATIONS BETWEEN CARBOXYLIC ACIDS AND AMINES CATALYZED BY BORONIC ACIDS (**2-21**) AND (**2-24**) AT ROOM TEMPERATURE 73

TABLE 2-6: DIRECT AMIDATIONS BETWEEN HIGHLY FUNCTIONALIZED CARBOXYLIC ACIDS AND AMINES CATALYZED BY BORONIC ACIDS (**2-21**) AND (**2-24**) AT ROOM TEMPERATURE 74

TABLE 2-7: EFFECT OF ADDITIVES ON CATALYTIC DIRECT AMIDE BOND FORMATION 77

TABLE 2-8: DIELS–ALDER CYCLOADDITIONS OF FREE α,β-UNSATURATED CARBOXYLIC ACIDS CATALYZED BY BORONIC ACIDS (**2-21**) AND (**2-24**).....79

TABLE 3-1: SELECTED BOND DISTANCES AND ANGLES FOR CATALYSTS (**3-1**, **3-22**) AND (**3-23**).....110

TABLE 3-2: SELECTED BOND DISTANCES AND ANGLES FOR CATALYSTS (**3-1**) AND (**3-27**). 114

TABLE 3-3: SELECTED BOND DISTANCES AND ANGLES FOR CATALYSTS (**3-32**) AND (**3-33**). 116

TABLE 3-4: SELECTED BOND DISTANCES AND ANGLES FOR CATALYSTS (**3-1**, **3-42**) AND (**3-43**)..... 123
TABLE 3-5: OPTIMIZATION OF REACTION SOLVENT. 130
TABLE 3-6: OPTIMIZATION OF AMINE STOICHIOMETRY. 131
TABLE 3-7: OPTIMIZATION OF REACTION CONCENTRATION. 132
TABLE 3-8: SUBSTRATE SCOPE IN THE SECOND-GENERATION CATALYTIC DIRECT AMIDE BOND FORMATION OF CARBOXYLIC ACIDS UNDER OPTIMIZED CONDITIONS. 134
TABLE 4-1: EFFECT OF DIFFERENT IODINATING AGENTS IN THE DIRECT *ORTHO*-IODINATION OF 3-METHOXYPHENYLBORONIC ACID 180
TABLE 5-1: SYNTHESIS OF α-HYDROXYALKYL PYRANS FROM (*E*)-3-BORONOACROLEIN PINACOL ESTER (**5-1**), ENOL ETHER (**5-2(A-C)**) AND ALDEHYDE (**5-3(A-U)**)..... 209
TABLE 5-2: ACETAL REDUCTION OF α-HYDROXYALKYL DIHYDROPYRANS USING $BF_3{\cdot}Et_2O/Et_3SiH$..... 214
TABLE 5-3: DIHYDROXYLATION OF α-HYDROXYALKYL 2H-PYRANS USING OsO_4/NMO CONDITIONS. 216
TABLE 5-4: SELECTED BOND LENGTHS (Å) AND ANGLES (DEG) FOR (2*S*,3*R*,4*R*) TETRAHYDRO-2-((*R*)-HYDROXY(4-NITROPHENYL) METHYL)-2H-PYRAN-3,4-DIOL (**5-105**). 220

LIST OF SCHEMES

SCHEME 1-1: ESTER BOND VERSUS AMIDE BOND FORMATION. 4

SCHEME 1-2: AMIDE BOND FORMATION BY REACTION BETWEEN CARBOXYLIC ACID AND AMINE 5

SCHEME 1-3: MECHANISM FOR ACID CHLORIDE FORMATION USING THIONYL CHLORIDE OR OXALYL CHLORIDE. 7

SCHEME 1-4: ACYL CHLORIDE FORMATION USING CYANURIC CHLORIDE. 8

SCHEME 1-5: ACID CHLORIDE FORMATION USING TPP AND CCl_4 9

SCHEME 1-6: SYMMETRICAL ANHYDRIDE FORMATION USING DCC. 11

SCHEME 1-7: TWO STEP COUPLING PROCEDURE USING PIVALIC ANHYDRIDE (**1-4**). 12

SCHEME 1-8: *N*-CARBOXY ANHYDRIDE (NCA) FORMATION 13

SCHEME 1-9: COMMONLY USED ALCOHOLS FOR THE FORMATION OF ACTIVE ESTERS IN AMIDE BOND FORMATION. 15

SCHEME 1-10: USE OF ACTIVATOR HOBT TO MINIMIZE THE FORMATION OF THE UNREACTIVE *N*-ACYLUREA 17

SCHEME 1-11: AMIDE BOND FORMATION USING CDI REAGENT 17

SCHEME 1-12: AMIDE BOND FORMATION USING BOP REAGENT. 20

SCHEME 1-13: PROPOSED OVERALL MECHANISM FOR THERMAL AMIDE FORMATION. 24

SCHEME 1-14: PROPOSED MECHANISM FOR DIRECT AMIDE BOND FORMATION FROM MIXING CARBOXYLIC ACIDS WITH TRISDIALKYLAMINOBORANES. 29

SCHEME 1-15: DIRECT AMIDE BOND FORMATION THROUGH ACYLOXYDIALKYL-BORANE. 30

SCHEME 1-16: (A) LIBERATION OF ALCOHOL; (B) FORMATION OF UNREACTIVE AMMONIUM CARBOXYLATE SALT. 30

SCHEME 1-17: FORMATION OF AN AMINODIALKYLOXYBORANE SPECIES. 31

SCHEME 1-18: GANEM'S AMIDE BOND FORMATION USING CATECHOLBORANE. 31

SCHEME 1-19: WANG'S SOLID-SUPPORTED CATECHOLBORANE SOLID-PHASE FOR DIRECT AMIDE BOND FORMATION. 32

SCHEME 1-20: PROPOSED CYCLE FOR BORONIC ACID CATALYZED DIRECT AMIDE BOND FORMATION. 33

Scheme 1-21: Proposed catalytic cycle for the direct amide bond formation with boric acid. 38
Scheme 1-22: Proposed catalytic cycle for direct amide bond formation using 4,5,6,7-tetrachlorobenzo[d][1,3,2]dioxaborol-2-ol (**1-31**). 39
Scheme 1-23: General direct amide bond formation and structure of boron catalysts. 40
Scheme 1-24: Whiting's bifunctional catalysts for direct amide bond formation 42
Scheme 1-25: Direct amide bond formation with chiral bifunctional aminoboronic acid under azeotropic fluorobenzene conditions. 44
Scheme 2-1: Yamamoto's electron-poor phenylboronic acid catalysts for direct amidation. 57
Scheme 2-2: Whiting's bifunctional catalysts for direct amide bond formation. 58
Scheme 2-3: Screening of benzoboroxole (**2-14**) and other *ortho*-substituted phenylboronic acids (**2-15**–**2-19**) in toluene at 25 °C for amide bond formation. 61
Scheme 2-4: Screening of benzoboroxole (**2-14**) and other *ortho*-substituted phenylboronic acids (**2-15**–**2-19**) in DCM at 40 °C for amide bond formation 62
Scheme 2-5: Deleterious effect of water on direct amide bond formation catalyzed by phenylboronic acids. 63
Scheme 2-6: Other active *ortho*-substituted phenylboronic acids under optimized conditions. 66
Scheme 2-7: *Ortho*-Halophenylboronic acids as catalysts in direct amide bond formation under the optimized reaction conditions at 25 °C 67
Scheme 2-8: Comparison between *ortho*-iodo and *ortho*-bromophenylboronic acids (**2-24**) and (**2-21**) in a direct amidation reaction under optimized conditions 68

SCHEME 2-9: THE INFLUENCE OF STERIC EFFECTS OF *ORTHO*-SUBSTITUTED PHENYLBORONIC ACID CATALYSTS ON AMIDE BOND FORMATION REACTION 70

SCHEME 2-10: THE EFFECT OF *ORTHO*-DIHALOPHENYLBORONIC ACID CATALYSTS ON DIRECT AMIDE BOND FORMATION 71

SCHEME 2-11: COMPARISON IN PRODUCT YIELD BETWEEN *ORTHO*-IODO AND PARA-IODOPHENYLBORONIC ACIDS (**2-24**) AND (**2-32**) RESPECTIVELY IN DIRECT AMIDATION REACTION UNDER OPTIMIZED CONDITIONS 71

SCHEME 2-12: COMPARISON IN PRODUCT YIELDS BETWEEN THE LITERATURE PHENYLBORONIC ACIDS IN DIRECT AMIDE BOND FORMATION UNDER OUR OPTIMIZED CONDITIONS 72

SCHEME 2-13: POSTULATED MECHANISMS FOR DIRECT AMIDE BOND FORMATION WITH CATALYSTS **2-21** AND **2-24** 76

SCHEME 2-14: ORGANOCATALYTIC ACTIVATION OF α,β-UNSATURATED CARBOXYLIC ACIDS 78

SCHEME 2-15: DIELS-ALDER CYCLOADDITION REACTIONS OF ACRYLIC ACID WITH CYCLOPENTADIENE 79

SCHEME 2-16: THE PROPOSED CATALYTIC CYCLE FOR THE BORONIC ACID CATALYZED [4+2] CYCLOADDITIONS OF A,B-UNSATURATED CARBOXYLIC ACIDS 80

SCHEME 2-17: POSSIBLE METHODS FOR THE SYNTHESIS OF *ORTHO*-IODOPHENYLBORONIC ACID. 82

SCHEME 3-1: POSTULATED MECHANISM FOR BORONIC ACID CATALYZED AMIDATIONS. 100

SCHEME 3-2: COMPARISON IN PRODUCT YIELD BETWEEN *ORTHO*-IODOPHENYLBORONIC ACIDS (**3-1**) AND (**3-8**) IN A DIRECT AMIDATION REACTION BETWEEN PHENYLACETIC ACID AND BENZYLAMINE UNDER OPTIMIZED CONDITIONS 102

SCHEME 3-3: COMPARISON IN PRODUCT YIELD BETWEEN *ORTHO*-IODOPHENYLBORONIC ACIDS (**3-1**) AND (**3-8**) IN A DIRECT AMIDATION REACTION BETWEEN PHENYLACETIC ACID AND PYRROLIDINE UNDER OPTIMIZED CONDITIONS 103

SCHEME 3-4: ATTEMPTS TOWARD THE SYNTHESIS OF 3-TERT-BUTYL-2-IODOPHENYLBORONIC ACID (**3-10**). 105

SCHEME 3-5: ATTEMPTS TOWARD THE SYNTHESIS OF 3-PHENYL-2-IODOPHENYLBORONIC ACID (**3-12**). 106

SCHEME 3-6: COMPARISON IN PRODUCT YIELD BETWEEN ELECTRON-POOR *ORTHO*-HALOARYL BORONIC ACIDS (**3-21**, **3-22**, **3-23**) AND NEUTRAL *ORTHO*-HALOPHENYLBORONIC ACID (**3-1**, **3-2**) IN A DIRECT AMIDATION REACTION BETWEEN PHENYLACETIC ACID AND BENZYLAMINE UNDER OPTIMIZED CONDITIONS. 108

SCHEME 3-7: COMPARISON IN PRODUCT YIELD BETWEEN ELECTRON RICH *ORTHO*-IODOARYL BORONIC ACIDS (**3-26**, **3-27**) AND NEUTRAL ONES (**3-1**, **3-8**) IN A DIRECT AMIDATION REACTION BETWEEN PHENYLACETIC ACID AND BENZYLAMINE UNDER OPTIMIZED CONDITIONS. 112

SCHEME 3-8: COMPARISON IN PRODUCT YIELD BETWEEN ELECTRON RICH *ORTHO*-IODOARYL BORONIC ACIDS (3-26, 3-27) AND NEUTRAL ONES (**3-1**, **3-8**) IN A DIRECT AMIDATION REACTION BETWEEN PHENYLACETIC ACID AND PYRROLIDINE UNDER OPTIMIZED CONDITIONS 113

SCHEME 3-9: POSSIBLE WAYS TO ACCESS BORONIC ACID (**3-28**) AND (**3-29**). 115

SCHEME 3-10: EXAMINING THE CATALYTIC REACTIVITY OF ELECTRON RICH *ORTHO*-IODOARYL BORONIC ACIDS (**3-32**) AND (**3-33**) IN A DIRECT AMIDATION REACTION BETWEEN PHENYLACETIC ACID AND PYRROLIDINE UNDER OPTIMIZED CONDITIONS 116

SCHEME 3-11: SYNTHESIS OF 4,5-DIMETHOXY-2-IODOPHENYLBORONIC ACID (**3-26**). 117

SCHEME 3-12: SYNTHESIS OF 2-IODO-4,5-DIMETHOXY-3-METHYLPHENYLBORONIC ACID (**3-27**)..... 118

SCHEME 3-13: SYNTHESIS OF 2-IODO-6-METHOXYPHENYLBORONIC ACID (**3-32**)..... 119

SCHEME 3-14: SYNTHESIS OF 2-IODO-5,6-DIMETHOXYPHENYLBORONIC ACID (**3-33**). 119

SCHEME 3-15: DIRECT AND REGIOSELECTIVE *ORTHO*-IODINATION OF PHENYLBORONIC ACIDS..... 120

SCHEME 3-16: COMPARISON IN AMIDE PRODUCT YIELD BETWEEN ELECTRON RICH *ORTHO*-IODOPHENYLBORONIC ACIDS (**3-42**) TO (**3-45**) IN A DIRECT AMIDATION REACTION BETWEEN PHENYLACETIC ACID AND PYRROLIDINE UNDER OPTIMIZED CONDITIONS..... 122

SCHEME 3-17: COMPARISON IN AMIDE PRODUCT YIELD BETWEEN ELECTRON RICH *ORTHO*- IODOPHENYLBORONIC ACIDS (**3-46**) TO (**3-48**) IN A DIRECT

AMIDATION REACTION BETWEEN PHENYLACETIC ACID AND PYRROLIDINE UNDER OPTIMIZED CONDITIONS..... 124

SCHEME 3-18: COMPARISON IN AMIDE PRODUCT YIELD BETWEEN *ORTHO*-IODOPHENYLBORONIC ACID DERIVATIVES (**3-49**) TO (**3-51**) IN A DIRECT AMIDATION REACTION BETWEEN PHENYLACETIC ACID AND PYRROLIDINE UNDER OPTIMIZED CONDITIONS..... 125

SCHEME 3-19: ATTEMPTS TOWARD ELECTROPHILIC IODINATION OF PHENYLBORONIC ACID. 127

SCHEME 3-20: SYNTHESIS OF 8-IODONAPHTHALENEBORONIC ACID (**3-52**). 129

SCHEME 3-21: CONTROL EXPERIMENT WITH PHENYLBORONIC ACID AND 4-IODOANISOLE ON CATALYTIC AMIDE BOND FORMATION REACTION. 135

SCHEME 3-22: THE EFFECT OF BORON REPLACEMENT ON CATALYTIC DIRECT AMIDATION REACTION UNDER THE OPTIMIZED CONDITIONS. 136

SCHEME 3-23: PUTATIVE B-TO-I-TO-N ACYL TRANSFER MECHANISM..... 137

SCHEME 3-24: THE PROPOSED EFFECT OF THE 3-METHYL GROUP ON ENHANCING THE CATALYTIC REACTIVITY. 137

SCHEME 3-25: PROPOSED MECHANISTIC CYCLE FOR THE CATALYTIC DIRECT AMIDE BOND FORMATION USING *ORTHO*-IODOPHENYLBORONIC ACID CATALYST SYSTEM. 138

SCHEME 3-26: RETROSYNTHETIC ANALYSIS FOR 4-IODO-3-FURANBORONIC ACID (**3-75**). 140

SCHEME 3-27: SYNTHESIS OF 4-IODO-3-FURANBORONIC ACID (FIBA, **3-75**). 141

SCHEME 3-28: EXAMINING THE CATALYTIC REACTIVITY OF 4-IODO-3-FURANBORONIC ACID (FIBA, **3-75**) ON DIRECT AMIDE BOND FORMATION. 141

SCHEME 3-29: COMPARISON IN PRODUCT YIELD BETWEEN CATALYSTS (**3-75**, **3-44**) AND (**3-1**) IN DIRECT AMIDATION REACTIONS UNDER OPTIMIZED CONDITIONS. 143

SCHEME 3-30: COMPARISON IN PRODUCT YIELD BETWEEN CATALYSTS (**3-75**), (**3-44**) AND (**3-1**) IN A DIRECT AMIDATION REACTION BETWEEN IBUPROFEN AND PYRROLIDINE UNDER OPTIMIZED CONDITIONS. 144

SCHEME 3-31: SUBSTRATES AND CATALYSTS USED FOR THE CALCULATIONS. 144

SCHEME 3-32: LOWEST-ENERGY INTERMEDIATES CALCULATED FOR AMIDATION REACTIONS CATALYZED BY BORONIC ACID. 146

SCHEME 4-1: THE CONCEPT OF ELECTROPHILIC (LUMO-LOWERING) ACTIVATION OF UNSATURATED CARBOXYLIC ACIDS USING BORONIC ACID CATALYSIS..... 174
SCHEME 4-2: ELECTROPHILIC *IPSO*-HALOGENATION OF PHENYLBORONIC ACIDS. 175
SCHEME 4-3: PALLADIUM MEDIATED *IPSO*-FLUORINATION OF PHENYLBORONIC ACIDS..... 175
SCHEME 4-4: SILVER (I) TRIFLATE MEDIATED *IPSO*-FLUORINATION OF PHENYLBORONIC ACIDS. 176
SCHEME 4-5: METAL-FREE ELECTROPHILIC *IPSO*-FLUORINATIONS OF TRIFLUOROBORATES AND BORONIC ACIDS. 176
SCHEME 4-6: *IPSO*-NITRATION OF PHENYLBORONIC ACIDS USING TMSCL/NITRATE SALTS. 177
SCHEME 4-7: PROPOSED MECHANISM FOR *IPSO*-NITRATION OF PHENYLBORONIC ACIDS USING TMSCl/NITRATE SALTS. 177
SCHEME 4-8: *IPSO*-AMIDATION OF PHENYLBORONIC ACIDS USING XeF_2/NITRILES..... 178
SCHEME 4-9: PROPOSED MECHANISM FOR *IPSO*-AMIDATION OF PHENYLBORONIC ACIDS USING XeF_2/NITRILES. 178
SCHEME 4-10: DIRECT *ORTHO*-IODINATION AND BROMINATION OF PHENYLBORONIC ACIDS..... 182
SCHEME 4-11: THE PROPOSED MECHANISM FOR DIRECT *ORTHO*-IODINATION OF PHENYLBORONIC ACID. 184
SCHEME 4-12: CHEMOSELECTIVE SUZUKI-MIYAURA COUPLING FOR *ORTHO*-IODOPHENYLBORONIC ACIDS. 184
SCHEME 4-13: ONE-POT CHEMOSELECTIVE DOUBLE SUZUKI-MIYAURA COUPLING OF 3-METHOXYPHENYLBORONIC ACID. 185
SCHEME 5-1: THREE-COMPONENT HETERO [4+2] CYCLOADDITION/ALLYLBORATION REACTION APPROACH TO THIOMARINOL ANALOGUES..... 207
SCHEME 5-2: PREPARATION OF (*E*)-3-BORONOACROLEIN PINACOL ESTER (**5-1**)..... 208
SCHEME 5-3: STEREOSELECTIVITY OF TANDEM THREE-COMPONENT OXA[4+2] CYCLOADDITION/ ALLYLBORATION REACTION..... 211
SCHEME 5-4: THE EFFECT OF ACID/Et_3SiH CONDITIONS ON ACETAL REDUCTION OF α-HYDROXYALKYL DIHYDROPYRANS. 213
SCHEME 5-5: OBSERVED STEREOCHEMISTRY UPON DIHYDROXYLATION OF α-HYDROXYALKYL 2H-PYRANS. 220

LIST OF EQUATIONS

EQUATION 1-1: EQUILIBRIUM BETWEEN URONIUM AND GUANIDINIUM SPECIES..... 21

EQUATION 1-2: THE CATALYTIC ACTIVITY OF $FeCl_3.6H_2O$ ON AMIDATION REACTION UNDER AZEOTROPIC-REFLUX CONDITIONS.....27

EQUATION 1-3: THE CATALYTIC ACTIVITY OF K60 ON AMIDATION REACTIONS UNDER AZEOTROPIC-REFLUX CONDITIONS. 27

EQUATION 1-4: BORONIC ACID (**1-67**) CATALYZED POLYAMIDATION BETWEEN ADIPIC ACID AND HEXANEDIAMINE.....34

EQUATION 1-5: PHENYLBORONIC ACID CATALYZED *N*-ACYLCARBAMATE FORMATION BETWEEN 4-PHENYLBUTYRIC ACID AND UREA.....35

EQUATION 2-1: DIRECT AMIDE BOND FORMATION USING CATALYST (**2-19**) AND 4 Å MOLECULAR SIEVES AT 25 °C.....64

EQUATION 2-2: (A) CHEMOSELECTIVE DIELS-ALDER CYCLOADDITION BETWEEN AN α,β-UNSATURATED CARBOXYLIC ACID AND AN ESTER USING CATALYST (**2-24**) AT AMBIENT TEMPERATURE. (B) ONE-POT DIELS-ALDER/AMIDATION USING CATALYST (**2-21**) AT AMBIENT TEMPERATURE. 81

EQUATION 2-3: SYNTHESIS OF ORTHO-IODOPHENYLBORONIC ACID (**2-24**) BY ELECTROPHILIC BORATE TRAPPING WITH ARYLMETAL. 82

EQUATION 3-1: DIRECT AMIDATION CATALYZED BY 2-IODOPHENYLBORONIC ACID (**3-1**)..... 98

EQUATION 3-2: SELECTIVE METALATION REACTION FOR THE SYNTHESIS OF 3,5-DIMETHYL-2-IODOPHENYLBORONIC ACID (**3-8**).....102

EQUATION 3-3: DIRECT METALATION REACTION FOR THE SYNTHESIS OF 3,5-DIMETHYL-2-IODOPHENYLBORONIC ACID (**3-8**).....104

EQUATION 3-4: SYNTHESIS OF 3,4,5-TRIFLUORO-2-BROMOPHENYLBORONIC ACID (**3-23**).....111

EQUATION 3-5: SYNTHESIS OF 5-FLUORO-2-IODOPHENYLBORONIC ACID (**3-21**). 111

EQUATION 3-6: ELECTROPHILIC IODINATION OF MIDA BORONATE (**3-53**). 127

EQUATION 5-1: PREPARATION OF (*Z*)-1-ETHOXYOCT-1-ENE..... 208

EQUATION 5-2: ACETAL REDUCTION OF ONE OF THE α-HYDROXYALKYL DIHYDROPYRAN DERIVATIVES USING $TiCl_4/Et_3SiH$. 212

EQUATION 5-3: ACETAL REDUCTIVE CLEAVAGE OF GLYCOSIDES USING $BF_3{\cdot}Et_2O$/TFA/Et_3SiH CONDITIONS. 212

EQUATION 5-4: ACETAL REDUCTIVE CLEAVAGE USING $BF_3{\cdot}Et_2O/Et_3SiH$ CONDITIONS 213

Direct Amide Bond Formation and Peptide Synthesis [General Background]

Amide bonds are crucial to every form of life. Without them, peptides and proteins would not form. Twenty different amino acids are joined together by amide bonds to form peptides and are the basic building blocks for proteins. Amide bonds do not form only between amino acids; they can form between different amine and carboxylic acid functional groups and are found in more than 25% of the known pharmaceutical drugs and many active compounds.[1]

In this introductory chapter, a delineated background about the importance of the amide bond and the challenge of forming this bond directly from carboxylic acids and amines is presented, and the objectives of this PhD project are outlined. The first section focuses on using non-boron reagents for direct amide bond formation, stoichiometric in the use of coupling reagents or catalytic in the use of multimetal salts and additives. In the second section, the use of boron reagents for direct amide bond formation, currently the most attractive approach for the activation of carboxylic acids, is described. The detailed mechanisms for the use of catalytic and stoichiometric boron reagents are outlined. Lastly, the conclusion and the project objectives are presented.

1.1 Introduction

The amide bond is ubiquitous in nature. It links amino acids together to form peptides and proteins and is an important component of many natural and pharmaceutical products.[1] This can be expected since this bond is neutral, stable and has substantial double-bond character in the carbon-nitrogen amide bond due to its resonance structure, as described in **Figure 1-1 (a)**. The amide bond has several structural characteristics that are important in peptide and protein structures. It is flat, with the carbonyl carbon, oxygen, nitrogen and amide hydrogen all lying in the same plane. No free rotation occurs about the carbon-nitrogen bond

because of the partial double bond character (the barrier to rotation is about 25 kcal/mol). The torsional angle of this bond, ω, is defined by Cα–C(O)–N–Cα. Due to the partial double-bond character, there are two rotational isomers for molecules containing an amide bond: *trans* (ω = 180°) and *cis* (ω = 0°), as shown in **Figure 1-1 (b)**. The lower energy isomer is the *trans* amide bond, which is the isomer generally found in all peptides not involving proline. The resonance forms of the amide bond represent an extremely important characteristic in peptide and protein structures. The amide bond is quite polar and has a significant dipole moment, which makes the amide carbonyl oxygen a particularly good hydrogen-bond acceptor and the amide NH a particularly good hydrogen-bond donor.[2]

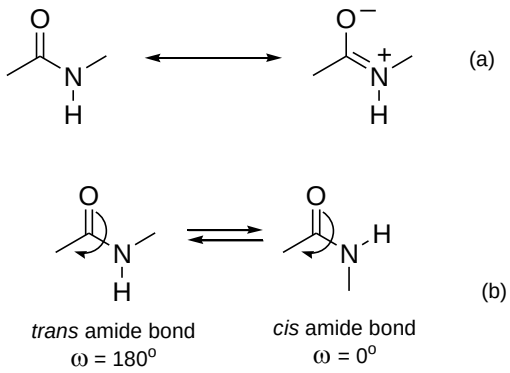


Figure 1-1: Amide bonds, (a) Resonance forms of amide bond, (b) *trans* and *cis* amide bonds.[3]

Proteins are generally assembled by amide-bond formation between peptides and/or amino acid residues. Proteins contain at least 50 residues and sometimes over 1000 residues. Proteins play a crucial role in practically all biological processes, such as enzymatic catalysis (nearly all known enzymes are peptides and proteins), transport/storage (hemoglobin), immune protection (antibodies), and mechanical support (collagen), and posses a well-defined three-dimensional structure. For example, carboxypeptidase A is one of many enzymatic proteins that break down food in the stomach. In contrast, skin has a much less precise molecular structure, but its toughness is mainly due to a protein called collagen.

Peptides are rather smaller molecules, which usually contain less than 50 amino acid residues connected by amide-bonds and do not possess a well-defined three-dimensional structure.[2] Peptides can act as hormones, poisons,

antibiotics and carry out many other functions. For example, angiotensin II (an octapeptide) is produced by our body and causes an increase in blood pressure, so synthetic angiotensin II could be used as a drug for the treatment of low blood pressure. Penicillin (a modified tripeptide) is known to destroy bacterial infections. Aspartame (dipeptide) is an artificial sweetener, about 100 times sweeter than sucrose (**Figure 1-2**).[3-6]

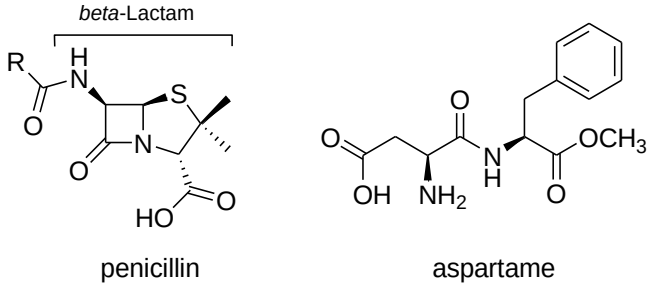


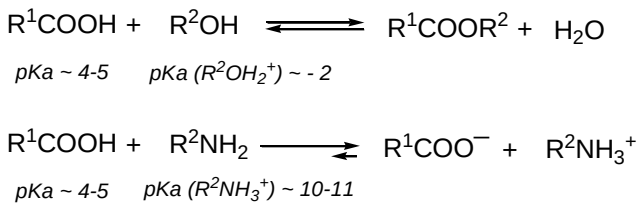
Figure 1-2: Structures of penicillin (a modified tripeptide) and aspartame (dipeptide).[3-6]

Peptides are extremely diverse in their structure and properties. There are only 20 natural amino acids, thus; there are a total of 20^5 possible combinations for a simple pentapeptide.[2] This allows nature to have almost unlimited possibilities of peptides and proteins, possessing unlimited structures and medicinal properties. In general, the amide bond is the golden key that connects together amino acids to form peptides and proteins. That such a small bond as the amide bond makes such important molecules leads to the question: how can this amide bond be formed?

1.2 Methods and Strategies for Amide Bond Formation

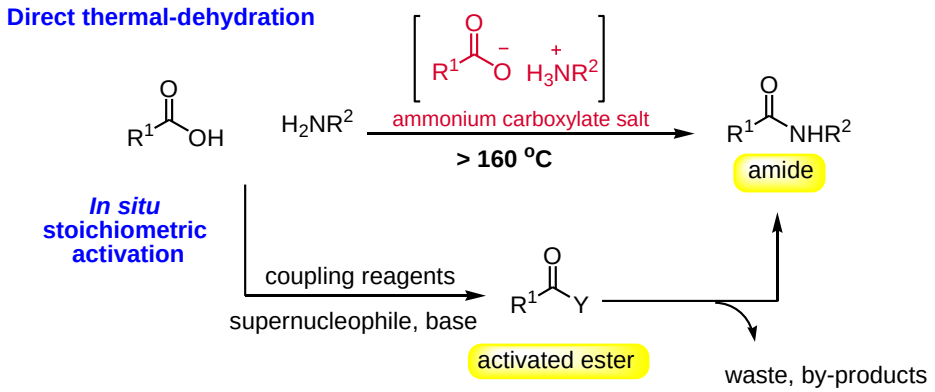
Amide or ester bond formation between, respectively, an acid and an amine or an alcohol, is, formally, a condensation reaction. The usual esterification reaction is an equilibrium reaction, whilst the mixing of an amine with a carboxylic acid at ambient temperature generates an acid-base reaction that forms a thermodynamically stable ammonium carboxylate salt. In other words, direct amide bond formation has to fight against adverse thermodynamics as the equilibrium lies on the side of hydrolysis rather than synthesis, as shown in **Scheme 1-1**.[7] The transformation of this salt directly into amides requires severe heating (over 160 ^{o}C), which is quite incompatible with most functionalized molecules.[8] Acidic

catalysis, which is effective in a condensation reaction between an alcohol and carboxylic acid without any other activation, is of no help in direct amide bond formation since amines are basic and their reactivity/nucleophilicity is diminished under acidic conditions.[6]



Scheme 1-1: Ester bond versus amide bond formation.[8]

Consequently, appropriate activation is required to perform amide bond formation under mild conditions. Theoretically, there are two types of activation strategies for making an amide bond: amino activation and carboxyl activation. The former has rarely been applied due to its drastic reaction conditions and racemization problems. Carboxyl activation has been used widely;[4] it is based on the attachment of a leaving group to the acyl carbon to facilitate the nucleophilic attack by the amino group.[4] Common methods of activating carboxylic acids for forming amide bonds involve the use of stoichiometric excesses of expensive and often toxic coupling reagents, such as carbodiimides or phosphonium or uronium salts, to activate and dehydrate the carboxylic acid.[9] These reagents and their associated co-reagents, including bases, supernucleophiles, and other additives, generate large amounts of wasteful by-products that complicate the isolation of the desired amide product (**Scheme 1-2)**. In other words, chemists are required to screen a variety of conditions to find the method best adapted to their reactions while avoiding poor reactivity, racemization, low yield, large amounts of by-products, poor selectivity, complicated purification and more recently, avoiding poor atom economy reagents (environmentally friendly reaction conditions). A recent survey in 2007 revealed that amide bond formation was, not only one of the top 15 reactions currently used in the drug discovery industry, but was also identified as a priority research area by the American Chemical Society (ACS) Green Chemistry Institute (GCI) and several leading global pharmaceutical corporations, as shown in **Table 1-1**.[1]



Scheme 1-2: Amide bond formation by reaction between carboxylic acid and amine.[8]

Consequently, the development of efficient amidation methods targeting high atom economy continues to be an important scientific pursuit.[9, 10]

Table 1-1: Roundtable leading pharmaceutical companies voting results for finding better reagents in priority areas of research.[1]

Research area	Number of roundtable companies voting for this research area as a priority area
Amide formation avoiding poor atom economy reagents	6 votes
OH activation for nucleophilic substitution	5 votes
Reduction of amides without hydride reagents	4 votes
Oxidation/epoxidation methods without the use of chlorinated solvents	4 votes
Safer and more environmentally friendly Mitsunobu reactions	3 votes
Friedel–Crafts reaction on unactivated systems	2 votes
Nitrations	2 votes

More recently, boron reagents and, especially, boronic acids and boric acid have provided a possible benign alternative and the most attractive approach for this long-standing problem. Boron reagents have been developed and used catalytically and stoichiometrically for the direct amide bond formation between carboxylic acids and amines. These methods considerably reduce the required reaction temperatures for this transformation and allow high atom economy towards a greener and milder amide bond formation.

1.2.1 Non-Boron Reagents for Direct Amide Bond Formation

Indeed, a plethora of methods and tactics have been developed for the direct and non-direct formation of amide bonds and these strategies are now available for synthetic, pharmaceutical and medicinal chemists. For the direct amide bond formation between a carboxylic acid and an amine, the carboxylic acid moiety needs to be activated before adding the amine. However, there are different strategies for activating the carboxylic acid and coupling it with an amine:

- The intermediate acylating agent is formed independently, isolated and then subjected to aminolysis.
- The reactive acylating agent is formed in separate steps, then immediately treated with the amine.
- The acylating agent is generated *in situ* from the acid in the presence of the amine by addition of an activating reagent.

Several stoichiometric and catalytic non-boron methods have been developed for activating the carboxylic acid moiety. However, there are many challenges that chemists might face during the activation of the carboxylic acid for amide bond formation, including racemization, low yields, degradations and tedious purifications.

1.2.1.1 Stoichiometric Activation of Carboxylic Acids

1.2.1.1.1 Acyl Halide Reagents

The use of acid halides (fluorides, chlorides or bromides) is one of the most common tactics for activation of the carboxylic acid moiety. It is recommended for extremely hindered substrates.[12] However, these intermediates are highly activated and can be easily racemized and, therefore, practical applications are restricted in spite of their high reactivity and the low cost.

Acid chlorides were first introduced by Emil Fisher in 1903. Since then, various chlorinating reagents have been discovered, such as *thionyl chloride* $SOCl_2$, [11-13] *oxalyl chloride* $(COCl)_2$, [14-16] *phosphorus trichloride* PCl_3,[13] *phosphorus oxychloride* $POCl_3$ [17] and *phosphorus pentachloride* PCl_5 [13, 18], as shown in **Figure 1-3**. This is

usually a two-step process, making the acyl chloride first then following with the treatment with amine to form the amide bond.

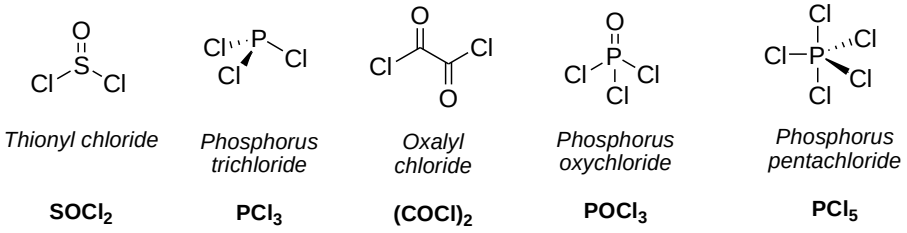
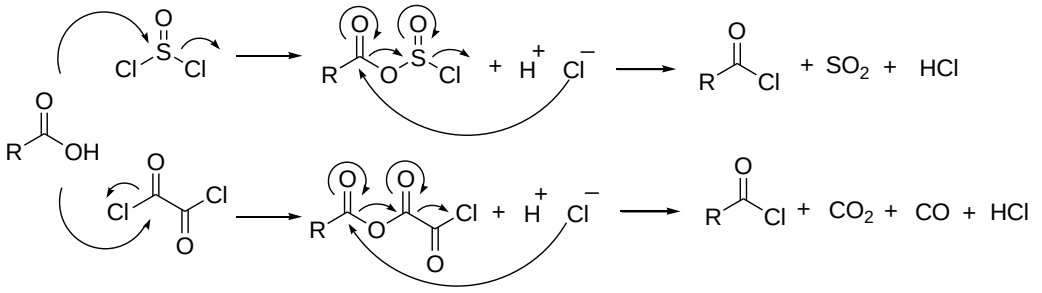


Figure 1-3: Common chlorinating reagents for amide bond formation.

One of the major disadvantages of using these chlorinating agents is the stoichiometric production of HCl. The mechanism of acid chloride formation using *thionyl chloride* and *oxalyl chloride* is outlined in **Scheme 1-3**. The use of *oxalyl chloride* is accompanied not only by a stoichiometric amount of HCl but also with two molecules of gas, one being carbon monoxide, which is highly toxic and therefore safety hazards should be taken into consideration in large scale transformations.[19]



Scheme 1-3: Mechanism for acid chloride formation using thionyl chloride (top) and oxalyl chloride (bottom).[19]

Reactions using these reagents are usually promoted with a catalytic amount of dimethylformamide (DMF).[20, 21]

Many substrates are acid sensitive and they are of course not suitable under these highly acidic conditions. To solve this problem, stoichiometric base is usually added to maintain neutral pH conditions throughout the reaction. Other acid chloride reagents are cyanuric chloride, CDMT and BTC, as shown in **Figure 1-4**. For example, cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) is used in the presence of a

stoichiometric amount of trimethylamine to maintain a basic medium as described in **Scheme 1-4**.[22].

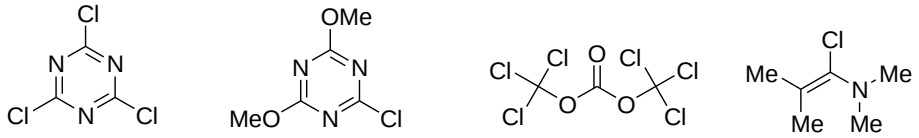
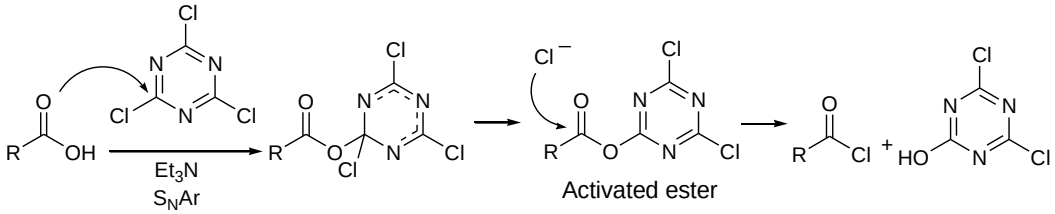


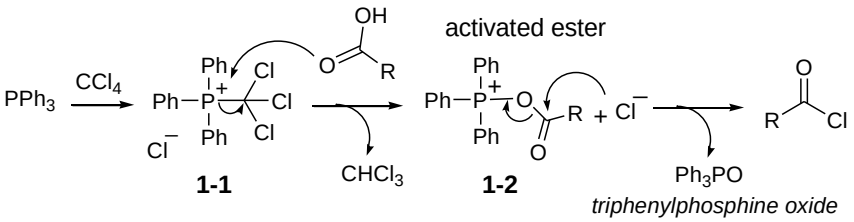
Figure 1-4: Structures of other chlorinating agents for direct amide bond formation.



Scheme 1-4: Acyl chloride formation using cyanuric chloride.[22]

Ghosez and co-workers described another neutral method to form the acid chloride by using tetramethyl-α-chloroenamine (**Figure 1-4**). In this process, the formation of hydrogen chloride is avoided, which is useful for acid-labile protecting groups.[23]

Gilon and co-workers described the use of BTC (**Figure 1-4**) as a chlorinating agent in solid-phase chemistry, which provided good yields for Fmoc-amino acids containing acid labile side chains.[24-26] Neutral methods have also been developed in this field. For example, triphenylphosphine (TPP) is used in the presence of CCl_4 as a source of chloride ions to form the acyl chloride, as described in **Scheme 1-5**. It is proposed that triphenylphosphine reacts with CCl_4 to form the triphenylphosphonium chloride (**1-1**), which is then attacked by the carboxylic acid to form the activated ester (**1-2**). The chloride ion then attacks the activated carboxyl carbon to form the acyl chloride and triphenylphosphine oxide, which is notorious for complicating the purification of the desired product. The toxicity and environmental risks associated with the use of CCl_4 limit the application of this method, especially if it is employed in a large scale to form pharmaceutical agents. [27, 28]



Scheme 1-5: Acid chloride formation using TPP and CCl_4.[27, 28]

Acyl chloride formation is one of the easiest methods to activate the carboxylic acid moiety. However, its application in amide bond formation and peptide synthesis has a limited value due to the ease of hydrolysis, racemization, cleavage of the protecting groups and other side reactions. Under basic conditions, the racemization of acyl chlorides is explained by ketene formation.[29]

Acyl fluorides are usually formed and reacted the same way as chlorides. However, they display better stability towards moisture[30] and acid-labile functional groups[31] than acid chlorides. In contrast, the corresponding acid fluorides suffer from less limitations than the chlorides. Several fluorinating agents have been developed and are shown in **Figure 1-5**.

Cyanuric fluoride is used in the same way as cyanuric chloride and CDMT in the presence of pyridine according to the general technique of Olah.[32, 33] The most notable advance in acid halogenation is the development of fluoroformamidinium intermediates. Carpino and co-workers reported the use of TFFH, BTFFH and DFIH (**Figure 1-5**), which act by *in situ* generating the acid fluorides in amide bond formation reactions.[34] These fluorinating reagents are useful but they are not stable, having a short shelf life, and the toxicity of the by-products (e.g. TFFH) has restricted the use of these reagents in direct amide bond formation.[34]

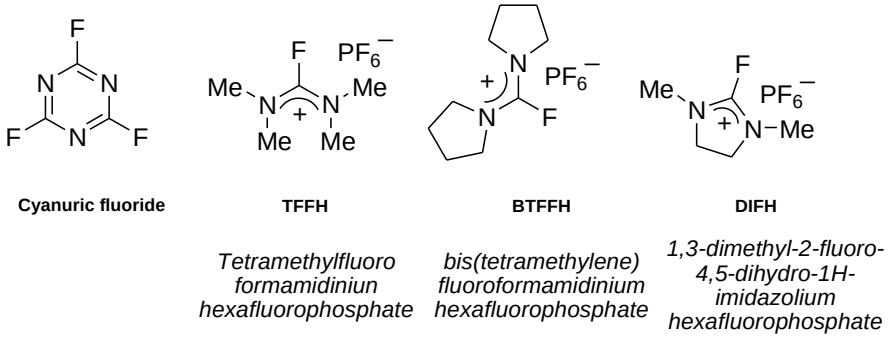


Figure 1-5: Common fluorinating agents for amide bond formation.[34]

Recently, diethylaminosulphur trifluoride (DAST) Et_2NSF_3[35, 36] and deoxo-fluor™ $(MeOEt)_2NSF_3$[37] have also been developed and used in amide bond formation (**Figure 1-6**). However, DAST rapidly decomposes upon heating. Lal *et al.* reported that DAST analogue Deoxo-fluor has a comparable reactivity and superior thermal stability than DAST.[36-38]

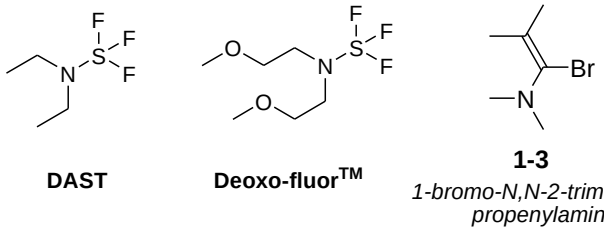


Figure 1-6: Structures of fluorinating and brominating agents.[35-38, 45]

Acid bromides are rarely used to generate amide bonds. Several brominating reagents have been developed, such as PBr_5,[39] Ph_3P/Br_2,[40] Ph_3P/NBS,[41] $SOBr_2$,[42 36] BBr_3/Al_2O_3,[43] and $(BrCO)_2$[44]. More recently, 1-bromo-*N*,*N*-2-trimethyl-1-propenylamine **1-3** (**Figure 1-6**) was also used to form acyl bromides under milder reaction conditions.[45] These reagents are usually effective for α-brominations which is one of the major limitations when using these reagents.[39]

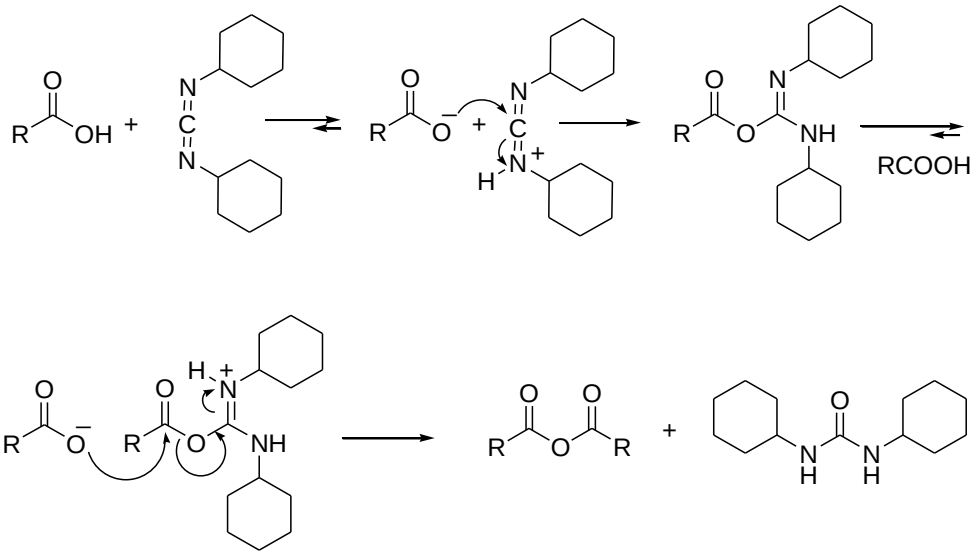
1.2.1.1.2 Anhydride Reagents

Anhydrides are intermediates that are formally derived by the condensation of a carboxy component with another acidic species by removing one molecule of water. They have a wide range of reactivity and different nucleophiles, such as alcohols,

thiols, amines and others, can attack the electrophilic carbonyl carbon to form other products. Simple symmetrical anhydrides or mixed anhydrides can be used in this strategy.

Symmetrical anhydrides are formed either by azeotropic distillation of the corresponding acid or by using one equivalent of dicyclohexyl carbodiimide (DCC) (**Scheme 1-6**).[46] After forming the anhydride in the first step, it reacts with the amine in the second step to form the amide. However, there are a few limitations associated with this strategy:

1. Only half of the acid precursor is reacted to form the amide and the second half is wasted.
2. The toxicity of the urea (DCU) by-product formed during the anhydride preparation.

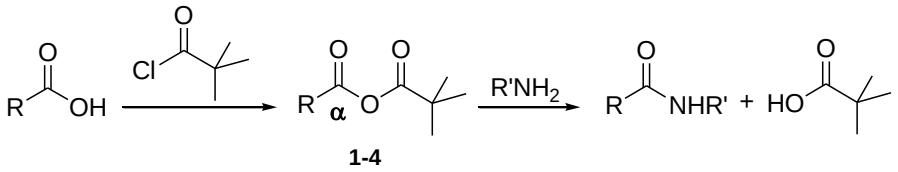


Scheme 1-6: Symmetrical anhydride formation using DCC.[46]

Mixed anhydrides overcome the waste problem associated with the use of symmetrical anhydrides. The only concern is the regioselectivity during the nucleophilic addition by the amine. There are four mixed anhydride methodologies:

1. Mixed carboxylic anhydrides: In this method, the second carboxylic acid moiety comes from a cheap and available acid. To overcome the regioselectivity problem, the sacrificial acid should have a physical property that allows it to be differentiated

from the targeted carbonyl group. One common example is the mixed pivalic anhydride **1-4**, which gives complete selectivity towards the desired carbonyl group denoted **α** in **Scheme 1-7**. This selectivity is believed to arise from the steric nature of the *tert*-butyl group.[47]



Scheme 1-7: Two step coupling procedure using pivalic anhydride 1-4. [47]

2. Mixed carbonic anhydrides: In this method, the difference in chemical nature of the two reactive centers is used to discriminate the reactivity of the two centers. One of the best examples is mixed anhydride **1-5** (**Figure 1-7**), where the carbonate electrophilic carbonyl center **α** is more reactive than the carbonyl site **β** due to the resonance stabilization effect. Mixed anhydrides can be prepared using different reagents, such as ethyl chloroformate[11] or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EDDQ)[48].

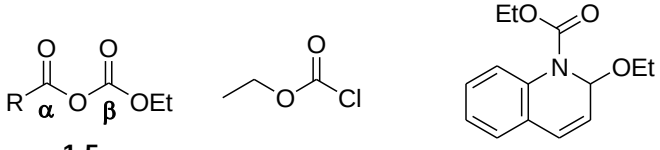
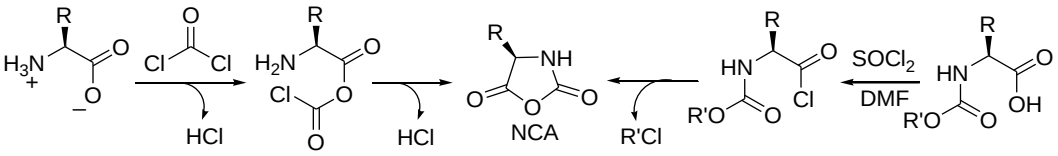


Figure 1-7: Common reagents for making mixed carbonic anhydride.[48]

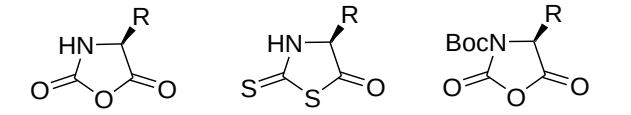
3. N-carboxy anhydride (NCA) or Leuch's anhydride is a cyclic anhydride **1-6** made from free amino acids with phosgene or by *N*-protected (Boc, Cbz, Fmoc) amino acids with thionyl chloride and DMF as shown in **Scheme 1-8**.[49, 50] The amine then reacts with NCA to form a chain followed by decarboxylation, which leads to the formation of homopolyamino acids. The double-coupling is the major limitation of this methodology. However, more carefully controlled conditions lead to the requisite mono-coupled product when the NCA is added slowly to a basic aqueous solution of the amino acid at 0 ^{o}C.[49, 50]



1-6

Scheme 1-8: *N*-carboxy anhydride (NCA) formation.[49, 50]

Other derivatives of NCA, such as the TCA[49] **1-7** (thiocarbamic acid) and the Fuller's UNCA[51] **1-8** (urethane N-carboxy anhydrides), have been made and used in amide bond formation (**Figure 1-8**).



1-6
NCA
N-carboxy anhydride

1-7
TCA
thiocarbamic acid

1-8
UNCA
urethane N-carboxy anhydrides

Figure 1-8: Structures of some *N*-carboxy anhydrides. [49, 51]

4. Organophosphorus anhydride is a mixed carboxylic-phosphoric anhydride, developed by Yamada and co-workers using diphenylphosphinic chloride DPPA, which is made from the reaction between diphenylphosphorochloride and sodium azide.[52, 53] Since then, various organophosphorus reagents have been made and developed, as shown in **Figure 1-9**. This method usually gives a higher regioselectivity towards nucleophilic attack by the amine compared to the mixed anhydride methods. DECP is made by the reaction between triethylphosphite and cyanogen bromide.[54, 55] DPP-Cl was first introduced by Yamada and co-workers and shortly after, Palomo-Coll and co-workers developed BOP-Cl, which is well known as a powerful reagent for amide bond formation.[56, 57] Many other organophosphorus reagents have been developed and described in the literature, such as MPTO [58], FDPP [59], NDPP [60], BMP-Cl [61], DEBP [62], BDP [63], and more recently, DEPBT, DEPBO and DOPBO.[64]

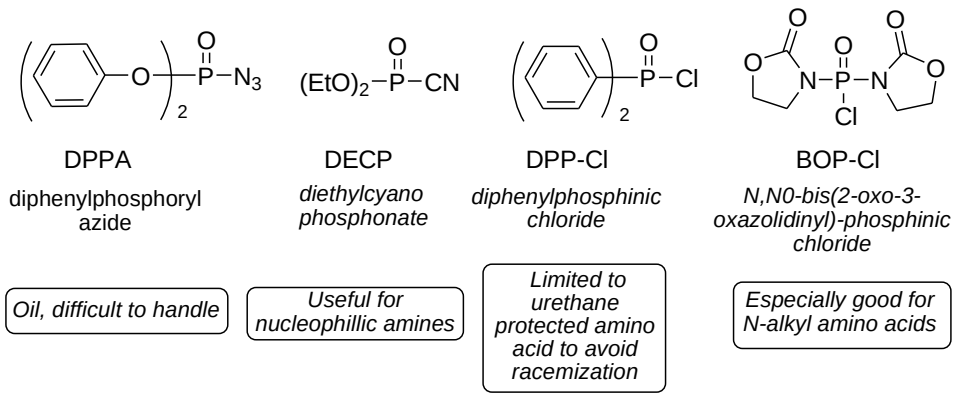


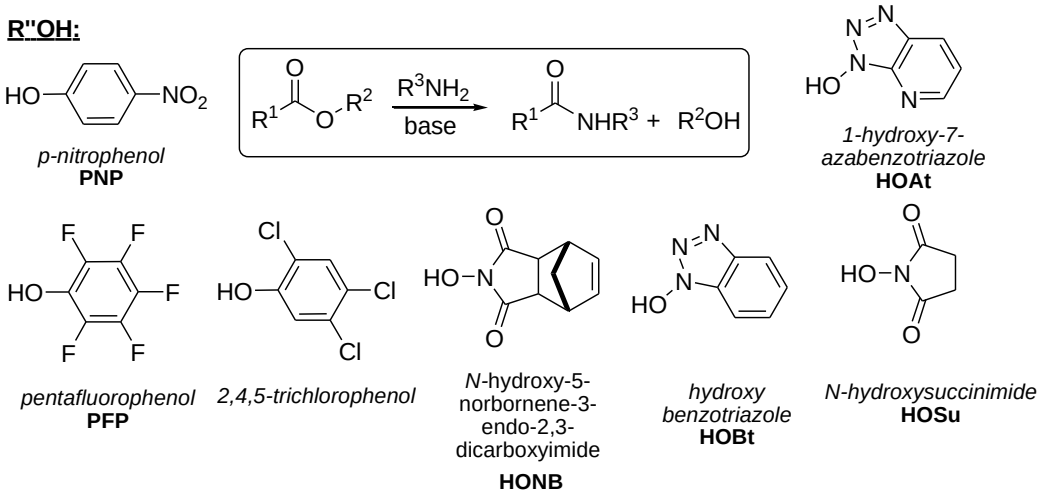
Figure 1-9: Common organophosphorus reagents for amide-bond formation.

1.2.1.1.3 Ester Reagents

There are two types of esters, the *alkyl esters* and the *active esters*:

Alkyl esters (e.g. methyl, ethyl, benzyl, *etc*.) are not considered to be useful, active species for amide bond formation under mild conditions. Generally, they are rather used as protecting groups in peptide synthesis. Under forcing conditions, such as the use of high temperature or the addition of Lewis acids, they can be displaced with other nucleophiles. In general, alkyl esters are stable under usual coupling conditions.

Active esters are usually easier to hydrolyze than alkyl esters and thus more prone to react with different nucleophiles. They react cleanly with amines under mild conditions with less racemization. Different active esters are shown in **Scheme 1-9**. Overall, these esters of aromatic alcohols have higher electrophilicity of the carbonyl carbon (a result of their electron-drawing character) and therefore increased reactivity towards nucleophiles. The most commonly used esters are HOBt,[65] PNP[66] and PFP[67]. Others, such as 2,4,5-trichlorophenol derived esters, are reported to be more active than both PNP esters[68] and *N*-hydroxy-5-norbornene-endo-2,3-dicarboxyimide HONB esters.[69, 70] HOSu esters are good alternatives as they are water-soluble and the resulting alcohol is easy to remove at the purification stage.



Scheme 1-9: Commonly used alcohols for the formation of active esters in amide bond formation.

Hydroxyl-7-azabenzotriazole HOAt has been reported to be more reactive than HOBt for some difficult cases. This reactivity might be due to the additional coordination from the pyridine nitrogen during the aminolysis step, as described in **Figure 1-10**.[71]

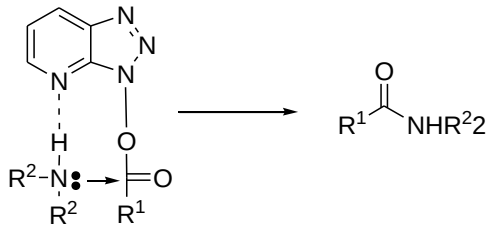


Figure 1-10: The additional chelation effect of HOAt with amine.[71]

1.2.1.1.4 Carbodiimide Reagents

Carbodiimide reagents have been used widely in amidation chemistry and peptide synthesis due to their reasonable price and moderate reactivity. Some carbodiimide reagents are shown in **Figure 1-11**. No additional amine is theoretically needed during this one-pot procedure. The carboxylic acid reacts with the carbodiimide to form an *O*-acylisourea mixed anhydride **1-9**, which then reacts with the amine to form the amide product and the urea by-product (**Scheme 1-10**).[9] Potential racemization of the amide product, reactivity of the carbodiimide and the toxicity of

the urea by-product are the major disadvantages of this methodology. The racemization can be suppressed by reacting the acid and the carbodiimide at 0 °C.

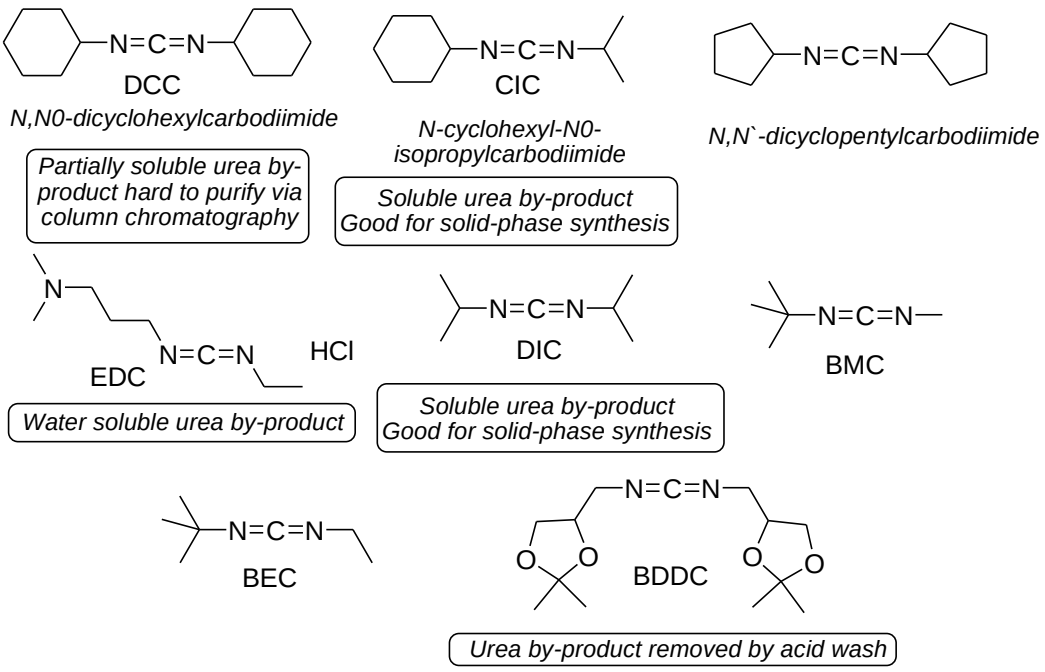
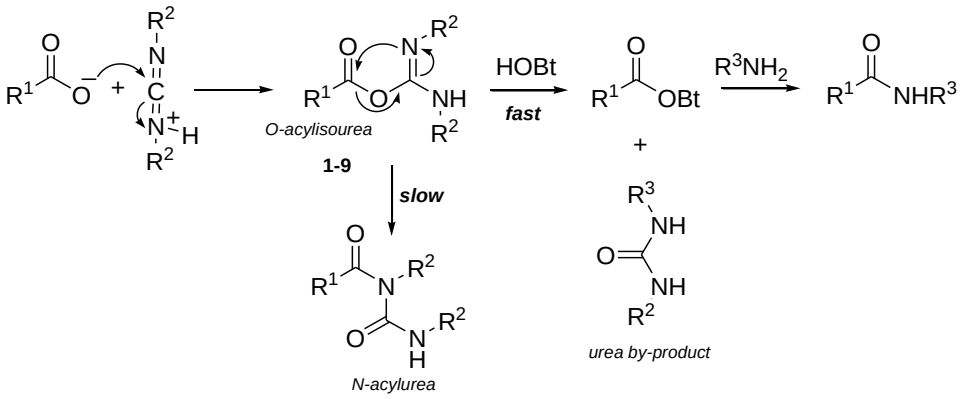


Figure 1-11: Commonly used carbodiimide reagents employed in amide bond formation.[9]

However, the reactivity of these reagents is diminished at this temperature and, consequently, an additional nucleophile is required to accelerate the reaction. Such "super-nucleophiles" are exemplified by DMAP and HOBt (**Figure 1-9**).[72] Since the pioneering work by Bodanszky on the successful combination of DCC/PNP,[73] carbodiimides have been dramatically expanded in their application in amide bond formations and various additives/activators have been reported (**Scheme 1-10**). These additives/activators have complemented the rate of the reaction and reduced racemization.

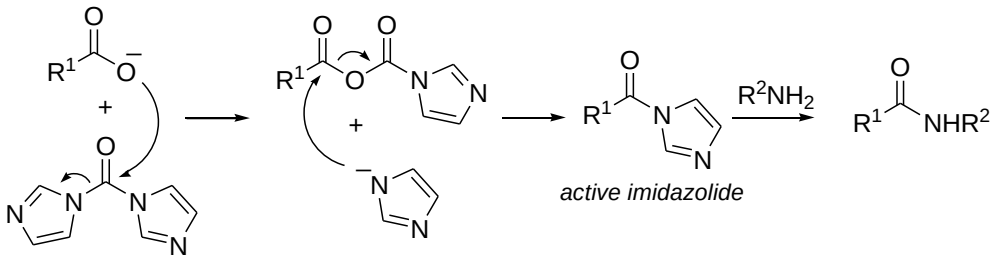


Scheme 1-10: Use of activator HOBt to minimize the formation of the unreactive N-acylurea.[9]

Other carbodiimides, such as BMC, BEC and *N,N'*-dicyclopentylcarbodiimide, have also been developed. Rapoport and co-workers developed the hydrophilic side-chain carbodiimide BDDC, which gives good yields and the by-product can be removed by an acid wash.[74]

1.2.1.1.5 Imidazolium Reagents

The search for better reagents based on DCC led to the development of carbonyl diimidazole (CDI).[75, 76] The mechanism is believed to be a nucleophilic carboxylate attack on the carbonyl carbon of CDI followed by the nucleophilic attack of the counteranion of imidazole to produce the active imidazolide (**Scheme 1-11**). Then the amine is added, and attacks the carbonyl carbon on the active imidazolide to form the amide product. No additional base is needed under these reaction conditions.[77] Imidazolium reagents are useful in one-pot amide bond formation. Some imidazolium reagents are shown in **Figure 1-12**.



Scheme 1-11: Amide bond formation using CDI reagent.[75, 76]

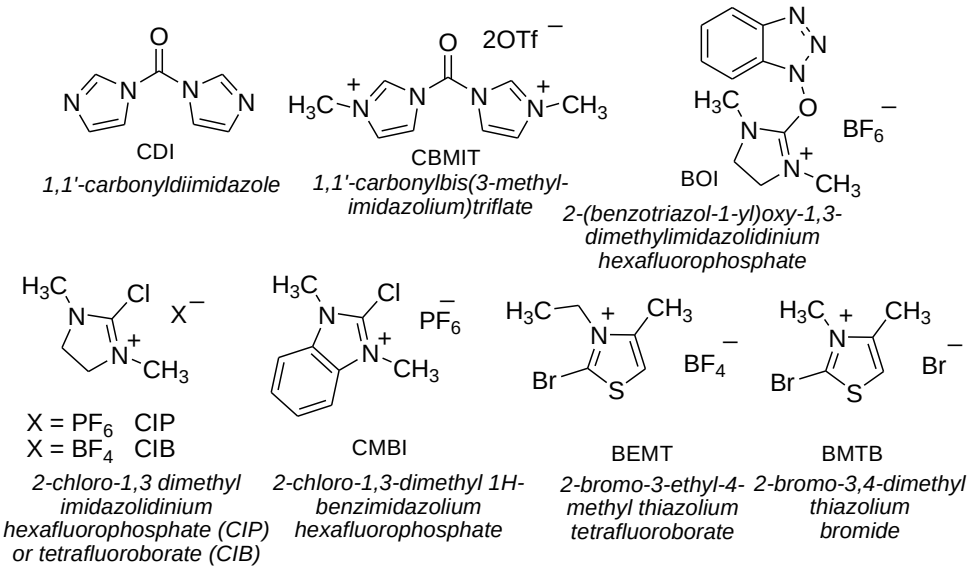


Figure 1-12: Imidazolium reagents for amide bond formation.[75, 76]

Rapoport and co-workers developed the imidazolium reagent CBMIT by dimethylation of CDI with methyl triflate.[78] Compared to CDI, CBMIT showed superior reactivity towards hindered substrates and no sign of racemization in the presence of $CuCl_2$ or $Cu(OTf)_2$.[79] However, CBMIT is moisture sensitive and should be handled for a very short time. One more limitation for this reagent is its polarity. Due to the high polarity of CBMIT, the choice of solvent is restricted to nitromethane.[79] A few years later, Kiso and co-workers made BOI and its precursors CIP and CIB. The efficiency of these reagents was evaluated for sterically hindered α,α-dialkylated amino acids.[80] The combination of CIP/HOAt showed good results in dipeptide formation. This combination was also applied successfully to the synthesis of (–)-mirabazole C.[81]

Recently, Xu and co-workers developed CMBI, a benzene derivative of CIP as a new imidazolium reagent during the synthesis of a pentadepsipeptide intermediate of actinomycin D, an anticancer drug.[82] The same group also developed the BEMT reagent.[83] The mechanism for this reagent is believed to be a sequential conversion of carboxylic acid into the acyloxythiazolium salt, which then adds to the acid bromide leaving *N*-ethyl-4-methylthiazolidone as a by-product. Even though BEMT showed good reactivity toward *N*-alkylated amino acids, it tends to suffer from low yields and racemization.[84] In 2003, Wischnat and co-workers introduced BMTB as

a new imidazolium reagent. BMTB proved to be better than BEMT since it is crystalline and non-hygroscopic.[85]

1.2.1.1.6 Ammonium Reagents

Ammonium reagents are useful in one-pot amide and ester formation. *Mukaiyama's reagent* **1-10**, 2-chloro-1-methylpyridinium iodide, the first example of this type of reagent, activates the carboxylic acid in the presence of base to give the activated pyridinium ester, which reacts with a variety of nucleophiles.[86, 87] This reagent is not often used in amide formation reactions due to its poor solubility in many solvents. The reaction requires refluxing conditions in order to be performed successfully. Xu and co-workers developed different alternatives to Mukaiyama's reagent in order to improve the solubility of the pyridinium compounds, which they achieved by changing the counteranion from iodide to tetrafluoroborate and hexachloroantimonate.[82, 83] Different reagents were made, such as 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP), 2-fluoro-1-ethylpyridinium tetrafluoroborate (FEB), 2-bromo-1-ethylpyridinium hexachloroantimonate (BEPH), and 2-fluoro-1-ethylpyridinium hexachloroantimonate (FEPH) (**Figure 1-13**). These reagents showed better solubility and were used in amide formation, especially for substrates containing *N*-methyl amino acids.

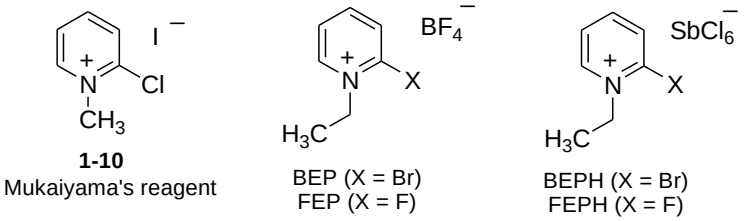
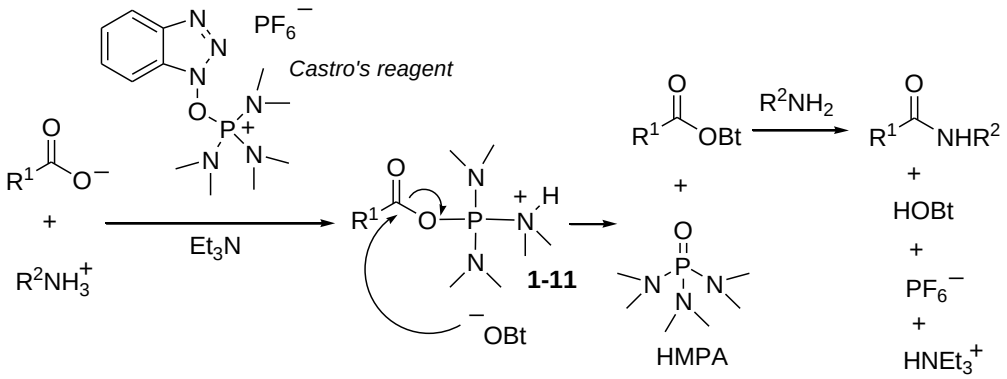


Figure 1-13: Ammonium reagents: Mukaiyama-type alternatives with improved solubility.[82, 83]

1.2.1.1.7 Phosphorus Reagents

Many phosphorus reagents have been developed for amide-bond formation. Castro's reagent, *benzotriazol-1-yl-oxytris-(dimethylamino)-phosphonium hexa fluorophosphate* (BOP), was the first published example of this type of reagent based on a combination of HOBt-onium salt in the presence of a base, such as

triethylamine or Hünig's base.[88] The proposed mechanism is described in **Scheme 1-12**. The deprotonated acid reacts with BOP to generate the activated acylphosphonium intermediate **1-11**. The deprotonated HOBt then reacts with the activated species to form the activated acid, which finally reacts with the amine to form the amide product. The driving force for this reaction is the formation of HMPA and its strong P=O double bond.[89]



Scheme 1-12: Amide bond formation using BOP reagent.[88]

Even though Castro's reagent is very effective, racemization may occur and the generation of HMPA, which is known to be very toxic, hampers the use of this method in synthesis. Later on, as shown in **Figure 1-14**, different phosphonium reagents, such as AOP,[90] PyCloP,[91] PyBroP,[91, 92] PyBOP [91, 92] and PyAOP [93], were prepared in which the dimethylamine moiety was replaced with pyrrolidine to avoid the generation of HMPA,

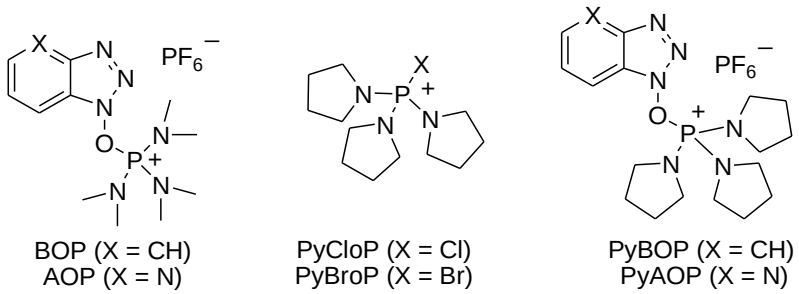
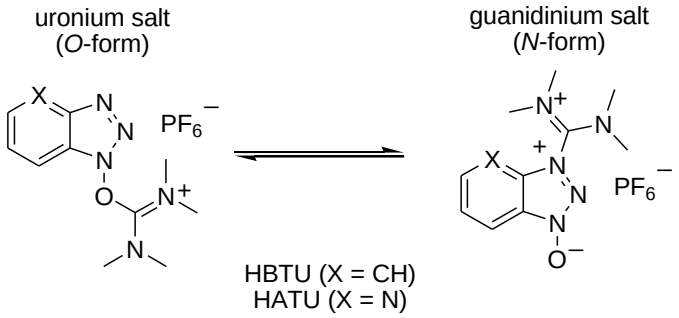


Figure 1-14: Phosphonium reagents employed in amide bond formation.[91- 93]

1.2.1.1.8 Uronium/Guanidinium Reagents

Another notable family of reagents developed in this active research field is the uronium/guanidinium reagents, for which the coupling is performed in the same way as phosphonium reagents. The original members of this family were *O*-(1*H*-benzotrizol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HBTU)[94] and *O*-(1*H*-benzotrizol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium trifluoroborate (TBTU)[95]. The counteranion has no apparent effect on the reactivity of these reagents. The driving force for these reagents is the formation of urea by-products. In the solution phase, the uronium species (*O*-form) are in equilibrium with the (*N*-form), as described in **Equation 1-1**.[96]



Equation 1-1: Equilibrium between uronium and guanidinium species. [96]

Even though the *N*-form and the *O*-form were found to be active reagents, they suffer from various limitations:

1. Uronium species (*O*-form) are known to be guanidylating agents, such that some side-product (guanidine) might occur, thus reducing the yield of the desired amide product. To overcome this problem, HOBt is added to form the active ester before aminolysis and reduce the reactivity of these reagents because of the sterically hindered structure of the HOBt.[97]
2. Noticeable racemization occurs, causing a loss of chiral integrity.
3. Many chemicals/reagents are involved in the reaction, which results in cumbersome purification.

Several uronium/guanidinium reagents have been developed in combination with different activators, and the structures of some of them are shown in **Figure 1-15**.[9]

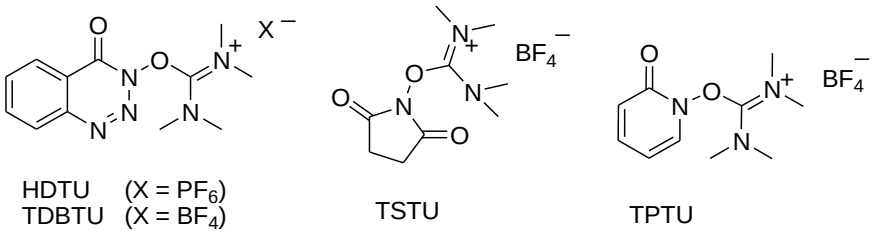


Figure 1-15: Some uronium reagents employed in amide-bond formation.[9]

In summary, certainly, there is no such thing as a general method or technique for amide-bond formation. Every method has its own advantages and disadvantages and, therefore, chemists need to screen a variety of methods for preparing the desired amide product in good yield, avoiding as much as possible degradation and formation of side product(s).

It should be noted that all the above stoichiometric synthetic methods for activation of the carboxylic acid moiety have significant drawbacks: toxic/corrosive by-products, shock sensitivity (racemization or degradation), high cost of coupling reagents and waste streams. Indeed, these methods need to be replaced since they are not "atom economical" and generate a lot of waste by-products. Accordingly, chemists are starting to search for and develop alternative methods for activation of carboxylic acids, aiming at a lower mass intensity factor "MI" (defined as the ratio of the total mass in a process divided by the mass of product in kg) or environmental impact factor "E-factor" (defined as the ratio of the total mass of waste divided by the mass of product).[98-100] Certainly, the development of a catalytic process would favorably impact the environmental profile of this process.

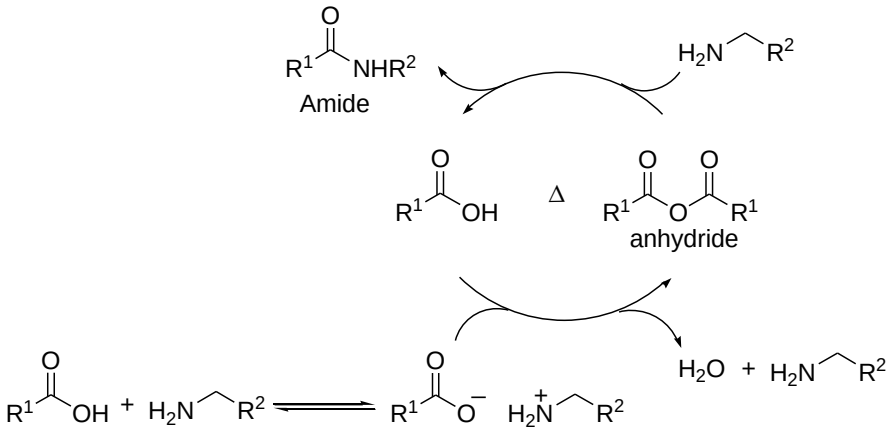
1.2.1.2 Catalytic Activation of Carboxylic Acids

In order to develop a catalytic process for amide bond formation that works at lower reaction temperatures, it is necessary to have a comprehensive understanding of how amines and carboxylic acids interact with or without a catalyst in solution phase. Lewis acid catalysis, which is well known to activate carbonyl derivatives toward nucleophilic substitution and other reactions, is of no use to the reaction of carboxylic acids with amines. This is due to the basicity of the

amine, which reacts with the Lewis acid and therefore diminishes its reactivity. For that reason, the development of any catalyst needs to activate the carboxylic acid in the presence of the amine without suppressing the nucleophilicty of the amine.

Something as simple as the acid-base reaction to form the ammonium carboxylate salt can be more complicated than normally assumed. In aqueous solution, the pKa of most carboxylic acids is significantly below that of most of protonated aliphatic amines and under the required conditions, the formation of an ammonium carboxylate salt is almost complete. However, in organic solvent, the relative pKa values of carboxylic acids and protonated aliphatic amines are usually reversed. For instance, the pKa for protonated *n*-butylamine is significantly higher than n-butyric acid in water (10.59 and 4.82, respectively) but lower in acetonitrile (18.26 and 22.70, respectively).[101] On the other hand, the charge separation of the ammonium carboxylate salt is considerably less favorable in organic solutions than in aqueous solutions and the ionic products do not separate but rather remain associated as ion-pairs.[101] Consequently, the reaction between amines and carboxylic acids is highly substrate-dependent. For example, some combinations favor the formation of neutral carboxylic acid and free amine and others favor salt formation. In both cases, possible H-bonding remains between both reactants. However, the process might be more complicated if there are traces of water in the organic solvent or if a reagent or a catalyst is used.

Under pyrolysis conditions, different monocarboxylic acids were found to undergo dehydration when refluxed at high temperatures between 250 and 350 ^{o}C to provide the anhydride product.[102, 103] Consequently, it is not surprising that adding an amine to the heated solution of a carboxylic acid will form the amide product since a well-known synthesis of amides is through the anhydride intermediates, as described in **Scheme 1-13**.



Scheme 1-13: Proposed overall mechanism for thermal amide formation.[102, 103]

In 1993, Jursic *et al.* prepared a range of amides by heating a neat mixture of different amines and carboxylic acids in the absence of any catalyst.[8] The optimum conditions for the heating of carboxylic acid and amine mixtures so far were found to be between 160 and 180 ^{o}C. However, under these thermal conditions, both the amines and carboxylic acids need to be thermally stable, non-volatile, have a low melting point and have a high boiling point. Extreme heating might lead to decomposition and tar formation, whereas heating below the required reaction temperature will provide incomplete transformation to the amide product. As a result, this method has not been widely used since it is not compatible with many functionalized and sensitive substrates.

Microwave irradiation has also been used for direct amide bond formation. It was reported to simplify the reaction and lead to higher conversion to the amide product under shorter reaction times than conventional heating methods. [104-107] However, this method is limited to simple achiral substrates since decomposition and racemization were observed. For example, benzylamine reacted with benzoic acid to provide the corresponding amide product in 80% yield after 30 min and with using 1.5 equivalents of amine. However, when the same reaction was heated using an oil bath only 8% yield of the amide was isolated. Moreover, it was also found that having an excess amount of either the amine or carboxylic acid was favorable for the reaction between benzylamine and benzoic acid, as described in **Table 1-2**. It was proposed that excess carboxylic acid or amine reacted with the carbonyl group at

the carboxylic acid by hydrogen bonding, thus enhancing the nucleophilic attack of the amine, as shown in **Figure 1-16**.[105]

Table 1-2: The effect of relative ratio of amine : acid in direct amidation under microwave conditions.[105]

Reaction time (min)	Relative ratio (acid:amine)	Yield%
30	1 : 1	10
30	1.5 : 1	75
30	1 : 1.5	80

Wang and co-workers claimed that the use of one equivalent of imidazole to a mixture of benzylamine and benzoic acid under microwave conditions facilitated the amide formation reaction and the yield increased from 13 to 61%.[108] The imidazole is assumed to activate the carbonyl group in the same way as using excess amine or carboxylic acid.

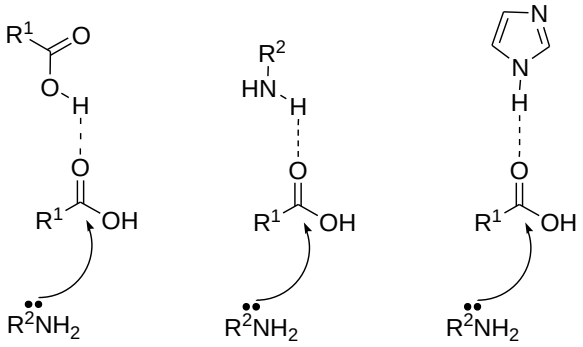


Figure 1-16: H-bonding assisted nucleophilic attack of amine in direct amide formation.[105, 108]

1.2.1.2.1 3 Å and 4 Å Molecular Sieves

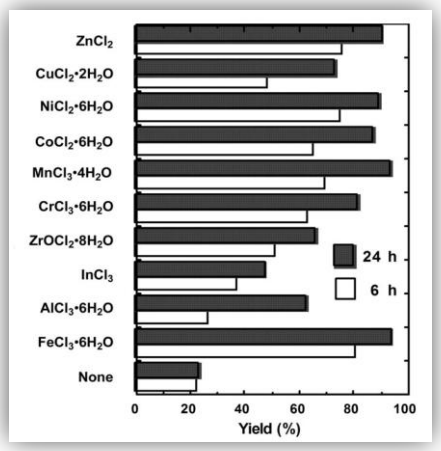
In 1989, Cossy and co-workers described the use of 4 Å molecular sieves for direct amide bond formation.[109] They have shown that neat mixtures of amines and carboxylic acids in combination with 4 Å molecular sieves provide the corresponding amide products in good yield. Primary amines react at 140 °C with saturated or unsaturated carboxylic acids to provide the amides, while amides from aromatic amines require a temperature of 170 °C. In contrast, the reaction of secondary amines with carboxylic acids gave the ammonium salts and no amide products were observed at all, even at 180 °C. One exception, however, was

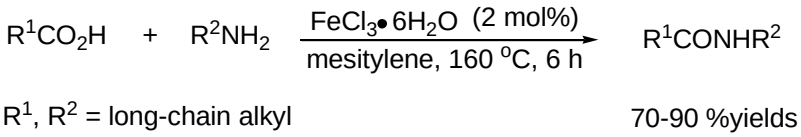
pyrrolidine. A background reaction to show the yield without using the sieves was not reported.

Very recently, Gooβen and co-workers explored the role of different dehydrating agents on a model amidation reaction between benzylamine and 10-decanoic acid at 160 °C under microwave heating. The use of activated 4 Å molecular sieves gave 59% of the amide product. Other dehydrating agents, Lewis acids or Brønsted acids, such as $MgSO_4$, $Yb(OTf)_3$ or H_2SO_4, led to lower yields. Furthermore, changing from 4 Å to 3 Å molecular sieves, the pretreatment (drying or grinding) or changing the amount of the molecular sieves provided only marginal differences. A control experiment in the absence of drying agent or mediators led to the same yield, which clearly supports the idea that the role of the molecular sieves is merely to trap the water by-product and is not part of the mechanism.[110]

1.2.1.2.2 Multivalent Metal Salts

In 2008, Sugi and co-workers examined the effect of multivalent metal salts on a model amidation reaction between long chain aliphatic carboxylic acids and aliphatic amines under azeotropic-reflux conditions, as shown in **Equation 1-2**.[111] They reported that the catalytic activity of multivalent metal chlorides decreases in the order: $FeCl_3.6H_2O$>$ZnCl_2$>$NiCl_2.6H_2O$>$MnCl_2.6H_2O$> $CoCl_2.6H_2O$>$CrCl_3.6H_2O$>$ZrOCl_2.8H_2O$>$CuCl_2.4H_2O$> $InCl_3$>$AlCl_3.6H_2O$. Different aromatic hydrocarbon solvents were examined using the best catalyst, $FeCl_3.6H_2O$, and revealed that the catalytic activity enhanced with increasing reaction temperature in the order: benzene << toluene < *m*-xylene << mesitylene (bp: 80, 110, 140 and 160 °C, respectively).



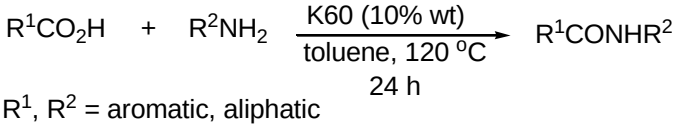


Equation 1-2: The catalytic activity of $FeCl_3.6H_2O$ on amidation reaction under azeotropic-reflux conditions.[111]

Moreover, exploring different Fe (III) salts under the optimized reaction conditions showed that sulfates, nitrates, and acetates are active for this reaction as well as chlorides. These results confirm that the active center for the amidation is on the metal cation and that the anionic counter anion has no influence on the catalytic activity. This methodology has major limitations because it requires temperatures as high as 160 °C, which are not compatible with many functional groups and low boiling point substrates.

1.2.1.2.3 Activated K60 (Kieselgel 60) Silica Gel

Very recently, in 2009, Clark and co-workers reported the use of a heterogeneous silica catalyst which can catalyze the amidation reaction in toluene under azeotropic-reflux conditions.[112] Using a model amidation reaction between butyric acid and aniline, the highest activity was found with thermally activated Kieselgel 60 (average pore size 6 nm), as shown in **Equation 1-3**.



Equation 1-3: The catalytic activity of K60 on amidation reactions under azeotropic-reflux conditions.[112]

Using Lewis acids, such as $FeCl_3$ or $ZnCl_2$, had only a slight influence on the activity. Lewis acids supported on K60 had negative effects and lower yields of products were observed (**Table 1-3**). The activation temperature was investigated; it was found that the activation at 700 °C gave the highest yields in amidation products. Porosimetry data shows that the catalyst surface changes over a range of temperature. The authors proposed that the combination between the weak acidity and hydrophobicity of the silica provides the best environment for amide formation and the silanol groups are not acidic enough to protonate the amine.

Table 1-3: The effect of additives on amidation under azeotropic-reflux conditions.[112]

Catalyst	Activation temperature (°C)	Yield%
$FeCl_3$.anhydrous	-	7
$ZnCl_2$.anhydrous	-	9
K60 silica	700	55
$FeCl_3$/K60 silica	700	50
$ZnCl_2$/K60 silica	700	41
Zeolite B25	260	19
Zeolite B150	260	33
None	-	6

1.2.2 Boron Reagents for Direct Amide Bond Formation

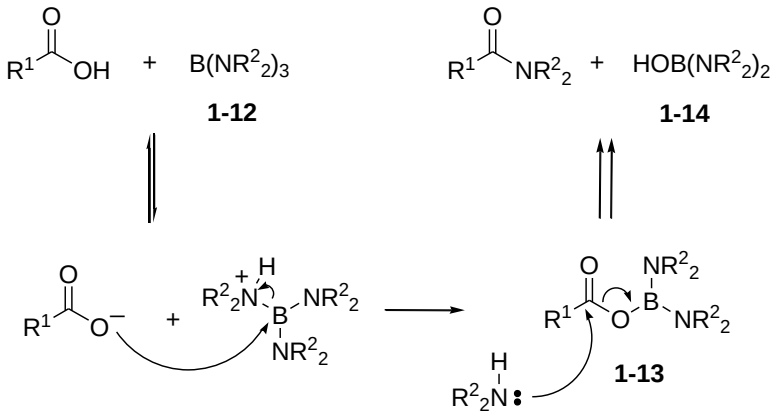
1.2.2.1 Stoichiometric Activation of Carboxylic Acids

Back in 1965, Pelter and co-workers reported the use of boranes as effective reagents for certain functional group transformations, such as converting ketones to enamines, β-ketoesters to enamine amides, β-ketones to β-enaminoketones and, especially, converting carboxylic acids to amides.[113]

1.2.2.1.1 Trisdialkylaminoborane [$B(NR'_2)_3$]

The mixing of carboxylic acids with *trisdialkylaminoboranes* [$B(NR'_2)_3$] **1-12** in inert conditions is found to be exothermic. Depending on the carboxylic acid used, the reaction might need cooling or refluxing at 120 °C for several hours to provide the desired amide product. There is no need for any additional reagents to be added. Interestingly, only one of the dialkylamino groups was consumed for this amide transformation (**Scheme 1-14**).[113, 114] In the proposed mechanism, mixing the acid and the borane reagent **1-12** initiates salt formation followed by the attack of carboxylate to form the activated mixed anhydride **1-13**. Once this mixed anhydride **1-13** is formed, nucleophilic attack of the amine at the acyl carbon provides the amide product and the borane species **1-14**. The limitations of this methodology are: only one of the amino groups is utilized; potential racemizations; and limited

substrate scope since aminoboranes are reactive reagents and few organic functional groups are tolerant of these reaction conditions.[115]



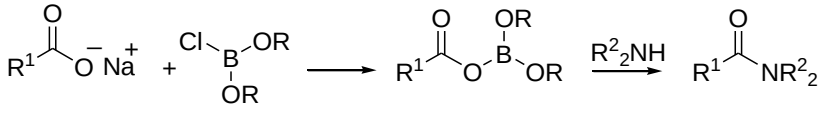
Scheme 1-14: Proposed mechanism for direct amide bond formation from mixing carboxylic acids with trisdialkylaminoboranes.[113, 114]

1.2.2.1.2 Trialkylboranes [BR_3] & Trialkoxyboranes [$B(OR)_3$]

Using a model amidation reaction between hexanoic acid and butylamine, different borane reagents have been examined. The use of *trialkylboranes* [BR_3] was found to be less active than the borane **1-12** and the amide product only formed when refluxing at temperatures upwards of 138 °C for several hours. On the other hand, a high excess of *trialkoxyboranes* [$B(OR)_3$] is necessary for this reaction, no product was formed at room temperature, and heating for several hours was required in order to provide the amide product alongside trace amounts of ester.[115]

1.2.2.1.3 Chlorodialkoxyboranes [$ClB(OR')_2$]

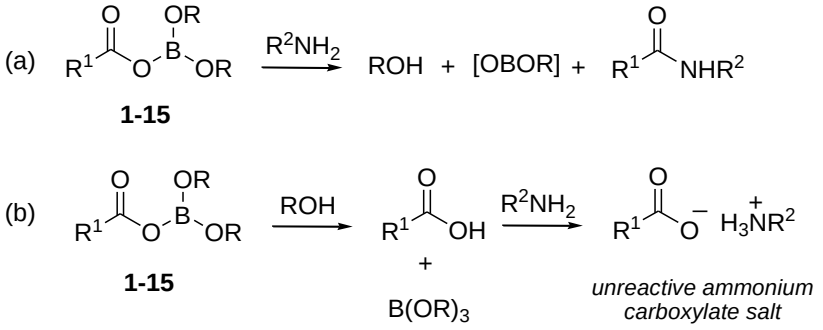
Further studies by the same group demonstrated that *acyloxydialkoxyboranes* [$RCO_2B(OR')_2$] were promising candidates for direct amide bond formation.[115, 116] These intermediates can be formed by the reaction between *chlorodialkoxyboranes* [$ClB(OR')_2$] and the sodium salt of carboxylic acids, as outlined in **Scheme 1-15**. This reaction proceeded quickly and there was infrared evidence (1710 cm^{-1}) for the formation of the mixed anhydride **1-15**. More interestingly, the addition of methanol to the mixed intermediate **1-15** at room temperature gave no ester. In contrast, the addition of amine at room temperature rapidly gave the amide product in **44% yield**. This was increased to **70%** by heating the reaction mixture.[115, 116]



1-15

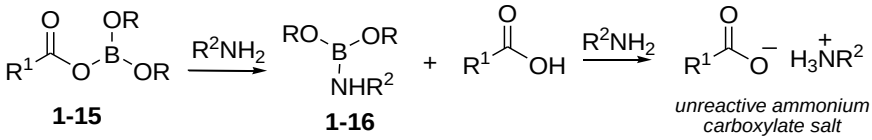
Scheme 1-15: Direct amide bond formation through acyloxydialkylborane.[115, 116]

The efficiency of this method was tested in peptide synthesis by the preparation of benzoyl-L-leucylglycine ethyl ester. The sodium salt of benzoyl-L-leucine was reacted with *chlorodialkyloxyborane* in benzene at room temperature and then glycine ethyl ester was added. The desired benzoyl-L-leucylglycine ethyl ester was isolated in **31%** yield with **10%** racemization. Heating the reaction to 55 °C gave complete racemization. Further studies were carried out to investigate the reason why low conversions were obtained at room temperature. It was found that the reaction between the amine and the mixed anhydride **1-15** ejects one equivalent of alcohol (**Scheme 1-16**). This alcohol reacts with the mixed anhydride **1-15** at the boron atom, which competitively destroys it and results in the formation of the stable ammonium carboxylate salts and therefore low conversions.[115, 116]



Scheme 1-16: (a) Liberation of alcohol; (b) formation of unreactive ammonium carboxylate salt.[115, 116]

One other explanation is that the amine can attack the boron on mixed anhydride **1-15**, giving the aminodialkyloxyborane **1-16** and the stable ammonium carboxylate salt (**Scheme 1-17**).[116]

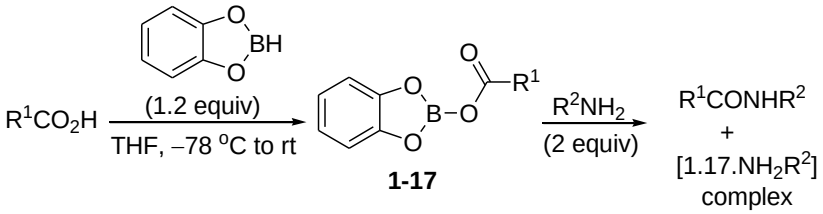


Scheme 1-17: Formation of an aminodialkyloxyborane species.[116]

1.2.2.1.4 Borane and Catecholborane

Trapani *et al*.[117] described the use of borane trimethylamine complex in direct amide-bond formation. The molar ratio 1:1:3 between the amine: borane: carboxylic acid, respectively, provided the amide product in good yield under refluxing xylene conditions. It was claimed that the triacyloxyborane intermediate is the activated acylating species. However, there was no evidence for this conclusion.

In 1978, Ganem and co-workers described the use of a stoichiometric amount of catecholborane and other catechol derivatives as effective boron reagents for the direct amide formation between carboxylic acids and amines under mild conditions, such as THF, –78 °C to room temperature, as outlined in **Scheme 1-18**.[118]

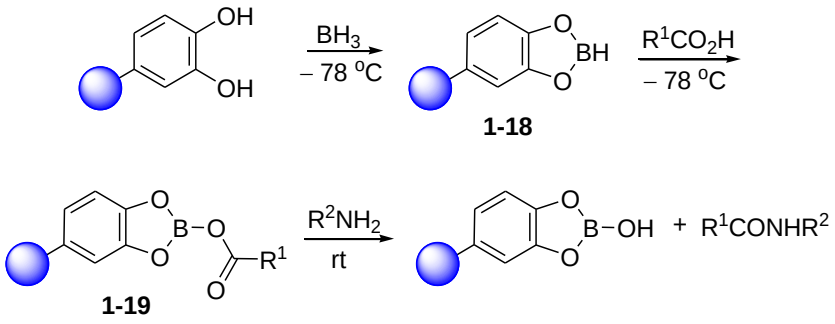


Scheme 1-18: Ganem's amide bond formation using catecholborane.[118]

The authors claimed that the mixing of carboxylic acid and catecholborane gave the active intermediate 2-acyloxy-1,2,3-benzodioxaborolane **1-17** (1740 cm^{-1} carbonyl absorption). The reaction requires two equivalents of amine, since it proceeds by the nucleophilic attack of the amine onto the intermediate **1-17** at the boron atom to form [**1-17**.amine] complex. [118]

In 2002, Wang and co-workers described the use of solid-phase catecholborane **1-18** as an effective solid-phase boron reagent for direct amide bond formation between amines and carboxylic acids (**Scheme 1-19**).[119] After forming the solid-phase catecholborane by reacting the catechol with BH_3, the carboxylic acid was

added and the mixture was shaken to form the activated mixed anhydride **1-19**. The amine was then added at ambient temperature to form the desired amide product in moderate yields.



Scheme 1-19: Wang's solid-supported catecholborane solid-phase for direct amide bond formation.[119]

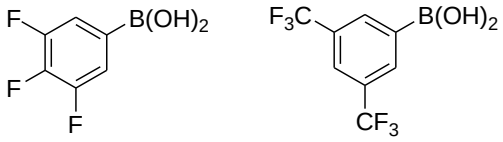
1.2.2.2 Catalytic Activation of Carboxylic Acids

The development of a catalytic method or ideally, a lower EI-factor method, is the most desirable approach to optimize the environmental profile of many processes. The formation of amide bonds is one of the most common transformations carried out in the pharmaceutical industry. The direct catalytic condensation between carboxylic acids and amines is generally understood to be impossible, due to the formation of an unreactive carboxylate–ammonium salt. Moreover, as explained before (c.f. Section 1.2.1.2.), the use of Lewis or Brønsted acids, which is well known to activate the carbonyl group, is of no help in the presence of the amine. Although the direct thermal formation of amide bonds without catalysts has been known since 1858,[120] to this day this process has found little synthetic utility. Very recently, boric acid and boronic acids have provided the most promising approach to this long-standing problem in chemical synthesis.

1.2.2.2.1 Electron-poor Arylboronic Acids

In 1996, Yamamoto and co-workers described for the first time the use of catalytic arylboronic acids for direct amide bond formation at reflux temperature in toluene.[121] These authors found that arylboronic acids bearing electron-withdrawing groups at *meta*- or *para*- positions are active in nonpolar solvents at

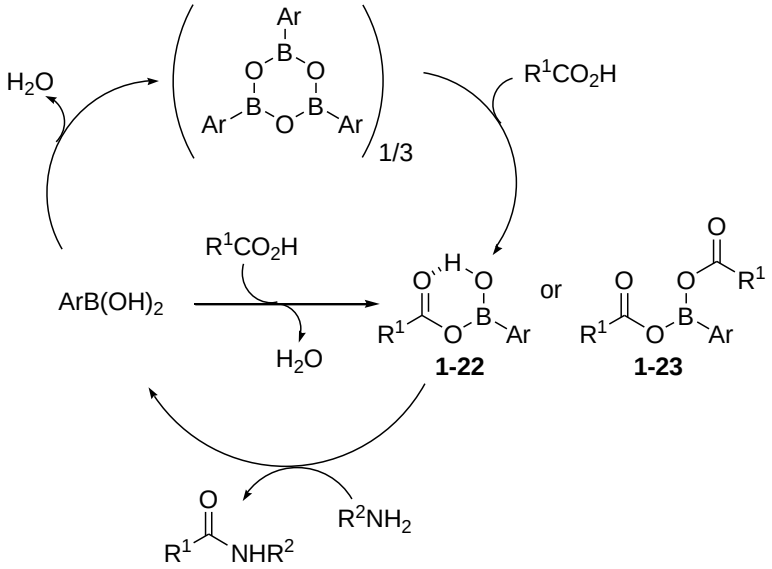
azeotropic-reflux using 4 Å molecular sieves to remove the water in a Soxhlet thimble. 3,4,5-Trifluorophenylboronic acid (**1-20**) and 3,5-bis(trifluoromethyl)phenylboronic acid (**1-21**) catalyzed the amide bond formation in toluene, as shown in **Figure 1-17**. 3,4,5-Trifluorophenylboronic acid (**1-20**) was found to be the most active arylboronic acid. However, the reaction still required a high reaction temperature of reflux in toluene for several hours to produce a 96% yield when using simple substrates, such as 4-phenylbutyric acid and benzylamine.



1-20 **1-21**

Figure 1-17: Structures of 3,4,5-trifluorophenylboronic acid 1-20 (Yamamoto catalyst) and 3,5-trifluoromethylphenylboronic acid 1-21.[121]

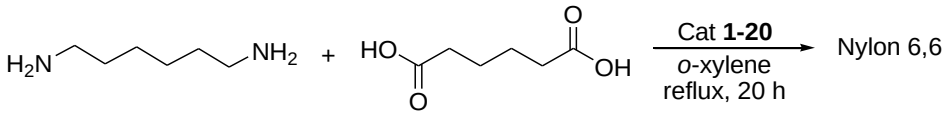
For more demanding substrates, like aniline instead of benzylamine, more forcing conditions were employed and the reaction required refluxing in mesitylene (163 – 166 °C) for several hours to provide the amide in 99% yield.[121] The rate-determining step for this catalyzed reaction was proposed to be the formation of the mixed anhydride, monoacyloxyboronate intermediate **1-22** or the diacylboronate **1-23**.[121-123] The proposed mechanism is outlined in **Scheme 1-20**.[121]



Scheme 1-20: Proposed cycle for boronic acid catalyzed direct amide bond formation.[121]

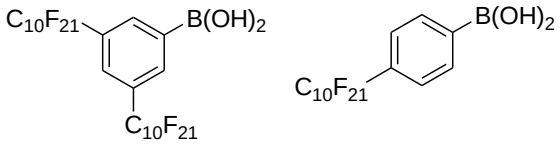
The authors claimed that monoacyloxyboronate **1-22** "the mixed anhydride" is produced, which is then attacked by the amine to form the amide product. The reported ^{1}H-NMR and IR data for the active intermediate are inconclusive without any ^{11}B-NMR data. It was claimed that the peak at 1586 cm^{-1} in the IR spectrum is for the monoacylboronate **1-22**. According to Ganem's work, the monoacylboronate **1-22** was observed at 1740 cm^{-1} by IR and the free acid at 1709 cm^{-1}. Indeed, further investigations are required to determine whether the monoacylboronate **1-22** is the active species or whether other species are involved. However, the scope of suitable substrates for this methodology was limited because the catalytic activities of these neutral boronic acids are greatly reduced in polar solvents and with sterically demanding substrates.

In 2000, the same group showed that 3,4,5-trifluorophenylboronic acid (**1-20**) is also an effective catalyst for the polycondensation of dicarboxylic acids and diamines.[122] For instance, the direct condensation between adipic acid and hexamethylenediamine was achieved with 10 mol% of the catalyst **1-20** at reflux in *o*-xylene with the presence of 4 Å molecular sieves in a Soxhlet thimble (**Equation 1-4**) The polyamide product was isolated in 89% yield after 20 h and the average molecular weight number was estimated to be 2680. This result is increased to 4690 with the use of a 1 : 3 mixture of *m*-cresol and *o*-xylene.[122]



Equation 1-4: Boronic acid 1-20 catalyzed polyamidation between adipic acid and hexanediamine.[122]

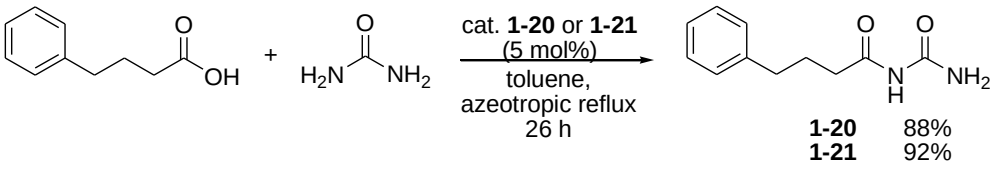
In 2001, other arylboronic acids, such as 3,5-bis(perfluorodecyl)phenylboronic acid **1-24** and 4-(perfluorodecyl)phenylboronic acid **1-25** (**Figure 1-18**), were developed and their catalytic reactivity was tested toward direct amide bond formations.[124] The catalytic activity of **1-24** was found to be greater than **1-25** under the same reaction conditions. Even though the catalytic activity of catalyst **1-24** was found to be less active than both **1-20** and **1-21**, it can be efficiently recovered after the reaction by extraction with a fluorous phase.[124]



1-24 **1-25**

Figure 1-18: Structures of 3,5-bis(perfluorodecyl)phenylboronic acid (1-24) and 4-(perfluorodecyl)phenylboronic acid (1-25).[124]

In 2002, Yamamoto and co-workers found that catalysts **1-20** and **1-21** are also good catalysts for the formation of *N*-acylurea, which can be formed by the reaction between carboxylic acids and urea.[125] Ureas are known to be less nucleophilic than amines. However, the *N*-acylurea products were formed in good yields between 4-phenylbutyric acid and urea (**Equation 1-5**).[125] The mechanism of this reaction is proposed to be the same as described in **Scheme 1-20**.



Equation 1-5: Arylboronic acid catalyze *N*-acylcarbamate formation between 4-phenylbutyric acid and urea.[125]

The major limitation of using all of these catalysts in amidation reactions is the use of elevated temperatures, "which is not compatible with many functionalized substrates and drugs".[8] Moreover, these methods tend to fail with sterically hindered substrates and the activity of these catalysts is restricted to use in non-polar solvents. To overcome some of these limitations, cationic arylboronic acids and solid-supported boronic acids have been developed.

In 2005, Ishihara and co-workers developed *N*-alkyl-4-boronopyridinium iodide **1-26** (**Figure 1-19**) as a more active catalyst than the neutral arylboronic acids for amide bond formation in polar solvents, such as anisole, acetonitrile and *N*-methylpyrrolidinone (NMP).[126] When boronic acid **1-26** is heated in DMF at 120 °C, it polymerizes to give a dodecamer **[1-26]$_{12}$** form (**Figure 1-19**) that precipitates as a yellow solid within 1 hour.

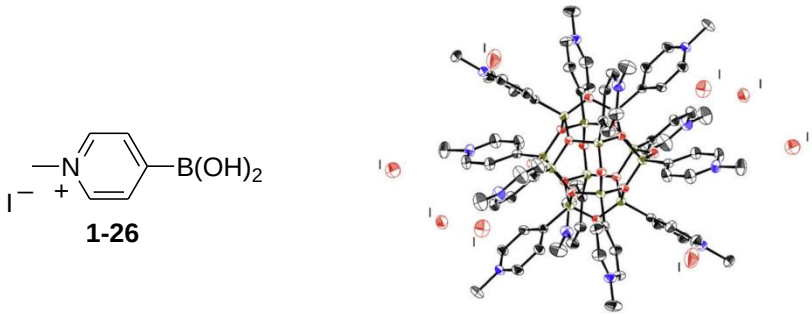
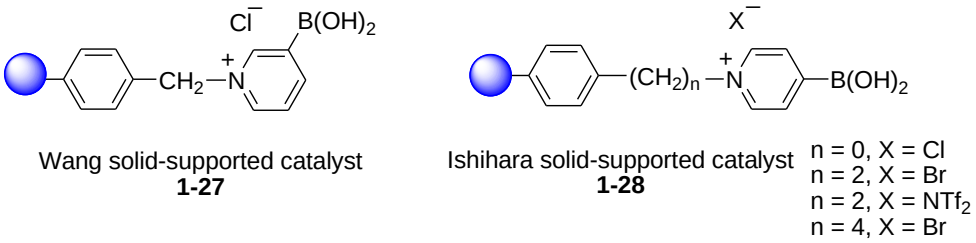


Figure 1-19: Structure of *N*-alkyl-4-boronopyridinium iodide 1-26 and X-ray structure of dodecamer [1-26]$_{12}$.[126]

The catalytic activities of **1-26** and [**1-26**]$_{12}$ (5 mol % for B atom) were compared in the amidation reaction between 4-phenylbutyric acid and benzylamine under azeotropic-reflux conditions in toluene with the removal of water. The catalytic activity of [**1-26**]$_{12}$ is much lower than that of **1-26**. However, the catalytic activity of **1-26** and the dodecamer **[1-26]$_{12}$** can be improved through the use of ionic-toluene biphasic solvents which were found to be a good mixture to regenerate **1-26** from [**1-26**]$_{12}$.[126]

Wang[127] and Ishihara[126] developed *N*-polystyrene-bound 4-boronopyridinium chloride **1-27** and *N*-polystyrene-bound 3-boronopyridinium chloride **1-28** in 2001 and 2005, respectively (**Figure 1-20**), aiming to recover and reuse the boronic acid catalysts in amidation reactions. Under azeotropic-reflux conditions, the required reaction conditions, a protodeboronation reaction was found to be one of the problems when using these heterogeneous catalysts. Under these harsh conditions, it is understandable that decomposition is taking place to give boric acid and *N*-polystyrene-bound pyridinium salts which indeed limits the long term use of these solid phase catalysts.[126-128] This decomposition in the form of "protodeboronation" is also expected to occur with other arylboronic acids under the same harsh conditions. This decomposition was further supported in 2005 when Tang and co-workers examined the catalytic activity of boric acid and other arylboronic acid in direct amide bond formation under azeotropic-reflux conditions.[129]



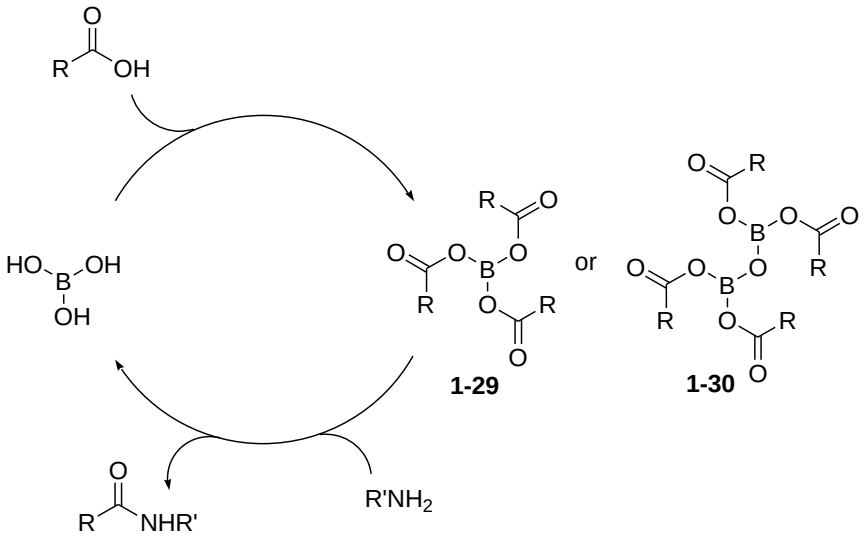
Wang solid-supported catalyst
1-27

Ishihara solid-supported catalyst
1-28

Figure 1-20: Structures of Wang and Ishihara solid-supported catalysts.[126, 127]

1.2.2.2.2 Boric Acid

In 2005, Tang and co-workers described the use of cheap and readily available boric acid alone as an efficient catalyst for direct amide bond formation under azeotropic-reflux conditions.[129] Benzylamines and cyclic aliphatic amines reacted with aliphatic carboxylic acids to provide the amide products in excellent yields with the use of a 5 mol% loading of $B(OH)_3$. It was observed that aromatic acids or amines required a longer reaction time and higher temperatures than the reaction between aliphatic acids and amines.[129] However, more demanding substrates required the use of higher loading of $B(OH)_3$ and higher reaction temperatures similar to those used in the case of anilines and benzoic acids. It was proposed that boric acid reacts with the carboxylic acid to form the mixed anhydride triacylborate **1-29** "the activated ester" or "tetraacyldiborate" species **1-30**,[75, 130, 131] which then reacts with the amine to form the desired amide product and boric acid is regenerated as described in **Scheme 1-21**.



Scheme 1-21: Proposed catalytic cycle for the direct amide bond formation with boric acid.

In 2007, Bandichhor and co-workers applied this methodology towards the synthesis of several active pharmaceutical ingredients (APIs) shown in **Figure 1-21**.[132] Using the same reaction procedure described by Tang and co-workers, this involved the addition of acid, amine derivative, and 10 mol% of boric acid under azeotropic-reflux conditions using a Dean–Stark apparatus and either toluene or xylene as solvent. A background reaction without the use of boric acid catalyst showed no or very low yields of the amide product.

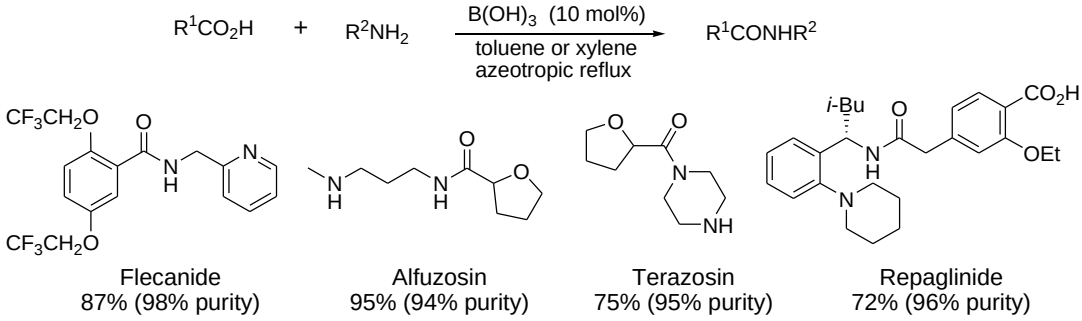
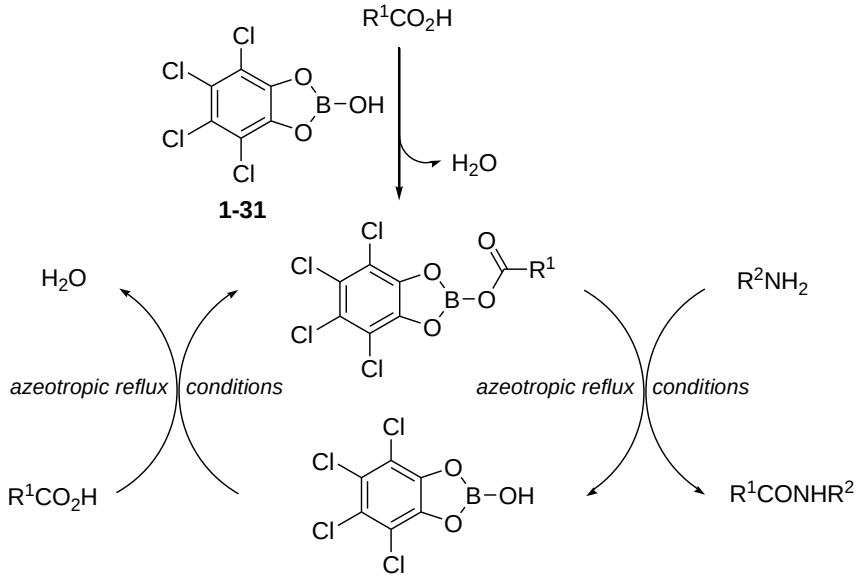


Figure 1-21: Boric acid catalyzed amide bond formation of some active pharmaceutical ingredients (APIs).[132]

Yamamoto and co-workers described the use of 4,5,6,7-tetrachlorobenzo-[*d*][1,2,3]dioxaborol-2-ol **1-31** as an effective catalyst for direct amide bond

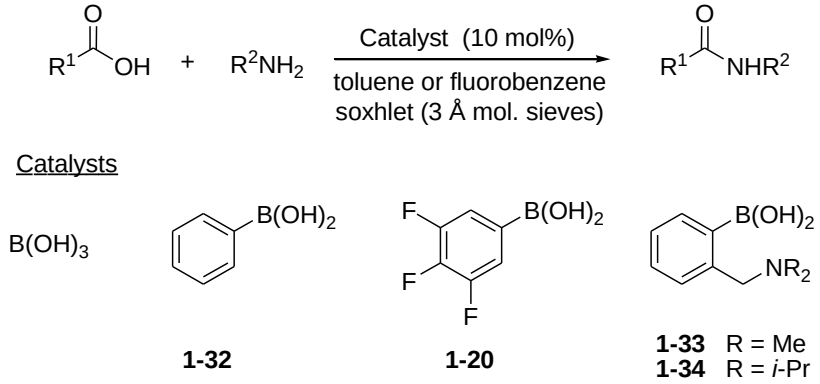
formation under azeotropic-reflux conditions.[133] According to Ganem's work, discussed in Section 1.2.2, page 30 of this thesis,[118] Yamamoto and co-workers found that **1-31** could be used to catalyze the amidation reaction between equimolar mixtures of carboxylic acids and amines with 5 mol% catalyst loading in toluene or *o*-xylene. The proposed mechanism is shown in **Scheme 1-22**. The 4,5,6,7-tetrachlorobenzo[d][1,3,2]dioxaborol-2-ol **1-31** is prepared in situ from tetrachlorocatechol and boric acid. The authors claimed that catalyst **1-31** is superior to boric acid for the direct amide bond formation between aliphatic and aromatic carboxylic acids.[128, 133] For example, catalyst **1-31** provided 94% of the desired amide product between 4-phenylbutyric acid and benzylamine in toluene under azeotropic conditions, while boric acid provided only 31% under the same reaction conditions. For more sterically demanding substrates, such as the reaction between cyclohexanecarboxylic acid and benzylamine, the product was isolated in 62% and 2% yields when using catalyst **1-31** and boric acid, respectively. Moreover, the catalytic activity of **1-31** is found to be the same as that of 3,5-bis(trifluoromethyl)phenylboronic acid (**1-21**) under the same azeotropic-reflux conditions.[133]



Scheme 1-22: Proposed catalytic cycle for direct amide bond formation using 4,5,6,7-tetrachlorobenzo[d][1,3,2]dioxaborol-2-ol 1-31.[101, 133]

1.2.2.2.3 Aminoarylboronic Acids

In 2006, Whiting and co-workers described the use of aminoarylboronic acids as efficient bifunctional catalysts for direct amide bond formation at lower reaction temperature.[123] They provided comparative kinetic studies of the uncatalyzed (thermal) and boric acid, arylboronic acids **1-32** and **1-20**, and the aminoarylboronic acids **1-33** and **1-34** catalyzed reactions in refluxing toluene (120 °C) and in fluorobenzene (85 °C) (**Scheme 1-23**).[123] These studies showed that the catalyst **1-34** clearly improved the amide bond formation for more difficult substrates, such as benzoic acid derivatives, and less electron-rich amines (aniline) at lower reaction temperatures than other monofunctional arylboronic acids **1-20** and **1-32**, and boric acid catalysts.



Scheme 1-23: General direct amide bond formation and structure of boron catalysts.[123]

Moreover, boric acid was found to be less reactive at lower temperature than other arylboronic acids. In contrast, in fluorobenzene (85 °C), it was shown that protodeboronation of arylboronic acids did not take place as was observed with the use of toluene (120 °C) or xylene (160 °C) and that catalytic effects assisted the reactions considerably above background uncatalyzed reactions.[123] One of the most attractive features of this study was demonstrated on the catalytic activity of the less basic and less hindered bifunctional catalyst **1-33**, which was found to be less reactive than **1-34** under the same substrate combinations and reaction conditions. Its reactivity was found to be close to **1-20**. The authors claimed that catalyst **1-34** showed no B–N coordination in both solution and the solid state, whereas **1-33** only

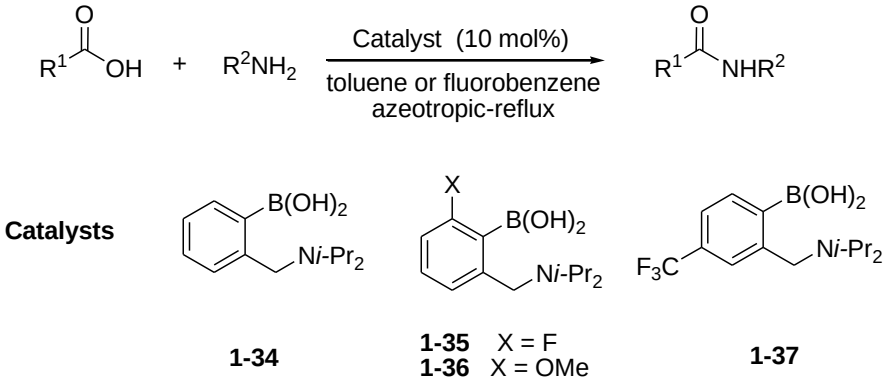
showed B–N coordination under these conditions.[134] This suggests that amine coordination might occur intramolecularly as in catalyst **1-33**, or intermolecularly by the use of excess amine and in both cases, the reactivity of these catalysts is diminished.

The authors also addressed more issues based on their kinetic studies, such as:

1. The thermal azeotropic reaction of ammonium carboxylate salts in non-polar solvent conditions, in which the salts quickly formed and precipitated, did produce amide products; however, the reaction was highly substrate and temperature dependent.
2. The more electron-deficient arylboronic acid catalyst **1-20** was an effective catalyst for amide formation reactions,[121, 135] and similar results were observed for boric acid at higher temperatures.
3. The general reactivity of boric acid at higher temperatures might be explained by forming the tetraacyldiborate intermediate **1-30** (**Scheme 1-21**)[130] or triacylborane intermediate **1-29** (**Scheme 1-21**), which has also been shown to react via amine complex intermediates to provide the desired amide products.[114, 116] It is possible that formation of these species is essential for the catalytic activity of boric acid and that the higher temperature (refluxing toluene) is assisting the catalyst recycling.
4. Hindered bifunctional catalyst **1-34** is assisting the amide bond formation of certain substrate-dependent reactions at lower temperature (fluorobenzene, bp: 85 ^{o}C) compared to less hindered bifunctional system **1-33**, unsubstituted **1-32** and the more electron deficient system **1-20**.[123] They also showed that the combination of both electron deficient arylboronic acid and an intermolecular base such as diisopropylamine, does not lead to significant enhancement of reactivity compared to bifunctional catalyst **1-34** under the same reaction conditions.[123]
5. NMR (^{1}H, ^{13}C and ^{11}B) and IR[121] spectroscopic studies are not sufficient to determine exactly which acylating species are produced during these amide formation reactions.[123]
6. The reaction was found to display first-order kinetics for the combination between 4-phenylbutyric acid and benzylamine and the rate determining step was most likely to be the formation of acyloxyboronate species “the

activated ester", the monoacylboronate **1-22** or the diacylboronate **1-23** species.[123]

In 2008, Whiting proposed that a combination of a more basic and hindered bifunctional system together with an electron-withdrawing group might enhance the catalytic activity of these bifunctional aminoarylboronic acids.[136] Thus, different *ortho*- and *para*- functionalized *N*,*N*-di-*iso*-propylbenzylaminoboronic acid derivatives were made (**Scheme 1-24**).[136, 137]



Scheme 1-24: Whiting's bifunctional catalysts for direct amide bond formation.[136, 137]

Ortho-fluorine derivative **1-35** decreased the reaction rate to a small extent compared to **1-34,** as outlined in **Figure 1-22**. The differences between catalysts **1-34**, **1-35** and **1-36** are not very significant. Switching to more electron-rich substituents, such as *ortho*-methoxy group **1-36**, led to a considerable decrease in reaction rate compared with other catalysts under the same reaction conditions. In contrast, increasing the acidity of **1-34** by adding a trifluoromethyl group at the *para* position as in **1-37**, increased the reaction rate for direct amide formation compared to catalyst **1-34** under lower temperature conditions (i.e. refluxing fluorobenzene).[136]

According to the results of the Yamamoto, Ishihara and Whiting groups, the rate determining step for direct amide bond formation is most likely to be the formation of the activated ester, either the monoacylboronate **1-22,** as proposed by Yamamoto *et al*.,[121] or the diacylboronate **1-23** proposed by Whiting and co-workers.[123] Indeed, different substituents on the arylboronic acid system have great influence

on the reactivity of these catalysts. The use of more electron poor substituents increased the Lewis acidity on the boron and therefore, increased the reactivity with the carboxylate to form the activated ester and consequently increased the rate of the amidation reaction. Moreover, the position of the electron withdrawing groups was also found to be crucial. For instance, having electron-withdrawing substituents at *ortho* positions, such as **1-35** and **1-36,** increased the Lewis acidity relatively to neutral arylboronic acid, but consequently decreased the reactivity of these catalysts by increasing the steric environment around the boron atom and hence disfavored the formation of the activated ester.

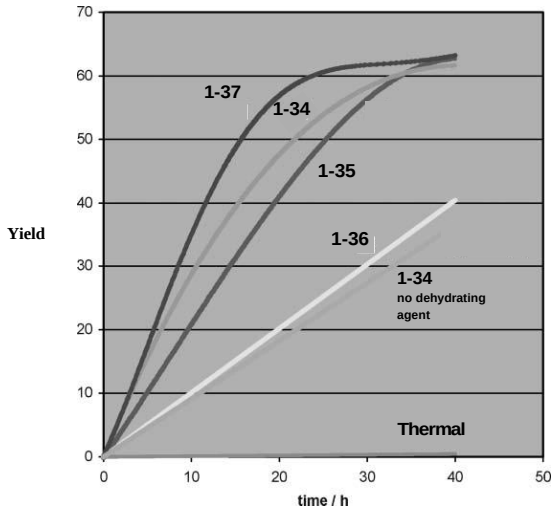
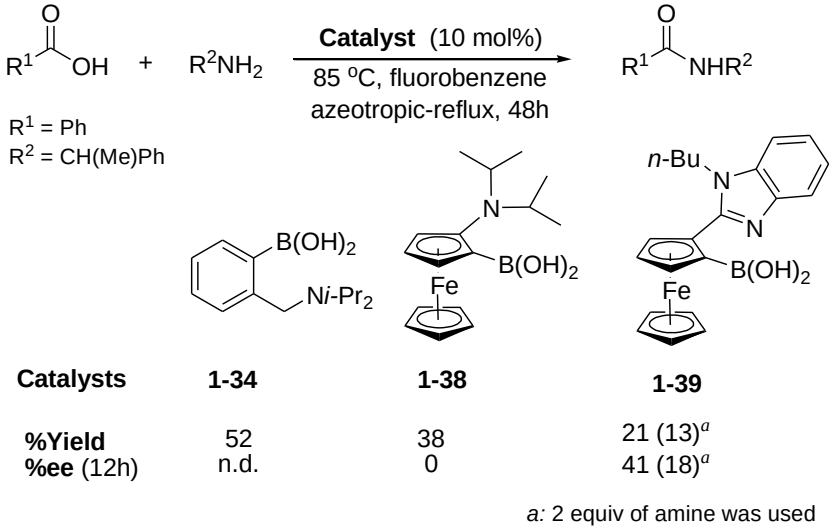


Figure 1-22: Yield *versus* time/h for catalyzed and thermal direct amide bond formation between benzoic acid and benzylamine in refluxing fluorobenzene.[136]

It is also relevant to note that Brown and co-workers reported the influence of the substituents on the formation of acyloxyboranes from the reaction between carboxylic acids and boranes.[138] The use of carboxylic acids with lower pKa values slowed the formation of acyloxyboranes. This result can be used to explain the difference in the rate of reaction, in addition to the steric factor, between aliphatic and aromatic carboxylic acids toward direct amide bond formation, such as 4-phenylbutyric acid (pKa = 4.76) and benzoic acid (pKa = 4.19).[123] Therefore, the more electron-rich carboxylic acid is essentially more reactive towards formation of the acyloxyboronate, and therefore leads to a faster amidation reaction.

In 2008, Whiting and co-workers reported the first asymmetric direct amide formation *via* kinetic resolution of racemic α-substituted benzylamines with achiral carboxylic acids using a planar, chiral ferrocene based bifunctional amino–boronic acid catalyst, such as (*p*S)-2-(2-boronoferrocenyl)-*N,N-diisopropylamine* **1-38** and (*p*S)-2-(2-boronoferrocenyl)-*N*-*n*-butylbenzimidazole **1-39** (**Scheme 1-25**).[139]

There are no published reports for direct amide formation involving asymmetric induction except the Whiting[139] work on chiral ferrocene-based bifunctional amino–boronic acids. This can be explained by the fact that this process usually requires high reaction temperatures, which would lead to reactant/product racemization or degradation; therefore, low chirality transfer to the desired amide product. The solution for this problem was the development of asymmetric induction processes that can occur efficiently at lower reaction temperatures.



Scheme 1-25: Direct amide bond formation with chiral bifunctional aminoboronic acid under azeotropic fluorobenzene conditions.[139]

Catalyst **1-38** provided 38% yield after 48 h as a racemic mixture, while **1-39** provided the desired amide product in 21% yield after 48 h, and 41% ee after 12 h (**Scheme 1-25**). It is noteworthy that with an increase of the reaction time, a lower enantioselectivity was observed. In addition, lower yields and enantioselectivity were observed when using 2 equivalents of amine (**Scheme 1-25**).[139] When more reactive achiral carboxylic acids were used, such as an aliphatic carboxylic acid, the enantioselectivity was reduced.[139] The authors claimed that the reason for

achieving low enantioselectivity was due to the protodeboronation reaction which led to competitive side reactions from boric acid. It was proposed[139] that the nitrogen-boron distance had a major impact on the enantioselectivity of the final amide product. This proximity facilitates the postulated hydrogen bonding between the benzimidazole group and the incoming ammonium salt, which reacts with the activated ester, the monoacylboronate **1-22** or diacylboronate **1-23** intermediates.[123] Consequently, catalyst **1-39** was able to select one amine enantiomer of α-chiral benzylamine at the hydrogen bonding stage to provide the desired amide product with low to moderate enantioselectivity, as depicted in **Figure 1-23.**[101, 137, 139]

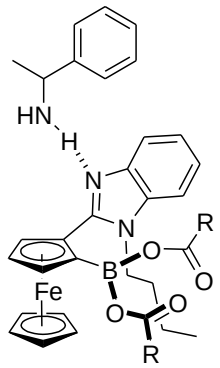


Figure 1-23: Proposed transition state for the enantioselectivity in amidation using catalyst 1-39.[101, 137, 139]

1.3 Conclusion

Although the thermal direct formation of amide bonds has been known since 1858,[120] the mechanism of the reaction remains poorly understood and is still a major scientific issue. The direct reaction between amines and carboxylic acids generates a thermodynamically stable ammonium carboxylate salt. In order to generate amide bonds from these salts, harsh reaction conditions with temperatures as high as 250 °C are required. Consequently, a preactivation of the acid is necessary. The majority of the published methods use stoichiometric reagents that have very poor atom economy and are associated with many limitations, such as poor reactivity, low conversions, toxicity, side reactions, racemizations, high costs and cumbersome purifications. For instance, uronium salts, such as HATU and HBTU, have become widely used in research but have poor atom economy by

producing a lot of by-products. The phosphorus-based reagents, BOP and PyBOP, have even worse atom economy. BOP has the further major disadvantage that its manufacture and use involve HMPA, a known carcinogenic agent. Dicyclohexyl carbodiimide (DCC) and diisopropyl carbodiimide (DIC) are two of the most common reagents used in the pharmaceutical industry; but they are not "green" and in recent years have become rarely used for scale-up.

Recently, boron reagents have provided a prospect for much "greener" alternatives and the most attractive approach for this long-standing problem. The use of a catalytic amount of arylboronic acids for direct amide formation offers generally more environmentally benign reaction conditions than most other reagents. However, there are a few limitations with the use of these catalysts. First, the reaction conditions require high temperatures in refluxing solvents, such as toluene (120 ^{o}C) or xylene (160 ^{o}C), for several hours, which is close to the optimum temperature required for classical thermal amidation conditions observed by Jursic and co-workers in 1993. These conditions are indeed harsh and incompatible with many substrates. Secondly, the stability of arylboronic acids at high temperatures is poor and they are known to decompose to form boric acid, as observed by Wang and Whiting in 2001 and 2008, respectively. These shortcomings will retard the long term use of these catalysts. Thirdly, the catalytic activities of these neutral arylboronic acids are greatly reduced in polar solvents, reducing the generality and limiting the substrate scope. Recently, Whiting and co-workers developed bifunctional aminoarylboronics acids as very active catalysts for direct amide bond formation. These catalysts are functional at lower temperatures than other arylboronic acids, for example, refluxing fluorobenzene (85 ^{o}C) for several hours. Unfortunately, these conditions are still harsh enough to decompose arylboronic acids. Tang and co-workers found that boric acid is also an active catalyst for direct amide bond formations. Boric acid, however, is a generally less active catalyst that requires higher reaction temperatures than normal arylboronic acid catalysts.

The development of a catalytic process in which the amide bond can form directly from amines and carboxylic acids at ambient temperature would be the optimum solution to overcome the limitations of racemization, decomposition, unwanted side reactions and poor atom economy.

1.4 Project Objectives

The objective of this research project was the identification of catalysts for direct amide bond formation that would function under practical, benign and mild conditions at room temperature and with high atom economy. The Hall group is interested in the synthesis and applications of *ortho*-functionalized arylboronic acids that can modulate or tune the reactivity of the boron atom towards different reactions.

A comprehensive overview on the catalytic and stoichiometric methods for direct amide bond formation between amines and carboxylic acids is given in Chapter One. This project started by screening different potential *ortho*-substituted arylboronic acids in order to find a promising catalyst that could activate carboxylic acids at ambient temperature. Chapter Two discusses our initial attempts towards identifying such a catalyst and the optimized reaction conditions for direct amide bond formation.

An improved second generation catalyst that exhibits superior reactivity toward direct amide bond formation over its predecessors is discussed in Chapter Three. Different investigations in the electronic and structural development of the second generation catalysts are also discussed, with an attempt to explain the unique reactivity of these catalysts.

In Chapter Four, a remarkable methodology for regioselective *ortho*-iodination of arylboronic acids is described. This methodology provided the desired iodoarylboronic acid catalysts in only one step directly from cheap and available starting materials.

1.5 References

[1] D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer Jr, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411.

[2] P. D. Bailey, *An Introduction to Peptide Chemistry*, Wiley: Verlag Sauerlander AG, Aarau, **1990**.

[3] G. A. E. Grant, *Synthetic Peptides*, UWBC, Newwork, **1992**.

[4] B. E. Gutte, *Peptides: Synthesis, Structures, and Applications*, Academic Press, London, **1995**.

[5] M. Bodanszky, *Principles of Peptide Synthesis*, Springer-Verlag, Berlin, **1993**.

[6] J. Jones, *The Chemical Synthesis of Peptides*, Oxford University Press, Oxford, **1994**.

[7] R. V. Ulijn, B. D. Moore, A. E. M. Janssen, P. J. Halling, *J. Chem. Soc. Perkin Trans. 2,* **2002**, 1024.

[8] B. S. Jursic, Z. Zdravkovski, *Synth. Commun.* **1993**, *23*, 2761.

[9] C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827.

[10] J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337.

[11] W. Chu, Z. Tu, E. McElveen, J. Xu, M. Taylor, R. R. Luedtke, R. H. MacH, *Bioorg. Med. Chem.* **2005**, *13*, 77.

[12] J. S. Pizey, Ed. , *Synthetic Reagents, Vol. 1*, Wiley: New York, **1974**.

[13] A. J. Pearson, W. R. Roush, Eds., *Handbook of Reagents for Organic Synthesis: Activating Agents and Protecting Groups*, Wiley, New York, **1999**.

[14] R. Adams, *J. Am. Chem. Soc.* **1920**, *42*, 599.

[15] S. Knapp, F. S. Gibson, *Org. Synth.* **1998**, *9*, 516.

[16] I. Kuwajima, H. Urabe, *Org. Synth.* **1993**, *8*, 486.

[17] J. Klosa, *J. Prakt. Chem. (Leipzig)* **1962**, *19 (1-2)*, 45.

[18] M. F. Antell, *The Chemistry of Acyl Halides*, Interscience, London, **1972**.

[19] R. Bruckner, *Advanced Organic Chemistry, Reaction Mechanisms*, Harcourt/Academic San Diego, **2002**.

[20] H. H. Bosshard, Mory, R., Schmid, M., Zollinger, H., *Helv. Chim. Acta* **1959**, *42*, 1653.

[21] Bruckner, R. *Advanced Organic Chemistry, Reaction Mechanisms*, Harcourt/Academic San Diego, **2002**, p. 239.

[22] K. Venkataraman, Wagle, D.R., *Tetrahedron Lett.* **1979**, *20*, 3037.

[23] A. Devos, J. Remion, A.-M. Frisque-Hesbain, A. Colens, L. Ghosez, *J. Chem. Soc., Chem. Commun.* **1979**, 1180.

[24] B. Thern, J. Rudolph, G. Jung, *Tetrahedron Lett.* **2002**, *43*, 5013.

[25] E. Falb, T. Yechezkel, Y. Salitra, C. Gilon, *J. Pept. Res.* **1999**, *53*, 507.

[26] M. Zouikri, A. Vicherat, A. Aubry, M. Marraud, G. Boussard, *J. Pept. Res.* **1998**, *52*, 19.

[27] I. M. Downie, J. B. Lee, M. F. S. Matough, *Chem. Commun.* **1968**, 1350.

[28] J. B. Lee, *J. Am. Chem. Soc.* **1966**, *88*, 3440.

[29] F. I. Luknitskii, B. A. Vovsi, *Usp. Khim.* **1969**, *38*, 1072.

[30] L. A. Carpino, M. Beyermann, H. Wenschuh, M. Bienert, *Acc. Chem. Res.* **1996**, *29*, 268.

[31] L. A. S.-A. Carpino, D.; Chao, H. G.; DeSelms, R. H., *J. Am. Chem. Soc.* **1990**, *112*, 9651.

[32] G. A. Olah, M. Nojima, I. Kerekes, *Synthesis* **1973**, 487.

[33] J. Savrda, L. Chertanova, M. Wakselman, *Tetrahedron* **1994**, *50*, 5309.

[34] L. A. Carpino, A. El-Faham, *J. Am. Chem. Soc.* **1995**, *117*, 5401.

[35] S. V. V. Badu, H. N. Gopi, K. Ananda, *Indian J. Chem. Sect. B* **2000**, *39*, 384.

[36] G. S. Lal, G. P. Pez, R. J. Pesaresi, F. M. Prozonic, H. Cheng, *J. Org. Chem.* **1999**, *64*, 7048.

[37] G. S. LaI, G. P. P. Pez, R. J., F. M. Prozonic, *Chem. Commun.* **1999**, 215.

[38] G. S. Lal, E. Lobach, A. Evans, *J. Org. Chem.* **2000**, *65*, 4830.

[39] K. E. Pryor, G. W. Shipps, Jr., D. A. Skyler, J. Rebek, Jr., *Tetrahedron* **1998**, *54*, 4107.

[40] H. J. Bestmann, R. Kunstmann, H. Schulz, *Justus Liebigs Ann. Chem.* **1966**, *699*.

[41] P. Froeyen, *Synth. Commun.* **1995**, *25*, 959.

[42] S. D. Saraf, M. Zaki, *Synthesis* **1973**, 612.

[43] S. Bains, J. Green, L. C. Tan, R. M. Pagni, G. W. Kabalka, *Tetrahedron Lett.* **1992**, *33*, 7475.

[44] L. E. Overman, A. L. Tomasi, *J. Am. Chem. Soc.* **1998**, *120*, 4039.

[45] A. DalPozzo, M. M. Ni, L., A. Caporale, R. de Castiglione, B. Kaptein, Q. B. Broxterman, F. Formaggio, *J. Org. Chem.* **2002**, *67*, 6372.

[46] M. Mikolajczyk, P. Kielbasinski, *Tetrahedron* **1981**, *37*, 233.

[47] S. J. Wittenberger, M. A. McLaughlin, *Tetrahedron Lett.* **1999**, *40*, 7175.

[48] B. Belleau, G. Malek, *J. Am. Chem. Soc.* **1968**, *90*, 1651.

[49] K. Poduska, H. Gross, *Chem. Ber.* **1961**, *49*, 527.

[50] H. Leuchs, *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 857.

[51] W. D. Fuller, M. P. Cohen, M. Shabankareh, R. K. Blair, M. Goodman, F. R. Naider, *J. Am. Chem. Soc.* **1990**, *112*, 7414.

[52] T. Shioiri, S.-I. Yamada, *Chem. Pharm. Bull.* **1974**, *22*, 849.

[53] T. Shioiri, K. Ninomiya, S. Yamada, *J. Am. Chem. Soc.* **1972**, *94*, 6203.

[54] S. Takuma, Y. Hamada, T. Shioiri, *Chem. Pharm. Bull.* **1982**, *30*, 3147.

[55] S.-I. Yamada, Y. Kasai, T. Shioiri, *Tetrahedron Lett.* **1973**, 14, 1595.

[56] R. D. Tung, D. H. Rich, *J. Am. Chem. Soc.* **1985**, *107*, 4342.

[57] J. Diago-Meseguer, A. L. Palomo-Coll, *Synthesis* **1980**, 547.

[58] T. Katoh, M. Ueki, *Int. J. Pept. Protein Res.* **1993**, *42*, 264.

[59] S. Chen, J. Xu, *Tetrahedron Lett.* **1991**, *32*, 6711.

[60] Y. Kiso, T. Miyazaki, M. Satomi, H. Hiraiwa, T. Akita, *J. Chem. Soc., Chem. Commun.* **1980**, 1029.

[61] G. T. Panse, S. K. Kamat, *Indian J. Chem. Sect. B* **1989**, 793.

[62] M. Miyake, M. Kirisawa, N. Tokutake, *Chem. Lett.* **1985**, 123.

[63] S. Kim, H. Chang, Y.-K. Ko, *Tetrahedron Lett.* **1985**, *26*, 1341.

[64] C.-X. Fan, X.-L. Hao, Y.-H. Ye, *Synth. Commun.* **1996**, *26*, 1455.

[65] J. C. Sheehan, G. P. Hess, *J. Am. Chem. Soc.* **1955**, *77*, 1067.

[66] G. M. Gangwar, T. Pauletti, J. Siahaan, V. J. Stella, R. T. Borchardt, *J. Org. Chem.* **1997**, *62*, 1356.

[67] L. Kisfaludy, I. Schón, T. Szirtes, O. Nyéki, M. Lów, *Tetrahedron Lett.* **1974**, *19*, 1785.

[68] P. H. Bentley, H. Gregory, A. H. Laird, J. S. Morley, *J. Chem. Soc., Suppl.* **1964**, 6130.

[69] C. Kitada, M. Fujino, *Chem. Pharm. Bull.* **1978**, *26*, 585.

[70] M. Fujino, S. Kobayashi, M. Obayashi, T. Fukuda, S. Shinagawa, O. Nishimura, *Chem. Pharm. Bull.* **1974**, *22*, 1857.

[71] L. A. Carpino, *J. Am. Chem. Soc.* **1993**, *115*, 4397.

[72] G. C. Windridge, E. C. Jorgensen, *J. Am. Chem. Soc.* **1971**, *17*, 6318.

[73] M. Bodanszky, *Nature* **1955**, *175*, 685.

[74] F. S. Gibson, M. S. Park, H. Rapoport, *J. Org. Chem.* **1994**, *59*, 7503.

[75] G. W. Anderson, R. Paul, *J. Am. Chem. Soc.* **1958**, *80*, 4423.

[76] R. Paul, W. Anderson, *J. Am. Chem. Soc.* **1960**, *82*, 4596.

[77] H. A. Staab, M. Lueking, F. H. Duerr, *Chem. Ber.* **1962**, *95*, 1275.

[78] A. K. Saha, P. Schultz, H. Rapoport, *J. Am. Chem. Soc.* **1989**, *111*, 4856.

[79] F. S. Gibson, H. Rapoport, *J. Org. Chem.* **1995**, *60*, 2615.

[80] F. Albericio, M. A. Bailén, R. Chinchilla, D. J. Dodsworth, C. Nájera, *Tetrahedron* **2001**, *57*, 9607.

[81] K. Akaji, N. Kuriyama, Y. Kiso, *J. Org. Chem.* **1996**, *61*, 3350.

[82] P. Li, J. C. Xu, *Tetrahedron* **2000**, *56*, 9949.

[83] P. Li, J. C. Xu, *Tetrahedron Lett.* **1999**, *40*, 8301.

[84] P. Li, J. C. Xu, *J. Org. Chem.* **2000**, *65*, 2951.

[85] R. Wischnat, J. Rudolph, R. Hanke, R. Kaese, A. May, H. Theis, U. Zuther, *Tetrahedron Lett.* **2003**, *44*, 4393.

[86] T. Mukaiyama, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 707.

[87] E. Bald, K. Saigo, T. Mukaiyama, *Chem. Lett.* **1975**, 1163.

[88] B. Castro, J.-R. Dormoy, G. Evin, C. Selve, *Tetrahedron Lett.* **1975**, 14, 1219.

[89] B. Castro, J.-R. Dormoy, B. Dourtoglou, G. Evin, C. Selve, J.-C. Ziebler, *Synthesis* **1976**, 751.

[90] L. A. Carpino, A. El-Faham, F. Albericio, *Tetrahedron Lett.* **1994**, *35*, 2279.

[91] J. Coste, E. Frérot, P. Jouin, B. Castro, *Tetrahedron Lett.* **1991**, *32*, 1967.

[92] J. Coste, D. Le-Nguyen, B. Castro, *Tetrahedron Lett.* **1990**, *31*, 205.

[93] F. Albericio, M. Cases, J. Alsina, S. A. Triolo, L. A. Carpino, S. A. Kates, *Tetrahedron Lett.* **1997**, *38*, 4853.

[94] R. Knorr, A. Trzeciak, W. Bannwarth, D. Gillessen, *Tetrahedron Lett.* **1989**, *30*, 1927.

[95] G. R. Pettit, S. R. Taylor, *J. Org. Chem.* **1996**, *61*, 2322.

[96] I. Abdelmoty, F. Albericio, L. A. Carpino, B. M. Foxman, S. A. Kates, *Lett. Pept. Sci.* **1994**, *1*, 57.

[97] B. Stowasser, K.-H. Budt, L. Jian-Qi, A. Peyman, D. Ruppert, *Tetrahedron Lett.* **1992**, *33*, 6625.

[98] R. A. Sheldon, *Chem. Ind. (London)* **1997**, 12.

[99] R. A. Sheldon, *Chem. Tech.* **1994**, 38.

[100] R. A. Sheldon, *Chem. Ind. (London)* **1992**, 903.

[101] H. Charville, D. Jackson, G. Hodges, A. Whiting, *Chem. Commun.* **2010**, *46*, 1813.

[102] T. Higuchi, T. Miki, A. C. Shah, A. K. Herd, *J. Am. Chem. Soc.* **1963**, *85*, 3655.

[103] D. Davidson, P. Newman, *J. Am. Chem. Soc.* **1952**, *74*, 1515.

[104] X. J. Wang, Q. Yang, F. Liu, Q. D. You, *Synth. Commun.* **2008**, *38*, 1028.

[105] L. Perreux, A. Loupy, F. Volatron, *Tetrahedron* **2002**, *58*, 2155.

[106] R. S. Varma, *Green Chem.* **1999**, *1*, 43.

[107] S. Caddick, *Tetrahedron* **1995**, *51*, 10403.

[108] B. W. Baldwin, T. Hirose, Z. H. Wang, *Chem. Commun.* **1996**, 2669.

[109] J. Cossy, C. Pale-Grosdemange, *Tetrahedron Lett.* **1989**, *30*, 2771.

[110] L. J. Gooβen, D. M. Ohlmann, P. P. Lange, *Synthesis* **2009**, 160.

[111] Y. Terada, N. Ieda, K. Komura, Y. Sugi, *Synthesis* **2008**, 2318.

[112] J. W. Comerford, J. H. Clark, D. J. MacQuarrie, S. W. Breeden, *Chem. Commun.* **2009**, 2562.

[113] P. Nelson, A. Pelter, *J. Chem. Soc.* **1965**, 5142.

[114] A. Pelter, T. E. Levitt, *Tetrahedron* **1970**, *26*, 1899.

[115] A. Pelter, T. E. Levitt, P. Nelson, *Tetrahedron* **1970**, *26*, 1539.

[116] A. Pelter, T. E. Levitt, *Tetrahedron* **1970**, *26*, 1545.

[117] G. Trapani, A. Reho, A. Latrofa, *Synthesis* **1983**, 1013.

[118] D. B. Collum, S. C. Chen, B. Ganem, *J. Org. Chem.* **1978**, *43*, 4393.

[119] W. Yang, X. Gao, G. Springsteen, B. Wang, *Tetrahedron Lett.* **2002**, *43*, 6339.

[120] J. A. Mitchell, E. E. Reid, *J. Am. Chem. Soc.* **1931**, *53*, 1879.

[121] K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4196.

[122] K. Ishihara, S. Ohara, H. Yamamoto, *Macromolecules* **2000**, *33*, 3511.

[123] K. Arnold, B. Davies, R. L. Giles, C. Grosjean, G. E. Smith, A. Whiting, *Adv. Synth. Catal.* **2006**, *348*, 813.

[124] K. Ishihara, S. Kondo, H. Yamamoto, *Synlett* **2001**, 1371.

[125] T. Maki, K. Ishihara, H. Yamamoto, *Synlett* **2004**, 1355.

[126] T. Maki, K. Ishihara, H. Yamamoto, *Org. Lett.* **2005**, *7*, 5043.

[127] R. Latta, G. Springsteen, B. Wang, *Synthesis* **2001**, 1611.

[128] K. Ishihara, *Tetrahedron* **2009**, *65*, 1085.

[129] P. Tang, *Org. Synth.* **2005**, *81*, 262.

[130] A. D. Negro, L. Ungaretti, A. Perotti, *J. Chem. Soc., Dalton Trans.* **1972**, 1639.

[131] R. G. Hayter, A. W. Laubengayer, P. G. Thompson, *J. Am. Chem. Soc.* **1957**, *79*, 4243.

[132] R. K. Mylavarapu, G. C. M. Kondaiah, N. Kolla, R. Veeramalla, P. Koilkonda, A. Bhattacharya, R. Bandichhor, *Org. Process Res. Dev.* **2007**, *11*, 1065.

[133] T. Maki, K. Ishihara, H. Yamamoto, *Org. Lett.* **2006**, *8*, 1431.

[134] S. W. Coghlan, R. L. Giles, J. A. K. Howard, L. G. F. Patrick, M. R. Probert, G. E. Smith, A. Whiting, *J. Organomet. Chem.* **2005**, *690*, 4784.

[135] K. Ishihara, S. Ohara, H. Yamamoto, D. T. Amos, R. L. Danheiser, *Org. Synth.* **2002**, *79*, 167.

[136] K. Arnold, A. S. Batsanov, B. Davies, A. Whiting, *Green Chem.* **2008**, *10*, 124.

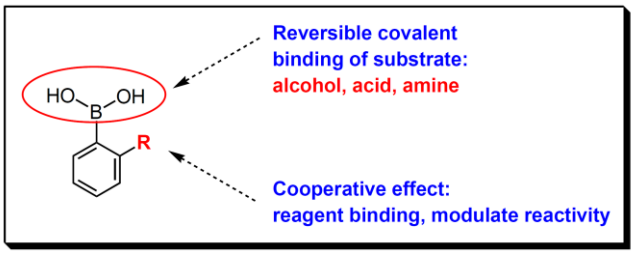
[137] I. Georgiou, G. Ilyashenko, A. Whiting, *Acc. Chem. Res.* **2009**, *42*, 756.

[138] H. C. Brown, T. P. Stocky, *J. Am. Chem. Soc.* **1977**, *99*, 8218.

[139] K. Arnold, B. Davies, D. Hérault, A. Whiting, *Angew. Chem. Int. Ed.* **2008**, *47*, 2673.

Catalytic Amide Bond Formation by Ortho-Haloarylboronic Acids: First Generation Catalysts

A method for the organocatalytic activation of carboxylic acids using *ortho*-substituted arylboronic acids as bifunctional catalysts towards direct and waste-free, room-temperature amide bond formation has been discovered. This new catalytic system represents a significant advance over the previously reported catalysts by both the Yamamoto and Whiting groups and demonstrates the strong potential of boronic acid-catalysis towards activation of the carboxylic acid moiety.

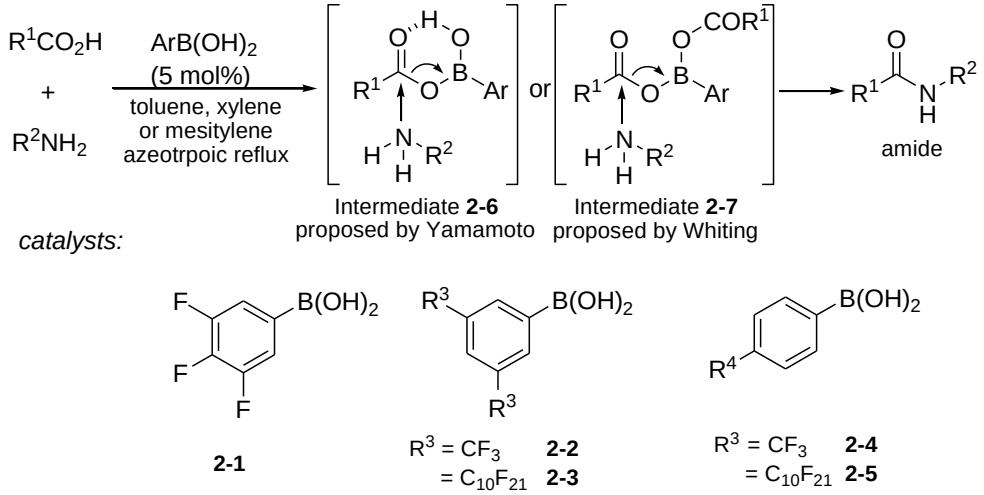


In the first section, a class of *ortho*-halogenated arylboronic acids is presented. Within this class of arylboronic acids, the *ortho*-iodo derivative was found to be the most active catalyst enhancing the reaction rate and providing the highest yields of amide products over a short reaction time. Moreover, secondary and tertiary amides were successfully made in high yields, as well as highly functionalized and biologically active amides, such as indomethacin, leelamine, and ibuprofen amides, with <5% epimerization of the chiral α-substituted carboxyl substrates. The effect of drying agents on catalytic direct amidation reactions, the steric effect of *ortho*-substituted arylboronic acids and a second round of evaluation of different *ortho*-substituted arylboronic acids are discussed in the second section. In the third section, a new organocatalytic activation of unsaturated carboxylic acids for Diels-Alder reactions is described.

2.1 Introduction

As mentioned in Chapter One, the catalytic use of arylboronic acids and boric acid has provided a possible benign alternative solution for direct amide bond formation

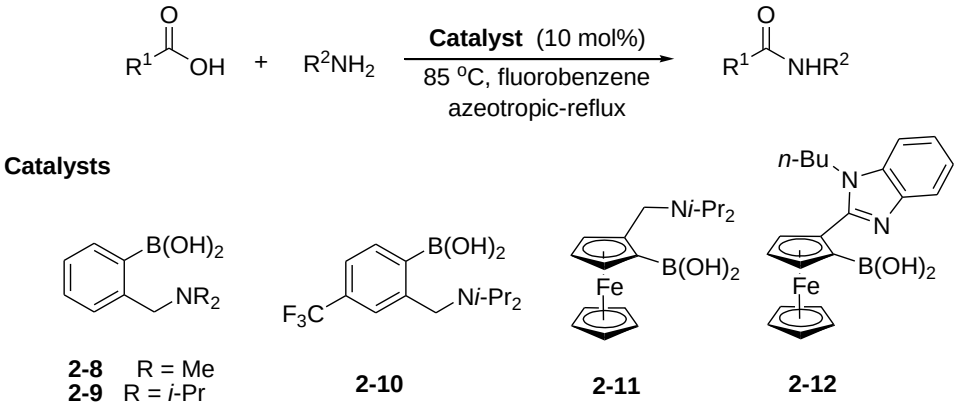
between carboxylic acids and amines. This chemistry was popularized by Yamamoto and co-workers in 1996 when they cleverly described the use of electron-poor arylboronic acids in direct amide bond formation at azeotropic-reflux conditions.[1-4] The most active catalyst identified was 3,4,5-trifluorophenylboronic acid **2-1**, which provided the highest yields of the desired amide products. Other electron-poor arylboronic acid catalysts, **2-2**,[3] **2-3**,[5] **2-4**[3] and **2-5**[5] (**Scheme 2-1**), developed by Yamamoto and Ishihara were also evaluated. It is known that electron-withdrawing groups increase the Lewis acidity of the boron atom and therefore may increase the reactivity of the boron with carboxylic acids towards forming the monoacylboronate intermediate **2-6** or the diacylboronate intermediate **2-7**, which are the proposed activated esters.



Scheme 2-1: Yamamoto's electron-poor arylboronic acid catalysts for direct amidation.[1-5]

More recently, Whiting and co-workers described the use of *ortho*-dialkylaminomethylarylboronic acids as active catalysts for direct amide bond formation.[6] They showed that *ortho*-substituents, such as the dimethylaminomethyl in catalyst **2-8** and diisopropylaminomethyl in catalyst **2-9,** activate the boron atom towards direct amidation at azeotropic-reflux conditions (**Table 2-2**). They claimed that these catalysts work as bifunctional catalysts and the role of these amine substituents is to deprotonate the ammonium to regenerate the amine. Moreover, it forms H-bonding with both the amine and carboxylic acid,

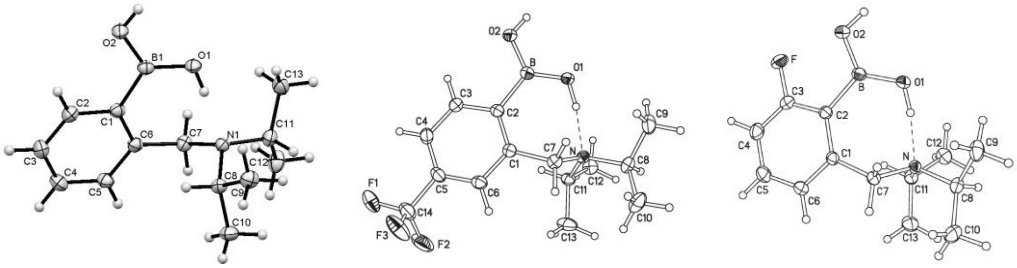
consequently increasing the proximity of the starting materials with the catalyst.[6, 7] Catalyst **2-9** with a diisopropylaminomethyl substituent at the *ortho* position is found to be more active than catalyst **2-8** with a dimethylaminomethyl group under the same reaction conditions.[7]

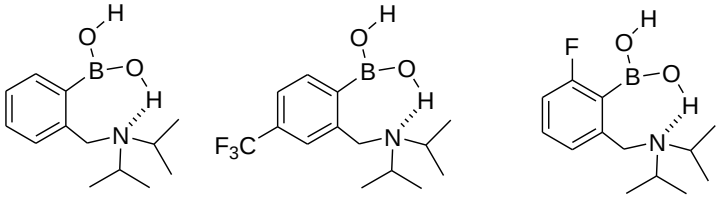


Scheme 2- 2: Whiting's bifunctional catalysts for direct amide bond formation.[6-9]

X-ray crystallographic data showed that catalyst **2-8** has a B–N coordination bond.[10] This coordination is believed to decrease the reactivity of the boron atom by forming a tetrahedral boronate which becomes less reactive in amidation.[7, 10] In contrast, catalyst **2-9** shows no B–N coordination bond and hence the boronic acid group is still reactive as a consequence of its trigonal planar geometry and the empty p-orbital.[7] It is remarkable to see how the *ortho* substituents on the arylboronic acids can affect their reactivity towards direct amide bond formation. In 2008, the same group further slightly improved their catalyst by placing the electron-withdrawing group, trifluoromethyl, at the *para* position to the boronic acid group in catalyst **2-10** (**Table 2-2**).[7] Catalyst **2-10** was found to be beneficial compared to catalyst **2-9**. It is worth noting that the difference in reaction rate and reactivity between these catalysts is not very significant, with only a small difference in the yields of amide products, whereas the addition of the fluorine substituent at the *ortho* position in **2-13** decreases the reaction rate to a small extent.[7]

Table 2-1: Selected bond lengths (Å) for Whiting catalysts 2-9, 2-10 and 2-13.[7]





2-9 **2-10** **2-13**

Bond	bond lengths (Å)		
	2-9	**2-10**	**2-13**
C(2)-B	1.588(2)	1.5965(14)	1.5876(17)
B-O(1)	1.356(2)	1.3547(13)	1.3575(15)
B-O(2)	1.366(2)	1.3581(13)	1.3609(16)
O···N	2.637(1)	2. 607(1)	2.623(1)
C(1)-C(2)	1.412(2)	1.4204(12)	1.4169(16)

In 2008, the same group reported the first asymmetric direct amidation *via* kinetic amine resolution of racemic α-substituted benzylamines with achiral carboxylic acids using (*p*S)-2-(2-boronoferrocenyl)-*N*-*n*-butylbenzimidazole **2-12** and (*p*S)-2-(2-boronoferrocenyl)-*N,N*-diisopropylamine **2-11** as planar, chiral ferrocene-based bifunctional amino–boronic acid catalysts under azeotropic-reflux in fluorobenzene.

Even catalyst **2-11** was found to be more active than **2-12**, providing **35%** and **21%** of the desired amide product, respectively; however, no kinetic resolution was detected compared to 41% *ee* for catalyst **2-12** under the same reaction conditions.[9] Although this report was the first one in asymmetric direct amidation reactions, low yields and enantioselectivity (only up to 41% *ee*) were observed. It is worth noting that increasing the reaction time and the quantity of the amine (from 1

equivalent to 2 equivalents), lowered yields and enantioselectivities were detected.[8, 9] The authors claimed that the low enantioselectivity observed in the amidation reaction is due to the *ipso*-protodeboronation reaction of the catalyst **2-12.** This decomposition produces boric acid, which is known to be an active catalyst in direct amide bond formation, as described by Tang and co-workers.[11]

All of the catalysts described above provide a remarkable foundation for the activation of carboxylic acids in direct amide bond formations. However, the reaction conditions are still harsh as azeotropic-reflux conditions at elevated temperature for several hours in high boiling solvents, such as toluene (110 °C), xylene (120 °C) or mesitylene (160 °C), are needed for more demanding substrates. While the use of Whiting's catalysts requires lower temperatures, such as the use of fluorobenzene at 85 °C, these conditions are certainly not compatible with many functionalized substrates. Furthermore, the fact that these catalysts are also partially decomposed to form the deprotonated derivatives and boric acid, as described by Whiting[9] and Wang[12], impedes the popular use of these methodologies.

The Hall group is interested in the application of *ortho*-functionalized arylboronic acids to modulate the reactivity of the boronic acid group in different organic reactions. Recently, Hall and co-workers discovered for the first time the remarkable ability of benzoboroxole **2-14** to complex glycopyranosides (6-membered sugars) like those found on the surfaces of cells under physiological conditions (**Figure 2-1**).[13-15] Due to the relatively weak binding of benzoboroxoles to glycopyranosides, a peptide-based library of carboxy-functionalized benzoboroxoles was developed in order to increase the binding affinity.[14, 15]

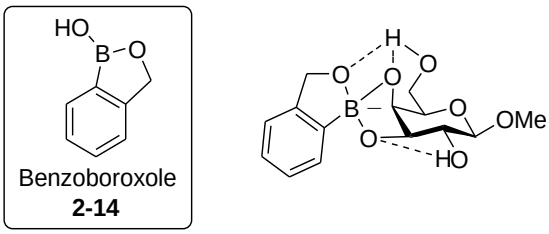


Figure 2-1: Complexation of hexopyranosides using benzoboroxole 2-14.[13-15]

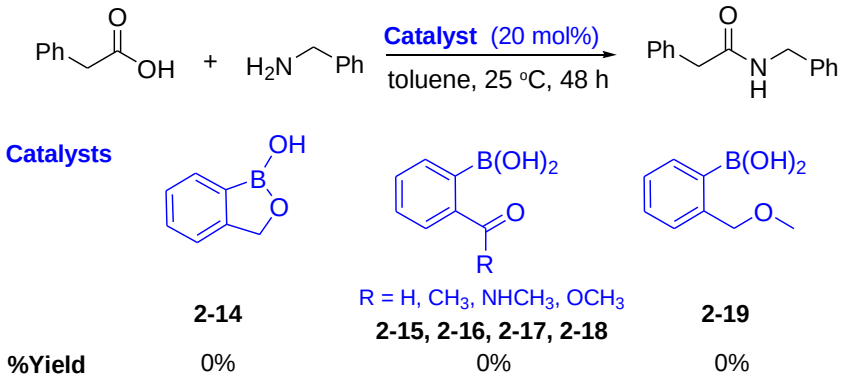
This unique binding ability of benzoboroxole **2-14** and more precisely, the effect of the alcohol side chain at the *ortho* position on increasing the binding affinity motivated us to screen the catalytic activity of benzoboroxole **2-14** and other *ortho*-functionalized arylboronic acids toward amide bond formation and other reactions.

We became highly interested in the prospect of finding a catalyst that can activate carboxylic acids to make the amide bond under more benign conditions, such as room temperature, the most favorable temperature for any organic reaction. These conditions would favorably impact the stability profile of arylboronic acid catalysts with regard to *ipso*-deboronation reactions and also provide benign conditions for the use of highly functionalized and sensitive substrates.

2.2 Results[16]

2.2.1 Initial Screening of *Ortho*-Functionalized Arylboronic Acids

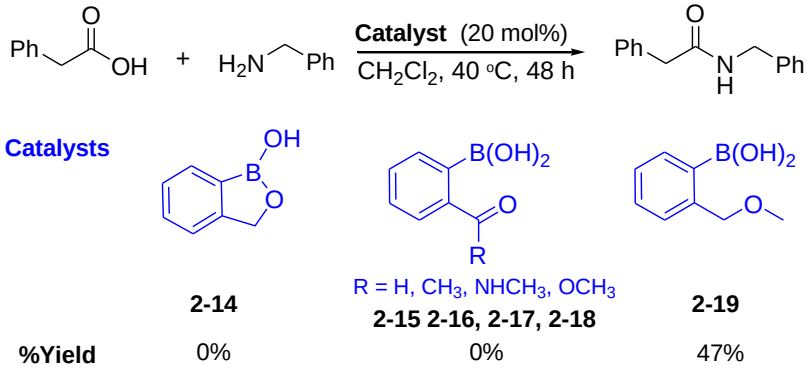
Having realized the unique binding ability of benzoboroxole **2-14** to glycopyranosides, we decided to examine the effectiveness of benzoboroxole **2-14** and other *ortho*-substituted arylboronic acids, such as **2-15**, **2-16**, **2-17**, **2-18** and **2-19,** on direct amide bond formation reactions at ambient temperature. We used the combination of benzylamine and phenylacetic acid as a model reaction in toluene for 48 hours as described in **Scheme 2-3**.



Scheme 2-3: Screening of benzoboroxole 2-14 and other *ortho*-substituted arylboronic acid 2-15–2-19 in toluene at 25 °C for amide bond formation.

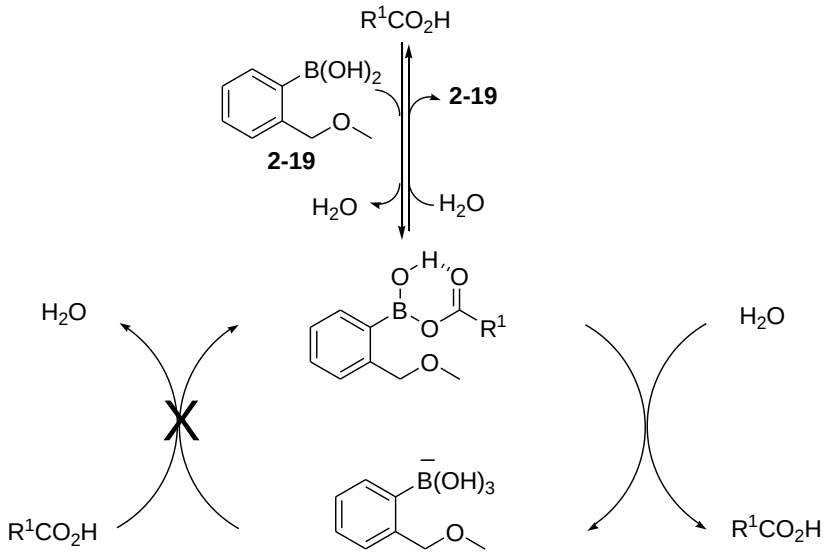
It was found that all chosen arylboronic acids, including benzoboroxole **2-14,** were ineffective at promoting the desired amide product. The solubility of the resulting salt, the ammonium carboxylate salt, was an issue in this reaction.

Next, we decided to switch to using other solvents and higher reaction temperatures to overcome the solubility issue. Methylene choride (dichloromethane DCM) was chosen (40 °C), and again most arylboronic acids were inactive except arylboronic acid **2-19**, which provided 47% of the desired amide product. This result provided the impetus for us to further optimize the reaction conditions. Consequently, we decided to examine the effect of water on the reaction in order to enhance the solubility of the ammonium carboxylate salt. The addition of one equivalent of water completely suppressed the reactivity of the catalyst and resulted in no amide bond formation, whereas the addition of 10 mol% (0.1 equiv) dramatically lowered the conversion from 47% to 3%.



Scheme 2-4: Screening of benzoboroxole 2-14 and other *ortho*-substituted arylboronic acids 2-15–2-19 in CH_2Cl_2 at 40 °C for amide bond formation

These early results clearly indicated that the addition of water inhibits the reactivity of the arylboronic acid catalyst. This is understandable since the nucleophilicity of water is superior to that of carboxylate and therefore, decreases the formation of the activated esters, as proposed in **Scheme 2-5**.

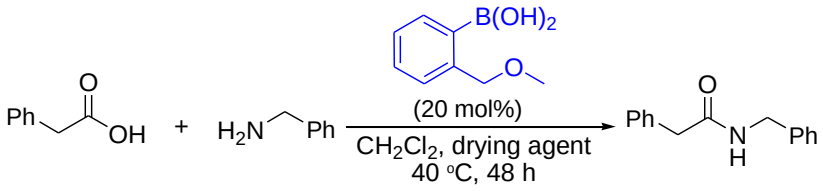


Scheme 2-5: Deleterious effect of water on direct amide bond formation catalyzed by arylboronic acids.

2.2.2 The Effect of Drying Agents on Catalytic Direct Amide Bond Formation

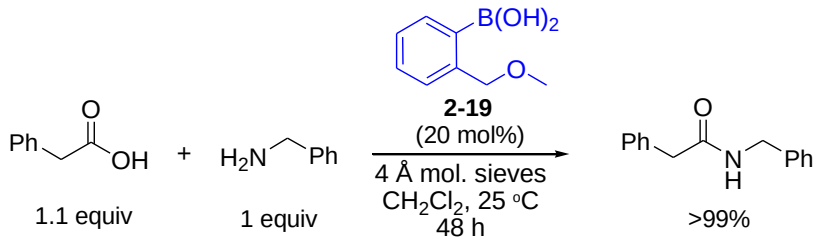
As water is the only by-product in catalytic amide bond formation, we decided to apply Le Chatelier's Principle to increase the formation of the amide product by using a drying agent to remove the water from the reaction. Different drying agents were examined, such as $MgSO_4$, Na_2SO_4, LiCl, molecular sieves and trimethyl orthoformate (**Table 2-2**). This examination revealed that 4 Å molecular sieves were the most effective drying agent by providing the desired amide product in >99% yield after 48 hours. Surprisingly, no amide product was observed using other drying agents.

Table 2-2: Effect of drying agents on direct amide bond formation using catalyst 2-19



Entry	Drying agent	%Yield	Entry	Drying agent	%Yield
1	None	47%	4	4 Å Molecular Sieves	99%
2	Na_2SO_4	0%	5	$HC(OCH_3)_3$	0%
3	LiCl	0%	6	$MgSO_4$	0%

Further optimizations were performed by examining different solvents which led to the identification of methylene chloride, toluene and tetrahydrofuran (a non-halogenated polar solvent) as the optimal solvents. As excess of amine was found to slow down the reactions; it was deemed preferable to use a slight excess of the carboxylic acid. We repeated the reaction at room temperature using these optimized reaction conditions and were very satisfied to observe an almost complete consumption of the carboxylic acid at ambient temperature after 48 h reaction time (**Equation 2-1**).

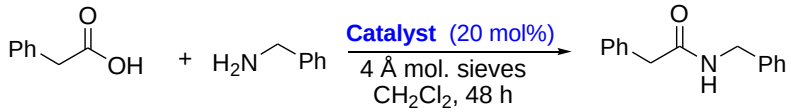


Equation 2-1: Direct amide bond formation using catalyst 2-19 and 4 Å molecular sieves at 25 °C

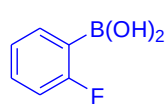
2.2.3 Second Round of Evaluation of Different *Ortho*-Substituted Arylboronic Acids Under Optimized Reaction Conditions

From here onwards, we decided to screen different *ortho*-functionalized arylboronic acids and others under the optimized reaction conditions at ambient temperature. We conducted a systematic evaluation of over 45 candidates in different solvents and at different temperatures, as shown in **Table 2-3**. A handful were active at room temperature, and in all cases it was found essential to scavenge the water by-product of the reaction, which was accomplished by the use of activated 4 Å molecular sieves.

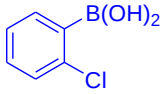
Table 2-3: List of tested arylboronic acids under optimized reaction conditions.



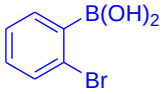
Catalysts



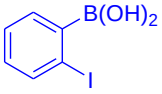
25 °C
98%



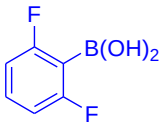
25 °C
99%



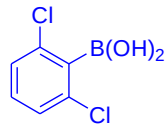
25 °C
99%



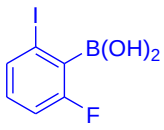
25 °C
99%



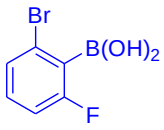
35-40°C **85%**
25°C **42%**



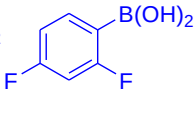
25 °C
10%



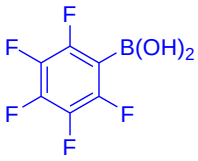
25 °C
50%



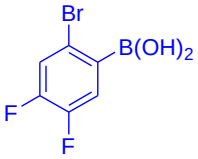
25 °C
33%



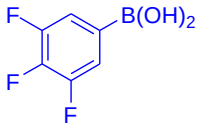
35-40°C **99%**
25°C **63%**



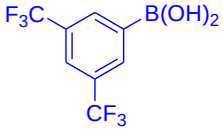
35-40°C
11%



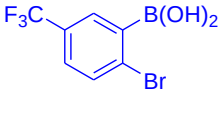
35-40°C
64%



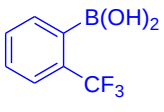
35-40°C **85%**
25°C **56%**



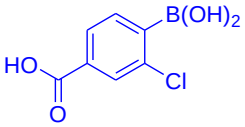
35-40°C
92%



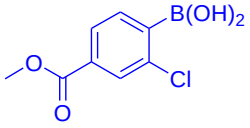
25 °C
60%



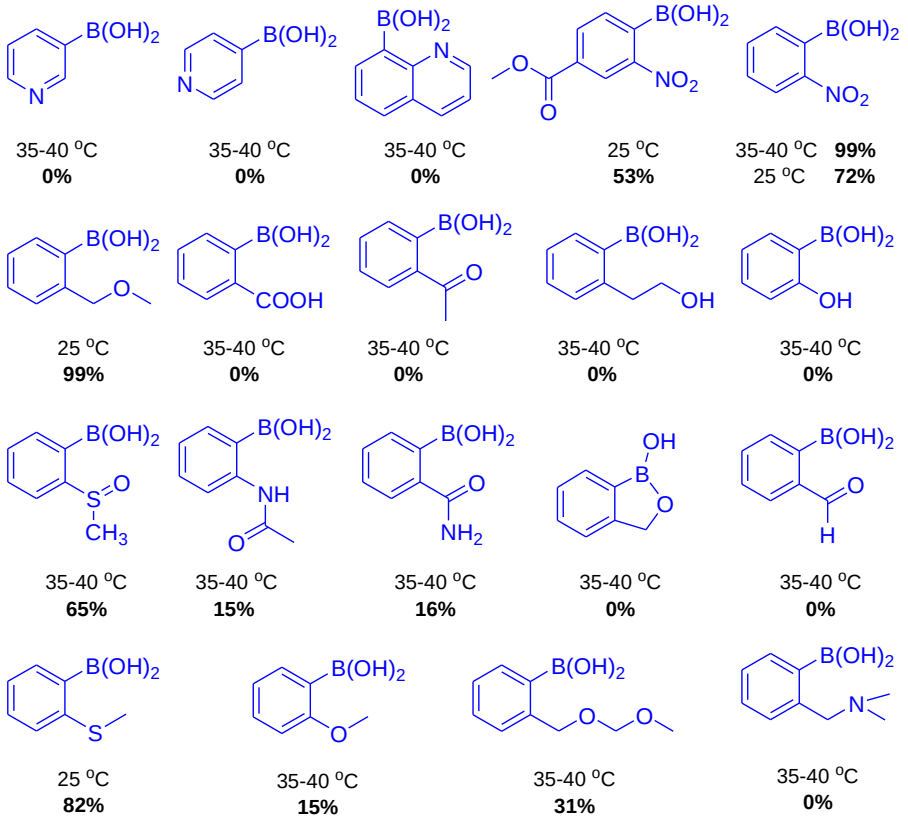
35-40°C
28%



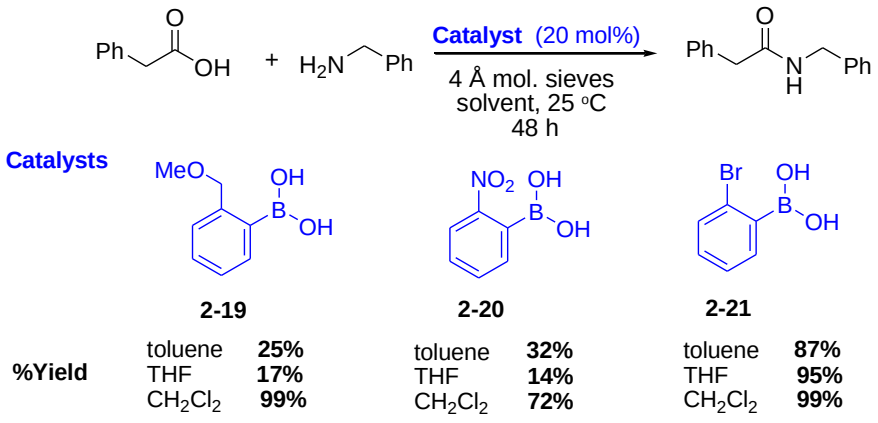
25 °C
49%



25 °C
77%

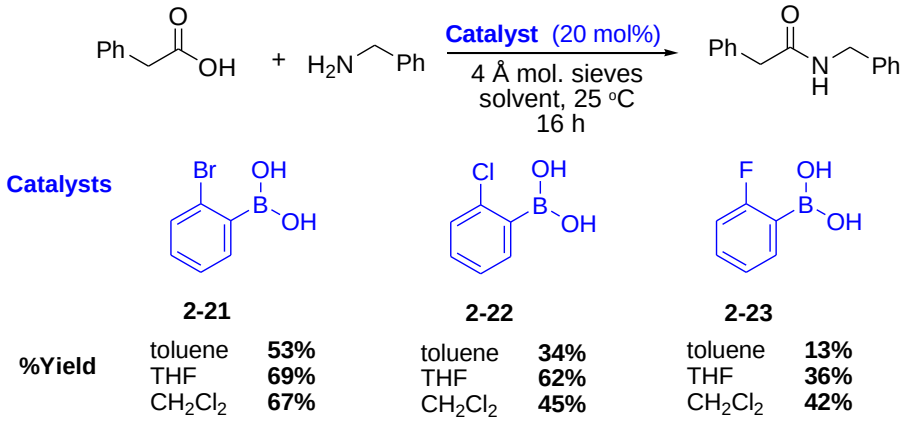


This evaluation revealed a few other active *ortho*-functionalized arylboronic acids in the direct amidation reaction between benzylamine and phenylacetic acid (**Scheme 2-6**). For instance, catalyst **2-20** provided the desired amide product in 72% yield, while both catalysts **2-21** and **2-19** provided 99% of the desired amide product in dichloromethane.



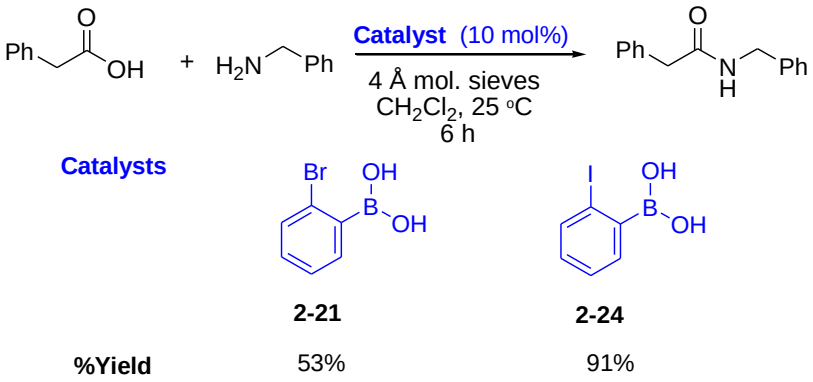
Scheme 2-6: Other active *ortho*-substituted arylboronic acids under optimized conditions.

A second round of evaluation of the most promising candidates under the same optimized conditions with different solvents revealed *ortho*-bromoarylboronic acid **2-21** as the most efficient catalyst. This was an unexpected result, since a bromo substituent is neutral and cannot undergo H-bonding. Therefore, a systematic evaluation of the *ortho*-halogenated arylboronic acids (Br **2-21**, Cl **2-22**, F **2-23**) under the same optimized conditions but for shorter reaction time (16 h) showed once again the superior activity of *ortho*-bromoarylboronic acid **2-21** over other *ortho*-haloarylboronic acids (**Scheme 2-7**).



Scheme 2-7: *Ortho*-Haloarylboronic acids as catalysts in direct amide bond formation under the optimized reaction conditions at 25 °C.

Because of the reverse trend observed in reactivity for the *ortho*-haloarylboronic acid series (F<Cl<Br), we were encouraged to synthesize the unknown *ortho*-iodoarylboronic acid **2-24**. Different approaches were undertaken to make this boronic acid. After the successful synthesis of *ortho*-iodoarylboronic acid **2-24** (see Section 2.4), a side-by-side evaluation between *ortho*-bromoarylboronic acid **2-21** and *ortho*-iodoarylboronic acid **2-24** using the model amidation reaction between phenylacetic acid and benzylamine for 6 h reaction time using 10 mol% loading of the catalyst confirmed the superiority of the *ortho*-iodophenylboronic acid **2-24** over *ortho*-bromoarylboronic acid **2-21** (**Scheme 2-8**).



Scheme 2-8: Comparison between *ortho*-iodo and *ortho*-bromoarylboronic acids 2-24 and 2-21 respectively, in a direct amidation reaction under optimized conditions.

Due to the reverse trend of electronegativity in the reactivity of *ortho*-haloarylboronic acids, inductive effects alone cannot account for the superiority of *ortho*-iodoarylboronic acid **2-24** over other *ortho*-haloarylboronic acids. As discussed by Yamamoto and Whiting, the more acidic the arylboronic acid, the more effective it is in catalyzing the amidation reaction. Consequently, we decided to measure the acidity of catalyst **2-24**. Following the reported literature,[14] the pKa for this catalyst was measured by Olivier Marion, a former Postdoctoral fellow in our group, and found to be 8.9, as shown in **Figure 2-2**, which is similar to that of phenylboronic acid (pKa = 8.8).[17] Thus, the acidity cannot explain the unique catalytic activity of *ortho*-iodoarylboronic acid **2-24**.

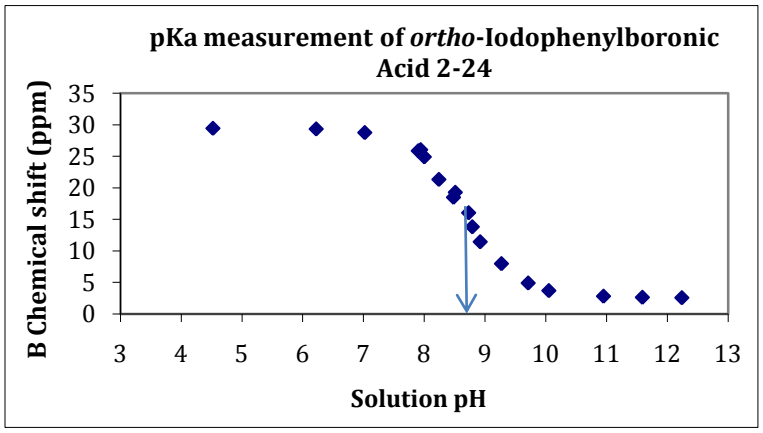
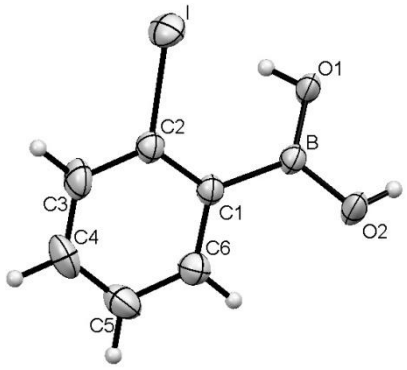


Figure 2-2: pKa measurement graph of *ortho*-iodoarylboronic acid 2-24 using ^{11}B-NMR titration.

X-ray crystallographic data of this catalyst showed an unusual angular distortion of the B-C-C bonds (117°, 126°) due to the size and the electron density of the iodo group, and as a result, subtle electronic or structural effects may be at play. It is interesting to note that the *ortho*-iodoarylboronic acid **2-24** exhibits a 1.569 Å C–B bond length (**Table 2-4**), which is slightly shorter than those of Whiting's catalysts (**Table 2-1**). It should be noted that ^{11}B-NMR does not seem to suggest significant differences in the properties of the arylboronic acid functionality, showing resonances at δ 28.8,[10] 28.4,[7] 28.5[7] and 29.10[16] for **2-9**, **2-10**, **2-13** and **2-24**, respectively.

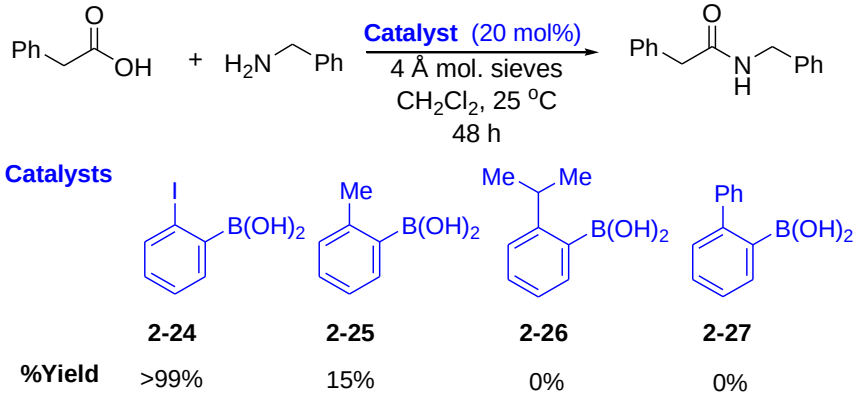
Table 2-4: Selected bond lengths (Å) and angles (deg) for *ortho*-iodoarylboronic acid 2-24.



	Atoms	*Ortho*-iodoarylboronic acid 2-24	
Bond	I-C(2)	Selected atomic distance (Å)	2.115(3)
	O(1)-B		1.363(4)
	O(2)-B		1.363(3)
	C(1)-B		1.569(4)
	C(1)-C(2)		1.402(4)
	C(1)-C(6)		1.403(4)
Angle	C(2)-C(1)-B	Selected atomic angles (deg)	126.9(3)
	C(6)-C(1)-B		117.0(3)
	I-C(2)-C(1)		121.5(2)
	I-C(2)-C(3)		116.1(2)

2.2.4 The Steric Influence of *Ortho*-Substituted Arylboronic Acid Catalysts on Direct Amide Bond Formation

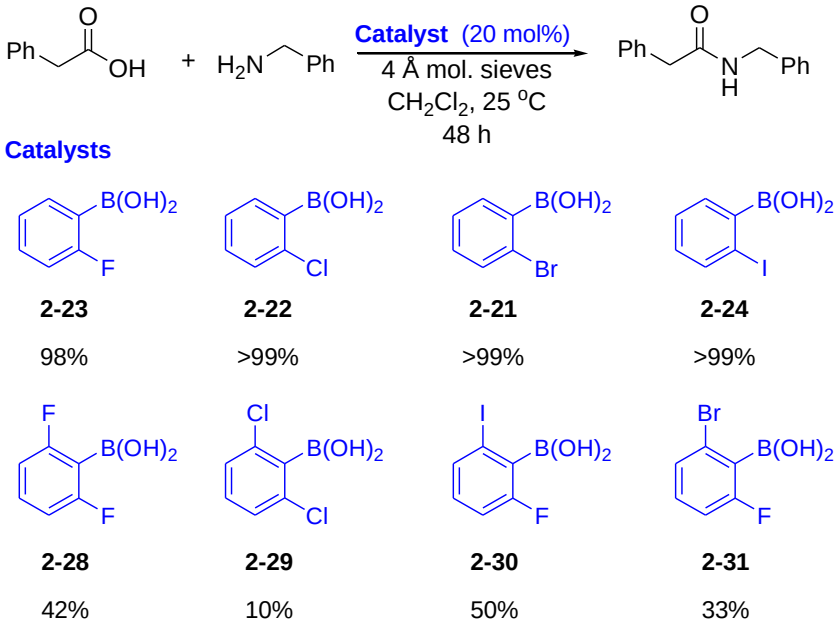
At this stage, we had realized the large size of the iodine atom (atomic radius = 133 pm) compared with other halogens (113, 100, 72 pm for Br, Cl and F, respectively), helps explain the unusual angular distortion of the B-C-C bonds. We decided to explore the importance of steric effects by comparing the reactivity of *ortho*-iodoarylboronic acid **2-24** with other *ortho*-substituted arylboronic acids having different groups under the same optimized conditions, as illustrated in **Scheme 2-9**. Different *ortho*-substituted arylboronic acid catalysts were used in this study, and in all cases the reactivity of these catalysts was very low in comparison to the *ortho*-iodoarylboronic acid **2-24**. For example, **2-25** provided only 15% of the desired amide product after a 48 hour reaction time. Catalysts **2-26** and **2-27** showed no sign of activity by providing no amide product after 48 hours compared to >99% for the use of catalyst **2-24** under the same reaction conditions. The basis of the exceptional activity of *ortho*-iodophenylboronic acid was unclear at this moment, and probably not due to steric effects or acidity.



Scheme 2-9: The influence of steric effects of *ortho*-substituted arylboronic acid catalysts on amide bond formation reaction.

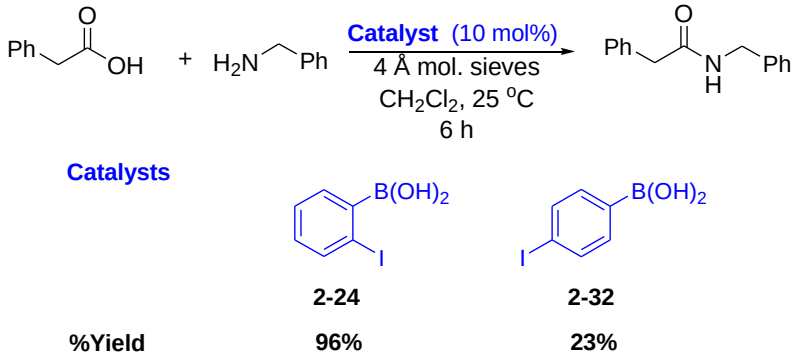
In light of this, we proposed that having two halogens at both *ortho* positions might enhance the reactivity of catalyst **2-24**. A systematic study using different arylboronic acid catalysts was performed under the same optimized conditions. As shown in **Scheme 2-10**, doubly *ortho*-dihaloarylboronic acids were found to be less effective than mono *ortho*-halo substituted catalysts. Other substituents were also

examined and found to be less effective, which is clearly consistent with the need for one unsubstituted *ortho* position next to the boronic acid group. For instance, the use of catalyst **2-28** provided 42% of the desired amide product, 33%, 50% and 33% yields for catalysts **2-29** and **2-30** and **2-31,** respectively.



Scheme 2-10: The effect of *ortho*-dihaloarylboronic acid catalysts on direct amide bond formation.

Accordingly, we decided to inspect the importance of the *ortho* position by comparing the reactivity of *ortho* versus *para* iodoarylboronic acid **2-24** and **2-32** under the same conditions, as outlined in **Scheme 2-11**.

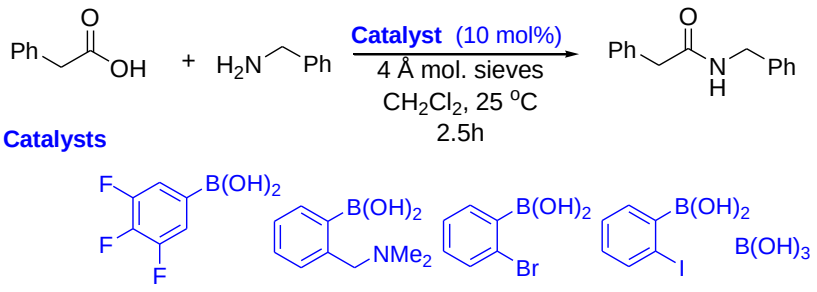


Scheme 2-11: Comparison in product yield between *ortho*-iodo and *para*-iodoarylboronic acids 2-24 and 2-32 in direct amidation reaction under optimized conditions.

In this event, the *para* isomer was found to be significantly less effective than the *ortho* isomer by providing a 23% yield compared to 96%. This fact confirms the crucial importance of the *ortho* position in the reactivity of the *ortho*-iodoarylboronic acid **2-24**.

2.2.5 Comparison Between our Catalytic System (*Ortho*-Bromo and *Ortho*-Iodoarylboronic Acids) and Promising Arylboronic Acids Found in the Literature.

Having all these systematic studies that clearly showed the superiority of the *ortho*-iodoarylboronic acid catalyst, we decided to examine the efficiency of boric acid as well as Yamamoto and Whiting catalysts **2-1** and **2-9** and compare them with our best catalysts **2-21** and **2-24** under our optimized reaction conditions. It turned out that there was no sign of any reactivity for both the Whiting catalyst **2-9** and boric acid using our model amidation reaction between phenylacetic acid and benzylamine. Surprisingly, Yamamoto catalyst **2-1** provided the amide product in moderate yields, as shown in **Scheme 2-12**. This is indicative that the acidity might explain the reactivity of Yamamoto catalyst **2-1**, which is obviously not the case with the *ortho*-haloarylboronic acid catalysts. However, the basis of the exceptional reactivity of *ortho*-iodo and *ortho*-bromoarylboronic acid catalysts might come from a different mode of reactivity.



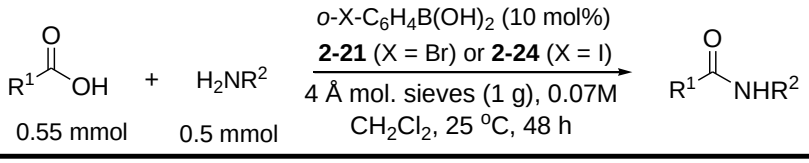
%Yield	2-1	2-9	2-21	2-24	
THF	22%	0%	49%	71%	0%
DCM	42%	0%	76%	91%	0%

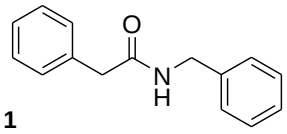
Scheme 2-12: Comparison in product yields between the literature arylboronic acids in direct amide bond formation under our optimized conditions.

2.2.6 Substrate Scope of Catalytic Direct Amide Bond Formation at Ambient Temperature.[16]

With the exceptional reactivity of *ortho*-bromophenylboronic acid **2-21** and the hitherto unknown *ortho*-iodophenylboronic acid **2-24** as the most efficient catalysts for direct amide bond formation, we chose to demonstrate the versatility and scope of these new catalysts at room temperature. A panel of model carboxylic acids, including aliphatic, functionalized aliphatic, unsaturated and aromatic carboxylic acid substrates, was studied, as shown in **Table 2-5**.

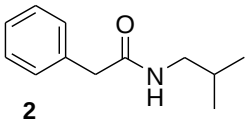
Table 2-5: Direct amidations between carboxylic acids and amines catalyzed by boronic acids 2-21 and 2-24 at room temperature.





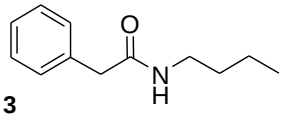
1

99% (**2-21**)



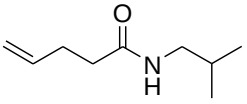
2

64% (with **2-21** in CH_2Cl_2)
91% (with **2-21** in THF)



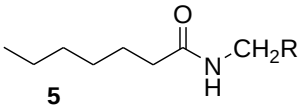
3

66% (with **2-21** in CH_2Cl_2)
87% (with **2-24** in THF)



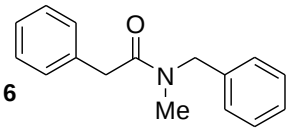
4

80% (**2-21**)



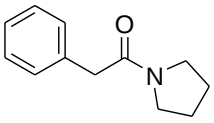
5

R = Ph **99%** (**2-21**)
R = C_5H_{11} **51%** (**2-21**)



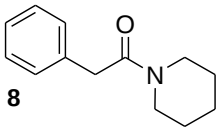
6

0%



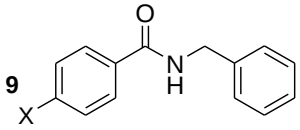
7

41% (with **2-21** in CH_2Cl_2)
76% (with **2-24** in CH_2Cl_2)



8

52% (with **2-24** in CH_2Cl_2)
97% (with **2-24** in THF)



9

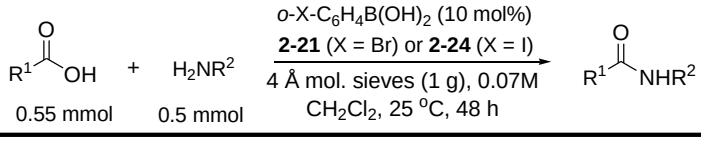
X = H **22%**
X = I **24%**
(with 20 mol% of **2-24** in toluene at 50 °C)

Standard conditions employed the use of the commercially available catalyst **2-21** in methylene chloride containing 4 Å molecular sieves. To ensure reaction completion in the case of slower substrates, a reaction time of 48 h was chosen. Different carboxylic acids and primary amines containing aromatic substituents, straight aliphatic chains, or branched aliphatic chains, are suitable substrates providing good

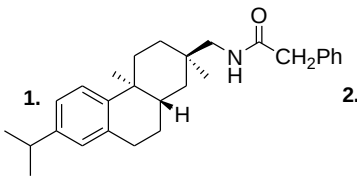
to excellent yields, as outlined in **Table 2-5, entries 1-5**. Although an acyclic secondary amine failed to react at room temperature (**Table 2-5, entry 6**), cyclic ones provided the expected tertiary amides (**Table 2-5, entries 7 and 8**).

Aromatic carboxylic acids were found to require a higher temperature and afforded lower yields after 48 h (**Table 2-5, entry 9**). In other difficult cases, such as the formation of cyclic tertiary amides, the superior *ortho*-iodo catalyst **2-24** is more appropriate, as shown in **entry 7**. Likewise, with some substrates the use of THF as solvent gives higher yields (e.g., **Table 2-5, entries 2 and 8**). Highly functionalized substrates were successfully employed to make biologically important amide products using this simple and highly atom-economical process. For example, the hindered hydrophobic amine, leelamine, reacted in good yield (**Table 2-6, entry 1**).

Table 2-6: Direct amidations between highly functionalized carboxylic acids and amines catalyzed by boronic acids 2-21 and 2-24 at room temperature



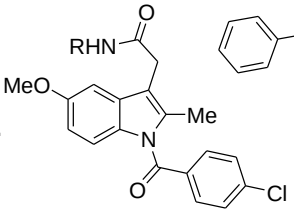
1.



Leelamine amide

74% (with **2-24** in CH_2Cl_2)

2.

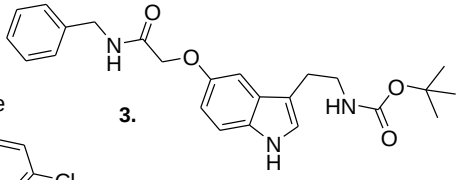


Indomethacin amides

COX-II inhibitor

R = $CH_2CH(CH_3)_2$ **73%**
R = CH_2Ph **93%**
(with **2-21** in CH_2Cl_2)

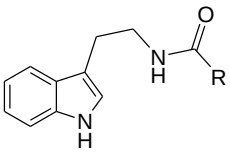
3.



Serotonin conjugate

95% (with 20 mol% **2-24** in CH_2Cl_2)

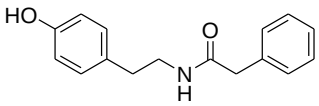
4.



Tryptamine amide

R = CH_2Ph **54%**
R = $CH_2CH_2CHCH_2$ **72%**
(with **2-24** in CH_2Cl_2)

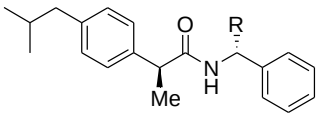
5.



Tyramine amide

31% (with **2-24** in CH_2Cl_2)

6.



Ibuprofen amides

NSAID with reduced toxicity

R = H **73%**, **>95%*ee*** (with **2-24** in THF)
R = CH_3 **70%**, **>95%*de*** (with 20 mol% **2-24** in THF for 16 h)

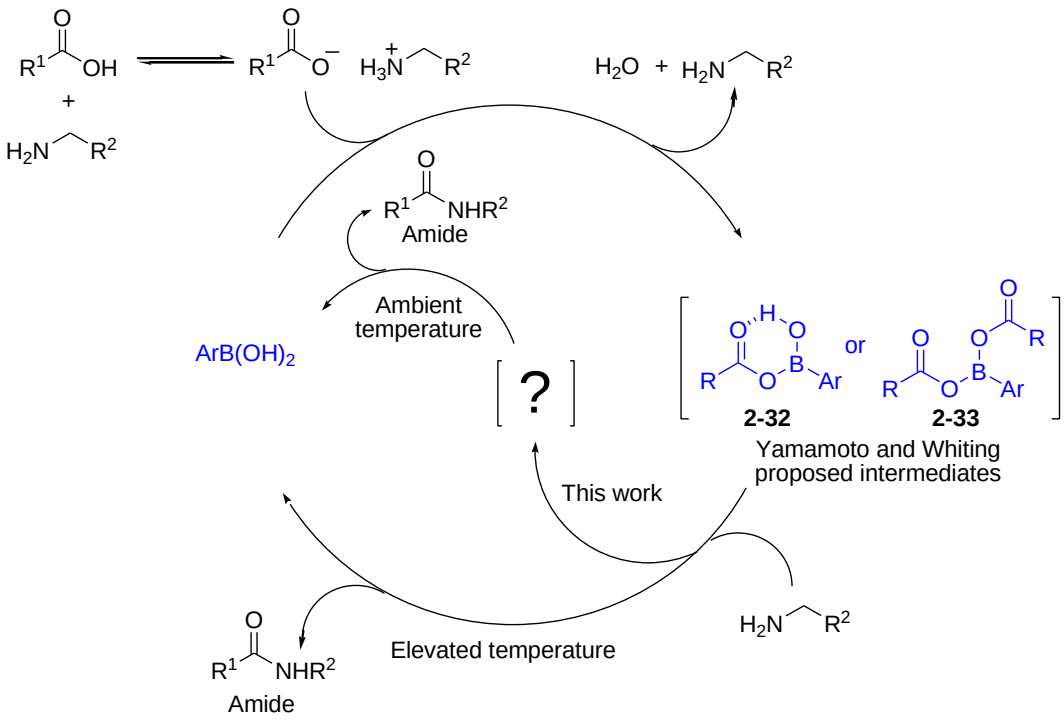
Amides of the drug indomethacin are known to display potent biological properties, such as the inhibition of COX-2 enzymes.[18, 19] Considering their reported method of preparation using excess coupling reagents and chromatographic purification, as described in Chapter 1, it is remarkable that indomethacin amides can be made with such ease using the new catalysts (**Table 2-6, entry 2**). A protected serotonin derivative was prepared in pure form with a high yield (**entry 3**). Tryptamine and tyramine amides were successfully prepared in good yields, as shown in **entries 4 and 5**.

Ibuprofen amides have been reported to display improved anti-inflammatory activity with less toxicity.[20] In this case, the amidation of optically active (S)-ibuprofen with both benzylamine and (*R*)-(+)-α-methylbenzylamine in THF led to the corresponding amides with good yields and >95% ee and >95% de, respectively (**Table 2-6, entry 6**). Given the propensity of ibuprofen and its amides to racemize,[21] this result provides a clear testimony to the mildness of these low temperature conditions. These direct catalytic amidations are operationally very simple. They employ equimolar amounts of acid and amine substrates, require no heating or cooling source, generate no by-products, and they afford pure amide products after a simple filtration and acid–base extractions to remove any unreacted substrates and the catalyst.

The previously proposed mechanism for boronic acid catalyzed direct amidations was inclusively supported by the isolation of a monoacylboronate intermediate **2-32** by Yamamoto[3] or by the diacylboronate **2-33** proposed by Whiting.[6] Intermediate **2-32** would provides electrophilic activation of the carboxylate group through boron conjugation and internal H-bonding. The intermediacy of carboxylic acid anhydrides has been ruled out.[6] Indeed, we observed no formation of acetic anhydride when acetic acid and **2-24** were mixed alone under the same amidation conditions. Moreover, in the same conditions, butyric anhydride reacted efficiently with *N*-methylbenzylamine, a substrate that failed direct amidation catalyzed by **2-24** under the optimal reaction conditions.

It is worth noting that the amide products from these proposed intermediates required elevated temperature to form. With our catalysts **2-21** and **2-24**, the halo

group at the *ortho* position might provide another intermediate (possibly multiple intermediates), which is most likely to be highly reactive in order to allow the reaction to proceed at ambient temperature, as shown in **Scheme 2-13**. Further investigations are required to explain the actual role of the iodo substituent in the mechanism.



Scheme 2-13: Postulated mechanisms for direct amide bond formation with catalysts 2-21 and 2-24.

2.2.7 Effect of Additives on Catalytic Direct Amide Bond Formation

Having identified the optimal catalyst and solvent for catalytic amide bond formation and found that there were still some limitations for this catalytic amidation method, such as the use aromatic carboxylic acids, we examined the effect of additives to improve further this catalytic methodology as a way to finding solutions to these limitations. Different additives were used, as summarized in **Table 2-7**. For example, the use of Et_3N, TFA, Triton X, Na_2CO_3, proton sponge, *n*-Bu_4NBr and crown ether completely shut down the catalytic activity and no amide products were detected. The use of DMAP had no effect and the same yield was isolated. Furthermore, it is known that HOBt is used as an activator during stoichiometric

amidation reaction conditions.[13, 14, 16] Unfortunately, it did not improve the yield or enhance the reactivity of the catalytic amidation reaction even with shorter reaction time. These are preliminary results and further investigations were made by my laboratory partner, Sam Mothana.

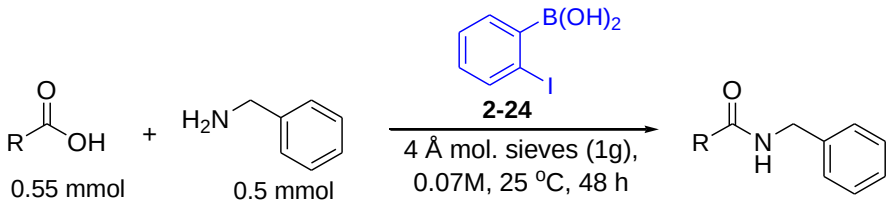
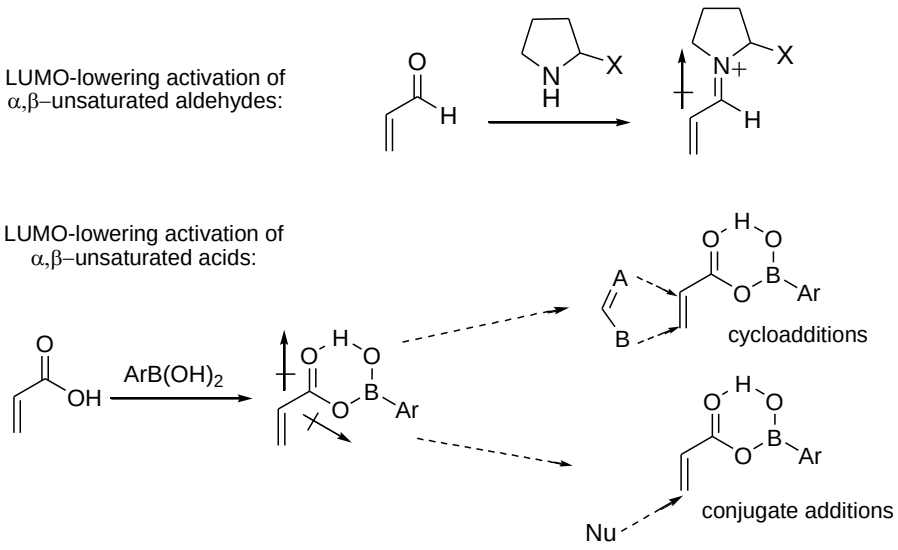


Table 2-7: Effect of additives on catalytic direct amide bond formation

Entry	Additive/solvent	Additive equivalency	R	Conversion (%)
1	none	-	$PhCH_2$	99
2	Et_3N/DCM	1.0	$PhCH_2$	0
3	TFA/DCM	1.0	$PhCH_2$	0
4	TFA/THF	1.0	$PhCH_2$	0
5	*n*-Bu_4NBr/DCM	0.10	$PhCH_2$	0
6	*n*-Bu_4NBr/THF	0.10	$PhCH_2$	0
7	DMAP/DCM	0.10	$PhCH_2$	99
8	DMAP/DCM	0.10	Ph	0
9	Proton sponge/THF	0.10	$PhCH_2$	0
10	Proton sponge/DCM	0.10	$PhCH_2$	0
11	DBU/DCM	0.10	$PhCH_2$	0
12	HOBt/DCM	1.0	$PhCH_2$	95
13	Triton X/DCM	0.1	$PhCH_2$	0
14	12-Crown-4/THF	0.10	$PhCH_2$	0
15	18-Crown-6/THF	0.10	$PhCH_2$	0
16	Na_2CO_3/THF	1.0	$PhCH_2$	0

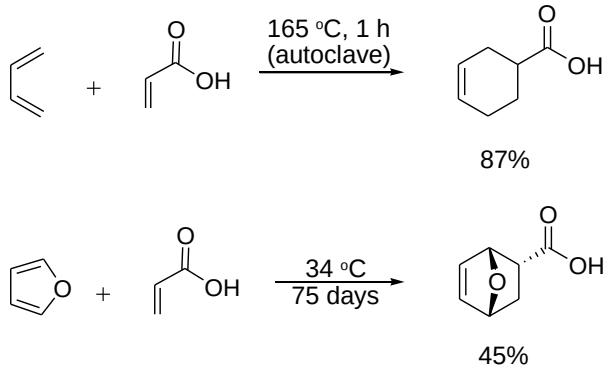
2.3 Organocatalytic Activation of Unsaturated Carboxylic Acids for Diels-Alder Reactions

Beyond its use in amidation chemistry, the carboxylic acid group tends to be a difficult functional group that is incompatible or unreactive in several important chemical reactions. It can be envisaged that the same catalytic activation mechanism could be exploited in cycloadditions of unsaturated carboxylic acids (**Scheme 2-14**). Such a concept, using boronic acids as organocatalysts, would complement the pyrrolidine-catalyzed iminium ion activation of α,β-unsaturated ketones and aldehydes, as depicted in **Scheme 2-14**.[22]



Scheme 2-14: Organocatalytic activation of α,β-unsaturated carboxylic acids.

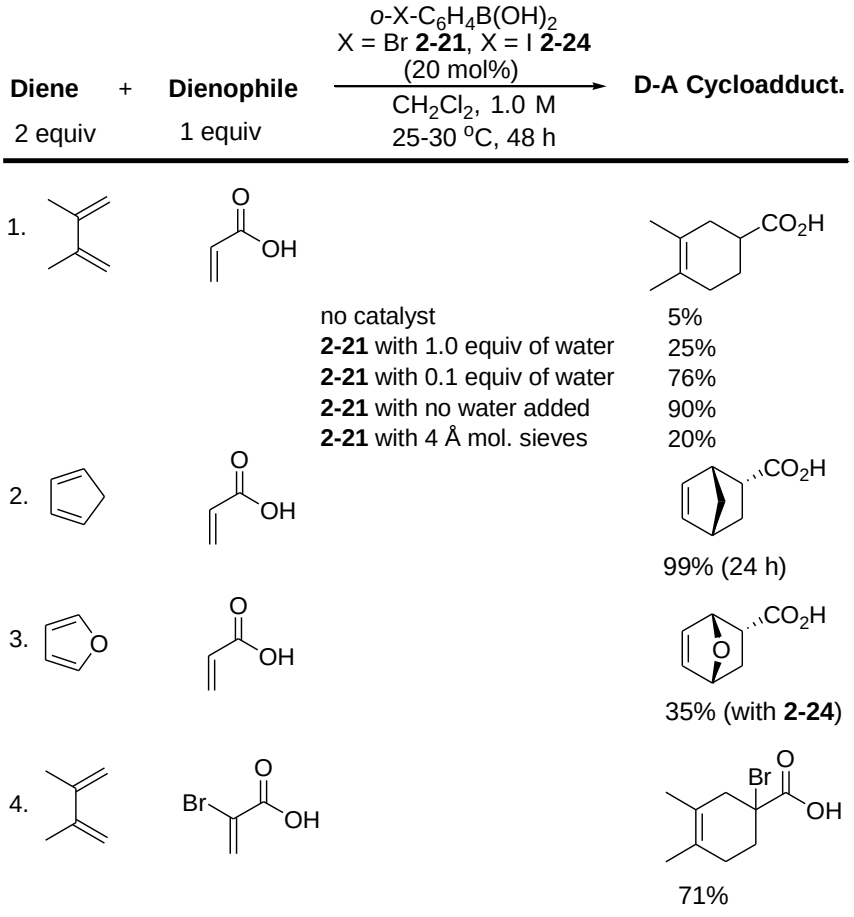
In a partnership with Olivier Marion, we chose to explore the notoriously difficult thermal Diels–Alder reactions of α,β-unsaturated carboxylic acids. Indeed, acrylic acid is known to induce decomposition of functionalized dienes at high temperatures, and it is quite unreactive at low temperatures.[23, 24] For example, the Diels–Alder reactions between acrylic acid and cyclopentadiene and furan require, respectively, one hour at 165 °C and 75 days at 35 °C, respectively, to achieve reasonable yields of the desired products (**Scheme 2-15**).



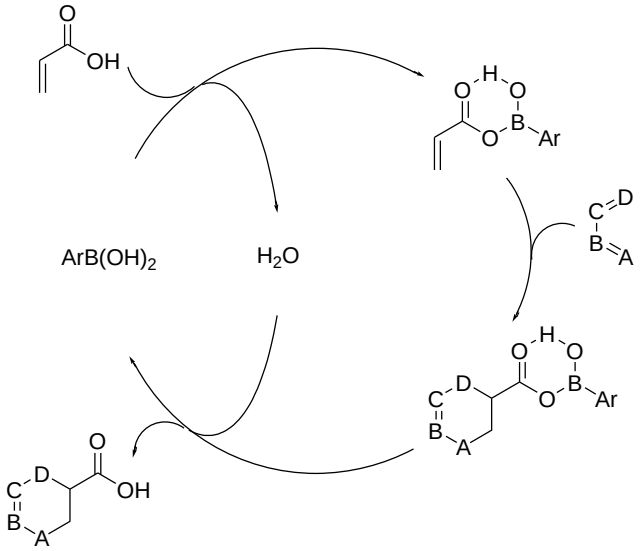
Scheme 2-15: Diels-Alder cycloaddition reactions of acrylic acid with cyclopentadiene and furan.[23, 24]

We found that boronic acids **2-21** and **2-24** catalyze Diels–Alder reactions of acrylic acid and α-bromoacrylic acid in good to high yields at room temperature (**Table 2-8**). Phenylboronic acid gave only 25% yield under the same reaction conditions.

Table 2-8: Diels–Alder cycloadditions of free α,β-unsaturated carboxylic acids catalyzed by boronic acids 2-21 and 2-24.

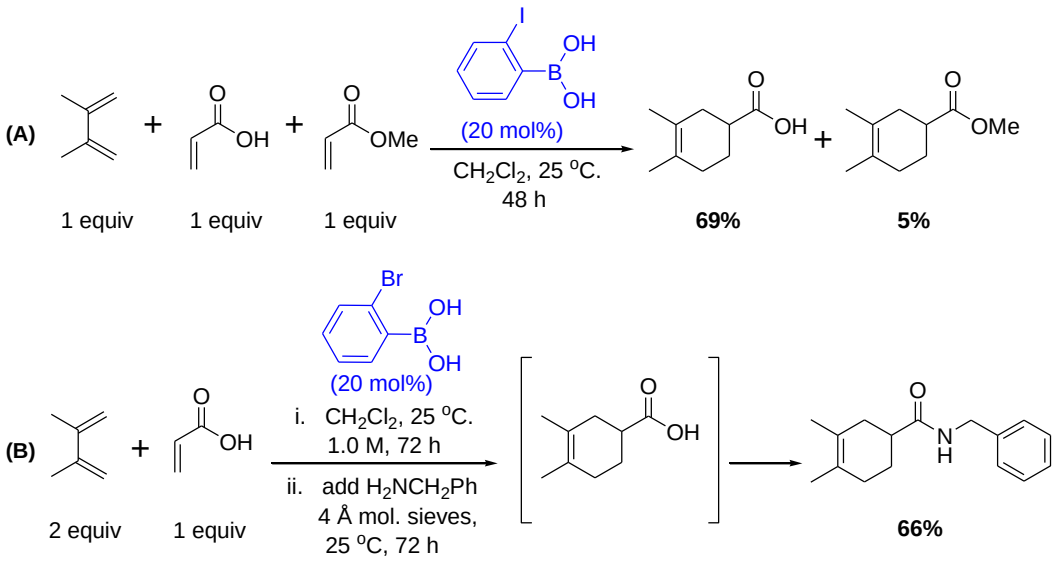


Furthermore, the reactions proceed with less than 5% yield in the absence of the catalyst. Interestingly, the absence of water (i.e., when using molecular sieves) does not allow catalyst turnover and leads to low yields. We observed that a small amount of water (from condensation of the acid and the catalyst) is required to regenerate the catalyst from the cycloadduct. The catalytic cycle is proposed in **Scheme 2-16**. Although there are a few reported cases of Lewis acid catalyzed [4+2] cycloadditions of acrylic acid,[25, 26] the current system permits a remarkable selectivity over the corresponding esters that would be difficult to achieve with noncovalent catalysis, as shown in **Equation 2-2 (A)**.



Scheme 2-16: The proposed catalytic cycle for the boronic acid catalyzed [4+2] cycloadditions of α,β-unsaturated carboxylic acids.

The possibility to perform cascade reactions with the help of simple organocatalysts is very attractive from the standpoint of step economy and synthetic efficiency.[27] Pleasingly, we found a possible way to combine the two reactions, which was achieved in a remarkable "one-pot" sequential Diels–Alder cycloaddition/amidation with a single catalyst, the *ortho*-iodoarylboronic acid **2-24** (**Equation 2-2 (B)**).

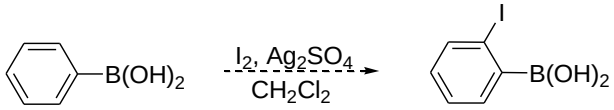


Equation 2-2: (A) Chemoselective Diels-Alder cycloaddition between an α,β-unsaturated carboxylic acid and an ester using catalyst 2-24 at ambient temperature. (B) One-pot Diels-Alder/amidation using catalyst 2-21 at ambient temperature.

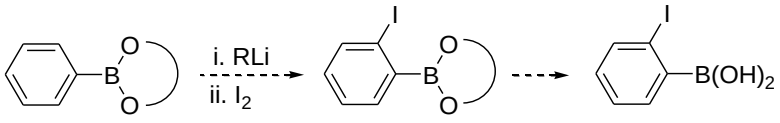
2.4 Synthesis of *Ortho*-Iodoarylboronic Acid

It was envisaged that *ortho*-iodoarylboronic acid **2-24** could be made by three different approaches (**Scheme 2-17**). The first one is the directed Friedel-Crafts iodination of arylboronic acids. Secondly, directed *ortho*-metalation followed by iodine trapping and thirdly, electrophilic borate trapping of an arylmetal intermediate from commercial *ortho*-diiodobenzene. Arylboronic acids are known to be susceptible to chemoselectivity issues that render them difficult to derivatize further after introduction of the boronic acid. As a result, a protection of the boronic acid group is necessary for both Friedel-Crafts and directed *ortho*-metallation approaches.

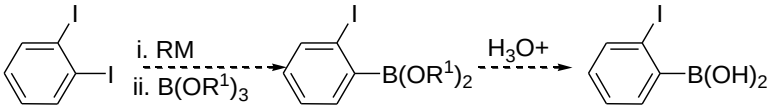
1. Electrophilic Friedel-Crafts iodination of phenylboronic acid



2. Electrophilic iodine trapping of arylboronate intermediate from directed ortho-iodination

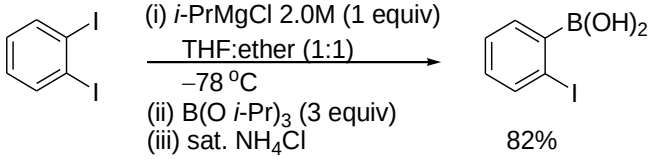


3. Electrophilic borate trapping of arylmetal intermediate from ortho-diiodobenzene



Scheme 2-17: Possible methods for the synthesis of ortho-iodoarylboronic acid.

In order to avoid the protection/deprotection steps, we decided to examine the first and the third approaches. The first approach failed to provide the desired product with and without protection of the boronic acid group. The third approach based on a procedure by Scott and coworkers[28] was pleasingly successful in providing the *ortho*-iodoarylboronic acid **2-24** in 82% yield in one step. The crude product was effectively purified without the need for any protection of the boronic acid group during purification (**Equation 2-3**). An X-ray crystal structure (**Table 2-4**) was also accessible by successful recrystallization in an ether/hexanes mixture.



Equation 2-3: Synthesis of ortho-iodoarylboronic acid 2-24 by electrophilic borate trapping with arylmetal.

2.5 Conclusion–First Generation Catalyst System

During this initial stage, the exceptional and remarkable ability of *ortho*-bromo- **2-21** and, especially, *ortho*-iodophenylboronic acid **2-24** to serve as catalysts for direct amide bond formation and cycloadditions of carboxylic acids under mild and waste-free conditions at room temperature was uncovered. In this methodology, the

reaction procedure is operationally very simple. It employs equimolar amounts of acid and amine substrates, requires no heating or cooling source, generates only water as a by-product, and affords pure amide products after a simple filtration and acid–base extractions to remove any unreacted substrates and the catalyst. This new catalytic system represents a significant advance over the previous catalysts reported by both the Yamamoto and Whiting groups and demonstrates the strong potential of boronic acid-catalysis towards activation of the carboxylic acid moiety. With three other ring positions that can be electronically modulated with various substituents, improved catalysts could be designed to expand further the substrate scope of these reactions which will be discussed in Chapter Three. Along with a better mechanistic understanding, this concept of organocatalytic activation of carboxylic acids could become broadly applicable to other important synthetic transformations.

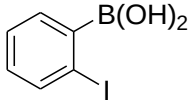
2.6 Experimental

2.6.1 General Information

Unless otherwise stated, all reactions were performed under argon atmosphere using flame-dried glassware. Toluene and CH_2Cl_2 were distilled from CaH_2. THF was distilled from sodium with benzophenone as an indicator. Analytical thin layer chromatography was performed on Merck Silica Gel 60 F254 plates. NMR spectra were recorded on Varian INOVA-300, INOVA-400 or INOVA-500 MHz instruments. *J* accuracy: (+/−) 0.5 Hz. The residual solvent protons (^{1}H) or the solvent carbon (^{13}C) were used as internal standards. Carbon attached to $B(OH)_2$ group was generally not detected by ^{13}C-NMR (exhaustive peak broadening due to quadrupolar relaxation of ^{11}B). ^{1}H-NMR data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet; sept, septet. High-resolution mass spectra were recorded by the University of Alberta mass spectrometry service laboratory using either electron impact (EI) or electrospray ionization (ESI) techniques. Infrared spectra were obtained on a Nicolet Magna-IR 750 with frequencies expressed in cm^{-1}. X-ray crystallography was performed using

a Bruker P4/RA/SMART 1000 CCD diffractometer. Powdered 4 Å molecular sieves (< 5 micron, Aldrich) were dried overnight in an oven (250 °C) prior to use.

2.6.2 Preparation and Characterization Data for *Ortho*-Iodophenylboronic Acid (2-24)



To a solution of 1,2-diiodobenzene (1.02 g, 3.08 mmol) in 300 mL of a mixture of THF and Et_2O (1:1) at –78 °C isopropyl magnesium chloride (2 M in THF, 15.4 mL, 30.8 mmol) was added dropwise. The mixture was stirred at that temperature for 2 h and then triisopropyl borate (17.4 g, 92.4 mmol) was added. The solution was slowly warmed to room temperature and stirred overnight. HCl (10% aq., 400 mL) was added and the resulting mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with Et_2O (3 x 500 mL). After drying the organic phase with Na_2SO_4, the solution was filtered and then the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (100% hexane then hexane/EtOAc; 4:1) to yield the desired product (0.62 g, 82% yield) as a white solid.

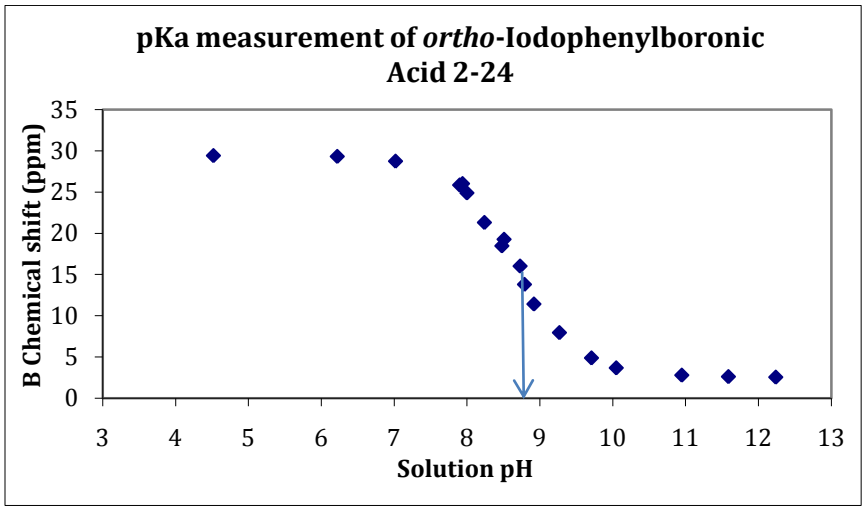
^{1}H-NMR (400 MHz, CD_2Cl_2) δ 7.86 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.77 (dd, *J* = 1.8, 7.6 Hz, 1H), 7.41 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.14 (dt, *J* = 1.8, 7.6 Hz, 1H), 5.22 (s, 2 H). **^{13}C-NMR** (125 MHz, CD_2Cl_2) δ 139.8, 136.9, 132.5, 128.0, 100.7, (C attached to B not seen on the NMR at 27 °C). **^{11}B-NMR** (125 MHz, CD_2Cl_2) δ 29.10. **IR** (Microscope, cm^{-1}) 3306, 1581, 1352, 999, 820, 752. **HRMS** (EI) for $C_6H_6O_2{}^{11}BI$: calcd. 247.95056; found, 247.95068.

CCDC 664933

pKa (^{11}B NMR titration) 8.90.

NMR titration assay. Phosphate buffer solution: In a volumetric flask (50 mL), 690 mg of NaH_2PO_4 were dissolved in 5 mL of D_2O. The flask was filled to 50 mL with H_2O. Boronic acid solution: In a volumetric flask (25 mL), 99 mg of boronic acid **2-24** was dissolved in a minimum amount of DMSO. The flask was filled to 25 mL with the phosphate buffer solution (resulting solution: 16 mM of **2-24** in 0.1 M phosphate buffer; 90/10 H_2O/D_2O). Solution for ^{11}B NMR: 1 mL of the boronic acid

solution was placed in a vial. This solution was adjusted to the desired pH with an aqueous NaOH solution. The ^{11}B NMR is made from this solution. The pKa is determined using the plot of the boron chemical shift *vs*. the pH of the solution.

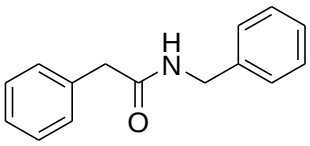


2.6.3 General Procedure for Organocatalytic Amidations

Into a 25 mL round bottom flask equipped with a stir bar were added carboxylic acid (0.55 mmol, 1.1 equiv), *ortho*-bromophenylboronic acid (0.05 mmol, 10 mol%) and 1 g of activated 4Å molecular sieves (preactivation overnight in an oven at ~250 °C or by Kugelrohr for 2h at 250 °C under high vacuum). Dichloromethane (7 mL) was added and the mixture was stirred for 10 min. Then, amine (0.5 mmol, 1 equiv) was added (in order to get reproducible results, it was necessary to use a gastight 100 μL syringe). The resulting mixture was stirred for 48 h at room temperature (24-25 °C). The reaction mixture was filtered through a pad of Celite® 545, the filtrate was washed with aqueous hydrochloric solution (pH = 4), aqueous sodium hydroxide solution (pH = 10-11) and brine, respectively. The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and evaporated to yield the title amide product.

2.6.3.1 Amides Preparation and Characterization Data

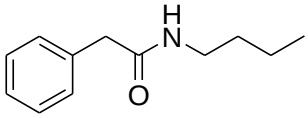
2.6.3.1.1.1 N-Benzyl-2-Phenyl-Acetamide (**Table 2-5, entry 1**)



The title compound was prepared using the general procedure for the organocatalytic amidations (0.123 g, 99% yield in DCM).

The characterization of the compound matched previous reports: (a) W. K. Chan, C. M. Ho, M. K. Wong, C. M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 14796. (b) D. C. Dittmer, Q. Li, D. V. Avilov, *J. Org. Chem.* **2005**, *70*, 4682.

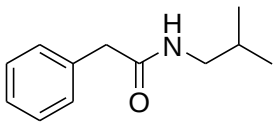
2.6.3.1.1.2 N-Butyl-2-Phenyl-Acetamide (**Table 2-5, entry 3**)



The title compound was prepared using the general procedure for the organocatalytic amidations (66% yield in DCM, 87% yield in THF).

The characterization of the compound matched previous reports: (a) S. D. Petrovic, N. D. Stojanovic, O. K. Stojanovic, N. L. Fac. Kobilaov, T. Metall. *J. Serb. Chem. Soc.* **1986**, *51*, 395. (b) R. N. Ram, R. Ashare, A. K. Mukerjee, *Chem. Indust.* (London, United Kingdom) **1983**, *14*, 569.

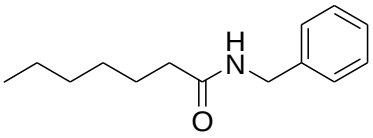
2.6.3.1.1.3 Pent-4-enoic Acid Isobutylamide (**Table 2-5, entry 4**)



The title compound was prepared using the general procedure for the organocatalytic amidations (80% yield).

The characterization of the compound matched previous reports: (a) F. Gagosz, C. Moutrille, S. Z. Zard, *Org. Lett.* **2002**, *4*, 2707. (b) P. R. Blakemore, *Sci. Synth.* **2005**, *21*, 833.

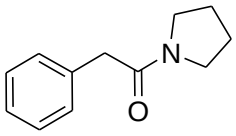
2.6.3.1.1.4 Heptanoic Acid Benzylamide (**Table 2-5, entry 5**)



The title compound was prepared using the general procedure for the organocatalytic amidations (99% yield).

The characterization of the compound matched previous reports: (a) J. M. Hoeter, K. M. Otte, S. H. Gellman, S. S. Stahl, *J. Am. Chem. Soc.* **2006**, *128*, 5177. (b) H. L. Lee, J. Aube, *Tetrahedron* **2007**, *63*, 9007. (c) C. M. Bell, D. A. Kissounko, S. H. Gellman, S. S. Stahl *Angew. Chem. Int. Ed.* **2007**, *46*, 761.

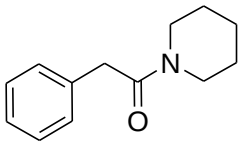
2.6.3.1.1.5 2-Phenyl-1-Pyrrolidin-1-yl-Ethanone (**Table 2-5, entry 7**)



The title compound was prepared using the general procedure for the organocatalytic amidations (41% yield, 76% yield with catalyst **2-24**).

The characterization of the compound matched previous reports: (a) J. H. Smitrovich, L. DiMichele, C. Qu, G. N. Boice, T. D. Nelson, M. A. Huffman, J. Murry, *J. Org. Chem.* **2004**, *69*, 1903. (b) A. R.; Katrizky, H. Y. He, K. Suzuki, *J. Org. Chem.* **2000**, *65*, 8210. (c) T. D. Nelson, *Chirality* **2004**, *16*, 609. (d) S. Hackett, *J. Org. Chem.* **1986**, *51*, 879.

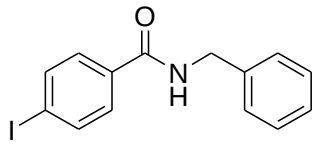
2.6.3.1.1.6 2-Phenyl-1-Piperdin-1-yl-Ethanone **(Table 2-5, entry 8)**



The title compound was prepared using the general procedure for the organocatalytic amidations. Catalyst **2-24** was used (52% yield in DCM, 97% yield in THF).

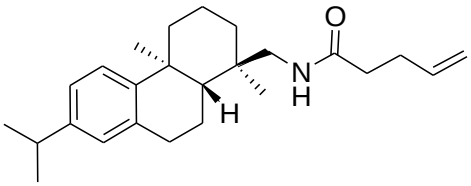
The characterization of the compound matched previous reports: (a) W. Shen,; A. Kunzer, *Org. Lett.* **2002**, *4*, 1315. (b) W. B. Wang, E. J. Roskamp, *J. Org. Chem.* **1992**, *57*, 6101.

2.6.3.1.1.7 N-Benzyl-4-Iodobenzamide (**Table 2-5, entry 6**)



The title compound was prepared using the general procedure for the organocatalytic amidations. The solvent for the reaction was toluene, the temperature was 50 °C and catalyst **2-24** (20 mol%) was used (24% yield after flash chromatography (25% EtOAc/hexanes).

The characterization of the compound matched a previous report: A. Klapars, Antilla, J. C. X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727.

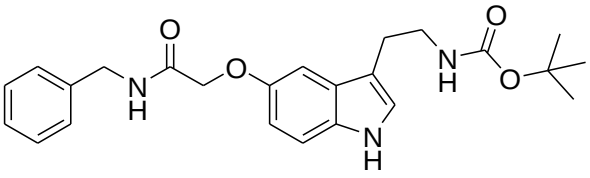


2.6.3.1.1.8 Pent-4-enoic Acid (7-Isopropyl-1,4a-Dimethyl-1,2,3,4,4a,9,10,10a-Octahydro Phenanthren-1-ylmethyl)-Amide (**Table 2-6, entry 1**)

The title compound was prepared using the general procedure for the organocatalytic amidations. Catalyst **2-24** was used (74% yield after chromatography (20% EtOAc/hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.4 Hz, 1H), 7.00 (dd, *J* = 1.8, 8.4 Hz, 1H), 6.89 (s, 1H), 5.79 (m, 1H), 5.38 (br s, 1H), 5.00 (dd, *J* = 18.0, 18.4 Hz, 2H), 3.00 (m, 3H), 2.25 (m, 4H), 1.75-0.81 (m, 23H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 172.3, 147.0, 145.5, 137.0, 134.7, 126.8, 124.0, 123.7, 115.5, 49.7, 45.2, 38.3, 37.3, 37.2, 36.1, 35.9, 33.3, 30.1, 29.6, 25.2, 23.90, 23.87, 18.9, 18.6, 18.5. **IR** (Cast film, cm^{-1}) 3305, 3078, 2956, 2925, 2853, 1711, 1644, 1553, 1498. **HRMS** (ESI) for $C_{25}H_{37}NONa$: calcd. 390.27674; found, 390.27689.

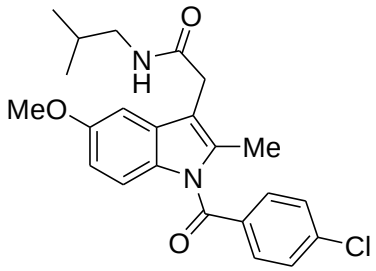
2.6.3.1.1.9 {2-[5-(Benzylcarbomoyl-Methoxy)-1H-Indol-3-yl] Ethyl}-Carbamic Acid Tert-Butyl Ester (**Table 2-6, entry 3**)



The title compound was prepared using the general procedure for the organocatalytic amidations. Catalyst **2-24** (20 mol%) was used (95% yield).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.24 (m, 6H), 7.05 (m, 1H), 6.85 (dd, *J* = 2.8, 8.7 Hz, 1H), 4.60 (s, 2H), 4.50 (d, *J* = 3.6 Hz, 2H), 3.43 (m, 2H), 2.90 (t, *J* = 6.7 Hz, 2H), 1.44 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 168.9, 155.9, 151.4, 137.8, 132.2, 128.6, 127.7, 127.6, 127.5, 123.4, 112.8, 112.1, 111.8, 102.8, 79.1, 68.6, 42.9, 40.7, 28.3, 25.7. **IR** (Cast film, cm^{-1}) 3430, 3319, 2976, 2930, 1692, 1672, 1533,1174, 733. **HRMS** (ESI) for $C_{24}H_{29}N_3O_4Na$: calcd. 446.20503, found; 446.20537.

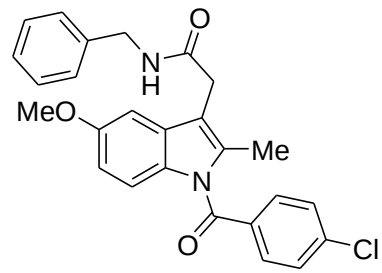
2.6.3.1.1.10 2-[1-(4-Chloro-Benzoyl)-5-Methoxy-2-Methyl-1H-Indol-3-yl]-N-iso-Butyl-Acetamide (**Table 2-6, entry 2**)



The title compound was prepared using the general procedure for the organocatalytic amidations (73% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 2.8 Hz, 1H), 6.88 (d, *J* = 9.2 Hz, 1H), 6.68 (d, *J* = 2.4 Hz, 1H), 5.77 (t, *J* = 5.6 Hz, 1H), 3.80 (s, 3H), 3.64 (s, 2H), 3.02 (t, *J* = 6.4 Hz, 2H), 2.37 (s, 3H), 1.67 (sept, *J* = 6.8 Hz, 1H), 0.78 (d, *J* = 6.8 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 169.8, 168.2, 156.2, 139.4, 136.2, 133.5, 131.0, 130.8, 130.2, 129.1, 115.0, 112.8, 112.4, 100.6, 55.6, 46.8, 32.1, 28.3, 19.8, 13.1. **IR** (Cast film, cm^{-1}) 3296, 3086, 2960, 2929, 1680, 1647, 1592, 1478, 1359, 1324, 1225, 1090, 734. **HRMS** (ESI) for $C_{23}H_{25}N_2O_3ClNa$: calcd. 435.14459; found 435.14489.

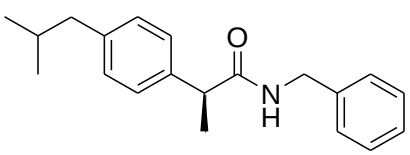
2.6.3.1.1.11 N-Benzyl-2-[1-(4-Chloro-Benzoyl)-5-Methoxy-2-Methyl-1H-Indol-3-yl]-Acetamide (**Table 2-6, entry 2**)



The title compound was prepared using the general procedure for the organocatalytic amidations (93% yield).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.25 (m, 3H), 7.18 (m, 2H), 6.90 (m, 1H), 6.85 (d, *J* = 9.0 Hz, 1H), 6.70 (d, *J* = 5.7 Hz, 1H), 6.18 (t, *J* = 5.7 Hz, 1H), 4.41 (d, *J* = 6.0 Hz, 2H), 3.78 (s, 3H), 3.70 (s, 2H), 2.34 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 169.9, 168.1, 156.2, 139.4, 138.0, 136.2, 133.5, 131.0, 130.8, 130.2, 129.05, 128.97, 128.5, 127.3, 115.0, 112.7, 112.3, 100.7, 55.6, 43.4, 32.1, 13.2. **IR** (Cast film, cm^{-1}) 3297, 3065, 2929, 1679, 1650, 1478, 1359, 1324, 1226, 1089, 733. **HRMS** (ESI) for $C_{26}H_{23}N_2O_3ClNa$: calcd. 469.12894; found 469.12918.

2.6.3.1.1.12 (S)-N-Benzyl-2-(4-Isobutylphenyl)-Propionamide (**Table 2-6, entry 6**)

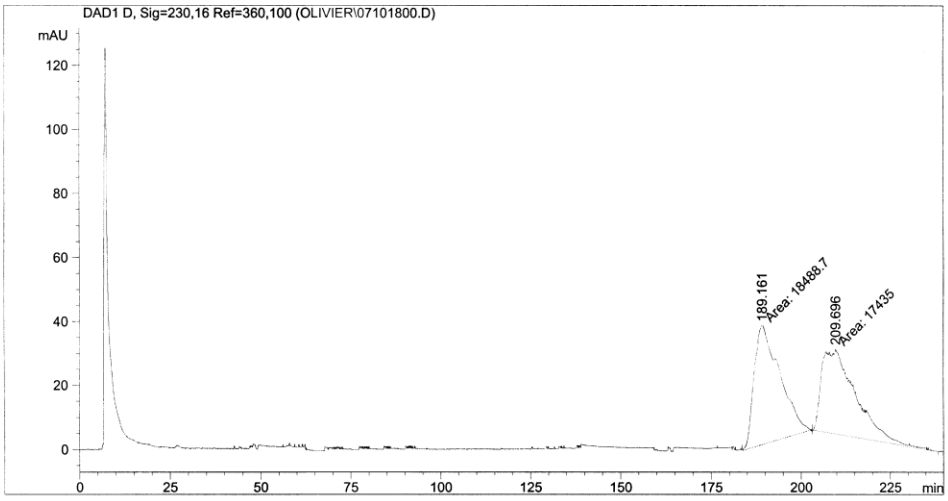


The title compound was prepared using the general procedure for the organocatalytic amidations. The solvent for the reaction was THF and catalyst **2-24** was used (73% yield after chromatography, 25% EtOAc/hexanes). Special care should be taken with the basic extraction for base sensitive substrates. A pH higher then 9 for the aqueous solution should be avoided.

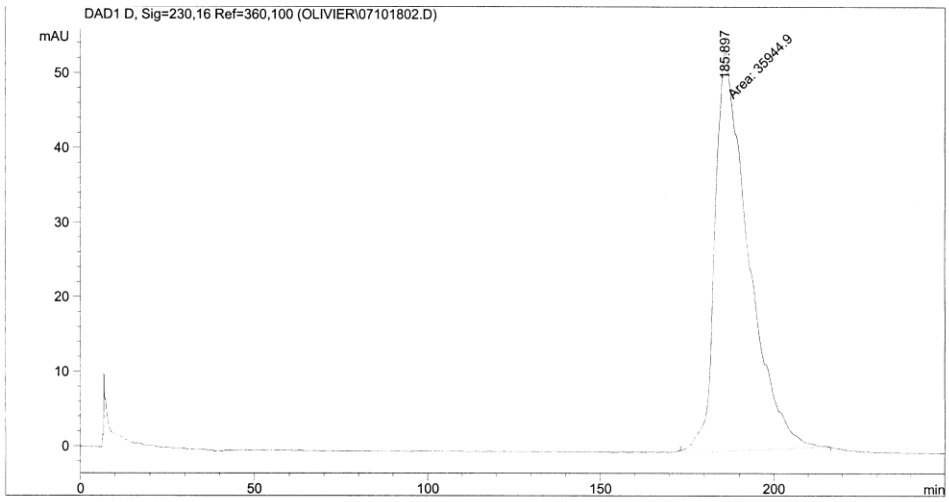
The characterization of the compound matched a previous report: S. G. Sudrik, S. P. Chavan, K. R. S. Chandrakumar, S. Pal, S. K. Date, S. P. Chavan, H. R. Sonawane, *J. Org. Chem.* **2002**, *67*, 1574-1579.

HPLC (Chiralcel OD column. Hexane/isopropanol 99/1. Flow rate of 0.5 mL/min. Temperature at 0.5 ^{0}C. UV detection at 230 nm)

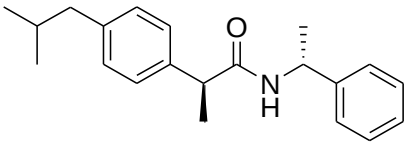
Racemic mixture (prepared from racemic ibuprofen):



Chiral product:



2.6.3.1.1.13 (S,R)-2-(4-Isobutyl-Phenyl)-N-(1-Phenyl-Ethyl)-Propionamide (**Table 2-6, entry 6**).

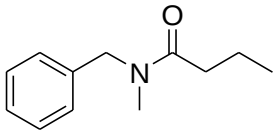


The title compound was prepared using the general procedure for the organocatalytic amidations but the reaction was stopped after 16 h. The solvent for the reaction was THF and catalyst **2-24** (20 mol%) was used (70% yield after chromatography, 25% EtOAc/hexanes). Special care should be taken with the basic extraction for base sensitive substrates. A pH higher then 9 for the aqueous solution should be avoided. Some racemization has been observed when using a basic solution at pH 11.

The ^{1}H-NMR of the compound matched a previous report: E. J. Ebbers, G. J. A. Ariaans, A. Bruggink, B. Zwanenburg, *Tetrahedron: Asymmetry* **1999**, *10*, 3701-3718.

2.6.3.1.1.14 N-Benzyl-N-Methyl-Butyramide

The title compound was prepared using the general procedure for the organocatalytic amidations (with the boronic acid catalyst and the molecular sieves) but butyric anhydride was used instead of the acid. The reaction was stopped after 24 h (95% yield).



The title compound was reported before (S. Sugasawa, T. Fujii, *Chem. & Pharm. Bull.* **1958**, *6*, 587) but full characterization was not given. Both amide rotamers can be observed on the ^{1}H and ^{13}C-NMR at 27 ^{o}C.

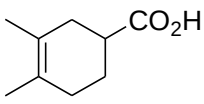
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5H), 4.58 (2*s, 2H), 2.94 (2*s, 3H), 2.37 (m, 2H), 1.72 (m, 2H), 0.97 (2*t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 173.5 (173.2), 137.6 (136.7), 128.9 (128.5), 128.0 (127.5), 127.2 (126.3), 53.3 (50.7), 35.5 (35.1), 34.8 (33.8), 18.8 (18.6), 14.0. **IR** (Cast film, cm^{-1}) 3295, 3063, 2963, 2933, 2874, 1645, 1453, 1402, 1076, 731, 699.

2.6.3.2 General Procedure for the Diels-Alder Reaction.

To a solution of carboxylic acid (1.39 mmol) in dichloromethane (2 mL) was added the *ortho*-bromophenylboronic acid (20 mol%), followed by the diene (2.78 mmol). This solution was stirred at 25 ^{o}C for 48 h. Upon completion, the product was directly purified by column chromatography (diethyl ether/pentane 1:1) to yield the title cycloadduct compound.

2.6.3.2.1 Cyloadduct Preparation and Characterization Data

2.6.3.2.1.1 3,4-Dimethyl-Cyclohex-3-Enecarboxylic Acid (**Table 2-7, entry 1**)

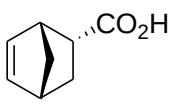


The title compound was prepared using the general procedure for the Diels-Alder reaction but the reaction was stopped after 48 h (90% yield) as a white solid.

The characterization of the compound matched previous reports: (a) P. P. Pescarmona, *J. Mol. Cat. A: Chem.* **2004**, *220*, 37. (b) K. Furuta, Y. Miwa, K. Iwanaga, H. Yamamoto, *J. Am. Chem. Soc.* **1988**, *110*, 6254. (c) G. B. Bachman, *J. Org. Chem.*

1939, *4*, 493.

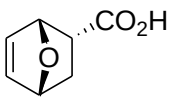
2.6.3.2.1.2 Bicyclo[2.2.1]Hept-5-ene-2-Carboxylic Acid (**Table 2-7, entry 2**)



The title compound was prepared using the general procedure for the Diels-Alder reaction but the reaction was stopped after 24 h (99% yield).

The characterization of the compound matched a previous report: R. Akkari, *Euro. J. Org. Chem.* **2004**, *11*, 2441.

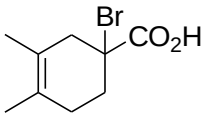
2.6.3.2.1.3 7-Oxa-Bicyclo[2.2.1]Hept-5-ene-2-Carboxylic Acid (**Table 2-7, entry 3**)



The title compound was prepared using the general procedure for the Diels-Alder reaction but catalyst **2-24** was used (20 mol%) (35% yield). A longer reaction time failed to increase the yield.

The characterization of the compound matched a previous report: J. A. Moore, E. M. III. Partain, *J. Org. Chem.* **1983**, *48*, 1105.

2.6.3.2.1.4 1-Bromo-3,4-Dimethyl-Cyclohex-3-Enecarboxylic Acid (**Table 2-7, entry 4**)

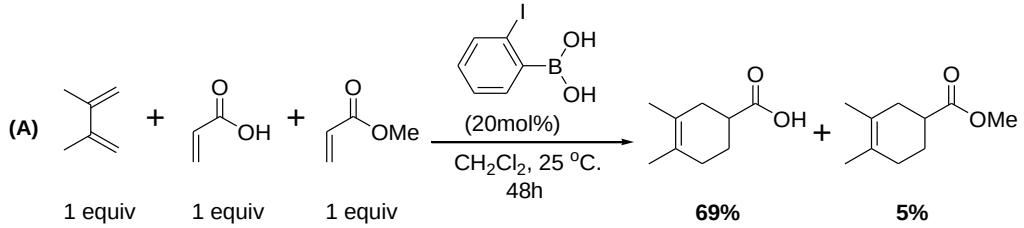


The title compound was prepared using the general procedure for the Diels-Alder reaction (71% yield).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 11.58 (br s, 1H), 2.87 (d, *J* = 17.5 Hz, 1H), 2.67 (d, *J* = 17.5 Hz, 1H), 2.28 (m, 2 H), 2.20 (m, 2 H), 1.63 (s, 6 H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 177.3, 125.0, 122.7, 59.2, 43.0, 34.1, 30.3, 19.0, 18.6. **IR** (Microscope, cm^{-1}) 2903, 2606, 1701, 1413, 1294, 1229, 934. **HRMS** (EI) for $C_9H_{13}O_2{}^{81}Br$: calcd. 234.00784; found, 234.00760; for $C_9H_{13}O_2{}^{79}Br$: calcd. 232.00989; found, 232.00964.

2.6.3.3 Procedure for Competition Reaction Between Carboxylic Acid and Ester Toward Diels-Alder Cycloaddition.

2.6.3.3.1 3,4-Dimethyl-Cyclohex-3-Enecarboxylic Acid and Methyl 3,4-Dimethyl Cyclohex-3-Enecarboxylate *(Equation 2-2 (A))*

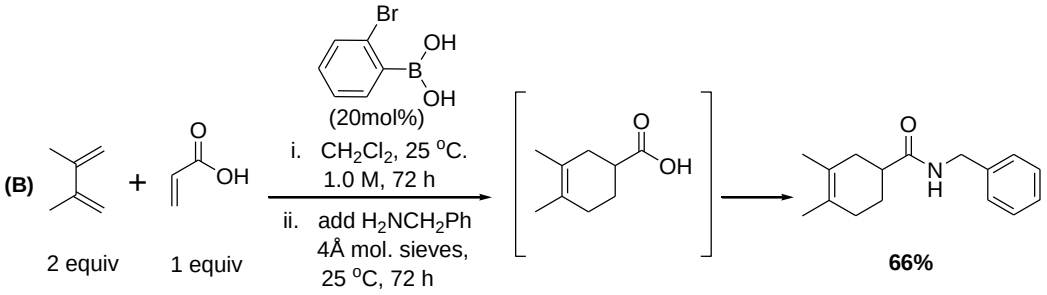


To a solution of acrylic acid (0.10 g, 1.39 mmol) and methyl acrylate (0.12 g, 1.39 mmol) in dichloromethane (2 mL) was added the *ortho*-bromophenylboronic acid (58 mg, 20 mol%) followed by the 2,3-dimethyl-1,3-butadiene (0.12 g, 1.39 mmol). This solution was stirred at 25 °C for 48 h. Upon completion, the product was directly purified by column chromatography (diethyl ether/pentane 1:1) the yield 3,4-dimethyl-cyclohex-3-enecarboxylic acid (0.15 g, 69%) and methyl 3,4-dimethyl cyclohex-3-enecarboxylate (0.012 g, 5%).

The characterization of methyl 3,4-dimethylcyclohex-3-enecarboxylate matched a previous report: K. Hara, R. Akiyama, M. Sawamura, *Org. Lett.* **2005**, *7*, 5621.

2.6.3.4 Procedure for the Sequential One-pot Diels-Alder/Amidation Reaction.

2.6.3.4.1 3,4-Dimethyl-Cyclohex-3-Enecarboxylic Acid Benzylamide *(Equation 2-2 (B))*



To a solution of acrylic acid (0.10 g, 1.39 mmol) in dichloromethane (2 mL) was added the *ortho*-iodophenylboronic acid (60 mg, 20 mol%) followed by the 2,3-dimethyl-1,3-butadiene (0.23 g, 2.78 mmol). This solution was stirred at 25 °C for 72

h. After this time, molecular sieves were added and the volume of solvent was increased to 8 mL. This mixture was stirred for 1 h and benzylamine (0.10 g, 1.04 mmol) was added. The reaction was stirred for 72 h at 25 °C. Upon completion, the mixture was filtered through Celite and the Celite was washed with dichloromethane (2x10 mL). The filtrate was then extracted with aqueous NaOH solution (pH 10-11, 2x20 mL), aqueous HCl solution (pH 4, 2x20 mL) and brine. The organic phase was dried with sodium sulphate and filtered. Concentration of the organic yielded the pure amide (0.17 g, 66%) as a white solid.

The characterization of the compound matched a previous report: R. Akkari, *Tetrahedron: Asymmetry* **2004**, *15*, 2515.

2.7 References

[1] K. Ishihara, S. Ohara, H. Yamamoto, *Macromolecules* **2000**, *33*, 3511.

[2] K. Ishihara, H. Yamamoto, *Eur. J. Org. Chem.* **1999**, 527.

[3] K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4196.

[4] K. Ishihara, *Tetrahedron* **2009**, *65*, 1085.

[5] K. Ishihara, S. Kondo, H. Yamamoto, *Synlett* **2001**, 1371.

[6] K. Arnold, B. Davies, R. L. Giles, C. Grosjean, G. E. Smith, A. Whiting, *Adv. Synth. Catal.* **2006**, *348*, 813.

[7] K. Arnold, A. S. Batsanov, B. Davies, A. Whiting, *Green Chem.* **2008**, *10*, 124.

[8] H. Charville, D. Jackson, G. Hodges, A. Whiting, *Chem. Commun.* **2010**, *46*, 1813.

[9] K. Arnold, B. Davies, D. Hérault, A. Whiting, *Angew. Chem. Int. Ed.* **2008**, *47*, 2673.

[10] S. W. Coghlan, R. L. Giles, J. A. K. Howard, L. G. F. Patrick, M. R. Probert, G. E. Smith, A. Whiting, *J. Organomet. Chem.* **2005**, *690*, 4784.

[11] P. Tang, *Org. Synth.* **2005**, *81*, 262.

[12] R. Latta, G. Springsteen, B. Wang, *Synthesis* **2001**, 1611.

[13] A. Pal, M. Bérubé, D. G. Hall, *Angew. Chem. Int. Ed.* **2010**, *49*, 1492.

[14] M. Bérubé, M. Dowlut, D. G. Hall, *J. Org. Chem.* **2008**, *73*, 6471.

[15] M. Dowlut, D. G. Hall, *J. Am. Chem. Soc.* **2006**, *128*, 4226.

[16] R. M. Al-Zoubi, O. Marion, D. G. Hall, *Angew. Chem. Int. Ed.* **2008**, *47*, 2876.

[17] D. G. Hall, Ed. *Boronic Acids*; Wiley-VCH: Weinheim, **2005**

[18] C. W. Moth, J. J. Prusakiewicz, L. J. Marnett, T. P. Lybrand, *J. Med. Chem.* **2005**, *48*, 3613

[19] A. S. Kalgutkar, A. B. Marnett, B. C. Crews, R. P. Remmel, L. J. Marnett, *J. Med. Chem.* **2000**, *43*, 2860

[20] L. V. Anikina, G. L. Levit, A. M. Demin, Y. B. Vikharev, V. A. Safin, T. V. Matveeva, V. P. Krasnov, *Pharm. Chem. J.* **2002**, *36*, 237.

[21] X. Yuchun, L. Huizhou, C. Jiayong, *Int. J. Pharm.* **2000**, *196*, 21.

[22] A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416.

[23] J. A. Moore, E. M. Partain III, *J. Org. Chem.* **1983**, *48*, 1105.

[24] F. X. Werber, J. E. Jansen, T. L. Gresham, *J. Am. Chem. Soc.* **1952**, *74*, 532.

[25] D. Hyun Ryu, T.W. Lee, E. J. Corey, *J. Am. Chem. Soc.* **2002**, *124*, 9992.

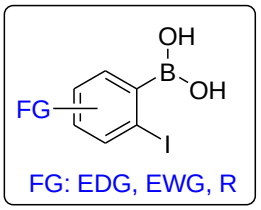
[26] K. Furuta, Y. Miza, K. Iwanaga, H. Yamamoto, *J. Am. Chem. Soc.* **1988**, *110*, 6254.

[27] A. M. Walji, D.W. C. MacMillan, *Synlett* **2007**, 1477.

[28] H. A. Wegner, H. Reisch, K. Rauch, A. Demeter, K. A. Zachariasse, A. De Meijere, L. T. Scott, *J. Org. Chem.* **2006**, *71*, 9080.

A Second Generation Catalyst System for Direct Amide Bond Formation: Implication of Steric and Electronic Effects

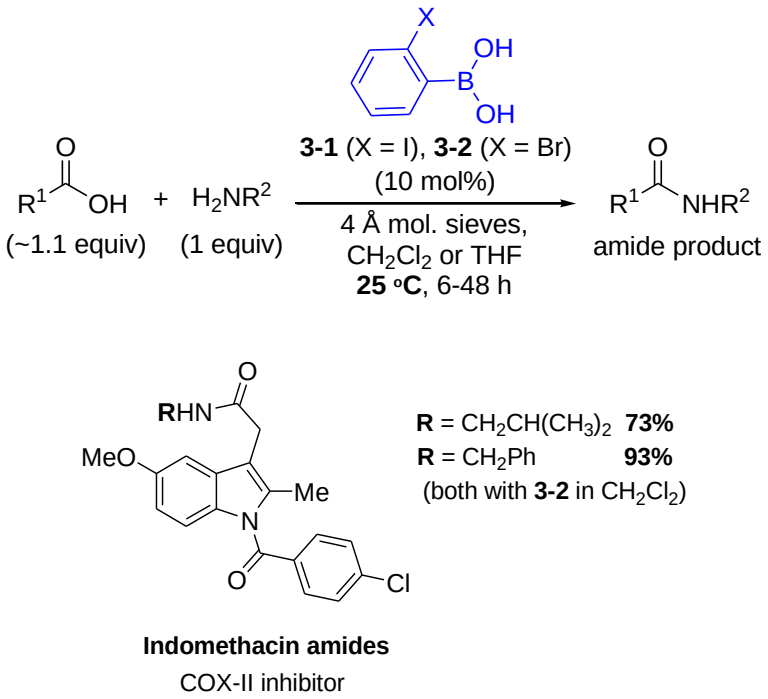
The purpose of this chapter is to delineate steric and electronic effects on the reactivity of the first generation boronic acid catalyst in order to design a better catalyst for direct amide bond formation. The first section considers the three possible positions in the aromatic ring for catalyst optimization. In the second section, the steric effects on the substitution of the 3-position are clarified. The implication of the electronic effects on the reactivity of *ortho*-iodoarylboronic acid is elucidated in the third section. Optimization of the reaction parameters is examined. Some mechanistic aspects of catalyzed direct amidation reactions using *ortho*-iodoarylboronic acid catalysts are presented. In the last section, a third generation catalytic system for direct amide bond formation that provides a superior catalytic reactivity over the first and second generation catalytic systems is revealed.



3.1 Introduction

As described in Chapter Two, in 2008 we reported the first example of a mild, and waste-free direct amidation by organocatalytic activation of carboxylic acids at room temperature.[1] Utilizing *ortho*-haloarylboronic acids as active catalysts toward direct amidations between amines and carboxylic acids (c.f. Chapter 2.2.3), we showed that *ortho*-iodophenylboronic acid (**3-1**) and *ortho*-bromophenylboronic acid (**3-2**) were the most active catalysts providing the highest yields of secondary and tertiary amides in a very high atom-economical fashion that gave only water as a by-product, as shown in **Equation 3-1**. The reaction is operationally very simple, requires no heating or cooling source, uses simple and inexpensive molecular sieves to trap the water by-product, and affords pure amide products after simple filtration

and acid–base extractions. For example, indomethacin amides were made using catalyst **3-1** in good to excellent yields.[1]



Equation 3-1: Direct amidation catalyzed by 2-iodophenylboronic acid (3-1).

These amides are viewed as potential therapeutic agents through their potent biological properties, such as inhibition of COX-2 enzymes.[2, 3] Considering the reported method of preparation using excess coupling reagents and chromatographic purification, it is remarkable that indomethacin amides can be made so easily with this new methodology. Furthermore, it is equally impressive that highly functionalized substrates can be employed, as shown with the example of a serotonin conjugate.[1] These examples and others[1] showed that this new catalyst provide a glimpse of its potential to solve the long standing problem of amidation. In spite of the impressive performance of catalyst **3-1** towards aliphatic carboxylic acids,[1] unfortunately, aromatic carboxylic acids, which are important substrates in pharmaceuticals and agrochemicals, and sterically hindered carboxylic acids, unfortunately, tend to provide low yields using *ortho*-iodophenylboronic acids (**3-1**) (c.f. Chapter 2.2.6), and thus an improved catalyst is desirable in order to overcome these limitations.

The successful development of improved catalysts could revolutionize the generality of this method and make it widely applicable in the field of amide coupling and peptide synthesis which is indeed a multi-million dollar business.

Three possible positions on the aromatic ring scaffold (3-4-5) are still available for further manipulation. As shown in **Figure 3-1**, catalysts might be optimized by exploiting ring substitution at carbons 3, 4 or 5 to provide an improved catalytic system which would be broadly applicable to a wide scope of substrates and effect the amide bond formation within hours at room temperature.

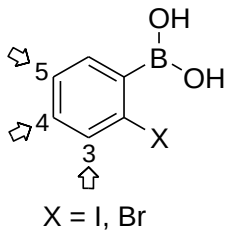
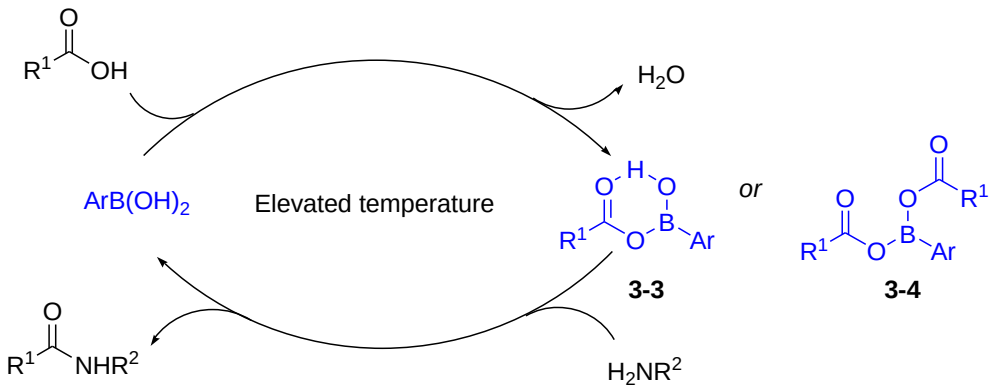


Figure 3-1: Possible positions in the aromatic ring for catalyst optimization.

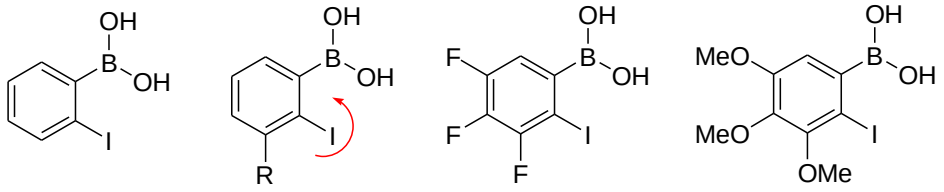
3.2 The Design of an Improved Catalyst for Direct Amide Bond Formation

The previous report on boronic acid catalyzed amidations was supported by the isolation of a monoacylboronate intermediate **3-3** or by diacylboronate intermediate **3-4,** as shown in **Scheme 3-1**. Intermediate **3-3** would provide electrophilic activation of the carboxylate group via boron conjugation and internal H-bonding.[4-7]



Scheme 3-1: Postulated mechanism for boronic acid catalyzed amidations.

With respect to Yamamoto's[4-7] and Whiting's[8, 9] catalysts, the acidity is found to be crucial for catalyst activity.[6-9] In our work, *ortho*-iodophenylboronic acid **3-1** was measured to have a pKa of 8.9, which is not abnormal (e.g. $PhB(OH)_2$: 8.8) and thus cannot explain its exceptional catalytic activity.[1] Because a reverse trend of efficiency is observed in the *ortho*-halo series (I > Br > Cl > F), inductive effects alone cannot account for the superiority of catalyst **3-1**.[1] Due to the size and electron density of the iodo group and X-ray crystallographic observations, such as the unusual angular distortion of the B-C-C bonds (117°, 126°),[1] subtle electronic or structural effects may be at play. For example, we suspected that the perturbation of the boron centre by the electronic density of the large iodo substituent could be responsible for the outstanding catalytic activity of **3-1**. To emphasize this effect, two approaches were taken. The first one was to design catalysts of type **3-5** with a substituent at carbon 3 to enforce the proximity between the iodo group and the boron unit, as depicted in **Figure 3-2**. Secondly, even though the optimal electronic effects were unclear at this stage, we suspected that a combination between electron-poor substituents (Yamamoto's catalysts) and *ortho*-iodo (our catalytic system) may be preferable. Therefore, catalysts of type **3-6** were evaluated.



3-1 **3-5** **3-6** **3-7**

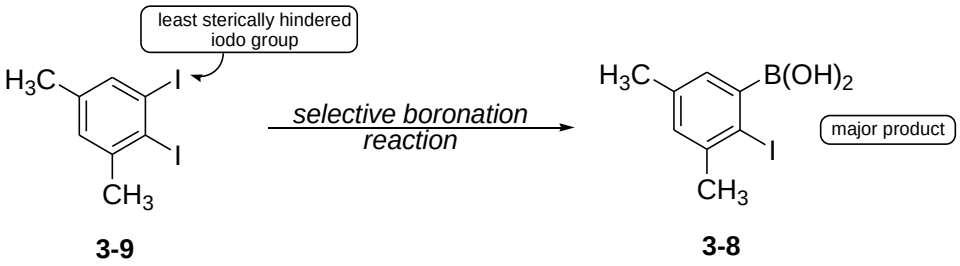
Figure 3-2: Exploiting the ring substitution at carbons 3-4-5 for catalyst optimization.

However, because the electronic density of the iodo substituent seems to be important, based on the catalytic reactivity between *ortho*-haloarylboronic acids (c.f. Chapter 2.2.3), catalysts of type **3-7** containing electron donating groups at carbons 3-4-5 in the aromatic ring were examined as well.

3.2.1 Implication of the Steric Effects on Reactivity of 3-Substituted-2-Iodoarylboronic Acids

At the onset, steric manipulation of the 3-substituted-2-iodoarylboronic acids **3-5** was unappealing since the *ortho*-iodophenylboronic acid **3-1** itself is not commercially available and a careful synthetic procedure is necessary because of the high lability of both the boronic acid and iodo groups, as described in Chapter 2.4. Indeed, multistep syntheses are required for the synthesis of 3-substituted-2-iodophenylboronic acids of type **3-5**. Consequently, we decided to examine the steric hypothesis by evaluating a simple derivative of **3-5** with a group like methyl positioned at C3 in the aromatic scaffold.

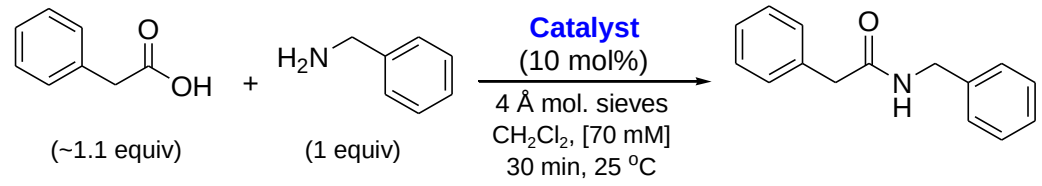
After a careful examination of the literature, we came across an idea to make catalyst **3-8**. Since the starting material for the diiodo derivative **3-9** was found to be commercially available, catalyst **3-8** was proposed to be made in a similar approach to that of catalyst **3-1**, through a selective metalation reaction (**Equation 3-2**).



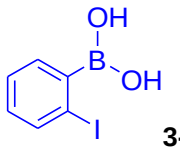
3-9 **3-8**

Equation 3-2: Selective metalation reaction for the synthesis of 3,5-dimethyl-2-iodophenylboronic acid (3-8).

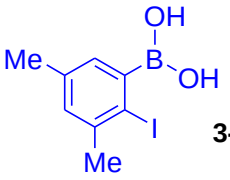
After the successful synthesis of this catalyst containing a methyl group at position 3 next to the iodo substituent, we subjected it to a model amidation reaction between phenylacetic acid and benzylamine. We noticed that the substitution at position 3 next to the iodo group had a small benefit on catalytic activity (**Scheme 3-2**). For instance, replacement of the hydrogens at positions 3 and 5 of catalyst **3-1** with methyl groups, as in catalyst **3-8,** provided a considerable increase in amide product: from a yield of 54% with catalyst **3-1** to 80% yield for catalyst **3-8**.



Catalysts:



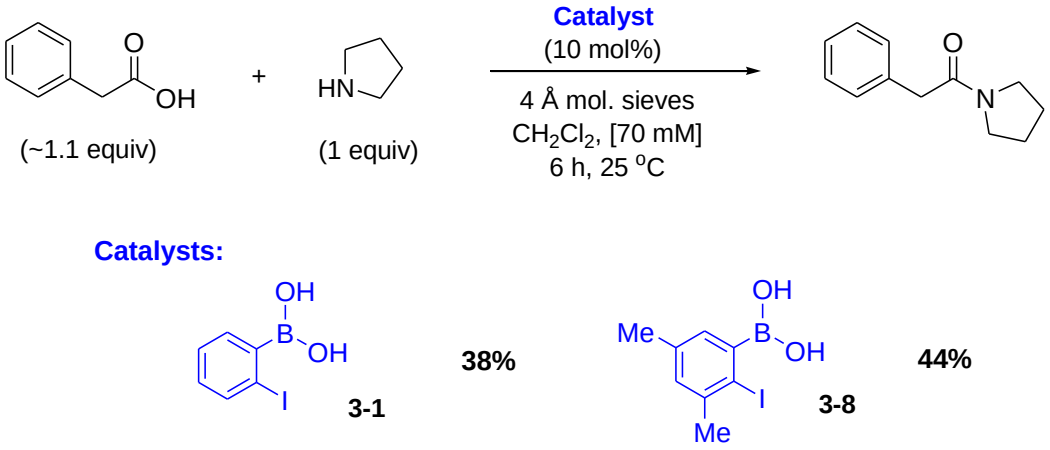
3-1 **54%**



3-8 **80%**

Scheme 3-2: Comparison in product yield between *ortho*-iodophenylboronic acids 3-1 and 3-8 in a direct amidation reaction between phenylacetic acid and benzylamine under optimized conditions

Using the more demanding substrate. pyrrolidine, instead of benzylamine, also showed a moderate increase in the amide yield from 38% to 44% (**Scheme 3-3**) which seemed to validate our hypothesis.



Scheme 3-3: Comparison in product yield between *ortho*-iodophenylboronic acids 3-1 and 3-8 in a direct amidation reaction between phenylacetic acid and pyrrolidine under optimized conditions

After these results, we decided to make more arylboronic acids of type **3-4** with larger groups, such as **3-10** and **3-11,** and examine their catalytic activity in amidation reactions. However, the syntheses of these catalysts unfortunately were not achieved. After several steps making the required diiodides **3-12** and **3-13**, the selective metalation steps of the corresponding diiodo precursors followed by borate trapping were unsuccessful and complex mixtures of unknown products were observed.

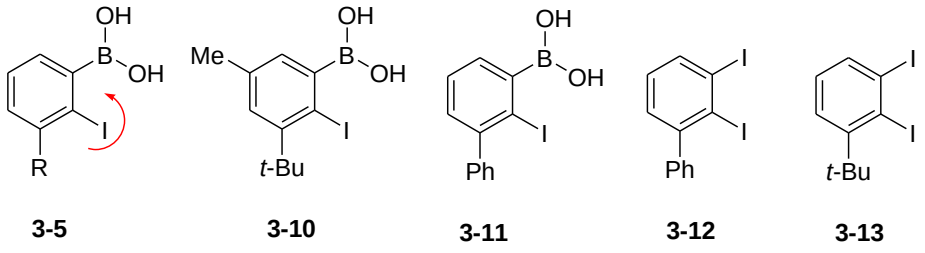
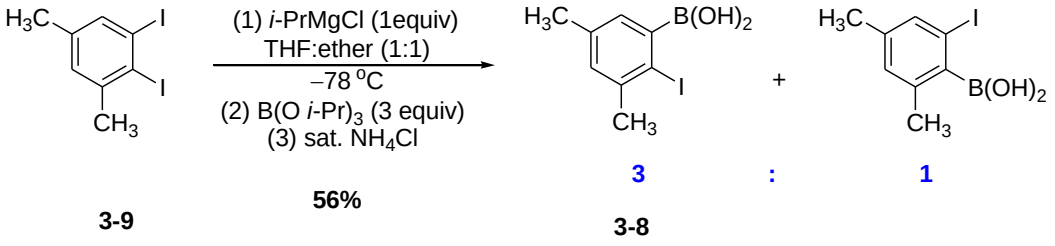


Figure 3-3: Promising catalysts with larger groups at carbon 3 and their diiodide starting materials.

3.2.1.1 Synthesis of 3,5-Dimethyl-2-Iodophenylboronic Acid (3-8)

The synthesis of arylboronic acid **3-8** was based on a one-step synthesis from the commercially available 3,5-dimethyl-1,2-diiodobenzene. The direct metalation of the diiodo precursor with *iso*propylmagnesium chloride followed by triisopropylborate trapping led to the desired boronic acid in good yield as a 3:1 regioisomeric mixture (**Equation 3-3**). A successful purification of this arylboronic acid **3-8** was done by recrystallization using an ether/hexanes mixture.

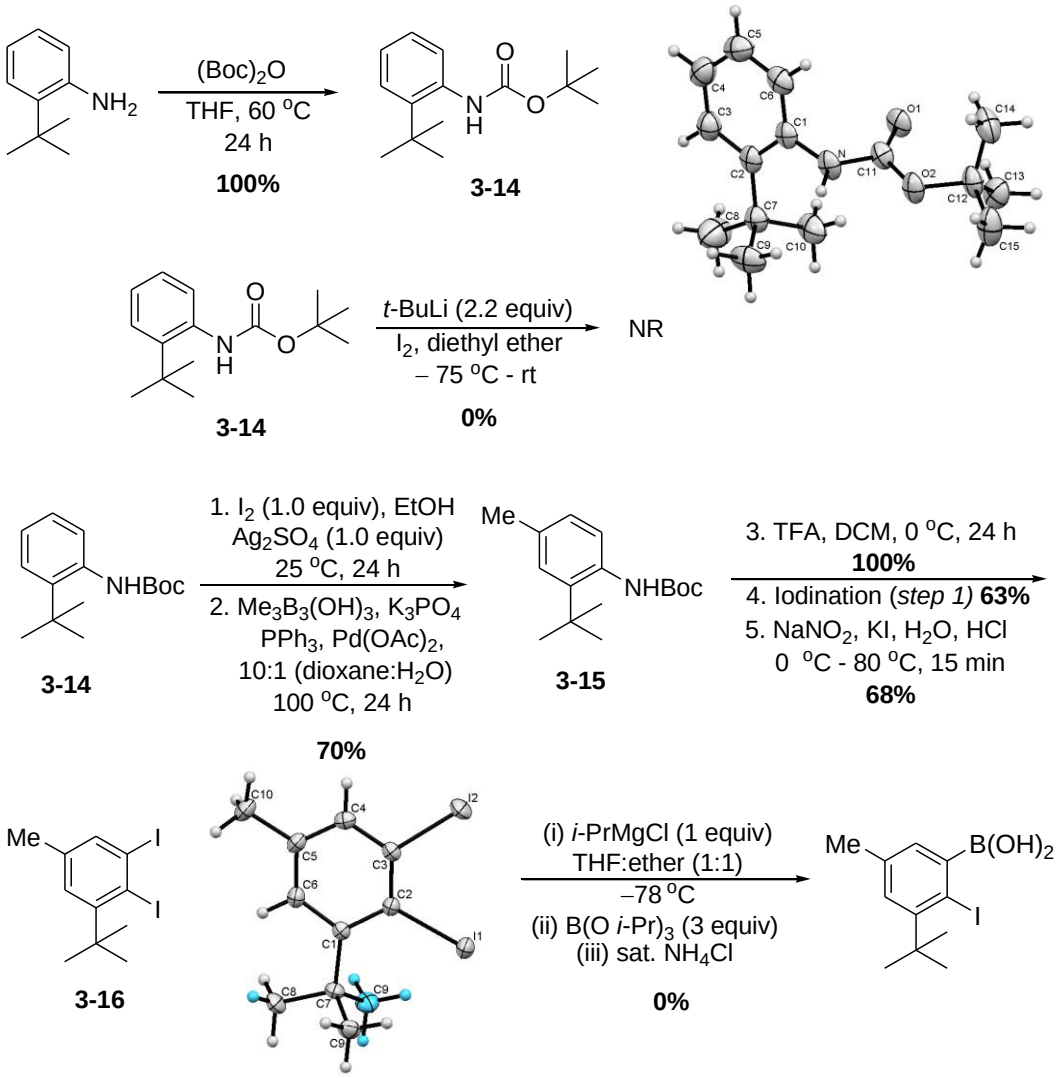


Equation 3-3: Direct metalation reaction for the synthesis of 3,5-dimethyl-2-iodophenylboronic acid (3-8).

3.2.1.2 Attempts Toward the Synthesis of 3-Tert-Butyl-2-Iodophenylboronic Acid (3-10) and 3-Phenyl-2-Iodophenylboronic Acid (3-11)

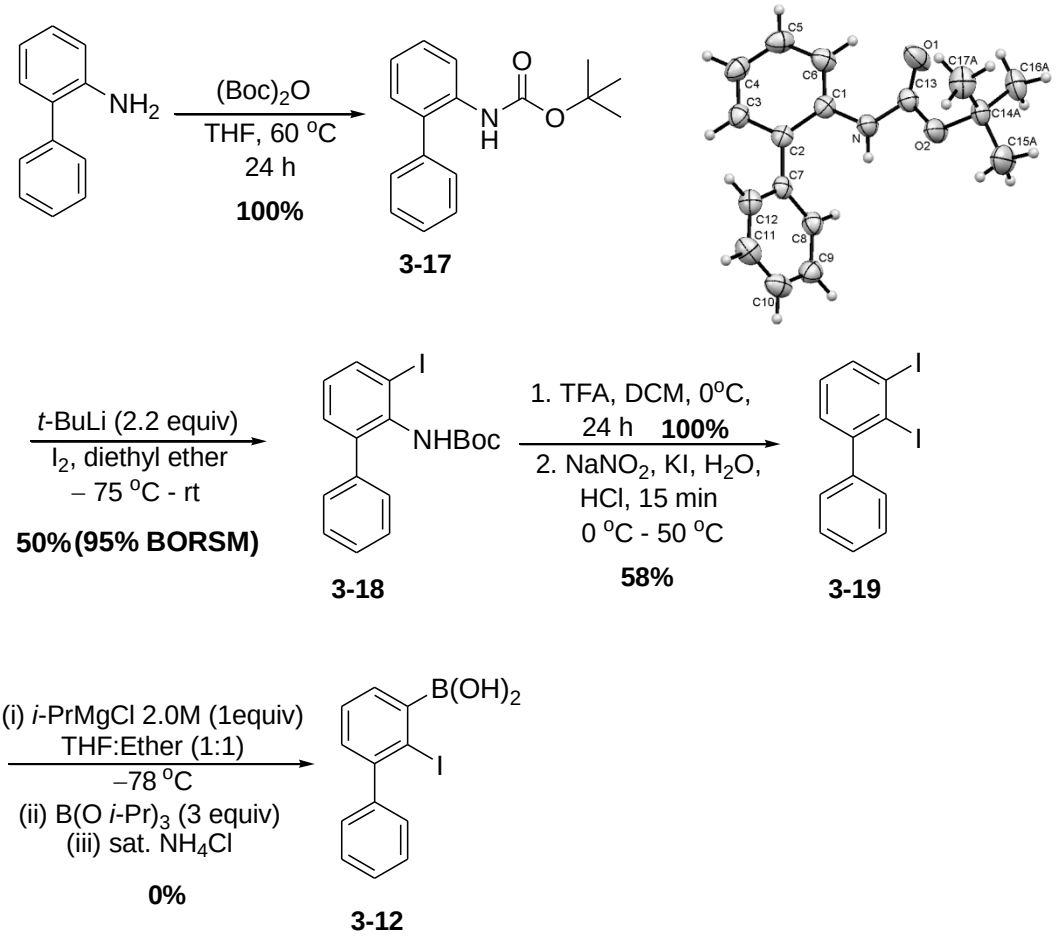
The synthesis of **3-10** and **3-11** was based on a similar approach to catalyst **3-1** through a selective metalation with Grignard reagent followed by a borate trapping approach from the diiodo precursors. The synthesis of **3-10** started from the commercially available ortho-tert-butylaniline which was protected with di-*tert*-butyl dicarbonate $(Boc)_2O$ to form the amide **3-14**. Directed lithiation with different alkyl lithium reagents was unsuccessful and only starting material was recovered after the reaction. Having the amide **3-14** to hand, regioselective iodination promoted by silver sulfate, followed by Suzuki coupling led to the amide **3-15** in 70% yield over two steps. Amine deprotection with TFA (trifluoroacetic acid) at 0 °C in THF, followed by iodination at the *ortho* position provided the free amine in quantitative yield. A successful diazotization reaction afforded the requisite diiodo intermediate **3-16** in 68% yield. The structure of **3-16** was supported by X-ray crystallography. Finally, selective metalation followed by borate trapping was

unfortunately not successful, providing side reactions and decompositions (**Scheme 3-4**).



Scheme 3-4: Attempts toward the synthesis of 3-*tert*-butyl-2-iodophenylboronic acid (3-10).

The synthesis of **3-12** (**Scheme 3-5**) commenced with Boc protection of the commercially available *ortho*-biphenylamine to provide the carbamate **3-17** in quantitative yield. Directed *ortho* lithiation followed by iodine trapping led to the desired iodinated product **3-18**. Deprotection of the amine followed by a diazotization reaction afforded the requisite diiodo product **3-19** in good yields over two steps. Finally, the desired selective metalation followed by different borate trapping was unfortunately not successful.



Scheme 3-5: Attempts toward the synthesis of 3-phenyl-2-iodophenylboronic acid (3-12).

Having a large group next to the diiodo groups presumably increases the formation of benzyne, which is a very reactive intermediate, during the metal-halogen exchange reaction, leading to other side reactions. To overcome this decomposition, a metalation reaction at –100 °C was done for both of these diiodo precursors **3-16** and **3-19** but there was no improvement in the outcome.

3.2.2 Implication of Electronic Effects on the Reactivity of 2-Iodoarylboronic Acids

3.2.2.1 Electron-poor Ortho-Iodoarylboronic Acid

Having identified a steric effect on the catalytic activity of 2-iodophenylboronic acid **3-1** under the optimized reaction conditions, we began to explore electronic modifications of the aryl ring (**Figure 3-1**).

The most important aspect of this manipulation is not to alter the free *ortho* position next to the boronic acid, which would suppress the reactivity of the catalyst (c.f. Chapter 2.2.4).[1] The catalyst candidates at this stage were directly related to the idea of a combination between Yamamoto's catalyst **3-20**,[7] which has three fluoro groups at positions 3, 4 and 5 on the aryl ring, and our catalytic system with an iodo or bromo substituent at position 2, as depicted in **Figure 3-4**.

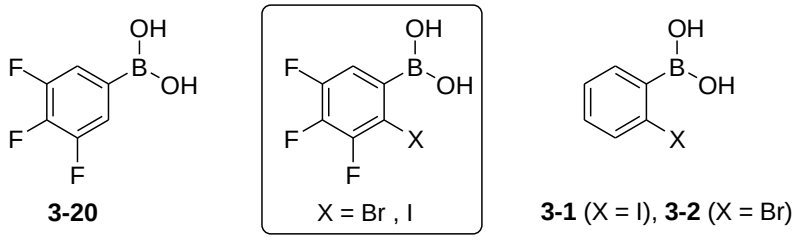
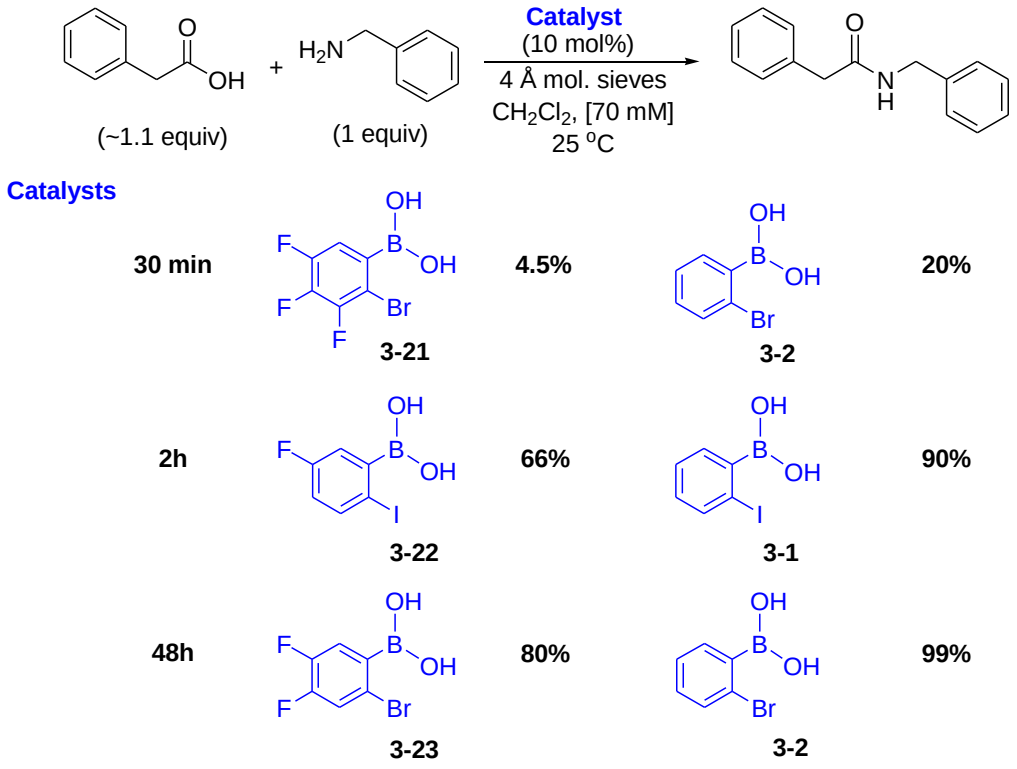


Figure 3-4: A plausible combination between Yamamoto's catalyst 3-20 and our catalyst system.

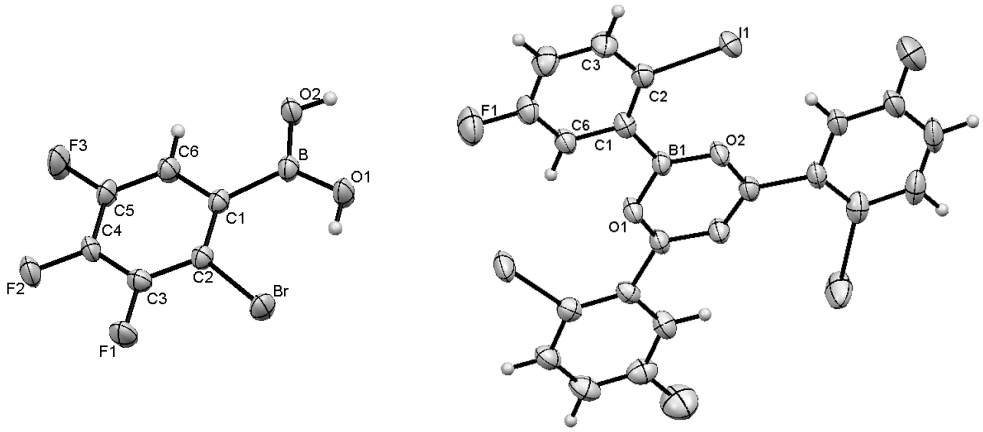
In the event, three different electron-poor arylboronic acids were chosen. Both catalysts **3-21** and **3-22** were successfully synthesized by direct metalation of the diiodo or bromo-iodo precursors, respectively, as shown in **Equations 3-4** and **3-5,** respectively, while **3-23** was commercially available. We then subjected these catalysts to a model amidation reaction between phenylacetic acid and benzylamine. Side-by-side reactions were carefully examined to compare the reactivity of these catalysts in comparison with the neutral *ortho*-iodo or bromophenylboronic acids **3-1** and **3-2**, respectively (**Scheme 3-6**).

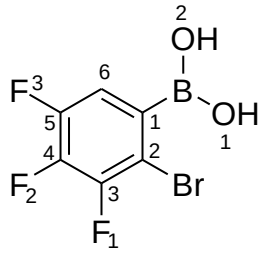


Scheme 3-6: Comparison in product yield between electron-poor *ortho*-halophenyl boronic acids 3-21, 3-22, 3-23 and neutral ortho-halophenylboronic acid 3-1, 3-2 in a direct amidation reaction between phenylacetic acid and benzylamine under optimized conditions.

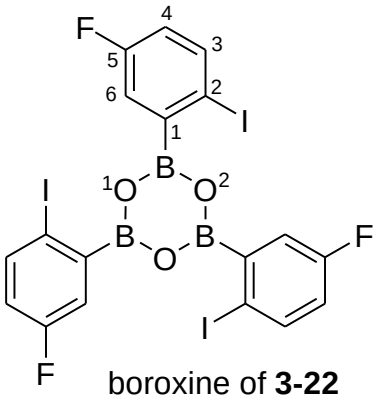
In this context, the use of electron-poor *ortho*-halophenylboronic acids clearly showed a decrease in the catalytic reactivity of these arylboronic acids under the optimized reaction conditions for direct amide bond formation. For instance, replacement of the hydrogen at position 5 of catalyst **3-1** with a fluoro group, as in **3-22,** provided a considerable decrease in amide product yields from 90% to 66% for the 2 hour reaction between phenylacetic acid and benzylamine. While the replacement of both protons at positions 4 and 5 with fluoro groups, as in **3-23,** provided an 80% yield of the amide product compared to 99% for the neutral 2-bromophenylboronic acid. Furthermore, the use of 3,4,5-trifluoro-2-bromophenylboronic acid **3-21** led to a 4.5% yield of the desired amide compared to 20% for 2-bromophenylboronic acid **3-2** under a 30 minute reaction time between the same substrates. This result was particularly surprising to us since both Yamamoto's and Whiting's catalysts showed increased catalytic reactivity with more electron-poor arylboronic acids.[6-9] Their observations regarding catalytic

reactivity appeared reasonable since the greater Lewis acidity of the boron atom is associated with the more electron-poor substituents at the aryl ring, which plausibly enhances the formation of monoacyl **3-3** or diacylboronate intermediates **3-4,** as explained in Chapter 1.2.2.2. However, in our system, we observed a different trend of catalytic reactivity. It confirmed that electron-poor arylboronic acids are less reactive catalysts toward direct amide bond formation than the neutral ones. Catalyst **3-22** is expected to be more acidic than catalyst **3-1**; the acidity of catalyst **3-1** was measured to have a pKa of 8.9 which is not abnormal (e.g. $PhB(OH)_2$: 8.8, Chapter 2.2.3) and thus cannot explain its catalytic activity. On the other hand, shorter C(1)-B and C(2)-I bond lengths are also expected with more electron withdrawing groups on the backbone aryl ring. For example, based on the X-ray crystallographic data, catalyst **3-22** has 1.559 Å and 2.106 Å for the C(1)-B and C(2)-I, respectively, compared to 1.569 Å and 2.115 Å for catalyst **3-1** (**Table 3-1**). These bond lengths present only tiny differences and are not likely to explain the catalytic reactivity as well. The last variable is the electronic density of the iodine (halogen next to the boronic acid group), which indeed is also subjected to change based on the electronic environment of the aromatic ring. We can imagine that the electron densities of the *ortho*-halo group in catalysts **3-21**, **3-22** and **3-23** are lower than **3-1** and **3-2** due to the presence of electron withdrawing groups.





3-21



boroxine of **3-22**

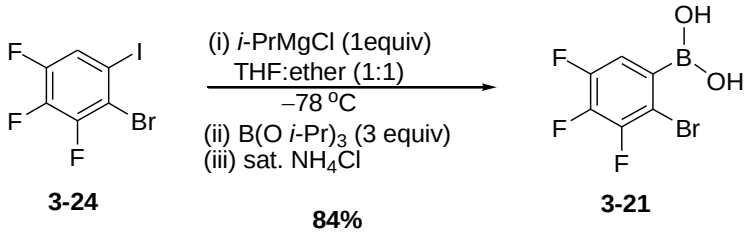
Table 3-1: Selected bond distances and angles for catalysts 3-1, 3-21 and 3-22

Atoms			Catalyst		
			3-1	**3-22**	**3-21**
Bond	X-C(2)	Atomic distance (Å)	2.115(3)	1.894(3)	2.106 (7)
	O(1)-B		1.363(4)	1.359(4)	1.392(9)
	O(2)-B		1.363(3)	1.340(4)	1.365(8)
	C(1)-B		1.569(4)	1.588(6)	1.559(9)
	C(1)-C(2)		1.402(4)	1.393(5)	1.420(1)
	C(1)-C(6)		1.403(4)	1.400(4)	1.403(9)
	B ←→ I		3.496	3.443	3.607
Angle	C(2)-C(1)-B	Atomic angles (deg)	126.9(3)	127.5(3)	128.9(5)
	C(6)-C(1)-B		117.0(3)	115.8(3)	115.8(5)
	X-C(2)-C(1)		121.5(2)	123.5(3)	123.7(4)
	X-C(2)-C(3)		116.1(2)	115.1(2)	114.1(5)

3.2.2.1.1 Synthesis of 5-Fluoro-2-Iodophenylboronic Acid **3-22** and 3,4,5-Trifluoro-2-Bromophenylboronic Acid **3-21**

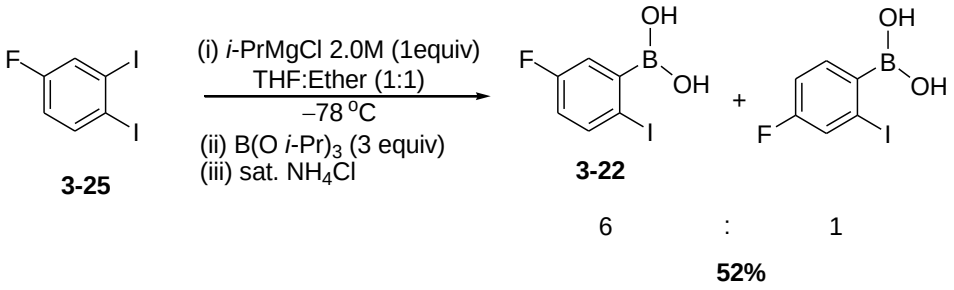
The syntheses of arylboronic acids **3-21** and **3-22** were based on one chemoselective metalation step from commercially available diiodo or bromo-iodo precursors. For the synthesis of 3,4,5-trifluoro-2-bromophenylboronic acid **3-21**, direct regioselective metalation of the commercially available 1-iodo-2-bromo-3,4,5-trifluorobenzene **3-24** precursor with isopropylmagnesium chloride followed by triisopropylboroate trapping led to the desired boronic acid **3-21** in 84% yield after recrystallization in an ether/hexanes mixture (**Equation 3-4**). The use of all alkyllithium reagents was unsuccessful and complex mixtures were observed. The

use of this Grignard reagent[10] was found to be sufficient to chemoselectively exchange only the iodo substituent in the presence of other halogens.



Equation 3-4: Synthesis of 3,4,5-trifluoro-2-bromophenylboronic acid (3-21).

The same chemistry was used for the synthesis of catalyst **3-21**. Starting from the commercially available 4-fluoro-1,2-diiodobenzene **3-25** and under the same reaction conditions, the desired boronic acid **3-22** was isolated as a major product in a 6:1 regioisomeric ratio in overall 52% yield. The major product (5-fluoro-2-iodophenylboronic acid **3-22**) was successfully purified by recrystallization from ether/hexanes to yield cubic crystals.



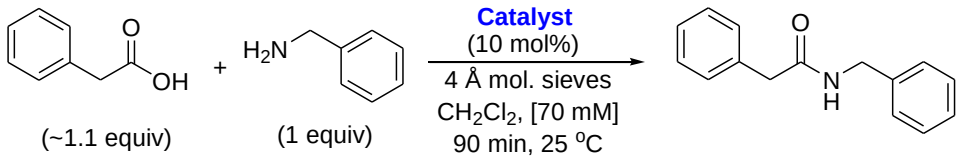
Equation 3-5: Synthesis of 5-fluoro-2-iodophenylboronic acid 3-22.

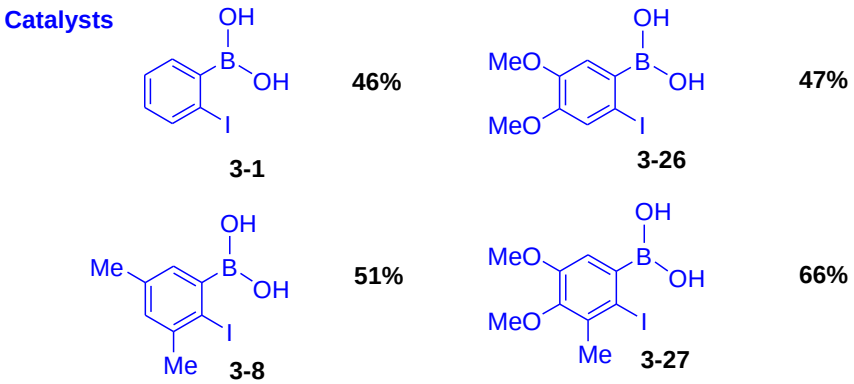
3.2.2.2 Electron-rich Ortho-Iodoarylboronic Acids

Having recognized the antagonistic effect of electron-withdrawing groups and especially fluorine on the reactivity of *ortho*-halophenylboronic acids **3-1** and **3-2**, we started to investigate the reactivity of electron-rich *ortho*-haloarylboronic acids. The synthesis of these catalysts was more challenging than the electron-poor ones since not many commercially available electron-rich aryliodides are available.

It was envisioned that these compounds would be made in a similar approach to that of electron-poor arylboronic acids **3-21** and **3-22**, through monometalation of the diiodide or bromoiodide intermediates followed by trapping with a borate

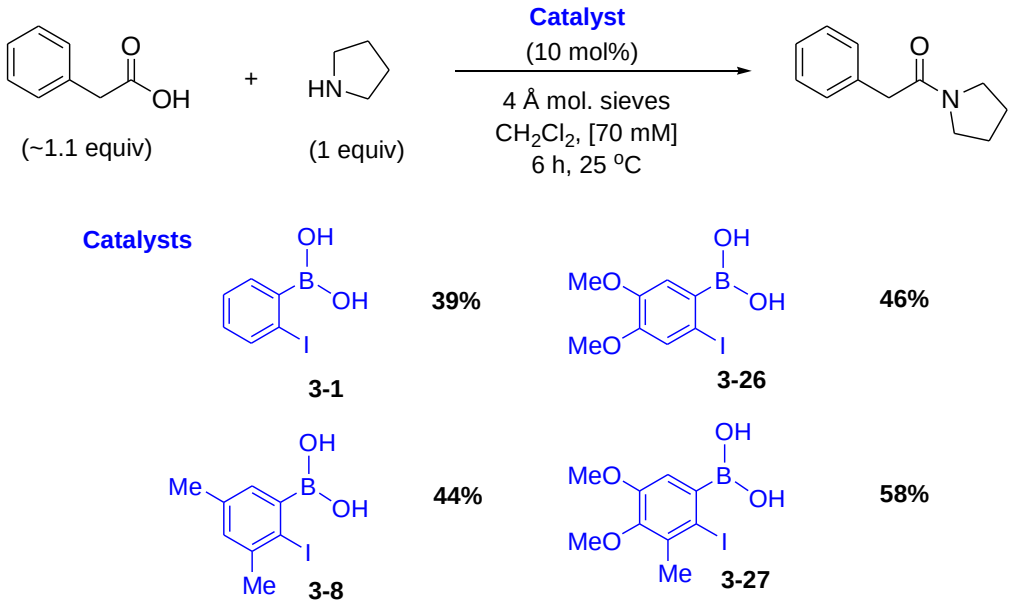
reagent. A careful examination of the literature revealed a mild and regioselective method for direct iodination of aniline derivatives in ethanol.[11] In order to avoid the basicity and the coordination ability of the nitrogen donating group, we decided to start by examining this methodology on a system containing oxygen donating groups. Due to the ability of phenol to direct *ortho* halogenations, we decided to use a methoxy donating group. Using this methodology, two different diiodoarene compounds were made and purified and were then subjected to a metal-halogen exchange reaction with the Grignard reagent *iso*propylmagnesium chloride, providing the expected electron-rich *ortho*-iodophenylboronic acids **3-26** and **3-27** in good yields. We then subjected these catalysts to the model amidation reaction between phenylacetic acid and benzylamine. Side-by-side reactions of these catalysts were carefully examined in comparison with the neutral *ortho*-iodophenylboronic acid **3-1** (**Scheme 3-7**). From the results obtained, we were very pleased to see that electron-rich *ortho*-iodophenylboronic acids **3-26** and **3-27** were found to be more active than catalyst **3-1,** providing 47% and 66% under the same reaction conditions.





Scheme 3-7: Comparison in product yield between electron rich *ortho*-iodophenyl boronic acids 3-26, 3-27 and neutral ones 3-1, 3-8 in a direct amidation reaction between phenylacetic acid and benzylamine under optimized conditions.

For the more demanding amidation of pyrrolidine, a model amidation reaction between phenylacetic acid and pyrrolidine was chosen as shown in **Scheme 3-8**. Pyrrolidine is known to be a difficult amine substrate. A 6 hour reaction provided amide yields of 44%, 46% and 58% with **3-8**, **3-26** and **3-27**, respectively. On the other hand, catalyst **3-1** provided only 39% under the same reaction conditions.



Scheme 3-8: Comparison in product yield between electron rich *ortho*-iodophenyl boronic acids 3-26, 3-27 and neutral ones 3-1, 3-8 in a direct amidation reaction between phenylacetic acid and pyrrolidine under optimized conditions

At this stage, it appeared that a combination of electron rich substituent and an alkyl group at position 3 provides the best catalyst so far. A comparison between the X-ray crystallographic data from the best catalyst **3-27** and *ortho*-iodophenylboronic acid **3-1** is highlighted in **Table 3-2**. Catalyst **3-27** has 1.584 Å bond length for the C(1)-B bond, which is longer than 1.569 Å for catalyst **3-1**. This difference is reasonable due to the resonance effect from the strongly donating methoxy group. There was no noticeable difference in the bond length of C(2)-I between the two catalysts, which might be explained by favoring the conjugation between the boronic acid group with its *para* methoxy rather than the iodo with its own *para* methoxy group. Even with the longer C(1)-B bond in catalyst **3-27** compared to catalyst **3-1**, surprisingly, the distance between the boron and the iodo group is shorter in **3-27** than in catalyst **3-1**. From these data, it was envisioned that as the

distance between the iodo group and the boron atom in the catalyst backbone becomes closer the catalytic performance might increase.

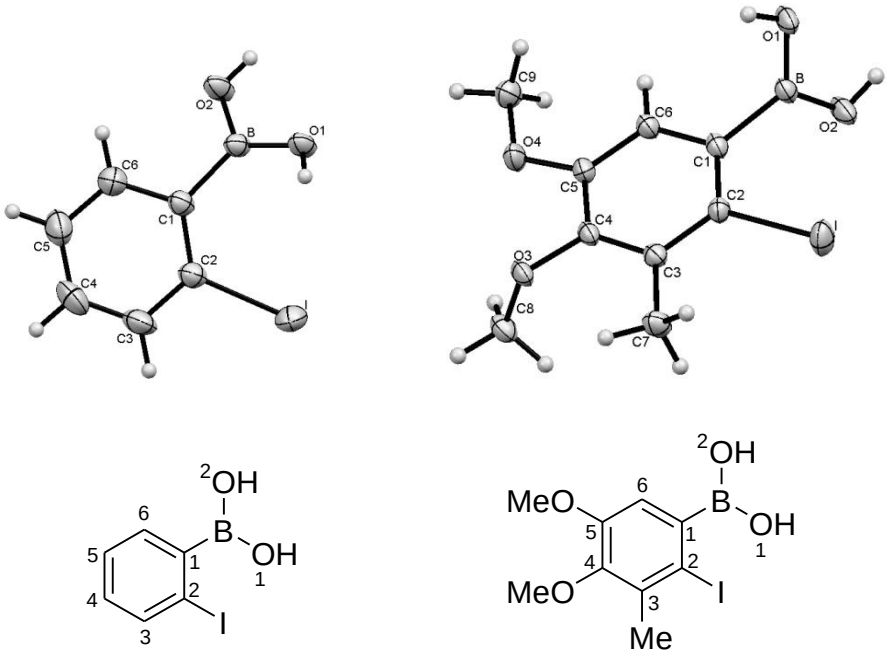
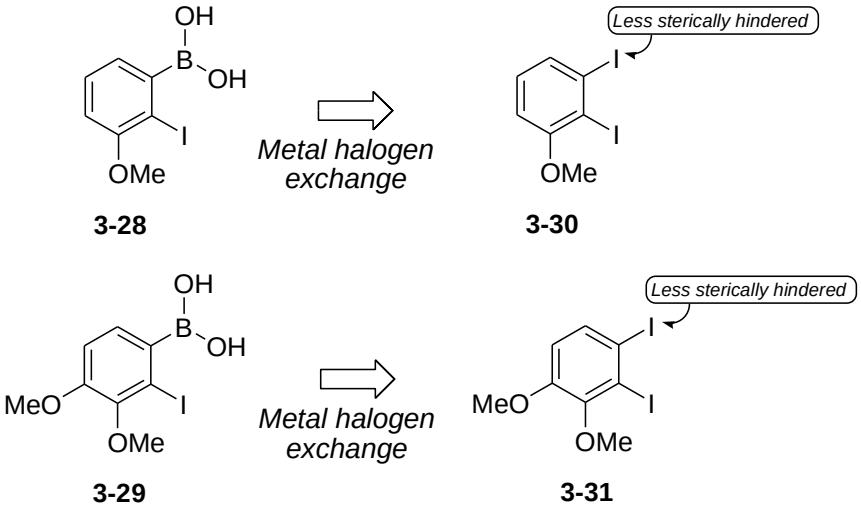


Table 3-2: Selected bond distances and angles for catalysts 3-1 and 3-27.

	Atoms		Catalyst	
			3-1	3-27
Bond	I-C(2)	Atomic distance (Å)	2.115(3)	2.110(3)
	O(1)-B		1.363(4)	1.367(5)
	O(2)-B		1.363(3)	1.346(4)
	C(1)-B		1.569(4)	1.584(5)
	C(1)-C(2)		1.402(4)	1.393(4)
	C(1)-C(6)		1.403(4)	1.405(4)
	B ←→ I		3.496	3.319
Angle	C(2)-C(1)-B	Atomic angles (deg)	126.9(3)	124.4(3)
	C(6)-C(1)-B		117.0(3)	117.9(3)
	I-C(2)-C(1)		121.5(2)	117.8(2)
	I-C(2)-C(3)		116.1(2)	118.9(2)

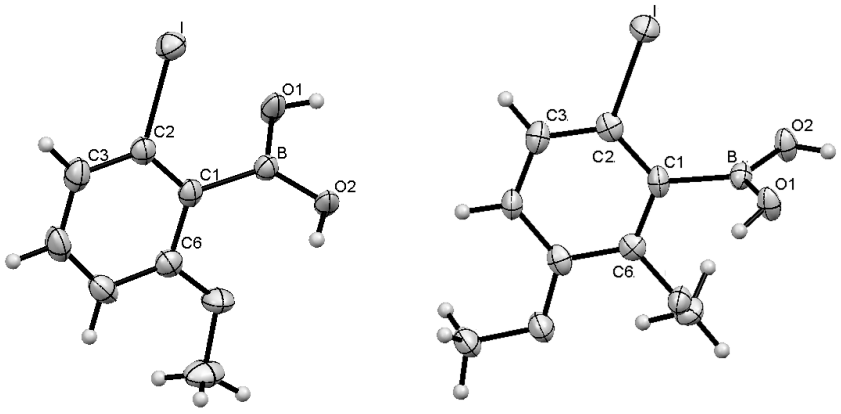
This hypothesis seems to be reasonable since the reactivities of both catalysts **3-26** and **3-27** were superior to catalyst **3-1** under the same reaction conditions. To accentuate this effect, we predicted that catalysts, such as **3-28** and **3-29,** would enhance the catalytic performance by affording the needed steric effect at position 3 and enrich the ring by resonance effect. For making these compounds, we

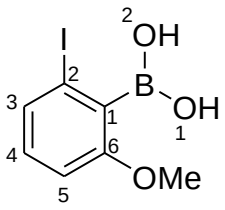
envisioned that these catalysts would be synthesized in the same way as before by direct metalation with *iso*propylmagnesium chloride from the diiodo precursors **3-30** and **3-31,** favoring exchange of the less sterically hindered iodo group (**Scheme 3-9**).



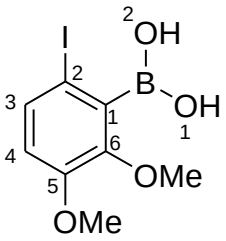
Scheme 3-9: Possible ways to access boronic acid 3-28 and 3-29.

Unfortunately, despite all the efforts at making these diiodo compounds, the metalation step was unsuccessful. It was directed by the methoxy group to afford the other regioisomers **3-32** and **3-33**, which were proved by X-ray crystallography, as outlined in **Table 3-3**. Examining these catalysts under the optimized amidation reaction conditions on a model amidation reaction between phenylacetic acid and pyrrolidine led to no amide bond formation at all (**Scheme 3-10**), which again supported the idea of the necessity of having one *ortho* unsubstituted position next to the boronic acid group for optimal reactivity, as explained in Chapter 2.2.4.





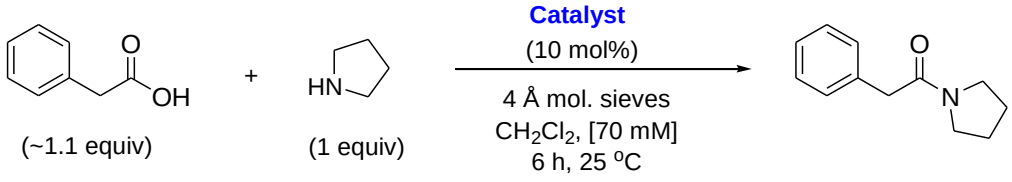
3-32



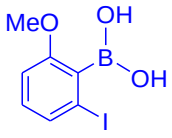
3-33

Table 3-3: Selected bond distances and angles for catalysts 3-32 and 3-33.

	Atoms		Catalyst	
			3-32	**3-33**
Bond	I-C (2)	Atomic distance (Å)	2.125(2)	2.110(3)
	O(1)-B		1.350(3)	1.367(5)
	O(2)-B		1.356(3)	1.346(4)
	C(1)-B		1.581(4)	1.584(5)
	C(1)-C(2)		1.381(3)	1.393(4)
	C(1)-C(6)		1.411(3)	1.405(4)
	B ←→ I		3.426	3.325
Angle	C(2)-C(1)-B	Atomic angles (deg)	124.7(2)	124.2(6)
	C(6)-C(1)-B		118.7(2)	117.8(5)
	I-C(2)-C(1)		121.1(2)	119.8(4)
	I-C(2)-C(3)		115.5(2)	118.8(2)

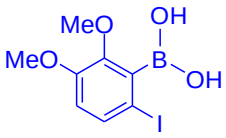


Catalysts



3-32

0%



3-33

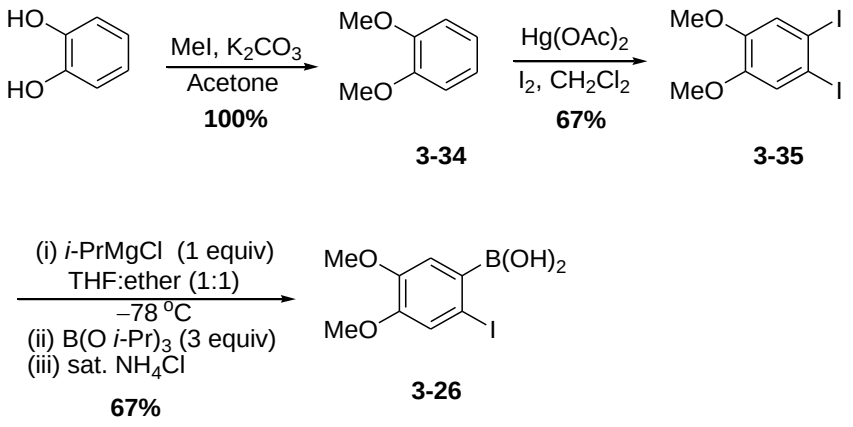
0%

Scheme 3-10: Examining the catalytic reactivity of electron rich *ortho*-iodophenyl boronic acids 3-32 and 3-33 in a direct amidation reaction between phenylacetic acid and pyrrolidine under optimized conditions.

3.2.2.2.1 Synthesis of **3-26** and **3-27**

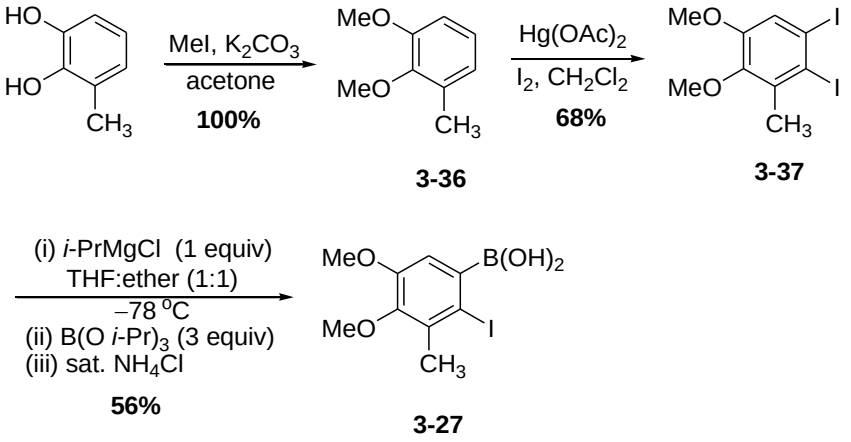
As discussed in the previous section, the arylboronic acids **3-32** and **3-33** were proposed to be made in a similar approach to that of arylboronic acids **3-1** and **3-8**, through a selective metal-iodo exchange reaction of the polyiodinated arenes with *iso*propylmagnesium chloride followed by borate trapping.

Therefore, for the synthesis of 4,5-dimethoxy-2-iodophenylboronic acid **3-26**, the readily available catechol was methylated to provide, in quantitative yield, the ether **3-34,** which, when iodinated under the conditions described by Pak and co-workers[12], led to a 67% yield of the desired diiodide **3-35** after two steps. Diiodide **3-35** was then subjected to a careful metalation/boronation step with *iso*propylmagnesium chloride and the pure boronic acid product **3-26** was isolated in good yield after recrystallization using an ether/hexanes mixture (**Scheme 3-11**).



Scheme 3-11: Synthesis of 4,5-dimethoxy-2-iodophenylboronic acid 3-26.

Following the same chemistry, 2-iodo-3-methyl-4,5-dimethoxyphenylboronic acid **3-27** was synthesized from the commercially available 3-methylcatechol in three steps and in a 38% overall yield (**Scheme 3-12**). At the outset, methylation of 3-methylcatechol provided the ether **3-36** in quantitative yield, which was then followed by iodination to give the requisite diiodide **3-37** in 68% yield after two steps.

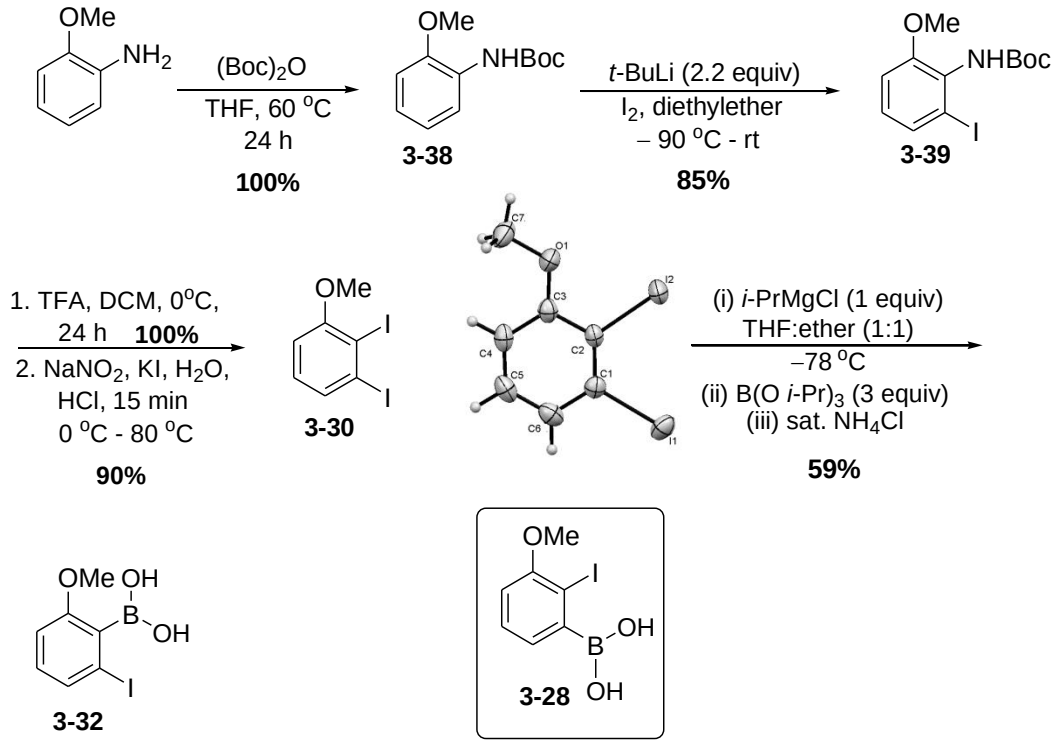


Scheme 3-12: Synthesis of 2-iodo-4,5-dimethoxy-3-methylphenylboronic acid (3-27).

Diiodide **3-37** was subjected to a careful metalation/boronation step with isopropylmagnesium chloride and the desired boronic acid product **3-27** was isolated in good yield as cubic crystals after recrystallization using an ether/hexanes mixture.

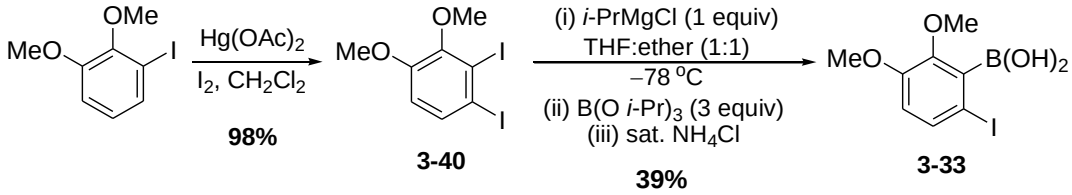
3.2.2.2.2 Attempts Toward the Synthesis of **3-28** and **3-29**

The syntheses of **3-28** and **3-29** were envisioned through a selective metalation from the diiodo precursors **3-30** and **3-31,** respectively. The synthesis of **3-28** started from the commercially available *ortho*-anisidine which was protected with di-*tert*-butyl dicarbonate $(Boc)_2O$ to provide the carbamate **3-38** in quantitative yield (**Scheme 3-13**). Directed *ortho* lithiation followed by iodine trapping led to the iodide **3-39** in 85% yield. Amine deprotection with trifluoroacetic acid (TFA) was then followed by a diazotization reaction to afford the requisite diiodo intermediate **3-30** in 76% yield over two steps. The structure of **3-30** was confirmed by X-ray crystallography. It was proposed that the terminal iodo group is more reactive with the Grignard reagent since it is less sterically hindered. Unfortunately, the selective metalation followed by borate trapping was not successful, providing the other undesired regioisomer **3-32** in 59% as a white solid after recrystallization in an ether/hexanes mixture.



Scheme 3-13: Synthesis of 2-iodo-6-methoxyphenylboronic acid 3-32.

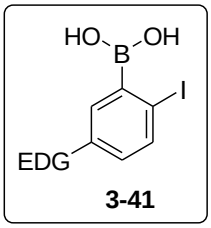
The synthesis of **3-33** commenced with the direct iodination of the commercially available 1-iodo-2,3-dimethoxybenzene to the diiodide **3-40** in 98% yield as the sole product (**Scheme 3-14**). Finally, a selective metalation followed by triisopropyl borate trapping provided the arylboronic acid **3-33** as cubic crystals in 39% yield after recrystallization in an ether/hexanes mixture.



Scheme 3-14: Synthesis of 2-iodo-5,6-dimethoxyphenylboronic acid 3-33.

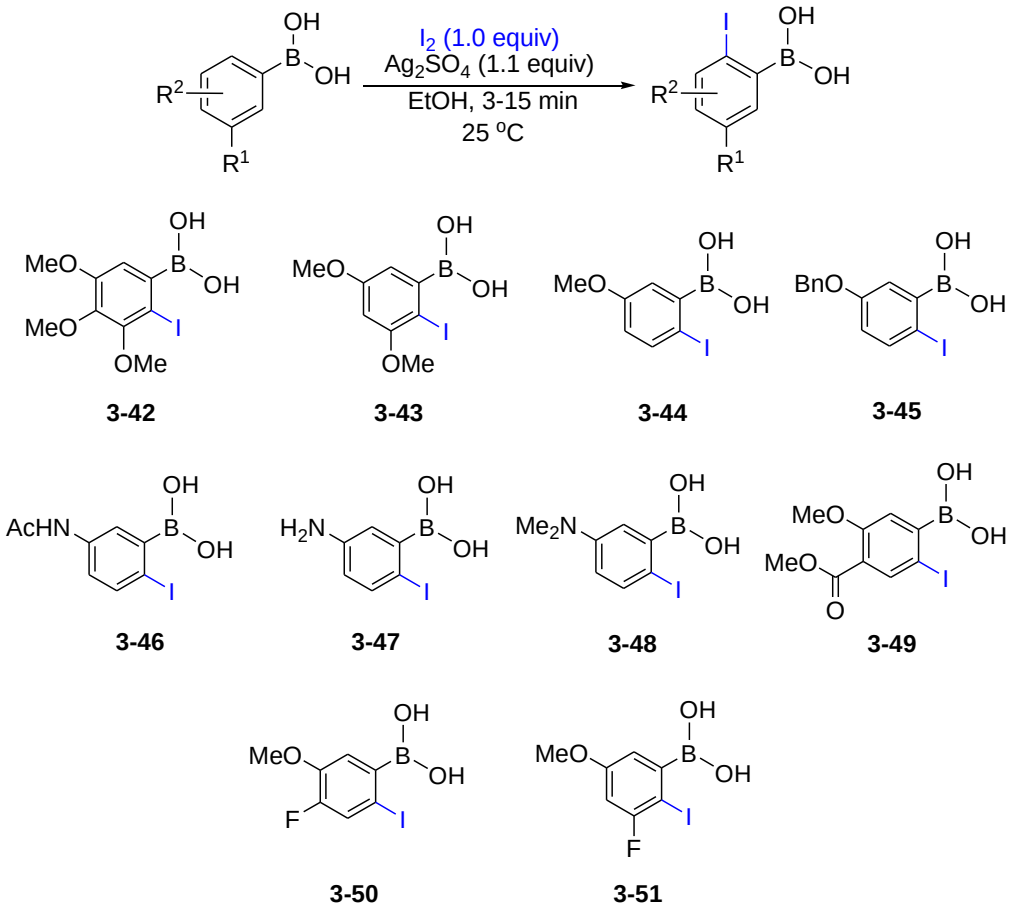
From this context, we decided to try and make catalysts of type **3-41** with at least one electron-donating substituent only *para* to the iodo group while trying to avoid any donating group positioned para to the boronic acid group. This perhaps would

maximize the electron density on the iodo group while keeping the boronyl group electron-poor, and therefore, could enhance the catalytic performance.



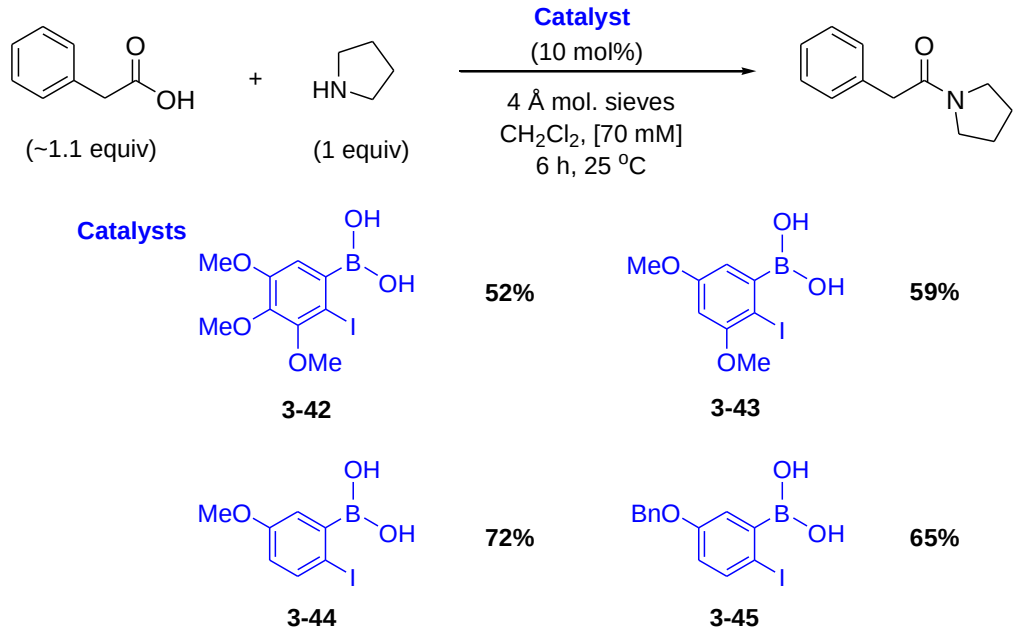
3-41

After examining the literature carefully, we realized that the direct iodination of electron rich arylboronic acids would be the easiest and the most direct way to make these compounds since the desired diiodide intermediates are not commercially available and are challenging to synthesize. Arylboronic acids are known to be susceptible to chemoselectivity issues which typically cause a simple protodeboronation or a substitution of the boronic acid group. After several unsuccessful experiments, a new methodology, which will be discussed in detail in Chapter 4, was developed using mild silver (I) mediated regioselective iodination and bromination of arylboronic acids. Using this method, we prepared electron rich arylboronic acids **3-42** to **3-51** as shown in **Scheme 3-15**.



Scheme 3-15: Direct and regioselective *ortho*-iodination of arylboronic acids.

We then subjected these electron-rich arylboronic acids to a model amidation reaction between phenylacetic acid and pyrrolidine. At the outset, the use of all new electron-rich arylboronic acids **3-42** to **3-51** in a catalytic direct amidation reaction under the optimized reaction conditions showed superior reactivity compared to *ortho*-iodoarylboronic acid **3-1**. For example, the use of highly electron-rich **3-42** led to 52% of the amide product, while catalyst **3-1** provided only 38%. This result was similar to the result when we used catalyst **3-27** (i.e. 56%, **Scheme 3-7**) under the same reaction conditions. Accordingly, we thought that highly electron-rich arylboronic acid catalysts might be not very helpful for the catalytic reactivity. We decided to examine more arylboronic acid catalysts with two donating groups. Since we did examine the reactivity of catalysts **3-26** and **3-27** and showed that having a methyl group at position 3 enhanced the reactivity of **3-27** compared to **3-26**, we proposed that a catalyst with two methoxy groups, where one is *para* to the iodo group and the second methoxy at position 3 (i.e. **3-43**), would enhance the catalytic activity even more towards the direct amide bond formation reaction. Even though catalyst **3-43** led to 59% yield of the desired amide product (**Scheme 3-16**), which is a higher yield compared to catalyst **3-26** (i.e. 46%, **Scheme 3-7**), it did not lead to a sharp increase in product yield compared to catalyst **3-42** (59% vs. 52%). X-ray crystallographic structures and data for both **3-42** and **3-43** are highlighted in **Table 3-4**.



Scheme 3-16: Comparison in amide product yield between electron rich *ortho*-iodoarylboronic acids 3-42 to 3-45 in a direct amidation reaction between phenylacetic acid and pyrrolidine under optimized conditions.

The results from catalysts **3-43** and **3-26**, clearly showed the importance of position 3 on catalyst performance. However, they also demonstrated that having an electron donating group *para* to the boronic acid would decrease the catalytic activity. From this point, we decided to make compounds with only one donating group on the ring and in a position which is *para* to the iodo substituent. Both catalysts **3-44** and **3-45** were made and examined in direct amide bond formation under the same reaction conditions. We were pleased that placement of an electron donating substituent at the *para*- position to the iodo group on the aromatic ring did render some significant effects. For example, introduction of a methoxy group at position 5 of the aromatic ring, as in **3-44,** led to a significant increase in observed amide yields (72% compared to 38% for catalyst **3-1**), while having a benzyloxy group, as in **3-45,** led to 65% of the desired amide product (**Scheme 3-15**).

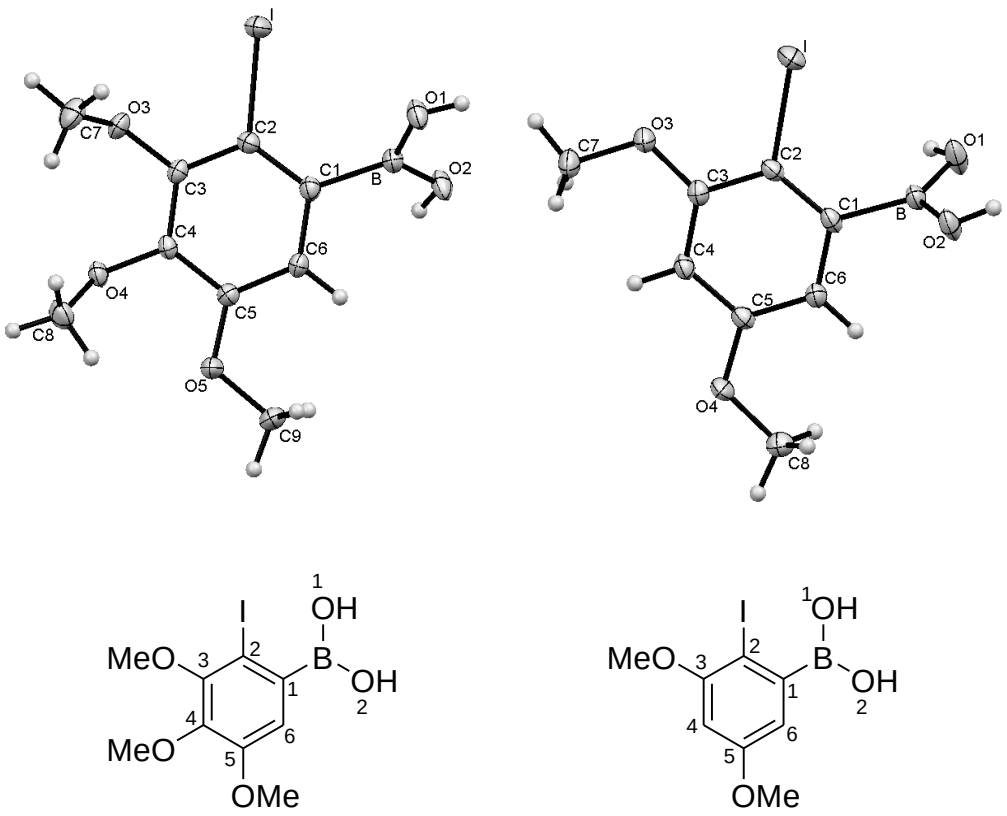


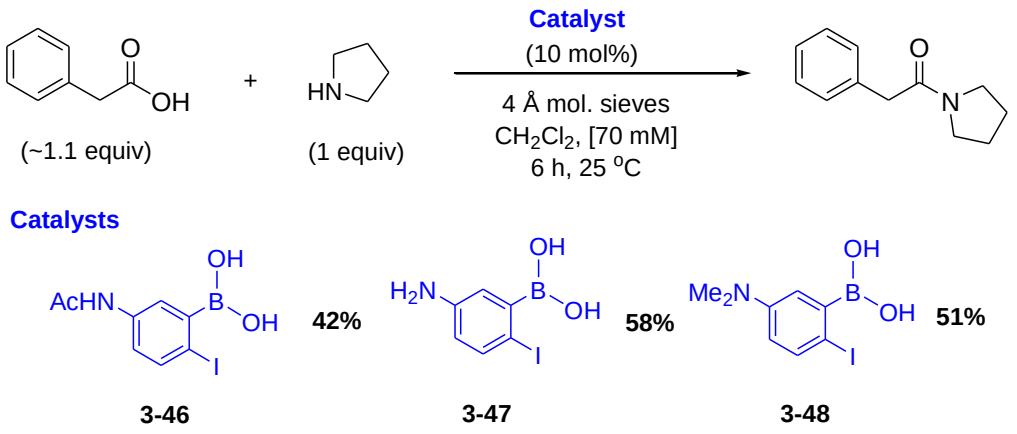
Table 3-4: Selected bond distances and angles for catalysts 3-1, 3-42 and 3-43.

Atoms			Catalyst		
			3-1	**3-42**	**3-43**
Bond	I-C(2)	Atomic distance (Å)	2.115(3)	2.104(2)	2.103 (2)
	O(1)-B		1.363(4)	1.349(2)	1.346(2)
	O(2)-B		1.363(3)	1.373(2)	1.366(2)
	C(1)-B		1.569(4)	1.582(3)	1.585(3)
	C(1)-C(2)		1.402(4)	1.397(2)	1.387(2)
	C(1)-C(6)		1.403(4)	1.407(3)	1.408(2)
	B ←→ I		3.496	3.443	3.369
Angle	C(2)-C(1)-B	Atomic angles (deg)	126.9(3)	124.6(2)	123.7(2)
	C(6)-C(1)-B		117.0(3)	117.2(2)	117.6(1)
	I-C(2)-C(1)		121.5(2)	121.9(1)	120.4(1)
	I-C(2)-C(3)		116.1(2)	116.8(1)	117.8(1)

These results supported our hypothesis regarding the important role of the electron density of the iodo group on the reactivity of these catalysts and also corroborated the previous results that we observed with electron-poor arylboronic acids. It is known that nitrogen containing donating groups are more electron rich than oxygen

containing donating groups. Therefore, we decided to examine some of these catalysts in our model amidation reactions. Three different arylboronic acids, **3-46**, **3-47** and **3-48,** were successfully made and examined under the optimized amidation reaction conditions which led to 42%, 58% and 51% of the desired amide product, respectively (**Scheme 3-17**).

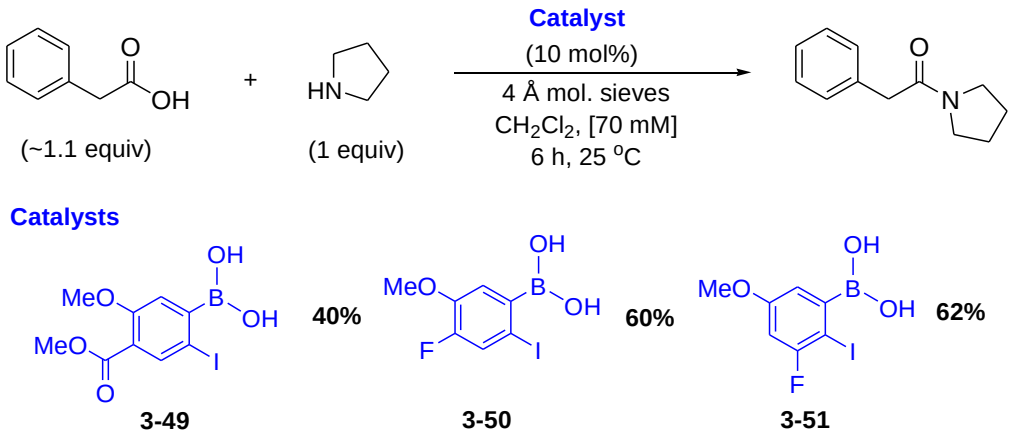
Because of the resonance effect of the nitrogen lone-pair with the carbonyl group in catalyst **3-46**, less electronic donation into the aromatic ring is expected and therefore, less amide product was observed. While the reason for having less amide product for both catalysts **3-47** and **3-48** was unclear, it could be due to the high basicity of these groups, which may interfere with the reaction mechanism.



Scheme 3-17: Comparison in amide product yield between electron rich *ortho*-iodoarylboronic acids 3-46 to 3-48 in a direct amidation reaction between phenylacetic acid and pyrrolidine under optimized conditions.

The previous results, especially from the comparison between **3-26** and **3-43**, showed that having an electron-donating group *para* to the boronic acid group. such as in **3-26,** was not favorable for the catalytic activity. We decided to make a few more arylboronic acids with both an electron-donating group (i.e methoxy) at carbon 5 and an electron-withdrawing group (i.e. F or CO_2R) at carbon 4 (*para* to the boronic acid group) on the aromatic ring. For instance, catalysts **3-49** with a fluoro group and **3-50** with a methyl ester were made using the same iodination methodology. Unfortunately, these catalysts under the optimized amidation reaction conditions did not lead to a further increase in amide product yield (**Scheme 3-18**).

While moving the fluoro group from position 4 to position 3 (i.e. **3-51**) on the aromatic ring, did slightly increase the amide yield in comparison to catalyst **3-50**, it was still less effective than catalyst **3-44**.

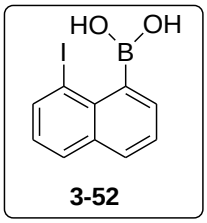


Scheme 3-18: Comparison in amide product yield between *ortho*-iodoarylboronic acid derivatives 3-49 to 3-51 in a direct amidation reaction between phenylacetic acid and pyrrolidine under optimized conditions.

It seems from these results that there is a specific electron density required for optimal reactivity of these catalysts. One consideration is that the Lewis acidity of the boronic acid group might be affected by the electronic nature of different substituents on the aromatic ring, as well as by the electron density of the iodo group. For instance, a donating group at carbon 4 (para to the $B(OH)_2$ group) decreased the Lewis acidity of the boronic acid group, while at carbon 5 (*para* to the iodo group) increased the electron density of the iodo substituent and therefore enhanced the catalytic reactivity of the catalyst. More precisely, a greater electron density on the iodo group is expected to increase the nucleophilicity of the iodo substituent. On the other hand, a comparison of the results for catalyst **3-26** and **3-27** and for **3-26** and **3-43**, also showed that having a group on position 3. such as a methyl and methoxy in **3-27** and **3-43,** respectively, enhanced the reactivity of the catalyst by forcing closer proximity between the iodine atom and the boronic acid groups. This hypothesis was supported by X-ray crystallographic structures which clearly showed a decrease in the I-C(2)-C(1) bond angle, such as 117.8 deg and 120.4 deg for both catalysts **3-27** and **3-43**, respectively, compared to 121.5 deg for **3-1**. Furthermore, a shorter distance between B ←→ I was also observed for these

catalysts. For instance, 3.319 Å and 3.369 Å were observed for catalysts **3-27** and **3-43**, respectively, compared to 3.469 Å for **3-1**.

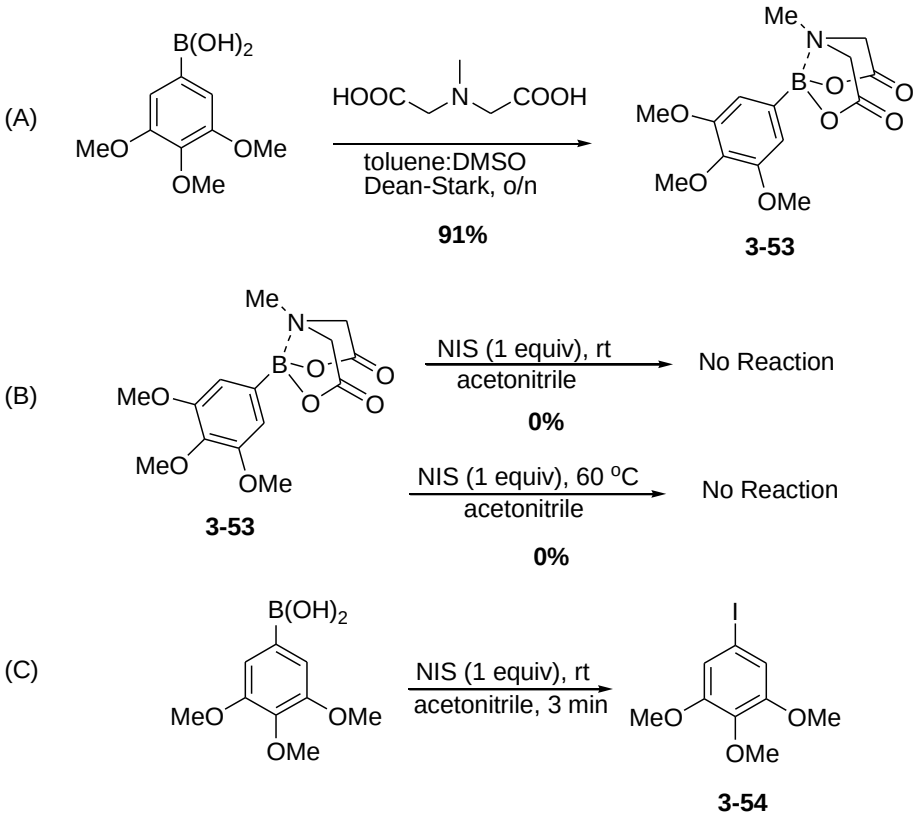
As a result of these observations, we thought that a catalyst, such as **3-52**, which displays a smaller distance between the iodine atom and the $B(OH)_2$ group, might dramatically enhance the catalytic reactivity. Unfortunately, this catalyst led to less than 5% yield of the desired amide product, also suggesting that a precise distance between the iodine atom and the $B(OH)_2$ groups is needed. Consequently, the highest performing *ortho*-iodoarylboronic acid derivative turned out to be 5-methoxy-2-iodophenylboronic acid (MIBA) **3-44** (**Scheme 3-15**), which provided the highest amide product yield in the model reactions.



3-52

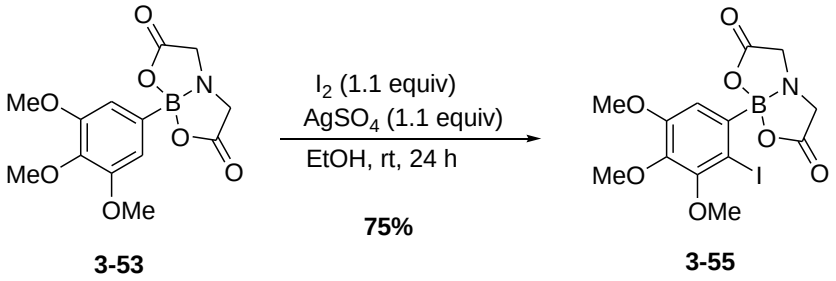
3.2.2.2.3 Synthesis of **3-42** to **3-51**

Arylboronic acids **3-41** to **3-51** were envisioned to be made in a similar approach to that of iodination of electron-rich arenes, such as phenol and aniline, through an electrophilic iodination reaction. It is known that arylboronic acids are oxidatively sensitive compounds and a simple displacement of the boronic acid group through an *ipso*-substitution reaction can form other products. To test this idea, we decided to protect the boronic acid group with MIDA (*N*-methyliminodiacetic acid).[13, 14] Thus, 3,4,5-trimethoxyphenylboronic acid was chosen. After making the MIDA boronate **3-53**, we then subjected it to a direct iodination reaction using NIS in acetonitrile (**Scheme 3-19**).[15] Unfortunately, no product was observed under these conditions and only starting material was recovered, whereas the use of free boronic acid led to only the ipso-iodinated product **3-54** in excellent yields.



Scheme 3-19: Attempts toward electrophilic iodination of arylboronic acid. [13-15]

On changing the reaction conditions from NIS/MeCN to I_2/EtOH, we were pleased to isolate the expected iodinated product **3-55** in 75% yield (**Equation 3-6**). To avoid the solubility problem that is associated with MIDA boronates during purification, we decided to change the protecting group.



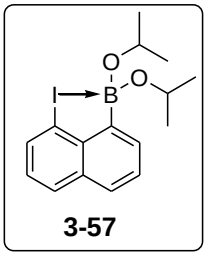
Equation 3-6: Electrophilic iodination of MIDA boronate 3-53.

After surveying the literature, it was decided that using ethanol as a solvent for the reaction would stabilize the iodonium species as well as protecting the boronic acid

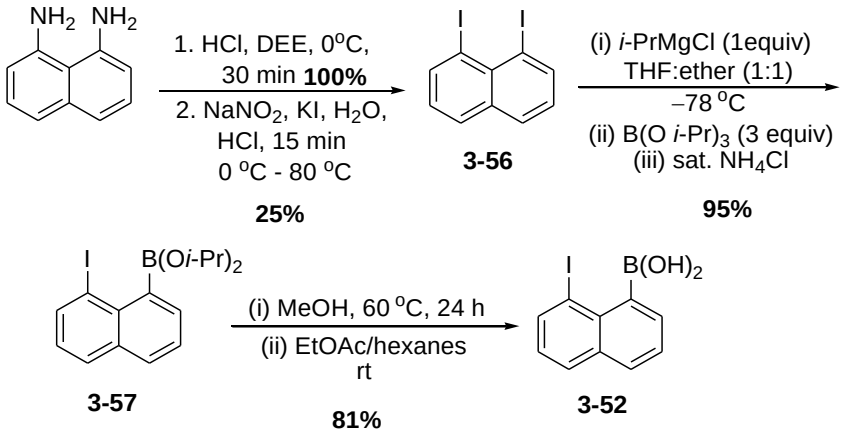
by forming the ethylboronate intermediate. Ethyl boronate is known to be an easily hydrolyzable boronate compared to other boron protecting groups. We were glad to see that these conditions were quite efficient in providing the desired iodinated arylboronic acids in a one step synthesis from cheap and available starting materials in a highly regioselective fashion and in good to high yields. More information about the exact conditions, substrate scope and the proposed mechanism of this new iodination and bromination methodology of arylboronic acid is described in Chapter 4.

3.2.2.2.4 Synthesis of **3-52**

The synthesis of **3-52** was planned through a metalation reaction from the diiodo precursor **3-56** using *iso*propylmagnesium chloride followed by trapping with the triisopropyl borate reagent. The synthesis of the diiodide **3-56** was initiated with a diazotization reaction from the commercially available 1,8-diaminonaphthalene to provide the requisite 1,8-diiodonaphthalene **3-56** in 25% yield (**Scheme 3-20**). A careful metalation reaction followed by borate trapping was successful, providing the isopropylborate **3-57** in 95% yield as a pale yellow oil after flash chromatography. It was surprising to us how stable this borate was on silica compared to other arylborate intermediates. This could be explained by the formation of a tetrahedral borate intermediate **3-58** with the proximal iodo group at carbon 8 on the naphthalene ring. Different methods were used to hydrolyze this isopropyl boronate intermediate **3-58** but without any success. Finally, forming the methyl boronate **3-59** by reflux conditions in methanol followed by evaporation of the solvent and recrystallization in an ethyl acetate/hexanes mixture was effective at hydrolyzing it to form the desired 8-iodonaphthalene-1-boronic acid **3-52** in 81% recrystallization yield as a white solid.



3-57



Scheme 3-20: Synthesis of 8-iodonaphthaleneboronic acid 3-52.

3.2.3 Optimization of Reaction Parameters

Having identified the optimal catalyst, 5-methoxy-2-iodophenylboronic acid (MIBA) **3-44**, and prepared this compound in multi-gram amounts, we turned our attention to the optimization of reaction parameters, including reaction solvent, amine stoichiometry, and the concentration of the reaction.

3.2.3.1 Optimization of Reaction Solvent

According to our first solvent examinations, amidation reactions catalyzed by arylboronic acids were found to perform best in solvents such as CH_2Cl_2, THF and toluene. Accordingly, we decided to examine these solvents again to see which one is the best, including mixed solvent systems (**Table 3.5**). Accordingly, CH_2Cl_2 was found to be the solvent of choice. However, only small differences in the amide yields were observed between solvents. Moreover, we also observed that using different carboxylic acid-amine combinations favored different solvent systems in a manner similar to the observations in our first generation catalyst (**c.f. Chapter 2.2.6**).

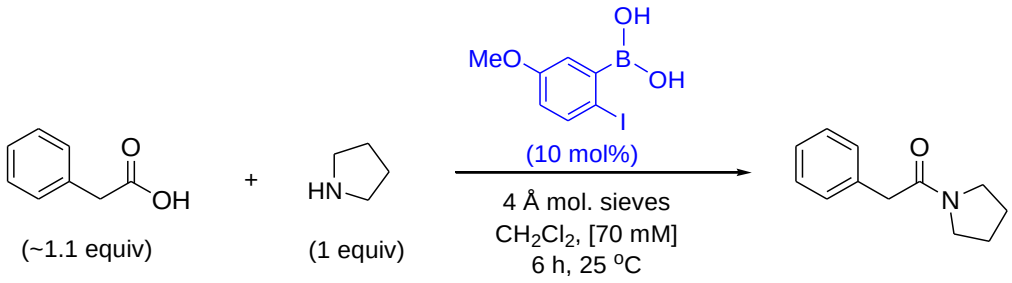


Table 3-5: Optimization of reaction solvent.

Entry	Solvent	%Yield (%)
1	CH_2Cl_2	72
2	THF	68
3	toluene	56
4	CH_2Cl_2:THF, 1:1	71
5	CH_2Cl_2:THF, 2:1	71
6	toluene:hexane, 1:1	43
7	diethyl ether	0.0
8	DMF	0.0
9	acetone	0.0
10	EtOH	0.0
11	acetonitrile	0.0
12	NMP	0.0

3.2.3.2 Optimization of Amine Stoichiometry

With CH_2Cl_2 as the optimal solvent, we then proceeded to optimize the stoichiometry of the amine substrate. Although this study had been done with the first generation catalyst (**Chapter 2.2.2**), we decided to repeat it with our optimal catalyst **3-44**. Along this line, we chose the reaction between phenylacetic acid and pyrrolidine as a model amidation reaction. A 20-mol% excess loading of the acid provided a 77% conversion of the amide product after 6 hours at room temperature (**Table 3-6, entry 1**), whereas using 10-mol% excess did not lead to a significant increase in observed amide yields (**Table 3-6, entry 2**). On the other hand, the use of a 10-mol% and a 20-mol% excess of the amine led to a significant decrease in amide product and provided only 42.5% and 33% yields, respectively (**Table 3-6, entries 4**

and 5). Thus, this result confirms again that a slight excess of amine inhibits the catalytic reactivity of these catalysts.

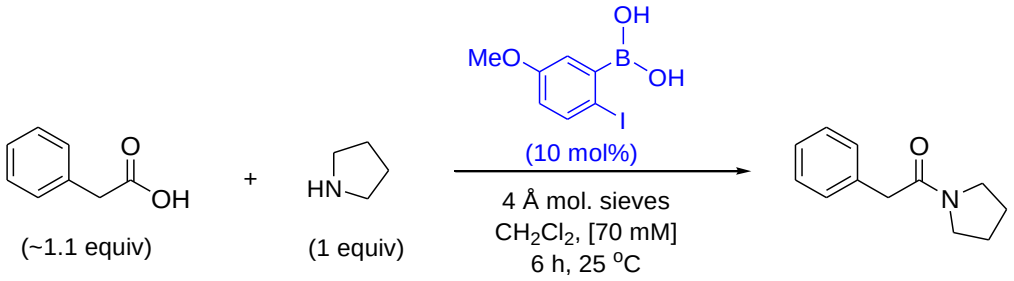
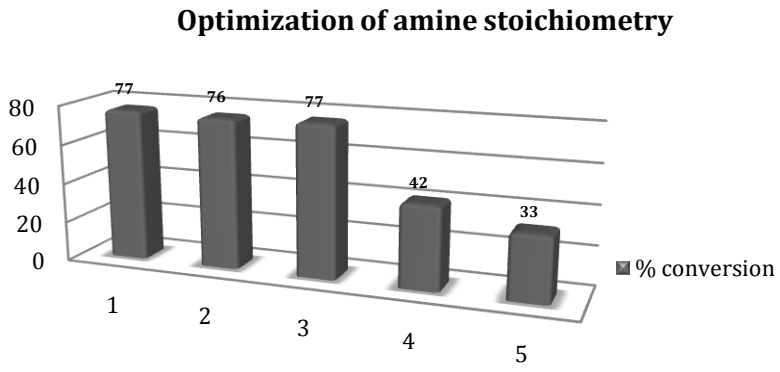


Table 3-6: Optimization of amine stoichiometry.

Entry	Acid	Amine (equiv)	Conversion
1	1.2	1.0	77
2	1.1	1.0	76
3	1.0	1.0	77
4	1.0	1.1	42
5	1.0	1.2	33



3.2.3.3 Optimization of Reaction Concentration

In Chapter 1, we performed the catalytic amidation reaction at 0.07 M concentration of carboxylic acid substrate.[1] With the new catalyst **3-44**, it was found that an increase in the operating reaction concentration led to faster reactions and more amide product was isolated. Specifically, a 0.100 M concentration was the optimal concentration upon using 10-mol% of the catalyst **3-44**, providing 94% conversion to the desired amide product (**Table 3.7, entry 2**). Taking advantage of increased

reaction rates at higher concentrations, the loading of the catalyst was lowered to 5-mol% of catalyst **3-44** to see if it would be possible to optimize further without negative impact on the product yield. Unfortunately, lower catalyst loading provides the requisite product in a slightly lower yirld. The optimal conditions were found at 0.125 M concentration providing 74% conversion to the amide product (**Table 3.7, entry 9**). Since the reaction is slower with 5-mol%, we opted to use a 10-mol% catalyst loading. The direct amide bond formation reaction using 5-methoxy-2-iodophenylboronic acid **3-44** provided an improved reactivity and faster reactions when compared to our first-generation catalyst system. Overall, it is remarkable that the amidation reaction is performed catalytically within a few hours in excellent yields and at ambient temperature, making it clearly advantageous over the most popular stoichiometric reagents.[16-18]

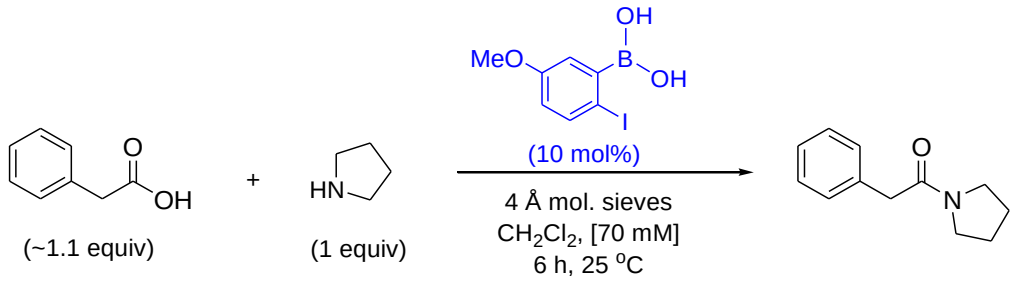
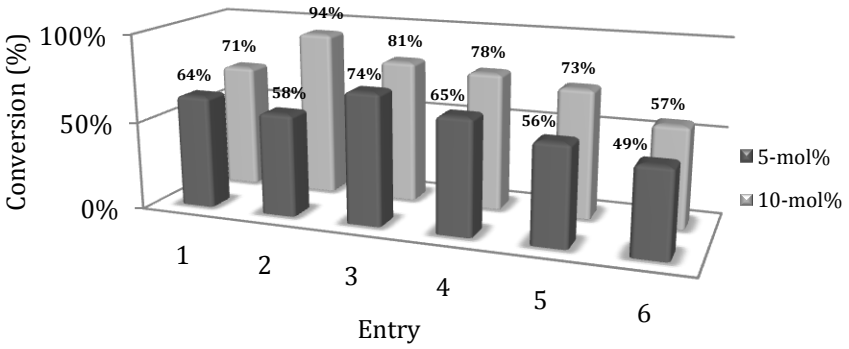


Table 3-7: Optimization of reaction concentration.

10-mol%			5-mol%		
Entry	Conc. (M)	Conversion (%)	Entry	Conc. (M)	Conversion (%)
1	0.071	71 %	7	0.071	64 %
2	0.100	94 %	8	0.100	58 %
3	0.125	81 %	9	0.125	74 %
4	0.166	78 %	10	0.166	65 %
5	0.250	73 %	11	0.250	56 %
6	0.500	57 %	12	0.500	49 %

Optimization of reaction concentration



3.2.4 Substrate Scope for Catalytic Direct Amide Bond Formation

Having optimized reaction parameters with the MIBA catalyst **3-44**, we then explored the scope of the amidation reaction using the optimized conditions (**Table 3-8**). Analogous to our previous report,[1] the preferred substrates for this second generation catalyst system turned out to be aliphatic carboxylic acids. The reaction gave excellent yields within two hours for the majority of aliphatic substrates (**Table 3-8, entries 1-4 and 6-12**). Although acyclic secondary amines did not work (**Entry 5)**, cyclic amines worked well and provided near quantitative yields of the desired amides within 3-4 hours (**Entries 4, 6 and 10)**. Acyclic secondary amines are known to have lower reactivity compared to cyclic ones due to steric effects.[19] Furthermore, the use of different amino acids provided the desired amide products in good to excellent yield (**Entries 6-9)**. For instance, the reaction of *N*-Boc-γ-aminoacid with hexylamine led to 87% and 65% of the amide product in DCM and THF. respectively (**Entry 7)**. While the use of *N*-Boc-β-alanine provided the desired amide product in excellent yields (**Entry 8**), unfortunately, *N*-Boc-α-glycine did not lead to any amide product, which might be explained by Boc carbamate carbonyl complexation to boron (**Entry 9**). For the amidation reaction of ibuprofen with pyrrolidine, the requisite amide product was isolated in 26% and 51% yields in 3 and 8 hours, respectively, without any traces of epimerization. Unfortunately, no amidation reactions were observed for aromatic carboxylic acids at room temperature and only trace amounts of amide product were observed at 50 °C (**Entries 13 and 14**).

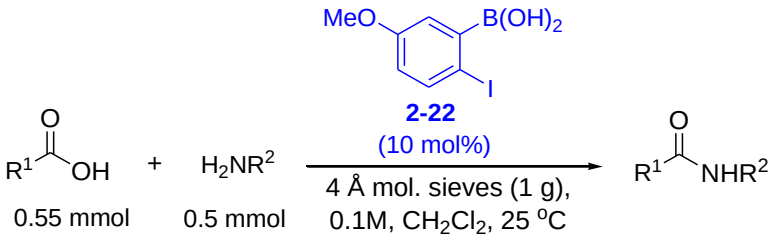


Table 3-8: Substrate scope in the second-generation catalytic direct amide bond formation of carboxylic acids under optimized conditions.

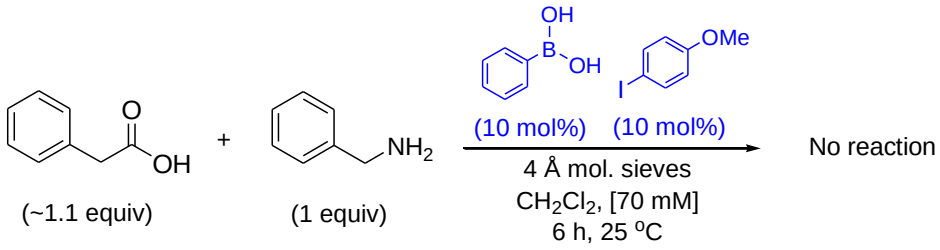
Entry	Amine	Carboxylic acid	Product	%Yield/time (h)
1	$PhCH_2NH_2$	$PhCH_2CO_2H$	**3-60**	99/3
2	$PhCH_2NH_2$	$Ph(CH_2)_3CO_2H$	**3-61**	91/2.5
3	$CH_3(CH_2)_3NH_2$	$Ph(CH_2)_3CO_2H$	**3-62**	90/2.5
4	pyrrolidine	$PhCH_2CO_2H$	**3-63**	94/6
5	$PhCH_2NHCH_3$	$PhCH_2CO_2H$	**3-64**	0 (0) [a]/48
6	pyrrolidine	*N*-Boc-7-aminoheptanoic acid	**3-65**	95 (85) [a]/6
7	$C_6H_{13}NH_2$	*N*-Boc-γ-aminobutanoic acid	**3-66**	87 (65)[a]/2
8	$C_6H_{13}NH_2$	*N*-Boc-β-aminopropanoic acid	**3-67**	86 (73)[a]/2
9	$C_6H_{13}NH_2$	*N*-Boc-α-aminoethanoic acid	**3-68**	0 (0)[a]/2
10	pyrrolidine	Ibuprofen	**3-69**	26 (31)[a]/3
11	pyrrolidine	Ibuprofen	**3-69**	51 (70)[a]/8
12	(R)-(+)$PhCH(CH_3)NH_2$	ibuprofen	**3-70**	62 (83)[a]/2
13	$PhCH_2NH_2$	4-I-$C_6H_4CO_2H$	**3-71**	0/48
14	$PhCH_2NH_2$	4-I-$C_6H_4CO_2H$	**3-71**	0/24 [b]

The boronic acid **3-44** (0.05 mmol), carboxylic acid (0.55 mmol), and the amine (0.5 mmol) were stirred at 24–25 °C in solvent containing powdered activated 4Å molecular sieves (1 g). Unless indicated otherwise, amidations took place in CH_2Cl_2 with catalyst **3-44** (10-mol%). Product purity after acid-base extraction was greater than 95% according to ^1H NMR spectroscopic analysis.
Boc = butoxycarbonyl. [a] Reaction in THF. [b] Reaction was carried out at 50 °C.

3.2.5 Mechanistic Aspects of the Direct Amidation Catalyzed With *Ortho*-Iodoarylboronic Acids

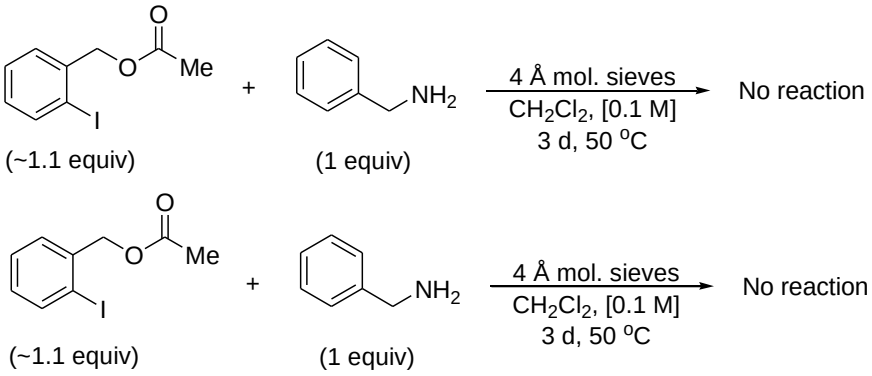
Having optimized the electronic and steric effects on the activity of *ortho*-iodophenylboronic acid toward catalytic direct amide bond formation, we started to validate the role of the iodo group on the reactivity of these catalysts. As previously described, we have found that electron-rich *ortho*-iodoarylboronic acids and especially the MIBA catalyst **3-44** (Second generation catalyst) are reproducibly

more reactive catalysts under the optimized conditions than the original first-generation catalyst **3-1**. Apparently, increasing the electron density of the iodine atom increases the basicity or nucleophilicity of this substituent. This effect may explain the reactivity of these catalysts by supporting a different mechanism using the electron-rich iodo substituent for a nucleophilic substitution reaction. To validate this hypothesis, we subjected a model amidation reaction between phenylacetic acid and benzylamine using 10-mol% of each phenylboronic acid and 4-iodoanisole, side-by-side with another reaction using 10-mol% of MIBA catalyst under the optimized reaction conditions. We observed no catalysis for the former reaction while a quantitative yield of the desired amide product was isolated with the use of MIBA **3-44** (**Scheme 3-21**). This result shows that the close proximity of the *ortho*-iodo substituent and the boronic acid is crucial for catalysis to occur.



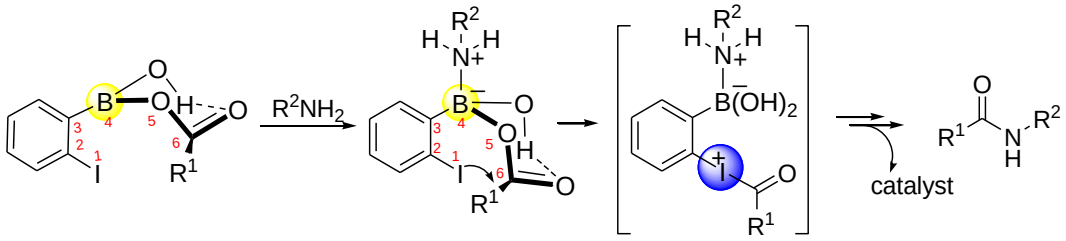
Scheme 3-21: Control experiment with phenylboronic acid and 4-iodoanisole on catalytic amide bond formation reaction.

Moreover, we then decided to study the effect of the iodo substituent on a substrate such as 2-iodobenzyl acetate to see if there could be any acyl transfer to the iodo substituent by a nucleophilic iodide transfer mechanism under the same reaction conditions but at higher reaction temperature. At the outset, direct acylation reactions used acetic anhydride with both benzyl alcohol and 2-iodobenzyl alcohol to form the acylated products **3-72** and **3-73** in 97% and 96%. respectively. We then subjected these compounds to the amidation reaction conditions as shown in **Scheme 3-22**. After three days, we did not observe any amide bond formation in either reactions. This result clarified the important role of the boron in catalysis.



Scheme 3-22: The effect of boron replacement on catalytic direct amidation reaction under the optimized conditions.

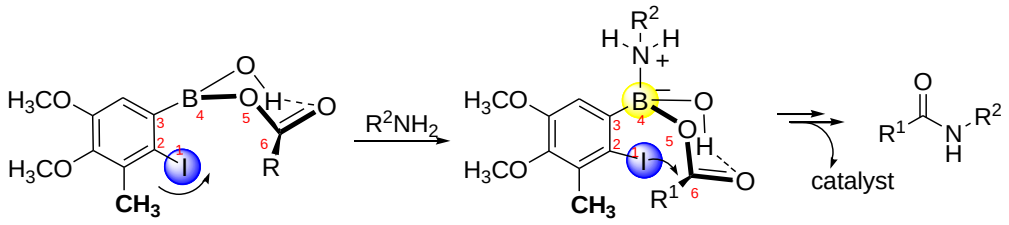
During the course of the synthesis of new catalysts for direct amide bond formation, one of the catalysts (catalyst **3-48**) turned out to be purple in color. While I was testing this colored catalyst, the color did not change while the solution was a mixture of carboxylic acid, catalyst and 4Å molecular sieves. However, once the amine was added to the reaction mixture, the color immediately disappeared and the amide product started to be formed. It was isolated in 51% yield after 6 hours (**Scheme 3-17**). This event suggests a coordination between the amine and the empty p-orbital on the boron which, presumably, changes the electronic environment and results in a color change. This coordination is supported by ^{11}B-NMR, wherein the boron peak was shifted from 24 ppm to 3 ppm. On the other hand, the coordination between the amine and the boron would also change the geometry of the boron atom from trigonal planar to tetrahedral (**Scheme 3-23**). This tetrahedral structure would enforce a closer proximity between the acyl group and the electron-rich iodo substituent. Although we have not yet clarified the detailed mechanism of direct amide bond formation catalyzed by *ortho*-iodoarylboronic acid catalysts, it seems conceivable to invoke a B-I acyl transfer that results in the formation of an activated acyliodonium intermediate **3-74**, which would, undoubtedly, be a potent acylating agent.



3-74

Scheme 3-23: Putative B-to-I-to-N acyl transfer mechanism.

We had previously observed a small benefit from the group [i.e. CH_3 (**3-8**), F (**3-51**)] at position 3 in the aromatic ring. In line with the proposed acyliodonium mechanism, such a group (i.e. CH_3) may further enforce a close proximity between the iodo substituent and the boron center, which would facilitate the acyl transfer (**Scheme 3-24**).



Scheme 3-24: The proposed effect of the 3-methyl group on enhancing the catalytic reactivity.

Moreover, electron-rich *ortho*-iodoarylboronic acids were found to be more reactive catalysts than neutral and electron-poor *ortho*-iodoarylboronic acids. The reactivity of the catalyst was found to be optimal with only one donating group (OMe, **3-44**) at position 5 in the aromatic ring. Seemingly, increasing the electron density of the iodine atom by resonance increases the nucleophilicity of this substituent (**Figure 3-5**).

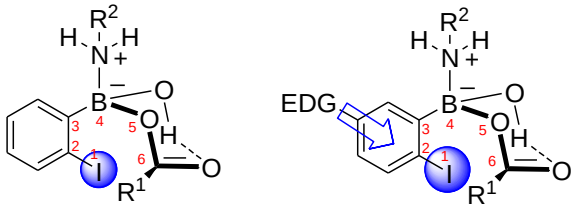
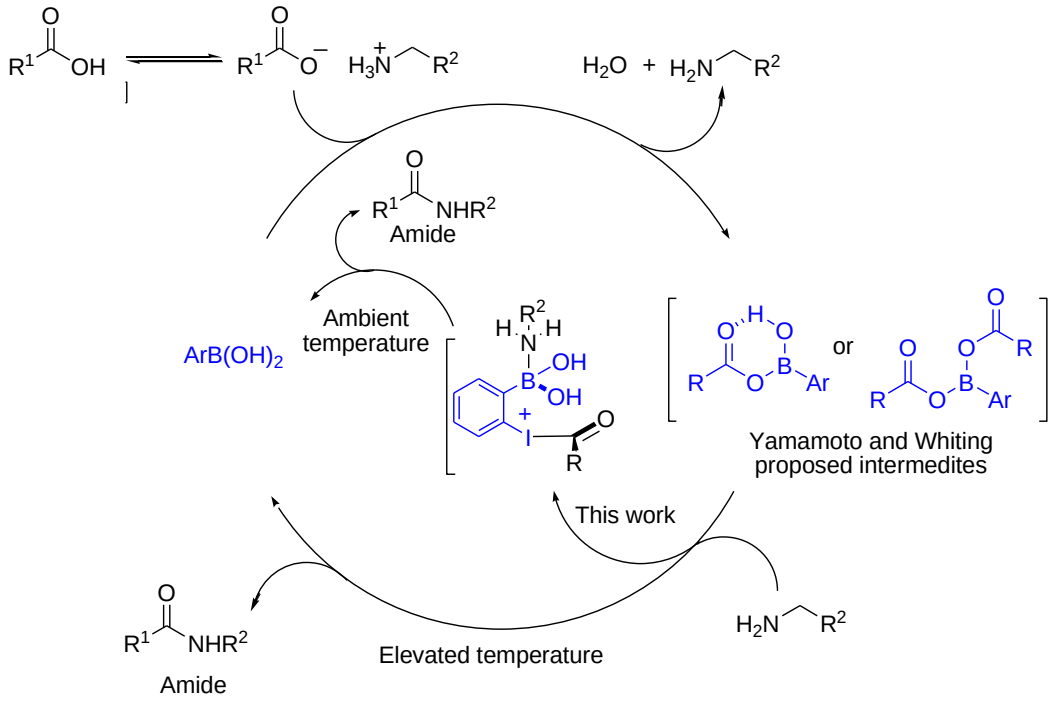


Figure 3-5: The effect of electron donating groups on the reactivity of *ortho*-iodoarylboronic acid system.

As described in Chapter One, mixing of the carboxylic acid and the boronic acid catalyst under the same reaction conditions did not lead to formation of the anhydride intermediate. This also supported our hypothesis regarding the need of the amine to be a part of the mechanism by forming a tetrahedral geometry and, presumably, changing the electronic environment around the boron centre. Moreover, when alcohols or thiols were used instead of amines for direct catalytic ester and thioester formation, these reactions were unsuccessful and only starting materials were detected and isolated. These results support the important role of the amine in the mechanism.

The amidation reaction conditions require the use of 4 Å activated molecular sieves as a drying agent. A reactivation of the molecular sieves by oven heating at 250 °C for few days or by Kugelrohr for 2 h under high vacuum is necessary for the reproducibility of this direct amidation method. It indicates that the reactive intermediate(s) formed are highly moisture sensitive and completely dry conditions are necessary. The proposed catalytic cycle is highlighted in **Scheme 3-25**.



Scheme 3-25: Proposed mechanistic cycle for the catalytic direct amide bond formation using *ortho*-iodoarylboronic acid catalyst system.

3.3 Rational Design of an Improved Catalytic System for the Direct Amide-Bond Formation: Third Generation Catalyst

To summarize my results up to this point, an efficient catalyst system was developed for direct amide bond formation at ambient temperature. Secondary and tertiary amides were obtained in good to excellent yields in less than 3 hours with the second generation catalyst "5-methoxy-2-iodophenylboronic acid **3-44**". Remarkably, the amide products of β and γ–aminoacids were obtained with excellent yields and high atom economy compared to the known stoichiometric amidation methods.[1] Using control reactions and X-ray crystallographic analyses of several *ortho*-iodoarylboronic acid catalysts, we noticed an intimate steric relationship between the iodo substituent and the boronic acid requiring a specific distance between the B ←→ I. It was also shown that there was a precise electron density required in the aromatic backbone of the catalyst to increase the nucleophilicity of the iodo substituent without affecting the boron's Lewis acidity. Accordingly, the most active catalyst was found to be catalyst **3-44** with only one electron-donating group at position 5 in the aromatic ring. Although this new catalytic methodology was found to be superior to known published methods, providing the amide products in simple, green and highly atom economical fashion, it still suffers from a few limitations, such as its use with aromatic carboxylic acids and α-aminoacids, which are important precursors in pharmaceutical and medicinal chemistry.

Since there are only three available positions (C3, C4, and C5) on the aromatic backbone of the *ortho*-iodoarylboronic acid catalyst (**Figure 3-1**) to functionalize, and we had already exhausted many possibilities in the process of discovering catalyst **3-44** (second generation catalyst), further derivatization was unfortunately not an option to overcome the aforementioned limitations.

As previously noted, electron-rich *ortho*-iodoarylboronic acids were found to be more active catalysts than the neutral *ortho*-iodoarylboronic acid in direct amide bond formation. We rationalized that changing the aromatic backbone on these catalysts and using different aromatic rings, such as heteroarenes that are known to

be more electron-rich than cyclohexatriene systems, could enhance the catalytic reactivity.

In this regard, it was expected that heteroaromatic rings, such as furan and pyrrole, could provide the required electron density for reactivity and open a new avenue in the synthesis and understanding of this catalytic direct amidation reaction. To this end, I decided to synthesize a furanboronic acid equipped with *ortho*-iodo substituent (**Figure 3-6**) and compare it with catalyst **3-44** under the optimized reaction conditions. After reviewing the literature carefully, I came up with an idea for making 4-iodo-3-furanboronic acid **3-75**.

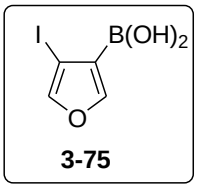
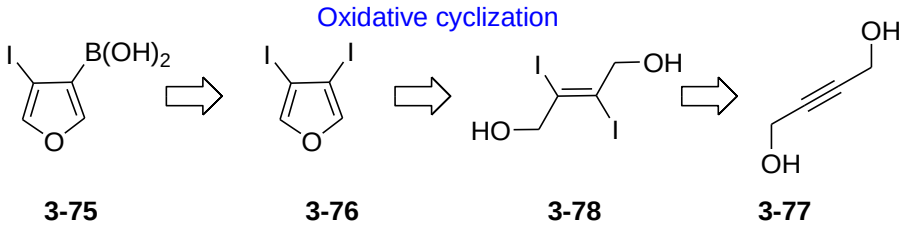


Figure 3-6: Proposed iodo-furanboronic acid 3-75.

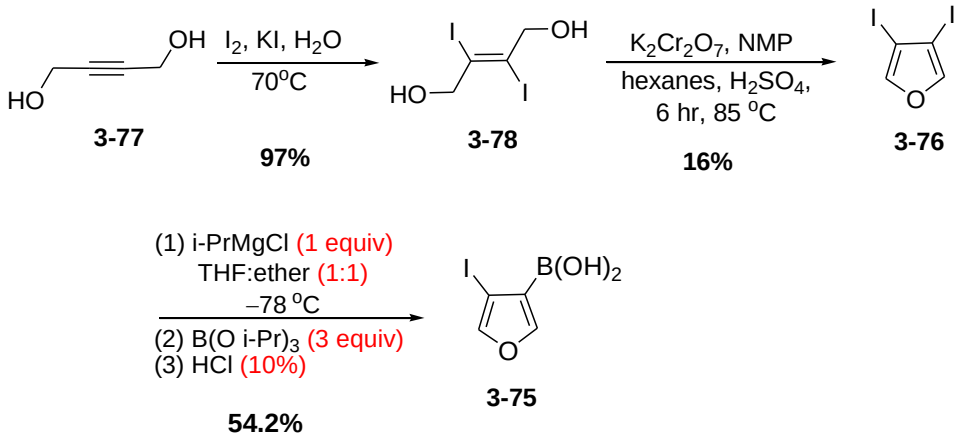
It is known that some furans are sensitive and may easily decompose under certain conditions. Therefore, a similar approach was used as before, wherein the boronic acid **3-75** was prepared by a metal-halogen exchange reaction followed by borate trapping from the diiodo precursor **3-76,** as described in **Scheme 3-26**. The diiodofuran **3-76** was made according to a published report by Wang.[20]



Scheme 3-26: Retrosynthetic analysis for 4-iodo-3-furanboronic acid 3-75.

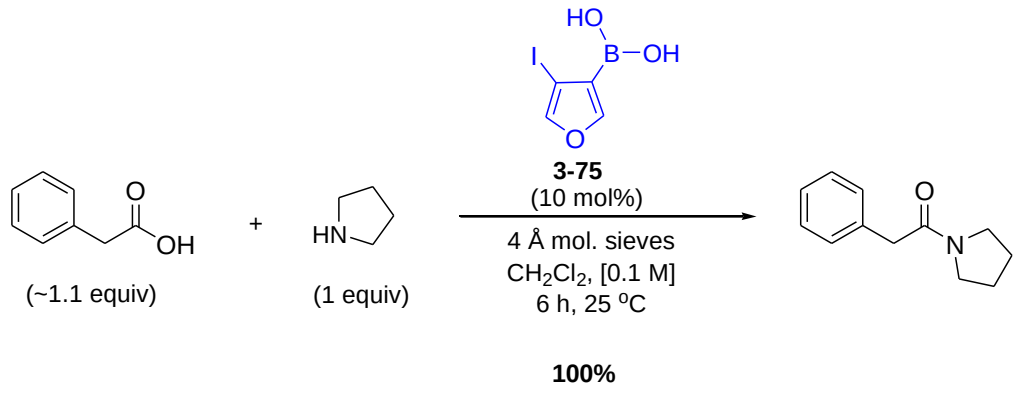
The synthesis started by iodination of cheap and commercially available propargylic diol **3-77** leading to diiodoalkene **3-78**. An oxidative cyclization reaction with dichromate provided the requisite diiodide **3-76** in 7% isolated yield (b.p. = 71 ^{o}C, 1.1 mm Hg).[20] A metalation reaction from the diiodide **3-76** using

*iso*propylmagnesium chloride followed by trapping with triisopropylborate reagent led to the desired boronic acid **3-75** in three steps overall and with 8.4% yield (**Scheme 3-27**).



Scheme 3-27: Synthesis of 4-iodo-3-furanboronic acid (FIBA) 3-75.

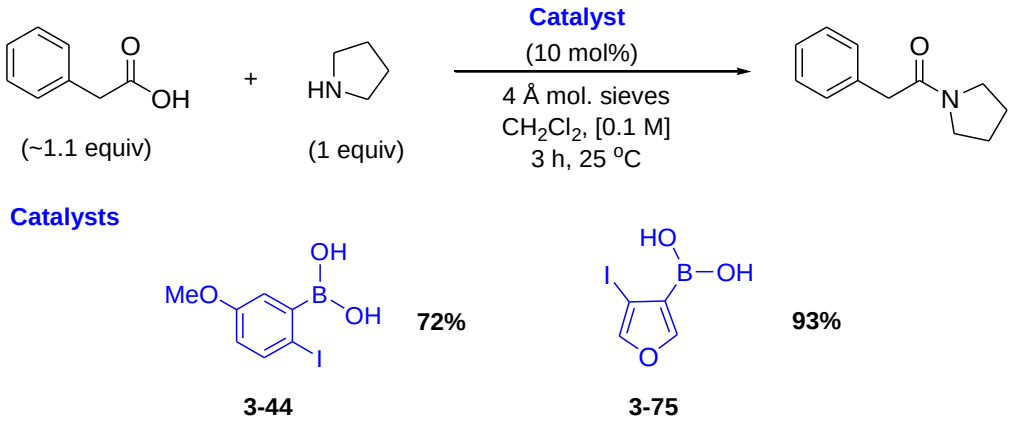
We then subjected this new boronic acid catalyst **3-75** to a model amidation reaction between phenylacetic acid and pyrrolidine under the optimized reaction conditions. In this event, catalyst **3-75** provided a quantitative yield of the desired amide product after 6 hours of reaction (**Scheme 3-28**).



Scheme 3-28: Examining the catalytic reactivity of 4-iodo-3-furanboronic acid (FIBA) 3-75 on direct amide bond formation.

To compare the performance between both 5-methoxy-2-iodophenylboronic acid **3-44** and 4-iodo-3-furanboronic acid **3-75** catalysts under the optimized reaction conditions, three hour long side-by-side reactions were planned (**Scheme 3-29**).

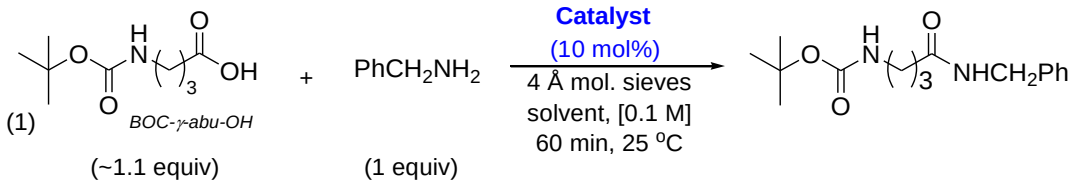
Pleasingly, catalyst **3-75** was superior, providing 93% yield while only a 72% yield was obtained with catalyst **3-44**.

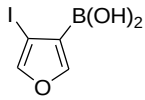


FIBA catalyst **3-75** led to a relatively faster catalyzed amidation reaction providing a higher yield of one of the most demanding amidation reactions (tertiary amide) between phenylacetic acid and pyrrolidine, its effect on the preparation of other aliphatic amides (**Scheme 3-29**) and α-substituted amides (**Scheme 3-30**) is significant, providing the desired products in shorter reaction time avoiding epimerization side reactions and thus appears to be general. Unfortunately, the new catalyst system, FIBA **3-75** did not fare as well with aromatic carboxylic acids and α-amino acids providing very low yields even after 24 hours.

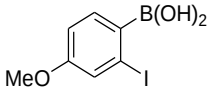
3.3.1 Efficiency of FIBA (3-75) in Direct Amide Bond Formation at Ambient Temperature

Having identified the superiority of the 4-iodo-3-furanboronic acid **3-75**, we then compared this new catalyst system with both our first and second generation catalysts **3-1** and **3-44,** respectively in side-by-side reactions using more demanding substrates and in three different solvents (**Scheme 3-29**). While only a small panel of carboxylic acids and amines were employed in this comparison, all examples gathered thus far have led to an increase of isolated amide yield with FIBA catalyst **3-75** over both **3-44** and **3-1**, suggesting that its reactivity is general and applicable to other substrates that were previously studied with both catalysts **3-44** and **3-1** (see Chapter 2.2.6).

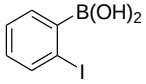




3-75

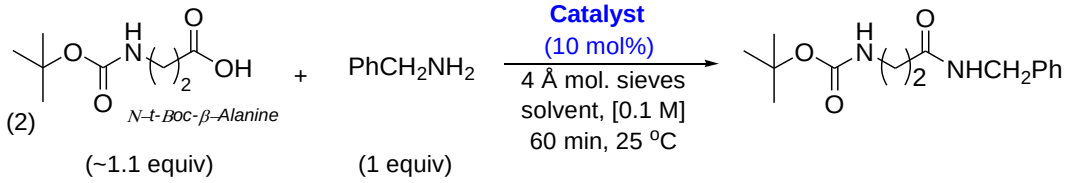


3-44



3-1

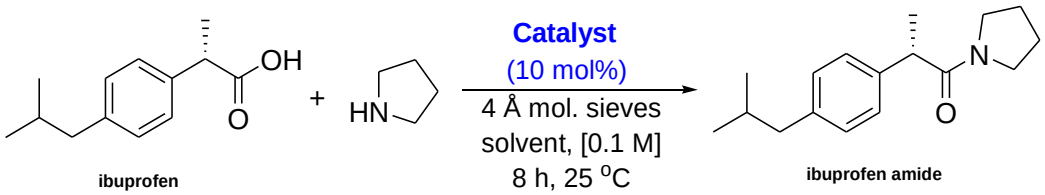
	CH_2Cl_2	THF	toluene
3-75	86%	74%	77%
3-44	73%	53%	62%
3-1	63%	46%	41%



	CH_2Cl_2	THF	toluene
3-75	68%	43%	75%
3-44	59%	35%	71%
3-1	48%	24%	47%

Scheme 3-29: Comparison in product yield between catalysts 3-75, 3-44 and 3-1 in direct amidation reactions under optimized conditions.

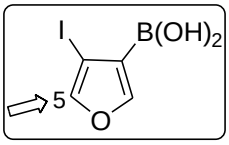
To determine the relative rates of catalyzed direct amidation reactions using *ortho*-iodoboronic acid catalysts **3-75**, **3-44** and **3-1**, a model reaction between ibuprofen and pyrrolidine was decided upon and terminated after exactly 8.0 hours. In the event, the model amidation reaction gave 68% conversion in CH_2Cl_2 with **3-75**, and 51% and 43% conversions with **3-44** and **3-1,** respectively (**Scheme 3-30**).



	CH_2Cl_2	THF	toluene
3-75	68%	78%	81%
3-44	51%	69%	77%
3-1	43%	52%	65%

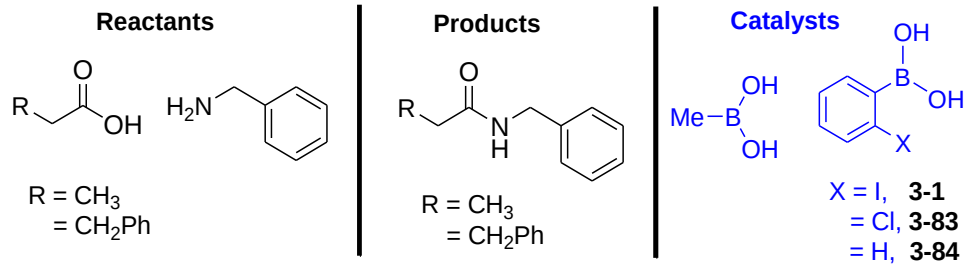
Scheme 3-30: Comparison in product yield between catalysts 3-75, 3-44 and 3-1 in a direct amidation reaction between ibuprofen and pyrrolidine under optimized conditions.

In line with *ortho*-iodophenylboronic acid **3-2**, the same manipulations could also be done to optimize this catalytic system. Indeed, small electronic and steric differences either by different possible substitutions at carbon 5 in the furan ring in catalyst **3-75** or with the use of different heteroaromatic rings could significantly enhance the catalytic activity of this system towards direct amide bond formation.



3.4 Recent Quantum Chemical Studies From Marcelli[21]

While this thesis was being completed, Tommaso Marcelli reported a detailed study on the role of halogens at the *ortho* position for direct amide bond formation catalyzed by boronic acids using DFT calculations (**Scheme 3-31**). In this study, the author indicated that the remarkable catalytic activity of *ortho*-haloarylboronic acids was due to their activity as bifunctional Lewis acid/Lewis base catalysts in direct amidation reactions.[21]



Scheme 3-31: Substrates and catalysts used for the calculations.[21]

As concluded in this study, the Lewis basicity of halogens and their ability to form O–H···X hydrogen bonds, which was found to be greater for iodine than for chlorine, is exceptional and has been found in other systems[22, 23]. It is noteworthy that these observations were found to be in line with our recent results showing that electron-rich *ortho*-iodoarylboronic acids are more reactive catalysts than neutral and electron-poor *ortho*-iodoarylboronic acids. However, it failed to provide an explanation of the difference in reactivity between aliphatic and aromatic carboxylic acids.

Furthermore, the author found a larger activation barrier for the amidation reaction of ionized reactants (c.f. carboxylate and ammonium) than those involving neutral species.[4, 21, 24-26] Moreover, the reaction sequences involving diacylboronate intermediate **3-4** (**Scheme 3-1**) as proposed by Whiting and co-workers was found to have a significantly higher barrier than the monoacylboronate intermediate **3-3** (**Scheme 3-1**).[21]

Accordingly, using the lowest-energy monoacylboronate intermediate **3-3**, the author claimed that the formation of the boron-bound amide intermediate **3-79** from the corresponding hemiaminal **3-80** (hemiaminal dehydration step) was found to be the rate determining step of this transformation, as shown in the lowest-energy catalytic cycle (**Scheme 3-32**).[21] The formation of *cis*-amide **3-81** was found to be 5 kcal/mol more favored than the *trans*-isomer **3-82** due to the benefit of forming intramolecular N–H···O hydrogen bonding in *cis*-amide **3-81** and the build up of steric interactions between the amine substituent and the hydroxyl group of the boronic acid catalyst in *trans*-amide **3-82** (**Figure 3-7**).[21]

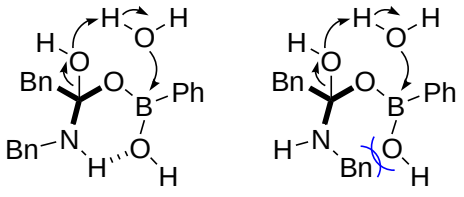
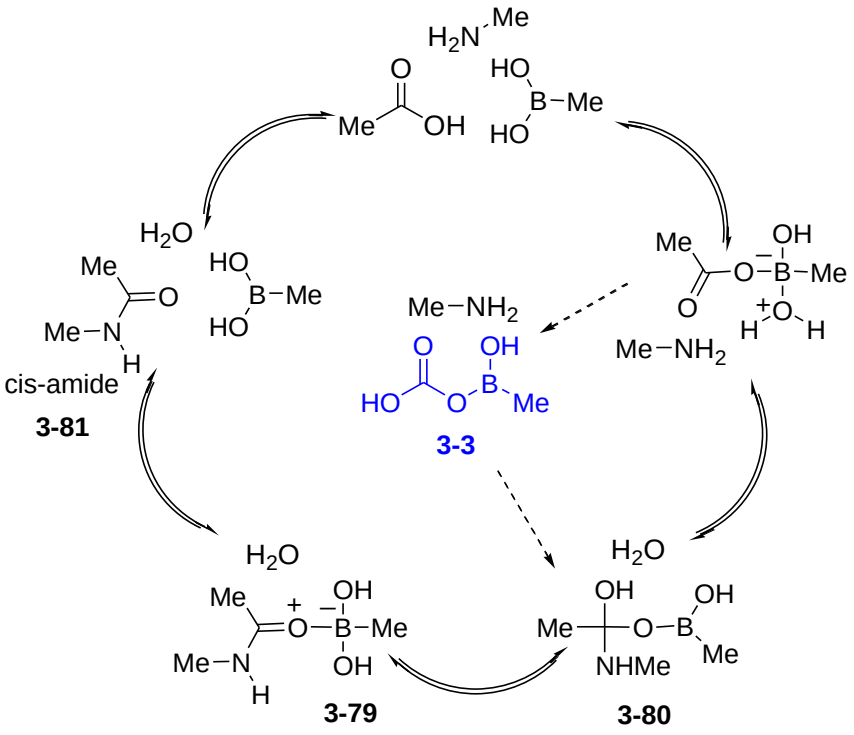


Figure 3-7: Lowest-energy water elimination for the formation of *cis*-amide catalyzed by phenylboronic acid.[21]



Scheme 3-32: Lowest-energy intermediates calculated for amidation reaction catalyzed by boronic acid.[21]

Moreover, the computationally most energetically accessible transition states for both catalysts **3-83** and **3-1** were found to demonstrate a short distance between the proton of the hydroxyl group on the boron and the halogen atom (**Figure 3-8**).[21]

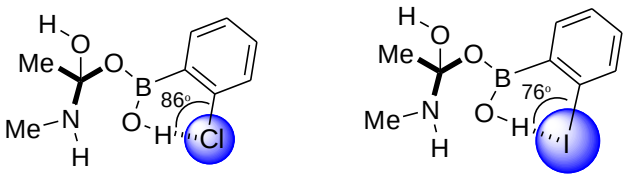


Figure 3-8: Most energetically accessible transition states for the use of boronic acids 3-1 and 3-83.[21]

The author also claimed that this computational study was in excellent agreement with our experimental results,[1] and the overall barriers for the amidation catalyzed by **3-83** and **3-1** were, respectively, 0.9 and 1.7 kcal/mol lower than the value obtained with boronic acid **3-84** (**Scheme 3-31**) (**3-84** : 28.1 kcal/mol, **3-83**: 27.2 kcal/mol, **3-1**: 26.4 kcal/mol). In other words, the DFT calculations predicted that this hydrogen bonding (O–H···X) could be the reason for the improved activity of catalysts **3-83** and **3-1** compared to **3-84**.[22, 23] The geometry of the C–X···H

interaction displayed an angle close to 90°, which is in line with the anisotropic electron distribution of the carbon-halogen bond.[27] Additionally, the distortion of the iodine's electron density in the *ortho*-iodo catalyst clearly enhanced the O–H···X hydrogen bonding, providing a more active catalyst.[21]

3.5 Conclusion

Following the lead hypothesis of steric and electronic manipulations on the catalyst system and then by studying their effects on the direct amide bond formation, we were able to design an improved boronic acid catalyst, MIBA (**3-44**). The direct amidation reactions using MIBA catalyst **3-44** were shown to deliver the desired amides without racemization and in higher yield when compared to the parent IBA **3-1** catalyst under the optimized conditions. A small benefit was found for a steric alkyl substituent at the 3-position. While electron-poor substituents were found to inhibit the catalytic reactivity, electron-rich ones were found to increase the performance of the catalyst. A precise tuning of electron densities was required for optimal reactivity of the catalyst by having only one donating group at the 5-position, whilst more electron-donating groups inhibited the reactivity. likely by affecting the boron's Lewis acidity. Under this second-generation catalyst system, the aliphatic amide products were obtained in up to 99% yield and without any racemization in the case of ibuprofen. Additionally, β-amino acids and γ-amino acids were subjected to the reaction conditions and the amide products were isolated in very high yield within 2 hours of reaction time and without the need for chromatography.

A third generation catalyst system (FIBA **3-75**) was also discovered and showed a consistent superiority over the second generation catalyst in providing the amide products in higher yields with shorter reaction times. Different manipulations are still possible for optimizing this catalytic system. For instance, substitution of the hydrogen at the 5-position next to the iodo group with an alkyl group or with a methoxy could enhance the catalytic system toward direct amide bond formation. In general, the ease of amidation reaction conditions, ease of work-up and the easily accessible iodoarylboronic acid catalysts by one step synthesis from cheap and readily available starting materials using the developed direct iodination

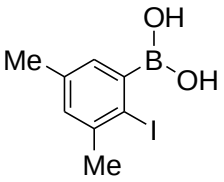
methodology (Chapter 4), are the most advantageous aspects of this amidation method.

3.6 Experimental

3.6.1 General Information

The methods described in Section 2.6.1 also apply here.

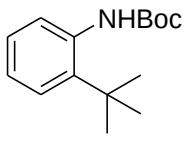
3.6.1.1 Preparation and Analytical Data of 3,5-Dimethyl-2-Iodophenylboronic Acid (3-10)



To a solution of 1,2-diiodo-3,5-dimethylbenzene (0.50 g, 1.40 mmol) in 60 mL of a mixture of THF and Et_2O (1:1) was added dropwise at -78 °C isopropylmagnesium chloride (2 M in THF, 0.70 mL, 1.40 mmol). After the mixture was stirred for 2 h at that temperature, B(O*i*-Pr)$_3$ (0.96 mL, 4.19 mmol) was added. The solution was warmed to room temperature overnight; then a saturated aqueous solution of NH_4Cl was added, and the resulting mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with Et_2O (50 mL, 3 times and the extract was dried over Na_2SO_4, filtered and concentrated. To the concentrated sample, hexane was added and the resulting precipitate was isolated to give the desired product in 56% yield as a 3:1 mixture of non separable regioisomers (**Equation 3-3**).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 2H), 7.06 (d, J = 2.4 Hz, 1H), 6.76 (d, J = 2.4 Hz, 1H), 2.30 (s, 3H), 2.18 (s, 3 H). **^{13}C-NMR** (100 MHz, DMSO-d_6) δ 139.2, 136.2, 130.6, 129.8, 101.4, 28.0, 20.0 (C attached to B not seen on the NMR at 27 °C). **IR** (Microscope, cm^{-1}) 2951, 1587, 1386, 1342, 1296, 1270, 1000. **HRMS** (EI) for $C_8H_{10}{}^{11}BIO_2$: calcd. 275.98185; found, 275.98239.

3.6.1.2 Preparation and Data Analytical of Tert-Butyl 2-Tert-Butylphenyl Carbamate (3-14)

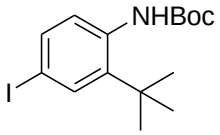


A dry, 50-mL RBF connected to a supply of argon was equipped with a Teflon-coated magnetic stirring bar and a condenser. The flask was charged with 2-tert-butylaniline (0.65 g, 4.36 mmol), (*t*-

$C_4H_9OOC)_2O$ (1.00 g, 4.60 mmol) and THF (20 mL) and the reaction mixture was stirred at 60 °C for 4 h. After removal of the solvent under reduced pressure, the residue was dissolved in dichloromethane (20 mL), and then poured into water (30 mL). The organic layer was separated, and the aqueous layer was extracted three times with dichloromethane (20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the desired product in 100% yield (1.1 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 1H, *J* = 7.8 Hz), 7.36 (dd, 1H, *J* = 1.6 Hz, *J* = 8.0 Hz), 7.22 (ddd, 1H, *J* = 1.6 Hz, *J* = 7.6 Hz, *J* = 9.2 Hz), 7.11 (ddd, 1H, *J* = 1.6 Hz, *J* = 7.6 Hz, *J* = 8.0 Hz), 6.35 (bs, 1H), 1.52 (s, 9H), 1.42 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 153.6, 135.6, 126.8, 126.6, 126.2, 125.0, 80.1, 34.4, 30.5, 28.3. **IR** (Microscope, cm^{-1}) 3326, 2969, 1809, 1735, 1698, 1510, 1366, 1161. **HRMS** (EI) for $C_{15}H_{23}O_2N$: calcd. 249.17288; found, 249.17257.

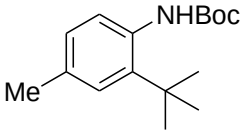
3.6.1.3 Preparation and Analytical Data of Tert-Butyl 2-Tert-Butyl-4-Iodophenyl Carbamate (Scheme 3-4, Step 1)



tert-Butyl 2-tert-butylphenylcarbamate **3-14** (1.0 g, 4.0 mmol) was added to a mixture of iodine (1.00 g, 4.0 mmol) and silver (I) sulfate (1.25 g, 4.0 mmol) in 1,2-ethanediol (40 mL) at room temperature. The reaction was stirred until the iodine color completely disappeared. The reaction mixture was filtered through a pad of Celite ® 545 using ethyl acetate. Water (100 mL) was added to the filtrate and the mixture was extracted with ethyl acetate (2 X 30 mL). The combined organic layers were washed with aqueous sodium sulfite, brine, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel (hexane/ethyl acetate 3:1) to yield the pure iodinated product in 81% yield as 1.2 g.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.63 (d, 1H, *J* = 2.1 Hz), 7.52 (ddd, 1H, *J* = 0.5 Hz, *J* = 2.1 Hz, *J* = 8.5 Hz), 7.37 (d, 1H, *J* = 8.2 Hz), 6.31 (s, 1H), 1.51 (s, 9H), 1.39 (s, 9H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 153.2, 143.7, 143.7, 135.7, 135.5, 128.1, 89.7, 80.6, 34.5, 30.4, 28.4. **IR** (Microscope, cm^{-1}) 3309, 2969, 1698, 1502, 1366, 1242, 1162, 1042, 1162. **HRMS** (EI) for $C_{15}H_{22}O_2NI$: calcd. 375.06952; found, 375.06967.

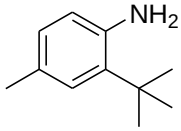
3.6.1.4 Preparation and Analytical Data of Tert-Butyl 2-Tert-Butyl-4-Methylphenyl Carbamate (3-15)



A flame dried flask was charged with the above iodinated product (1.00 g, 2.67 mmol), $Me_3B_3O_3$ (0.33 g, 2.67 mmol), palladium II acetate (90 mg, 5 mol%), dioxane (20 mL), water (2.0 mL), K_3PO_4 (1.7 g, 8.00 mmol) and PPh_3 (0.17 g, 0.66 mmol) under argon. The mixture was heated to 100 °C for 12-14 h. The mixture was then cooled down to room temperature. Ethyl acetate (30 mL) was added and the organic layer was separated, washed twice with water, brine, dried over Na_2SO_4 and filtered. The solvent was removed and the crude product purified by flash chromatography (20% EtOAc/hexanes) to provide the desired product (0.42 g as 59% yield).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 (d, 1H, *J* = 7.7 Hz), 7.16 (d, 1H, *J* = 1.6 Hz), 7.02 (dd, 1H, *J* = 1.5 Hz, *J*= 8.1 Hz), 6.21 (bs, 1H), 2.32 (s, 3H), 1.51 (s, 9H), 1.40 (s, 9H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 154.0, 142.4, 134.8, 132.9, 128.7, 127.2, 127.1, 80.0, 34.5, 30.7, 28.4, 21.2. **HRMS** (EI) for $C_{16}H_{25}O_2N$: calcd. 263.18854; found, 263.18841.

3.6.1.5 Preparation and Analytical Data of 2-Tert-Butyl-4-Methylaniline (Scheme 3-4, Step 3)

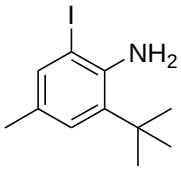


To a solution of tert-butyl 2-tert-butyl-4-methylphenyl carbamate **3-15** (1.00 g, 3.79 mmol, 0.2 M) in CH_2Cl_2 (20 mL) was added CF_3COOH (3.8 mL, 49.3 mmol) dropwise at 0 °C under argon atmosphere and the mixture was stirred for overnight at room temperature. After consumption of the starting material, water was added to the reaction solution. The mixture was neutralized using 3N aqueous NaOH and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The desired product was isolated as a pale orange oil in quantitative yield and used without further purification in the following step.

^{1}H-NMR (300 MHz, $CDCl_3$) 7.04 (d, 1H, *J* = 2.2 Hz), 6.85 (dd, 1H, *J* = 2.2 HZ, *J* = 7.9 Hz), 6.57 (d, 1H, *J* = 7.9 Hz), 3.69 (s, 2H), 2.25 (s, 3H), 1.42 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 142.2, 133.9, 127.6, 127.5, 127.3, 118.1, 34.3, 29.8, 20.9. **IR**

(Microscope, cm^{-1}) 3323, 2965, 1692, 1514, 1390, 1287, 1049. **HRMS** (EI) for $C_{11}H_{17}N$: calcd. 163.13609; found, 163.13600.

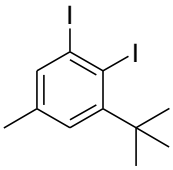
3.6.1.6 Preparation and Analytical Data of 2-Tert-Butyl-6-Iodo-4-Methylaniline (Scheme 3-4, Step 4-5)



2-tert-Butyl-4-methylaniline (0.4 g, 2.45 mmol) was added to a mixture of iodine (0.68 g, 2.45 mmol) and silver (I) sulfate (0.84 g, 2.65 mmol) in 1,2-ethanediol (40 mL) at room temperature. The reaction was stirred until the iodine color completely disappeared. The reaction mixture was filtered through a pad of Celite® 545 using ethyl acetate, Water (100 mL) was added to the filtrate and the mixture was extracted with ethyl acetate (2 X 30 mL). The combined organic layers were washed with aqueous sodium sulfite, brine, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel (hexane/ethyl acetate 3:1) to yield the pure iodinated product in 63% yield as 0.44 g.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.47 (d, 1H, *J* = 0.5 Hz), 7.06 (d, 1H, *J* = 0.5 Hz), 4.26 (bs, 2H), 2.24 (s, 3H), 1.44 (s, 9H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 141.8, 137.4, 134.1, 128.7, 127.8, 89.1, 34.9, 29.7, 20.2. **IR** (Microscope, cm^{-1}) 3498, 3379, 2964, 1614, 1592, 1467, 1443, 1250, 856. **HRMS** (EI) for $C_{11}H_{16}NI$: calcd. 289.03275; found, 289.03275.

3.6.1.7 Preparation and Analytical Data of 1-Tert-Butyl-2,3-diiodo-5-Methylbenzene (3-16)

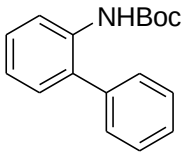


A solution of $NaNO_2$ (0.08 g, 1.14 mmol) in water (0.30 mL) was added dropwise to a mixture of 2-tert-butyl-6-iodo-4-methylaniline (0.30 g, 1.04 mmol) in water (1.8 mL) and concentrated hydrochloric acid (0.50 mL) kept below 5 °C, and the mixture was stirred for 10 min. Then a solution of potassium iodide (0.26 g, 1.55 mmol) in water (0.3 mL) was added. The mixture was stirred for 15 min without cooling, then at 50 °C for 15 min and at 80 °C for 15 min. After that the mixture was cooled to 0 °C, and a solution of 5% aqueous sodium sulfite (15 mL) was added. The organic layer was separated, and the water layer extracted with Et_2O (30 mL, 3 times). The combined organic phases were dried over $MgSO_4$. After removal of the solvents under reduced

pressure the crude product was purified by column chromatography (*n*-pentane) to provide 0.28 g of the desired product as a pale orange solid in 68% yield.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.77 (d, 1H, J = 2.0 Hz), 7.18 (d, 1H, J = 1.9 Hz), 2.23 (s, 3H), 1.55 (s, 9H). **^{13}C-NMR** (100 MHz, DMSO-d_6) δ 153.6, 139.0, 138.4, 128.0, 116.0, 104.5, 38.3, 30.2, 20.6. **IR** (Microscope, cm^{-1}) 2997, 2957, 2917, 1580, 1394, 1254, 996. **HRMS** (EI) for $C_{11}H_{14}I_2$: calcd. 399.91852; found, 399.91828.

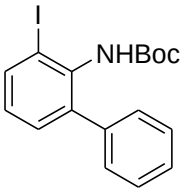
3.6.1.8 Preparation and Analytical Data of Tert-Butyl 2-Biphenylcarbamate (3-17)



A dry, 100 mL RBF connected to a supply of argon was equipped with a Teflon-coated magnetic stirring bar and a condenser. The flask was charged with 2-biphenylamine (10 g, 59.1 mmol), (t-$C_4H_9OOC)_2O$ (15.5 g, 70.9 mmol) and THF (65 mL) and the reaction mixture was stirred at 60 °C overnight. After removal of the solvent under reduced pressure, the residue was dissolved in dichloromethane (50 mL), and then poured into water (50 mL). The organic layer was separated, and the aqueous layer was extracted three times with dichloromethane (25 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the desired product in quantitative yield.

The characterization of the compound matched the previous report: W. M. Seganish, P. DeShong, *J. Org. Chem.* **2004**, *69*, 6790.

3.6.1.9 Preparation and Analytical Data of Tert-Butyl 6-Iodo-2-Biphenylcarbamate (3-18)

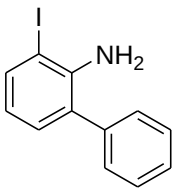


A 50 mL RBF and syringes were carefully flame-dried for the following procedure. To a solution of tert-butyl 2-biphenylcarbamate (1.0 g, 3.71 mmol) in diethyl ether (4.0 mL) was added t-BuLi (1.7 M solution in pentane, 4.8 mL, 8.17 mmol) dropwise at -20 °C under argon atmosphere and the mixture was stirred for 3 hours at the same temperature. The reaction mixture was then cooled down to -90 °C, and a solution of iodine (1.45 g, 4.64 mmol) in diethyl ether (10 mL)

was added dropwise. After adding iodine, the reaction mixture was allowed to be warmed to room temperature and stirred overnight. To the reaction mixture was added saturated aqueous $Na_2S_2O_3$, and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered The crude mixture was purified by silica gel column chromatography using hexane/ethyl acetate (3/1) to provide the desired product in 50% yield (95% BORSM).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, 1H, J = 1.5 Hz, J = 7.9 Hz), 7.36 (m, 6H), 7.03 (dd, 1H, J = 7.8 Hz), 5.98 (bs, 1H), 1.37 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 153.0, 141.8, 139.6, 138.5, 136.2, 130.8, 128.7, 128.6, 128.2, 127.5, 101.2, 80.2, 28.1 . **IR** (Microscope, cm^{-1}) 3280, 2977, 1702, 1484, 1391, 1166, 1085, 756. **HRMS** (EI) for $C_{17}H_{18}O_2IN$: calcd. 395.03824; found, 395.03830.

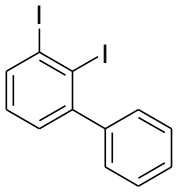
3.6.1.10 Preparation and Analytical Data of Tert-Butyl 6-Iodo-2-Biphenylamine (Scheme 3-5, Step1)



To a solution of tert-butyl 6-iodo-2-biphenylcarbamate **3-18** (1.0 g, 2.53 mmol, 0.2 M) in CH_2Cl_2 (14 mL) was added CF_3COOH (2.5 mL, 33.0 mmol) dropwise at 0 °C under argon atmosphere and the mixture was stirred overnight at room temperature. After consumption of the starting material, water was added to the reaction solution. The mixture was neutralized using 3N aqueous NaOH and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The desired product was isolated in quantitative yield and used without further purification in the following step.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, 1H, *J* = 1.5 Hz, *J* = 7.9 Hz), 7.44 (m, 5H), 7.10 (dd, 1H, *J* = 1.5 Hz, *J* = 7.5 Hz), 6.57 (t, 1H, *J* = 7.7 Hz), 4.23 (s, 2H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 143.9, 139.4, 138.4, 130.6, 129.0, 129.0, 127.8, 127.7, 119.8, 85.0, 53.5. **IR** (Microscope, cm^{-1}) 3469, 3371, 3056, 1607, 1452, 143, 1012, 778. **HRMS** (EI) for $C_{12}H_{10}IN$: calcd. 294.98581; found, 294.98584.

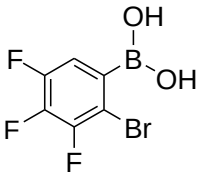
3.6.1.11 Preparation and Analytical Data of 2,3-Diiodobiphenyl (3-19)



A solution of $NaNO_2$ (12.8 mg, 0.186 mmol) in water (40 µL) was added dropwise to a mixture of tert-butyl 6-iodo-2-biphenylamine (50.0 mg, 0.170 mmol) in water (0.3 mL) and concentrated hydrochloric acid (73 µL) kept below 5 °C, and the mixture was stirred for 10 min. Then a solution of potassium iodide (42.2 mg, 0.254 mmol) in water (45 µL) was added. The mixture was stirred for 15 min without cooling, then at 50 °C for 30 min. The mixture was cooled to 0 °C, and a solution of 5% aqueous sodium sulfite (10 mL) was added. The organic layer was separated, and the water layer extracted with Et_2O (15 mL, 3 times). The combined organic phases were dried over $MgSO_4$ and filtered. After removal of the solvents under reduced pressure the crude product was purified by column chromatography (*n*-pentane) to provide 40 mg of the desired product in 68% (98% BORSM).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.89 (dd, 1H, *J* = 1.8 Hz, *J* = 7.8 Hz), 7.42 (m, 3H), 7.26 (m, 2H), 7.22 (dd, 1H, *J* = 1.8 Hz, *J* = 7.5 Hz), 7.10 (dd, 1H, *J* = 7.5 Hz, *J* = 7.8 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 149.7, 146.6, 138.5, 129.2, 128.8, 128.5, 128.0, 127.9, 112.6, 110.0. **IR** (Microscope, cm^{-1}) 3054, 3025, 1606, 1543, 1442, 1378, 757. **HRMS** (EI) for $C_{12}H_8I_2$: calcd. 405.87155; found, 405.87202.

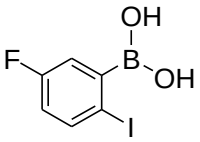
3.6.1.12 Preparation and Analytical Data of 2-Bromo-3,4,5-Trifluorophenyl Boronic Acid (3-21)



To a solution of 1-iodo-2-bromo-3,4,5-trifluorolbenzene (0.5 g, 1.48 mmol) in 40 mL of a mixture of THF and Et_2O (1:1) was added dropwise at -78 °C *iso*propylmagnesium chloride (2 M in THF, 0.74 mL, 1.48 mmol). After the mixture was stirred for 2 h at that temperature, B(O*i*-Pr)$_3$ (1.0 mL, 4.44 mmol) was added. The solution was warmed to room temperature overnight; then a saturated solution of NH_4Cl was added, and the resulting mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with Et_2O (50 mL, 3 times) and dried over Na_2SO_4, filtered and concentrated. To the concentrated sample, hexane was added and the resulting precipitate was isolated to give the desired product in 84% yield.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 2H), 7.35 (m, 1H). **^{13}C-NMR** (125 MHz, DMSO-d_6, ^{1}H and ^{19}F decoupled) δ 149.2, 147.1, 139.1, 116.3, 107.1 (C attached to B not seen on the NMR at 27 0°C). **^{13}C-NMR** (125 MHz, DMSO-d_6, ^{1}H decoupled) δ 149.2 (dd, *J* = 9.2 Hz, *J* = 201.4 Hz), 147.1 (dd, *J* = 9.2 Hz, *J* = 235.2 Hz), 139.1 (ddd, *J* = 16.4 Hz, *J* = 32.0 Hz, *J* = 251.3Hz), 116.3 (d, *J* = 15.9 Hz), 107.1 (d, *J* = 16.2 Hz) (C attached to B not seen on the NMR at 27 0°C). **IR** (Microscope, cm^{-1}) 3224, 3067, 1642, 1595, 1514, 1412, 1359, 1209, 1058. **HRMS** (EI) for $C_6H_3{}^{11}B^{79}BrF_3O_2$: calcd. 253.93616; found, 253.93690.

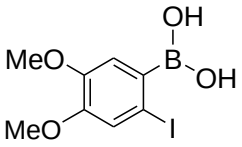
3.6.1.13 Preparation and Analytical Data of 5-Fluoro-2-Iodophenylboronic Acid (3-22)



To a solution of 4-fluoro-1,2-diiodobenzene (1.0 g, 3.08 mmol) in 60 mL of a mixture of THF and Et_2O (1:1) was added dropwise at –78 °C *iso*propylmagnesium chloride (2 M in THF, 1.54 mL, 3.08 mmol). After the mixture was stirred for 2 h at that temperature, B(O*i*-Pr)$_3$ (2.0 mL, 9.20 mmol) was added. The solution was warmed to room temperature overnight; then a saturated solution of NH_4Cl was added, and the resulting mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with Et_2O (50 mL, 3 times) and dried over Na_2SO_4, filtered and concentrated. To the concentrated sample, hexane was added and the resulting precipitate was isolated to give the desired product in 52% yield as a 6:1 mixture of regioisomers.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, 1H, *J* = 5.1 Hz, *J* = 8.7 Hz), 7.5 (dd, 1H, *J* = 3.3 Hz, *J* = 8.9 Hz), 6.87 (ddd, 1H, *J* = 3.2 Hz, *J* = 7.9 Hz, *J* = 8.6 Hz), 5.33 (s, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 140.7 (d, *J* = 7.1 Hz), 123.8 (d, *J* = 20.9 Hz), 119.69 (d, *J* = 22.0 Hz). **IR** (Microscope, cm^{-1}) 3356, 1583, 1566, 1476, 1454, 1387, 1328, 1264. **HRMS** (EI) for $C_6H_5{}^{11}BFIO_2$: calcd. 265.94113; found, 265.94121.

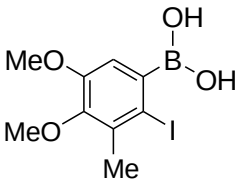
3.6.1.14 Preparation and Analytical Data of 2-Iodo-4,5-Dimethoxyphenyl Boronic Acid (3-26)



To a solution of 1,2-diiodo-4,5-dimethoxybenzene (2.0 g, 5.13 mmol) in 120 mL of a mixture of THF and Et_2O (1:1) was added dropwise at -78 °C isopropylmagnesium chloride (2 M in THF, 2.67 mL, 5.39 mmol). After the mixture was stirred for 2 h at that temperature, B(O*i*-Pr)$_3$ (10.89 mL, 15.39 mmol) was added. The solution was warmed to room temperature overnight; then a saturated solution of NH_4Cl was added, and the resulting mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with Et_2O (50 mL, 3 times) and dried over Na_2SO_4, filtered and concentrated. To the concentrated sample, hexane was added and the resulting precipitate was isolated to give 1.05 g of the pure product in 67% yield.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 2H), 7.17 (s, 1H), 6.80 (s, 1H), 3.69 (s, 3H), 3.68 (s, 3H). **^{13}C-NMR** (125 MHz, DMSO-d_6) δ 149.3, 147.8, 121.0, 116.6, 87.5, 55.4, 55.2 (C attached to B not seen on the NMR at 27 °C). **IR** (Microscope, cm^{-1}) 2959, 1585, 1506, 1373, 1310, 1263, 1199. **HRMS** (ESI) for $C_{10}H_{14}{}^{11}BIO_4INa$ (dimethylester): calcd. 358.99221; found, 358.99259.

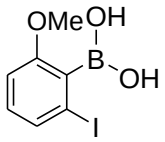
3.6.1.15 Preparation and Analytical Data of 2-Iodo-4,5-Dimethoxy-3-Methylphenylboronic Acid (3-27)



To a solution of 1,2-diiodo-4,5-dimethoxy-3-methylbenzene (2.0 g, 4.95 mmol) in 120 mL of a mixture of THF and Et_2O (1:1) was added dropwise at -78 °C isopropylmagnesium chloride (2 M in THF, 2.72 mL, 5.44 mmol). After the mixture was stirred for 2 h at that temperature, B(O*i*-Pr)$_3$ (10.50 mL, 14.84 mmol) was added. The solution was warmed to room temperature overnight; then saturated solution of NH_4Cl was added, and the resulting mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with Et_2O (50 mL, 3 times) and dried over Na_2SO_4, filtered and concentrated. To the concentrated sample, hexane was added and the resulting precipitate was isolated to give 0.90 g of the pure product in 56% yield.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.14 (s, 2H), 6.73 (s, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 2.27 (s, 3H). **^{13}C-NMR** (100 MHz, DMSO-d_6) δ 152.1, 146.8, 133.9, 114.9, 95.2, 60.2, 55.9, 21.8. (C attached to B not seen on the NMR at 27 °C). **IR** (Microscope, cm^{-1}) 3283, 2944, 1577, 1939, 1344, 1077, 993. **HRMS** (EI) for $C_9H_{12}{}^{11}BIO_4$: calcd. 321.98733; found, 321.98740.

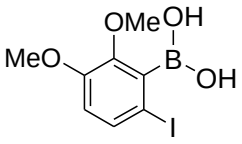
3.6.1.16 Preparation and Analytical Data of 2-Iodo-6-Methoxyphenylboronic Acid (3-32)



To a solution of 1,2-diiodo-3-methoxybenzene (0.45 g, 1.25 mmol) in 30 mL of a mixture of THF and Et_2O (1:1) was added dropwise at -78 °C *iso*propylmagnesium chloride (2 M in THF, 0.70 mL, 1.37 mmol). After the mixture was stirred for 2 h at that temperature, B(O*i*-Pr)$_3$ (2.7 mL, 3.75 mmol) was added. The solution was warmed to room temperature overnight; then a saturated solution of NH_4Cl was added, and the resulting mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with Et_2O (50 mL, 3 times) and dried over Na_2SO_4, filtered and concentrated. To the concentrated sample, hexane was added and the resulting precipitate was isolated to give the desired product in 59% yield.

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.11 (bs, 2H), 7.26 (d, 1H, *J*=7.7Hz), 6.99 (dd, 1H, *J* = 7.9 Hz, *J* = 8.0 Hz), 6.91 (d, 1H, *J* = 8.3 Hz), 3.68 (s, 3H). **^{13}C-NMR** (125 MHz, DMSO-d_6) δ 161.5, 130.6, 129.7, 109.5, 98.7, 55.5 (C attached to B not seen on the NMR at 27 °C). **IR** (Microscope, cm^{-1}) 3220, 2970, 2836, 1579, 1554, 1455, 1420, 1327, 1141. **HRMS** (EI) for $C_7H_8{}^{11}BIO_3$: calcd. 277.85209; found, 277.96168.

3.6.1.17 Preparation and Analytical Data of 6-Iodo-2,3-Dimethoxyphenyl boronic Acid (3-33)

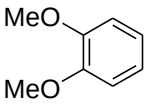


To a solution of 1,2-diiodo-3,4-dimethoxybenzene (0.68 g, 1.74 mmol) in 40 mL of a mixture of THF and Et_2O (1:1) was added dropwise at -78 °C *iso*propylmagnesium chloride (2 M in THF, 0.96 mL, 1.91 mmol). After the mixture was stirred for 2 h at that temperature, B(O*i*-Pr)$_3$ (3.7 mL, 5.23 mmol) was added. The solution was warmed to room temperature overnight; then a saturated solution of NH_4Cl was

added, and the resulting mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with Et_2O (40 mL, 3 times) and dried over Na_2SO_4, filtered and concentrated. To the concentrated sample, hexane was added and the resulting precipitate was isolated and recrystallized in ether/hexanes mixture to give the desired product in 39% yield.

^{1}H-NMR (500 MHz, CD_3OD) δ 7.40 (d, 1H, *J* = 8.7 Hz), 6.76 (d, 1H, *J* = 8.6 Hz), 3.82 (s, 3H), 3.77 (s, 3H). **^{13}C-NMR** (125 MHz, CD_3OD) δ 153.5, 152.2, 135.3, 116.4, 85.8, 61.360, 56.251. **IR** (Microscope, cm^{-1}) 2967, 1596, 1458, 1377, 1265, 1232, 998. **HRMS** (EI) for $C_8H_{10}{}^{11}BIO_4$: calcd. 307.97168; found, 307.97176.

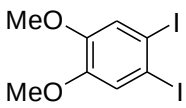
3.6.1.18 Preparation and Analytical Data of 1,2-Dimethoxybenzene (3-34)



In a round bottom flask, catechol (10.0 g, 90.0 mmol), MeI (50.0 g, 354.0 mmol), and K_2CO_3 (42.7 g, 309.0 mmol) were dissolved in acetone (40.0 mL). The reaction mixture was stirred at room temperature for 1 h, then at 60 °C overnight. The reaction mixture was concentrated and chromatographed on silica gel using EtOAc/Hexanes (5:95). A colorless liquid was isolated in 100% yield (12.43 g).

The characterization of the compound matched previous report: (a) P. M. Paduraru; R. T. W. Popoff; R. Nair; R. Gries; G. Gries; E. Plettner, *J. Comb. Chem.* **2008**, *10* (1), 123.

3.6.1.19 Preparation and Analytical Data of 1,2-Diiodo-4,5-Dimethoxybenzene (3-35)

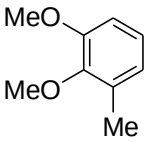


In a round bottom flask, 1,2-dimethoxybenzene (2.1 g, 15.2 mmol), I_2 (10.42 g, 33.44 mmol), and $Hg(OAc)_2$ (10.65 g, 33.44 mmol) were dissolved in CH_2Cl_2 (40.0 mL). The reaction mixture was stirred at room temperature and monitored by TLC. Upon completion, the reaction mixture was filtered and washed with an aqueous solution of sodium thiosulfate, extracted with CH_2Cl_2 and washed with brine. The CH_2Cl_2 solution was

dried with Na_2SO_4, filtered, concentrated and chromatographed on silica gel using EtOAc/hexane (10:90). A light orange solid was isolated in 67% yield (4.0 g).

The characterization of the compound matched previous report: (a) J. J. Pak; J. L. Mayo; E. Shurdha, *Tetrahedron Lett.* **2006**, *47*, 233.

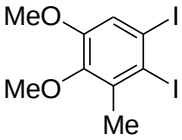
3.6.1.20 Preparation and Analytical Data of 1,2-Dimethoxy-3-Methylbenzene (3-36)



In a round bottom flask, 3-methyl catechol (5.0 g, 40.3 mmol), MeI (22.3 g, 157.1 mmol), and K_2CO_3 (18.9 g, 136.9 mmol) were dissolved in acetone (20.0 mL). The reaction mixture was stirred at room temperature for 1 h, then at 60 ^oC overnight. The reaction mixture was concentrated and chromatographed on silica gel using EtOAc/Hexane (5:95). A pale yellow liquid was isolated in 100% (6.13 g).

The characterization of the compound matched previous report: (a) L. Xing; X. Wang; X. Cheng; R. Zhu; B. Liu; Y. Hu, *Tetrahedron Lett.* **2007**, *63, (38)*, 9382.

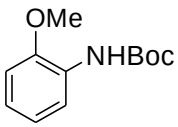
3.6.1.21 Preparation and Analytical Data of 1,2-Diiodo-4,5-Dimethoxy-3-Methylbenzene (3-37)



In a round bottom flask, 1,2-dimethoxy-3-methylbenzene (2.0 g, 13.15 mmol), I_2 (9.02 g, 28.92 mmol), and $Hg(OAc)_2$ (9.22 g, 28.92 mmol) were dissolved in CH_2Cl_2 (40.0 mL). The reaction mixture was stirred at room temperature and monitored by TLC. Upon completion, the reaction mixture was filtered and washed with aqueous solution of sodium thiosulfate, extracted with CH_2Cl_2 and washed with brine. The CH_2Cl_2 solution was dried with Na_2SO_4, filtered, concentrated and chromatographed on silica gel using EtOAc/hexane (10:90). A light orange solid was isolated in 68% yield (3.61 g).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 2.53 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 153.3, 146.8, 138.1, 121.2, 104.7, 102.6, 60.7, 56.3, 25.7. **IR** (Microscope, cm^{-1}) 2998, 2959, 1562, 1466, 1436, 1288, 1252, 1223, 1006, 833. **HRMS** (EI) for $C_9H_{10}I_2O_2$: calcd. 403.87704; found, 403.87682.

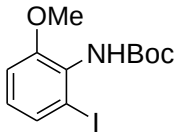
3.6.1.22 Preparation and Analytical Data of Tert-Butyl 2-Methoxyphenylcarbamate (3-38)



A dry, 100 mL RBF connected to a supply of argon was equipped with a Teflon-coated magnetic stirring bar and a condenser. The flask was charged with *ortho*-anisidine (5.0 g, 40.6 mmol), (t-$C_4H_9OOC)_2O$ (9.74 g, 44.6 mmol) and THF (60 mL) and the reaction mixture was stirred at 60 °C overnight. After removal of the solvent under reduced pressure, the residue was dissolved in dichloromethane (50 mL), and then poured into water (50 mL). The organic layer was separated, and the aqueous layer was extracted three times with dichloromethane (15 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the desired product in 100% yield (9.0 g).

The characterization of the compound matched the previous report: I. Nakamura, U. Yamagishi, D. Song, S. Konta, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2007**, *46*, 2284.

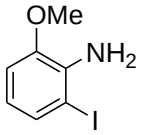
3.6.1.23 Preparation and Analytical Data of Tert-Butyl 2-Iodo-6-Methoxyphenylcarbamate (Scheme 3-12, Step 1)



A 250 mL RBF and syringes were carefully flame-dried for the following procedure. To a solution of tert-butyl 2-methoxyphenylcarbamate **3-38** (1.5 g, 6.73 mmol) in diethyl ether (13 mL) was added *t*-BuLi (1.7 M solution in pentane, 15.8 mL, 26.9 mmol) dropwise at -20 °C under argon atmosphere and the mixture was stirred for 3 hours at the same temperature. The reaction mixture was then cooled down to -90 °C, and a solution of iodine (7.38 g, 23.5 mmol) in diethyl ether was added dropwise. After adding iodine, the reaction mixture was allowed to warm to room temperature and stirred overnight. To the reaction mixture was then added saturated aqueous $Na_2S_2O_3$, and the mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The crude mixture was purified by silica gel column chromatography using hexane/ethyl acetate (3/1) to provide the desired product in 50% yield (1.2 g) (95% BORSM).

The characterization of the compound matched the previous report: I. Nakamura, U. Yamagishi, D. Song, S. Konta, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2007**, *46*, 2284.

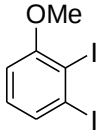
3.6.1.24 Preparation and Analytical Data of 2-Iodo-6-Methoxybenzenamine (3-39)



To a solution of tert-butyl 2-iodo-6-methoxyphenylcarbamate (1.0 g, 2.86 mmol, 0.2 M) in CH_2Cl_2 (14 mL) was added CF_3COOH (2.87 mL, 37.2 mmol) dropwise at 0 °C under argon atmosphere and the mixture was stirred for overnight at room temperature. After consumption of the starting material, water was added to the reaction solution. The mixture was neutralized using 3N aqueous NaOH and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The desired product was isolated in 100% yield (0.71 g) and used without further purification in the following step.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.27 (dd, 1H, *J* = 1.2 Hz, *J* = 8.1 Hz), 6.75 (dd, 1H, *J* = 1.2 Hz, *J* = 8.0 Hz), 6.49 (t, 1H, *J* = 8.0 Hz), 4.26 (s, 1H), 3.85 (s, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 146.5, 137.4, 130.4, 119.2, 109.9, 83.2, 55.7. **IR** (Microscope, cm^{-1}) 3466, 3368, 3063, 2958, 2834, 1605, 1568, 1478, 1278, 1210, 1031. **HRMS** (EI) for C_7H_8INO: calcd. 248.96507; found, 248.96570.

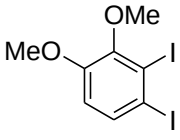
3.6.1.25 Preparation and Analytical Data of 1,2-Diiodo-3-Methoxybenzene (3-30)



A solution of $NaNO_2$ (0.18 g, 2.65 mmol) in water (0.60 mL) was added dropwise to a mixture of 2-iodo-6-methoxybenzenamine **3-39** (0.50 g, 2.40 mmol) in water (4.0 mL) and concentrated hydrochloric acid (1.0 mL) below 5 °C, and the mixture was stirred for 10 min. Then a solution of potassium iodide (0.56 g, 3.4 mmol) in water (0.60 mL) was added. The mixture was stirred for 15 min without cooling, then at 50 °C for 15 min and at 80 °C for 15 min. After that the mixture was cooled to 0 °C, and a solution of 5% aqueous sodium sulfite (15 mL) was added. The organic layer was separated, and the water layer extracted with Et_2O (30 mL, 3 times). The combined organic phases were dried over $MgSO_4$ and filtered. After removal of the solvents under reduced pressure the crude product was purified by column chromatography (*n*-pentane) to provide 0.63 g of the desired product in 90% yield as an orange solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, 1H, *J* = 1.3 Hz, *J* = 7.9 Hz), 7.04 (dd, 1H, *J* = 7.9 Hz, *J* = 8.1 Hz), 6.74 (dd, 1H, *J* = 1.2 Hz, *J* = 8.3 Hz), 3.85 (s, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 159.8, 132.0, 130.8, 110.1, 109.8, 100.8, 57.1. **IR** (Microscope, cm^{-1}) 3062, 2962, 1562, 1452, 1277, 1258, 1032, 1009, 764. **HRMS** (EI) for $C_7H_6I_2O$: calcd. 359.85083; found, 359.85073.

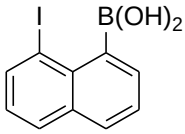
3.6.1.26 Preparation and Analytical Data of 1,2-Diiodo-3,4-Dimethoxybenzene (3-40)



In a round bottom flask, 1-iodo-2,3-dimethoxybenzene (0.5 g, 1.89 mmol), I_2 (1.30 g, 4.16 mmol), and $Hg(OAc)_2$ (1.33 g, 4.16 mmol) were dissolved in CH_2Cl_2 (35 ml). The reaction mixture was stirred at room temperature and monitored by TLC. Upon completion, the reaction mixture was filtered and washed with an aqueous solution of sodium thiosulfate, extracted with CH_2Cl_2 and washed with brine. The CH_2Cl_2 solution was dried with Na_2SO_4, filtered, concentrated and chromatographed on silica gel using EtOAc/hexanes (1/4) to provide the desired product in 98% yield (0.72 g) as a colorless liquid.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.21 (d, 1H, *J* = 8.7 Hz), 6.34 (d, 1H, *J* = 8.7 Hz), 3.48 (s, 1H), 3.45 (s, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 151.7, 149.9, 134.2, 114.3, 106.6, 96.1, 59.9, 55.8. **IR** (Microscope, cm^{-1}) 3001, 2852, 1565, 1507, 1462, 1371, 1286, 1028, 1000, 794. **HRMS** (EI) for $C_8H_8I_2O_2$: calcd. 389.86139; found, 389.86158.

3.6.1.27 Preparation and Analytical Data of 8-Iodonaphthalen-1-yl-1-Boronic Acid (3-52)

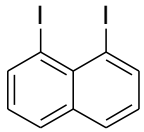


Diisopropyl 8-iodonaphthalen-1-yl-1-boronate **3-57** was dissolved in methanol and the solvent was evaporated under reduced pressure three times. After concentrating the mixture under reduced pressure, a drop of water was added to the residue and the desired product was isolated as colorless crystals in 73% yield.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.15 (dd, 1H, *J* = 1.3 Hz, *J* = 7.3 Hz), 8.10 (s, 2H), 7.94 (dd, 1H, *J* = 1.2 Hz, *J* = 8.3 Hz), 7.84 (dd, 1H, *J* = 1.9 Hz, *J* = 7.7 Hz), 7.49 (m, 2H), 7.20 (dd, 1H, *J* = 7.3 Hz, *J* = 8.0 Hz). **^{13}C-NMR** (125 MHz, DMSO-d_6) δ 138.4, 135.7, 134.2,

131.8, 129.3, 128.7, 126.5, 125.5, 100.1(C attached to B not seen on the NMR at 27 °C). **IR** (Microscope, cm^{-1}) 3314, 3049, 1601, 1368, 1328, 1216, 813, 765. **HRMS** (ESI) for $C_{10}H_8{}^{11}BClIO_2$ $(M+Cl)^-$: calcd. 332.93579; found, 332.93511.

3.6.1.28 Preparation and Analytical Data of 1,8-Diiodonaphthalene (3-56)

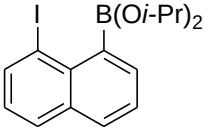


To a solution of 1,8-naphthalenediamine (5.0 g, 31.6 mmol) in ether, HCl (1.0 mL, 12 M) was added dropwise at 0 °C. The mixture was stirred for 30 min at the same temperature. Reaction mixture was filtered and the solid was washed with ether and dried under reduced pressure. The desired chloride salt was isolated in quantitative yield and used without further purification in the following step.

A solution of $NaNO_2$ (1.66 g, 24.1 mmol) in water (10 mL) was added dropwise to a mixture of 1,8-naphthalenediammonium chloride (2.53 g, 10.9 mmol) in water (15 mL) and concentrated hydrochloric acid (3.0 mL) below 5 °C, and the mixture was stirred for 10 min. Then a solution of potassium iodide (6.36 g, 38.3 mmol) in water (6.0 mL) was added. The mixture was stirred for 15 min without cooling, then at 50 °C for 15 min and at 80 °C for 40 min. After that the mixture was cooled to 0 °C, and a solution of 5% aqueous sodium sulfite (30 mL) was added. The organic layer was separated, and the water layer extracted with Et_2O (30 mL, 3 times). The combined organic phases were dried over $MgSO_4$ and filtered. After removal of the solvents under reduced pressure the crude product was purified by column chromatography (*n*-pentane) to provide the desired product as a white solid in 25% yield (3.0 g).

The characterization of the compound matched the previous report: P. Prabhakaran, V. G. Puranik, J. N. Chandran, P. R. Rajamohanan, H. J. Hofmann, G. J. Sanjayan, *Chem. Commun.* **2009**, 3446.

3.6.1.29 Preparation and Analytical Data of Diisopropyl 8-Iodonaphthalen-1-yl-1-Boronate (3-57)

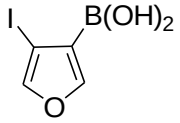


To a solution of 1,8-diiodonaphthalene (0.70 g, 1.84 mmol) in 40 mL of a mixture of THF and Et_2O (1:1) was added dropwise at –78 °C *iso*propylmagnesium chloride (2 M in THF, 1.0 mL, 2.02 mmol). After the mixture was stirred for 2 h at that temperature, $B(Oi\text{-}Pr)_3$ (3.9 mL,

5.52 mmol) was added. The solution was warmed to room temperature overnight; then a saturated solution of NH_4Cl was added, and the resulting mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with Et_2O (40 mL, 3 times). the combined ether extracts were dried over Na_2SO_4, filtered, concentrated and the crude product was purified by column chromatography (hexanes/ethyl acetate 3/1) to provide the desired product in 95% yield (0.66 g).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, 1H, *J* = 1.3 Hz, *J* = 7.3 Hz), 7.85 (dd, 1H, *J* = 1.3 Hz, *J* = 8.2 Hz), 7.78 (ddd, 1H, *J* = 0.36 Hz, *J* = 1.4 Hz, *J* = 8.0 Hz), 7.57 (dd, 1H, *J* = 1.4 Hz, *J* = 6.8 Hz), 7.48 (dd, 1H, *J* = 6.8 Hz, *J* = 8.1 Hz), 7.15 (dd, 1H, *J* = 7.3 Hz, *J* = 8.1 Hz), 4.27 (sept, 2H, *J* = 6.1 Hz), 1.30 (d, 6H, *J* = 6.1 Hz), 1.14 (d, 6H, *J* = 6.1 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 138.8, 136.8, 134.8, 132.4, 129.8, 129.6, 126.5, 125.6, 99.5, 66.7, 24.1, (C attached to B not seen on the NMR at 27 °C). **IR** (Microscope, cm^{-1}) 2971, 2927, 1375, 1314, 1295, 1138, 1117, 805. **HRMS** (ESI) for $C_{16}H_{21}{}^{11}BIO_2$ $(M+H)^+$: calcd. 383.06767; found, 383.06693.

3.6.1.30 Preparation and Analytical Data of 4-Iodofuran-3-yl-3-Boronic Acid (3-75)

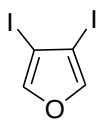


To a solution of 3,4-diiodofuran **3-76** (1.27 g, 3.98 mmol) in 60 mL of a mixture of THF and Et_2O (1:1) was added dropwise at –78 °C *iso*propylmagnesium chloride (2 M in THF, 4.37 mmol). After the mixture was stirred for 2 h at that temperature, B(O*i*-Pr)$_3$ (6.91 mL, 11.9 mmol) was added. The solution was warmed to room temperature overnight; then a saturated solution of NH_4Cl was added, and the resulting mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with Et_2O (40 mL, 3 times) and the ether extracts were dried over Na_2SO_4, filtered, concentrated and the crude product was purified by column chromatography (hexanes/ethyl acetate 3/1) to give the desired product in 54% yield (0.51 g).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 2H), 7.77 (d, 1H, *J* = 2.0 Hz), 7.75 (d, 1H, *J* = 2.0 Hz). **^{13}C-NMR** (125 MHz, DMSO-d_6) δ 151.6, 147.2, 70.8 (C attached to B not seen

on the NMR at 27 °C). **IR** (Microscope, cm^{-1}) 3127, 1537, 1368, 1333, 1112, 982. **HRMS** (ESI) for $C_4H_3{}^{11}BIO_3$ $(M-H)^-$: calcd. 236.9226; found, 236.9222.

3.6.1.31 Preparation and Analytical Data of 3,4-Diiodofuran (3-76)

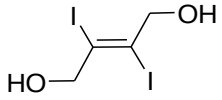


To a 2 L three-neck flask fitted with a stirrer, a water cooled condenser, and a 100 mL dropping funnel was added 2,3-diiodo-2-butene-1,4-diol (25 g, 73.5 mmol), NMP (300 mL), and hexanes (500 mL). The mixture was stirred vigorously at 85 °C. To this solution was added a preheated (85 °C) solution of $K_2Cr_2O_7$ (21.6 g, 73.5 mmol) in H_2SO_4 (3 M, 90 mL) dropwise in portions (30 mL) over 1 h. The biphasic mixture was stirred at 85 °C for 5 h and then allowed to cool to room temperature. The hexane layer was decanted, and the remaining solvent was extracted once with hexanes (250 mL).

The hexane layers were combined, washed successively with water (2 x 120 mL), a saturated $Na_2S_2O_3$ solution (120 mL), and brine (120 mL), dried, passed over a short plug of silica gel, and concentrated to give the desired product in 7% yield (1.6 g) as a pale yellow liquid

The characterization of the compound matched the previous report: C. C. Hughes, J. J. Kennedy-Smith, D. Trauner, *Org. Lett.* **2003**, *5*, 4113.

3.6.1.32 Preparation and Analytical Data of (E)-2,3-Diiodobut-2-ene-1,4-Diol (3-80)



2-Butyne-1,4-diol (2.0 g, 23.2 mmol), iodine (6.0 g, 23.6 mmol), potassium iodide (8.0 g, 48.2 mmol) and water (70 mL) were heated to 70 °C on a steambath for an hour. The precipitate was separated, washed and crystallized from water to provide the desired iodinated product in 81% yield (6.4 g).

^{1}H-NMR (400 MHz, CD_3COCD_3, D_2O) δ 4.36 (s, 4H), 3.68 (s, 2H). **^{13}C-NMR** (100 MHz, CD_3COCD_3, D_2O) δ 96.5, 69.4.

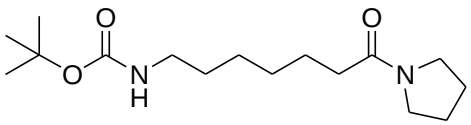
3.6.2 General Procedure for Direct Amidation

Into a 25 mL round bottom flask equipped with a stir bar was added carboxylic acid (0.55 mmol, 1.1 equiv), 5-methoxy-2-iodophenylboronic acid **3-44** (0.05 mmol, 10 mol%) and 1 g of activated 4Å molecular sieves (preactivation overnight in an oven

at ~250 °C or 2h in a Kugelrohr at 250 °C under high vacuum). Solvent (5 mL) was added and the mixture was stirred for 10 min. Then, amine (0.5 mmol, 1 equiv) was added (in order to get reproducible results, it is necessary to use a gas tight 100 µl syringe). The resulting mixture was stirred at room temperature (24-25 °C). The reaction mixture was filtered through a pad of Celite ® 545, the filtrate was washed with aqueous acidic solution (pH = 4), aqueous basic solution (pH = 10-11) and brine. The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and evaporated to yield the title amide product.

3.6.2.1 Amide Preparation and Characterization Data

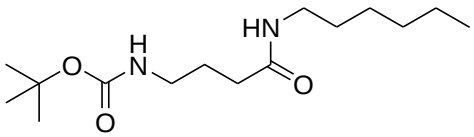
3.6.2.1.1 *Tert*-Butyl 7-Oxo-7-(Pyrrolidin-1-yl)Heptylcarbamate **3-65** (**Table 3-8, Entry 6**)



The title compound was prepared using the general procedure for the organocatalytic amidations. (6 h reaction time, 95% yield in DCM, 85% yield in THF).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.65 (s, 1H), 3.35 (td, 4H, *J* = 6.9 Hz, *J* = 18.4 Hz), 3.02 (dd, 2H, *J* = 6.5 Hz, *J* = 13.1 Hz), 2.17 (t, 2H, *J* = 7.4 Hz), 1.87 (m, 2H) , 1.77 (m, 2H), 1.56 (m, 2H), 1.36 (m, 11H), 1.26 (m, 4H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ171.6, 155.9, 79.5, 46.5, 45.5, 34.5, 29.0, 28.3, 26.5, 26.0, 24.6, 24.3. **IR** (Microscope, cm^{-1}) 3325, 2973, 2932, 1708, 1631, 1526, 1446, 1173. **HRMS** (ESI) for $C_{16}H_{31}N_2O_3$ $(M+H)^+$: calcd. 299.2329; found, 299.2337.

3.6.2.1.2 *Tert*-Butyl 3-(Hexylcarbamoyl)Propylcarbamate **3-66** (**Table 3-8, Entry 7**)

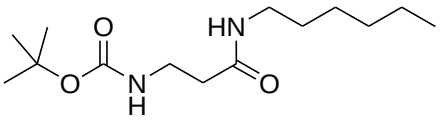


The title compound was prepared using the general procedure for the organocatalytic amidations (2 h reaction time, 87% yield in DCM, 65% yield in THF).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.67 (dd, 1H, *J* = 3.1 Hz, *J* = 8.6 Hz), 6.41 (bs, 1H), 3.17 (m, 6H), 2.38 (t, 2H, *J* = 7.2 Hz), 2.21 (t, 2H, *J* = 7.0 Hz), 1.79 (m, 4H), 1.23-1.55 (m,

14H). **^{13}C-NMR** (100 MHz, $CDCl_3$) 177.0, 159.2, 79.8, 39.7, 31.4, 31.2, 29.3, 28.3, 26.5, 26.5, 25.2, 22.5, 13.9. **IR** (Microscope, cm^{-1}) 3320, 2958, 2931, 1692, 1651, 1534, 1172. **HRMS** (ESI) for $C_{15}H_{31}N_2O_3$ $(M+H)^+$: calcd. 287.2329; found, 287.2333.

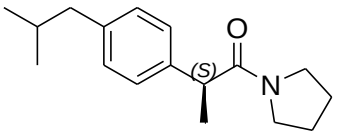
3.6.2.1.3 *Tert*-Butyl 2-(Hexylcarbamoyl)Ethylcarbamate **3-67** (**Table 3-8, Entry 8**)



The title compound was prepared using the general procedure for the organocatalytic amidations (2 h reaction time, 86% yield in DCM, 73% yield in THF).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.62 (dd, 1H, *J* = 3.2 Hz, *J* = 8.6 Hz), 6.45 (s, 1H), 3.35 (m, 2H), 3.18 (m, 1H), 2.51 (m, 2H), 2.39 (m, 1H), 1.10-1.40 (m, 18H), 1.24 (m, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$) 176.1, 156.0, 79.5, 39.7, 35.9, 34.4, 31.4, 29.2, 28.3, 26.5, 22.4, 13.9. **IR** (Microscope, cm^{-1}) 3340, 2977, 2933, 1699, 1521, 1393, 1282, 1171. **HRMS** (ESI) for $C_{14}H_{28}N_2NaO_3$ $(M+Na)^+$: calcd. 295.1992; found, 295.1994.

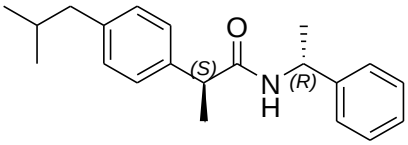
3.6.2.1.4 (S)-2-(4-Isobutylphenyl)-1-(Pyrrolidin-1-Yl)Propan-1-One **3-69** (**Table 3-8, Entry 10**)



The title compound was prepared using the general procedure for the organocatalytic amidations. (8 h reaction time, 51% yield in DCM, 70% yield in THF after chromatography, 25% EtOAc/hexanes). Special care should be taken with the basic extraction for base sensitive substrates. A pH higher than 9 for the aqueous solution should be avoided.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.19 (d, 2H, *J* = 8.0 Hz), 7.07 (d, 2H, *J* = 8.3 Hz), 3.70 (q, 1H, *J* = 6.9Hz), 3.53 (m, 1H), 3.43 (m, 2H), 3.17 (m, 1H), 2.43 (d, 2H, *J* = 7.2 Hz), 1.81 (m, 5H), 1.43 (d, 3H, *J* = 6.9 Hz), 0.89 (d, 6H, *J* = 6.6 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) 172.4, 140.0, 138.9, 129.4, 127.2, 46.2, 45.9, 45.0, 44.6, 30.2, 26.0, 24.1, 22.4, 20.3. **IR** (Microscope, cm^{-1}) 2954, 2869, 1642, 1453, 1340. **HRMS** (ESI) for $C_{17}H_{26}NO$ $(M+H)^+$: calcd. 260.2009; found, 260.2014.

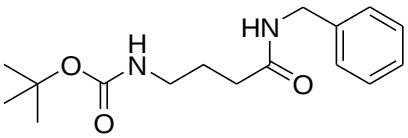
3.6.2.1.5 (2S)-2-(4-Isobutylphenyl)-*N*-((R)-1-Phenylethyl)Propanamide **3-70** (**Table 3-8, Entry 11**)



The title compound was prepared using the general procedure for the organocatalytic amidations (2 h reaction time, 62% yield in DCM, 83% yield in THF after chromatography, 25% EtOAc/hexanes). Special care should be taken with the basic extraction for base sensitive substrates. A pH higher than 9 for the aqueous solution should be avoided.

The characterization of the compound matched previous result: (a) R. M. Al-Zoubi, O. Marion, D. G. Hall, *Angew. Chem. Int. Ed.* **2008**, *47*, 2876.

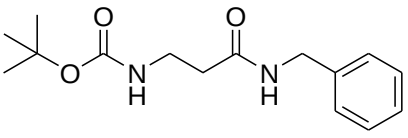
3.6.2.1.6 *Tert*-Butyl 3-(Benzylcarbamoyl)Propylcarbamate (**Scheme 3-8, Eq.1**)



The title compound was prepared using the general procedure for the organocatalytic amidations. (60 min reaction time, 73% yield in DCM, 53% yield in THF, 62% in toluene). Using catalyst **3-75** (60 min reaction time, 86% yield in DCM, 74% yield in THF, 77% in toluene).

The characterization of the compound matched previous reports: (a) M. S. Coumar, et. al., *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1274. (b) H. Tsu, et. al. *J. Med. Chem.* **2006**, *49*, 373.

3.6.2.1.7 Tert-Butyl 2-(Benzylcarbamoyl)Ethylcarbamate (**Scheme 3-8, Eq.2**)



The title compound was prepared using the general procedure for the organocatalytic amidations. (60 min reaction time, 59% yield in DCM, 35% yield in THF, 71% in toluene). Using catalyst **3-75** (60 min reaction time, 68% yield in DCM, 43% yield in THF, 75% in toluene).

The characterization of the compound matched previous report: H. Kotsuki, M. Iwasaki, H. Nishizawa, *Tetrahedron Lett.* **1992**, *33*, 4945.

3.7 References

[1] R. M. Al-Zoubi, O. Marion, D. G. Hall, *Angew. Chem. Int. Ed.* **2008**, *47*, 2876.

[2] C. W. Moth, J. J. Prusakiewicz, L. J. Marnett, T. P. Lybrand, *J. Med. Chem.* **2005**, *48*, 3613

[3] A. S. Kalgutkar, A. B. Marnett, B. C. Crews, R. P. Remmel, L. J. Marnett, *J. Med. Chem.* **2000**, *43*, 2860

[4] K. Ishihara, *Tetrahedron* **2009**, *65*, 1085.

[5] T. Maki, K. Ishihara, H. Yamamoto, *Synlett* **2004**, 1355.

[6] K. Ishihara, S. Ohara, H. Yamamoto, D. T. Amos, R. L. Danheiser, *Org. Synth.* **2002**, *79*, 176.

[7] K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4196.

[8] K. Arnold, A. S. Batsanov, B. Davies, A. Whiting, *Green Chem.* **2008**, *10*, 124.

[9] K. Arnold, B. Davies, R. L. Giles, C. Grosjean, G. E. Smith, A. Whiting, *Adv. Synth. Catal.* **2006**, *348*, 813.

[10] H. A. Wegner, H. Reisch, K. Rauch, A. Demeter, K. A. Zachariasse, A. de Meijere, L. T. Scott, *J. Org. Chem.* **2006**, *71*, 9080.

[11] Y. Zhang, T. Ren, W. Zhu, Y. Xie, *Org. Prep. Proced. Int.* **2007**, *39*, 90.

[12] J. J. Pak, J. L. Mayo, E. Shurdha, *Tetrahedron Lett.* **2006**, *47*, 233.

[13] E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2008**, *130*, 14084.

[14] E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2007**, *129*, 6716.

[15] R. Johnsson, A. Meijer, U. Ellervik, *Tetrahedron* **2005**, *61*, 11657.

[16] C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827.

[17] S.-Y. Han, Y.-A. Kim, *Tetrahedron* **2004**, *60*, 2447.

[18] F. Albericio, *Curr. Opin. Chem. Biol.* **2004**, *8*, 211.

[19] F. Brotzel, Y. C. Chu, H. Mayr, *J. Org. Chem.* **2007**, *72*, 3679.

[20] G. A. Kraus, X. Wang, *Synth. Commun.* **1998**, *28*, 1093.

[21] T. Marcelli, *Angew. Chem. Int. Ed.* **2010**, *49*, 6840.

[22] A. Kovács;, Z. Varga, *Coord. Chem. Rev.* **2006**, *250*, 710

[23] L. Brammer, E. A. Bruton, P. Sherwood, *Cryst. Growth Des.* **2001**, *1*, 277

[24] H. Charville, D. Jackson, G. Hodges, A. Whiting, *Chem. Commun.* **2010**, *46*, 1813.

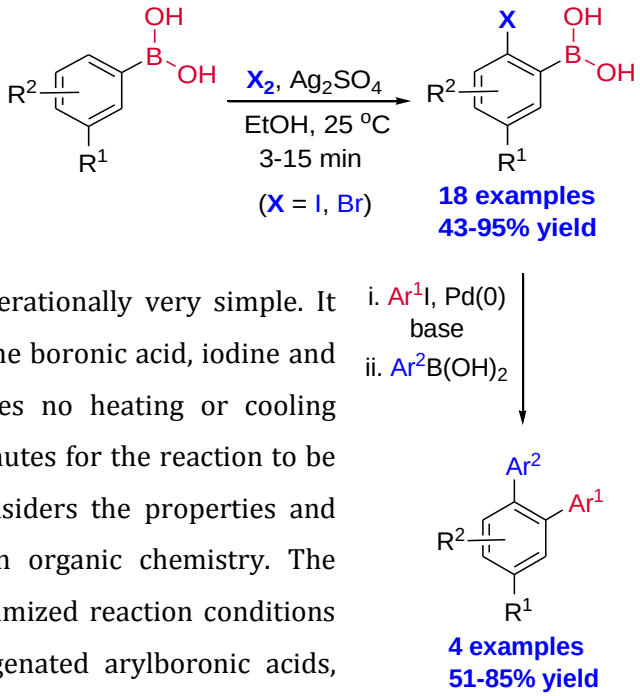
[25] I. Kaljurand, A. Kütt, L. Sooväli, T. Rodima, V. Mäemets, I. Leito, I. A. Koppel, *J. Org. Chem.* **2005**, *70*, 1019

[26] A. Kütt, I. Leito, I. Kaljurand, L. Sooväli, V. M. Vlasov, L. M. Yagupolskii, I. A. Koppel, *J. Org. Chem.* **2006**, *71*, 2829

[27] T. Clark, M. Hennemann, J. S. Murray, P. Politzer, *J. Mol. Model.* **2007**, *13*, 291

Mild Silver(I)-Mediated Regioselective Iodination and Bromination of Arylboronic Acids and Their Application Toward Chemoselective Suzuki-Miyaura Coupling

A convenient and effective method for mild and regioselective iodination and bromination of free arylboronic acids has been discovered. This method provides the desired *ortho*-halogenated aryboronic acids in moderate to high yield (43% - 95%). In this methodology, the reaction is operationally very simple. It employs equimolar amounts of the boronic acid, iodine and silver sulfate or nitrate, requires no heating or cooling source, and needs only a few minutes for the reaction to be completed. The first section considers the properties and applications of boronic acids in organic chemistry. The second section discloses the optimized reaction conditions for the synthesis of *ortho*-halogenated arylboronic acids, which are known to be very active catalysts toward direct amidation and cycloaddition, as demonstrated in Chapters Two and Three. In the third section, a remarkably chemoselective Suzuki-Miyaura coupling is developed in one-pot fashion to provide the di– and triaryl derivatives in good yields, which are core chemical structures in a number of biologically active natural products.



4.1 Introduction

Boronic acids and their ester derivatives have been the subject of research for 150 years, and their synthesis, applications and properties in organic chemistry and medicine have been recently reviewed.[1]

Structurally, boronic acids comprise a trivalent boron connected to one organic substituent and two hydroxyl groups. Three covalent bonds with 6 valence electrons make the boron deficient of two more electrons. An empty low energy P orbital is orthogonal to the other three covalent bonds which are oriented in a trigonal planar geometry.[1] Boronic acids are relatively more stable to air oxidation than other organoboron compounds, such as borinic acids which result from the first oxidation of boranes. The third oxidation of borane results in boric acid which is very stable and relatively benign to humans. The structure of boronic acid and other types of organoboron compounds are presented in **Figure 4-1**.[1]

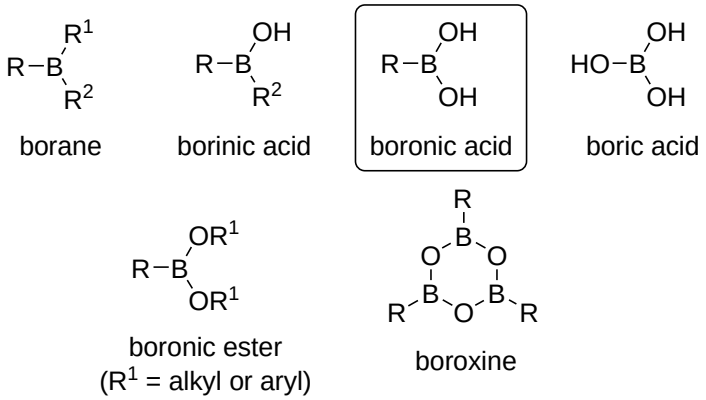
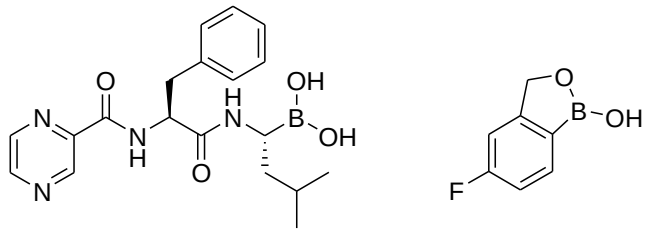


Figure 4-1: Oxygenated organoboron compounds.[1]

Furthermore, boronic acids have become an increasingly important class of compounds for biological and synthetic applications[1] due to: (1) their inter-convertibility between the sp^2 and sp^3 forms, (2) their strong interaction with diol-containing compounds, (3) their Lewis acidity, (4) their relatively low toxicity[2, 3] [phenylboronic acid: LD_{50}, oral-rat = 740 mg/kg] and, (5) their stability and commercial availability. For all these unique properties, boronic acids have been used as pharmaceuticals,[4-7] receptors in carbohydrate recognition,[1-3] boron neutron capture therapy agents,[1-3] catalysts,[1, 8-24] and synthetic reagents.[25, 26]

The potential of boronic acid-based therapeutics has finally been recognized. For instance, bortezomib (Velcade®, PS-341) **4-1** (**Figure 4-2**) is a boronic acid-based thrombin inhibitor that was approved by the US Food and Drug Administration in 2008 after its successful phase III clinical trials.[27-30] Bortezomib represents the first FDA-approved boronic acid agent for cancer therapy and as a single agent for the

treatment of multiple myeloma. Furthermore, AN-2690 **4-2** is a fluoroarene boroxole-based broad-spectrum antifungal agent developed specifically for the treatment of onychomycosis, a fungal infection that affects fingers and toes, causing the nails to become brittle and discoloured with soreness of the surrounding skin.[31] AN-2690 has retention of antifungal activity and a nail penetration efficiency coefficient 50-fold higher than that of topical ciclopirox.[32] It is currently in phase II/III clinical trials by the US Food and Drug Administration. These two compounds and other boronic acids have initiated significant interest in boron-based small molecules in drug discovery.



bortezomib (Velcade®, PS-341) **4-1**

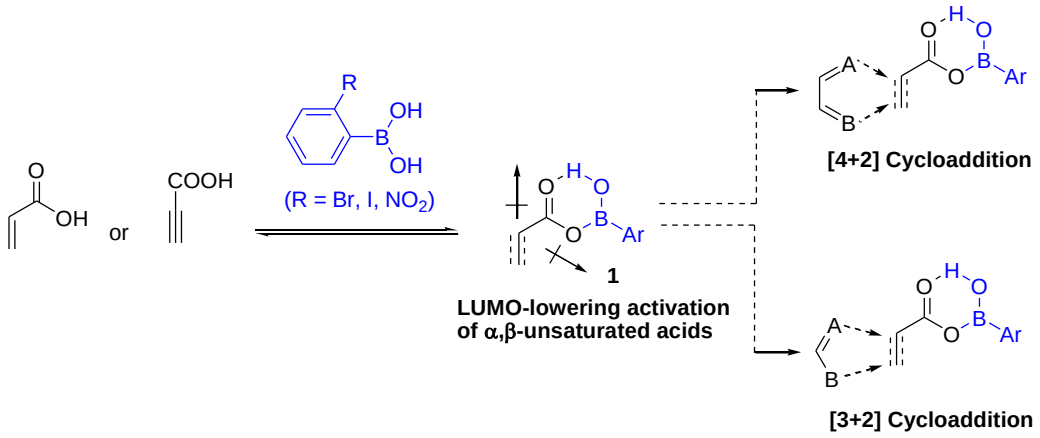
AN-2690 **4-2**

Figure 4-2: Structure of bortezomib (Velcade®, PS-341) (4-1) and AN-2690 (5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole) (4-2).

Furthermore, boronic acids and their esters have been extensively used not only as versatile intermediates in organic synthetic transformations, such as Suzuki-Miyaura[25, 26, 33] and Chan-Lam[34] couplings, allylborations[35, 36] and multi-component reactions for the synthesis of various amino acids,[37, 38] but also as efficient catalysts for cycloaddition, aldol and amidation reactions,[1, 8-24] and as synthetic reagents.[25, 26]

The remarkable activity of *ortho*-halogenated arylboronic acids as effective catalysts and especially the *ortho*-iodoarylboronic acids towards direct, mild and waste-free amidations, as discussed in Chapters Two and Three, motivated our group to start discovering more possible organic transformations that can be catalyzed by *ortho*-haloarylboronic acids. In 2010, Hall and co-workers developed mild and selective [3+2] dipolar cycloadditions to unsaturated carboxylic acids and [4+2] cycloadditions to propargylic carboxylic acids.[8, 9] As shown in **Figure 4-1**, *ortho*-iodo

and nitroarylboronic acids were found to be the best catalysts for these transformations.

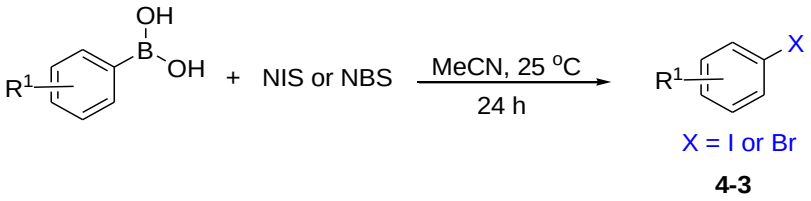


Scheme 4-1: The concept of electrophilic (LUMO-lowering) activation of unsaturated carboxylic acids using boronic acid catalysis.

With these remarkable foundations regarding the activity of *ortho*-iodoarylboronic acids toward direct amidation and cycloadditions, we aimed at optimizing this catalyst and developing new methods that would provide a variety of substituted *ortho*-iodoarylboronic acids.

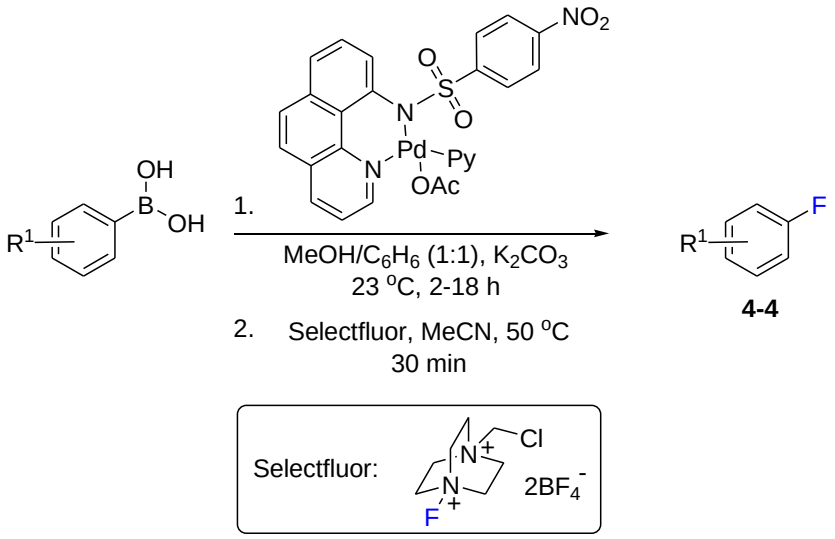
Even though arylboronic acids have been available for several years, are easy to handle, and are relatively stable, they are susceptible to chemoselectivity issues that render them difficult for further derivatization after introduction of the boronic acid. Their Lewis acidic nature makes them prone to react with commonly used organic reagents, such as strong acids, bases, oxidants and metal salts. This reactivity typically causes a simple protodeboronation or a substitution of the boronic acid group, thus forming other products, such as haloarenes,[39-43] amidoarenes[44] and nitroarenes.[45]

For instance, Olah and co-workers published in 1998 the first report on the synthesis of iodo and bromoarenes from arylboronic acids by using *N*-halosuccinaimides as electrophilic halogenation reagents to provide the desired *ipso*-halogenated products **4-3** in good to excellent yields at ambient temperatures (**Scheme 4-2**).[43]



Scheme 4-2: Electrophilic *ipso*-halogenation of arylboronic acids.[43]

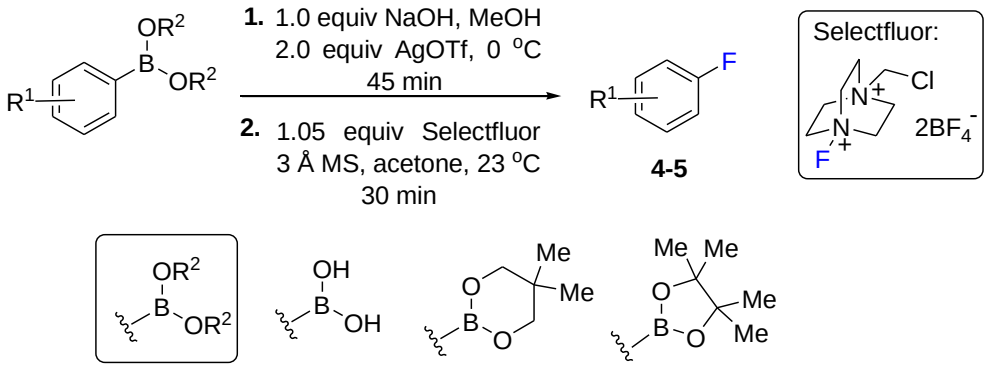
In 2008, Ritter and co-workers reported palladium mediated *ipso*-fluorination of arylboronic acids at 50 °C in acetonitrile to provide the *ispo*-fluorinated products **4-4** in moderate to good yields (**Scheme 4-3**).[40]



Scheme 4-3: Palladium mediated *ipso*-fluorination of arylboronic acids.[40]

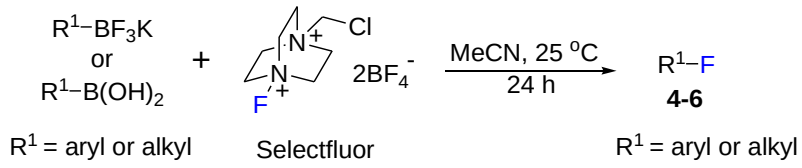
In 2009, the same group described milder reaction conditions for the *ipso*-fluorination of arylboronic acids using silver (I) triflate (AgOTf) under basic conditions to provide the desired products in good yields (**Scheme 4-4**).[39] It was claimed that the use of silver (I) triflate in basic medium accelerated the transmetalation step. Furthermore, the authors found that the use of excess NaOH (more basic conditions) in the reaction conditions reduced the yields of the isolated *ipso*-fluorinated products. This is due to the side oxidation reaction of silver (I) triflate which forms insoluble silver oxide (Ag_2O). Moreover, the use of 2.0 equivalents of silver (I) triflate and 1.0 equivalent of NaOH afforded an 82% yield of the *ipso*-fluorinated product "4-biphenylfluoride", while the yield increased to 95% when they used 3.0 equivalent of AgOTf and 1.2 equivalents of NaOH. Different

arylboronic esters, such as neopentylate and pinacolate, can also participate in the *ipso*-fluorination reaction conditions without prior hydrolysis to afford the desired fluoroarenes **4-5** in, albeit, lower yield than the boronic acids.[39]



Scheme 4-4: Silver (I) triflate mediated *ipso*-fluorination of arylboronic acids. [39]

In both of the *ipso*-fluorination methodologies described above, the authors used commercially available "Selectfluor" F-TEDA-BF_4 (1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) as the electrophilic fluorinating agent. In 2009, Lemaire and co-workers described a metal-free electrophilic *ipso*-fluorination of aryl and secondary alkyl trifluoroborates and boronic acids in acetonitrile at ambient temperature affording the desired *ipso*-fluorinated products **4-6** in good to excellent yields (**Scheme 4-5**).[41]

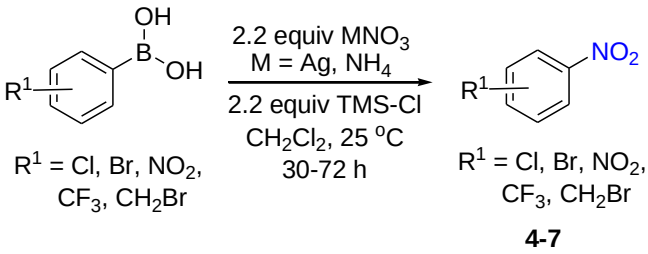


$R^1 = aryl\ or\ alkyl$ $R^1 = aryl\ or\ alkyl$

Scheme 4-5: Metal-free electrophilic *ipso*-fluorinations of trifluoroborates and boronic acids.[41]

In 2004, Olah and co-workers developed a convenient method for the *ipso*-nitration of arylboronic acids using a mixture of nitrate salt and chlorotrimethylsilane. This mixture was found to be an efficient regioselective nitrating agent producing the corresponding nitroarenes **4-7** in moderate to excellent yields (**Scheme 4-6**). TMS-Cl reacts with nitrate salts to generate the TMS-O-NO_2 species, which was found to be the active nitrating agent in this reaction. These reaction conditions, however, were

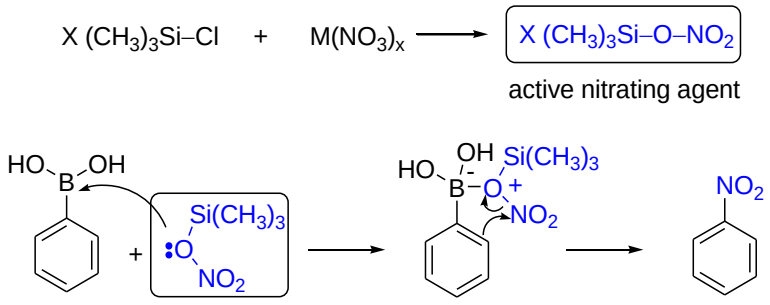
effective with arylboronic acids but not with aliphatic boronic acids. Moreover, arylboronic acids bearing electron neutral groups gave nitroarenes in high yields, while moderate to low yields were observed for those bearing electron withdrawing groups.



4-7

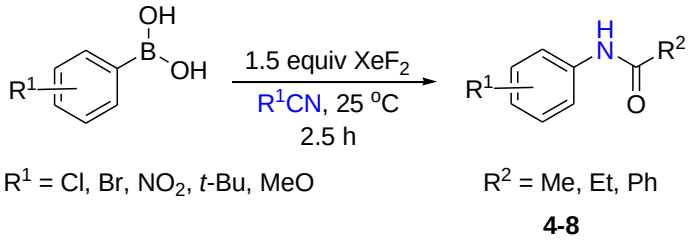
Scheme 4-6: *Ipso*-nitration of arylboronic acids using TMSCl/nitrate salts.[45]

The proposed mechanism for *ipso*-nitration of arylboronic acids is described in **Scheme 4-7**. The authors claimed that there is an electronic interaction between the boronic acid group and the intermediate nitrating agent TMS-O-NO_2 species through boron and the siloxy group. This most likely helps the nitration to occur at the *ipso*-position.[45]



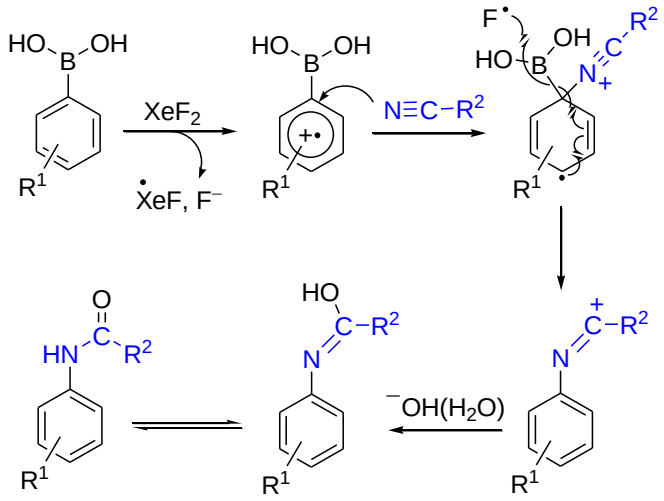
Scheme 4-7: Proposed mechanism for *ipso*-nitration of arylboronic acids using TMSCl/nitrate salts.[45]

In 2009, Prakash *et al.* developed an *ipso*-amidation of arylboronic acids mediated by xenon difluoride and acetonitrile under mild conditions (**Scheme 4-8**).[44] This new method provided a simple one-pot procedure for the synthesis of anilides from the corresponding arylboronic acids and alkyl/aryl nitriles. Arylboronic acids bearing electron donating groups gave anilides **4-8** in high yields, while moderate yields were observed for those bearing electron withdrawing groups.[44]



Scheme 4-8: *Ipso*-amidation of arylboronic acids using XeF_2/nitriles.[44]

The proposed mechanism involves the formation of an aryl radical cation through single electron transfer (SET) by the use of xenon difluoride, followed by the nucleophilic addition of the nitrile, as demonstrated in **Scheme 4-9**.[44]



Scheme 4-9: Proposed mechanism for *ipso*-amidation of arylboronic acids using XeF_2/nitriles. [44]

All these transformations shown above are believed to proceed via boron activation followed by an *ipso* displacement mechanism. As a result of this reactivity, boronic acids are very labile and rarely left intact after being carried through a number of synthetic chemical reactions.[46, 47]

In 1962, Kuivila and co-workers reported direct halogenations of arylboronic acids.[48] Although their direct bromination and chlorination worked to provide polyhalogenated arylboronic acids,[49] their direct iodination was not successful. The reaction was hampered by the formation of HI, which causes protolytic cleavage of

the $B(OH)_2$ group to provide the iodoarene. While the halogenation of aromatic compounds is one of the most widely studied reactions in the literature,[50] a practical iodination of arylboronic acids to access iodinated arylboronic acids had not been reported.

We became interested to find such a method that can effectively provide direct and regioselective *ortho*-halogenated arylboronic acids under benign conditions avoiding the *ipso*-decomposition reactions of the boronic acid group. These conditions would favorably provide an easy and convenient pathway for the synthesis of *ortho*-iodoarylboronic acids compounds, which, as described in this thesis, are found to be very active catalysts toward direct amide bond formations and cycloadditions.

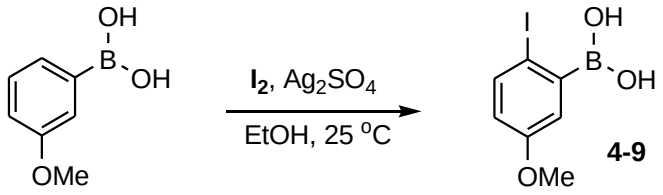
4.2 Results[51]

4.2.1 Initial Screening for a Mild and Convenient Iodination Method of Arylboronic Acids[51]

This project was initiated by looking for a milder and convenient iodination agent. There have been a number of reports on direct aromatic iodination,[52] however, few Lewis acids have been examined. The most common Lewis acids are silver and mercuric salts in combination with I_2 due to the fact that silver and mercury can remove iodide efficiently from solution by precipitation. We decided to explore conditions with different solvents using 3-methoxyphenylboronic acid as a model substrate. First, a combination of silver sulfate and iodine was utilized as an iodinating agent at room temperature. A brief optimization of solvent revealed that ethanol and 1,2-ethanediol were the most suitable solvents for the desired transformation. The iodine color disappeared within a few minutes to provide the desired product without the *ipso* deboronation side product (**Table 4-1, entries 4 and 5**). All other solvents were found to be unsuitable for this reaction (**Entries 1-3**). Using ethanol as a solvent, we examined the influence of different reagents on iodination of 3-methoxyphenylboronic acid to establish further the reaction conditions. We found that when a mixture of $Hg(OAc)_2/I_2$ was used instead of Ag_2SO_4/I_2, the yield of *ortho*-iodination product **4-9** decreased and formation of 10-15% of the *ipso*-iodination was observed (**Entry 7**). Using $AgNO_3/I_2$ led to a similar

result as with Ag_2SO_4/I_2 (**Entry 6**). No *ortho*-iodination was observed with NIS (**Entries 8**) while, NIS in acetonitrile gave only the *ipso*-iododeboronation product in excellent yield (**Entry 9**). Furthermore, when the reaction times exceeded 3 min, further decomposition occurred and less *ortho*-iodination product **4-9** was observed.

Table 4-1: Effect of different iodinating agents in the direct *ortho*-iodination of 3-methoxyphenylboronic acid.[a]



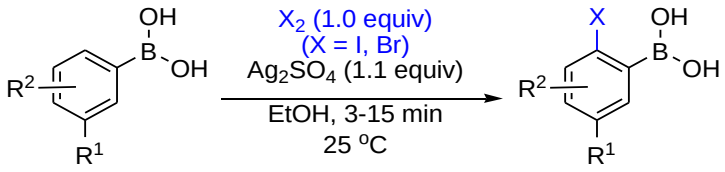
Entry	Solvent	Iodinating agents	*T*(min)	%Yields[b]
1	CH_2Cl_2	Ag_2SO_4/I_2	2.5	0
2	THF	Ag_2SO_4/I_2	2	0
3	CH_3CN	Ag_2SO_4/I_2	2	27
4	$HOCH_2CH_2OH$	Ag_2SO_4/I_2	3	77
5	EtOH	Ag_2SO_4/I_2	2.5	79
6	EtOH	$AgNO_3/I_2$	3	75
7	EtOH	$Hg(OAc)_2/I_2$	20	40
8	EtOH	NIS	>15	0
9	CH_3CN	NIS	2	0
10	EtOH	Ag_2SO_4/I_2[c]	2.5	81
11	EtOH	Ag_2SO_4/I_2[d]	2.5	82
12[e]	EtOH	Ag_2SO_4/I_2[c]	2.5	78

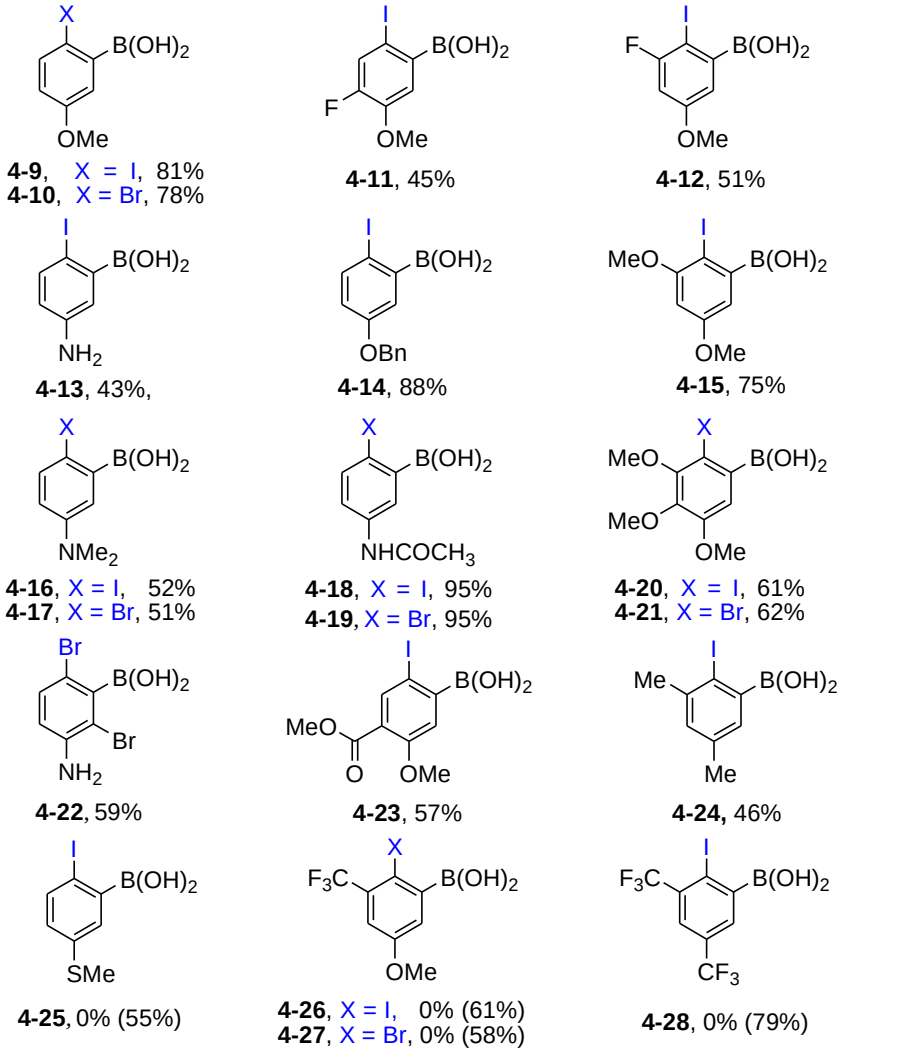
[a]Conditions: All the reactions were carried out using 1 equiv of iodinating agent and stirred at 25 °C for the time specified. [b]Isolated yield. [c]Ag_2SO_4 (1.1 equiv of Ag). [d]Ag_2SO_4 (1.5 equiv of Ag). [e]5 gram scale (32.9 mmol).

The best yield of *ortho*-iodination product was obtained when 1.1 equivalents of Ag_2SO_4 or $AgNO_3$ was used with 1.0 equivalent of I_2 (**Table 4-1, entry 10**). The reaction also worked well on a multigram scale (5.0 g, 32.9 mmol) (**Entry 12**). Although the stoichiometric use of metal salts should be avoided as much as possible, it is tolerable for transformations that provide products that are difficult or impossible to access by any other means. In this regard, the substrate scope of the

Ag(I)-mediated direct iodinaton of boronic acids using the optimized reaction conditions was evaluated, as demonstrated in **Scheme 4-10**. Different electron-rich, neutral and electron-poor arylboronic acids bearing protic, basic, electrophilic, or nucleophilic functional groups were subjected to the optimal reaction conditions to provide the *ortho*-halogenated products without any traces of other regioisomers. Substrates with electron-donating substituents, such as a methoxy, amido or amino, provided the desired products in higher yield and shorter reaction times of 2-5 min (**Scheme 4-10: 4-9, 4-10, 4-13** to **4-21**), whereas when two equivalents of Br_2 were used with 3-aminoarylboronic acid, only the dibrominated product at ortho positions to the boronic acid group was isolated (**Scheme 4-10: 4-22**). In contrast, arylboronic acids bearing electron-withdrawing substituents decreased the reaction efficiency and increased the required reaction time to 10-15 min (**Scheme 4-10: 4-11, 4-12** and **4-23**). The neutral substrate 3,5-dimethylphenylboronic acid was also subjected to the same reaction conditions to provide the desired iodinated product within 10 min (**Scheme 4-10: 4-24**). Substrates with methylthio- and trifluoromethyl- substituents did not provide the desired products and starting materials were recovered (**Scheme 4-10: 4-25** to **4-28**). This is likely due to the nucleophilicity of sulfur and the sterically hindered triflouromethyl group.

Electron-rich groups with their ability for conjugation enhance the reactivity of *ortho* and *para* positions toward electrophilic substitution reactions. The iodination of highly activated aromatic compounds, like aniline, provides the *para*-iodinated product in 66% yield as well as *ortho*- and *para*-diiodinated products in 13% yield at room temperature.[50] Using our conditions, the fact that the substitution occurs only *ortho* to the $B(OH)_2$ group and *para* to the electron donating group even, with multiple electron donating groups (**Scheme 4-10: 4-15**), indicates that electronic effects are not the only significant factor in these reactions. Indeed, the observed regioselectivity suggests that a strong *ortho* directing group effect from the $B(OH)_2$ group is operative. Moreover, when there are two distinct *ortho* positions available for iodination, the site which is the least sterically hindered and *para* to the electron-donating group is iodinated (**Scheme 4-10: 4-9** to **4-14**, **4-16** to **4-19**).





Scheme 4-10: Direct *ortho*-iodination and bromination of arylboronic acids.

The regiochemistry in these examples is supported by X-ray crystallographic analyses of several products, such as **4-15** and **4-20,** as shown in **Figure 4-3**,[53] which clearly indicate the position of the electrophilic iodination. For example, the

precursor to 2-iodo-3,5-dimethoxyphenyl boronic acid (**Figure 4-3, 4-15**) has two positions available for iodination, *ortho* and *para* to the boronic acid group. The *ortho* position is iodinated exclusively under the optimized reaction conditions.

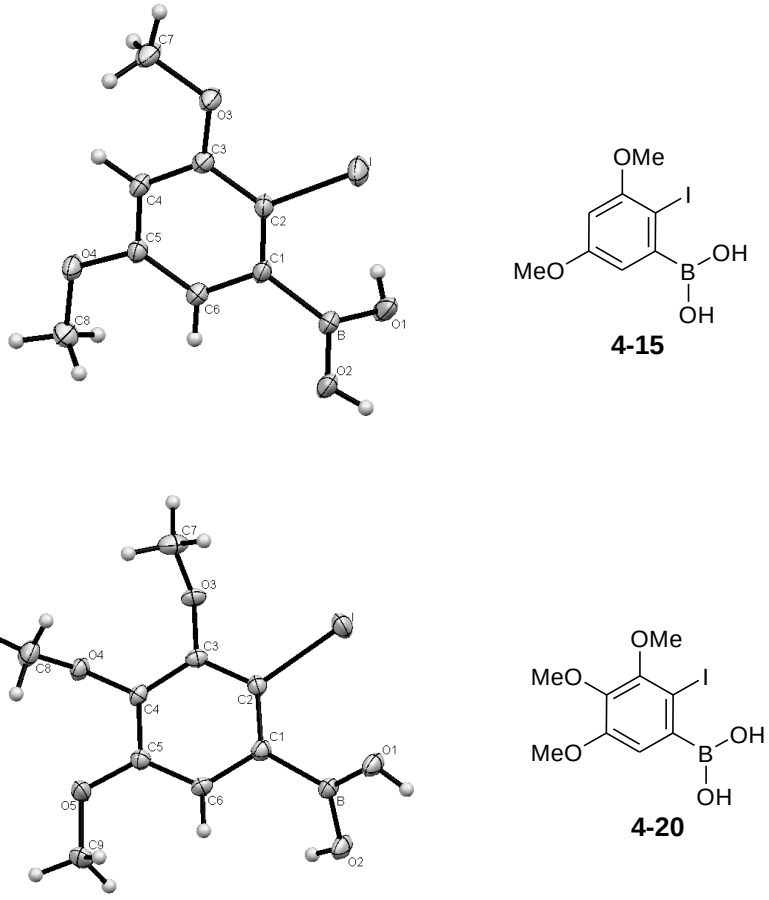
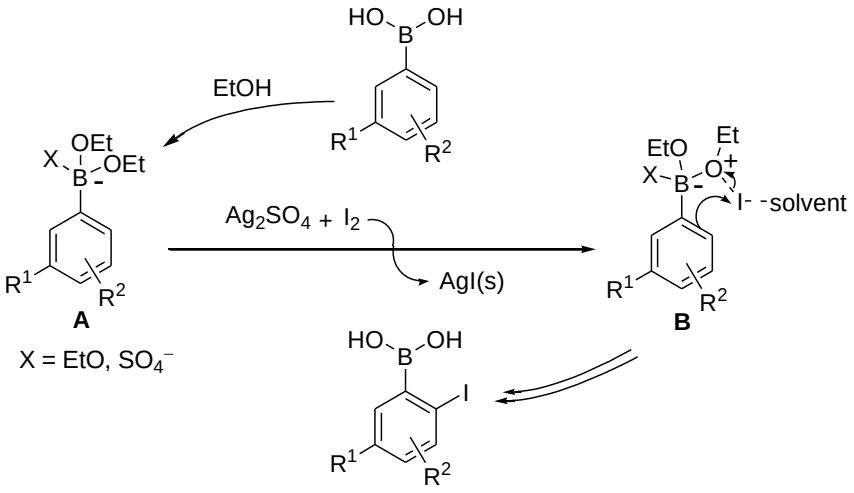


Figure 4-3: ORTEP view of 2-iodo-3,5-dimethoxyphenylboronic acid (4-15) and 2-iodo-3,4,5-trimethoxyphenylboronic acid (4-20). Thermal Gaussian ellipsoids at 20% probability level.

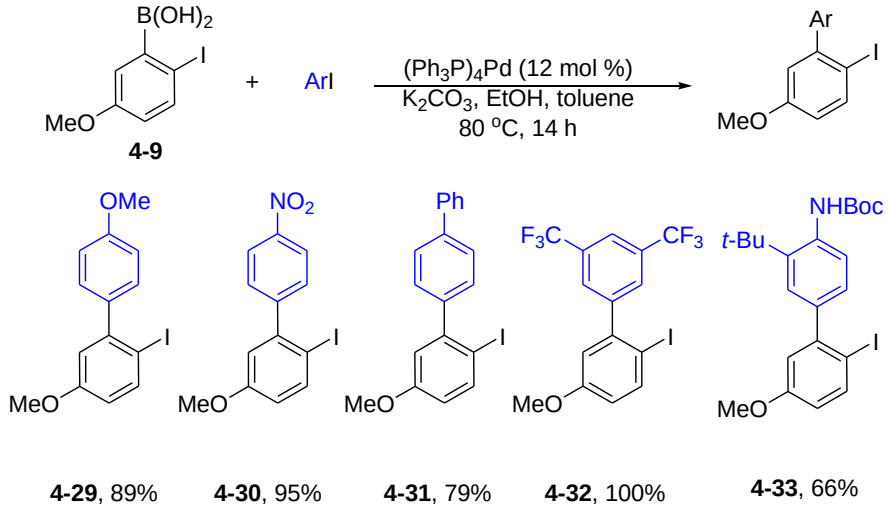
Since other regioisomers in the reaction were not observed, it is likely that there exists a prominent interaction between the boronyl group and the active iodonium intermediate, as shown in the proposed mechanism (**Scheme 4-11**). In ethanol, in the presence of anionic species, the formation of borate intermediate A is likely. Formation of this boronate anion activates the ring for electrophilic iodination while fostering electrostatic attraction with the iodonium reagent. This directing effect leads to iodination at the *ortho* position to the boronic acid, as depicted in intermediate B.



Scheme 4-11: The proposed mechanism for direct *ortho*-iodination of arylboronic acid.

4.3 Chemoselective Suzuki-Miyaura Coupling for *Ortho*-Iodoarylboronic Acids[51]

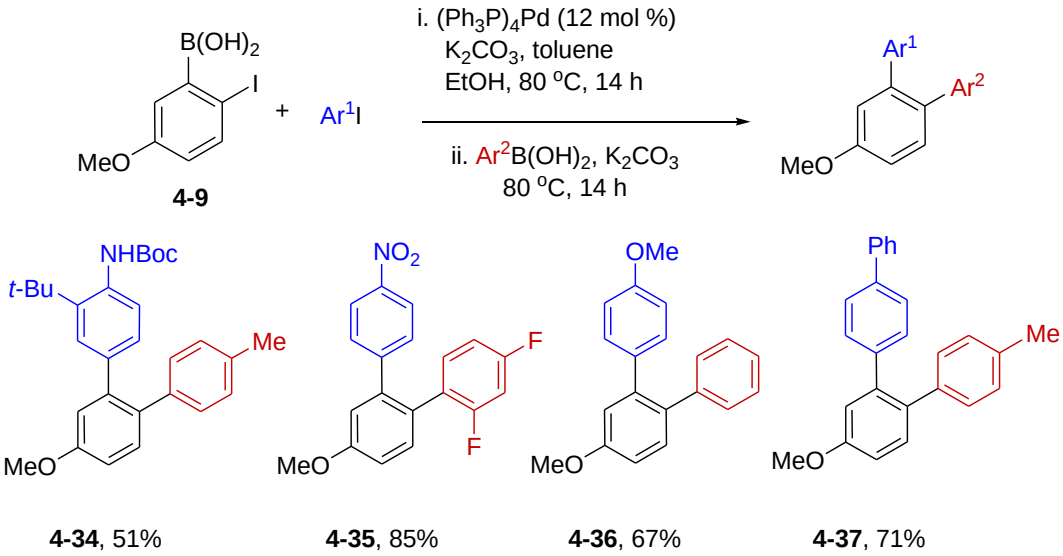
Besides catalytic direct amidations and cycloadditions, we wished to demonstrate the utility of these *ortho*-iodoarylboronic acids as useful intermediates in different synthetic transformations. For example, 5-methoxy-2-iodophenylboronic acid **4-9** was converted into biaryl derivatives by a highly chemoselective Suzuki-Miyaura coupling reaction with good to excellent yields (**Scheme 4-12:** **4-29** to **4-33**).



4-29, 89% **4-30**, 95% **4-31**, 79% **4-32**, 100% **4-33**, 66%

Scheme 4-12: Chemoselective Suzuki-Miyaura coupling for *ortho*-iodoarylboronic acids.

Furthermore, one-pot double Suzuki-Miyaura couplings were also successful at providing the expected *ortho* triaryl derivatives in good yields (Scheme 4-13: **4-34** to **4-37**).



Scheme 4-13: One-pot chemoselective double Suzuki-Miyaura coupling of 2-iodo-5-methoxyphenylboronic acid.

4.4 Conclusion

The first direct method for mild and regioselective direct iodination and bromination of arylboronic acids was developed. The functional group tolerance, broad substrate scope, and regioselectivity of the reaction provide a general method for halogenated arylboronic acids that are difficult to access otherwise. In this methodology, the reaction is operationally very simple. It employs equimolar amounts of the boronic acid, iodine and silver sulfate or nitrate, requires no heating or cooling source, and needs only a few minutes for the reaction to be completed. This process generates silver iodide or bromide as a precipitate, which can easily be isolated and used for different applications, and affords the desired halogenated arylboronic acids after flash chromatography. The stability of *ortho*-iodoarylboronic acids during silica purification was remarkable when compared with other arylboronic acids. This new methodology represents a significant way for simple

and easy access to *ortho*-iodinated arylboronic acids by a short one step synthesis from cheap and commercially available starting materials. The resulting boronic acids are known to be very active catalysts toward direct amidation and cycloaddition, as shown in Chapters Two and Three. To demonstrate the utility of these *ortho*-iodinated arylboronic acids in synthesis, a remarkably chemoselective Suzuki-Miyaura couplings in a one-pot fashion to provide bi and triaryl derivatives which are a basic chemical strucure in a number of biologically active natural products.

4.5 Experimental[51]

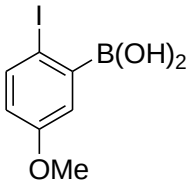
4.5.1 General Information

Toluene, CH_3CN and CH_2Cl_2 were distilled from CaH_2. EtOH (100%), Ag_2SO_4 (BDH, analytical reagent), $AgNO_3$ (EM Science, 99% tech powder), HgO (Aldrich, 99% tech powder and I_2 (Caledon, 99.8%) were used as supplied. Analytical thin layer chromatography was performed on Merck Silica Gel 60 F254 plates and visualized with UV light and 1% $KMnO_4$ (aq). NMR spectra were recorded on Varian INOVA-300, INOVA-400 or INOVA-500 MHz instruments. The residual solvent protons (^1H) or the solvent carbon (^{13}C) were used as internal standards. ^1H-NMR data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, integration, coupling constant). Carbon attached to $B(OH)_2$ group was generally not detected by ^{13}C-NMR (exhaustive peak broadening due to quadrupolar relaxation of ^{11}B). The following abbreviations are used in reporting NMR data: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; dq, doublet of quartets; dd, doublet of doublets; m, multiplet. High resolution mass spectra were recorded by the University of Alberta mass spectrum service laboratory using either electron impact (EI) or electrospray (ESI) ionization techniques. Infrared spectra were obtained on a Nicolet Magna-IR 750 with frequencies expressed in cm^{-1}. Optical rotations were measured using a 1 mL cell with a 1 dm length on a Perkin Elmer 241 polarimeter.

4.5.2 General Procedure for Halogenation of Arylboronic Acids

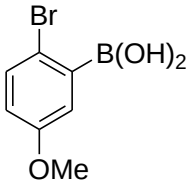
A solution of iodine in EtOH (4.72 mmol, 1.00 equiv, 0.30 M) was added dropwise to a mixture of arylboronic acid (4.72 mmol, 1.00 equiv) and silver (I) sulfate (2.36 mmol, 0.55 equiv) in EtOH (15 mL) at room temperature. After complete addition of iodine the reaction was stirred at room temperature until the purple color completely disappeared. The reaction mixture was filtered through a pad of Celite ® 545 using ethyl acetate, water (50 mL) was added to the filtrate and the mixture was extracted with ethyl acetate (2 X 30 mL). The combined organic layers were washed with aqueous sodium sulfite, brine, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel (hexane/ethyl acetate 3:1) to yield the pure desired product.

4.5.2.1 Synthesis of 2-Iodo-5-Methoxyphenylboronic Acid (4-9)



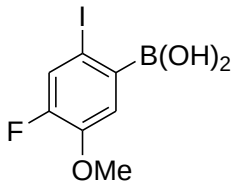
The title compound was prepared using the general procedure for halogenation of arylboronic acids and isolated in **81%** yield as a white solid. **IR** (Cast film, cm^{-1}) 3373, 1563, 1441, 1398, 1334, 1281, 1231, 1035, 810. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ: 8.22 (bs, 2H), 7.58 (d, 1H, *J* = 8.6 Hz), 6.79 (d, 1H, *J* = 3.2 Hz), 6.66 (dd, 1H, *J* = 3.2 Hz, *J* = 8.6 Hz), 3.71 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 159.1, 139.2, 119.6, 116.9, 88.2, 55.8. **HRMS** (ESI) for $C_7H_8BClIO_3$ $[M+Cl]^-$: calcd. 312.93065; found, 312.92965.

4.5.2.2 *Synthesis of 2-Iodo-5-Methoxyphenylboronic Acid* (4-10)



The title compound was prepared using the general procedure for halogenation of arylboronic acids and isolated in **78%** yield as a white solid. **^{1}H-NMR** (500 MHz, DMSO-d_6) δ: 8.28 (bs, 2H), 7.49 (d, 1H, *J* = 3.2 Hz), 7.44 (d, 1H, *J* = 8.7 Hz), 6.86 (dd, 1H, *J* = 3.1 Hz, *J* = 8.7 Hz), 3.74 (s, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 157.7, 133.4, 118.7, 118.7, 117.8, 55.0. **HRMS** (ESI) for $C_7H_8BBrClO_3$ $[M+Cl]^-$: calcd. 264.9444; found, 264.9442.

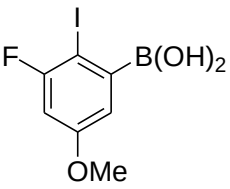
4.5.2.3 *Synthesis of 4-Fluoro-2-Iodo-5-Methoxyphenylboronic Acid* (4-11)



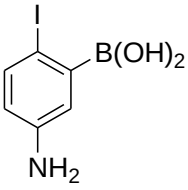
The title compound was prepared using the general procedure for halogenation of arylboronic acids and isolated in **45%** yield as a white solid. **IR** (Cast film, cm^{-1}) 3070, 2960, 1593, 1498, 1456, 1392, 1370, 1303, 1185, 1174, 730. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ: 8.27 (bs, 2H), 7.55 (d, 1H, *J* = 11.0 Hz), 7.01 (d, 1H, *J* = 9.6 Hz), 3.80 (s, 3H). **^{13}C-NMR** (100 MHz, DMSO-d_6) δ: 153.3 (d, *J* = 248Hz), 147.2 (d, *J* = 9.4Hz), 125.6 (d, *J* = 19Hz), 119.1, 86.6 (d, *J* = 6.2Hz), 56.7. **HRMS** (ESI) for $C_7H_6BFIO_3$: calcd. 294.94455; found, 294.94478.

4.5.2.4 *Synthesis of 3-Fluoro-2-Iodo-5-Methoxyphenylboronic Acid* (4-12)

The title compound was prepared using the general procedure for halogenation of arylboronic acids and isolated in **51%** yield as a white solid. **IR** (Cast film, cm^{-1}) 3420, 3238, 3065, 1596, 1575, 1438, 1383, 1187, 852. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ: 8.33 (bs, 2H), 6.83 (dd, 1H, *J* = 2.8 Hz, *J* = 10.3 Hz), 6.65 (d, 1H, *J* = 2.8 Hz), 3.74 (s, 3H). **^{13}C-NMR** (100 MHz, DMSO-d_6) δ: 162.6 (d, *J* = 240.4Hz,) , 161.0 (d, *J* = 9.7Hz,), 115.6 (d, *J* = 2.4Hz,), 102.2 (d, *J* = 18.0Hz,), 74.6 (d, *J* = 24.0Hz,), 56.4. **HRMS** (ESI) for $C_7H_6BFIO_3$: calcd. 294.94455; found, 294.4455.

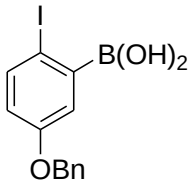


4.5.2.5 *Synthesis of 5-Amino-2-Iodophenylboronic Acid* (4-13)



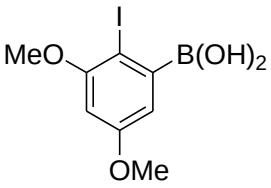
The title compound was prepared using the general procedure for halogenation of arylboronic acids and isolated in **43%** yield as a white solid. **IR** (Cast film, cm^{-1}) 3377, 3928, 3223, 3037, 2957, 2926, 1616, 1587, 1565, 1460, 1419, 1287, 1167, 1111, 1004, 900. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ : 8.05 (s, 2H), 7.26 (d, 1H, *J* = 8.4 Hz), 6.48 (d, 1H, *J* = 2.9 Hz), 6.30 (dd, 1H, *J* = 2.9 Hz, *J* = 8.4 Hz). **^{13}C-NMR** (100 MHz, DMSO-d_6) δ: 148.1, 138.3, 119.9, 116.9, 81.5. **HRMS** (ESI) for $C_6H_8BINO_2$: calcd. 263.96884; found, 263.96854.

4.5.2.6 Synthesis of 5-(Benzyloxy)-2-Iodophenylboronic Acid (4-14)



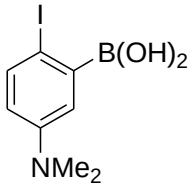
The title compound was prepared using the general procedure for halogenation of arylboronic acids and isolated in **88%** yield as a white solid. **IR** (Cast film, cm^{-1}) 3332, 3059, 1582, 1493, 1472, 1460, 1338, 1278, 1167, 1137, 1000. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ: 8.26 (s, 2H), 7.58 (d, 1H, *J* = 8.6 Hz), 7.35 (m, 5H), 6.88 (d, 1H, *J* = 3.1 Hz), 6.74 (dd, 1H, *J* = 3.2 Hz, *J* = 8.7 Hz), 5.06 (s, 2H). **^{13}C-NMR** (100 MHz, DMSO-d_6) δ: 158.2, 139.3, 137.6, 129.1, 128.5, 128.2, 120.7, 117.7, 88.5, 69.8. **HRMS** (ESI) for $C_{13}H_{12}BINaO_3$: calcd. 376.98188; found, 376.98168.

4.5.2.7 Synthesis of 2-Iodo-3,5-Dimethoxyphenylboronic Acid (4-15)



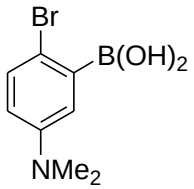
The title compound was prepared using the general procedure for halogenation of arylboronic acids and isolated in **75%** yield as a white solid. **IR** (Cast film, cm^{-1}) 3333, 2978, 1579, 1453, 1441, 1405, 1347, 1194, 1175, 1155, 1074, 837. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ: 8.16 (bs, 2H), 6.50 (d, 1H, *J* = 2.7 Hz), 6.38 (d, 1H, *J* = 2.7 Hz), 3.77 (s, 3H), 3.74 (s, 3H). **^{13}C-NMR** (100 MHz, DMSO-d_6) δ: 160.1, 157.5, 109.4, 98.6, 78.8, 56.2, 55.2. **HRMS** (ESI) for $C_8H_9BIO_4$: calcd. 306.96456; found, 306.96389.

4.5.2.8 Synthesis of 5-(Dimethylamino)-2-Iodophenylboronic Acid (4-16)



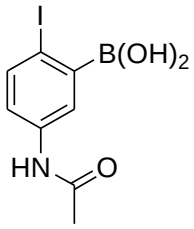
The title compound was prepared using the general procedure for halogenation of arylboronic acids and isolated in **52%** yield as a purple solid. **IR** (Cast film, cm^{-1}) 3467, 2887, 1582, 1551, 1481, 1399, 1355, 1304, 1263, 1172, 756. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ: 8.11 (bs, 2H), 7.43 (dd, 1H, *J* = 1.2 Hz, *J* = 8.7 Hz), 6.59 (d, 1H, *J* = 3.2 Hz), 6.45 (dd, 1H, *J* = 3.2 Hz, *J* = 8.7 Hz), 2.83 (s, 6H). **^{13}C-NMR** (100 MHz, DMSO-d_6) δ: 149.8, 138.4, 118.2, 115.5, 83.2, 40.7. **HRMS** (ESI) for $C_8H_{11}BClINO_2$: calcd. 325.96231; found, 325.96262.

4.5.2.9 *Synthesis of 5-(Dimethylamino)-2-Bromophenylboronic Acid* (4-17)



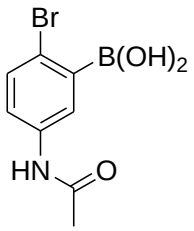
The title compound was prepared using the general procedure for halogenation of arylboronic acids and isolated in **51%** yield as a purple solid. **^{1}H-NMR** (500 MHz, DMSO-d_6) δ: 8.16 (bs, 2H), 7.45 (d, 1H, J = 3.2 Hz), 7.31 (d, 1H, J = 8.7 Hz), 6.64 (dd, 1H, J = 3.2 Hz, J = 8.7 Hz), 2.87 (s, 6H). **^{13}C-NMR** (125 MHz, DMSO-d_6) δ: 148.8, 132.8, 120.9, 115.2, 114.2, 40.2. **HRMS** (ESI) for $C_8H_{11}BBrClNO_2$: calcd. 277.976; found, 277.976.

4.5.2.10 *Synthesis of 5-Acetamido-2-Iodophenylboronic Acid* (4-18)



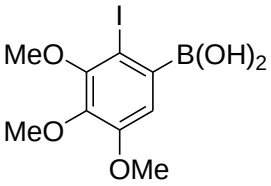
The title compound was prepared using the general procedure for halogenation of arylboronic acids and isolated in **95%** yield as a white solid. **IR** (Cast film, cm^{-1}) 3483, 3339, 3126, 3099, 1636, 1595, 1581, 1538, 1331, 1268, 1117, 1026, 832. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ: 9.91 (bs, 1H), 8.23 (bs, 2H), 7.60 (d, 1H, J = 9.0 Hz), 7.37 (m, 2H), 2.01 (s, 3H). **^{13}C-NMR** (100 MHz, DMSO-d_6) δ: 169.1, 139.0, 138.5, 124.2, 121.5, 91.4, 24.7. **HRMS** (ESI) for $C_8H_8BINO_3$: calcd. 303.96489; found, 303.96463.

4.5.2.11 *Synthesis of 5-Acetamido-2-Bromophenylboronic Acid* (4-19)



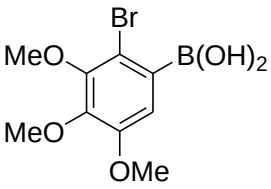
The title compound was prepared using the general procedure for halogenation of arylboronic acids and isolated in **95%** yield as a white solid. **IR** (Cast film, cm^{-1}) 3470, 3345, 2977, 1714, 1139, 1456, 1423, 1304, 1100, 789. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ: 9.94 (bs, 1H), 8.27 (bs, 2H), 7.54 (dd, 1H, J = 2.8 Hz, J = 8.8 Hz), 7.50 (d, 1H, J = 2.4 Hz), 7.39 (d, 1H, J = 8.4 Hz), 2.02 (s, 3H). **^{13}C-NMR** (100 MHz, DMSO-d_6) δ: 168.3, 137.8, 131.5, 123.7, 120.6, 117.9, 23.9. **HRMS** (ESI) for $C_{10}H_{14}BBrNO_3$: calcd. 286.02465; found, 286.02482.

4.5.2.12 Synthesis of 2-Iodo-3,4,5-Trimethoxyphenylboronic Acid (4-20)



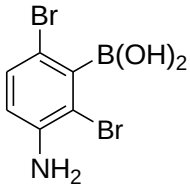
The title compound was prepared using the general procedure for halogenation of arylboronic acids and isolated in **61%** yield as a white solid. **IR** (Cast film, cm^{-1}) 3340, 2941, 1578, 1555, 1438, 1359, 1295, 1099, 1012, 997. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ: 7.28 (s, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H). **^{13}C-NMR** (100 MHz, DMSO-d_6) δ: 153.6, 152.2, 144.4, 116.1, 89.3, 60.9, 60.8, 56.1. **HRMS** (ESI) for $C_9H_{12}BClIO_5$ $[M+Cl]^-$: calcd. 372.95182; found, 372.95151.

4.5.2.13 Synthesis of 2-Bromo-3,4,5-Trimethoxyphenylboronic Acid (4-21)



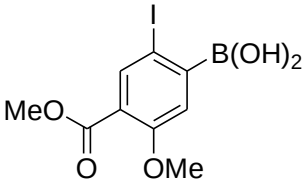
The title compound was prepared using the general procedure for halogenation of arylboronic acids and isolated in **62%** yield as a white solid. **^{1}H-NMR** (500 MHz, DMSO-d_6) δ: 8.22 (bs, 2H), 7.48 (s, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.76 (s, 3H). **^{13}C-NMR** (125 MHz, DMSO-d_6) δ: 151.6, 149.8, 143.7, 115.1, 113.7, 60.4, 60.3, 55.7. **HRMS** (ESI) for $C_9H_{12}BBrNaO_5$: calcd. 312.9855; found, 312.9856.

4.5.2.14 Synthesis of 5-Amino-2,6-Dibromophenylboronic Acid (4-22)



The title compound was prepared using the general procedure for halogenation of arylboronic acids and isolated in **59%** yield as a white solid. **^{1}H-NMR** (500 MHz, DMSO-d_6) δ : 8.31 (s, 2H), 7.13 (d, 1H, J = 8.5 Hz), 6.65 (dd, 1H, J = 0.8 Hz, J = 8.5 Hz), 5.30 (s, 2H). **^{13}C-NMR** (125 MHz, DMSO-d_6) δ: 144.2, 130.4, 115.6, 110.4, 108.7. **HRMS** (ESI) for $C_6H_6BBr_2NO_2$: calcd. 327.8552; found, 327.8551.

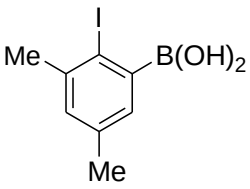
4.5.2.15 Synthesis of 4-(Methoxycarbonyl)-2-Iodo-5-Methoxyphenylboronic Acid (4-23)



The title compound was prepared using the general procedure for halogenation of arylboronic acids and isolated in **57%** yield as a white solid. **IR** (Cast film, cm^{-1}) 3461, 3360, 2951, 1710, 1462, 1435, 1421, 1298, 1178, 1094, 788. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ: 8.42 (bs, 2H), 7.89 (s, 1H), 6.99 (s, 1H),

3.78 (s, 3H), 3.75 (s, 3H). **^{13}C-NMR** (100 MHz, DMSO-d_6) δ: 165.4, 157.8, 139.6, 122.2, 118.0, 87.1, 56.6, 52.7. **HRMS** (ESI) for $C_9H_9BIO_5$: calcd. 334.95949; found, 334.95867.

4.5.2.16 *Synthesis of 3,5-Dimethyl-2-Iodophenylboronic Acid* (4-24)

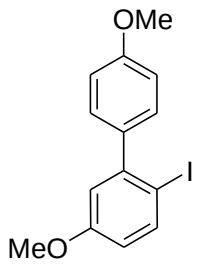


The title compound was prepared using the general procedure for halogenation of arylboronic acids and isolated in **46%** yield as a white solid. **^{1}H-NMR** (500 MHz, DMSO-d_6) δ: 8.15 (bs, 2H), 7.07 (d, 1H, J = 2.5 Hz), 6.78 (d, 1H, J = 2.5 Hz), 2.32 (s, 3H), 2.20 (s, 3H). **^{13}C-NMR** (125 MHz, DMSO-d_6) δ: 139.4, 136.3, 130.7, 129.9, 101.5, 28.2, 20.2. **HRMS** (ESI) for $C_8H_{10}BClIO_2$ $[M+Cl]^-$: calcd. 310.9513; found, 310.9513.

4.5.3 General Procedure for Chemoselective Suzuki-Miyaura Cross-Couplings

A flame dried flask was charged with 2-iodo-5-methoxyphenylboronic acid (0.10 g, 0.36 mmol), aryl iodide (0.33 mmol), tetrakis(triphenylphosphine)palladium (0) (46 mg, 12 mol%), toluene (2.0 mL), ethanol (0.20 mL) and a 2M solution of potassium carbonate (0.70 mL) under argon. The mixture was heated to 80 °C for 12-14 h. The mixture was cooled down to room temperature, the organic layer was separated, washed twice with water, brine, dried over Na_2SO_4 and filtered. The solvent was removed and the crude residue purified by flash chromatography (20% EtOAc/hexanes) to provide the desired product.

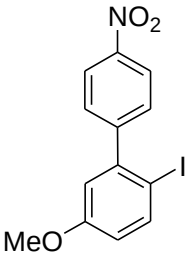
4.5.3.1 *Synthesis of 2-(4-Methoxyphenyl)-4-Methoxyiodobenzene* (4-29)



The title compound was prepared using the general procedure for the chemoselective Suzuki-Miyaura cross-coupling (**89%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.80 (d, 1H, J = 8.7 Hz), 7.66 (d, 1H, J = 7.8 Hz), 7.38 (d, 1H, J = 2.1 Hz), 7.20 (dd, 1H, J = 2.1 Hz, J = 8.2 Hz), 6.90 (d, 1H, J = 3.1 Hz), 6.64 (dd, 1H, J = 3.1 Hz, J = 8.7 Hz), 6.47 (bs, 1H), 3.80 (s, 3H), 1.54 (s, 9H), 1.46 (s, 9H). **^{13}C-NMR** (125

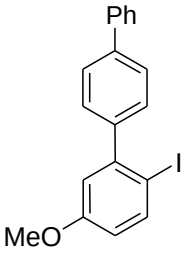
MHz, $CDCl_3$) δ: 159.8, 153.6, 147.4, 140.1, 135.2, 127.9, 127.2, 116.0, 115.0, 87.2, 80.4, 55.4, 36.6, 34.7, 30.7, 28.4, 24.7, 23.4. **HRMS** (EI) for $C_{14}H_{13}IO_2$: calcd. 339.99608; found, 339.99597.

4.5.3.2 *Synthesis of 2-(4-Nitrophenyl)-4-Methoxyiodobenzene* (4-30)



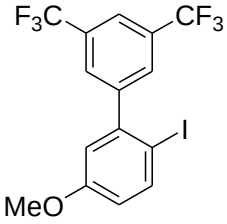
The title compound was prepared using the general procedure for the chemoselective Suzuki-Miyaura cross-coupling (**95%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ : 8.28 (ddd, 2H, *J* = 1.2 Hz, *J* = 2.3 Hz, *J* = 8.1 Hz), 7.83 (d, 1H, *J* = 8.7 Hz), 7.52 (d, 2H, *J* = 8.3 Hz), 6.86 (d, 1H, *J* = 3.0 Hz), 6.72 (dd, 1H, *J* = 3.0 Hz, *J* = 8.8 Hz), 3.82 (s, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 159.9, 150.3, 147.3, 145.2, 140.4, 130.3, 123.3, 115.9, 115.9, 85.7, 55.5. **HRMS** (EI) for $C_{13}H_{10}INO_3$: calcd. 354.97054; found, 354.97112.

4.5.3.3 Synthesis of 2-(4-Biphenyl)-4-Methoxyiodobenzene (4-31)



The title compound was prepared using the general procedure for the chemoselective Suzuki-Miyaura cross-coupling (**79%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ : 7.86 (d, 1H, *J* = 8.7 Hz), 7.70 (m, 4H), 7.51 (m, 4H), 7.47 (m, 1H), 6.97 (d, 1H, *J* = 3.0 Hz), 6.70 (dd, 1H, *J* = 3.1 Hz, *J* = 8.7 Hz), 3.84 (s, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 159.9, 147.5, 143.0, 140.7, 140.5, 140.1, 129.7, 128.8, 127.4, 127.2, 126.7, 116.0, 115.3, 87.1, 55.5. **HRMS** (EI) for $C_{19}H_{15}IO$: calcd. 386.01700; found, 386.01676.

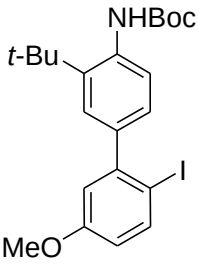
4.5.3.4 Synthesis of 2-(3,5-Bis(Trifluoromethyl)Phenyl)-4-Methoxyiodobenzene (4-32)



The title compound was prepared using the general procedure for the chemoselective Suzuki-Miyaura cross-coupling (**100%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ : 7.94 (bs, 1H), 7.86 (m, 2H), 7.35 (m, 1H), 6.91 (d, 1H, *J* = 3.0 Hz), 6.74 (dd, 1H, *J* = 3.0 Hz, *J* = 8.8 Hz), 3.85 (s, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 160.1, 145.6, 144.3, 140.5, 133.7 (q, *J* = 19.4 Hz), 131.4 (q, *J* = 33.5 Hz), 129.7, 128.6 (q, *J* =

7.2 Hz), 123.3 (q, *J* = 272.8 Hz), 116.1, 86.0, 55.5. **HRMS** (EI) for $C_{15}H_9F_6IO$: calcd. 445.96024; found, 445.96061.

4.5.3.5 *Synthesis of Tert-Butyl 2-Tert-Butyl-4-(2-Iodo-5-Methoxyphenyl) Phenylcarbamate* (4-33)

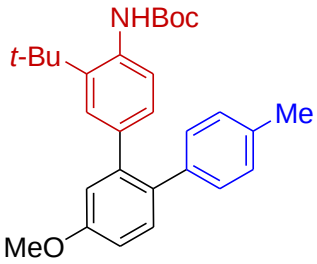


The title compound was prepared using the general procedure for the chemoselective Suzuki-Miyaura cross-coupling (**66%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ : 7.80 (d, 1H, *J* = 8.7 Hz), 7.66 (d, 1H, *J* = 7.8 Hz), 7.38 (d, 1H, *J* = 2.1 Hz), 7.20 (dd, 1H, *J* = 2.1 Hz, *J* = 8.2 Hz), 6.90 (d, 1H, *J* = 3.1 Hz), 6.64 (dd, 1H, *J* = 3.1 Hz, *J* = 8.7 Hz), 6.47 (bs, 1H), 3.80 (s, 3H), 1.54 (s, 9H), 1.46 (s, 9H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 159.8, 153.6, 147.4, 140.1, 135.2, 127.9, 127.2, 116.0, 115.0, 87.2, 80.4, 55.4, 36.6, 34.7, 30.7, 28.4, 24.7, 23.4. **HRMS** (EI) for $C_{22}H_{28}INO_3$: calcd. 481.11139; found, 481.11200.

4.5.4 General Procedure for One-pot Chemoselective Double Suzuki-Miyaura Couplings

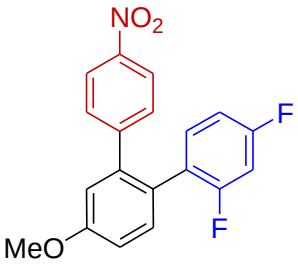
A flame dried flask was charged with 2-iodo-5-methoxyphenylboronic acid (0.10 g, 0.36 mmol), aryl iodide (0.33 mmol), tetrakis(triphenylphosphine)palladium (0) (46 mg, 12 mol%), toluene (2.0 mL), ethanol (0.20 mL) and a 2M solution of potassium carbonate (0.70 mL) under argon. The mixture was heated to 80 °C for 12-14 h. The mixture was cooled down to room temperature. Phenylboronic acid (0.36 mmol), and a 2M solution of potassium carbonate (0.70 mL) were added to the crude mixture. The mixture was heated again to 80 °C for 12 h. The reaction mixture was cooled to room temperature, the organic layer was separated, washed twice with water, brine, dried over Na_2SO_4 and filtered. The solvent was removed and the crude was purified by flash chromatography (20% EtOAc/hexanes) to provide the desired product.

4.5.4.1 Synthesis of 1-(4-Tolyl)-2-(3-Tert-Butyl-4-Tert-Butylcarbamatyl phenyl)-4-Methoxybenzene (4-34)



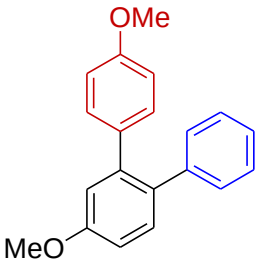
The title compound was prepared using the general procedure for the chemoselective double Suzuki-Miyaura cross-couplings (**51%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ : 7.60 (s, 1H), 7.35 (d, 1H, *J* = 8.4 Hz), 7.25 (d, 1H, *J* = 11.2 Hz), 7.21 (dd, 1H, *J* = 1.9 Hz, *J* = 8.2 Hz), 7.03-6.93 (m, 7H), 6.33 (bs, 1H), 3.88 (s, 3H), 2.30 (s, 3H), 1.52 (s, 9H), 1.15 (s, 9H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 158.8, 153.6, 141.6, 138.5, 135.5, 134.2, 133.3, 131.5, 129.9, 129.2, 128.5, 127.4, 115.5, 112.8, 80.2, 55.4, 30.3, 28.4, 24.7, 20.9. **HRMS** (EI) for $C_{29}H_{35}NO_3$: calcd. 445.26169; found, 445.26080.

4.5.4.2 Synthesis of 1-(2,4-Difluorophenyl)-2-(4-Nitrophenyl)-4-Methoxy Benzene (4-35)



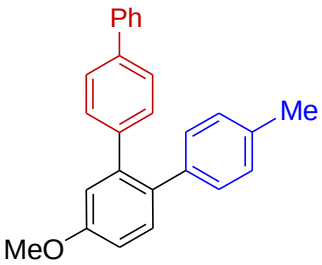
The title compound was prepared using the general procedure for the chemoselective double Suzuki-Miyaura cross-couplings (**85%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ : 8.09 (d, 2H, *J* = 8.9 Hz), 7.33 (d, 1H, *J* = 8.5 Hz), 7.30 (d, 2H, *J* = 8.9 Hz), 7.10 (ddd, 1H, *J* = 6.4 Hz, *J* = 8.5 Hz , *J* = 8.5 Hz), 7.04 (dd, 1H, *J* = 2.7 Hz, *J* = 8.5 Hz), 6.97 (d, 1H, *J* = 2.7 Hz), 6.81 (ddd, 1H, *J* = 1.0 Hz, *J* = 2.5 Hz , *J* = 8.2 Hz), 6.67 (ddd, 1H, *J* = 2.5 Hz, *J* = 8.9 Hz, *J* = 9.8 Hz), 3.90 (s, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 159.6, 147.5 (d, *J* = 154.5 Hz), 140.7, 132.7, 132.6, 132.5, 132.4, 129.9, 125.9, 123.2, 114.3 (d, *J* = 192.1 Hz), 111.4 (d, *J* = 3.6 Hz), 111.3 (d, *J* = 3.9 Hz), 104.2, 104.0, 103.8, 55.5. **HRMS** (EI) for $C_{19}H_{13}F_2NO_3$: calcd. 341.08636; found, 341.08626.

4.5.4.3 *Synthesis of 2-(4-Methoxyphenyl)-4-Methoxy-1-Phenylbenzene* (4-36)



The title compound was prepared using the general procedure for the chemoselective double Suzuki-Miyaura cross-couplings (**67%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ : 7.35 (dd, 1H, *J* = 1.0 Hz, *J* = 7.8 Hz), 7.21 (m, 3H), 7.14 (d, 1H, *J* = 1.7 Hz), 7.13 (d, 1H, *J* = 1.5 Hz), 7.09 (d, 2H, *J* = 8.9 Hz) , 6.98 (m, 1H), 6.78 (m, 2H), 3.89 (s, 3H), 3.79 (s, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 158.9, 158.4, 141.4, 141.3, 133.9, 133.2, 131.7, 130.8, 129.9, 128.2, 127.8, 125.9, 115.8, 114.1, 113.4, 112.7, 55.4, 55.1. **HRMS** (EI) for $C_{20}H_{18}O_2$: calcd. 290.13068; found, 290.13060.

4.5.4.4 *Synthesis of 1-(4-Tolyl)-2-(4-Biphenyl)-4-Methoxybenzene* (4-37)



The title compound was prepared using the general procedure for the chemoselective double Suzuki-Miyaura cross-couplings (**71%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ : 7.64 (ddd, 2H, *J* = 1.6 Hz, *J* = 3.2 Hz, *J* = 4.2 Hz), 7.53 (d, 2H, *J* = 8.5 Hz), 7.46 (m, 2H), 7.41 (d, 1H, *J* = 8.4 Hz), 7.37 (m, 1H), 7.29 (d, 2H, *J* = 8.5 Hz), 7.07 (m, 5H), 7.02 (dd, 1H, *J* = 2.7 Hz, *J* = 8.4 Hz), 3.93 (s, 3H), 2.35 (s, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 158.8, 141.2, 140.7, 139.2, 138.2, 135.7, 133.3, 131.8, 130.2, 129.8, 128.8, 128.7, 127.2, 126.9, 126.6, 115.8, 113.2, 55.4, 21.1. **HRMS** (EI) for $C_{26}H_{22}$: calcd. 350.16705 ; found, 350.16727.

4.6 References

[1] D. G. Hall, Ed. *Boronic Acids*; Wiley-VCH: Weinheim, **2005**

[2] W. Yang, X. Gao, B. Wang, *Med. Res. Rev.* **2003**, *23*, 346.

[3] N. Ni, G. Choudhary, H. Peng, M. Li, H. T. Chou, C. D. Lu, E. S. Gilbert, B. Wang, *Chem. Biol. Drug Des.* **2009**, *74*, 51.

[4] J. Y. Winum, A. Innocenti, A. Scozzafava, J. L. Montero, C. T. Supuran, *Bioorg. Med. Chem.* **2009**, *17*, 3649.

[5] B. E. Collins, S. Sorey, A. E. Hargrove, S. H. Shabbir, V. M. Lynch, E. V. Anslyn, *J. Org. Chem.* **2009**, *74*, 4055.

[6] T. M. Altamore, E. S. Barrett, P. J. Duggan, M. S. Sherburn, M. L. Szydzik, *Org. Lett.* **2002**, *4*, 3489.

[7] J. A. Riggs, K. A. Hossler, B. D. Smith, M. J. Karpa, G. Griffin, P. J. Duggan, *Tetrahedron Lett.* **1996**, *37*, 6303.

[8] H. Zheng, R. McDonald, D. G. Hall, *Chem. Eur. J.* **2010**, *16*, 5454.

[9] H. Zheng, D. G. Hall, *Tetrahedron Lett.* **2010**, *51*, 3561.

[10] H. Charville, D. Jackson, G. Hodges, A. Whiting, *Chem. Commun.* **2010**, *46*, 1813.

[11] I. Georgiou, G. Ilyashenko, A. Whiting, *Acc. Chem. Res.* **2009**, *42*, 756.

[12] K. Arnold, B. Davies, D. Hérault, A. Whiting, *Angew. Chem. Int. Ed.* **2008**, *47*, 2673.

[13] K. Arnold, A. S. Batsanov, B. Davies, A. Whiting, *Green Chem.* **2008**, *10*, 124.

[14] R. M. Al-Zoubi, O. Marion, D. G. Hall, *Angew. Chem. Int. Ed.* **2008**, *47*, 2876.

[15] T. Maki, K. Ishihara, H. Yamamoto, *Tetrahedron* **2007**, *63*, 8645.

[16] K. Arnold, B. Davies, R. L. Giles, C. Grosjean, G. E. Smith, A. Whiting, *Adv. Synth. Catal.* **2006**, *348*, 813.

[17] T. Maki, K. Ishihara, H. Yamamoto, *Org. Lett.* **2005**, *7*, 5043.

[18] T. Maki, K. Ishihara, H. Yamamoto, *Org. Lett.* **2005**, *7*, 5047.

[19] K. Ishihara, S. Ohara, H. Yamamoto, D. T. Amos, R. L. Danheiser, *Org. Synth.* **2002**, *79*, 167.

[20] K. Ishihara, S. Ohara, H. Yamamoto, D. T. Amos, R. L. Danheiser, *Org. Synth.* **2002**, *79*, 176.

[21] K. Ishihara, S. Kondo, H. Yamamoto, *Synlett* **2001**, 1371.

[22] K. Ishihara, S. Ohara, H. Yamamoto, *Macromolecules* **2000**, *33*, 3511.

[23] K. Ishihara, H. Yamamoto, *Eur. J. Org. Chem.* **1999**, 527.

[24] K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4196.

[25] A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147.

[26] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.

[27] J. Adams, *Drug Discovery Today* **2003**, *8*, 307.

[28] J. Adams, *Curr. Opin. Chem. Biol.* **2002**, *6*, 493.

[29] J. Adams, M. Behnke, S. Chen, A. A. Cruickshank, L. R. Dick, L. Grenier, J. M. Klunder, Y. T. Ma, L. Plamondon, R. L. Stein, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 333.

[30] T. Mc Cormack, W. Baumeister, L. Grenier, C. Moomaw, L. Plamondon, B. Pramanik, C. Slaughter, F. Soucy, R. Stein, F. Zuhl, L. Dick, *J. Bio. Chem.* **1997**, *272*, 26103.

[31] S. Kumar, A. B. Kimball, *Expert Opin. on Investigational Drugs* **2009**, *18*, 727.

[32] S. J. Baker, Y. K. Zhang, T. Akama, A. Lau, H. Zhou, V. Hernandez, W. Mao, M. R. K. Alley, V. Sanders, J. J. Plattner, *J. Med. Chem.* **2006**, *49*, 4447.

[33] N. Miyaura, T. Yanagi, A. Suzuki, *Synth. Commun.* **1981**, *11*, 513.

[34] P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan, A. Combs, *Tetrahedron Lett.* **1998**, *39*, 2941.

[35] D. G. Hall, *Synlett* **2007**, 1644.

[36] H. Lachance, D. G. Hall*, Vol. 73*, Ed: S.E. Denmark, Wiley, New York, **2009**.

[37] M. A. Beenen, D. J. Weix, J. A. Ellman, *J. Am. Chem. Soc.* **2006**, *128*, 6304.

[38] N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1997**, *119*, 445.

[39] T. Furuya, T. Ritter, *Org. Lett.* **2009**, *11*, 2860.

[40] T. Furuya, H. M. Kaiser, T. Ritter, *Angew. Chem. Int. Ed.* **2008**, *47*, 5993.

[41] C. Cazorla, E. Mètay, B. Andrioletti, M. Lemaire, *Tetrahedron Lett.* **2009**, *50*, 3936.

[42] A. Sniady, *Synlett* **2006**, 960.

[43] C. Thiebes, G. K. S. Prakash, N. A. Petasis, G. A. Olah, *Synlett* **1998**, 141.

[44] G. K. S. Prakash, M. D. Moran, T. Mathew, G. A. Olah, *J. Fluorine Chem.* **2009**, *130*, 806.

[45] G. K. Surya Prakash, C. Panja, T. Mathew, V. Surampudi, N. A. Petasis, G. A. Olah, *Org. Lett.* **2004**, *6*, 2205.

[46] S. Mothana, J. M. Grassot, D. G. Hall, *Angew. Chem. Int. Ed.* **2010**, *49*, 2883.

[47] S. Mothana, N. Chahal, S. Vanneste, D. G. Hall, *J. Comb. Chem.* **2007**, *9*, 193.

[48] H. G. Kuivila, L. E. Benjamin, C. J. Murphy, A. D. Price, J. H. Polevy, *J. Org. Chem.* **1962**, *27*, 825.

[49] All attempts to reproduce this work were not successful in my hands.

[50] R. Johnsson, A. Meijer, U. Ellervik, *Tetrahedron* **2005**, *61*, 11657.

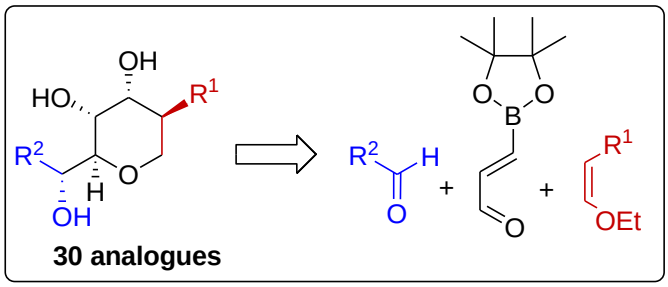
[51] R. M. Al-Zoubi, D. G. Hall, *Org. Lett.* **2010**, *12*, 2480.

[52] E. B. Merkushev, *Synthesis* **1988**, 923.

[53] CCDC-767421 and 767422 contain the supplementary crystallographic data for compounds **4-9** and **4-14**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Diversity-Oriented Synthesis of a 30 Member Library of Thiomarinol Analogues via oxa[4+2] Cycloaddition/Allylboration Methodology

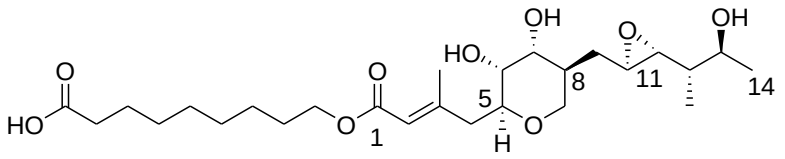
A small library of 30-thiomarinol analogues was successfully synthesized through a methodology involving a tandem oxa[4+2] cycloaddition/allylboration developed in the Hall Laboratory. The first section considers the synthesis of highly substituted α-hydroxyalkyl dihydropyran systems in a single step utilizing a wide variety of aldehydes, such as aromatic, heteroaromatic, unsaturated and aliphatic aldehydes with three different enol ethers. In the second section, a benign method for acetal reduction of α-hydroxyalkyl dihydropyrans without the need for hydroxyl group protection, which facilitated the synthesis of this library and affords α-hydroxyalkyl 2*H*–pyrans in good to excellent yields, is revealed. Lastly, dihydroxylations of α-hydroxyalkyl 2*H*–pyrans to provide the desired thiomarinol analogues with proof of stereochemistry are disclosed in the third section.



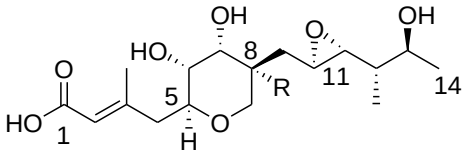
5.1 Introduction

Mupirocin (pseudomonic acid A, **Figure 5-1**) is one of the world's leading topical antibiotics commercialized by GlaxoSmithKline under the name Bactroban®.[1] It is produced by *Pseudomonas fluorescens* and reported to possess antibacterial activity as early as 1887.[2] In the 1960s, the mixture of pseudomonic acids was found to be the active component.[3] The major constituent was identified and characterized in the 1970s and named pseudomonic acid A (mupirocin).[4, 5] Mupirocin is active against Gram-positive aerobic bacteria and a few Gram-negative strains. It is

prescribed for treating skin infections, such as impetigo, candidiasis as well as burn wounds and cuts.



mupirocin (pseudomonic acid A, Bactroban®)
pseudomonic acid C (C10-C11 is an *E*-alkene)



monic acid

Figure 5-1: Structures of mupirocin (pseudomonic acid A) and monic acid.[1]

Furthermore, it inhibits the bacterial isoleucyl tRNA synthetase enzyme responsible for loading the amino acid isoleucine (Ile) onto its cognate tRNA, the required enzyme for ribosomal protein synthesis (**Figure 5-2**).[6] Aminoacyl tRNA synthetases belong to a superfamily of nucleotidyl transferase enzymes related to other ATP-binding proteins, such as dehydrogenases and photolyase. There is at least one discrete synthetase per specific amino acid. These enzymes are divided into two related classes, I or II, depending on whether they acylate the 2′ or 3′ end of the tRNA (**Figure 5-2**).[7, 8] The $tRNA^{Ile}$ synthetase (a class I synthetase) and some other synthetases even possess an editing site for correcting misloaded amino acids. Although the synthetase site of these enzymes holds substrates in place without involving any covalent bonds or proton exchange with the functional groups of the enzyme, it stabilizes with very conserved residues (the so-called HIGH box) the transition state for cleavage of the α-phosphate upon nucleophilic attack by the amino acid carboxylate.[9]

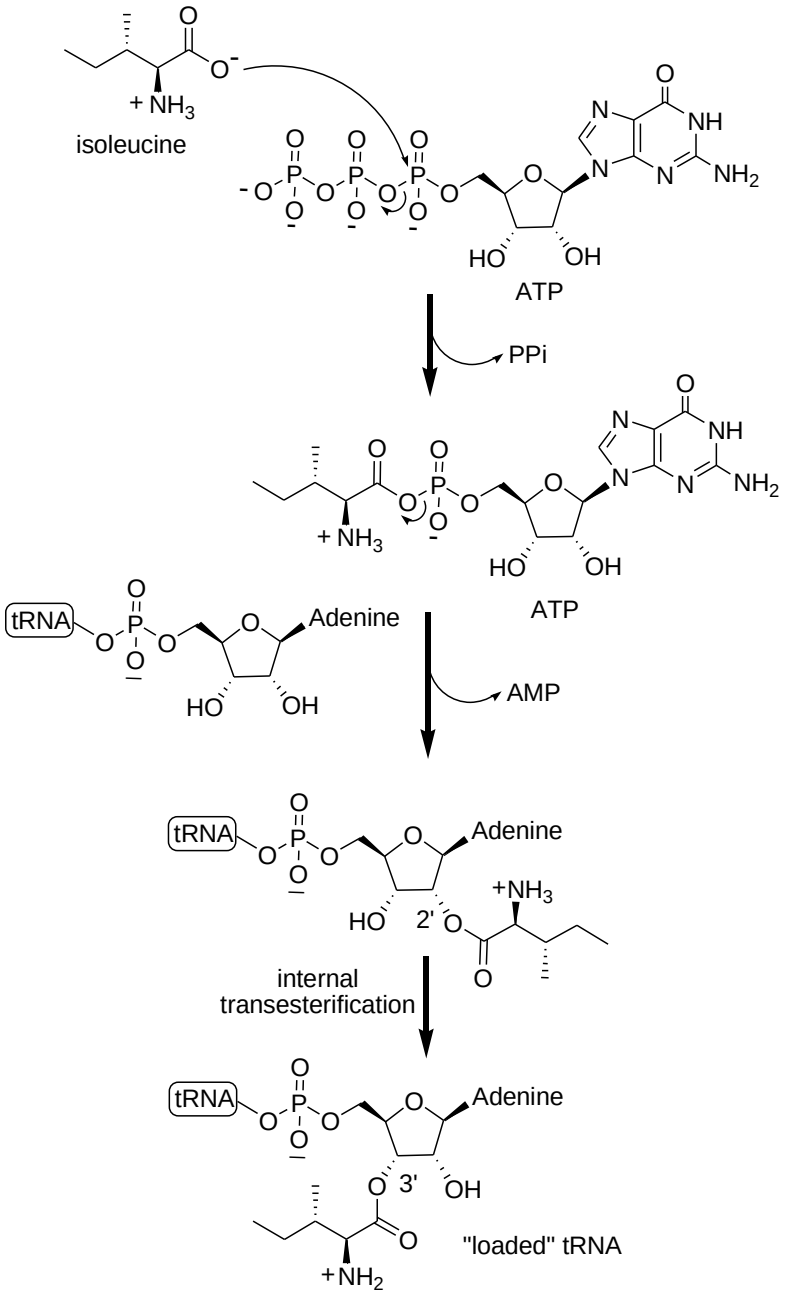


Figure 5-2: Mechanism of action for tRNA^{Ile} synthetase, a class I aminoacyl tRNA synthetase.[6]

Mupirocin is found to be 10,000 times more potent on the bacterial enzyme than on the human homologue, which ensures its selectivity as a pharmaceutical drug.[10, 11] The binding of mupirocin to the enzyme–tRNA complex is competitive with isoleucine and ATP, and also with Ile-AMP derivatives. The X-ray crystal structure of mupirocin bound to the complex between tRNA^{Ile} synthetase and its cognate tRNA

was solved in 1999.[12] The X-ray structure confirmed that the right-hand side chain of mupirocin does not occupy the site that would normally stabilize the phosphatidyl isoleucine. Furthermore, it also confirmed that mupirocin acts mainly as an ATP mimic and occupies the site normally occupied by the ribose ring. The map of the main molecular interactions in the mupirocin–tRNA^{Ile} complex is shown in **Figure 5-3**. Critical to the inhibitor complex is a π–π* interaction between Phe 587 and the acrylate moiety, which is also held in place with a backbone hydrogen bond between Val 588 and the carbonyl oxygen.

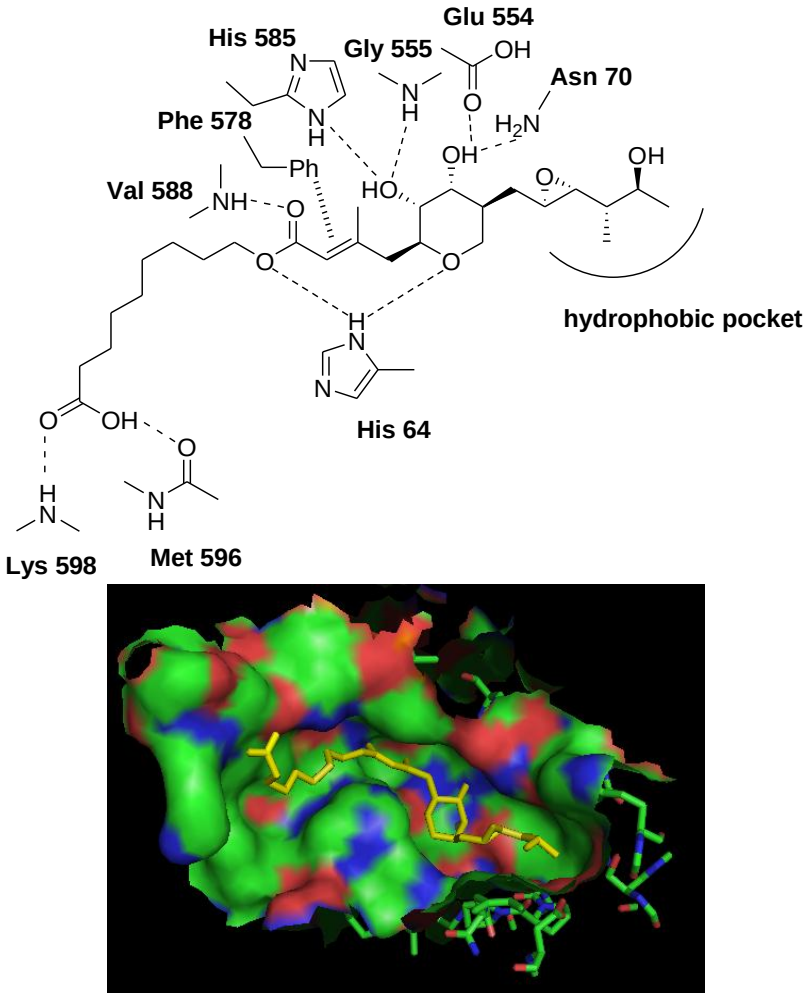


Figure 5-3: Map of main molecular interactions in the mupiroin-tRNA^{Ile} complex.[12, 13]

Pseudomonic acids have attracted considerable attention for their unique structure and biological activity.[14] Unfortunately, mupirocin displays poor oral absorptivity

and low metabolic stability. In the bloodstream, its ester linkage is quickly hydrolyzed to an inactive product, monic acid.[15] Consequently, there has been significant interest in the development of improved analogues that could also be suitable as oral antibiotics. Thiomarinol A[16] and thiomarinol H[17] and others[18, 19] (**Figure 5-4**) are rare marine natural products recently isolated from the bacterium *Alteromonas rava* sp. nov. SANK 73390. These closely related families of naturally occurring antibiotics display minor structural differences.

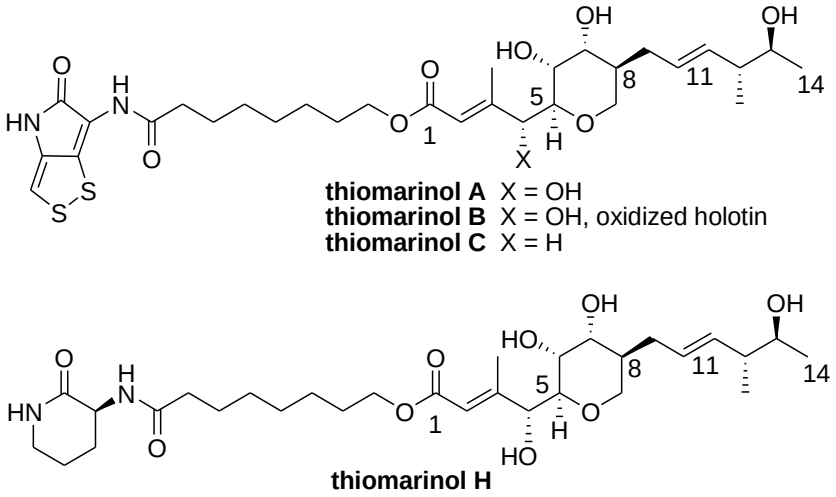


Figure 5-4: Structures of selected members of the thiomarinol family.[16,17, 18, 19]

The structures of thiomarinols A and H differ from mupirocin by the presence of a C4-hydroxyl, a shorter C1-alkoxy chain, and the replacement of the C10–C11 epoxide with an *E* alkene unit. Based on the X-ray crystal structure of the mupirocin–tRNA^{Ile} synthetase complex, an additional hydroxyl group at carbon 4 in thiomarinols might be able to form hydrogen bonds with His64 and Asp557 in the bacterial enzyme, thereby improving their antimicrobial activity (**Figure 5-4**). Thiomarinols A and H are distinguishable by their respective holotin and anhydroornithine C1 amide end-groups. These natural substances were found to be equally potent as pseudomonic acid A, and thiomarinol A was found to possess a wider spectrum of activity (against both Gram-positive and -negative bacteria).[16, 17] Our group has recently synthesized thiomarinol H[20] and other thiomarinol analogues[13] using a synthetic route that we postulated could be amenable to the design of simplified analogues.

It is believed that mupirocin and the thiomarinols share the same target, bacterial isoleucine tRNA synthetase. A pharmacophore model of mupirocin was developed even before the availability of X-ray crystallographic information,[12] which revealed that the dihydroxypyran core is essential for the antibacterial activity and it should be conserved. It was also shown that the left-hand and right-hand side chains are quite variable, as shown in **Figure 5-5**.

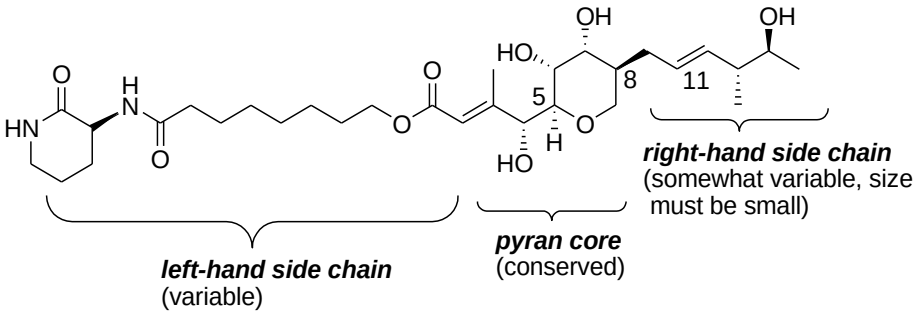


Figure 5-5: Qualitative pharmacophore model for mupirocin.

Professor Waldmann at the Max-Planck-Institute for Molecular Physiology in Dortmund, Germany, has been a strong advocate of the value of natural products in drug discovery. He believes that natural products are ideal lead structures in combinatorial library design with convincing examples in his review paper in **2002**.[21] A collaborative study between Professors Hall and Waldmann was planned using the Protein Structure Similarity Clustering (**PSSC**) computational approach developed in Waldmann's Laboratory.

PSSC is a novel approach for the identification of new groups of compounds based on structure by abstracting principles and similarity studies. This approach helps guide chemists in identifying targets for the synthesis of small focused libraries of biologically interesting and drug-like compounds. The steps for using the PSSC approach are summarized in **Figure 5-6**.[21]

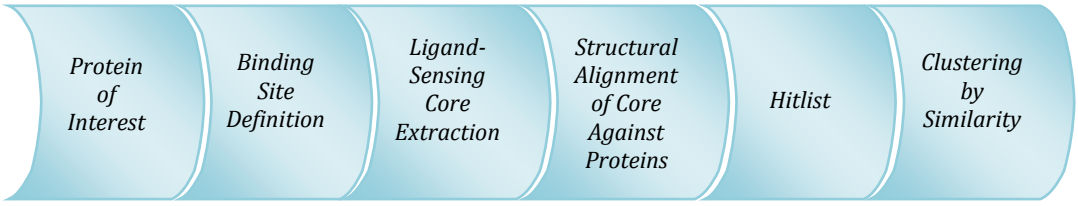


Figure 5-6: Automated Protein Structure Similarity Clustering (PSSC).[21]

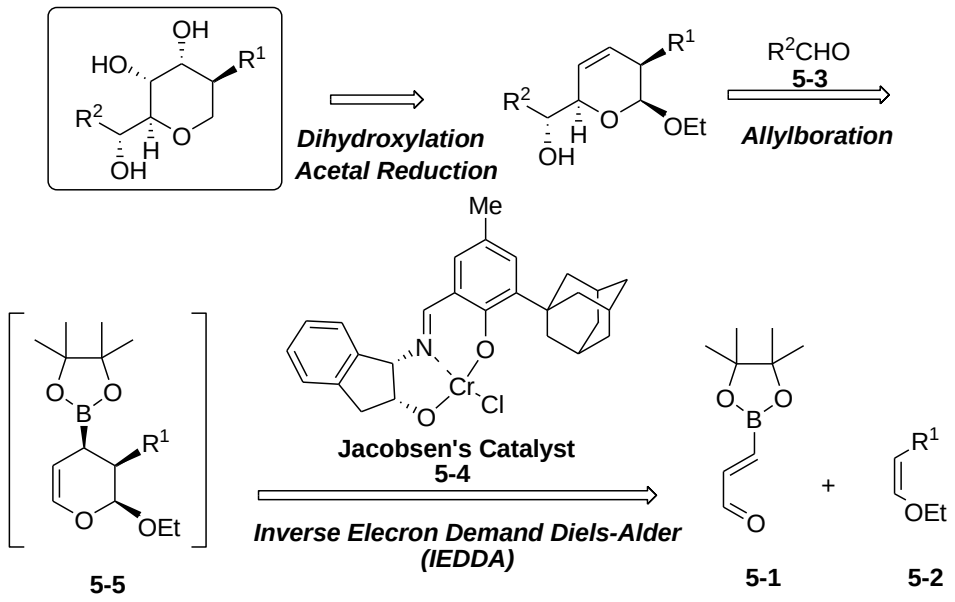
The first step of this approach is finding a protein of interest whose X-ray structure bound to a small-molecule is known. The second step is the studying of the maximum binding interactions (i.e. H-bonding, hydrophobic and hydrophilic interactions) between the bound molecule and the protein. Identifying the core structure that has the maximum interactions is the third step of this approach. Using this core structure is the guiding principle for finding other protein targets with similar binding scaffolds is the fourth step. Lastly, the identified protein hits that have similar folding are classified by similarity. Consequently, a small structural diversity library of compounds is then synthesized by addressing the core binding sites of the PSSC member proteins.[21]

This approach was applied to the known X-ray crystal structure[12] of mupirocin bound to the bacterial isoleucyl tRNA synthase, and revealed different protein targets for screening, such as *phosphopantetheine adenyltransferase, pantothenate synthetase, muconate lactonizing enzyme, glycerol-3-phosphate cytidylytransferase (GCT)* and *nicotinate mononucleotide adenylyltransferase.*

To address the effect of the structural differences between mupirocin and the thiomarinols on their respective antimicrobial activity, and to screen mupirocin analogues against some of the above PSSC targets, we planned to design a library of thiomarinol analogues. The library is small in size (30 members) because it has only two changeable parts around the pyran core (**Figure 5-5**): the left-hand and the right-hand side chains. The screening study of this library against the same target, the bacterial isoleucyl tRNA synthetase, will proceed in the laboratories of Professor Eric Brown at McMaster University.

5.2 Library of Thiomarinol Analogues Through Diversity-Oriented Synthesis

All the thiomarinol analogues were prepared though a catalytic enantioselective inverse electron demand hetero [4 + 2] cycloaddition/allylboration tandem reaction between boronoacrolein pinacol ester **5-1**, enol ether **5-2**, and aldehyde **5-3** developed in the Hall Laboratory (**Scheme 5-1**).[22] The cycloaddition step is catalyzed by Jacobsen's Cr(III) complex **5-4**.[23, 24] This multicomponent reaction functions well with a wide range of enol ethers and aldehydes, and was demonstrated successfully in the total synthesis of thiomarinol H.[20] Acetal reduction and a stereoselective dihydroxylation of dihydropyrans would afford the desired thiomarinol analogues.

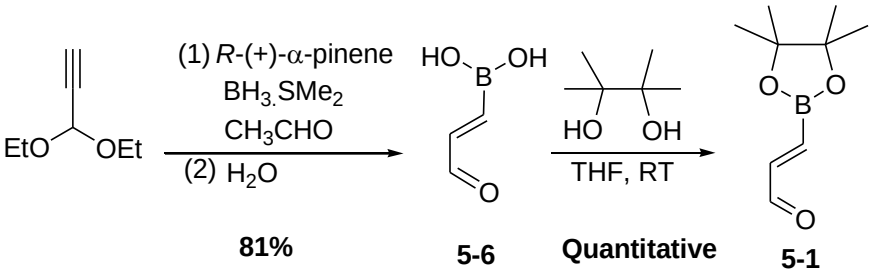


Scheme 5-1: Three-component hetero [4+2] cycloaddition/allylboration reaction approach to thiomarinol analogues.[22]

5.2.1 Synthesis of α-Hydroxyalkyl Dihydropyran Analogues

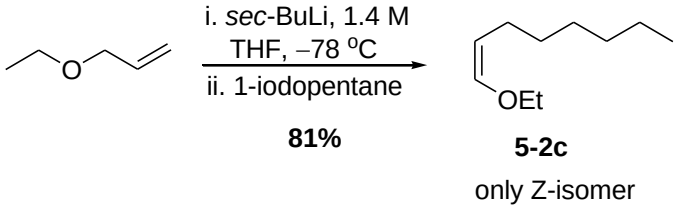
Based upon previous work in the Hall group[20, 22] revolving around the three-component oxa[4+2] cycloaddition/allylboration reaction, *(E)*-3-boronoacrolein **5-6** was made in good yield and the boronic acid group was protected with pinacol to

form the ester derivative **5-1** in two steps from readily available (*R*)-(+)-α-pinene in 90% overall yield (**Scheme 5-2**).



Scheme 5-2: Preparation of (*E*)-3-boronoacrolein pinacol ester 5-1.[20, 22]

Three different enol ethers **5-2a**, **5-2b** and **5-2c** were used during the synthesis of this library. **5-2c** was made using a known method as shown in **Equation 5-1**,[25, 26] while **5-2a** and **5-2b** were commercially available (**Figure 5-7**).



Equation 5-1: Preparation of (*Z*)-1-ethoxyoct-1-ene.[25, 26]

The previous work and expertise in the Hall group regarding the three-component [4+2] cycloaddition/ allylboration reaction meant that no further optimization was required. The thermal allylboration reaction requires longer reaction times and elevated temperatures with enol ether **5-2c** than with enol ethers **5-2a** and **5-2b**. Towards this end, (*E*)-3-boronoacrolein pinacol ester **5-1** was reacted with enol ethers **5-2(a-c)** to form the cycloadduct products **5-5** which then reacted with a wide variety of aldehydes **5-3(a-u)** (**Figure 5-7**) to provide the desired α-hydroxyalkyl dihydropyran analogues (**Table 5-1**).

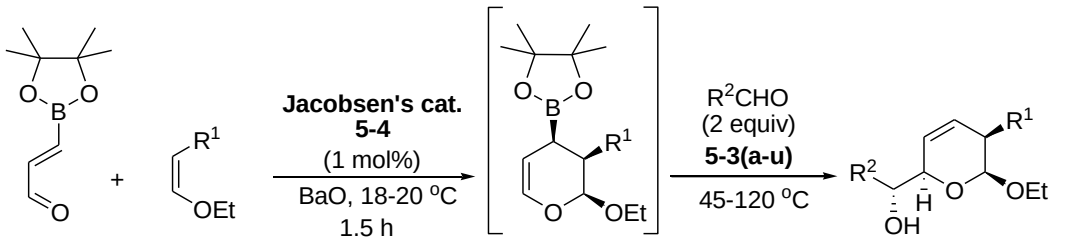


Table 5-1: Synthesis of α-hydroxyalkyl pyrans from (*E*)-3-boronoacrolein pinacol ester 5-1, enol ether 5-2(a-c) and aldehyde 5-3(a-u).

Entry	Enol ether	Aldehyde	α-Hydroxyalkyl dihydropyran	%Yields
1	**5-2a**	**5-3a**	**5-7**	67
2	**5-2a**	**5-3b**	**5-8**	65
3	**5-2a**	**5-3c**	**5-9**	38
4	**5-2a**	**5-3d**	**5-10**	62
5	**5-2a**	**5-3e**	**5-11**	75
6	**5-2a**	**5-3f**	**5-12**	73
7	**5-2a**	**5-3g**	**5-13**	47
8	**5-2a**	**5-3h**	**5-14**	51
9	**5-2a**	**5-3i**	**5-15**	71
10	**5-2a**	**5-3j**	**5-16**	81
11	**5-2a**	**5-3k**	**5-17**	49
12	**5-2a**	**5-3l**	**5-18**	81
13	**5-2a**	**5-3m**	**5-19**	79
14	**5-2a**	**5-3n**	**5-20**	36
15	**5-2a**	**5-3o**	**5-21**	69
16	**5-2a**	**5-3p**	**5-22**	54
17	**5-2a**	**5-3q**	**5-23**	59
18	**5-2a**	**5-3r**	**5-24**	65
19	**5-2b**	**5-3a**	**5-25**	79
20	**5-2b**	**5-3b**	**5-26**	50
21	**5-2b**	**5-3c**	**5-27**	65
22	**5-2b**	**5-3d**	**5-28**	61
23	**5-2b**	**5-3e**	**5-29**	63
24	**5-2b**	**5-3g**	**5-30**	93
25	**5-2b**	**5-3h**	**5-31**	97

26	**5-2b**	**5-3i**	**5-32**	59
27	**5-2b**	**5-3j**	**5-33**	78
28	**5-2b**	**5-3k**	**5-34**	53
29	**5-2b**	**5-3l**	**5-35**	74
30	**5-2b**	**5-3m**	**5-36**	59
31	**5-2b**	**5-3q**	**5-37**	58
32	**5-2b**	**5-3s**	**5-38**	84
33	**5-2b**	**5-3t**	**5-39**	63
34	**5-2b**	**5-3u**	**5-40**	70
35	**5-2c**	**5-3a**	**5-41**	79
36	**5-2c**	**5-3b**	**5-42**	72
37	**5-2c**	**5-3c**	**5-43**	65
38	**5-2c**	**5-3g**	**5-44**	67
39	**5-2c**	**5-3h**	**5-45**	62
40	**5-2c**	**5-3l**	**5-46**	72
41	**5-2c**	**5-3m**	**5-47**	43
42	**5-2c**	**5-3s**	**5-48**	75
43	**5-2c**	**5-3t**	**5- 49**	57

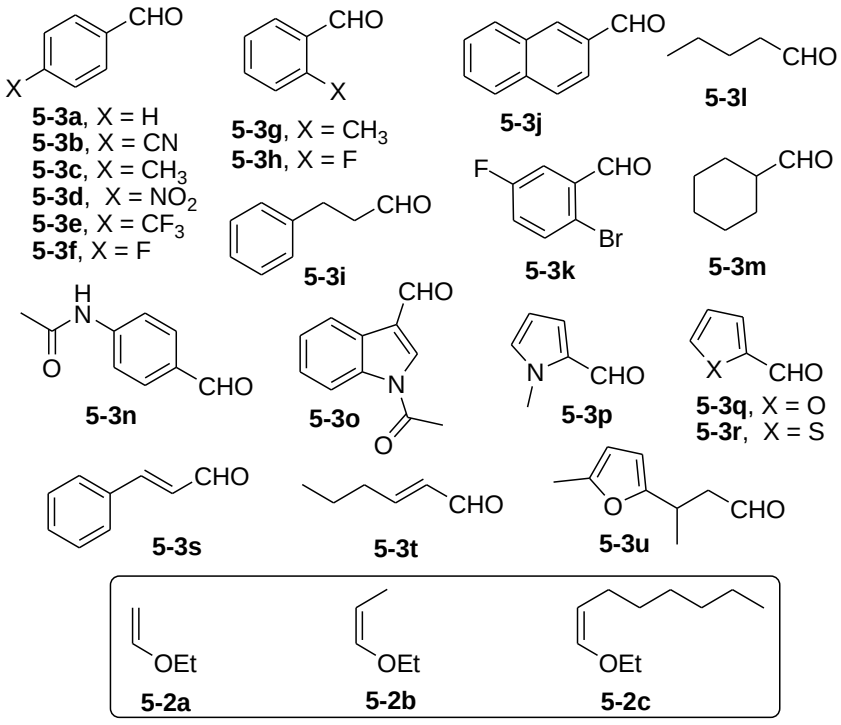
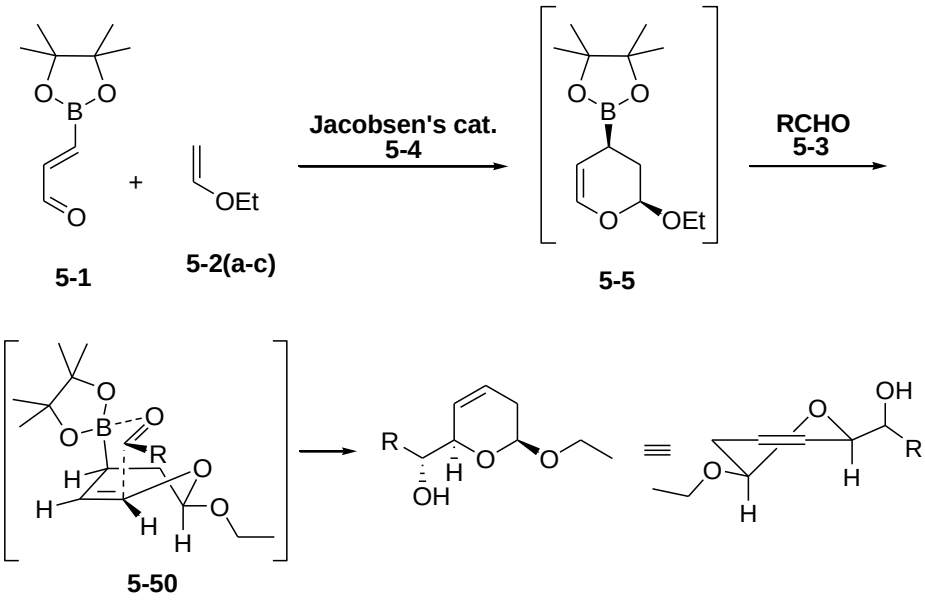


Figure 5-7: Aldehydes 5-3(a-u) and enol ethers 5-2(a-c) as diversity reagents.

One will observe the generality of aldehydes that can be utilized in the three-component oxa[4+2] cycloaddition/allylboration reaction. A variety of substituted aromatic, heteroaromatic, α,β-unsaturated and aliphatic aldehydes are all suitable substrates for this tandem reaction. All cycloaddition reactions were performed at a temperature between 18–20 °C, and purified by flash chromatography (deactivated silica) following the general published procedure from our group.[20, 22]

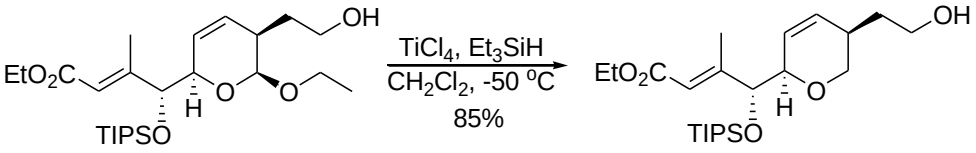
The relative stereochemistry of the optically enriched α-hydroxyalkyl dihydropyran products was confirmed by the X-ray crystallographic analysis of one of the library members (c.f. Section 5.2.3). Mechanistically, the [4+2] cycloaddition of 1-boronoacrolein pinacolate **5-1** with ethyl vinyl ether is expected to proceed with complete *endo* selectivity to give the allylboronate intermediate **5-5**. In the allylboration step, a boat-like transition state **5-50** with a pseudo-equatorial ethoxy substituent was proposed[22] leading to the desired α-hydroxyalkyl dihydropyran product as shown in **Scheme 5-3**.



Scheme 5-3: Stereoselectivity of tandem three-component oxa[4+2] cycloaddition/ allylboration reaction.[22, 27]

5.2.2 Acetal Reduction of α-Hydroxyalkyl Dihydropyrans

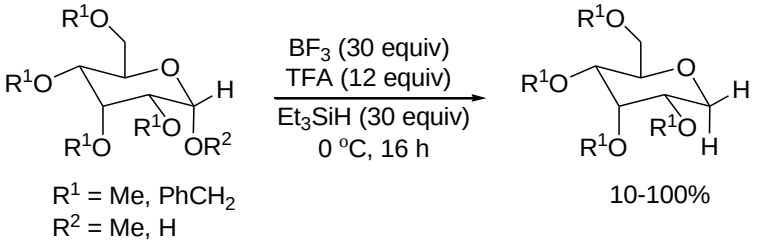
We then turned our attention to the acetal reduction of these α-hydroxyalkyl dihydropyran products. The previous expertise in the Hall group regarding this step was performed with a protected secondary alcohol using $TiCl_4/Et_3SiH$ conditions [20, 27, 28], as shown in **Equation 5-2**.



Equation 5-2: Acetal reduction of one of the α-hydroxyalkyl dihydropyran derivatives using $TiCl_4/Et_3SiH$.[20, 27, 28]

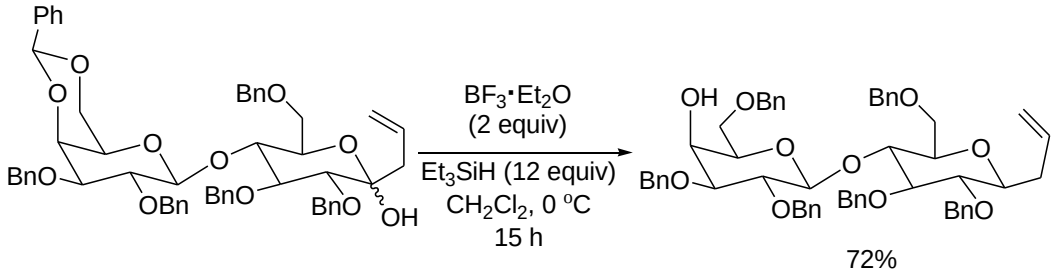
For simplification of the library work, it was obvious to try to reduce the acetal moiety directly from α-hydroxyalkyl dihydropyrans without protecting the α-hydroxyl group. Unfortunately, the acetal reduction reaction under $TiCl_4/Et_3SiH$ was unsuccessful for the unprotected α-hydroxyl dihydropyrans, providing other reduced products.

Nevertheless, many standard conditions for acetal reduction can be found in the literature. For instance, Gray and co-workers published in 1982 a report on the reductive cleavage of glycosides using $BF_3{\cdot}Et_2O/TFA/Et_3SiH$ conditions to provide the reduced acetal product in good to excellent yields at 0 °C, as demonstrated in **Equation 5-3**.[29]



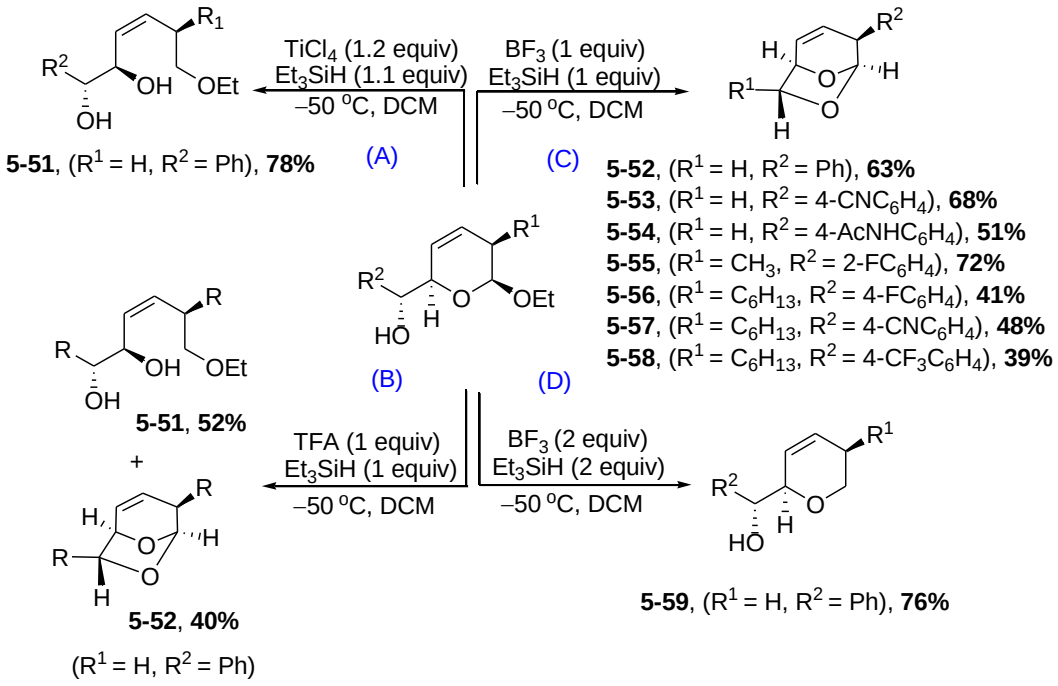
Equation 5-3: Acetal reductive cleavage of glycosides using $BF_3{\cdot}Et_2O/TFA/Et_3SiH$ conditions.[29]

In 2000, Toone and co-workers reported a regioselective reduction of 4,6-*O*-benzylidenes using $BF_3{\cdot}Et_2O/Et_3SiH$ at 0 °C (**Equation 5-4**).[30]



Equation 5-4: Acetal reductive cleavage using $BF_3{\cdot}Et_2O/Et_3SiH$ conditions.[30]

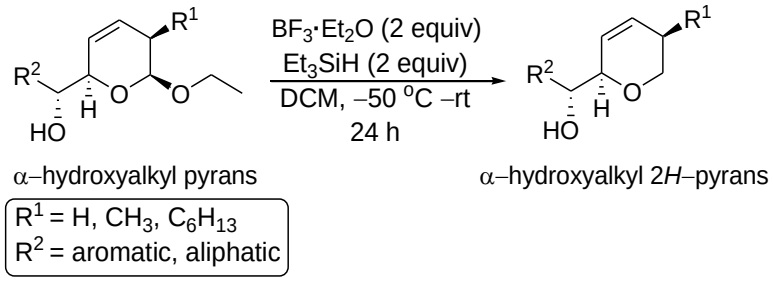
A number of different reagents have been employed for the reduction of acetal units by other investigators, such as $LiAlH_4–AlCl_3$[31], $NaCNBH_3/HCl$[32], Et_3SiH/TFA[33], and $EtAlCl_2/Et_3SiH$.[34] With this precedent in mind, initial trials were conducted to investigate the best conditions to provide the requisite acetal reduced products in our library synthesis without any decomposition and unwanted side products. For instance, the use of 1.2 equivalents of $TiCl_4/Et_3SiH$ at –50 °C provided the acetal ring open product **5-51** in 78% yield (**Scheme 5-4, Eq. A**), while the use of TFA/Et_3SiH provided a mixture of acetal ring open product **5-51** and bicyclic product **5-52** (**Scheme 5-4, Eq. B**).



Scheme 5-4: The effect of acid/Et_3SiH conditions on acetal reduction of α-hydroxyalkyl dihydropyrans.

The use of only 1 equivalent of $BF_3{\cdot}Et_2O/Et_3SiH$ cleanly provided the bicyclic products **5-52** to **5-58** in moderate to good yields (**Scheme 5-4, Eq. C**). The most suitable conditions were found to be the use of 2 equivalents of $BF_3{\cdot}Et_2O/Et_3SiH$ to provide the desired reduced product in good to excellent yields (**Table 5-2**).

With conditions in hand that would provide the desired α-hydroxyalkyl 2*H*–pyran products and would also be amenable to library synthesis, a subset of α-hydroxyalkyl dihydropyran substrates was selected for acetal reduction reaction under the optimized conditions. Towards this end, most of the α-hydroxyalkyl dihydropyrans were successfully reduced, generating the desired products, except those which have an allylic or benzylic alcohol (**Table 5-2, entries 32, 33, 42** and **43**) and also those bearing a heterocyclc ring (**Table 5-2, entries 15, 16, 17** and **18**), which decomposed immediately upon the addition of the boron trifluoride reagent.



α–hydroxyalkyl pyrans

R^1 = H, CH_3, C_6H_{13}
R^2 = aromatic, aliphatic

α–hydroxyalkyl 2*H*–pyrans

Table 5-2: Acetal reduction of α-hydroxyalkyl dihydropyrans using $BF_3{\cdot}Et_2O/Et_3SiH$.

Entry	α-Hydroxyalkyl dihydropyrans	R^1	R^2	Product	%Yields
1	**5-7**	H	C_6H_5	**5-59**	76
2	**5-8**	H	4-CNC_6H_4	**5-60**	31
3	**5-9**	H	4-MeC_6H_4	**5-61**	13
4	**5-10**	H	4-$NO_2C_6H_4$	**5-62**	74
5	**5-11**	H	4-$CF_3C_6H_4$	**5-63**	59
6	**5-12**	H	4-FC_6H_4	**5-64**	53
7	**5-13**	H	2-MeC_6H_4	**5-65**	57
8	**5-14**	H	2-FC_6H_4	**5-66**	91
9	**5-15**	H	$PhCH_2CH_2$	**5-67**	45
10	**5-16**	H	2-naphthyl	**5-68**	78

11	**5-17**	H	2-Br-5-FC_6H_3	**5-69**	88
12	**5-18**	H	C_4H_{11}	**5-70**	59
13	**5-19**	H	C_6H_{11}	**5-71**	73
14	**5-20**	H	4-AcNHC_4H_4	**5-72**	0
15	**5-21**	H	N-Ac-3-indolyl	**5-73**	0
16	**5-22**	H	N-CH_3-2-pyrolyl	**5-74**	0
17	**5-23**	H	furanyl	**5-75**	0
18	**5-24**	H	thiophen-2-yl	**5-76**	0
19	**5-25**	CH_3	C_6H_5	**5-77**	52
20	**5-26**	CH_3	4-CNC_6H_4	**5-78**	48
21	**5-27**	CH_3	$PhCH_2CH_2$	**5-79**	52
22	**5-28**	CH_3	4-MeC_6H_4	**5-80**	0
23	**5-29**	CH_3	2-MeC_6H_4	**5-81**	31
24	**5-30**	CH_3	4-$CF_3C_6H_4$	**5-82**	61
25	**5-31**	CH_3	4-FC_6H_4	**5-83**	60
26	**5-32**	CH_3	2-FC_6H_4	**5-84**	69
27	**5-33**	CH_3	2-naphthyl	**5-85**	0
28	**5-34**	CH_3	2-Br-5-F-C_6H_3	**5-86**	76
29	**5-35**	CH_3	C_4H_{11}	**5-87**	76
30	**5-36**	CH_3	C_6H_{11}	**5-88**	81
31	**5-37**	CH_3	Furanyl	**5-89**	0
32	**5-38**	CH_3	PhCHCH	**5-90**	0
33	**5-39**	CH_3	$CH_3(CH_2)_2CHCH$	**5-91**	0
34	**5-40**	CH_3	2-(5-methyl furan-2-yl)propyl	**5-92**	0
35	**5-41**	C_6H_{13}	C_6H_5	**5-93**	75
36	**5-42**	C_6H_{13}	4-CNC_6H_4	**5-94**	67
37	**5-43**	C_6H_{13}	$PhCH_2CH_2$	**5-95**	77
38	**5-44**	C_6H_{13}	4-$CF_3C_6H_4$	**5-96**	71
39	**5-45**	C_6H_{13}	4-FC_6H_4	**5-97**	51
40	**5-46**	C_6H_{13}	C_4H_{11}	**5-98**	97
41	**5-47**	C_6H_{13}	C_6H_{11}	**5-99**	67
42	**5-48**	C_6H_{13}	PhCHCH	**5- 100**	0
43	**5-49**	C_6H_{13}	$CH_3(CH_2)_2CHCH$	**5- 101**	0

The reactions were run independently at –50 °C for 1 hour and allowed to warm up to room temperature for 12 hours and once reactions were completed, they were basified with bicarbonate, extracted with dichloromethane, concentrated and autoflashed using combi*flash*® system to provide the desired α-hydroxyalkyl 2*H*-pyrans **in** yields ranging from 13-91%.

5.2.3 Dihydroxylation of α-Hydroxyalkyl 2*H*–Pyran Derivatives into "Thiomarinol Analogues"

After the successful optimization of the acetal reduction and without the need for alcohol protection, thiomarinol analogues were synthesized by dihydroxylation of the α-hydroxyalkyl 2*H*-pyrans following the standard published reaction conditions.[20, 22, 27, 35] A subset of α-hydroxyalkyl 2*H*–pyrans were subjected to the optimized reaction conditions and subsequently worked up and purified by combi*flash*® system. Towards this end, all α-hydroxyalkyl 2*H*–pyrans were successfully dihydroxylated to provide 30 derivatives of the requisite thiomarinol analogues (**Figure 5-8**) in isolated yields ranging from 35-95% (**Table 5-3**).

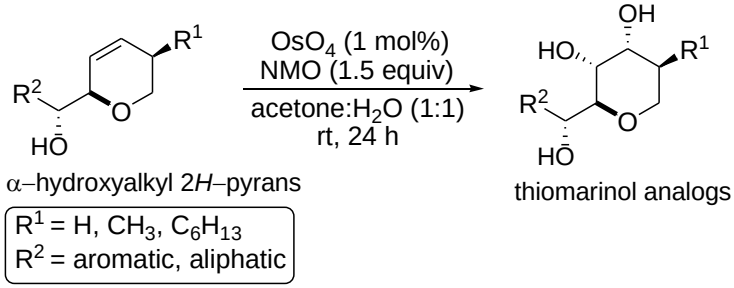
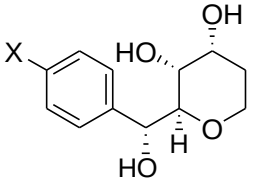


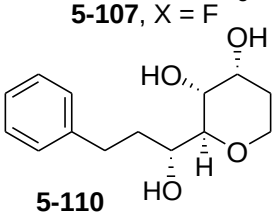
Table 5-3: Dihydroxylation of α-hydroxyalkyl 2*H*-pyrans using OsO_4/NMO conditions.

Entry	α-Hydroxyalkyl 2*H*–pyrans	R^1	R^2	Product	%Yields
1	**5-51**	H	C_6H_5	**5-102**	66
2	**5-52**	H	4-CNC_6H_4	**5-103**	75
3	**5-53**	H	4-MeC_6H_4	**5-104**	51
4	**5-54**	H	4-$NO_2C_6H_4$	**5-105**	72
5	**5-55**	H	4-$CF_3C_6H_4$	**5-106**	85
6	**5-56**	H	4-FC_6H_4	**5-107**	52
7	**5-57**	H	2-MeC_6H_4	**5-108**	51

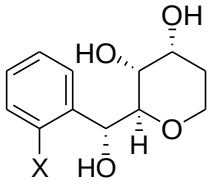
8	**5-58**	H	2-FC_6H_4	**5-109**	52
9	**5-59**	H	$PhCH_2CH_2$	**5-110**	78
10	**5-60**	H	2-naphthyl	**5-111**	71
11	**5-61**	H	2-Br-5-FC_6H_3	**5-112**	74
12	**5-65**	H	C_4H_{11}	**5-113**	89
13	**5-66**	H	C_6H_{11}	**5-114**	62
14	**5-67**	CH_3	C_6H_5	**5-115**	77
15	**5-69**	CH_3	4-CNC_6H_4	**5-116**	43
16	**5-70**	CH_3	$PhCH_2CH_2$	**5-117**	55
17	**5-71**	CH_3	2-MeC_6H_4	**5-118**	72
18	**5-72**	CH_3	4-$CF_3C_6H_4$	**5-119**	63
19	**5-74**	CH_3	4-FC_6H_4	**5-120**	80
20	**5-75**	CH_3	2-FC_6H_4	**5-121**	75
21	**5-76**	CH_3	2-Br-5-FC_6H_3	**5-122**	51
22	**5-81**	CH_3	C_4H_{11}	**5-123**	73
23	**5-82**	CH_3	C_6H_{11}	**5-124**	84
24	**5-83**	C_6H_{13}	C_6H_5	**5-125**	72
25	**5-84**	C_6H_{13}	4-CNC_6H_4	**5-126**	35
26	**5-85**	C_6H_{13}	$PhCH_2CH_2$	**5-127**	69
27	**5-86**	C_6H_{13}	4-$CF_3C_6H_4$	**5-128**	68
28	**5-87**	C_6H_{13}	4-FC_6H_4	**5-129**	61
29	**5-88**	C_6H_{13}	C_4H_{11}	**5-130**	76
30	**5-89**	C_6H_{13}	C_6H_{11}	**5-131**	95



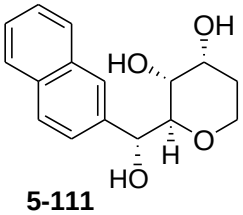
5-102, X = H
5-103, X = CN
5-104, X =Me
5-105, X =NO_2
5-106, X = CF_3
5-107, X = F



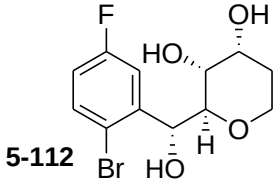
5-110



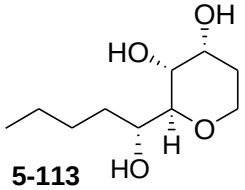
5-108, X = CH_3
5-109, X = F



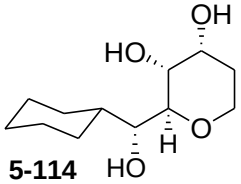
5-111



5-112



5-113



5-114

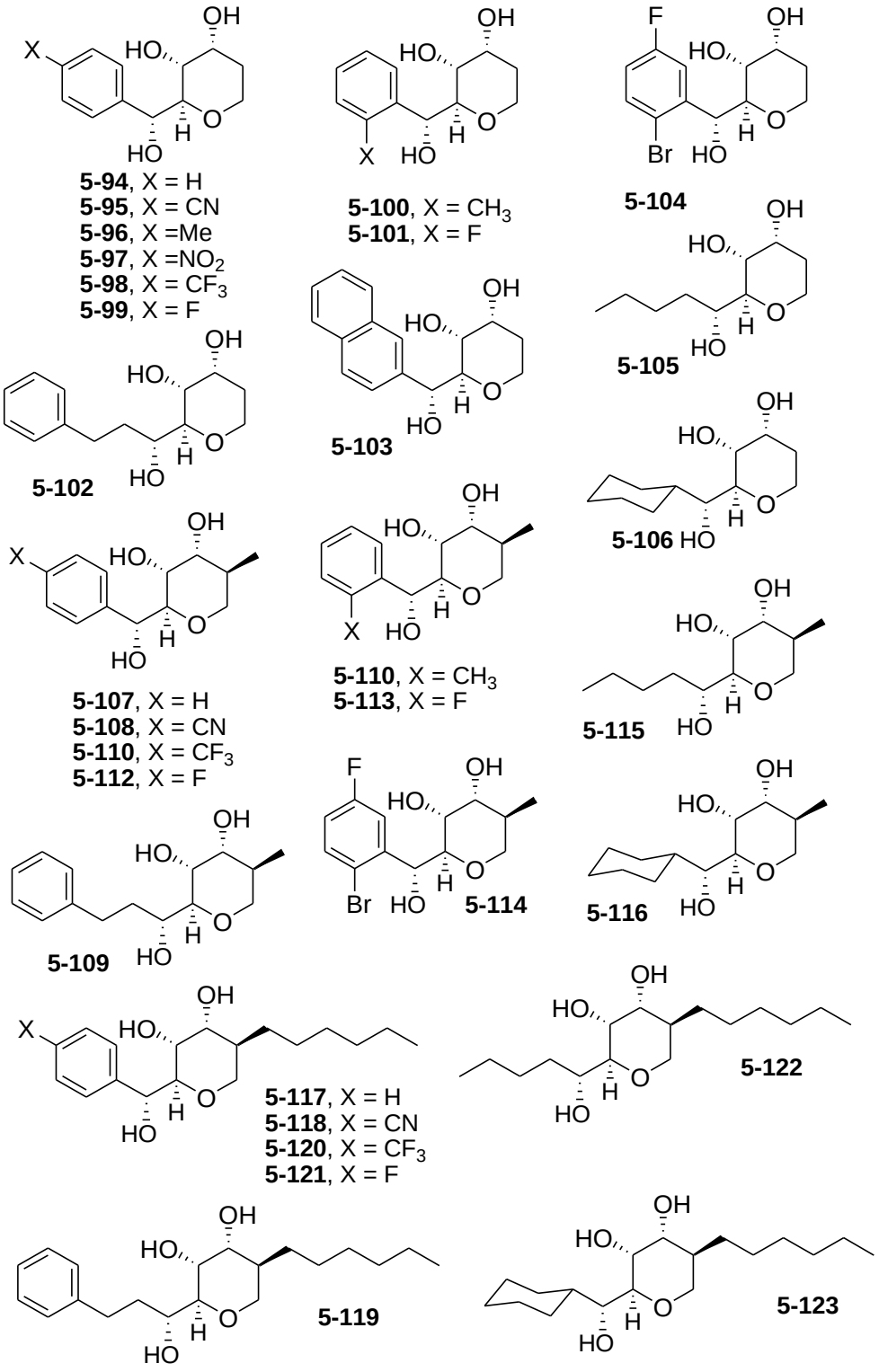


Figure 5-8: Structures of thiomarinol analogues.

According to previous work by Xuri Gao, a former member of the Hall group, who studied the relative stereochemistry of α-hydroxyalkyl dihydropyran products by NMR spectroscopy, the nOe result of one of the α-hydroxyalkyl dihydropyrans indicated that all three side chains on the pyran ring have a *cis* relationship, which is as expected when the reaction proceeds via complete *endo* selectivity in the [4+2] cycloaddition step (**Figure 5-9**).[20, 22, 27] Furthermore, the relationship between the catalyst configuration and the absolute stereochemistry of the optically enriched α-hydroxyalkyl dihydropyran products was substantiated by the total synthesis of two natural products (thiomarinol H, $[\alpha]^{23}_{D}$ –2.25° (c=0.004, MeOH), lit. $[\alpha]^{23}_{D}$ –1.8° (c=0.003, MeOH) and (5*R*, 6*S*)-6-acetoxy-5-hexadecanolide, $[\alpha]^{23}_{D}$ –35.1° (c=1.1, $CHCl_3$), lit. $[\alpha]^{23}_{D}$ –37.4° (c=2.2, $CHCl_3$)) as well as by X-ray crystallographic analysis.[20, 22, 27, 36, 37]

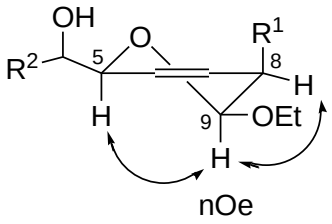


Figure 5-9: nOe result of one of the α-hydroxyalkyl dihydropyran products.[20, 22, 27]

According to this work, the relative stereochemistry of the final products was confirmed by X-ray crystallography on one of the thiomarinol analogues, **5-105** (**Table 5-4**), which clearly demonstrated the proposed structure of these analogues.

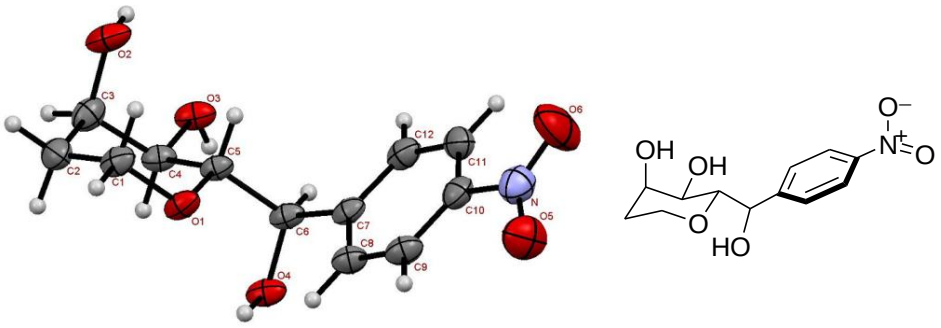
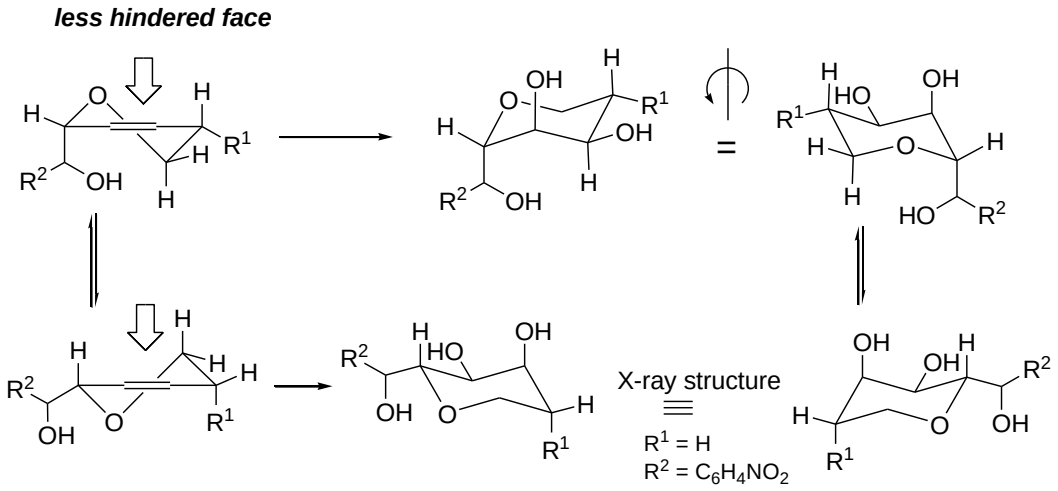


Table 5-4: Selected bond lengths (Å) and angles (deg) for (2S,3R,4R)-tetrahydro-2-((*R*)-hydroxy(4-nitrophenyl)methyl)-2H-pyran-3,4-diol 5-105.

	Atoms	Thiomarinol analog 5-105	
Bond	O(1)-C(1)	Selected atomic distance (Å)	1.446(2)
	O(1)-C(5)		1.424(2)
	O(2)-C(3)		1.427(3)
	O(3)-C(4)		1.429(3)
	O(4)-C(6)		1.417(3)
	C(6)-C(7)		1.511(3)
Angle	C(1)-O(1)-C(5)	Selected atomic angles (deg)	111.5(1)
	O(2)-C(3)-C(2)		107.2(2)
	O(2)-C(3)-C(4)		110.7(2)
	O(3)-C(4)-C(3)		109.3(2)
	O(3)-C(4)-C(5)		108.5(1)
	O(4)-C(6)-C(5)		111.5(1)
	O(4)-C(6)-C(7)		113.5(2)

The resulting observed stereochemistry in all thiomarinol analogues could be explained by dihydroxylation from the least hindered face of the double bond as demonstrated in **Scheme 5-5**.



Scheme 5-5: Observed stereochemistry upon dihydroxylation of α-hydroxyalkyl 2*H*-pyrans.

5.3 Conclusion

Through a methodology involving a tandem oxa[4+2] cycloaddition/allylboration reaction of aldehydes, I have successfully formed a small library of 30 thiomarinol analogues. This reaction sequence uses a wide variety of aldehydes, such as aromatic, heteroaromatic, unsaturated and aliphatic aldehydes, and with three different enol ethers to allow the generation of highly substituted α-hydroxyalkyl dihydropyran systems in a single step.

Furthermore, I have developed a method for mild acetal reduction of α-hydroxyalkyl dihydropyran systems without the need for hydroxyl group protection, which facilitated the synthesis of this library. Attempts were made to reduce unsaturated α-hydroxyalkyl dihydropyrans and those ones containing heterocycles; however, these compounds proved too sensitive and the products immediately decomposed upon the addition of different reagents.

Dihydroxylations of the double bond of α-hydroxyalkyl 2*H*–pyrans proceeded smoothly following the standard conditions, which was shown by X-ray crystallographic analysis to provide the requisite stereochemistry of thiomarinol analogues. This methodology proved to be quite general with substituted enol ethers and various aldehydes.

This library was designed using the protein structure similarity clustering (**PSSC**) computational approach through a collaboration study between Professors Hall and Waldmann in Germany. The screening study of this library against different protein targets is under investigation in the laboratories of Professor Eric Brown at McMaster University.

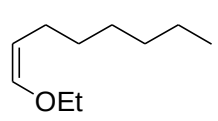
5.4 Experimental Details and Characterization Data

5.4.1 General Information

Catalyst **5-4** was prepared according to the procedure of Jacobsen.[23, 24] Boronate **5-1** was prepared according to our previously published procedure and purified by

Kugelrohr distillation (< 0.5 mm Hg).[22, 27] Toluene and CH_2Cl_2 were distilled from CaH_2. Ethyl vinyl ether was stirred over KOH for 30 min before distillation. All aldehydes were purified by Kugelrohr distillation prior to use. BaO (Acros) was used as supplied (90% tech powder). Powdered 4 Å molecular sieves (< 5 micron, Aldrich) were oven dried (138 °C) prior to use. Unless otherwise stated, all reagents were purchased from Aldrich and used as received. Analytical thin layer chromatography was performed on Merck Silica Gel 60 F254 plates and visualized with UV light and 1% $KMnO_4$ (aq). NMR spectra were recorded on Varian INOVA-300, INOVA-400 or INOVA-500 MHz instruments. The residual solvent protons (^1H) or the solvent carbon (^{13}C) were used as internal standards. ^1H-NMR data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, integration, coupling constant). The following abbreviations are used in reporting NMR data: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; dq, doublet of quartets; dd, doublet of doublets; m, mutiplet. *J*–accuracy = (+/_) 0.5 Hz. High resolution mass spectra were recorded by the University of Alberta mass spectrum service Laboratory using either electron impact (EI) or electrospray (ESI) ionization techniques. Infrared spectra were obtained on a Nicolet Magna-IR 750 with frequencies expressed in cm^{-1}. Optical rotations (deg ml dm^{-1} g^{-1}) were measured using a 1 mL cell with a 1 dm path-length on a Perkin Elmer 241 polarimeter.

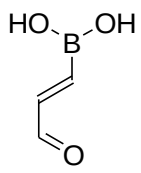
5.4.1.1 Preparation of (Z)-1-Ethoxyoct-1-ene (5-2c)



To a solution of *sec*-BuLi (1.40 M, 8.35 mL) in THF (10 mL) at –78 °C was added dropwise the allyl ethyl ether (1.00 g, 11.6 mmol) and the mixture was stirred at –78 °C for 1 h. 1-Iodopentane (1.40 g, 7.06 mmol) was added dropwise and the mixture was stirred for a further 3h at –78 °C. The reaction was allowed to warm up to room temperature and then quenched with a saturated aqueous solution of NH_4Cl (10 mL). The resulting mixture was extracted with ether (2 x 15 mL), the organic layers were combined, dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo and purified by flash chromatography on silica gel (100% hexanes) to afford the title compound (0.89 g, **81 %** yield).

Spectral data of the product matched that previous reported: (a) H. Yamamoto, M. Tsuda, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **1997**, *62*, 7174. (b) J. F. Normant, A. Commercon, M. Bourgain, J. Villiras, *Tetrahedron Lett.* **1975**, 3833.

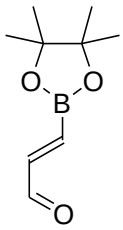
5.4.1.2 Preparation of (E)-3-Boronoacrolein (5-6)



(R)-(+)-α-Pinene (91% ee, 10.8 mL, 66.7 mmol) was slowly added to a solution of borane-dimethyl sulfide complex (3.30 mL, 33.0 mmol) in THF (10 mL) at 0 °C under argon. The solution was stirred for 10 min at 0 °C followed by 2 h at room temperature. The resulting white suspension was cooled to 0 °C and propionaldehyde diethyl acetal (4.50 mL, 31.0 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 h and further stirred at room temperature for an additional hour, the reaction vessel was cooled back again to 0 °C prior to the quick addition of freshly distilled acetaldehyde (20 mL). The mixture was stirred for 30 minutes at 0 °C, then refluxed for 16 h at 45 °C, water (12 mL) was added at 0 °C. After 3 h the solution was transferred to a separatory funnel. The aqueous layer was extracted with ether (2 x 50 mL) and ethyl acetate (2 x 50 mL). The organic layers were combined and concentrated under reduced pressure. The resulting suspension was then triturated with cooled hexanes and filtered to provide the boronic acid as a white solid (2.66 g, **81%** yield).

Spectral data of the product matched that of previous reports: (a) M. Gravel, B. B. Touré, D. G. Hall, *Org. Prep. Proc. Int.* **2004**, *36(6),* 573. (b) M. Deligny, F. Carreaux, B. Carboni, L. Toupet, G. Dujardin, *Chem. Commun.* **2003**, 276.

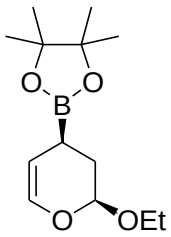
5.4.2 Synthesis of (E)-3-Boronoacrolein Pinacol Ester (5-1)



3-boronacrolein (200 mg, 2.00 mmol) and pinacol (236 mg, 2.00 mmol) were dissolved in THF (15 mL) at room temperature. The solution was stirred for 30 min then the solvent was evaporated under reduced pressure at 45 °C to afford a colorless oil. Addition of THF followed by concentration may be necessary to complete the condensation by azeotropic removal of the water. The crude oil was then purified by bulb to bulb distillation (1 mm Hg, 100 °C) to provide the aldehyde (364 mg, **100%** yield).

Spectral data of the product matched previous reports: M. Gravel, B. B. Touré, D. G. Hall, *Org. Prep. Proc. Int.* **2004**, *36(6)*, 573.

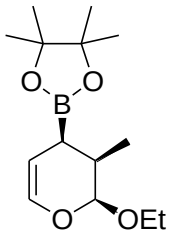
5.4.2.1 Synthesis of 2-((2S,4S)-2-Ethoxy-3,4-Dihydro-2H-Pyran-4-yl)-4,4,5,5-Tetramethyl -1,3,2-Dioxaborolane (5-5a)



A mixture of 3-boronoacrolein pinacolate **5-1** (364 mg, 2.00 mmol) and ethyl vinyl ether (1.90 mL, 20.0 mmol) was placed in an oven-dried 10 mL RBF with stirbar. To this solution was added **5-4** (9.60 mg, 1 mol %) and powdered BaO (300 mg). The reaction was allowed to stir for 14 h at ambient temperature then filtered through Celite and concentrated *in vacuo* to give the crude product (427 mg, **84%** yield, **98 : 2 dr**).

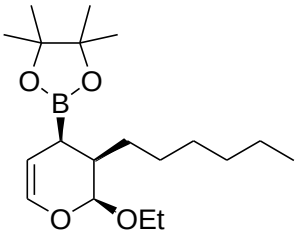
Spectral data of the product matched previous reports: (a) M. Deligny, F. Carreaux, L. Toupet, B. Carboni, *Adv. Synth. Catal.* **2003**, *345*, 1215. (b) X. Gao, D. G. Hall, M. Deligny, A. Favre, F. Carreaux, B. Carboni, *Chem. Eur. J*. **2006**, *12*, 3132.

5.4.2.2 Synthesis of 2-((2S,3R,4R)-2-Ethoxy-3,4-Dihydro-3-Methyl-2H-Pyran-4-yl)-4,4,5,5-Tetramethyl-1,3,2-Dioxaborolane (5-5b)



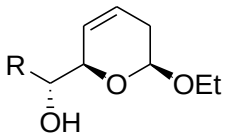
A mixture of 3-boronoacrolein pinacolate **5-1** (364 mg, 2.00 mmol) and ethyl 1-propenyl ether (Z/E 3:1)(2 mL) was placed in an oven dried 10 mL RBF with stirbar. To this solution was added **5-4** (30 mg, 3 mol %) and powdered BaO (300 mg). The reaction was allowed to stir for 14 h at ambient temperature then filtered through Celite and concentrated *in vacuo* to give the crude product (445 mg, **83%** yield, **dr** (**98.5 : 1.5**). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.21 (dd, 1H, *J* = 6.0 Hz, *J* = 2.4 Hz), 4.76 (d, 1H, *J* = 2.0 Hz), 4.75 (dd, 1H, *J* = 3.6 Hz, *J* = 6 Hz), 3.84 (dq, 1H, *J* = 9.6 Hz, *J* = 7.2 Hz), 3.84 (dq, 1H, *J* = 10 Hz, *J* = 7.2 Hz), 2.17 (m, 1H), 1.84 (m, 1H), 1.23 (d, 12H), 1.18 (dd, 3H, *J* = 2.4 Hz, *J* = 4.4 Hz), 1.04 (d, 3H, *J* = 6.8 Hz).

5.4.2.3 Synthesis of 2-((2S,3R,4R)-2-Ethoxy-3,4-Dihydro-3-Methyl-2H-Pyran-4-yl)-4,4,5,5-Tetramethyl-1,3,2-Dioxaborolane (5-5c)



A mixture of 3-boronoacrolein pinacolate **5-1** (364 mg, 2.00 mmol) and (*Z*)-1-ethoxyoct-1-ene (2 mL) was placed in an oven-dried 10 mL RBF with stirbar. To this solution was added **5-4** (30 mg, 3 mol %) and powdered BaO (300 mg). The reaction was allowed to stir for 14 h at ambient temperature, then filtered through Celite and concentrated *in vacuo* and the excess of (*Z*)-1-ethoxyoct-1-ene was recovered by bulb to bulb distillation to provide the title product. (478 mg, **71%** yield, **dr** (**99 : 1**). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 6.20 (dd, 1H, *J* = 6.5 Hz, *J* = 2.0 Hz), 4.86 (dd, 1H, *J* = 5.5 Hz, *J* = 6.0 Hz), 4.82 (d, 1H, *J* = 2.0 Hz,), 3.78 (dq, 1H, *J* = 10 Hz, , *J* = 7.0 Hz), 3.55 (dq, 1H, *J* = 10.5 Hz, , *J* = 7.0 Hz), 1.98 (m, 1H), 1.84 (m, 1H), 1.23 (d, 12H), 1.18 (dd, 3H, *J* = 2.4 Hz, , *J* = 4.4 Hz), 1.04(d, 3H, *J* = 6.8 Hz). **^{13}C-NMR** (MHz, $CDCl_3$) δ: 137.9, 104.0, 99.0, 82.8, 77.3, 77.0, 76.7, 63.3, 39.5, 31.7, 29.8, 29.8, 27.4, 25.1, 24.3, 22.6, 15.2, 14.1.

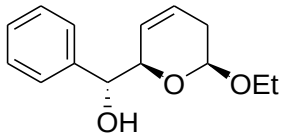
5.4.3 General Procedure for Cr(III)-Catalyzed Three-Component [4+2] Cycloaddition/ Allylboration Using Ethyl Vinyl Ether



A mixture of 3-boronoacrolein pinacolate **5-1** (364 mg, 2.00 mmol) and ethyl vinyl ether (1.90 mL, 20.0 mmol) was placed in an oven-dried 10 mL RBF with stirbar. To this solution was added **5-4** (9.6 mg, 1 mol %) and powdered 4 Å molecular sieve (300 mg). After stirring for 14 h at ambient temperature, aldehyde (4.00 mmol) was added to the reaction mixture. The reaction mixture was allowed to stir at 45 °C for 24 h, then diluted with ethyl acetate and filtered through Celite. The ethyl acetate solution was then stirred for 30 min with a saturated solution of $NaHCO_3$. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with saturated NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated to afford the title compound as a crude product.

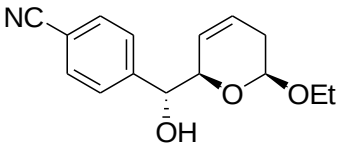
Purification by flash column chromatography (deactivated silica-gel, hexane:ether (9:1)) led to the pure product title compound.

5.4.3.1 Synthesis of (R)-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl)(Phenyl)Methanol (5-7)



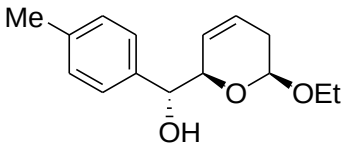
The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl vinyl ether and benzaldehyde (**76%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.35 (m, 5H), 5.77 (dddd, 1H, *J* = 2.3 Hz, *J* = 3.9 Hz, *J* = 8.0 Hz, *J* = 10.2 Hz), 5.39 (ddd, 1H, *J* = 2.1 Hz, *J* = 3.9 Hz, *J* = 10.3 Hz), 4.78 (dd, 1H, *J* = 5.0 Hz, *J* = 5.4 Hz), 4.58 (dd, 1H, *J* = 2.7 Hz, *J* = 7.5 Hz), 4.33 (m, 1H), 3.98 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.58 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.28 (d, 1H, *J* = 2.9 Hz), 2.25 (m, 2H), 1.27 (t, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 139.9, 128.3, 128.0, 127.3, 125.4, 124.8, 98.5, 78.7, 76.8, 64.5, 31.0, 15.2. **HRMS** (ESI) for $C_{14}H_{18}NaO_3$: calcd. 257.11507; found, 257.11526.

5.4.3.2 Synthesis of 4-((R)-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl)(Hydroxy) Methyl) Benzonitrile (5-8)



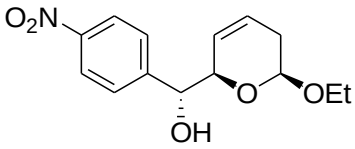
The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl vinyl ether and 4-cyanobenzaldehyde (**65%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.62 (dd, 2H, *J* = 1.6 Hz, *J* = 8.2 Hz), 7.50 (m, 2H), 5.82 (dddd, 1H, *J* = 2.3 Hz, *J* = 3.3 Hz, *J* = 4.5 Hz, *J* = 10.2 Hz), 5.44 (ddd, 1H, *J* = 1.9 Hz, *J* = 3.9 Hz, *J* = 10.3 Hz), 4.73 (dd, 1H, *J* = 4.0 Hz, *J* = 6.4 Hz), 4.65 (m, 1H), 4.35 (m, 1H), 3.85 (qd, 1H, *J* = 7.1 Hz, *J* = 9.5 Hz), 3.51 (m, 2H), 2.21 (m, 2H), 1.21 (t, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 145.9, 131.9, 127.7, 125.5, 124.8, 118.7, 111.5, 98.1, 77.8, 75.6, 64.5, 30.7, 15.1. **HRMS** (ESI) for $C_{15}H_{17}NNaO_3$: calcd. 282.11032; found, 282.11077.

5.4.3.3 Synthesis of (R)-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl)(P-Tolyl)Methanol (5-9)



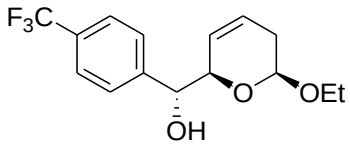
The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl vinyl ether and 4-methylbenzaldehyde (**38%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.28 (d, 2H, *J* = 8.1 Hz), 7.16 (d, 2H, *J* = 7.8 Hz), 5.74 (dddd, 1H, *J* = 2.3 Hz, *J* = 3.9 Hz, *J* = 3.9 Hz, *J* = 10.2 Hz), 5.38 (qd, 1H, *J* = 2.0 Hz, *J* = 10.3 Hz), 4.77 (m, 1H), 4.53 (d, 1H, *J* = 7.6 Hz), 4.31 (m, 1H), 3.99 (qd, 1H, *J* = 7.1 Hz, *J* = 9.5 Hz), 3.58 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.28 (bs, 1H), 2.34 (s, 1H), 2.23 (m, 2H), 1.27 (t, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 137.6, 136.9, 129.0, 127.2, 125.5, 124.6, 98.4, 78.7, 76.6, 64.4, 31.0, 21.1, 15.2. **HRMS** (ESI) for $C_{15}H_{20}NaO_3$: calcd. 271.13097; found, 271.13111.

5.4.3.4 Synthesis of (R)-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl)(4-Nitrophenyl) Methanol (5-10)



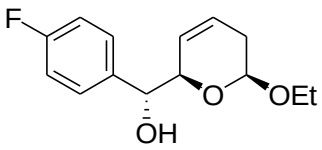
The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl vinyl ether and 4-nitrobenzaldehyde (**62%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 8.20 (d, 2H, *J* = 8.8 Hz), 7.58 (d, 2H, *J* = 8.8 Hz), 5.85 (dddd, 1H, *J* = 2.2 Hz, *J* = 3.4 Hz, *J* = 4.3 Hz, *J* = 10.1 Hz), 5.49 (ddd, 1H, *J* = 2.0 Hz, *J* = 3.9 Hz, *J* = 10.3 Hz), 4.75 (dd, 1H, *J* = 4.2 Hz, *J* = 6.1 Hz), 4.72 (bs, 1H), 4.39 (m, 1H), 3.86 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.52 (m, 2H), 2.24 (m, 2H), 1.23 (t, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 147.9, 147.5, 127.8, 125.6, 124.7, 123.3, 98.0, 77.7, 75.4, 64.5, 30.6, 15.1. **HRMS** (ESI) for $C_{14}H_{17}NNaO_5$: calcd. 302.10037; found, 302.10089.

5.4.3.5 Synthesis of (R)-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl)(4-(Trifluoro Methyl) Phenyl)Methanol (5-11)



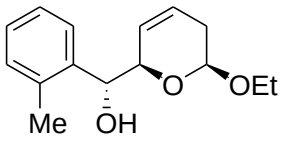
The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl vinyl ether and 4-trifluoromethylbenzaldehyde (**75%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.63 (dd, 2H, *J* = 0.6 Hz, *J* = 8.7 Hz), 7.54 (dd, 2H, *J* = 0.6 Hz, *J* = 8.1 Hz), 5.83 (m, 1H), 5.44 (ddd, 1H, *J* = 1.9 Hz, *J* = 4.0 Hz, *J* = 10.1 Hz), 4.78 (dd, 1H, *J* = 4.3 Hz, *J* = 6.0 Hz), 4.66 (m, 1H), 4.36 (m, 1H), 3.93 (qd, 1H, *J* = 7.2 Hz, *J* = 15.4 Hz), 3.57 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.36 (dd, 1H, *J* = 0.4 Hz, *J* = 3.9 Hz), 2.26 (m, 2H), 1.27 (t, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 142.0, 131.1 (q, *J* = 30.2 Hz), 123.4, 125.4, 124.2, 124.284, 123.1 (q, *J* = 271.3 Hz), 99.3, 77.3, 74.4, 63.5, 26.1, 14.1. **HRMS** (ESI) for $C_{15}H_{17}F_3NaO_3$: calcd. 325.10253; found, 325.10284.

5.4.3.6 Synthesis of (R)-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl)(4-Fluorophenyl) Methanol (5-12)



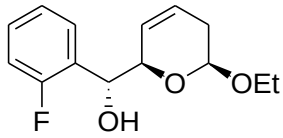
The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl vinyl ether and 4-fluorobenzaldehyde (**73%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.38 (ddd, 2H, *J* = 0.5 Hz, *J* = 5.4 Hz, *J* = 8.9 Hz), 7.06 (dd, 2H, *J* = 8.8 Hz, 8.7 Hz), 5.79 (m, 1H), 5.38 (ddd, 1H, *J* = 2.1 Hz, *J* = 3.9 Hz, *J* = 10.3 Hz), 4.78 (dd, 1H, *J* = 4.9 Hz, *J* = 5.8 Hz), 4.57 (dd, 1H, *J* = 2.3 Hz, *J* = 7.3 Hz), 4.29 (m, 1H), 3.97 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.59 (qd, 1H, *J* = 7.1 Hz, *J* = 9.5 Hz), 3.26 (d, 1H, *J* = 2.8 Hz), 2.26 (m, 2H), 1.28 (t, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 166.0 (d, *J* = 242.3 Hz), 135.9, 129.1 (d, *J* = 8.1 Hz), 127.2, 125.8, 125.3 (d, *J* = 3.1 Hz), 121.2, 115.4 (d, *J* = 21.3 Hz), 98.6, 78.8, 76.3, 64.7, 31.2, 15.4. **HRMS** (ESI) for $C_{14}H_{17}FNaO_3$: calcd. 275.10576; found, 275.10591.

5.4.3.7 Synthesis of (R)-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl)(O-Tolyl)Methanol (5-13)



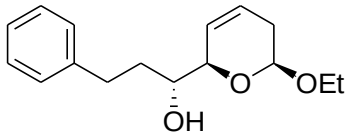
The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl vinyl ether and 2-methylbenzaldehyde (**47%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.49 (dd, 1H, *J* = 1.5 Hz, *J* = 7.6 Hz), 7.23 (ddd, 1H, *J* = 1.7 Hz, *J* = 7.5 Hz, *J* = 7.5 Hz), 7.19 (ddd, 1H, *J* = 1.6 Hz, *J* = 7.3 Hz, *J* = 7.3 Hz), 7.15 (m, 1H), 5.75 (dddd, 1H, *J* = 2.3 Hz, *J* = 3.5 Hz, *J* = 4.5 Hz, *J* = 10.2 Hz), 5.28 (ddd, 1H, *J* = 2.1 Hz, *J* = 3.9 Hz, *J* = 10.3 Hz), 4.91 (d, 1H, *J* = 7.8 Hz), 4.80 (dd, 1H, *J* = 4.7 Hz, *J* = 6.2 Hz), 4.36 (m, 1H), 4.02 (qd, 1H, *J* = 7.1 Hz, *J* = 9.5 Hz), 3.61 (qd, 1H, *J* = 7.1 Hz, *J* = 9.5 Hz), 3.17 (s, 1H), 2.34 (s, 1H), 2.25 (m, 2H), 1.28 (t, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 137.8, 135.7, 130.3, 127.7, 126.9, 126.1, 125.2, 124.9, 98.5, 78.9, 72.5, 64.4, 31.1, 19.7, 15.2. **HRMS** (ESI) for $C_{15}H_{20}NaO_3$: calcd. 271.13097; found, 271.13106.

5.4.3.8 Synthesis of (R)-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl)(2-Fluorophenyl) Methanol (5-14)



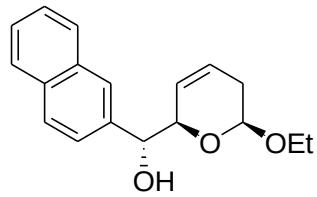
The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl vinyl ether and 2-fluorobenzaldehyde (**51%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.51 (ddd, 1H, *J* = 1.8 Hz, *J* = 7.5 Hz, *J* = 30.2 Hz), 7.23 (m, 1H), 7.12 (ddd, 1H, *J* = 1.1 Hz, *J* = 7.5 Hz, *J* = 8.4 Hz), 6.99 (ddd, 1H, *J* = 1.2 Hz, *J* = 8.2 Hz, *J* = 10.4 Hz), 5.77 (dddd, 1H, *J* = 2.3 Hz, *J* = 3.5 Hz, *J* = 4.4 Hz, *J* = 10.2 Hz), 5.46 (m, 1H), 4.95 (dd, 1H, *J* = 4.8 Hz, *J* = 6.0 Hz), 4.73 (dd, 1H, *J* = 4.5 Hz, *J* = 6.2 Hz), 4.40 (m, 1H), 3.88 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.51 (qd, 1H, *J* = 7.2 Hz, *J* = 9.6 Hz), 3.46 (d, 1H, *J* = 4.6 Hz), 2.21 (m, 2H), 1.20 (t, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 159.937 (d, *J* = 244.7 Hz), 129.1 (d, *J* = 8.2 Hz), 128.7 (d, *J* = 4.3 Hz), 127.6 (d, *J* = 12.9 Hz), 125.5, 125.0, 124.1 (d, *J* = 3.5 Hz), 115.1 (d, *J* = 2.2 Hz), 98.3, 77.7, 69.8, 64.3, 30.8, 15.1. **HRMS** (ESI) for $C_{14}H_{17}FNaO_3$: calcd. 275.10576; found, 275.10583.

5.4.3.9 Synthesis of (R)-1-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl)-3-Phenyl Propan-1-ol (5-15)



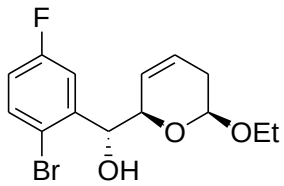
The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/allylboration using ethyl vinyl ether and hydrocinnamylaldehyde (**71%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.23 (m, 5H), 5.84 (m, 1H), 5.66 (ddd, 1H, *J* = 1.6 Hz, *J* = 3.6 Hz, *J* = 10.2 Hz), 4.76 (m, 1H), 4.19 (m, 1H), 3.98 (qd, 1H, *J* = 7.1 Hz, *J* = 9.5 Hz), 3.58 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 2.91 (m, 1H), 2.75 (m, 1H), 2.24 (m, 2H), 1.91 (m, 2H), 1.28 (t, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 142.1, 128.5, 128.3, 126.5, 125.8, 124.8, 98.4, 77.3, 72.6, 64.4, 35.0, 32.0, 31.0, 15.222. **HRMS** (ESI) for $C_{16}H_{22}NaO_3$: calcd. 285.14645; found, 285.14673.

5.4.3.10 Synthesis of (R)-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl) (Naphthalen-2-yl) Methanol (5-16)



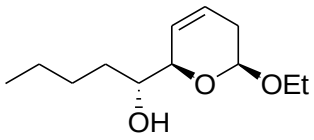
The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl vinyl ether and 2-naphthaldehyde (**81%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.85 (m, 4H), 7.54 (dd, 1H, *J* = 1.7 Hz, *J* = 8.5 Hz), 7.48 (m, 2H), 5.78 (m, 1H), 5.42 (ddd, 1H, *J* = 2.0 Hz, *J* = 4.0 Hz, *J* = 10.3 Hz), 4.80 (dd, 1H, *J* = 4.7 Hz, *J* = 6.0 Hz), 4.76 (m, 1H), 4.45 (m, 1H), 4.00 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.59 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.43 (d, 1H, *J* = 2.2 Hz), 2.25 (m, 2H), 1.28 (t, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 137.4, 133.2, 133.2, 128.1, 128.0, 127.7, 126.5, 126.0, 125.9, 125.4, 125.0, 124.8, 98.4, 78.6, 76.9, 64.5, 31.0, 15.2. **HRMS** (ESI) for $C_{18}H_{20}NaO_3$: calcd. 307.13119; found, 307.13114.

5.4.3.11 Synthesis of (R)-(2-Bromo-5-Fluorophenyl)((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl)Methanol (5-17)



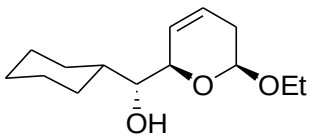
The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl vinyl ether and 2-bromo-5-fluorobenzaldehyde (**49%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.47 (dd, 1H, *J* = 5.2 Hz, *J* = 8.8 Hz), 7.31 (dd, 1H, *J* = 3.1 Hz, *J* = 9.7 Hz), 6.88 (ddd, 1H, *J* = 3.1 Hz, *J* = 7.7 Hz, *J* = 8.8 Hz), 5.88 (ddd, 1H, *J* = 2.4 Hz, *J* = 3.9 Hz, *J* = 10.3 Hz), 5.62 (ddd, 1H, *J* = 2.0 Hz, *J* = 4.0 Hz, *J* = 10.2 Hz), 5.03 (m, 1H), 4.75 (dd, 1H, *J* = 4.8 Hz, *J* = 5.7 Hz), 4.47 (m, 1H), 3.85 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.52 (m, 2H), 2.26 (m, 2H), 1.23 (t, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 162.1 (d, *J* = 245.4 Hz), 142.4, 142.3, 133.6, 133.5, 125.7, 125.3, 116.2 (d, *J* = 23.6 Hz), 98.1, 76.6, 74.0, 64.5, 30.6, 15.1. **HRMS** (ESI) for $C_{14}H_{16}BrFNaO_3$: calcd. 353.01653; found, 353.01642.

5.4.3.12 Synthesis of (R)-1-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl) Pentan-1-ol (5-18)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl vinyl ether and pentanal (**81%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 5.76 (m, 1H), 5.61 (ddd, 1H, *J* = 1.9 Hz, *J* = 3.7 Hz, *J* = 10.2 Hz), 4.69 (dd, 1H, *J* = 4.9 Hz, *J* = 6.1 Hz), 4.09 (m, 1H), 3.91 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.51 (m, 2H), 2.55 (bs, 1H), 2.16 (m, 2H), 1.10-1.90 (m, 6H), 1.20 (t, 3H, *J* = 7.1 Hz), 0.86 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 126.6, 124.6, 98.4, 77.2, 73.3, 64.3, 32.6, 31.0, 27.8, 22.7, 15.1, 13.9. **HRMS** (ESI) for $C_{12}H_{22}NaO_3$: calcd. 237.14671; found, 237.14667.

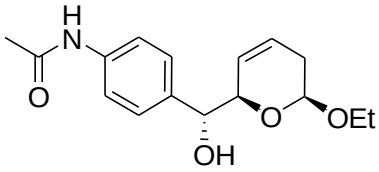
5.4.3.13 Synthesis of (R)-Cyclohexyl((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl)Methanol (5-19)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component

[4+2] cycloaddition/ allylboration using ethyl vinyl ether and cyclohexane carboxaldehyde (**79%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 5.83 (dddd, 1H, *J* = 2.4 Hz, *J* = 3.6 Hz, *J* = 4.3 Hz, *J* = 10.1 Hz), 5.65 (ddd, 1H, *J* = 2.0 Hz, *J* = 3.7 Hz, *J* = 10.1 Hz), 4.74 (dd, 1H, *J* = 5.2 Hz, *J* = 5.8 Hz), 4.37 (m, 1H), 3.95 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.56 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.23 (m, 1H), 2.24 (m, 3H), 1.97 (m, 1H), 1.40-1.87 (m, 6H), 1.25 (m, 7H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 127.7, 124.9, 98.7, 77.4, 74.7, 64.7, 40.5, 31.2, 29.8, 28.8, 26.6, 26.3, 26.1, 15.4. **HRMS** (ESI) for $C_{14}H_{24}NaO_3$: calcd. 263.16244; found, 263.16237.

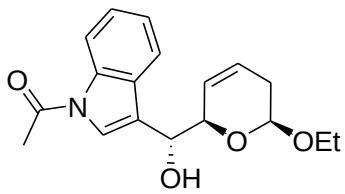
5.4.3.14 Synthesis of N-(4-((R)-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl)(Hydroxy)Methyl) Phenyl)Acetamide (5-20)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl vinyl ether and *N*-(4-formylphenyl)acetamide (**36%** yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.62 (bs, 1H), 7.48 (d, 2H, *J* = 8.4 Hz), 7.32 (d, 2H, *J* = 8.4 Hz), 5.75 (m, 1H), 5.36 (ddd, 1H, *J* = 1.6 Hz, *J* = 3.5 Hz, *J* = 10.2 Hz), 4.77 (dd, 1H, *J* = 5.4 Hz, *J* = 5.3 Hz), 4.53 (d, 1H, *J* = 7.4 Hz), 4.29 (m, 1H), 3.97 (qd, 1H, *J* = 7.1 Hz, *J* = 9.5 Hz), 3.57 (qd, 1H, *J* = 7.0 Hz, *J* = 9.5 Hz), 3.32 (bs, 1H), 2.23 (m, 2H), 2.14 (s, 3H), 1.25 (dd, 3H, *J* = 6.2 Hz, *J* = 8.0 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 168.5, 137.7, 135.6, 127.9, 125.3, 124.8, 119.7, 98.4, 78.6, 64.5, 31.0, 24.8, 24.5, 15.2.

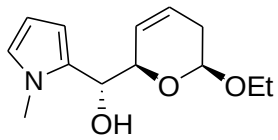
5.4.3.15 Synthesis of 1-(3-((R)-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl)(Hydroxy)Methyl)-1H-Indol-1-yl)Ethanone (5-21)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl vinyl ether and 1-acetyl-1*H*-indole-3-carbaldehyde (**69%** yield).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.64 (ddd, 1H, *J* = 0.7 Hz, *J* = 1.4 Hz, *J* = 7.6 Hz), 7.49 (s, 1H), 7.21-7.40 (m, 3H), 5.81 (dddd, 1H, *J* = 2.3 Hz, *J* = 3.9 Hz, *J* = 4.1 Hz, *J* = 10.2 Hz), 5.49 (ddd, 1H, *J* = 2.0 Hz, *J* = 4.1 Hz, *J* = 10.3 Hz), 4.87 (d, 1H, *J* = 6.9 Hz), 4.81 (dd, 1H, *J* = 5.3 Hz, *J* = 5.4), 4.56 (m, 1H), 3.98 (qd, 1H, *J* = 7.1 Hz, *J* = 9.5 Hz), 3.59 (qd, 1H, *J* = 7.1 Hz, *J* = 9.5Hz), 3.36 (bs, 1H), 2.59 (s, 3H), 2.27 (m, 2H), 1.22 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 168.5, 136.0, 135.0, 128.9, 126.8, 125.6, 125.4, 123.5, 123.6, 121.5, 119.8, 98.4, 77.7, 70.3, 64.5, 30.9, 23.9, 15.2.

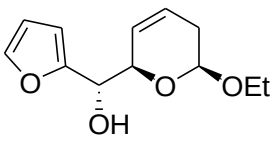
5.4.3.16 Synthesis of (R)-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl)(1-Methyl-1H-Pyrrol-2-yl)Methanol (5-22)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl vinyl ether and 1-methyl-1*H*-pyrrole-2-carbaldehyde (**54%** yield).

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.59 (dd, 1H, *J* = 1.8 Hz, *J* = 2.6 Hz), 6.16 (dd, 1H, *J* = 1.8 Hz, *J* = 3.6 Hz), 6.08 (dd, 1H, *J* = 2.7 Hz, *J* = 3.6 Hz), 5.78 (m, 1H), 5.52 (ddd, 1H, *J* = 2.0 Hz, *J* = 3.8 Hz, *J* = 10.2 Hz), 4.84 (dd, 1H, *J* = 4.8 Hz, *J* = 6.4 Hz), 4.62 (d, 1H, *J* = 7.5 Hz), 4.57 (m, 1H), 4.04 (qd, 1H, *J* = 7.1 Hz, *J* = 9.5 Hz), 3.67 (s, 3H), 3.62 (qd, 1H, *J* = 7.1 Hz, *J* = 9.5 Hz), 2.98 (bs, 1H), 2.26 (m, 2H), 1.28 (t, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 130.5, 126.2, 125.0, 123.0, 107.5, 106.8, 98.6, 76.8, 68.8, 64.5, 34.2, 31.1, 15.2.

5.4.3.17 Synthesis of (S)-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl)(Furan-2-yl)Methanol (5-23)

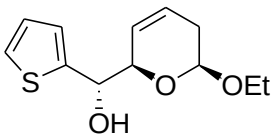


The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl vinyl ether and furan-2-carbaldehyde (**59%** yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39 (dd, 1H, *J* = 0.9 Hz, *J* = 1.8 Hz), 6.36 (ddd, 1H, *J* = 0.5 Hz, *J* = 0.9 Hz, *J* = 3.2 Hz), 6.35 (dd, 1H, *J* = 1.8 Hz, *J* = 3.3 Hz), 5.81 (dddd, 1H, *J* =

2.2 Hz, *J* = 3.3 Hz, *J* = 4.6 Hz, *J* = 10.2 Hz), 5.47 (ddd, 1H, *J* = 1.8 Hz, *J* = 4.1 Hz, *J* = 10.3 Hz), 4.81 (dd, 1H, *J* = 4.1 Hz, *J* = 6.4 Hz), 4.62 (d, 1H, *J* = 6.8 Hz), 4.58 (m, 1H), 3.95 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.56 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.25 (bs, 1H), 2.25 (m, 2H), 1.25 (t, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 153.1, 142.1, 125.2, 124.9, 110.2, 107.9, 98.2, 76.7, 70.3, 64.6, 30.9, 15.2. **HRMS** (ESI) for $C_{12}H_{16}O_4$: calcd. 224.10486; found, 224.10489.

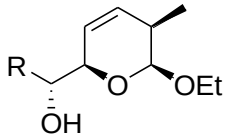
5.4.3.18 Synthesis of (S)-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl) (Thiophen-2-yl)Methanol (5-24)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl vinyl ether and thiophene-2-carbaldehyde (**65%** yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.28 (ddd, 1H, *J* = 0.3 Hz, *J* = 1.2 Hz, *J* = 5.0 Hz), 7.04 (ddd, 1H, *J* = 0.7 Hz, *J* = 1.2 Hz, *J* = 3.5 Hz), 6.97 (dd, 1H, *J* = 3.5 Hz, *J* = 5.1 Hz), 5.81 (dddd, 1H, *J* = 2.3 Hz, *J* = 3.6 Hz, *J* = 4.1 Hz, J = 10.2 Hz), 5.51 (ddd, 1H, *J* = 2.0 Hz, *J* = 4.1 Hz, *J* = 10.3 Hz), 4.85 (d, 1H, *J* = 6.7 Hz), 4.80 (dd, 1H, *J* = 4.6 Hz, *J* = 6.1 Hz), 4.40 (m, 1H), 4.00 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.58 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 2.25 (m, 2H), 1.27 (t, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 143.3, 126.4, 125.5, 125.3, 125.1, 98.4, 91.7, 78.3, 72.5, 64.6, 31.0, 15.3. **HRMS** (ESI) for $C_{12}H_{16}O_3S$: calcd. 240.08202; found, 240.08233.

5.4.4 General Procedure for Cr(III)-Catalyzed Three-Component [4+2] Cycloaddition/ Allylboration Using Ethyl 1-Propenyl Ether

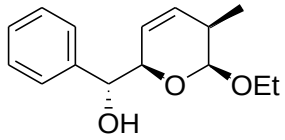


A mixture of 3-boronoacrolein pinacolate **5-1** (364 mg, 2.00 mmol) and ethyl 1-propenyl ether (Z/E 3:1) (1.90 mL) was placed in an oven-dried 10 mL RBF with stirbar. To this solution was added **5-4** (30 mg, 3 mol %) and powdered 4 Å MS (300 mg). After stirred for 14 h at ambient temperature, the reaction mixture was diluted with ether and filtered over Celite and concentrated under reduced

pressure. The catalyst was removed through a short column (deactivated silica gel, hexane 100%).

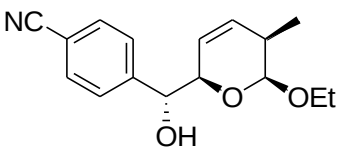
A mixture of hetero-Diels-Alder cycloadduct and aldehyde (4.00 mmol) were stirred at 110 °C for 24 h under argon. After being cooled to room temperature, a saturated solution of $NaHCO_3$ was added and the reaction mixture was stirred for 30 min. The reaction mixture was extracted with ether (2 x 20 mL), the organic layers were combined and washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered, and concentrated to afford title compound as a crude product. Purification by flash column chromatography (deactivated silica-gel, hexane:ether (9:1)) led to the pure product title compound.

5.4.4.1 Synthesis of (R)-((2R,5R,6S)-6-Ethoxy-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)(Phenyl) Methanol (5-25)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl 1-propenyl ether and benzaldehyde (**79%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.35 (m, 5H), 5.74 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.6 Hz, *J* = 10.2 Hz), 5.34 (ddd, 1H, *J* = 1.7 Hz, *J* = 1.7 Hz, *J* = 10.2 Hz), 4.74 (d, 1H, *J* = 3.3 Hz), 4.56 (dd, 1H, *J* = 2.9 Hz, *J* = 7.4 Hz), 4.33 (m, 1H), 3.97 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.57 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.40 (d, 1H, *J* = 2.9 Hz), 2.32 (m, 1H), 1.27 (t, 3H, *J* = 7.1 Hz), 1.06 (d, 3H, *J* = 7.0 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 140.0, 131.4, 128.3, 127.9, 127.2, 124.2, 100.0, 78.7, 76.8, 64.6, 33.7, 15.1, 13.9. **HRMS** (ESI) for $C_{15}H_{20}NaO_3$: calcd. 271.13119; found, 271.13107.

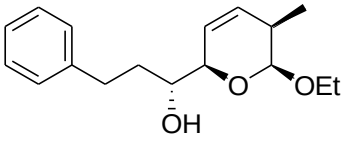
5.4.4.2 Synthesis of 4-((R)-((2R,5R,6S)-6-Ethoxy-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl) (Hydroxy)Methyl)Benzonitrile (5-26)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl 1-propenyl ether and 4-cyanobenzaldehyde (**50%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.64 (dd, 2H, *J* = 1.6 Hz, *J* = 6.4 Hz), 7.50 (m, 2H), 5.77 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.4

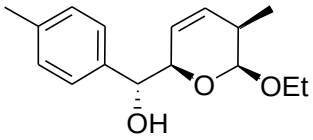
Hz, *J* = 10.1 Hz), 5.42 (ddd, 1H, *J* = 2.0 Hz, *J* = 4.2 Hz, *J* = 10.4 Hz), 4.68 (d, 1H, *J* = 13.6 Hz), 4.63 (dd, 1H, *J* = 2.8 Hz, *J* = 8.4 Hz), 4.34 (m, 1H), 3.86 (qd, 1H, *J* = 6.8 Hz, *J* = 9.6 Hz), 3.55 (d, 1H, *J* = 5.2 Hz), 3.53 (qd, 1H, *J* = 7.2 Hz, *J* = 9.7 Hz), 2.35 (m, 1H), 1.23 (t, 3H, *J* = 7.1 Hz), 0.99 (d, 3H, *J* = 7.2 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 146.1, 131.9, 127.7, 123.6, 118.8, 111.4, 99.7, 77.7, 75.6, 64.9, 33.4, 15.0, 14.0. **HRMS** (ESI) for $C_{16}H_{19}NNaO_3$: calcd. 296.12632; found, 296.12628.

5.4.4.3 Synthesis of (R)-1-((2R,5R,6S)-6-Ethoxy-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)-3-Phenylpropan-1-ol (5-27)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl 1-propenyl and hydrocinnamylaldehyde (**65%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.23 (m, 5H), 5.81 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.7 Hz, *J* = 10.2 Hz), 5.60 (ddd, 1H, *J* = 1.7 Hz, *J* = 1.7 Hz, *J* = 10.2 Hz), 4.72 (d, 1H, *J* = 3.3 Hz), 4.18 (m, 1H), 3.95 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.57 (m, 2H), 2.90 (m, 1H), 2.74 (m, 2H), 2.32 (m, 1H), 1.90 (m, 2H), 1.26 (t, 3H, *J* = 7.1 Hz), 1.06 (d, 3H, *J* = 7.0 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 142.2, 131.5, 128.5, 128.3, 125.7, 125.3, 100.0, 77.5, 72.6, 64.6, 35.0, 33.8, 32.0, 15.1, 13.9. **HRMS** (ESI) for $C_{17}H_{24}NaO_3$: calcd. 299.16177; found, 299.16139.

5.4.4.4 Synthesis of (R)-((2R,6S)-6-Ethoxy-5,6-Dihydro-2H-Pyran-2-yl)(1-Methyl-1H-Pyrrol-2-yl)Methanol (5-28)

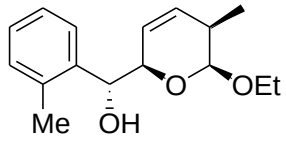


The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl 1-propenyl ether and 4-methylbenzaldehyde (**61%** yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.28 (d, 2H, *J* = 8.1 Hz), 7.16 (d, 2H, *J* = 7.8 Hz), 5.73 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.6 Hz, *J* = 10.2 Hz), 5.33 (ddd, 1H, *J* = 1.7 Hz, *J* = 1.7 Hz, *J* = 10.2 Hz), 4.74 (d, 1H, *J* = 3.3 Hz), 4.52 (dd, 1H, *J* = 2.4 Hz, *J* = 7.6 Hz), 4.30 (m, 1H),

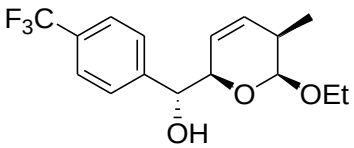
3.98 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.57 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.35 (d, 1H, *J* = 2.7 Hz), 2.34 (s, 3H), 2.31 (m, 1H), 1.27 (t, 3H, *J* = 7.1 Hz), 1.06 (d, 3H, *J* = 7.0 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 137.5, 137.0, 131.2, 128.9, 127.1, 124.3, 100.0, 78.8, 76.7, 64.6, 33.7, 21.1, 15.1, 13.9.

5.4.4.5 Synthesis of (R)-((2R,5R,6S)-6-Ethoxy-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)(o-Tolyl) Methanol (5-29)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl 1-propenyl ether and 2-methylbenzaldehyde (**63%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.48 (dd, 1H, *J* = 1.7 Hz, *J* = 7.5 Hz), 7.18 (m, 3H), 5.72 (dddd, 1H, *J* = 0.7 Hz, *J* = 2.4 Hz, *J* = 4.8 Hz, *J* = 10.2 Hz), 5.22 (ddd, 1H, *J* = 1.7 Hz, *J* = 1.7 Hz, *J* = 10.2 Hz), 4.88 (d, 1H, *J* = 7.7 Hz), 4.74 (dd, 1H, *J* = 0.6 Hz, *J* = 3.2 Hz), 4.34 (m, 1H), 4.00 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.59 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.14 (bs, 1H), 2.33 (s, 3H), 2.30 (m, 1H), 1.26 (t, 3H, *J* = 7.1 Hz), 1.06 (d, 1H, *J* = 7.0 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 138.0, 135.7, 131.5, 130.3, 127.6, 126.8, 126.1, 124.1, 100.1, 79.1, 72.7, 64.5, 60.3, 33.8, 19.7, 15.1, 14.1. **HRMS** (ESI) for $C_{16}H_{22}NaO_3$: calcd. 285.14671; found, 285.14668.

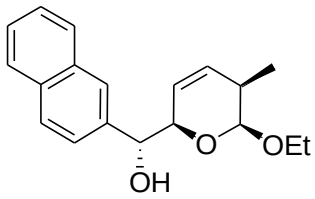
5.4.4.6 Synthesis of (R)-((2R,5R,6S)-6-Ethoxy-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)(4-(Trifluoromethyl) Phenyl)Methanol (5-30)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl 1-propenyl ether and 4-trifluoromethylbenzaldehyde (**93%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.61 (d, 2H, *J* = 8.1 Hz), 7.52 (dd, 2H, *J* = 0.6 Hz, *J* = 8.0 Hz), 5.77 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.4 Hz, *J* = 10.3 Hz), 5.39 (ddd, 1H, *J* = 1.8 Hz, *J* = 1.8 Hz, *J* = 10.3 Hz), 4.71 (d, 1H, *J* = 3.4 Hz), 4.64 (dd, 1H, *J* = 3.4 Hz, *J* = 6.4 Hz), 4.35 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.8 Hz, *J* = 6.5 Hz), 3.92 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.54 (m, 2H), 2.33 (m, 1H), 1.25 (t, 3H, *J* = 7.1 Hz), 1.04 (d, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (125 MHz,

$CDCl_3$) δ: 144.5, 131.7, 129.9 (q, *J* = 32.3 Hz), 127.4, 125.1 (q, *J* = 3.6 Hz), 124.1 (q, *J* = 271.6 Hz), 123.8, 99.9, 78.1, 75.9, 64.8, 33.6, 15.0, 13.9. **HRMS** (ESI) for $C_{16}H_{19}F_3NaO_3$: calcd. 339.11785; found, 339.11800.

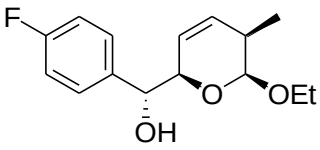
5.4.4.7 Synthesis of (R)-((2R,5R,6S)-6-Ethoxy-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)(Naphthalen-2-Yl)Methanol (5-31)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl 1-propenyl ether and 2-naphthaldehyde (**78%** yield).

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.88 (d, 1H, *J* = 0.9 Hz), 7.85 (m, 3H), 7.55 (dd, 1H, *J* = 1.7 Hz, *J* = 8.5 Hz), 7.48 (m, 2H), 5.75 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.6 Hz, *J* = 10.2 Hz), 5.38 (td, 1H, *J* = 1.7 Hz, *J* = 10.2 Hz), 4.76 (d, 1H, *J* = 3.3 Hz), 4.75 (d, 1H, *J* = 2.6 Hz), 4.45 (ddd, 1H, *J* = 2.5 Hz, *J* =4.5 Hz, *J* = 7.2 Hz), 4.00 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.59 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.54 (d, 1H, *J* = 2.9 Hz), 2.34 (m, 1H), 1.29 (t, 3H, *J* = 7.1 Hz), 1.10 (d, 3H, *J*=7.0Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 137.6, 133.2, 131.4, 128.0, 128.0, 127.6, 126.4, 126.0, 125.9, 125.0, 124.2, 100.1, 78.7, 76.9, 64.7, 33.7, 15.1, 14.0.

5.4.4.8 Synthesis of (R)-((2R,5R,6S)-6-Ethoxy-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)(4-Fluorophenyl)Methanol (5-32)

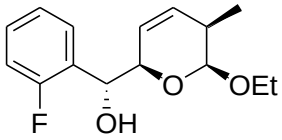


The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl 1-propenyl ether and 4-flourobenzaldehyde (**97%** yield).

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.35 (m, 2H), 7.02 (ddd, 1H, *J* = 2.5 Hz, *J* = 5.9 Hz, *J* = 10.8 Hz), 5.73 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.6 Hz, *J* = 10.2 Hz), 5.31 (ddd, 1H, *J* = 1.7 Hz, *J* = 1.7 Hz, *J* = 10.2 Hz), 4.71 (d, 1H, *J* = 3.3 Hz), 4.53 (d, 1H, *J* = 7.2 Hz), 4.27 (ddd, 1H, *J* = 2.5 Hz, *J* = 4.5 Hz, *J* = 7.1 Hz), 3.93 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.55 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.45 (bs, 1H), 2.30 (m, 1H), 1.24 (t, 3H, *J* = 7.1 Hz), 1.02 (d, 1H, *J* = 7.0 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 162.4 (d, *J* = 245.3 Hz), 135.9 (d, *J* =

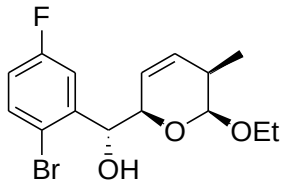
3.4 Hz), 131.6, 128.8 (d, *J* = 8.0 Hz), 123.9, 115.1 (d, *J* = 21.4 Hz), 100.0, 78.6, 76.0, 64.6, 33.7, 15.1, 13.8. **HRMS** (ESI) for $C_{15}H_{19}FNaO_3$: calcd. 289.12104; found, 289.12115.

5.4.4.9 Synthesis of (R)-((2R,5R,6S)-6-Ethoxy-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)(2-Fluorophenyl)Methanol (5-33)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl 1-propenyl ether and 2-flourobenzaldehyde (**59%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.54 (ddd, 1H, *J* = 1.8 Hz, *J* = 7.5 Hz, *J* = 7.5 Hz), 7.26 (dddd, 1H, *J* = 1.9 Hz, *J* = 5.3 Hz, *J* = 7.2 Hz, *J* = 8.2 Hz), 7.16 (ddd, 1H, *J* = 1.2 Hz, *J* = 7.5 Hz, *J* = 7.5 Hz), 7.02 (ddd, 1H, *J* = 1.2 Hz, *J* = 8.2 Hz, *J* = 10.5 Hz), 5.78 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.4 Hz, *J* = 10.2 Hz), 5.45 (ddd, 1H, *J* = 1.7 Hz, *J* = 2.9 Hz, *J* = 10.2 Hz), 4.94 (d, 1H, *J* = 6.1 Hz), 4.71 (d, 1H, *J* = 3.3 Hz), 4.45 (m, 1H), 3.93 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.54 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.40 (bs, 1H), 2.32 (m, 1H), 1.25 (t, 3H, *J* = 7.1 Hz), 1.06 (d, 1H, *J* = 7.1 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 159.9 (d, *J* = 244.5 Hz), 131.5, 129.1 (d, *J* = 8.2 Hz), 128.6 (d, *J* = 4.3 Hz), 127.7 (d, *J* = 12.9 Hz), 124.3, 124.0 (d, *J* = 3.4 Hz), 115.1 (d, *J* = 21.9 Hz), 99.8, 77.6, 70.1, 64.7, 33.6, 15.0, 14.0. **HRMS** (ESI) for $C_{15}H_{19}FNaO_3$: calcd. 289.12104; found, 289.12112.

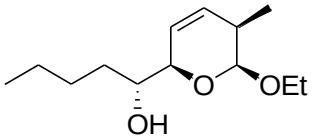
5.4.4.10 Synthesis of (R)-(2-Bromo-5-Fluorophenyl)((2R,5R,6S)-6-Ethoxy-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)Methanol (5-34)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl 1-propenyl ether and 2-bromo-5-flourobenzaldehyde (**53%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.48 (dd, 1H, *J* = 5.2 Hz, *J* = 8.7 Hz), 7.31 (dd, 1H, *J* = 3.1 Hz, *J* = 9.7 Hz), 6.88 (ddd, 1H, *J* = 3.1 Hz, *J* = 7.7 Hz, *J* = 8.7 Hz), 5.83 (ddd, 1H, *J* = 2.5 Hz, *J* = 4.2 Hz, *J* = 10.2 Hz), 5.60 (ddd, 1H, *J* = 1.8 Hz, *J* = 10.2 Hz, *J* = 10.2 Hz), 4.99 (dd, 1H, *J* = 4.7 Hz, *J* = 4.8 Hz), 4.70 (d, 1H, *J* = 3.4 Hz), 4.52 (m, 1H), 3.90 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.73 (d, 1H, *J* = 5.7 Hz), 3.55 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 2.34 (m,

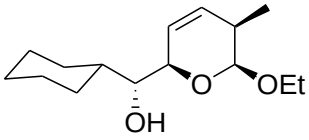
1H), 1.25 (t, 3H, *J* = 7.1 Hz), 1.08 (d, 1H, *J* = 7.1 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 162.1 (d, *J* = 246.3 Hz), 142.6 (d, *J* = 6.9 Hz), 133.6 (d, *J* = 7.6 Hz), 131.7, 124.6, 116.2 (d, *J* = 1.8 Hz), 116.0 (d, *J* = 5.6 Hz), 99.7, 76.4, 74.0, 65.1, 33.4, 15.0, 14.2. **HRMS** (ESI) for $C_{15}H_{18}FBrNaO_3$: calcd. 367.03261; found, 367.03288.

5.4.4.11 Synthesis of (R)-1-((2R,5R,6S)-6-Ethoxy-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)Pentan-1-ol (5-35)



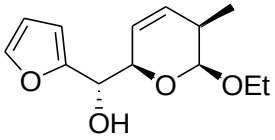
The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl 1-propenyl ether and pentanal (**74 %** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 5.77 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.7 Hz, *J* = 10.2 Hz), 5.58 (ddd, 1H, *J* = 1.7 Hz, *J* = 1.7 Hz, *J* = 10.2 Hz), 4.67 (d, 1H, *J* = 3.3 Hz), 4.11 (ddd, 1H, *J* = 1.7 Hz, *J* = 2.7 Hz, *J* = 5.1 Hz), 3.90 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.52 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.49 (bs, 1H), 2.27 (m, 1H), 2.58 (d, 1H, *J* = 4.0 Hz), 1.50 (m, 2H), 1.33 (m, 4H), 1.21 (t, 3H, *J* = 7.1 Hz), 1.01 (d, 3H, *J* = 7.0 Hz), 0.89 (t, 3H, *J* = 7.2 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 131.3, 125.4, 100.0, 77.4, 73.3, 64.5, 33.8, 32.7, 27.8, 22.7, 15.0, 14.0, 13.8. **HRMS** (ESI) for $C_{13}H_{24}NaO_3$: calcd. 251.16239; found, 251.16256.

5.4.4.12 Synthesis of (R)-Cyclohexyl((2R,5R,6S)-6-Ethoxy-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)Methanol (5-36)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl 1-propenyl ether and cyclohexane carboxaldehyde (**59%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 5.79 (ddd, 1H, *J* = 2.5 Hz, *J* = 4.7 Hz, *J* = 10.2 Hz), 5.58 (ddd, 1H, *J* = 1.7 Hz, *J* = 1.7 Hz, *J* = 10.2 Hz), 4.68 (d, 1H, *J* = 3.3 Hz), 4.35 (m, 1H), 3.91 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.53 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.18 (m, 1H), 2.38 (m, 1H), 2.28 (m, 1H), 1.96 (m, 1H), 1.40-1.96 (m, 6H), 1.23 (t, 3H, *J* = 7.1 Hz), 1.00-1.23 (m, 4H), 1.03 (d, 3H, *J* = 7.0 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 131.2, 126.2, 99.9, 77.4, 74.6, 64.6, 40.3, 33.6, 29.6, 28.5, 26.4, 26.3, 26.1, 15.0, 13.9. **HRMS** (ESI) for $C_{15}H_{26}NaO_3$: calcd. 277.17742; found, 277.17697.

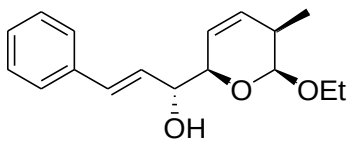
5.4.4.13 Synthesis of (S)-((2R,5R,6S)-6-Ethoxy-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)(Furan-2-yl)Methanol (5-37)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl 1-propenyl ether and furan-2-carbaldehyde (**58%** yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39 (dd, 1H, *J* = 0.9 Hz, *J* = 1.8 Hz), 6.35 (m, 1H), 5.76 (ddd, 1H, *J* = 2.2 Hz, *J* = 4.3 Hz, *J* = 10.3 Hz), 5.42 (td, 1H, *J* = 1.7 Hz, *J* = 10.2 Hz), 4.75 (d, 1H, *J* = 3.4 Hz), 4.58 (m, 1H), 3.94 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.55 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.38 (d, 1H, *J* = 4.1 Hz), 2.35 (m, 1H), 1.24 (t, 3H, *J* = 7.1 Hz), 1.04 (d, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 153.3, 142.1, 131.4, 124.0, 110.2, 107.8, 99.8, 76.0, 70.3, 64.7, 33.5, 15.0, 14.0. **HRMS** (ESI) for $C_{13}H_{18}NaO_4$: calcd. 261.10973; found. 261.10928.

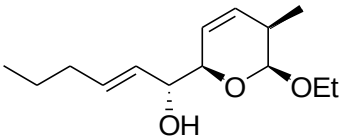
5.4.4.14 Synthesis of (R,2E)-1-((2R,5R,6S)-6-Ethoxy-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)-3-Phenyl Prop-2-en-1-ol (5-38)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl 1-propenyl ether and cinnamylaldehyde (**84%** yield).

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.39 (d, 2H, *J* = 7.4 Hz), 7.30 (t, 2H, *J* = 7.5 Hz), 7.23 (m, 1H), 6.71 (d, 1H, *J* = 16.0 Hz), 6.27 (dd, 1H, *J* = 6.4 Hz, *J* = 15.9 Hz), 5.79 (ddd, 1H, *J* = 2.3 Hz, *J* = 4.5 Hz, *J* = 10.2 Hz), 5.65 (td, 1H, *J* = 1.7 Hz, *J* = 10.2 Hz), 4.73 (d, 1H, *J* = 3.3 Hz), 4.25 (m, 2H), 3.96 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.55 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.25 (bs, 1H), 2.34 (m, 1H), 1.25 (t, 3H, *J* = 7.1 Hz), 1.06 (d, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 136.7, 132.4, 131.3, 128.5, 128.1, 127.6, 126.5, 124.5, 99.9, 77.6, 74.8, 64.6, 33.7, 15.0, 13.9.

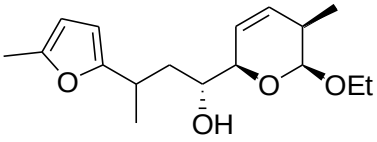
5.4.4.15 Synthesis of (R,2E)-1-((2R,5R,6S)-6-Ethoxy-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)Hex-2-en-1-ol (5-39)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl 1-propenyl ether and 2-hexenal (**63%** yield).

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.76 (m, 2H), 5.57 (td, 1H, *J* = 1.7 Hz, *J* = 10.2 Hz), 5.48 (tdd, 1H, *J* = 1.5 Hz, *J* = 7.3 Hz, *J* = 15.4 Hz), 4.70 (d, 1H, *J* = 3.3 Hz), 4.08 (m, 1H), 3.93 (m, 2H), 3.53 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 2.90 (d, 1H, *J* = 3.3 Hz), 2.29 (m, 1H), 1.40 (m, 2H), 1.23 (t, 5H, *J* = 7.1 Hz), 1.02 (d, 3H, *J* = 7.0 Hz), 0.89 (t, 3H, *J* = 7.4 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 134.8, 131.1, 128.3, 124.6, 100.0, 77.7, 75.1, 64.5, 34.4, 33.7, 22.1, 15.0, 13.8, 13.6. **HRMS** (ESI) for $C_{14}H_{24}NaO_3$: calcd. 263.16177; found. 263.16185.

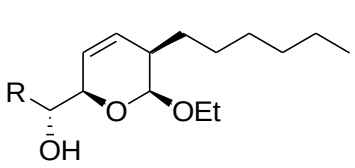
5.4.4.16 Synthesis of (1R)-1-((2R,5R,6S)-6-Ethoxy-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)-3-(5-Methyl Furan-2-Yl)Butan-1-ol (5-40)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using ethyl 1-propenyl ether and 3-(5-methylfuran-2-yl)butanal (**82%** yield).

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.85 (dd, 1H, *J* = 3.0 Hz, *J* = 10.2 Hz), 5.81 (m, 1H), 5.77 (m, 1H), 5.56 (tdd, 1H, *J* = 1.6 Hz, *J* = 10.2 Hz, *J* = 13.5 Hz), 4.68 (dd, 1H, *J* = 3.3 Hz, *J* = 11.2 Hz), 4.10 (m, 1H), 3.91 (dqd, 1H, *J* = 4.3 Hz, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.62 (bs, 1H), 3.51 (m, 2H), 3.07 (m, 1H), 2.28 (m, 1H), 2.21 (s, 3H), 1.10-1.30 (m, 8H), 1.02 (dd, 3H, *J* = 6.9 Hz, *J* = 9.4 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 158.8, 157.9, 150.0, 131.3, 125.5, 105.6, 104.6, 103.8, 99.9, 77.8, 77.4, 71.4, 70.8, 64.5, 33.7, 15.0, 13.4. **HRMS** (ESI) for $C_{17}H_{26}O_4$: calcd. 294.18311; found. 294.18319.

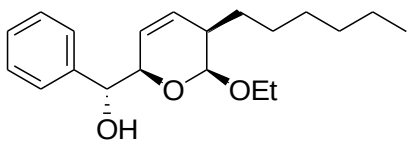
5.4.5 General Procedure for Cr(III)-Catalyzed Three-Component [4+2] Cycloaddition/ Allylboration Using (*Z*)-1-Ethoxyoct-1-ene



A mixture of 3-boronoacrolein pinacolate **5-1** (364 mg, 2.00 mmol) and ethyl (*Z*)-1-ethoxyoct-1-ene (2.0 mL) was placed in an oven-dried 10 mL RBF with a stirbar. To this solution was added **5-4** (30 mg, 3 mol%) and powdered 4 Å molecular sieve (300 mg). After stirring for 14 h at ambient temperature, the reaction mixture was diluted with ether and filtered over Celite and concentrated under reduced pressure. The catalyst was removed through a short column (deactivated silica gel, hexane 100%), and the excess of (*Z*)-1-ethoxyoct-1-ene was partly recovered by bulb to bulb distillation to provide the hetero-Diels-Alder cycloadduct product.

A mixture of hetero-Diels-Alder cycloadduct and aldehyde (4.00 mmol) was stirred at 110 ^{o}C for 24 h under argon. After being cooled to room temperature, a saturated solution of $NaHCO_3$ was added and the reaction mixture was stirred for 30 min. The reaction mixture was extracted with ether (2 x 20 mL), the organic layers were combined and washed with saturated NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated to afford the title compound as a crude product. Purification by flash column chromatography (deactivated silica-gel, hexane:ether (9:1)) led to the pure product title compound.

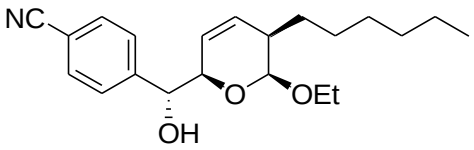
5.4.5.1 Synthesis of (R)-((2R,5R,6S)-6-Ethoxy-5-Hexyl-5,6-Dihydro-2H-Pyran-2-yl) (Phenyl) Methanol (5-41)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using (*Z*)-1-ethoxyoct-1-ene and benzaldehyde (**79%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.33 (m, 5H), 5.78 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.1 Hz, *J* = 10.4 Hz), 5.39 (ddd, 1H, *J* = 1.9 Hz, *J* = 1.9 Hz, *J* = 10.4 Hz), 4.76 (d, 1H, *J* = 3.4 Hz), 4.57 (d, 1H, *J* = 7.4 Hz), 4.33 (ddd, 1H, *J* = 2.3 Hz, *J* = 5.0 Hz, *J* = 7.3 Hz), 3.96 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.55 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6

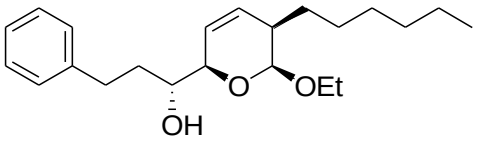
Hz), 3.50 (bs, 1H), 2.23 (m, 1H), 0.75-1.80 (m, 16H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 140.2, 129.6, 128.2, 127.8, 127.1, 124.4, 99.7, 78.4, 76.7, 64.6, 46.1, 38.6, 31.7, 29.5, 26.8, 22.6, 15.1, 14.0. **HRMS** (ESI) for $C_{20}H_{30}NaO_3$: calcd. 341.20931; found, 341.20965

5.4.5.2 Synthesis of 4-((R)-((2R,5R,6S)-6-Ethoxy-5-Hexyl-5,6-Dihydro-2H-Pyran-2-yl) (Hydroxy)Methyl)Benzonitrile (5-42)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using (*Z*)-1-ethoxyoct-1-ene and 4-cyanobenzaldehyde (**72%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.63 (d, 1H, *J* = 8.3 Hz), 7.51 (d, 1H, *J* = 8.6 Hz), 5.82 (ddd, 1H, *J* = 2.5 Hz, *J* = 3.8 Hz, *J* = 10.4 Hz), 5.46 (ddd, 1H, *J* = 2.0 Hz, *J* = 2.0 Hz, *J* = 10.4 Hz), 4.72 (d, 1H, *J* = 3.6 Hz), 4.65 (d, 1H, *J* = 5.8 Hz), 4.38 (ddd, 1H, *J* = 2.3 Hz, *J* = 5.5 Hz), 3.87 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.67 (bs, 1H), 3.50 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 2.22 (m, 1H), 1.10-1.70 (m, 13H), 0.87 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ. 146.3, 131.9, 130.3, 127.6, 123.8, 118.7, 111.3, 99.3, 77.4, 75.5, 64.9, 38.3, 31.7, 31.5, 29.5, 29.4, 26.7, 22.5, 15.0, 14.0. **HRMS** (ESI) for $C_{21}H_{29}NNaO_3$: calcd. 366.20449; found, 366.20476.

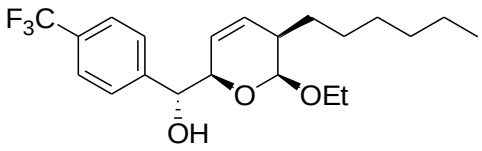
5.4.5.3 Synthesis of (R)-1-((2R,5R,6S)-6-Ethoxy-5-Hexyl-5,6-Dihydro-2H-Pyran-2-yl)-3-Phenylpropan-1-ol (5-43)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using (*Z*)-1-ethoxyoct-1-ene and hydrocinnamylaldehyde (**65%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.10-7.45 (m, 5H), 5.87 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.3 Hz, *J* = 10.3 Hz), 5.65 (ddd, 1H, *J* = 1.8 Hz, *J* = 1.8 Hz, *J* = 10.3 Hz), 4.75 (d, 1H, *J* = 3.5 Hz), 4.19 (m, 1H), 3.95 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.56 (m, 2H), 2.91 (m, 1H), 2.75 (ddd, 1H, *J* = 7.3 Hz, *J* = 9.4 Hz, *J* = 13.8 Hz), 2.24 (s, 1H), 1.90 (m, 2H), 1.13-1.62 (m, 10H), 1.26 (t, 1H, *J* = 7.1 Hz), 0.92 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 142.2, 129.7, 128.5, 128.3, 125.7, 125.5, 99.7,

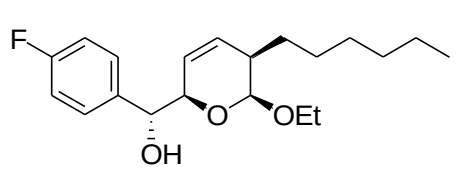
77.2, 72.6, 64.7, 38.7, 35.1, 32.0, 31.8, 29.5, 29.5, 26.9, 22.6, 15.0, 14.1. **HRMS** (ESI) for $C_{22}H_{34}NaO_3$: calcd. 369.24061; found, 369.24048.

5.4.5.4 Synthesis of (R)-((2R,5R,6S)-6-Ethoxy-5-Hexyl-5,6-Dihydro-2H-Pyran-2-yl)(4-(Trifluoromethyl)Phenyl)Methanol (5-44)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using (*Z*)-1-ethoxyoct-1-ene and 4-trifluoromethylbenzaldehyde (**67%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.62 (d, 1H, *J* = 8.1 Hz), 7.53 (d, 1H, *J* = 8.6 Hz), 5.83 (ddd, 1H, *J* = 2.5 Hz, *J* = 3.9 Hz, *J* = 10.4 Hz), 5.46 (ddd, 1H, *J* = 2.0 Hz, *J* = 2.0 Hz, *J* = 10.4 Hz), 4.76 (d, 1H, *J* = 3.5 Hz), 4.66 (d, 1H, *J* = 6.4 Hz), 4.38 (ddd, 1H, *J* = 2.3 Hz, *J* = 5.3 Hz, *J* = 6.3 Hz), 3.92 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.60 (m, 1H), 3.54 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 2.24 (m, 1H), 1.15-1.65 (m, 13H), 0.89 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 144.6, 130.1, 127.2, 126.6 (q, *J* = 272.9 Hz), 125.1 (q, *J* = 3.7 Hz), 125.1, 123.9, 99.4, 77.8, 75.8, 64.9, 38.4, 31.7, 29.5, 29.5, 26.8, 22.6, 15.0, 14.0. **HRMS** (ESI) for $C_{21}H_{29}F_3NaO_3$: calcd. 409.19657; found. 409.19661.

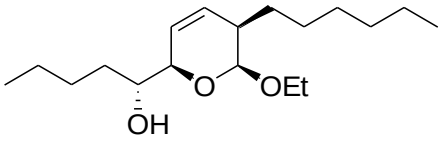
5.4.5.5 Synthesis of (R)-((2R,5R,6S)-6-Ethoxy-5-Hexyl-5,6-Dihydro-2H-Pyran-2-yl)(4-Fluorophenyl)Methanol (5-45)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using (*Z*)-1-ethoxyoct-1-ene and 4-fluorobenzaldehyde (**62%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.38 (ddd, 2H, *J* = 3.0 Hz, *J* = 5.5 Hz, *J* = 8.0 Hz), 7.05 (ddd, 2H, *J* = 3.0 Hz, *J* = 5.0 Hz, *J* = 10.0 Hz), 5.80 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.1 Hz, *J* = 10.4 Hz), 5.38 (ddd, 1H, *J* = 1.9 Hz, *J* = 1.9 Hz, *J* = 10.3 Hz), 4.77 (d, 1H, *J* = 3.5 Hz), 4.56 (d, 1H, *J* = 7.0 Hz), 4.29 (ddd, 1H, *J* = 2.4 Hz, *J* = 5.0 Hz, *J* = 7.3 Hz), 3.95 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.56 (qd, 1H, *J* = 7.1 Hz, *J* = 9.7 Hz), 3.43 (d, 1H, *J* = 2.3 Hz), 2.23 (m, 1H), 1.10-1.70 (m, 13H), 0.86 (m, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 162.4 (d, *J* = 245.2 Hz), 136.0 (d, *J* = 3.1 Hz),

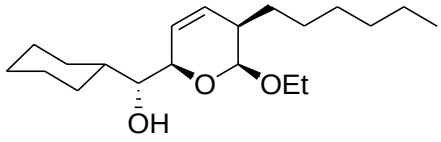
129.9, 128.7 (d, *J* = 8.1 Hz), 124.0, 115.1 (d, *J* = 21.3 Hz), 99.7, 78.3, 76.1, 64.8, 38.6, 36.6, 31.7, 29.5, 26.8, 22.6, 15.1, 14.0. **HRMS** (ESI) for $C_{20}H_{29}FNaO_3$: calcd. 359.19973; found, 359.19987.

5.4.5.6 Synthesis of (R)-1-((2R,5R,6S)-6-Ethoxy-5-Hexyl-5,6-Dihydro-2H-Pyran-2-yl) Pentan-1-ol (5-46)



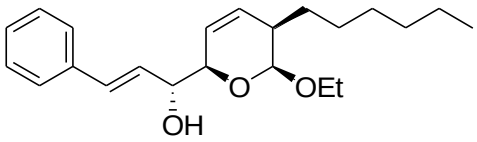
The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using (*Z*)-1-ethoxyoct-1-ene and pentanal (**72%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 5.80 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.3 Hz, *J* = 10.3 Hz), 5.60 (ddd, 1H, *J* = 1.8 Hz, *J* = 1.8 Hz, *J* = 10.3 Hz), 4.69 (d, 1H, *J* = 3.4 Hz), 4.10 (ddd, 1H, *J* = 2.5 Hz, *J* = 2.5 Hz, *J* = 5.0 Hz), 3.89 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.49 (m, 2H), 2.71 (m, 1H), 2.17 (m, 1H), 1.05-1.80 (m, 17H), 1.21 (dd, 3H, *J* = 10.0 Hz, *J* = 17.1 Hz), 0.86 (m, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 129.5, 125.6, 99.6, 77.1, 73.3, 64.6, 38.7, 32.8, 31.7, 29.5, 29.4, 27.8, 26.8, 22.7, 22.5, 14.9, 14.0, 13.9. **HRMS** (ESI) for $C_{18}H_{34}NaO_3$: calcd. 321.24049; found. 321.24076.

5.4.5.7 Synthesis of (R)-Cyclohexyl((2R,5R,6S)-6-Ethoxy-5-Hexyl-5,6-Dihydro-2H-Pyran-2-yl)Methanol (5-47)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using (*Z*)-1-ethoxyoct-1-ene and cyclohexane carboxaldehyde (**43%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 5.83 (ddd, 1H, *J* = 2.5 Hz, *J* = 4.2 Hz, *J* = 10.3 Hz), 5.61 (ddd, 1H, *J* = 1.8 Hz, *J* = 1.8 Hz, *J* = 10.3 Hz), 4.70 (d, 1H, *J* = 3.5 Hz), 4.37 (m, 1H), 3.90 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.51 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.16 (ddd, 1H, *J* = 3.9 Hz, *J* = 7.1 Hz, *J* = 7.1 Hz), 2.54 (d, 1H, *J* = 7.2 Hz), 2.18 (m, 1H), 1.97 (dd, 1H, *J* = 1.4 Hz, *J* = 11.6 Hz), 1.51-2.85 (m, 6H), 0.95-1.50 (m, 17H), 0.87 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 129.4, 126.4, 99.6, 77.4, 74.3, 64.7, 40.3, 38.6, 31.7, 29.6, 29.5, 28.5, 26.9, 26.4, 26.2, 26.1, 26.0, 22.6, 15.0, 14.0. **HRMS** (ESI) for $C_{20}H_{36}NaO_3$: calcd. 347.25634; found, 347.25651.

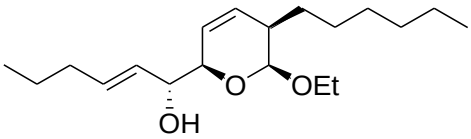
5.4.5.8 Synthesis of (S)-((2R,5R,6S)-6-Ethoxy-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)(Furan-2-yl)Methanol (5-48)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using (*Z*)-1-ethoxyoct-1-ene and cinnamylaldehyde (**75%** yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.40 (d, 1H, *J* = 7.0 Hz), 7.31 (dd, 1H, *J* = 7.7 Hz, *J* = 7.0 Hz), 7.24 (m, 1H), 6.73 (d, 1H, *J* = 15.9 Hz), 6.28 (dd, 1H, *J* = 6.3 Hz, *J* = 15.9 Hz), 5.85 (ddd, 1H, *J* = 2.3 Hz, *J* = 3.9 Hz, *J* = 10.4 Hz), 5.71 (ddd, 1H, *J* = 1.8 Hz, *J* = 1.9 Hz, *J* = 10.4 Hz), 4.78 (d, 1H, *J* = 3.5 Hz), 4.27 (m, 2H), 3.97 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.54 (qd, 1H, *J* = 7.1 Hz, *J* = 9.6 Hz), 3.27 (bs, 1H), 2.26 (m, 1H), 1.20–1.60 (m, 10H), 0.80–0.10 (m, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 136.7, 132.3, 129.6, 128.4, 128.3, 127.6, 126.5, 124.7, 99.5, 74.8, 64.8, 38.5, 31.8, 31.6, 29.5, 26.9, 22.6, 15.0, 14.1, 14.0.

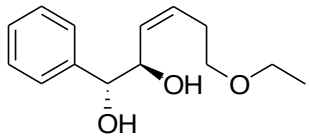
5.4.5.9 Synthesis of (R,2E)-1-((2R,5R,6S)-6-Ethoxy-5-Hexyl-5,6-Dihydro-2H-Pyran-2-yl)Hex-2-en-1-ol (5-49)



The title compound was prepared using the general procedure for the Cr(III)-catalyzed three-component [4+2] cycloaddition/ allylboration using (*Z*)-1-ethoxyoct-1-ene and 2-hexenal (**57%** yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.75 (m, 2H), 5.58 (d, 1H, *J* = 10.4 Hz), 5.45 (dd, 1H, *J* = 6.8 Hz, *J* = 7.2 Hz), 4.70 (d, 1H, *J* = 3.6 Hz), 4.10 (m, 1H), 3.90 (qd, 1H, *J* = 7.0 Hz, *J* = 9.7 Hz), 3.48 (m, 1H), 3.0 (bs, 1H), 2.18 (m, 1H), 0.95-1.80 (m, 21H), 0.86 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 134.5, 129.3, 128.5, 124.8, 99.6, 75.0, 64.5, 38.6, 34.4, 31.7, 31.5, 29.5, 29.4, 26.8, 22.5, 22.1, 14.9, 14.0, 13.5.

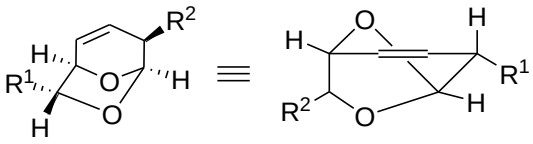
5.4.6 Synthesis of (Z,1R,2R)-6-Ethoxy-1-Phenylhex-3-ene-1,2-Diol (5-51)



Acetal **5-7** (1.0 mmol) and triethylsilane (1.1 mmol) were dissolved in CH_2Cl_2 (15 mL). $TiCl_4$ (1.2 mmol) was added dropwise at –50 °C. After being stirred for 2 h at –50 °C, the reaction mixture was allowed to warm up to ambient temperature. After 4h, the reaction was quenched with an aqueous saturated $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexane/EtOAc 5:1) to afford the title compound in 78% yield.

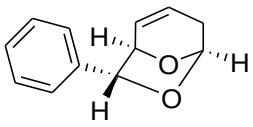
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1H-NMR (400 MHz), 7.20-7.40 (m, 5H), 5.56 (m, 2H), 4.56 (d, 1H, *J* = 7.6 Hz), 4.44 (dd, 1H, *J* = 7.2 Hz, *J* = 7.6 Hz), 3.44 (m, 3H), 3.29 (dt, 1H, *J* = 5.4 Hz, *J* = 9.0 Hz), 3.21 (dt, 1H, *J* = 4.5 Hz, *J* = 9.0 Hz), 2.37 (dddd, 1H, *J* = 5.4 Hz, *J* = 7.9 Hz, *J* = 9.0 Hz, *J* = 14.3 Hz), 2.00 (m, 1H), 1.18 (t, 3H, *J* = 7.1 Hz).
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 140.1, 131.0, 130.5, 128.1, 127.7, 127.0, 77.3, 71.2, 68.6, 66.3, 28.4, 14.7. **IR** (Cast film, cm^{-1}) 3387, 2974, 2867, 1652, 1558, 1455, 1109, 1047, 700. **HRMS** (EI) for $C_{14}H_{20}O_3$: M+ peak was not detected, fragments: 130.099907, 107.04957, 84.05758.

5.4.7 General Procedure for the Synthesis of Bicyclic Acetal Products



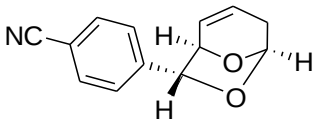
Acetal (1.0 mmol) and triethylsilane (1.0 mmol) were dissolved in CH_2Cl_2 (15 mL). $BF_3{\cdot}Et_2O$ (1.0 mmol) was added dropwise at –50 °C. After being stirred for 2 h at –50 °C, the reaction mixture was allowed to warm up to ambient temperature. After 16h, the reaction was quenched with an aqueous saturated $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexane/EtOAc 5:1) to afford the title compound.

5.4.7.1 Synthesis of (1R,5R,7R)-7-Phenyl-6,8-Dioxa-Bicyclo[3.2.1]Oct-2-ene (5-52)



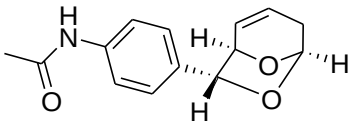
The title compound was prepared using the general procedure for the synthesis of acetal (**63%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.10-7.40 (m, 5H), 6.18 (m, 1H), 5.96 (dd, 1H, *J* = 2.0 Hz, *J* = 2.1 Hz), 5.76 (dddd, 1H, *J* = 1.8 Hz, *J* = 2.8 Hz, *J* = 3.9 Hz, *J* = 9.8 Hz), 5.17 (s, 1H), 4.43 (d, 1H, *J* = 4.6 Hz), 2.60 (ddd, 1H, *J* = 2.1 Hz, *J* = 5.1 Hz, *J* = 18.1 Hz), 2.20 (dddd, 1H, *J* = 0.8 Hz, *J* = 2.0 Hz, *J* = 3.9 Hz, *J* = 18.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 141.5, 129.1, 128.2, 127.5, 125.6, 124.5, 101.4, 86.1, 76.5, 34.1.

5.4.7.2 Synthesis of 4-((1R,5R,7R)-6,8-Dioxa-Bicyclo[3.2.1]oct-2-en-7-yl)Benzo Nitrile (5-53)



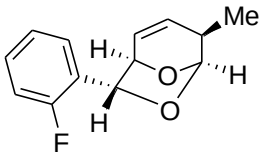
The title compound was prepared using the general procedure for the synthesis of acetal (**68%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.63 (d, 2H, *J* = 8.4 Hz), 7.43 (d, 2H, *J* = 8.4 Hz), 6.18 (m, 1H), 5.97 (m, 1H), 5.79 (m, 1H), 5.19 (d, 1H, *J* = 8.9 Hz), 4.40 (m, 1H), 2.60 (m, 1H), 2.20 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 147.0, 132.4, 128.7, 126.7, 125.2, 119.0, 111.7, 102.1, 85.6, 76.8, 34.3.

5.4.7.3 Synthesis of N-(4-((1R,5R,7R)-6,8-Dioxa-Bicyclo[3.2.1]oct-2-en-7-yl)Phenyl)Acetamide (5-54)



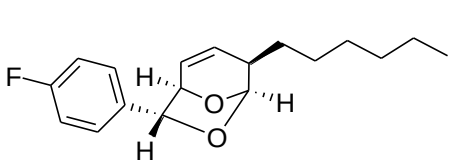
The title compound was prepared using the general procedure for the synthesis of acetal (**51%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.46 (d, 1H, *J* = 8.5 Hz), 7.34 (bs, 1H), 7.27 (d, 1H, *J* = 8.5 Hz), 6.17 (dddd, 1H, *J* = 1.9 Hz, *J* = 1.9 Hz, *J* = 4.1 Hz, *J* = 8.6 Hz), 5.94 (dd, 1H, *J* = 1.9 Hz, *J* = 2.0 Hz), 5.75 (m, 1H), 5.12 (s, 1H), 4.39 (d, 1H, *J* = 4.7 Hz), 2.59 (ddd, 1H, *J* = 2.3 Hz, *J* = 4.9 Hz, *J* = 17.8 Hz), 2.20 (m, 1H), 2.16 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 168.2, 137.6, 137.3, 129.1, 126.5, 124.5, 119.7, 101.5, 85.8, 77.2, 34.1, 24.5. **HRMS** (ESI) for $C_{14}H_{16}NO_3$ $(M+H)^+$: calcd. 264.11247; found, 246.11217.

5.4.7.4 Synthesis of (1R,4R,5R,7R)-7-(2-Fluorophenyl)-4-Methyl-6,8-Dioxa-Bicyclo[3.2.1]oct-2-ene (5-55)



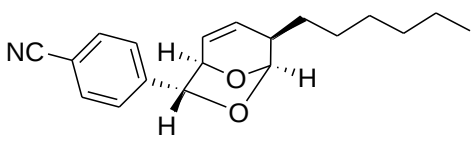
The title compound was prepared using the general procedure for the synthesis of acetal (**72%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.47 (ddd, 1H, *J* = 1.7 Hz, *J* = 7.6 Hz, *J* = 7.7 Hz), 7.27 (m, 1H), 7.16 (ddd, 1H, *J* = 1.2 Hz, *J* = 7.5Hz, *J* = 7.6 Hz), 7.02 (ddd, 1H, *J* = 1.2 Hz, *J* = 8.2 Hz, *J* = 10.5 Hz), 6.15 (ddd, 1H, *J* = 2.1 Hz, *J* = 4.4 Hz, *J* = 9.7 Hz), 5.75 (dd, 1H, *J* = 2.1 Hz, *J* = 2.2 Hz), 5.64 (ddd, 1H, *J* = 2.0 Hz, *J* = 2.1 Hz, *J* = 9.7 Hz), 5.38 (d, 1H, *J* = 0.7 Hz), 4.48 (dd, 1H, *J* = 0.7 Hz, *J* = 4.4 Hz), 2.72 (m, 1H), 1.14 (d, 3H, *J* = 7.4Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 159.5 (d, *J* = 244.6 Hz), 131.442, 129.2 (d, *J* = 8.1 Hz), 129.1 (d, *J* = 12.9 Hz), 127.9 (d, *J* = 4.2 Hz), 127.749, 124.3 (d, *J* = 3.4 Hz), 114.9 (d, *J* = 20.9 Hz), 105.1, 79.5, 76.3, 37.6, 14.6.

5.4.7.5 Synthesis of (1R,4R,5R,7R)-7-(4-Fluorophenyl)-4-Hexyl-6,8-Dioxa-Bicyclo[3.2.1]oct-2-ene (5-56)



The title compound was prepared using the general procedure for the synthesis of acetal (**41%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.30 (dd, 2H, *J* = 5.4 Hz, *J* = 8.9 Hz), 7.02 (dd, 2H, *J* = 8.9, *J* = 8.7 Hz), 6.11 (ddd, 1H, *J* = 2.1 Hz, *J* = 4.5 Hz, *J* = 9.8 Hz), 5.80 (dd, 1H, *J* = 2.2 Hz, *J* = 2.3 Hz), 5.68 (ddd, 1H, *J* = 2.1 Hz, *J* = 2.2 Hz, *J* = 9.8 Hz), 5.02 (s, 1H), 4.37 (d, 1H, *J* = 4.5 Hz), 2.55 (m, 1H), 1.10-1.70 (m, 10H), 0.90 (t, 3H, *J* = 6.8 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 162.3 (d, *J* = 244.1 Hz), 137.4 (d, *J* = 3.0 Hz), 130.1, 127.8, 127.6 (d, *J* = 8.2 Hz), 115.1 (d, *J* = 21.5 Hz), 104.1, 84.8, 76.9, 42.4, 31.7, 29.7, 29.5, 26.8, 22.6, 14.0. **HRMS** (ESI) for $C_{18}H_{23}FO_2$: calcd. 290.16821; found, 290.16784.

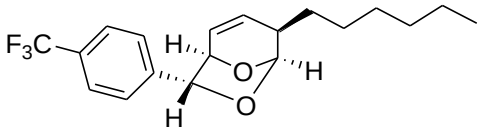
5.4.7.6 Synthesis of 4-((1R,4R,5R,7R)-4-Hexyl-6,8-Dioxa-Bicyclo[3.2.1]oct-2-en-7-yl)Benzonitrile (5-57)



The title compound was prepared using the general procedure for the synthesis of acetal (**48%** yield). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ: 7.62 (d, 2H, *J* = 8.5 Hz), 7.42 (d, 2H, *J* = 8.0 Hz), 6.10 (ddd, 1H, *J* = 2.0 Hz, *J* =

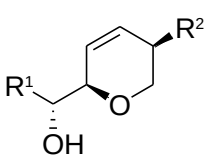
4.5 Hz, *J* = 9.8 Hz), 5.81 (dd, 1H, *J* = 2.2 Hz, *J* = 2.3 Hz), 5.69 (ddd, 1H, *J* = 2.2 Hz, *J* = 2.3 Hz, *J* = 9.8 Hz), 5.07 (s, 1H), 4.37 (d, 1H, *J* = 4.5 Hz), 2.56 (m, 1H), 1.10-1.70 (m, 10H), 0.89 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 146.8, 132.1, 130.4, 127.3, 126.5, 118.7, 111.4, 104.4, 84.6, 76.9, 42.4, 31.7, 29.6, 29.4, 26.7, 22.6, 14.0.

5.4.7.7 Synthesis of (1R,4R,5R,7R)-7-(4-(Trifluoromethyl)Phenyl)-4-Hexyl-6,8-Dioxa-Bicyclo[3.2.1]oct-2-ene (5-58)



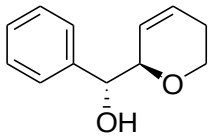
The title compound was prepared using the general procedure for the synthesis of acetal (**39%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.60 (d, 2H, *J* = 8.1 Hz), 7.44 (d, 2H, *J*=8.6Hz), 6.12 (ddd, 1H, *J* = 2.1 Hz, *J* = 4.5 Hz, *J* = 9.8 Hz), 5.83 (dd, 1H, *J* = 2.1 Hz, *J* = 2.2 Hz), 5.70 (ddd, 1H, *J* = 2.1 Hz , *J* = 2.2 Hz, *J* = 9.8 Hz), 5.10 (s, 1H), 4.39 (d, 1H, *J* = 4.5 Hz), 2.58 (tdd, 1H, *J* = 2.3 Hz, *J* = 4.9 Hz, *J* = 9.6 Hz), 1.10-1.70 (m, 10H), 0.90 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 145.5, 130.3, 127.5, 126.2 (q, *J* = 272.0 Hz), 126.1, 125.3, 125.2, 104.3, 84.7, 76.8, 42.4, 31.7, 29.7, 29.5, 26.7, 22.6, 14.0.

5.4.8 General Procedure for Acetal Reduction



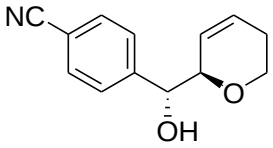
Acetal (1.0 mmol) and triethylsilane (2.0 mmol) were dissolved in CH_2Cl_2 (15 mL). $BF_3{\cdot}Et_2O$ (2.0 mmol) was added dropwise at –50 °C. After being stirred for 2 h at –50 °C, the reaction mixture was allowed to warm up to ambient temperature. After 16 h, the reaction was quenched with an aqueous saturated $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexane/EtOAc 4:1) to afford the title compound.

5.4.8.1 Synthesis of (R)-((R)-5,6-Dihydro-2H-Pyran-2-yl)(Phenyl)Methanol (5-59)



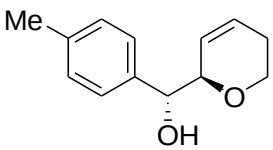
The title compound was prepared using the general procedure for acetal reduction (**76%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.36 (m, 5H), 5.91 (m, 1H), 5.36 (ddd, 1H, *J* = 2.1 Hz, *J* = 4.1 Hz, *J* = 10.4 Hz), 4.55 (d, 1H, *J* = 8.0 Hz), 4.15 (m, 1H), 4.04 (m, 1H), 3.74 (ddd, 1H, *J* = 4.3 Hz, *J* = 8.3 Hz, *J* = 11.2 Hz), 3.24 (bs, 1H), 2.25 (m, 1H), 2.04 (m, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 139.8, 128.3, 128.0, 127.3, 126.7, 125.8, 78.0, 76.3, 62.6, 25.1. **HRMS** (ESI) for $C_{12}H_{14}NaO_2$: calcd.213.08932; found, 213.08913.

5.4.8.2 Synthesis of 4-((R)-((R)-5,6-Dihydro-2H-Pyran-2-yl)(Hydroxy)Methyl) Benzonitrile (5-60)



The title compound was prepared using the general procedure for acetal reduction (**31%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.64 (dd, 2H, *J* = 1.8 Hz, *J* = 8.4 Hz), 7.50 (m, 2H), 5.96 (m, 1H), 5.37 (ddd, 1H, *J* = 2.0 Hz, *J* = 4.1 Hz, *J* = 10.4 Hz), 4.62 (dd, 1H, *J* = 1.9 Hz, *J* = 6.9 Hz), 4.12 (m, 1H), 4.00 (ddd, 1H, *J* = 3.7 Hz, *J* = 5.4 Hz, *J* = 11.3 Hz), 3.71 (ddd, 1H, *J* = 4.2 Hz, *J* = 8.6 Hz, *J* = 11.3 Hz), 3.26 (d, 1H, *J* = 2.6 Hz), 2.24 (m, 1H), 2.02 (m, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 145.5, 132.0, 127.9, 127.8, 125.0, 118.7, 111.6, 77.5, 75.5, 62.7, 25.0. **HRMS** (ESI) for $C_{13}H_{13}NNaO_2$: calcd. 238.08511; found, 238.08542.

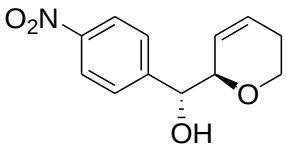
5.4.8.3 Synthesis of (R)-((R)-5,6-Dihydro-2H-Pyran-2-yl)(P-Tolyl)Methanol (5-61)



The title compound was prepared using the general procedure for acetal reduction (**13%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.27 (d, 1H, *J* = 8.1 Hz), 7.17 (d, 1H, *J* = 7.9 Hz), 5.90 (m, 1H), 5.36 (ddd, 1H, *J* = 2.0 Hz, *J* = 4.1 Hz, *J* = 10.4 Hz), 4.52 (d, 1H, *J* = 8.0 Hz), 4.13 (dq, 1H, *J* = 2.9 Hz, *J* = 5.2 Hz), 4.04 (m, 1H), 3.74 (ddd, 1H, *J* = 4.3 Hz, *J* = 8.3 Hz, *J* = 11.2 Hz), 3.11 (d, 1H, *J* = 0.5 Hz), 2.35 (s, 1H), 2.25 (dddd, 1H, *J* = 2.7 Hz, *J* = 5.4 Hz, *J* = 8.5 Hz, *J* = 19.8 Hz), 2.04 (m, 1H). **^{13}C-**

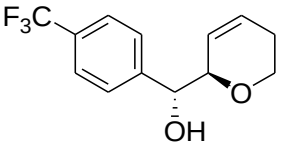
NMR (125 MHz, $CDCl_3$) δ: 137.7, 136.8, 129.0, 127.2, 126.6, 125.9, 78.0, 76.2, 62.6, 25.1, 21.1. **HRMS** (ESI) for $C_{13}H_{16}NaO_2$: calcd. 227.10478; found, 227.10497.

5.4.8.4 Synthesis of (R)-((R)-5,6-Dihydro-2H-Pyran-2-yl)(4-Nitrophenyl) Methanol (5-62)



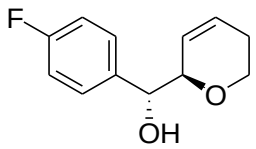
The title compound was prepared using the general procedure for acetal reduction (**74%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 8.21 (m, 2H), 7.57 (m, 1H), 5.98 (m, 1H), 5.40 (ddd, 1H, *J* = 1.9 Hz, *J* = 4.2 Hz, *J* = 10.4 Hz), 4.69 (d, 1H, *J* = 6.8 Hz), 4.15 (m, 1H), 4.01 (ddd, 1H, *J* = 3.7 Hz, *J* = 5.4 Hz, *J* = 11.3 Hz), 3.72 (ddd, 1H, *J* = 4.2 Hz, *J* = 8.6 Hz, *J* = 11.3 Hz), 3.25 (d, 1H, *J* = 2.3 Hz), 2.25 (m, 1H), 2.03 (m, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 147.5, 128.0, 127.9, 125.0, 123.4, 77.5, 75.4, 62.8, 25.0. **HRMS** (ESI) for $C_{12}H_{13}NNaO_4$: calcd. 258.07451; found, 258.07434.

5.4.8.5 Synthesis of (R)-(4-(Trifluoromethyl) Phenyl) ((R)-5,6-Dihydro-2H-Pyran-2-yl) Methanol (5-63)



The title compound was prepared using the general procedure for acetal reduction (**59%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.62 (d, 2H, *J* = 8.0 Hz), 7.52 (dd, 2H, *J* = 0.6 Hz, *J* = 8.0 Hz), 5.96 (m, 1H), 5.38 (ddd, 1H, *J* = 2.0 Hz, *J* = 4.1 Hz, *J* = 10.4 Hz), 4.63 (dd, 1H, *J* = 1.7 Hz, *J* = 7.4 Hz), 4.13 (m, 1H), 4.04 (m, 1H), 3.74 (ddd, 1H, *J* = 4.2 Hz, *J* = 8.4 Hz, *J* = 11.3 Hz), 3.23 (d, 1H, *J* = 2.3 Hz), 2.27 (m, 1H), 2.05 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 144.0, 130.1 (q, *J* = 32.2 Hz), 127.5, 127.4, 125.2, 125.2 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 270.5 Hz), 77.7, 75.7, 62.7, 25.0. **HRMS** (ESI) for $C_{13}H_{13}F_3NaO_2$: calcd. 281.07663; found, 281.07673.

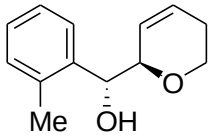
5.4.8.6 Synthesis of (R)-(4-Fluorophenyl)((R)-5,6-Dihydro-2H-Pyran-2-yl) Methanol (5-64)



The title compound was prepared using the general procedure for acetal reduction (**53%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.35 (m, 2H), 7.04 (m, 2H), 5.91 (m, 1H), 5.33 (ddd, 1H, *J* = 2.0 Hz, *J* = 4.1 Hz, *J* = 10.4 Hz), 4.53 (d, 1H, *J* = 7.9 Hz), 4.09 (dq, 1H, *J* =

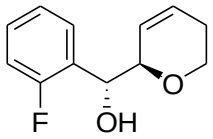
2.8 Hz, *J* = 5.2 Hz), 4.03 (ddd, 1H, *J* = 4.1 Hz, *J* = 5.2 Hz, *J* = 11.2 Hz), 3.73 (ddd, 1H, *J* = 4.3 Hz, *J* = 8.4 Hz, *J* = 11.2 Hz), 3.26 (s, 1H), 2.24 (m, 1H), 2.03 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 163.4 (d, *J* = 244.5 Hz), 135.6 (d, *J* = 3.1 Hz), 128.9 (d, *J* = 8.0 Hz), 127.0, 125.4, 115.1 (d, *J* = 21.3 Hz), 78.0, 75.6, 62.6, 25.0. **HRMS** (ESI) for $C_{12}H_{13}FNaO_2$: calcd. 231.07983; found, 231.07956.

5.4.8.7 Synthesis of (R)-((R)-5,6-dihydro-2H-pyran-2-yl)(o-tolyl)methanol (5-65)



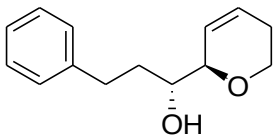
The title compound was prepared using the general procedure for acetal reduction (**57%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.49 (dd, 1H, *J* = 1.4 Hz, *J* = 7.6 Hz), 7.24 (m, 1H), 7.19 (m, 1H), 7.14 (dd, 1H, *J* = 1.5 Hz, *J* = 7.5 Hz), 5.90 (m, 1H), 5.28 (ddd, 1H, *J* = 2.1 Hz, *J* = 4.1 Hz, *J* = 10.4 Hz), 4.87 (d, 1H, *J* = 8.2 Hz), 4.19 (m, 1H), 4.06 (m, 1H), 3.76 (ddd, 1H, *J* = 4.3 Hz, *J* = 8.2 Hz, *J* = 11.3 Hz), 3.14 (bs, 1H), 2.35 (s, 3H), 2.27 (m, 1H), 2.05 (m, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 137.9, 135.7, 130.3, 127.6, 126.9, 126.8, 126.2, 125.7, 78.3, 72.0, 62.5, 25.1, 19.7. **HRMS** (ESI) for $C_{13}H_{16}NaO_2$: calcd. 227.10478; found, 227.10469.

5.4.8.8 Synthesis of (R)-(2-Fluorophenyl)((R)-5,6-Dihydro-2H-Pyran-2-yl)Methanol (5-66)



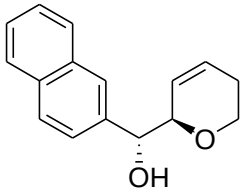
The title compound was prepared using the general procedure for acetal reduction (**91%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.53 (ddd, 1H, *J* = 1.8 Hz, *J* = 7.6 Hz, *J* = 7.6 Hz), 7.26 (dddd, 1H, *J* = 1.9 Hz, *J* = 5.3 Hz, *J* = 7.2 Hz, *J* = 8.2 Hz), 7.15 (ddd, 1H, *J* = 1.3 Hz, *J* = 7.6 Hz, *J* = 7.6 Hz), 7.01 (ddd, 1H, *J* = 1.2 Hz, *J* = 8.2 Hz, *J* = 10.4 Hz), 5.93 (m, 1H), 5.41 (ddd, 1H, *J* = 1.9 Hz, *J* = 1.9 Hz, *J* = 10.4 Hz), 4.94 (d, 1H, *J* = 7.2 Hz), 4.21 (m, 1H), 4.02 (ddd, 1H, *J* = 3.7 Hz, *J* = 5.4 Hz, *J* = 11.2 Hz), 3.71 (ddd, 1H, *J* = 4.2 Hz, *J* = 8.6 Hz, *J* = 11.2 Hz), 3.32 (m, 1H), 2.25 (m, 1H), 2.00 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 160.0 (d, *J* = 245.2 Hz), 129.2 (d, *J* = 8.2 Hz), 128.6 (d, *J* = 4.1 Hz), 127.3 (d, *J* = 12.9 Hz), 127.1, 125.6, 124.2 (d, *J* = 3.5 Hz), 115.1 (d, *J* = 21.9 Hz), 77.4 (d, *J* = 23.3 Hz), 69.4 (d, *J* = 1.6 Hz), 62.7, 25.0. **HRMS** (ESI) for $C_{12}H_{13}FNaO_2$: calcd. 231.07983; found, 231.07994.

5.4.8.9 Synthesis of (R)-1-((R)-5,6-Dihydro-2H-Pyran-2-yl)-3-Phenylpropan-1-ol (5-67)



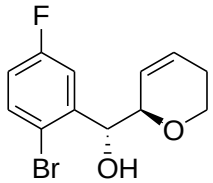
The title compound was prepared using the general procedure for acetal reduction (**45%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.24 (m, 5H), 5.97 (ddddd, 1H, *J* = 0.8 Hz, *J* = 2.2 Hz, *J* = 2.9 Hz, *J* = 5.0 Hz, *J* = 10.2 Hz), 5.67 (dddd, 1H, *J* = 1.7 Hz, *J* = 2.4 Hz, *J* = 3.5 Hz, *J* = 10.4 Hz), 4.00 (m, 2H), 3.70 (ddd, 1H, *J* = 4.0 Hz, *J* = 9.4 Hz, *J* = 11.2 Hz), 3.58 (dd, 1H, *J* = 6.0 Hz, *J* = 11.9 Hz), 2.91 (m, 1H), 2.73 (td, 1H, *J* = 8.2 Hz, *J* = 13.7 Hz), 2.51 (bs, 1H), 2.28 (m, 1H), 1.99 (m, 1H), 1.86 (dt, 2H, *J* = 6.7 Hz, *J* = 8.4 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 142.1, 128.5, 128.3, 127.0, 126.6, 125.7, 76.8, 72.5, 63.0, 34.5, 31.9, 25.2. **HRMS** (ESI) for $C_{14}H_{18}NaO_2$: calcd. 241.12038; found, 241.12053.

5.4.8.10 Synthesis of (R)-((R)-5,6-Dihydro-2H-Pyran-2-yl)(Naphthalen-2-yl)Methanol (5-68)



The title compound was prepared using the general procedure for acetal reduction (**78%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.85 (m, 4H), 7.50 (m, 3H), 5.92 (m, 1H), 5.39 (m, 1H), 4.74 (d, 1H, *J* = 7.8 Hz), 4.27 (m, 1H), 4.08 (m, 1H), 3.77 (m, 1H), 3.36 (bs, 1H), 2.28 (m, 1H), 2.05 (m, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ:137.3, 133.3, 133.2, 128.1, 128.0, 127.7, 126.8, 126.5, 126.0, 125.9, 125.8, 125.0, 78.0, 76.5, 62.6, 25.1. **HRMS** (ESI) for $C_{16}H_{16}NaO_2$: calcd. 263.10481; found, 263.10497.

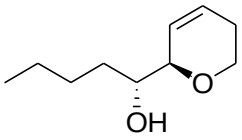
5.4.8.11 Synthesis of (R)-(2-Bromo-5-Fluorophenyl)((R)-5,6-Dihydro-2H-Pyran-2-yl) Methanol (5-69)



The title compound was prepared using the general procedure for acetal reduction (**88%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.48 (dd, 1H, *J* = 5.2 Hz, *J* = 8.8 Hz), 7.31 (dd, 1H, *J* = 3.1 Hz, *J* = 9.6 Hz), 6.89 (ddd, 1H, *J* = 3.1 Hz, *J* = 7.7 Hz, *J* = 8.7 Hz), 6.01 (m, 1H), 5.54 (ddd, 1H, *J* = 1.9 Hz, *J* = 4.0 Hz, *J* = 10.4 Hz), 5.01 (dd, 1H, *J* = 4.0 Hz, *J* = 4.3 Hz), 4.24 (m, 1H), 4.03 (ddd, 1H, *J* = 3.1 Hz, *J* = 5.5 Hz, *J* = 11.2 Hz), 3.70 (ddd, 1H, *J*

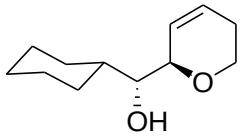
= 4.0 Hz, *J* = 9.1 Hz, *J* = 11.2 Hz), 3.18 (d, 1H, *J* = 4.2 Hz), 2.32 (m, 1H), 2.01 (m, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 162.1 (d, *J* = 246.5 Hz), 142.0 (d, *J* = 7.1 Hz), 133.7 (d, *J* = 7.8 Hz), 127.6, 126.0, 116.4 (d, *J* = 20.1 Hz), 116.2 (d, *J* = 21.4 Hz), 76.7, 73.9, 63.2, 25.0. **HRMS** (ESI) for $C_{12}H_{12}BrFNaO_2$: calcd. 308.99041; found, 308.99037.

5.4.8.12 Synthesis of (R)-1-((R)-5,6-Dihydro-2H-Pyran-2-yl)Pentan-1-ol (5-70)



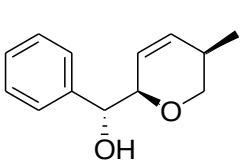
The title compound was prepared using the general procedure for acetal reduction (**59%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 5.91 (m, 1H), 5.63 (ddd, 1H, *J* = 2.0 Hz, *J* = 4.5 Hz, *J* = 10.5 Hz), 3.95 (m, 2H), 3.64 (m, 1H), 3.48 (bs, 1H), 2.48 (bs, 1H), 2.22 (m, 1H), 1.93 (m, 1H), 1.10-1.60 (m, 7H), 0.87 (t, 3H, *J* = 7.5 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 126.8, 126.7, 76.7, 73.1, 63.0, 32.3, 27.8, 25.2, 22.7, 13.9. **HRMS** (ESI) for $C_{10}H_{18}NaO_2$: calcd. 193.12039; found, 193.12053.

5.4.8.13 Synthesis of (R)-Cyclohexyl((R)-5,6-Dihydro-2H-Pyran-2-yl)Methanol (5-71)



The title compound was prepared using the general procedure for acetal reduction (**73%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 5.94 (m, 1H), 5.62 (ddd, 1H, *J* = 1.8 Hz, *J* = 4.1 Hz, *J* = 10.4 Hz), 4.13 (m, 1H), 3.97 (m, 1H), 3.64 (ddd, 1H, *J* = 4.0 Hz, *J* = 9.6 Hz, *J* = 11.2 Hz), 3.20 (dd, 1H, *J* = 5.2 Hz, *J* = 5.3 Hz), 2.25 (m, 2H), 1.64 (m, 7H), 1.16 (m, 5H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 127.6, 126.8, 77.3, 74.0, 63.1, 39.6, 29.7, 27.9, 26.4, 26.3, 26.1, 25.2. **HRMS** (ESI) for $C_{12}H_{20}NaO_2$: calcd. 219.13662; found, 219.13686.

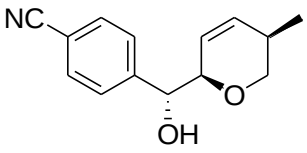
5.4.8.14 Synthesis of (R)-((2R,5R)-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)(Phenyl) Methanol (5-77)



The title compound was prepared using the general procedure for acetal reduction (**52%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.34 (m, 5H), 5.81 (ddd, 1H, *J* = 2.3 Hz, *J* = 3.9 Hz, *J* = 10.4 Hz), 5.29 (ddd, 1H, *J* = 2.0 Hz, *J* = 2.0 Hz, *J* = 10.4 Hz), 4.56 (d, 1H, *J* = 8.3 Hz), 4.10 (qd, 1H, *J* = 2.4 Hz, *J* = 8.1 Hz), 3.81 (dd, 1H, *J* = 4.4

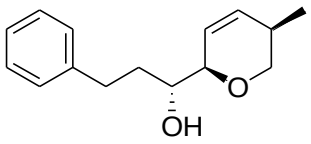
Hz, *J* = 11.1 Hz), 3.61 (dd, 1H, *J* = 5.0 Hz, *J* = 11.1 Hz), 3.24 (bs, 1H), 2.26 (m, 1H), 1.05 (d, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 139.8, 132.842, 128.3, 128.0, 127.3, 124.5, 77.9, 76.8, 68.0, 29.3, 17.8. **HRMS** (ESI) for $C_{13}H_{16}NaO_2$: calcd. 227.10483; found, 227.10491.

5.4.8.15 Synthesis of 4-((R)-((2R,5R)-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl) (Hydroxy)Methyl)Benzonitrile (5-78)



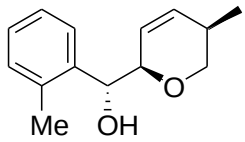
The title compound was prepared using the general procedure for acetal reduction (**48%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.64 (dd, 2H, *J* = 1.8 Hz, *J* = 8.4 Hz), 7.50 (m, 2H), 5.86 (ddd, 1H, *J* = 2.1 Hz, *J* = 3.9 Hz, *J* = 10.4 Hz), 5.30 (ddd, 1H, *J* = 2.0 Hz, *J* = 2.0 Hz, *J* = 10.5 Hz), 4.63 (d, 1H, *J* = 7.4 Hz), 4.06 (m, 1H), 3.79 (dd, 1H, *J* = 4.3 Hz, *J* = 11.1 Hz), 3.58 (dd, 1H, *J* = 4.7 Hz, *J* = 11.1 Hz), 3.26 (bs, 1H), 2.24 (m, 1H), 1.02 (d, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 145.4, 133.7, 132.0, 127.9, 123.6, 118.7, 111.7, 77.5, 75.3, 68.2, 29.3, 17.8. **HRMS** (ESI) for $C_{14}H_{15}NNaO_2$: calcd. 252.09952; found, 252.09977.

5.4.8.16 Synthesis of (R)-1-((2R,5R)-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)-3-Phenyl Propan-1-ol (5-79)



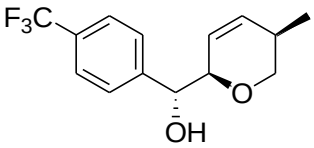
The title compound was prepared using the general procedure for acetal reduction (**52%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.24 (m, 5H), 5.89 (dddd, 1H, *J* = 0.7 Hz, *J* = 2.3 Hz, *J* = 4.3 Hz, *J* = 10.4 Hz), 5.63 (ddd, 1H, *J* = 1.9 Hz, *J* = 1.9 Hz, *J* = 10.4 Hz), 3.94 (ddd, 1H, *J* = 2.3 Hz, *J* = 4.7 Hz, *J* = 6.7 Hz), 3.78 (dd, 1H, *J* = 4.2 Hz, *J* = 11.1 Hz), 3.68 (m, 1H), 3.60 (dd, 2H, *J* = 3.8 Hz, *J* = 11.1 Hz), 2.91 (ddd, 1H, *J* = 6.3 Hz, *J* = 9.1 Hz, *J* = 13.9 Hz), 2.73 (ddd, 1H, *J* = 7.3 Hz, *J* = 9.3 Hz, *J* = 13.8 Hz), 2.21 (m, 1H), 1.85 (m, 2H), 1.06 (d, 3H, *J* =7.1 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 142.1, 132.9, 128.5, 128.3, 125.7, 125.2, 76.8, 72.3, 68.5, 34.5, 31.9, 29.5, 18.2. **HRMS** (ESI) for $C_{15}H_{20}NaO_2$: calcd. 255.13551; found, 255.13572.

5.4.8.17 Synthesis of (R)-((2R,5R)-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)(o-Tolyl)Methanol (5-81)



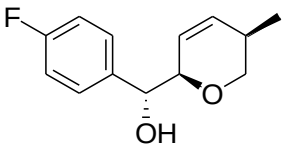
The title compound was prepared using the general procedure for acetal reduction (**31%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.50 (m, 1H), 7.19 (m, 3H), 5.80 (ddd, 1H, *J* = 2.3 Hz, *J* = 3.7 Hz, *J* = 10.4 Hz), 5.22 (ddd, 1H, *J* = 2.0 Hz, *J* = 2.0 Hz, *J* = 10.4 Hz), 4.90 (d, 1H, *J* = 8.3 Hz), 4.15 (m, 1H), 3.83 (dd, 1H, *J* = 4.5 Hz, *J* = 11.1 Hz), 3.62 (dd, 1H, *J* = 5.1 Hz, *J* = 11.1 Hz), 3.05 (bs, 1H), 2.35 (s, 3H), 2.26 (bs, 1H), 1.06 (d, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 138.2, 135.9, 133.2, 130.5, 127.9, 127.1, 126.4, 124.7, 78.5, 71.9, 68.2, 29.6, 19.9, 18.109. **HRMS** (ESI) for $C_{14}H_{18}NaO_2$: calcd. 241.12048; found, 241.12053.

5.4.8.18 Synthesis of (R)-(4-(Trifluoromethyl)Phenyl)((2R,5R)-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)Methanol (5-82)



The title compound was prepared using the general procedure for acetal reduction (**61%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.61 (d, 2H, *J* = 8.5 Hz), 7.50 (d, 2H, *J* = 8.0 Hz), 5.85 (ddd, 1H, *J* = 2.2 Hz, *J* = 3.9 Hz, *J* = 10.4 Hz), 5.28 (ddd, 1H, *J* = 2.0 Hz, *J* = 2.0 Hz, *J* = 10.4 Hz), 4.63 (d, 1H, *J* = 7.8 Hz), 4.08 (m, 1H), 4.01 (bs, 1H), 3.80 (dd, 1H, *J* = 4.4 Hz, *J* = 11.1 Hz), 3.59 (dd, 1H, *J* = 4.9 Hz, *J* = 11.1 Hz), 2.25 (m, 1H), 1.04 (d, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 143.8, 133.5, 130.2 (q, *J* = 32.3 Hz), 127.6, 126.2 (q, *J* = 271.6 Hz), 125.2 (q, *J* = 3.6 Hz), 123.8, 77.6, 75.5, 68.0, 29.3, 17.7. **HRMS** (ESI) for $C_{14}H_{15}F_3NaO_2$: calcd. 295.09164; found, 295.09243.

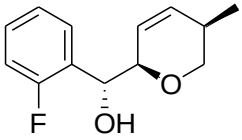
5.4.8.19 Synthesis of (R)-(4-Fluorophenyl)((2R,5R)-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)Methanol (5-83)



The title compound was prepared using the general procedure for acetal reduction (**60%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.36 (m, 2H), 7.05 (m, 2H), 5.82 (ddd, 1H, *J* =

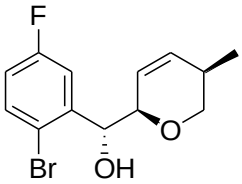
2.2 Hz, *J* = 3.9 Hz, *J* = 10.4 Hz), 5.27 (ddd, 1H, *J* = 2.0 Hz, *J* = 2.0 Hz, *J* = 10.4 Hz), 4.55 (dd, 1H, *J* = 1.7 Hz, *J* = 8.2 Hz), 4.05 (m, 1H), 3.81 (dd, 1H, *J* = 4.4 Hz, *J* = 11.1 Hz), 3.60 (dd, 1H, *J* = 4.9 Hz, *J* = 11.1 Hz), 3.19 (d, 1H, *J* = 1.7 Hz), 2.26 (m, 1H), 1.05 (d, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 162.5 (d, *J* = 245.5 Hz), 135.5 (d, *J* = 3.1 Hz), 133.1, 128.9 (d, *J* = 8.0 Hz), 124.1, 115.2 (d, *J* = 21.4 Hz), 77.9, 75.4, 68.0, 29.3, 17.8. **HRMS** (ESI) for $C_{13}H_{15}FNaO_2$: calcd. 245.09544; found, 245.09587.

5.4.8.20 Synthesis of (R)-(2-Fluorophenyl)((2R,5R)-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)Methanol (5-84)



The title compound was prepared using the general procedure for acetal reduction (**69%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.54 (ddd, H, *J* = 1.9 Hz, *J* = 7.4 Hz, *J* = 7.4 Hz), 7.27 (m, 1H), 7.17 (ddd, 1H, *J* = 1.2 Hz, *J* = 7.5 Hz, *J* = 7.5 Hz), 7.03 (ddd, 1H, *J* = 1.2 Hz, *J* = 8.2 Hz, *J* = 10.2 Hz), 5.85 (ddd, 1H, *J* = 2.3 Hz, *J* = 3.9 Hz, *J* = 10.4 Hz), 5.35 (ddd, 1H, *J* = 1.8 Hz, *J* = 3.6 Hz, *J* = 10.4 Hz), 4.96 (d, 1H, *J* = 7.6 Hz), 4.17 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.7 Hz, *J* = 7.5 Hz), 3.81 (dd, 1H, *J* = 4.4 Hz, *J* = 11.1 Hz), 3.62 (dd, 1H, *J* = 4.7 Hz, *J* = 11.1 Hz), 3.20 (bs, 1H), 2.25 (m, 1H), 1.06 (d, 1H, *J* = 7.1 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 160.1 (d, *J* = 245.4 Hz), 133.1 (d, *J* = 0.5 Hz), 129.3 (d, *J* = 8.3 Hz), 128.6 (d, *J* = 4.13 Hz), 127.2 (d, *J* = 12.9 Hz), 124.2 (d, *J* = 3.6 Hz), 115.2 (d, *J* = 22.0 Hz), 77.3, 69.2, 68.2, 29.3, 17.9. **HRMS** (ESI) for $C_{13}H_{15}FNaO_2$: calcd. 245.09544; found, 245.09563.

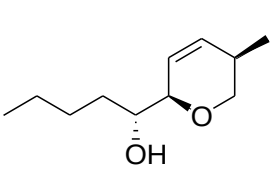
5.4.8.21 Synthesis of (R)-(2-Bromo-5-Fluorophenyl)((2R,5R)-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)Methanol (5-86)



The title compound was prepared using the general procedure for acetal reduction (**76%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.49 (dd, 1H, *J* = 5.2 Hz, *J* = 8.8 Hz), 7.32 (dd, 1H, *J* = 3.1 Hz, *J* = 9.6 Hz), 6.89 (ddd, 1H, *J* = 3.1 Hz, *J* = 7.7 Hz, *J* = 8.7 Hz), 5.92 (ddd, 1H, *J* = 2.2 Hz, *J* = 4.1 Hz, *J* = 10.3 Hz), 5.45 (ddd, 1H, *J* = 1.9 Hz, *J* = 10.3 Hz, *J* = 10.3 Hz), 5.04 (m, 1H), 4.17 (m, 1H), 3.80 (dd, 1H, *J* = 4.3 Hz, *J* = 11.1 Hz), 3.64 (dd, 1H, *J* = 4.2 Hz, *J* = 11.1 Hz), 3.13 (d, 1H, *J* = 3.7 Hz), 2.24 (m, 1H), 1.09 (d, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 162.1 (d, *J* = 246.5 Hz), 141.8

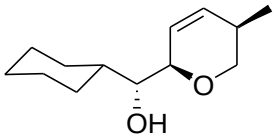
(d, *J* = 6.8 Hz), 133.7 (d, *J* = 8.0 Hz), 133.5, 124.5, 116.6 (d, *J* = 3.0 Hz), 116.4 (d, *J* = 22.4 Hz), 116.1 (d, *J* = 23.6 Hz), 77.0, 73.6, 68.5, 29.2, 18.1. **HRMS** (ESI) for $C_{13}H_{14}FBrNaO_2$: calcd. 323.00592; found, 323.00584.

5.4.8.22 Synthesis of (R)-1-((2R,5R)-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl)Pentan-1-ol (5-87)



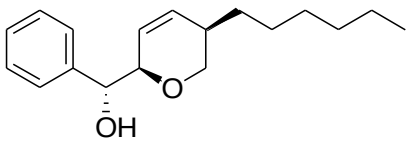
The title compound was prepared using the general procedure for acetal reduction (**76%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 5.87 (ddd, 1H, *J* = 2.3 Hz, *J* = 4.2 Hz, *J* = 10.4 Hz), 5.62 (ddd, 1H, *J* = 1.9 Hz, *J* = 1.9 Hz, *J* = 10.4 Hz), 3.88 (ddd, 1H, *J* = 2.3 Hz, *J* = 4.6 Hz, *J* = 6.7 Hz), 3.75 (dd, 1H, *J* = 4.2 Hz, *J* = 11.1 Hz), 3.57 (dd, 1H, *J* = 4.0 Hz, *J* = 11.1 Hz), 3.53 (m, 1H), 2.45 (dd, 1H, *J* = 0.6 Hz, *J* = 1.0 Hz), 2.20 (m, 1H), 1.30-1.60 (m, 6H), 1.03 (d, 3H, *J* = 7.1 Hz), 0.90 (t, 3H, *J* = 7.2 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 132.7, 125.4, 76.8, 72.9, 68.4, 65.8, 32.3, 29.5, 27.8, 22.7, 18.2, 15.2, 14.0. **HRMS** (ESI) for $C_{11}H_{20}NaO_2$: calcd. 207.13629; found, 207.13654.

5.4.8.23 Synthesis of (R)-Cyclohexyl((2R,5R)-5,6-Dihydro-5-Methyl-2H-Pyran-2-yl) Methanol (5-88)



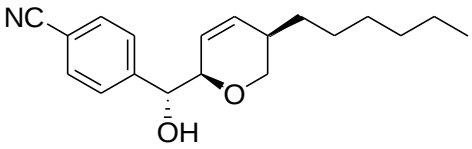
The title compound was prepared using the general procedure for acetal reduction (**81%** yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 5.87 (ddd, 1H, *J* = 2.3 Hz, *J* = 4.4 Hz, *J* = 10.3 Hz), 5.59 (ddd, 1H, *J* = 2.0 Hz, *J* = 2.0 Hz, *J* = 10.5 Hz), 4.08 (m, 1H), 3.73 (dd, 1H, *J* = 4.2 Hz, *J* = 11.1 Hz), 3.57 (dd, 1H, *J* = 3.6 Hz, *J* = 11.1 Hz), 3.24 (dd, 1H, *J* = 5.5 Hz, *J* = 5.5 Hz), 2.37 (m, 1H), 2.16 (m, 2H), 1.45-1.90 (m, 10H), 1.03 (d, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 132.7, 126.1, 76.9, 74.0, 68.5, 39.6, 29.9, 29.4, 27.5, 26.4, 26.4, 26.1, 18.3. **HRMS** (ESI) for $C_{13}H_{22}NaO_2$: calcd. 233.15183; found, 233.15165.

5.4.8.24 Synthesis of (R)-((2R,5R)-5-Hexyl-5,6-Dihydro-2H-Pyran-2-yl)(Phenyl) Methanol (5-93)



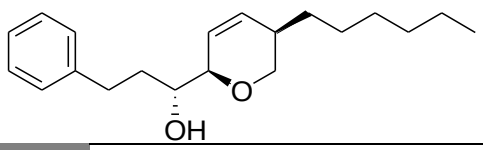
The title compound was prepared using the general procedure for acetal reduction (**75%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.32 (m, 5H), 5.83 (ddd, 1H, *J* = 2.2 Hz, *J* = 4.1 Hz, *J* = 10.5 Hz), 5.29 (ddd, 1H, *J* = 2.0 Hz, *J* = 2.0 Hz, *J* = 10.5 Hz), 4.53 (d, 1H, *J* = 8.1 Hz), 4.10 (ddd, 1H, *J* = 2.3 Hz, *J* = 4.8 Hz, *J* = 8.2 Hz), 3.77 (dd, 1H, *J* = 4.3 Hz, *J* = 11.2 Hz), 3.70 (dd, 1H, *J* = 4.4 Hz, *J* = 11.2 Hz), 3.37 (bs. 1H), 2.05 (m, 1H), 1.32 (m, 10H), 0.88 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 139.8, 131.5, 128.2, 127.9, 127.3, 124.8, 78.2, 76.2, 66.6, 34.4, 32.9, 31.7, 29.4, 27.0, 22.6, 14.0. **HRMS** (ESI) for $C_{18}H_{26}NaO_2$: calcd. 297.18327; found, 297.18343.

5.4.8.25 Synthesis of 4-((R)-((2R,5R)-5-Hexyl-5,6-Dihydro-2H-Pyran-2-yl)(Hydroxy) Methyl) Benzonitrile (5-94)



The title compound was prepared using the general procedure for acetal reduction (**67%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, 2H, *J* = 8.5 Hz), 7.49 (d, 2H, *J* = 8.1 Hz), 5.90 (ddd, 1H, *J* = 2.1 Hz, *J* = 4.3 Hz, *J* = 10.5 Hz), 5.33 (ddd, 1H, *J* = 10.4 Hz, *J* = 2 Hz, *J* = 2 Hz), 4.61 (dd, 1H, *J* = 2.4 Hz, *J* = 7.2 Hz), 4.07 (ddd, 1H, *J* = 2.3 Hz, *J* = 4.7 Hz, *J* = 7.1 Hz), 3.75 (dd, 1H, *J* = 4.2 Hz, *J* = 11.2 Hz), 3.68 (dd, 1H, *J* = 4.0 Hz, *J* = 11.2 Hz), 3.28 (d, 1H, *J* = 2.3 Hz), 2.03 (m, 1H), 1.10-1.45 (m, 10H), 0.88 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 145.4, 132.5, 131.9, 127.9, 124.0, 118.7, 111.6, 77.7, 75.4, 66.8, 34.3, 32.9, 31.7, 31.5, 29.3, 26.9, 22.5, 14.0, 14.0. **HRMS** (ESI) for $C_{19}H_{25}NNaO_2$: calcd. 322.17842; found, 322.17865.

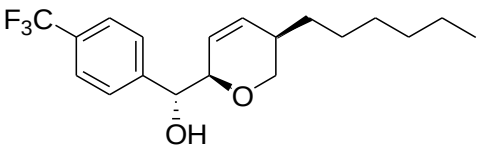
5.4.8.26 Synthesis of (R)-1-((2R,5R)-5-Hexyl-5,6-Dihydro-2H-Pyran-2-yl)-3-Phenylpropan-1-ol (5-95)



The title compound was prepared using the general procedure for acetal reduction

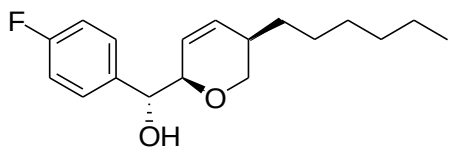
(**77%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.25 (m, 5H), 5.95 (ddd, 1H, *J* = 2.2 Hz, *J* = 4.5 Hz, *J* = 10.4 Hz), 5.65 (ddd, 1H, *J* = 1.8 Hz, *J* = 1.8 Hz, *J* = 10.4 Hz), 3.95 (m, 1H), 3.74 (m, 2H), 3.59 (m, 1H), 2.92 (m, 1H), 2.74 (td, 1H, *J* = 8.1 Hz, *J* = 13.8 Hz), 2.57 (d, 1H, *J* = 4.0 Hz), 2.04 (m, 1H), 1.85 (m, 2H), 1.15-1.66 (m, 10H), 0.92 (t, 3H, *J* = 6.8 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 142.2, 131.7, 128.5, 128.3, 125.7, 125.6, 77.1, 72.4, 67.0, 34.6, 34.5, 33.2, 31.9, 31.8, 29.4, 27.1, 22.6, 14.1. **HRMS** (ESI) for $C_{20}H_{30}NaO_2$: calcd. 325.21443; found, 325.21479.

5.4.8.27 Synthesis of (R)-(4-(Trifluoromethyl)Phenyl)((2R,5R)-5-Hexyl-5,6-Dihydro-2H-Pyran-2-yl)Methanol (5-96)



The title compound was prepared using the general procedure for acetal reduction (**71%** yield). **^{1}H-NMR** (100 MHz, $CDCl_3$) δ: 7.61 (d, 1H, *J* = 8.4 Hz), 7.50 (d, 1H, *J* = 8.1 Hz), 5.90 (ddd, 1H, *J* = 2.2 Hz, *J* = 4.2 Hz, *J* = 10.5 Hz), 5.33 (ddd, 1H, *J* = 1.6 Hz, *J* = 1.6 Hz, *J* = 10.4 Hz), 4.61 (dd, 1H, *J* = 1.8 Hz, *J* = 7.6 Hz), 4.10 (m, 1H), 3.77 (dd, 1H, *J* = 4.3 Hz, *J* = 10.8 Hz), 3.71 (dd, 1H, *J* = 4.2 Hz, *J* = 11.2 Hz), 3.37 (d, 1H, *J* = 1.9 Hz), 2.07 (m, 1H), 1.10-1.50 (m, 10H), 0.89 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 144.0, 132.1, 130.1 (q, *J* = 32 Hz), 127.6, 125.1 (q, *J* = 3.8 Hz), 124.6 (q, *J* = 268 Hz), 124.2, 77.9, 75.6, 66.7, 34.4, 32.9, 31.7, 29.4, 27.0, 22.6, 14.0. **HRMS** (ESI) for $C_{19}H_{25}F_3NaO_3$: calcd. 365.17052; found, 365.17041.

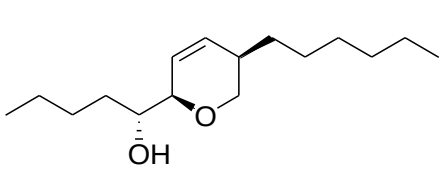
5.4.8.28 Synthesis of (R)-(4-Fluorophenyl)((2R,5R)-5-Hexyl-5,6-Dihydro-2H-Pyran-2-yl) Methanol (5-97)



The title compound was prepared using the general procedure for acetal reduction (**51%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.34 (m, 2H), 7.03 (m, 2H), 5.86 (ddd, 1H, *J* = 2.2 Hz, *J* = 4.2 Hz, *J* = 10.5 Hz), 5.29 (ddd, 1H, *J* = 1.9 Hz, *J* = 1.9 Hz, *J* = 10.5 Hz), 4.52 (dd, 1H, *J* = 1.6 Hz, *J* = 8.0 Hz), 4.06 (ddd, 1H, *J* = 2.3 Hz, *J* = 4.7 Hz, *J* = 8.0 Hz), 3.77 (dd, 1H, *J* = 4.3 Hz, *J* = 11.2 Hz), 3.70 (dd, 1H, *J* = 4.3 Hz, *J* = 11.2 Hz), 3.28 (d, 1H, *J* = 1.9 Hz), 2.06 (m, 1H), 1.41 (m, 1H), 1.10-1.40 (m, 10H), 0.87 (m. 3H). **^{13}C-NMR** (100

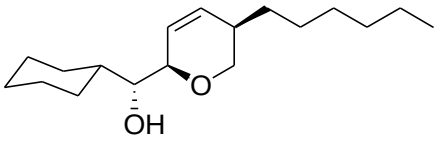
MHz, $CDCl_3$) δ: 162.4 (d, *J* = 244.7 Hz), 135.6 (d, *J* = 3.0 Hz), 131.8, 128.9 (d, *J* = 8.1 Hz), 124.5, 115.1 (d, *J* = 21.3 Hz), 78.1, 75.5, 66.6, 34.4, 32.9, 31.7, 29.4, 27.0, 22.6, 14.0. **HRMS** (ESI) for $C_{18}H_{25}FNaO_2$: calcd. 315.17368; found, 315. 17384.

5.4.8.29 Synthesis of (R)-1-((2R,5R)-5-hexyl-5,6-dihydro-2H-pyran-2-yl)pentan-1-ol (5-98)



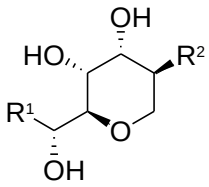
The title compound was prepared using the general procedure for acetal reduction (**97%** yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 5.90 (dddd, 1H, *J* = 0.8 Hz, *J* = 2.2 Hz, *J* = 4.4 Hz, *J* = 10.4 Hz), 5.62 (m, 1H), 3.87 (ddd, 1H, *J* = 2.2 Hz, *J* = 4.8 Hz, *J* = 6.2 Hz), 3.70 (m, 2H), 3.49 (m, 1H), 2.51 (d, 1H, *J* = 3.7 Hz), 2.00 (m, 1H), 1.10-1.70 (m, 17H), 0.83 (m, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 131.5, 125.7, 77.0, 73.0, 66.8, 34.6, 33.1, 32.3, 31.7, 29.3, 27.7, 27.0, 22.7, 22.5, 14.0, 13.9. **HRMS** (ESI) for $C_{16}H_{30}NaO_2$: calcd. 277.21438; found, 277.21475.

5.4.8.30 Synthesis of (R)-Cyclohexyl((2R,5R)-5-Hexyl-5,6-Dihydro-2H-Pyran-2-yl) Methanol (5-99)



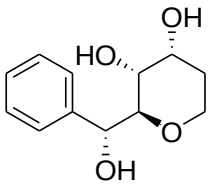
The title compound was prepared using the general procedure for acetal reduction (**67%** yield).**^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 5.94 (ddd, 1H, *J* = 2.2 Hz, *J* = 4.5 Hz, *J* = 10.4 Hz) , 5.62 (m, 1H), 4.11 (m, 1H), 3.72 (d, 1H, *J* = 3.7 Hz), 3.23 (m, 1H, *J* = 5.4 Hz), 2.19 (d, 1H, *J* = 5.0 Hz), 1.98 (m, 1H), 1.46-1.89 (m, 6H), 1.00-1.45 (m, 16H), 0.88-0.95 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ.131.5, 126.5, 77.1, 74.2, 67.0, 39.6, 34.6, 33.3, 31.7, 29.8, 29.4, 27.6, 27.1, 26.4, 26.3, 26.1, 22.6, 14.0. **HRMS** (ESI) for $C_{18}H_{32}NaO_2$: calcd. 303.23012; found, 303.23046.

5.4.9 General Procedure for Dihydroxylation



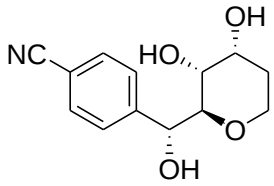
α-Hydroxyalkyl 2*H*–pyran (1.0 mmol), monohydrate of *N*-methylmorpholine *N*-oxide (1.5 mmol) and osmium tetroxide (2.5 wt% solution in 2-methyl-2-propanol) were dissolved in acetone/water (10 mL, 9:1) and the mixture was stirred at ambient temperature overnight. It was then diluted with aqueous sodium sulfite (5 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced presuure, and purified by flash column chromatography (hexane/EtOAc, 1:1) to afford the title compound as a white solid.

5.4.9.1 Synthesis of (2S,3R,4R)-Tetrahydro-2-((R)-Hydroxy(Phenyl)Methyl)-2H-Pyran-3,4-Diol (5-102)



The title compound was prepared using the general procedure for dihydroxylation (**66%** yield) as a white solid. $[\alpha]^{23}_D$ -18.12 (c = 0.33, MeOH). **IR** (Cast film, cm^{-1}) 3396, 3061, 2975, 2875, 1603, 1452, 1398, 1266, 1107, 1079, 1062, 1039, 1003, 925, 717. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.41 (m, 2H), 7.28 (m, 2H), 7.20 (m, 1H), 4.98 (d, 1H, *J* = 1.0 Hz), 4.09 (dd, 1H, *J* = 2.9 Hz, *J* = 6.5 Hz), 3.73 (dd, 1H, *J* = 3.1 Hz, *J* = 9.5 Hz), 3.66 (dd, 1H, *J* = 1.8 Hz, *J* = 9.6 Hz), 3.60 (m, 1H), 1.84 (m, 1H), 1.71 (m, 1H). **^{13}C-NMR** (100 M Hz, $CDCl_3$) δ: 143.3, 127.6, 126.6, 126.3, 78.8, 70.9, 67.9, 67.3, 61.5, 32.3. **HRMS** (ESI) for $C_{12}H_{16}NaO_4$: calcd. 247.09408; found. 247.09392.

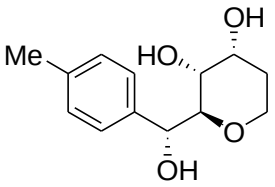
5.4.9.2 Synthesis of (2S,3R,4R)-Tetrahydro-2-((R)-Hydroxy(P-Cyanophenyl) Methyl)-2H-Pyran-3,4-Diol (5-103)



The title compound was prepared using the general procedure for dihydroxylation (**75%** yield) as a white solid. $[\alpha]^{23}_D$ -15.38 (c = 0.29, MeOH). **IR** (Cast film, cm^{-1}) 3426, 2927, 2877, 2229, 1609, 1463, 1412, 1412, 1268, 1203, 1108, 1072, 1040, 881. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.66 (dd, 1H, *J* = 1.6 Hz, *J* = 8.1 Hz), 7.58 (dd, 1H, *J* = 1.5 Hz, *J* = 8.1 Hz), 5.04 (bs, 1H), 4.10

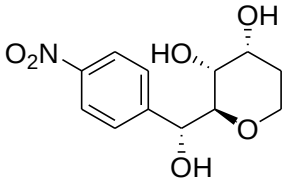
(m, 1H), 3.75 (dd, 1H, *J* = 3.1 Hz, *J* = 9.7 Hz), 3.66 (dd, 1H, *J* = 1.7 Hz, *J* = 9.7 Hz), 3.56 (m, 2H), 3.30 (m, 1H), 1.85 (m, 1H), 1.71 (dddd, 1H, *J* = 2.0 Hz, *J* = 2.0 Hz, *J* = 3.7 Hz, *J* = 14.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 149.6, 131.5, 127.3, 118.7, 110.2, 78.6, 70.5, 67.7, 67.2, 61.6, 32.4. **HRMS** (ESI) for $C_{13}H_{15}NNaO_4$: calcd. 272.08933; found. 272.08971.

5.4.9.3 Synthesis of (2S,3R,4R)-Tetrahydro-2-((R)-Hydroxy(P-Tolyl)Methyl)-2H-Pyran-3,4-Diol (5-104)



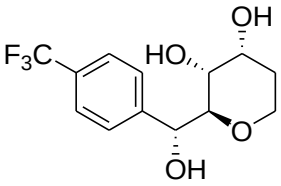
The title compound was prepared using the general procedure for dihydroxylation (**51%** yield) as a white solid. $[\alpha]^{23}_D$ -10.61 (c = 0.13, MeOH). **IR** (Cast film, cm^{-1}) 3391, 2924, 2875, 1662, 1604, 1515, 1412, 1266, 1107, 1072, 1038, 767. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.28 (d, 2H, *J* = 8.0 Hz), 7.11 (d, 2H, *J* = 7.8 Hz), 4.93 (dd, 1H, *J* = 0.5 Hz, *J* = 1.0 Hz), 4.08 (dd, 1H, *J* = 3.0 Hz, *J* = 6.6 Hz), 3.70 (dd, 1H, *J* = 3.1 Hz, *J* = 9.6 Hz), 3.60 (m, 2H), 3.30 (m, 1H), 2.31 (s, 3H), 1.84 (m, 1H), 1.71 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 140.1, 136.2, 128.2, 126.3, 78.8, 70.7, 67.9, 67.2, 61.5, 32.3, 19.9. **HRMS** (ESI) for $C_{13}H_{18}NaO_4$: calcd. 261.10973; found. 261.11009.

5.4.9.4 Synthesis of (2S,3R,4R)-Tetrahydro-2-((R)-Hydroxy(4-Nitrophenyl) Methyl)-2H-Pyran-3,4-Diol (5-105)



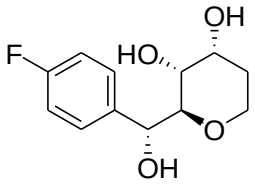
The title compound was prepared using the general procedure for dihydroxylation (**85%** yield) as a white solid. $[\alpha]^{23}_D$ -11.85 (c = 0.14, MeOH). **IR** (Cast film, cm^{-1}) 3404, 3078, 2927, 2877, 1604, 1519, 1349, 1107, 1072, 1040, 1003, 882, 763. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 8.18 (m, 2H), 7.63 (m, 2H), 5.10 (bs, 1H), 4.11 (dd, 1H, *J* = 2.9 Hz, *J* = 5.8 Hz), 3.76 (dd, 1H, *J* = 3.1 Hz, *J* = 9.7 Hz), 3.68 (dd, 1H, *J* = 1.6 Hz, *J* = 9.7 Hz), 3.56 (m, 2H), 1.86 (m, 1H), 1.71 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 151.6, 147.1, 127.3, 122.6, 78.6, 70.4, 67.7, 67.2, 61.7, 32.4. **HRMS** (ESI) for $C_{12}H_{15}NNaO_6$: calcd.292.07916; found. 292.07964.

5.4.9.5 Synthesis of (2S,3R,4R)-2-((R)-(4-(Trifluoromethyl)Phenyl) (Hydroxy) Methyl)-Tetrahydro-2H-Pyran-3,4-Diol (5-106)



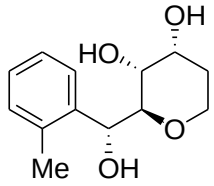
The title compound was prepared using the general procedure for dihydroxylation (**52%** yield) as a white solid. $[\alpha]^{23}_{D}$ -33.38 (c = 0.13, MeOH). **IR** (Cast film, cm^{-1}) 3398, 2927, 2874, 1719, 1619, 1511, 1327, 1122, 1069, 1039, 1017, 1004, 882. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.59 (m, 4H), 5.05 (bs, 1H), 4.10 (m, 1H), 3.75 (dd, 1H, *J* = 3.1 Hz, *J* = 9.7 Hz), 3.67 (dd, 1H, *J* = 1.7 Hz, *J* = 9.7 Hz), 3.59 (m, 1H), 3.30 (m, 1H), 1.84 (m, 1H), 1.71 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 148.2, 128.1 (q, *J* = 7.8 Hz), 127.3 (q, *J* = 268.9 Hz), 124.4 (q, *J* = 3.9 Hz), 114.1 (q, *J* = 21.2 Hz), 78.7, 70.5, 67.8, 67.2, 61.6, 32.4. **HRMS** (ESI) for $C_{13}H_{15}F_3NaO_4$: calcd. 315.08146; found. 315.08255.

5.4.9.6 Synthesis of (2S,3R,4R)-2-((R)-(4-Fluorophenyl)(Hydroxy)Methyl)-Tetrahydro-2H-Pyran-3,4-Diol (5-107)



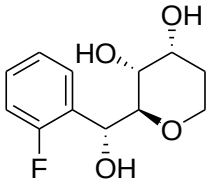
The title compound was prepared using the general procedure for dihydroxylation (**86%** yield) as a white solid. $[\alpha]^{23}_{D}$ -24.26 (c = 0.23, MeOH). **IR** (Cast film, cm^{-1}) 3541.8, 3440.1, 3344.8, 3057.6, 2960.0, 2923.4, 2890.8, 1602.3, 1510.8, 1421.7, 1302.0, 1214.9, 1112.6, 1046.3, 859.3. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.41 (m, 2H), 7.01 (ddd, 2H, *J* = 2.5 Hz, *J* = 5.9 Hz, *J* = 8.9 Hz), 4.97 (bs, 1H), 4.09 (m, 1H), 3.72 (dd, 1H, *J* = 3.1 Hz, *J* = 9.6 Hz), 3.61 (m, 4H), 1.84 (dddd, 1H, *J* = 2.6 Hz, *J* = 7.4 Hz, *J* = 10.3 Hz, *J* = 12.8 Hz), 1.71 (dddd, 1H, *J* = 2.1 Hz, *J* = 7.5 Hz, *J* = 3.9 Hz, *J* = 14.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 162.1 (d, *J* = 241.1 Hz), 139.3 (d, *J* = 3.1 Hz), 128.2 (d, *J* = 7.8 Hz), 114.1 (d, *J* = 21.2 Hz), 78.7, 70.3, 67.8, 67.2, 61.5, 32.3. **HRMS** (ESI) for $C_{12}H_{15}FNaO_4$: calcd.265.08466; found. 265.08506.

5.4.9.7 Synthesis of (2S,3R,4R)-Tetrahydro-2-((R)-Hydroxy(o-Tolyl)Methyl)-2H-Pyran-3,4-Diol (5-108)



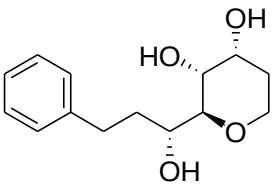
The title compound was prepared using the general procedure for dihydroxylation (**72%** yield) as a white solid. $[\alpha]^{23}_{D}$ -42.75 (c = 0.53, MeOH). **IR** (Cast film, cm^{-1}) 3403, 3059, 3026, 2926, 2877, 1711, 1605, 1488, 1404, 1266, 1218, 1105, 1065, 1037, 769, 736. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.53 (m, 1H), 7.12 (m, 3H), 5.27 (d, 1H, *J* = 1.5 Hz), 4.10 (m, 1H), 3.77 (dd, 1H, *J* = 3.2 Hz, *J* = 9.6 Hz), 3.60 (dd, 1H, *J* = 2.2 Hz, *J* = 7.8 Hz), 3.57 (m, 2H), 3.30 (m, 1H), 2.33 (s, 3H), 1.87 (dddd, 1H, *J* = 2.6 Hz, *J* = 7.5 Hz, *J* = 10.0 Hz, *J* = 14.0 Hz), 1.72 (dddd, 1H, *J* = 2.1 Hz, *J* = 4.0 Hz, *J* = 7.6 Hz, *J* = 14.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 141.0, 134.2, 129.7, 127.2, 126.5, 125.1, 77.2, 67.9, 67.3, 67.1, 61.5, 32.4, 18.2. **HRMS** (ESI) for $C_{13}H_{18}NaO_4$: calcd. 261.10973; found. 261.11044.

5.4.9.8 Synthesis of (2S,3R,4R)-2-((R)-(2-Fluorophenyl)(Hydroxy)Methyl)-Tetrahydro-2H-Pyran-3,4-Diol (5-109)



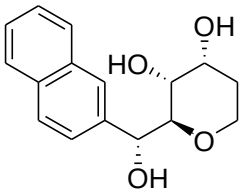
The title compound was prepared using the general procedure for dihydroxylation (**71%** yield) as a white solid. $[\alpha]^{23}_{D}$ -28.62 (c = 0.32, MeOH). **IR** (Cast film, cm^{-1}) 3404, 3067, 2928, 2878, 1616, 1488, 1456, 1403, 1267, 1222, 1105, 1069, 1038, 1002, 921, 793. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.60 (ddd, 1H, *J* = 1.1 Hz, *J* = 7.6 Hz, *J* = 7.6 Hz), 7.23 (m, 1H), 7.12 (dd, 1H, *J* = 7.5 Hz, *J* = 7.2 Hz), 7.00 (m, 1H), 5.37 (bs, 1H), 4.11 (dd, 1H, *J* = 3.0 Hz, *J* = 5.9 Hz), 3.79 (dd, 1H, *J* = 3.0 Hz, *J* = 9.5 Hz), 3.68 (d, 1H, *J* = 9.4 Hz), 3.60 (m, 1H), 1.86 (m, 1H), 1.72 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 159.6 (d, *J* = 242.0 Hz), 130.2 (d, *J* = 12.9 Hz), 129.1 (d, *J* = 4.3 Hz), 128.3 (d, *J* = 8.3 Hz), 123.5 (d, *J* = 3.3 Hz), 114.4 (d, *J* = 22.0 Hz), 77.8, 67.8, 67.3, 64.7 (d, *J* = 1.9 Hz), 61.6, 32.4. **HRMS** (ESI) for $C_{12}H_{15}FNaO_4$: calcd. 265.08466; found. 265.0851

5.4.9.9 Synthesis of (2S,3R,4R)-Tetrahydro-2-((R)-1-Hydroxy-3-Phenylpropyl)-2H-Pyran-3,4-Diol (5-110)



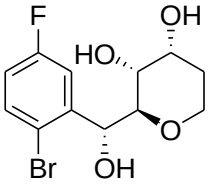
The title compound was prepared using the general procedure for dihydroxylation (**78%** yield) as a white solid. $[\alpha]^{23}_{D}$ -2.64 (c = 0.22, MeOH). **IR** (Cast film, cm^{-1}) 3486, 3377, 3280, 2946, 2920, 2879, 1603, 1496, 1454, 1401, 1278, 1080, 1054, 1019, 913, 735. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.19 (m, 5H), 4.06 (m, 1H), 3.83 (ddd, 1H, *J* = 1.4 Hz, *J* = 4.7 Hz, *J* = 8.9 Hz), 3.75 (dd, 1H, *J* = 2.3 Hz, *J* = 11.4 Hz), 3.69 (dd, 1H, *J* = 1.7 Hz, *J* = 9.1 Hz), 3.66 (dd, 1H, *J* = 3.1 Hz, *J* = 9.7 Hz), 3.41 (dd, 1H, *J* = 1.6 Hz, *J* = 9.8 Hz), 3.30 (m, 1H), 2.78 (m, 1H), 2.63 (ddd, 1H, *J* = 6.9 Hz, *J* = 9.7 Hz, *J* = 13.6 Hz), 1.94 (ddd, 2H, *J* = 4.8 Hz, *J* = 9.1 Hz, *J* = 18.8 Hz), 1.79 (m, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 142.5, 128.2, 128.1, 125.4, 76.9, 68.5, 67.6, 67.3, 61.5, 35.6, 32.5, 32.2. **HRMS** (ESI) for $C_{14}H_{20}NaO_4$: calcd. 275.12538; found. 275.12541.

5.4.9.10 Synthesis of (2S,3R,4R)-Tetrahydro-2-((R)-Hydroxy(Naphthalen-2-yl)Methyl)-2H-Pyran-3,4-Diol (5-111)



The title compound was prepared using the general procedure for dihydroxylation (**74%** yield) as a white solid. $[\alpha]^{23}_{D}$ -14.31 (c = 0.32, MeOH). **IR** (Cast film, cm^{-1}) 3529, 3429, 3312, 2944, 2877, 1402, 1274, 1259, 1129, 1070, 1047, 848. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.81 (m, 4H), 7.55 (dd, 1H, *J* = 1.6 Hz, *J* = 8.5 Hz), 7.43 (m, 2H), 5.15 (bs, 1H), 4.11 (m, 1H), 3.78 (m, 2H), 3.60 (m, 2H), 3.30 (m, 1H), 1.85 (m, 1H), 1.71 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 140.8, 133.5, 133.0, 127.6, 127.3, 127.1, 125.6, 125.2, 124.8, 124.8, 78.8, 71.0, 67.9, 67.3, 61.5, 32.3. **HRMS** (ESI) for $C_{16}H_{18}NaO_4$: calcd. 297.10973; found. 297.11016.

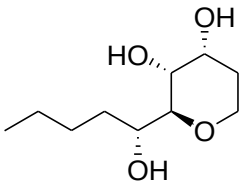
5.4.9.11 Synthesis of (2S,3R,4R)-2-((R)-(2-Bromo-5-Fluorophenyl) (Hydroxy Methyl) Tetrahydro-2H-Pyran-3,4-Diol (5-112)



The title compound was prepared using the general procedure for dihydroxylation (**89%** yield) as a white solid. $[\alpha]^{23}_{D}$ -28.86 (c = 0.44, MeOH). **IR** (Cast film, cm^{-1}) 3407, 3097, 2928, 2879, 1605,

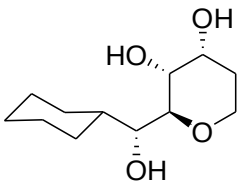
1581, 1465.7, 1411, 1348, 1265, 1219, 1152, 1110, 1070, 1039, 1001, 965. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.49 (dd, 1H, *J* = 5.3 Hz, *J* = 8.8 Hz), 7.37 (dd, 1H, *J* = 3.2 Hz, *J* = 10.2 Hz), 6.91 (m, 1H), 5.36 (bs, 1H), 4.13 (dd, 1H, *J* = 3.3 Hz, *J* = 6.2 Hz), 3.81 (dd, 1H, *J* = 3.1 Hz, *J* = 9.7 Hz), 3.72 (dd, 1H, *J* = 1.5 Hz, *J* = 9.7 Hz), 3.57 (m, 2H), 1.88 (dddd, 1H, *J* = 2.5 Hz, *J* = 6.5 Hz, *J* = 11.3 Hz, *J* = 14.0 Hz), 1.72 (dddd, 1H, *J* = 2.0 Hz, *J* = 3.8 Hz, *J* = 7.2 Hz, *J* = 14.0 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 162.1 (d, *J* = 242.3 Hz), 144.8 (d, *J* = 7.4 Hz), 133.4 (d, *J* = 7.8 Hz), 116.8 (d, *J* = 34.5 Hz), 115.4 (d, *J* = 23.0 Hz), 115.0 (d, *J* = 5.1 Hz), 76.4, 69.7, 67.9, 67.4, 61.7, 32.5. **HRMS** (ESI) for $C_{12}H_{14}BrFNaO_4$: calcd. 342.99517; found. 342.99500.

5.4.9.12 Synthesis of (2S,3R,4R)-Tetrahydro-2-((R)-1-Hydroxypentyl)-2H-Pyran-3,4-Diol (5-113)



The title compound was prepared using the general procedure for dihydroxylation (**62%** yield) as a white solid. $[\alpha]^{23}_{D}$ -29.27 (c = 1.24, MeOH). **IR** (Cast film, cm^{-1}) 3380, 2954, 2926, 2874, 2859, 1466, 1402, 1274, 1216, 1120, 1102, 1077, 1055, 919, 902, 665. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 4.06 (dd, 1H, *J* = 3.2 Hz, *J* = 6.1 Hz), 3.78 (m, 1H), 3.71 (dd, 1H, *J* = 2.4 Hz, *J* = 12.1 Hz), 3.65 (m, 2H), 3.38 (dd, 1H, *J* = 1.7 Hz, *J* = 9.8 Hz), 3.30 (ddd, 1H, *J* = 1.7 Hz, *J* = 2.0 Hz, *J* = 3.3 Hz), 1.83 (m, 1H), 1.73 (m,1H), 1.20-1.62 (m, 6H), 1.44 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 76.7, 69.0, 67.5, 67.3, 61.4, 33.2, 32.5, 28.2, 22.6, 13.2. **HRMS** (ESI) for $C_{10}H_{20}NaO_4$: calcd. 227.12538; found. 227.12536.

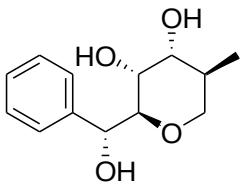
5.4.9.13 Synthesis of (2S,3R,4R)-2-((R)-Cyclohexyl(Hydroxy)Methyl)-Tetrahydro-2H-Pyran-3,4-Diol (5-114)



The title compound was prepared using the general procedure for dihydroxylation (**58%** yield) as a white solid. $[\alpha]^{23}_{D}$ -11.03 (c = 0.31, MeOH). **IR** (Cast film, cm^{-1}) 3383, 2922, 2850, 1398, 1113, 1075, 1058, 1031, 916, 668. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 4.08 (m, 1H), 3.44-3.86 (m, 3H), 3.58 (dd, 1H, *J* = 1.1 Hz, *J* = 9.7 Hz), 3.41 (d, 1H, *J* = 8.9 Hz), 3.30 (m, 1H), 2.08 (d, 1H, *J* = 11.6 Hz), 1.45-1.91 (m, 6H), 1.10-1.42 (m, 3H), 0.81-1.05 (dd, 2H, *J* = 7.3 Hz, *J* = 16.5 Hz). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 75.4, 74.4,

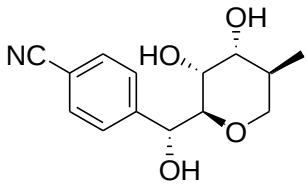
68.6, 68.5, 62.5, 41.2, 33.7, 31.4, 30.3, 27.7, 27.3, 27.2. **HRMS** (ESI) for $C_{12}H_{22}NaO_4$: calcd. 253.14103; found. 253.14104.

5.4.9.14 Synthesis of (2S,3R,4R,5S)-Tetrahydro-2-((R)-Hydroxy(Phenyl)Methyl)-5-Methyl-2H-Pyran-3,4-Diol (5-115)



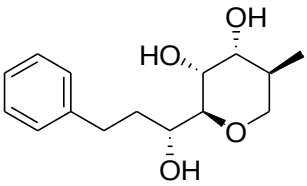
The title compound was prepared using the general procedure for dihydroxylation (**77%** yield) as a white solid. $[\alpha]^{23}_D$ -20.00 (c = 0.25, MeOH). **IR** (Cast film, cm^{-1}) 3525, 3424, 3275, 2996, 2979, 2923, 2875, 1497, 1454, 1401, 1383, 1306, 1072, 1054, 995, 789. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.32 (m, 5H), 4.96 (d, 1H, *J* = 2.8 Hz), 3.78 (m, 3H), 3.68 (dd, 1H, *J* = 3.0 Hz, *J* = 8.4 Hz), 3.39 (dd, 1H, *J* = 2.7 Hz, *J* = 11.3 Hz), 1.88 (m, 1H), 1.06 (d, 3H, *J* = 7.3 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 142.9, 127.7, 126.8, 126.4, 80.2, 72.2, 70.8, 66.6, 65.1, 36.3, 14.0. **HRMS** (ESI) for $C_{13}H_{18}NaO_4$: calcd. 261.10973; found. 261.11004.

5.4.9.15 Synthesis of (2S,3R,4R,5S)-2-((R)-(4-Cyanophenyl)(Hydroxy)Methyl)-Tetrahydro-5-Methyl-2H-Pyran-3,4-Diol (5-116)



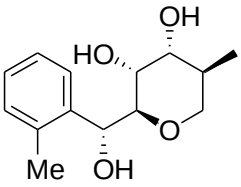
The title compound was prepared using the general procedure for dihydroxylation (**43%** yield) as a white solid. $[\alpha]^{23}_D$ -9.27 (c = 0.22, MeOH). **IR** (Cast film, cm^{-1}) 3422, 3058, 2964, 2931, 2878, 2229, 1609, 1412, 1326, 1267, 1203, 1065, 1013, 993, 772, 702. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.67 (dd, 2H, *J* = 1.8 Hz, *J* = 8.4 Hz),7.60 (m, 2H), 5.02 (d, 1H, *J* = 2.1 Hz), 3.88 (dd, 1H, *J* = 3.2 Hz, *J* = 9.4 Hz), 3.82 (dd, 1H, *J* = 3.3 Hz, *J* = 3.4 Hz), 3.72 (dd, 1H, *J* = 2.8 Hz, *J* = 11.3 Hz), 3.63 (dd, 1H, *J* = 2.1 Hz, *J* = 9.4 Hz), 3.35 (m, 1H), 3.30 (m, 1H), 1.85 (m, 1H), 1.09 (d, 3H, *J* = 7.4 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 149.5, 131.5, 127.3, 118.7, 110.2, 79.5, 72.1, 70.6, 66.7, 64.6, 36.8, 14.1. **HRMS** (ESI) for $C_{14}H_{17}NNaO_4$: calcd. 286.10498; found. 286.10520.

5.4.9.16 Synthesis of (2S,3R,4R,5S)-Tetrahydro-2-((R)-1-Hydroxy-3-Phenyl Propyl)-5-Methyl-2H-Pyran-3,4-Diol (5-117)



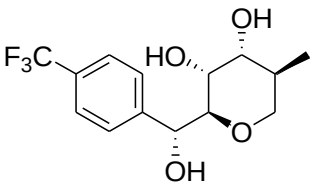
The title compound was prepared using the general procedure for dihydroxylation (**55%** yield) as a white solid. $[\alpha]^{23}_{D}$ -0.25 (c = 0.16, MeOH). **IR** (Cast film, cm^{-1}) 3398, 2927, 2877, 1602, 1518, 1349, 1268, 1215, 1107, 1071, 883, 763. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.20 (m, 5H), 5.04 (d, 1H, *J* = 2.1 Hz), 3.80 (m, 3H), 3.65 (dd, 1H, *J* = 2.3 Hz, *J* = 9.3 Hz), 3.44 (m, 1H, *J* = 11.2 Hz), 3.36 (dd, 1H, *J* = 2.0 Hz, *J* = 9.6 Hz), 3.30 (dd, 1H, *J* = 1.7 Hz, *J* = 3.3 Hz), 2.79 (ddd, 1H, *J* = 5.3 Hz, *J* = 9.9 Hz, *J* = 14.0 Hz), 2.64 (m, 1H), 1.94 (m, 2H), 1.31 (m, 2H), 1.09 (d, 3H, *J* = 7.4 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 142.5, 128.2, 128.1, 126.9, 77.9, 72.2, 68.4, 66.5, 64.4, 36.8, 34.4, 31.5, 14.1. **HRMS** (ESI) for $C_{15}H_{22}NaO_4$: calcd. 289.14103; found. 289.14071.

5.4.9.17 Synthesis of (2S,3R,4R,5S)-Tetrahydro-2-((R)-Hydroxy(o-Tolyl) Methyl)-5-Methyl-2H-Pyran-3,4-Diol (5-118)



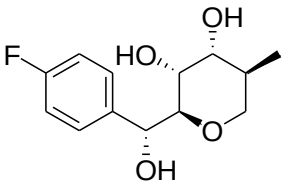
The title compound was prepared using the general procedure for dihydroxylation (**72%** yield) as a white solid. $[\alpha]^{23}_{D}$ -35.35 (c = 0.53, MeOH). **IR** (Cast film, cm^{-1}) 3405, 3055, 3025, 2961, 2930, 2877, 1489, 1462, 1384, 1266, 1219, 1111, 1059, 1010, 992, 779, 742. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.54 (m, 1H), 7.13 (m, 3H), 5.24 (d, 1H, *J* = 2.6 Hz), 3.87 (dd, 1H, *J* = 3.3 Hz, *J* = 8.7 Hz), 3.79 (dd, 1H, *J* = 3.5 Hz, *J* = 3.6 Hz), 3.74 (dd, 1H, *J* = 3.0 Hz, *J* = 11.4 Hz), 3.60 (dd, 1H, *J* = 2.6 Hz, *J* = 8.7 Hz), 3.41 (dd, 1H, *J* = 2.3 Hz, *J* = 11.3 Hz), 3.30 (m, 1H), 2.33 (s, 3H), 1.88 (m, 1H), 1.11 (dd, 3H, *J* = 3.9 Hz, *J* = 9.6 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 140.8, 134.4, 129.8, 127.1, 126.7, 125.3, 78.7, 72.4, 67.1, 66.6, 65.1, 36.4, 18.334, 14.0. **HRMS** (ESI) for $C_{14}H_{20}NaO_4$: calcd. 275.12538; found. 275.12605.

5.4.9.18 Synthesis of (2S,3R,4R,5S)-2-((R)-(4-(Trifluoromethyl) Phenyl) (Hydroxy) Methyl)-Tetrahydro-5-Methyl-2H-Pyran-3,4-Diol (5-119)



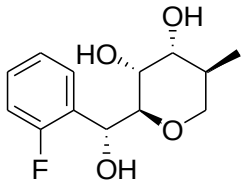
The title compound was prepared using the general procedure for dihydroxylation (**63%** yield) as a white solid. $[\alpha]^{23}_{D}$ -8.12 (c = 0.17, MeOH). **IR** (Cast film, cm^{-1}) 3394, 2930, 2878, 1662, 1620, 1416, 1328, 1124, 1164, 1068, 1015, 970, 951, 845. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.60 (m, 4H), 5.04 (d, 1H, *J* = 2.1 Hz), 3.88 (dd, 1H, *J* = 3.3 Hz, *J* = 9.2 Hz), 3.81 (dd, 1H, *J* = 3.2 Hz, *J* = 3.3 Hz), 3.73 (dd, 1H, *J* = 2.9 Hz, *J* = 11.3 Hz), 3.65 (dd, 1H, *J* = 2.3 Hz, *J* = 9.2 Hz), 3.37 (ddd, 1H, *J* = 0.8 Hz, *J* = 1.9 Hz, *J* = 11.4 Hz), 3.30 (m, 1H), 1.86 (m, 1H), 1.09 (d, 3H, *J* = 7.3 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 149.5, 131.5, 127.3, 118.7, 110.2, 79.5, 72.1, 70.6, 66.7, 64.6, 36.8, 14.1. **HRMS** (ESI) for $C_{14}H_{17}F_3NaO_4$: calcd. 329.09711; found. 329.09686.

5.4.9.19 Synthesis of (2S,3R,4R,5S)-2-((R)-(4-Fluorophenyl)(Hydroxy)Methyl)-Tetrahydro -5-Methyl-2H-Pyran-3,4-Diol (5-120)



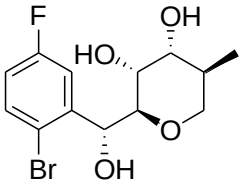
The title compound was prepared using the general procedure for dihydroxylation (**80%** yield) as a white solid. $[\alpha]^{23}_{D}$ -21.93 (c = 0.60, MeOH). **IR** (Cast film, cm^{-1}) 3519, 2284, 2209, 2930, 2898, 2873, 1601, 1510, 1386, 1250, 1220, 1095, 1037, 986, 851,789. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.42 (dd, 2H, *J* = 5.7 Hz, *J* = 8.2 Hz), 7.02 (m, 2H), 4.89 (d, 1H, *J* = 55.0 Hz), 3.78 (m, 3H), 3.64 (dd, 1H, *J* = 2.3 Hz, *J* = 8.5 Hz), 3.39 (dd, 1H, *J* = 1.4 Hz, *J* = 11.4 Hz), 1.87 (m, 1H), 1.06 (d, 3H, *J* = 7.3 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 162.2 (d, *J* = 241.8 Hz), 139.0 (d, *J* = 2.9 Hz), 128.3 (d, *J* = 7.8 Hz), 114.3 (d, *J* = 21.2 Hz), 79.8, 72.3, 70.4, 66.7, 65.0, 36.4, 14.1, **HRMS** (ESI) for $C_{13}H_{17}FNaO_4$:calcd. 279.10031; found. 279.10012.

5.4.9.20 Synthesis of (2S,3R,4R,5S)-2-((R)-(2-Fluorophenyl)(Hydroxy)Methyl)-Tetrahydro-5-Methyl-2H-Pyran-3,4-Diol (5-121)



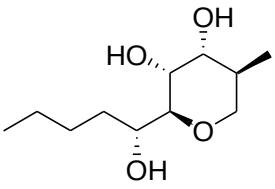
The title compound was prepared using the general procedure for dihydroxylation (**75%** yield) as a white solid. $[\alpha]^{23}_{D}$ -23.85 (c = 0.70, MeOH). **IR** (Cast film, cm^{-1}) 3403, 2964, 2933, 2878, 1617, 1489, 1456, 1312, 1223, 1152, 1061, 1011, 992, 841, 758. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.61 (ddd, 1H, *J* = 1.6 Hz, *J* = 7.6 Hz, *J* = 7.6 Hz), 7.24 (m, 1H), 7.13 (ddd, 1H, *J* = 1.1 Hz, *J* = 7.5 Hz, *J* = 7.5 Hz), 7.01 (ddd, 1H, *J* = 1.1 Hz, *J* = 8.2 Hz, *J* = 10.7 Hz), 5.34 (d, 1H, *J* = 2.7 Hz), 3.88 (dd, 1H, *J* = 3.1 Hz, *J* = 8.5 Hz), 3.79 (dd, 1H, *J* = 3.7 Hz, *J* = 3.7 Hz), 3.74 (dd, 1H, *J* = 3.0 Hz, *J* = 11.4 Hz), 3.68 (dd, 1H, *J* = 2.9 Hz, *J* = 8.5 Hz), 3.39 (dd, 1H, *J* = 2.7 Hz, *J*=11.3 Hz), 1.88 (m, 1H), 1.09 (d, 1H, *J* = 7.3 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 159.7 (d, *J* = 242.0 Hz), 130.0 (d, *J* = 13.0 Hz), 129.0 (d, *J* = 4.1 Hz), 128.5 (d, *J* = 8.2 Hz), 123.7 (d, *J* = 3.3 Hz), 114.5 (d, *J* = 22.0 Hz), 79.3, 72.3, 66.7, 65.1, 64.5, 36.3, 14.0. **HRMS** (ESI) for $C_{13}H_{17}FNaO_4$: calcd. 279.10031; found. 279.10095.

5.4.9.21 Synthesis of (2S,3R,4R,5S)-2-((R)-(2-Bromo-5-Fluorophenyl)(Hydroxyl) Methyl)-Tetrahydro-5-Methyl-2H-Pyran-3,4-Diol (5-122)



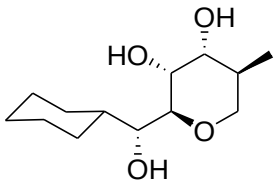
The title compound was prepared using the general procedure for dihydroxylation (**51%** yield) as a white solid. $[\alpha]^{23}_{D}$ -41.80 (c = 1.91, MeOH). **IR** (Cast film, cm^{-1}) 3368, 2959, 2937, 2882, 1605, 1582, 1466, 1413, 1358, 1267, 1107, 1066, 1044, 988, 916, 739. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.48 (dd, 1H, *J* = 5.3 Hz, *J* = 8.8 Hz), 7.41 (dd, 1H, *J* = 3.1 Hz, *J* = 10.2 Hz), 6.90 (m, 1H), 5.54 (d, 1H, *J* = 0.8 Hz), 3.96 (dd, 1H, *J* = 3.2 Hz, *J* = 9.3 Hz), 3.86 (dd, 1H, *J* = 3.2 Hz, *J* = 3.3 Hz), 3.71 (m, 2H), 3.38 (dd, 1H, *J* = 0.7 Hz, *J* = 11.3 Hz), 1.87 (m, 1H), 1.11 (d, 1H, *J* = 7.4 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 162.1 (d, *J* = 242.6 Hz), 144.7 (d, *J* = 7.0 Hz), 133.5 (d, *J* = 7.8 Hz), 116.8 (d, *J* = 24.3 Hz), 115.5 (d, *J* = 23.0 Hz), 106.0, 77.5, 72.4, 69.8, 66.9, 64.9, 36.8, 14.2. **HRMS** (ESI) for $C_{13}H_{16}FBrNaO_4$: calcd. 357.01082; found. 357.01024.

5.4.9.22 Synthesis of (2S,3R,4R,5S)-Tetrahydro-2-((R)-1-Hydroxypentyl)-5-Methyl-2H-Pyran-3,4-Diol (5-123)



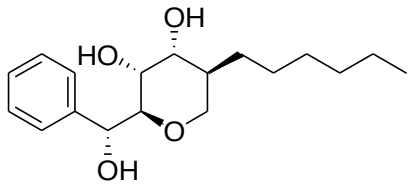
The title compound was prepared using the general procedure for dihydroxylation (**73%** yield) as a white solid. $[\alpha]^{23}_{D}$ -2.80 (c = 0.20, MeOH). **IR** (Cast film, cm^{-1}) 3392, 2956, 2931, 2872, 1461, 1382, 1346, 1258, 1107, 1053, 992, 949, 757. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 3.81 (m, 4H), 3.44 (dd, 1H, *J* = 1.3 Hz, *J* = 11.1 Hz), 3.34 (dd, 1H, *J* = 1.9 Hz, *J* = 9.5 Hz), 3.30 (m, 1H), 1.86 (m, 1H), 1.25-1.73 (m, 6H), 1.08 (d, 3H, *J* = 7.4 Hz), 0.92 (t, 3H, *J* = 7.1 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 77.7, 72.2, 69.0, 66.5, 64.4, 36.8, 33.2, 28.2, 22.6, 14.2, 13.2. **HRMS** (ESI) for $C_{11}H_{22}NaO_4$: calcd. 241.14103; found. 241.14131.

5.4.9.23 Synthesis of (2S,3R,4R,5S)-2-((R)-Cyclohexyl(Hydroxy)Methyl)-Tetrahydro-5-Methyl-2H-Pyran-3,4-Diol (5-124)



The title compound was prepared using the general procedure for dihydroxylation (**84%** yield) as a white solid. $[\alpha]^{23}_{D}$ -1.23 (c = 0.13, MeOH). **IR** (Cast film, cm^{-1}) 3456, 3351, 2923, 2974, 2851, 1448, 1384, 1091, 1071, 1054, 1007, 874. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 3.86 (m, 2H), 3.80 (dd, 1H, *J* = 2.7 Hz, *J* = 2.8 Hz), 3.54 (dd, 1H, *J* = 1.2 Hz, *J* = 9.5 Hz), 3.41 (m, 2H), 2.08 (d, 1H, *J* = 13.0 Hz), 1.47-1.94 (m, 6H), 1.15-1.40 (m, 3H), 1.08 (d, 3H, *J* = 7.4 Hz), 0.96 (m, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 75.1, 73.3, 72.3, 66.4, 64.1, 40.0, 37.0, 30.1, 29.1, 26.5, 26.1, 26.0, 14.2. **HRMS** (ESI) for $C_{13}H_{24}NaO_4$: calcd. 267.15668; found. 267.15657.

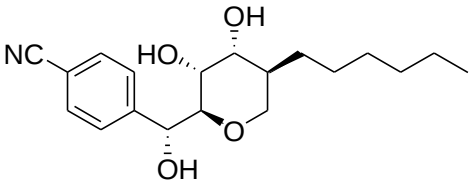
5.4.9.24 Synthesis of (2S,3R,4R,5S)-5-Hexyl-Tetrahydro-2-((R)-Hydroxy(Phenyl) Methyl)-2H-Pyran-3,4-Diol (5-125)



The title compound was prepared using the general procedure for dihydroxylation (**72%** yield). $[\alpha]^{23}_{D}$ -11.69 (c = 0.33, MeOH). **IR** (Cast film, cm^{-1}) 3504, 3417, 3321, 2925, 2887, 2855, 1496, 1456, 1402, 1378, 1342, 1097, 1045, 698. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.43 (m, 2H), 7.29 (m, 2H), 7.21 (m, 1H), 4.95 (d, 1H, *J* = 2.3 Hz), 3.86 (dd, 1H, *J* = 3.2 Hz, *J*

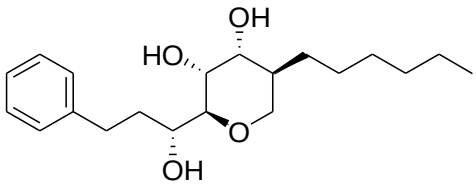
= 3.6 Hz), 3.80 (dd, 1H, *J* = 3.2 Hz, *J* = 9.1 Hz), 3.71 (dd, 1H, *J* = 2.8 Hz, *J* = 11.5 Hz), 3.66 (dd, 1H, *J* = 2.4 Hz, *J* = 9.1 Hz), 3.48 (m, 1H), 1.67 (m, 1H), 1.10-1.55 (m, 10H), 0.89 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 143.1, 127.6, 126.7, 126.3, 79.7, 71.3, 71.0, 65.2, 64.7, 42.2, 31.7, 29.3, 28.8, 27.5, 22.5, 13.2. **HRMS** (ESI) for $C_{18}H_{28}NaO_4$: calcd. 331.18798; found. 331.18785.

5.4.9.25 Synthesis of (2S,3R,4R,5S)-2-((R)-(4-Cyanophenyl)(Hydroxy)Methyl)-5-Hexyl-Tetrahydro-2H-Pyran-3,4-Diol (5-126)



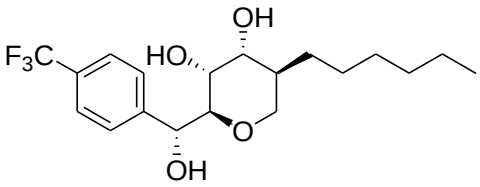
The title compound was prepared using the general procedure for dihydroxylation (**35%** yield). $[\alpha]^{23}_D$ -14.07 (c = 0.26, MeOH). **IR** (Cast film, cm^{-1}) 3500, 3407, 2954, 2926, 2857, 2233, 1606, 1502, 1466, 1412, 1324, 1135, 1098, 1065, 841. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.64 (m, 5H), 5.02 (d, 1H, *J* = 1.6 Hz), 3.89 (dd, 1H, *J* = 2.8 Hz, *J* = 3.2 Hz) 3.84 (dd, 1H, *J* = 3.2 Hz, *J* = 9.5 Hz), 3.67 (dd, 1H, *J* = 2.8 Hz, *J* = 11.7 Hz), 3.64 (dd, 1H, *J* = 1.9 Hz, *J* = 9.6 Hz), 3.46 (m, 2H), 3.30 (m, 1H), 1.63 (m, 1H), 1.33 (m, 1H), 1.10-1.55 (m, 10H), 0.90 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 149.5, 131.5, 127.3, 118.7, 110.2, 79.3, 71.2, 70.7, 64.9, 64.8, 42.6, 31.7, 29.3, 28.8, 27.6, 22.5, 13.2. **HRMS** (ESI) for $C_{19}H_{27}NNaO_4$: calcd. 356.18323; found. 356.18303.

5.4.9.26 Synthesis of (2S,3R,4R,5S)-5-Hexyl-Tetrahydro-2-((R)-1-Hydroxy-3-Phenyl Propyl)-2H-Pyran-3,4-Diol (5-127)



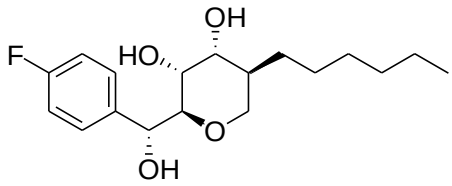
The title compound was prepared using the general procedure for dihydroxylation (**69%** yield). As a white solid. $[\alpha]^{23}_D$ 13.12 (c = 0.25, MeOH). **IR** (Cast film, cm^{-1}) 3477, 3376, 2953, 2925, 2857, 1467, 1379, 1114, 1098, 1061, 697. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.22 (m, 5H), 3.81 (m, 4H), 3.55 (d, 1H, *J* = 11.2 Hz), 3.36 (d, 1H, *J* = 9.7 Hz), 3.30 (m, 1H), 2.77 (m, 1H), 2.64 (m, 1H), 1.96 (m, 1H), 1.10-1.85 (m, 12H), 0.90 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 142.5, 128.2, 128.1, 125.4, 77.7, 71.3, 68.5, 64.7, 64.6, 42.6, 35.6, 32.2, 31.7, 29.3, 28.8, 27.6, 22.5, 13.2. **HRMS** (ESI) for $C_{20}H_{32}NaO_4$: calcd. 359.21928; found. 359.22032.

5.4.9.27 Synthesis of (2S,3R,4R,5S)-2-((R)-(4-(Trifluoromethyl)Phenyl) (Hydroxy)Methyl) -5-Hexyl-Tetrahydro-2H-Pyran-3,4-Diol (5-128)



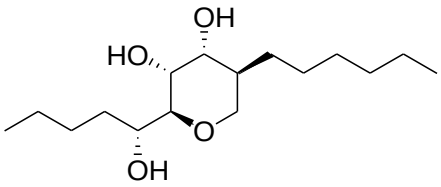
The title compound was prepared using the general procedure for dihydroxylation (**68%** yield) as a white solid. $[\alpha]^{23}_{D}$ -10.80 (c = 0.20, MeOH). **IR** (Cast film, cm^{-1}) 3503, 3384, 2927, 2858, 1468, 1329, 1166, 1125, 1070, 1045, 779. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.59 (m, 4H), 5.04 (bs, 1H), 3.90 (dd, 1H, *J* = 3.1 Hz, *J* = 3.2 Hz), 3.85 (dd, 1H, *J* = 3.2 Hz, *J* = 9.5 Hz), 3.70 (dd, 1H, *J* = 2.3 Hz, *J* = 11.6 Hz), 3.67 (dd, 1H, *J* = 2.0 Hz, *J* = 9.5 Hz), 3.47 (d, 1H, *J* = 11.4 Hz), 3.30 (bs, 1H), 1.64 (m, 1H), 1.56 (m, 1H), 1.20-1.47 (m, 9H), 0.89 (t, 3H, *J* = 6.8 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 148.0, 128.8 (q, *J* = 31.7 Hz), 126.9, 124.6 (q, *J* = 269.1 Hz), 124.4 (q, *J* = 3.8 Hz), 79.3, 71.3, 70.7, 65.0, 64.8, 42.6, 31.7, 29.3, 28.8, 27.6, 22.5, 13.2. **HRMS** (ESI) for $C_{19}H_{27}F_3NaO_4$: calcd. 399.17537; found. 399.17528.

5.4.9.28 Synthesis of (2S,3R,4R,5S)-2-((R)-(4-Fluorophenyl)(Hydroxy)Methyl)-5-Hexyl-Tetrahydro-2H-Pyran-3,4-Diol (5-129)



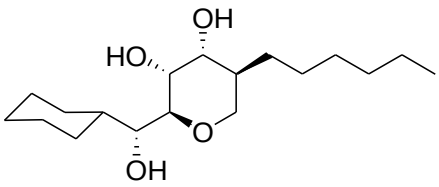
The title compound was prepared using the general procedure for dihydroxylation (**61%** yield) as a white solid. $[\alpha]^{23}_{D}$ -11.63 (c = 0.43, MeOH). **IR** (Cast film, cm^{-1}) 3503, 3417, 2955, 2825, 2847, 1605, 1514, 1425, 1397, 1266, 1063, 1044, 852. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.42 (m, 2H), 7.01 (m, 2H), 4.94 (d, 1H, *J* = 2.0 Hz), 3.86 (dd, 1H, *J* = 3.3 Hz, *J* = 3.2 Hz), 3.79 (dd, 1H, *J* = 3.2 Hz, *J* = 9.3 Hz), 3.71 (dd, 1H, *J* = 2.8 Hz, *J* = 11.4 Hz), 3.61 (dd, 1H, *J* = 2.3 Hz, *J* = 9.3 Hz), 3.48 (dd, 1H, *J* = 1.0 Hz, *J* = 11.5 Hz), 3.30 (m, 1H), 1.65 (m, 1H), 1.54 (m, 1H), 1.10-1.47 (m, 9H), 0.90 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 162.1 (d, *J* = 241.3 Hz), 139.1 (d, *J* = 3.1 Hz), 128.2 (d, *J* = 7.8 Hz), 114.2 (d, *J* = 21.2 Hz), 79.4, 71.2, 70.5, 65.1, 64.8, 42.4, 31.7, 29.3, 28.8, 27.5, 22.5, 13.2. **HRMS** (ESI) for $C_{18}H_{27}FNaO_4$: calcd. 349.17856; found. 349.17860.

5.4.9.29 Synthesis of (2S,3R,4R,5S)-5-Hexyl-Tetrahydro-2-((R)-1-Hydroxy pentyl)-2H-Pyran-3,4-Diol (5-130)



The title compound was prepared using the general procedure for dihydroxylation (**67%** yield) as a white solid. $[\alpha]^{23}_{D}$ 1.00 (c = 0.16, MeOH). **IR** (Cast film, cm^{-1}) 3481, 3380, 3256, 2954, 2925, 2857, 1467, 1402, 1379, 1236, 1124, 1100, 1058, 1042, 914. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 3.80 (m, 4H), 3.54 (d, 1H, *J* = 11.3 Hz), 3.34 (dd, 1H, *J* = 1.4 Hz, *J* = 9.6 Hz), 3.30 (m, 1H), 2.01 (bs, 1H), 1.20-1.75 (m, 16H), 0.89 (m, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 77.5, 71.3, 69.0, 64.7, 64.6, 42.6, 33.2, 31.8, 29.3, 28.8, 28.3, 27.6, 22.6, 22.5, 13.2, 13.2. **HRMS** (ESI) for $C_{16}H_{32}NaO_4$: calcd. 311.21928; found, 311.21932.

5.4.9.30 Synthesis of (2S,3R,4R,5S)-2-((R)-Cyclohexyl(Hydroxy)Methyl)-5-Hexyl-Tetrahydro-2H-Pyran-3,4-Diol (5-131)



The title compound was prepared using the general procedure for dihydroxylation (**95%** yield) as a white solid. $[\alpha]^{23}_{D}$ 6.31 (c = 0.39, MeOH). **IR** (Cast film, cm^{-1}) 3493, 3409, 2923, 2852, 1467, 1449, 1400, 1206, 1062, 1041, 890. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 3.87 (dd, 1H, *J* = 2.8 Hz, *J* = 2.8 Hz), 3.81 (m, 2H), 3.54 (m, 2H), 3.39 (dd, 1H, *J* = 0.6 Hz, *J* = 8.8 Hz), 3.30 (m, 1H), 2.08 (d, 1H, *J* = 12.4 Hz), 1.50-1.85 (m, 7H), 1.10-1.56 (m, 12H), 0.91 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 74.9, 73.3, 71.4, 64.5, 64.4, 42.7, 40.0, 31.8, 30.1, 29.3, 29.1, 28.8, 27.6, 26.5, 26.1, 26.0, 22.5, 13.2. **HRMS** (ESI) for $C_{18}H_{34}NaO_4$: calcd. 337.23493; found. 337.23482.

5.5 References

[1] R. Sutherland, R.J. Boon, K.E. Griffin, P.J. Masters, B. Slocombe, A.R. White, *Antimicrob. Agents Chemother.* **1985**, *27*, 495.

[2] A. Badder, C. Garre, *Corresp. Bl. Sweiz. Aertze* **1887**, *17*, 385.

[3] A.T. Fuller, G. Mellows, M. Woolford, G.T. Banks, K.D. Barrow, E.B. Chain, *Nature* **1971**, *234*, 416.

[4] E.B. Chain, G. Mellows, *J. Chem. Soc., Perkin Trans.* **1977**, *1* 318.

[5] R.G. Alexander, J.P. Clayton, K. Luk, N.H. Rogers, T.J. King, *J. Chem. Soc., Perkin Trans.* **1978**, *1*, 561.

[6] J. Hughes, G. Mellows, *Biochem. J.* **1978**, *176*, 305.

[7] M.G. Rossmann, D. Moras, K.W. Olsen, *Nature* **1974**, *250* 194.

[8] P. Bork, L. Holm, E.V. Koonin, C. Sander, *Proteins* **1995**, *22*, 259.

[9] J. Hughes, G. Mellows, *Biochem. J.* **1980**, *191*, 209.

[10] J. Hughes, G. Mellows, *J. Antibiot.* **1978**, *31*, 330.

[11] J. Hughes, G. Mellows, S. Soughton, *FEBS Lett.* **1980**, *122*, 322.

[12] L.F. Silvian, J. Wang, T.A. Steitz, *Science* **1999**, *285*, 1074.

[13] O. Marion, X. Gao, S. Marcus, D. G. Hall, *Bioorg. Med. Chem.* **2009**, *17*, 1006.

[14] Y.J. Class, P. DeShong, *Chem. Rev.* **1995**, *95*, 1843.

[15] J.P. Clayton, R.S. Oliver, N.P. Rogers, T.J. King, *J. Chem. Soc. Perkin Trans. I* **1979**, 838.

[16] H. Shiozawa, T. Kagasaki, T. Kinoshita, H. Haruyama, H. Domon, Y. Utsui, K. Kodama, S. Takahashi, *J. Antibiot.* **1993**, *46*, 1834.

[17] D.B. Stierle, A.A. Stierle, *Experientia* **1992**, *48*, 1165.

[18] H. Shiozawa, S. Takahashi, *J. Antibiot.* **1994**, *47*, 851.

[19] H. Shiozawa, T. Kagasaki, A. Torikata, N. Tanaka, K. Fujimoto, T. Hata, Y. Furukawa, S. Takahashi, *J. Antibiot.* **1995**, *48*, 907.

[20] X. Gao, D. G. Hall, *J. Am. Chem. Soc.* **2005**, *127*, 1628.

[21] a) R. Breinbauer, I. R. Vetter, H. Waldmann, *Angew. Chem. Int. Ed*. **2002**, *41*, 2878. b) M. A. Koch, H. Waldmann, *Drug Discovery Today* **2005**, *10*, 471.

[22] X. Gao, D. G. Hall, *J. Am. Chem. Soc.* **2003**, *125*, 9308.

[23] D.E. Chavez, E.N. Jacobsen, *Org. Synth.* **2005**, *82*, 34.

[24] K. Gademann, D.E. Chavez, E.N. Jacobsen, *Angew. Chem. Int. Ed.* **2002**, *41*, 3059.

[25] D. A. Evans, G. C. Andrews, B. Buckwalter, *J. Am. Chem. Soc.* **1974**, *96*, 5560.

[26] H. Yamamoto, M. Tsuda, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **1997**, *62*, 7174.

[27] X. Gao, Ph.D. Thesis, University of Alberta (Edmonton), **2003**.

[28] X. Li, T. Uchiyama, C. R. H. Raetz, O. Hindsgaul, *Org. Lett.* **2003**, *5*, 539.

[29] D. Rolf, G. R. Gray, *J. Am. Chem. Soc.* **1982**, *104*, 3539.

[30] S. D. Debenham, E. J. Toone, *Tetrahedron: Asymmetry* **2000**, *11*, 385.

[31] A. Lipták, I. Jodál, P. Nánási, *Carbohydr. Res.* **1975**, *1*, 44.

[32] P. J. Garegg, H. Hultberg, S. Wallin, *Carbohydr. Res.* **1982**, *108*, 97.

[33] M. P. Deninno, J. B. Etienne, K. C. Duplantier, *Tetrahedron Lett.* **1995**, *36*, 669.

[34] V. Balakumar, A. Aravind, S. Baskaran, *Synlett,* **2004**, 647.

[35] H. X. Zhang, P. Xia, W. S. Zhou, *Tetraherdron* **2003**, *59*, 2015.

[36] M. Deligny, F. Carreaux, L. Toupet, B. Carboni, *Chem. Commun*. **2003**, 276.

[37] M. Deligny, F. Carreaux, L. Toupet, B. Carboni, *Adv. Synth. Catal*. **2003**, *345*, 1215.

Conclusions and Future Directions

Part I: *Ortho*-Haloarylboronic Acids for Direct Amide Bond Formation

The research presented in this thesis addresses the development of a boron catalyst for an environmentally benign direct amide bond formation reaction at ambient temperature with high atom economy. The direct condensation between amines and carboxylic acids generates a thermodynamically stable "ammonium carboxylate salt", which requires harsh reaction conditions with temperatures as high as 250 °C for dehydrating. Consequently, the majority of the published methods require a preactivation step using stoichiometric reagents, which have very poor atom economy and are associated with many limitations, such as poor reactivity, low conversions, toxicity, side reactions, racemizations, high costs and cumbersome purifications.

Over the course of my research, I was able to discover that *ortho*-substituted arylboronic acids and, especially, the *ortho*-haloarylboronic acids are remarkable catalysts for direct amide bond formation at ambient temperature. *Ortho*-iodoarylboronic acid (IBA) was found to be the best *ortho*-haloarylboronic acid catalyst that provided the highest yields of the amide product under mild and waste-free conditions at room temperature. In this methodology, the reaction procedure is operationally very simple. It employs equimolar amounts of acid and amine substrates, requires no heating or cooling source, generates only water as a by-product, and affords pure amide products after a simple filtration and acid–base extractions to remove any unreacted substrates and the catalyst. This new catalytic system represents a significant advance over the previous catalysts reported by both the Yamamoto and Whiting groups and demonstrates the strong potential of boronic acid-catalysis towards activation of the carboxylic acid moiety.

Extensive optimization of the *ortho*-iodoarylboronic acid structure led us to find a more reactive catalyst, 5-methoxy-2-iodoarylboronic acid (MIBA), as a second generation catalyst for the direct amide bond formation reaction. In particular, the

MIBA catalyst was found to be effective for the direct amidation of aliphatic carboxylic acids, with the corresponding amide products isolated in up to 99% yield without any detected racemizations (with an optically pure α-substituted carboxylic acid). The MIBA catalyst also displayed reactivity for amide bond formation from β-amino acids and γ-amino acids and the amide products were isolated in high yield without the need for chromatography. Finally, a third generation catalyst, 4-iodo-3-furanboronic acid (FIBA), was discovered and showed a consistent superiority over the second generation catalyst by providing the amide products in higher yields with even shorter reaction times.

The stability of these *ortho*-iodoaryl and furanboronic acids on silica was comparable to other arylboronic acids. Unlike many arylboronic acids, these can be easily purified and stored for several months. The majority of these catalysts were prepared in a single step through a new mild and regioselective direct iodination methodology from cheap and commercially available arylboronic acids. These compounds are not only exceptional as catalysts for direct amidation reactions, but also as reagents for chemoselective Suzuki-Miyaura couplings in a one-pot fashion to provide bi- and triaryl derivatives, which are basic chemical structures in some biologically active natural products.

There are several areas where progress could be made: (1) optimizations of the third generation catalytic system (FIBA) with electron donating groups, (2) study of the additive effect on enhancing the reactivity of these catalysts, (3) synthesis of chiral iodoboronic acid catalysts for the kinetic resolution between racemic amines and carboxylic acids and (4) synthesis of solid-supported iodoboronic acid catalysts.

In conclusion, I was able to shed more light on the unique reactivity of boronic acid catalysts for the activation of carboxylic acids and design the first catalytic system toward direct amide bond formation at room temperature.

Part II: Diversity-Oriented Synthesis of a 30-Member Library of Thiomarinol Analogues via oxa[4+2] Cycloaddition/Allylboration Methodology

A successful synthesis of a small library of 30 thiomarinol analogues was outlined in the second part of my thesis. This library was made through a known methodology

developed in the Hall Laboratory, involving a tandem oxa[4+2] cycloaddition/allylboration reaction of aldehydes and enol ethers in highly enantio- and distereoselective fashion. This reaction sequence can be carried out with a wide variety of aldehydes including aromatic, heteroaromatic, unsaturated and aliphatic aldehydes and with three different enol ethers, allowing the generation of highly substituted α-hydroxyalkyl dihydropyran systems in a single step.

A mild method for acetal reduction of α-hydroxyalkyl dihydropyran systems without the need for hydroxyl group protection was developed, which was followed by dihydroxylations of the double bond to provide the requisite thiomarinol analogues in good yields. The absolute stereochemistry of one of the library members was proven by X-ray crystallography.

This library was designed through a collaboration study between Professors Hall and Waldmann in Germany using the protein structure similarity clustering (**PSSC**) computational approach. The screening study of this library against the bacterial isoleucyl tRNA synthetase is under investigation in the laboratories of Professor Eric Brown at McMaster University.

X-Ray Crystallography Reports

1. X-Ray Crystallography Report of 2-Iodoarylboronic acid

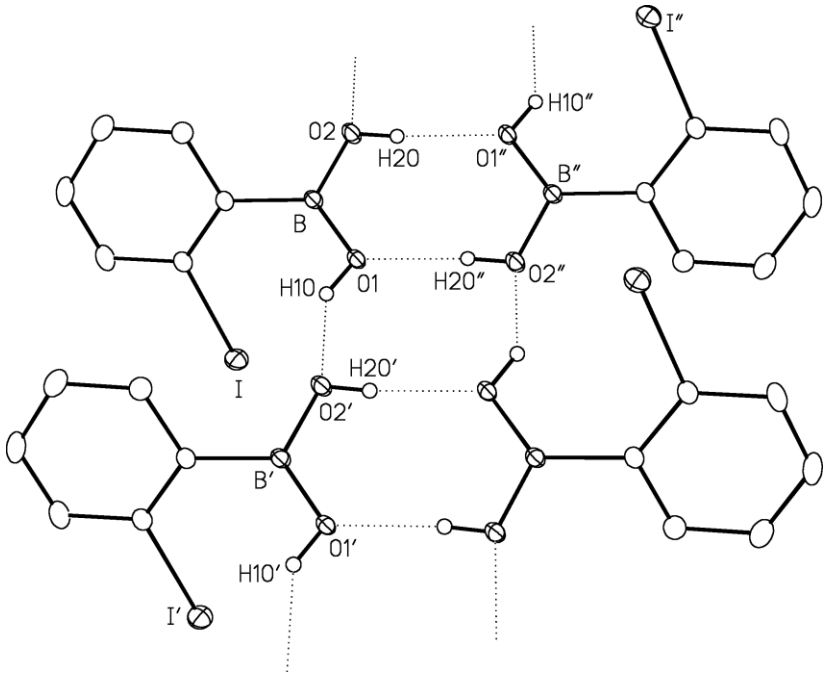
UNIVERSITY OF ALBERTA
X-Ray Crystallography Laboratory
Department of Chemistry • University of Alberta
Edmonton, Alberta T6G 2G2 Canada

Phone: +1 780 492 2485
Fax: +1 780 492 8231
Bob.McDonald@ualberta.ca • Michael.Ferguson@ualberta.ca
http://xray.chem.ualberta.ca/

XCL Code: DGH0712 **Date:** 29 August 2007

Compound: 2-Iodophenylboronic acid
Formula: $C_6H_6BIO_2$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta

2. X-Ray Crystallography Report 2-Bromo-3,4,5-Trifluoro phenylboronic Acid

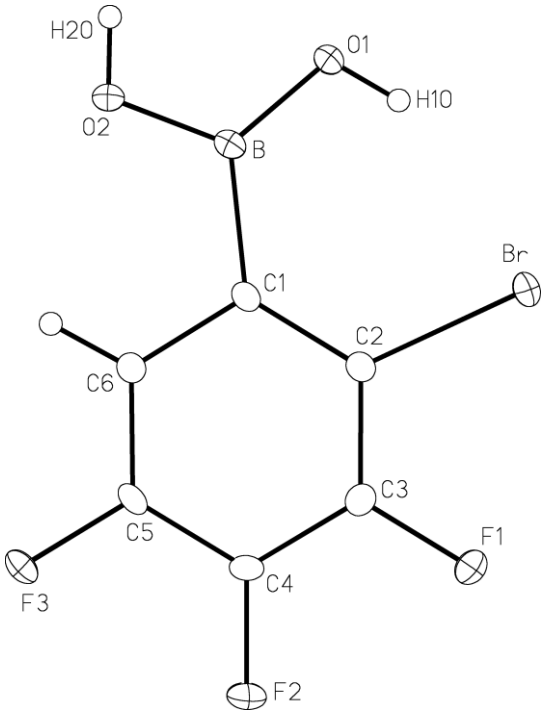
UNIVERSITY OF ALBERTA
X-Ray Crystallography Laboratory
Department of Chemistry • University of Alberta
Edmonton, Alberta T6G 2G2 Canada

Phone: +1 780 492 2485
Fax: +1 780 492 8231
Bob.McDonald@ualberta.ca • Michael.Ferguson@ualberta.ca
http://xray.chem.ualberta.ca/

XCL Code: DGH0718 **Date:** 21 December 2007

Compound: 2-Bromo-3,4,5-trifluorophenylboronic acid
Formula: $C_6H_3BBrF_3O_2$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta

3. X-Ray Crystallography Report of 5-Fluoro-2-Iodophenyl boronic Acid (85%) / 4-Fluoro-2-iodophenylboronic Acid (15%)

UNIVERSITY OF ALBERTA
X-Ray Crystallography Laboratory
Department of Chemistry • University of Alberta
Edmonton, Alberta T6G 2G2 Canada

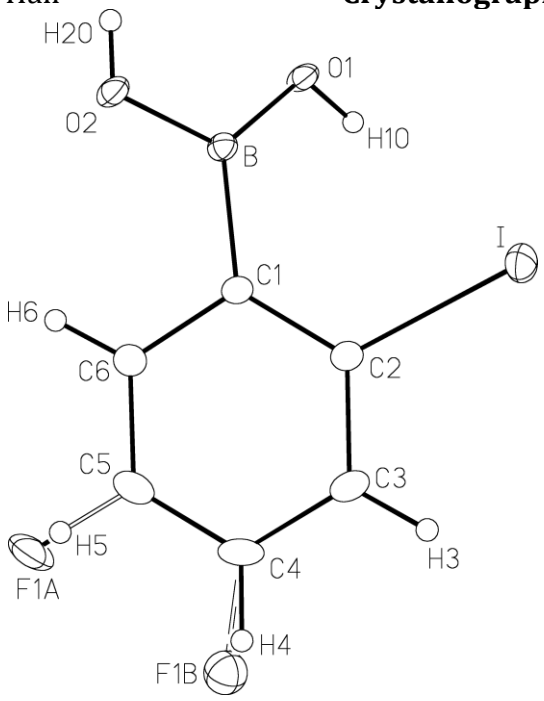
Phone: +1 780 492 2485
Fax: +1 780 492 8231
Bob.McDonald@ualberta.ca • Michael.Ferguson@ualberta.ca
http://xray.chem.ualberta.ca/

XCL Code: DGH0715 **Date:** 27 November 2007

Compound: 5-Fluoro-2-iodophenylboronic acid (85%) / 4-fluoro-2-iodophenylboronic acid (15%)

Formula: $C_6H_5BFIO_2$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta

4. X-Ray Crystallography Report of 1,3,5-Tris(5-fluoro-2-iodoaryl)boroxine

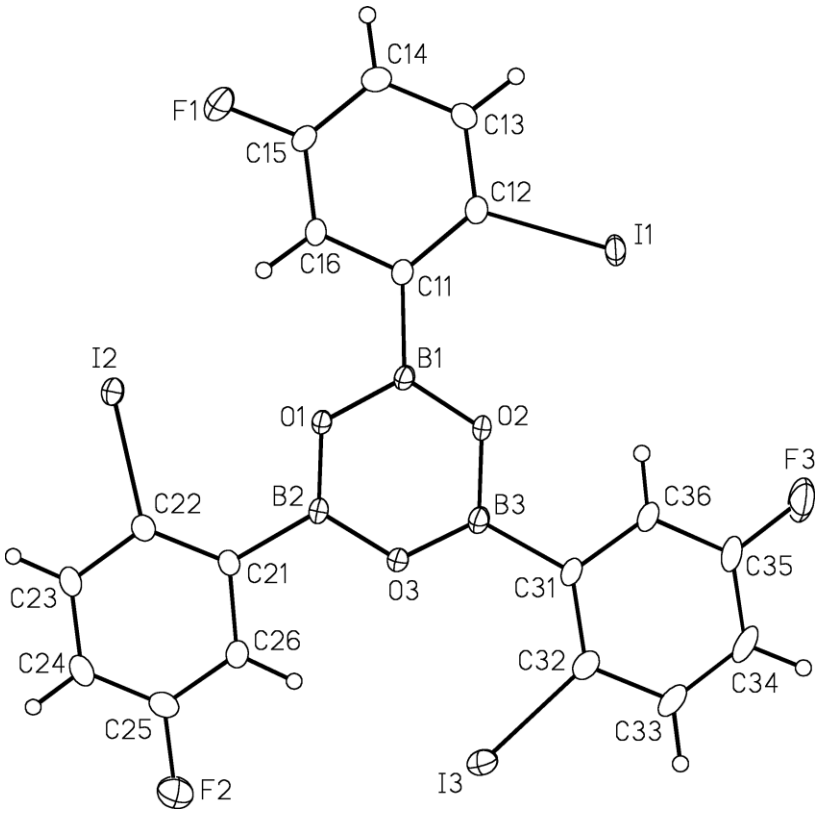
UNIVERSITY OF ALBERTA
X-Ray Crystallography Laboratory
Department of Chemistry • University of Alberta
Edmonton, Alberta T6G 2G2 Canada

Phone: +1 780 492 2485
Fax: +1 780 492 8231
Bob.McDonald@ualberta.ca • Michael.Ferguson@ualberta.ca
http://xray.chem.ualberta.ca/

XCL Code: DGH0713 **Date:** 2 November 2007

Compound: 1,3,5-Tris(5-fluoro-2-iodophenyl)boroxine
Formula: $C_{18}H_9B_3F_3I_3O_3$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta

5. X-Ray Crystallography Report of 2-Iodo-4,5-dimethoxy-3-methylarylboronic Acid

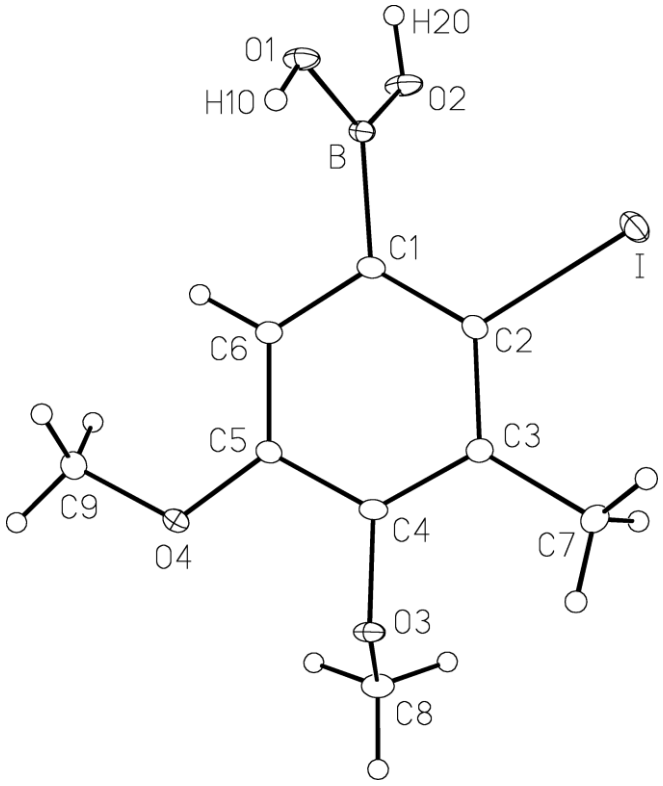
UNIVERSITY OF ALBERTA
X-Ray Crystallography Laboratory
Department of Chemistry • University of Alberta
Edmonton, Alberta T6G 2G2 Canada

Phone: +1 780 492 2485
Fax: +1 780 492 8231
Bob.McDonald@ualberta.ca • Michael.Ferguson@ualberta.ca
http://xray.chem.ualberta.ca/

XCL Code: DGH0820 **Date:** 25 August 2008

Compound: (2-Iodo-4,5-dimethoxy-3-methylphenyl)boronic acid
Formula: $C_9H_{12}BIO_4$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta

6. X-Ray Crystallography Report of 2-Iodo-6-methoxyaryl boronic Acid

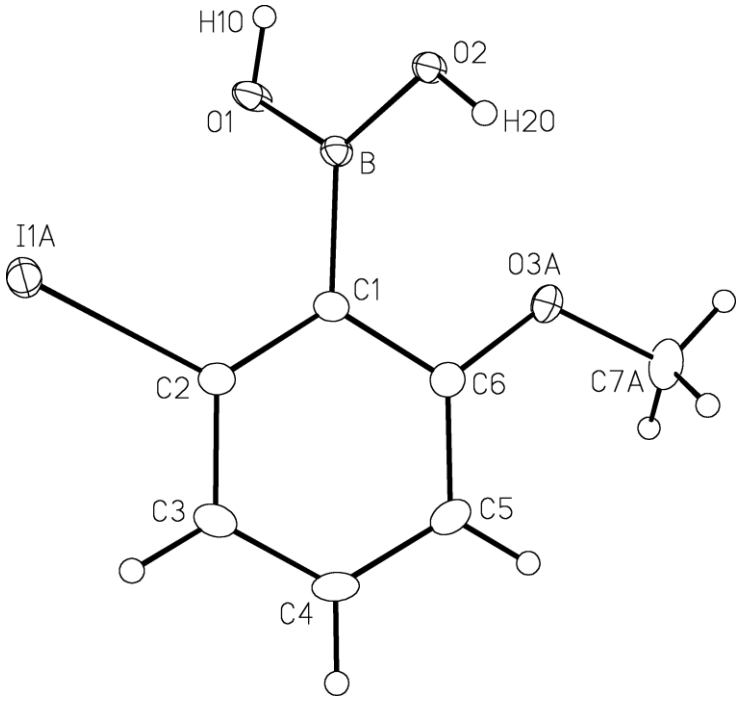
UNIVERSITY OF ALBERTA
X-Ray Crystallography Laboratory
Department of Chemistry • University of Alberta
Edmonton, Alberta T6G 2G2 Canada

Phone: +1 780 492 2485
Fax: +1 780 492 8231
Bob.McDonald@ualberta.ca • Michael.Ferguson@ualberta.ca
http://xray.chem.ualberta.ca/

XCL Code: DGH0825 **Date:** 16 October 2008

Compound: 2-Iodo-6-methoxyphenylboronic acid
Formula: $C_7H_8BIO_3$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta

7. X-Ray Crystallography Report of 6-Iodo-2,3-dimethoxy arylboronic Acid

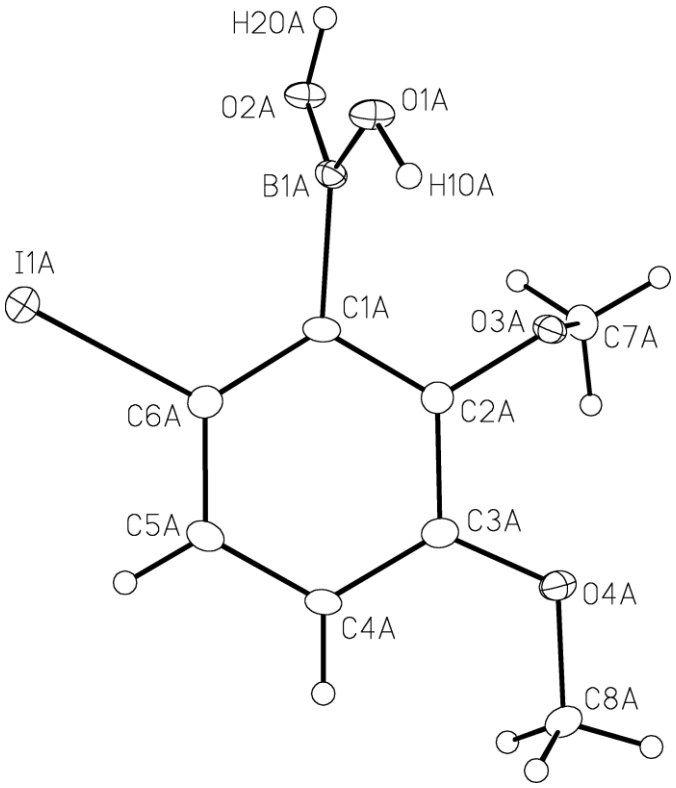
UNIVERSITY OF ALBERTA
X-Ray Crystallography Laboratory
Department of Chemistry • University of Alberta
Edmonton, Alberta T6G 2G2 Canada

Phone: +1 780 492 2485
Fax: +1 780 492 8231
Bob.McDonald@ualberta.ca • Michael.Ferguson@ualberta.ca
http://xray.chem.ualberta.ca/

XCL Code: DGH0822 **Date:** 16 October 2008

Compound: (6-Iodo-2,3-dimethoxyphenyl)boronic acid
Formula: $C_8H_{10}BIO_4$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta

8. X-Ray Crystallography Report of 1,2-diiodo-3-methoxybenzene

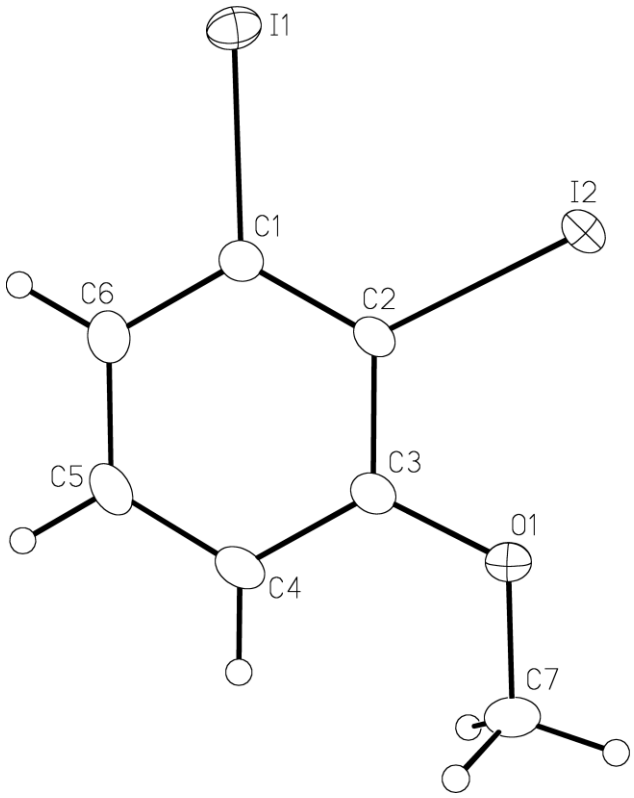
UNIVERSITY OF ALBERTA
X-Ray Crystallography Laboratory
Department of Chemistry • University of Alberta
Edmonton, Alberta T6G 2G2 Canada

Phone: +1 780 492 2485
Fax: +1 780 492 8231
Bob.McDonald@ualberta.ca • Michael.Ferguson@ualberta.ca
http://xray.chem.ualberta.ca/

XCL Code: DGH0819 **Date:** 28 July 2008

Compound: 1,2-diiodo-3-methoxybenzene
Formula: $C_7H_6I_2O$

Supervisor: D. G. Hall **Crystallographer:** M. J. Ferguson



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta

9. X-Ray Crystallography Report of 2-Iodo-3,4,5-Trimethoxyaryl boronic Acid

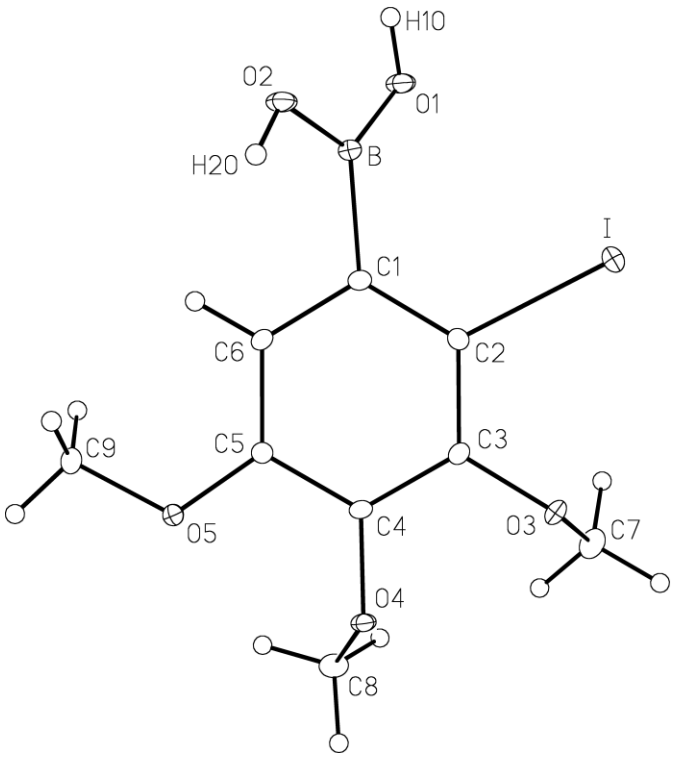
UNIVERSITY OF ALBERTA
X-Ray Crystallography Laboratory
Department of Chemistry • University of Alberta
Edmonton, Alberta T6G 2G2 Canada

Phone: +1 780 492 2485
Fax: +1 780 492 8231
Bob.McDonald@ualberta.ca • Michael.Ferguson@ualberta.ca
http://xray.chem.ualberta.ca/

XCL Code: DGH0903 **Date:** 23 June 2009

Compound: (2-Iodo-3,4,5-trimethoxyphenyl)boronic acid
Formula: $C_9H_{12}BIO_5$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta

10. X-Ray Crystallography Report of 2-Iodo-3,5-Dimethoxy arylboronic Acid

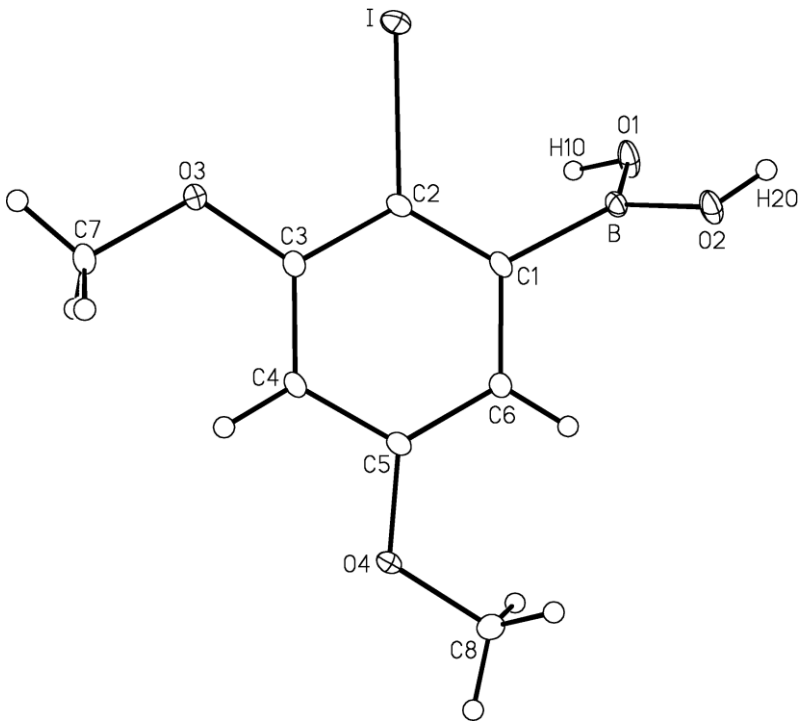
UNIVERSITY OF ALBERTA
X-Ray Crystallography Laboratory
Department of Chemistry • University of Alberta
Edmonton, Alberta T6G 2G2 Canada

Phone: +1 780 492 2485
Fax: +1 780 492 8231
Bob.McDonald@ualberta.ca • Michael.Ferguson@ualberta.ca
http://xray.chem.ualberta.ca/

XCL Code: DGH0905 **Date:** 28 July 2009

Compound: (2-iodo-3,5-dimethoxyphenyl)boronic acid
Formula: $C_8H_{10}BIO_4$

Supervisor: D. G. Hall **Crystallographer:** M. J. Ferguson



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta

11. X-Ray Crystallography Report of *t*-butyl (2-*t*-butyl phenyl)carbamate

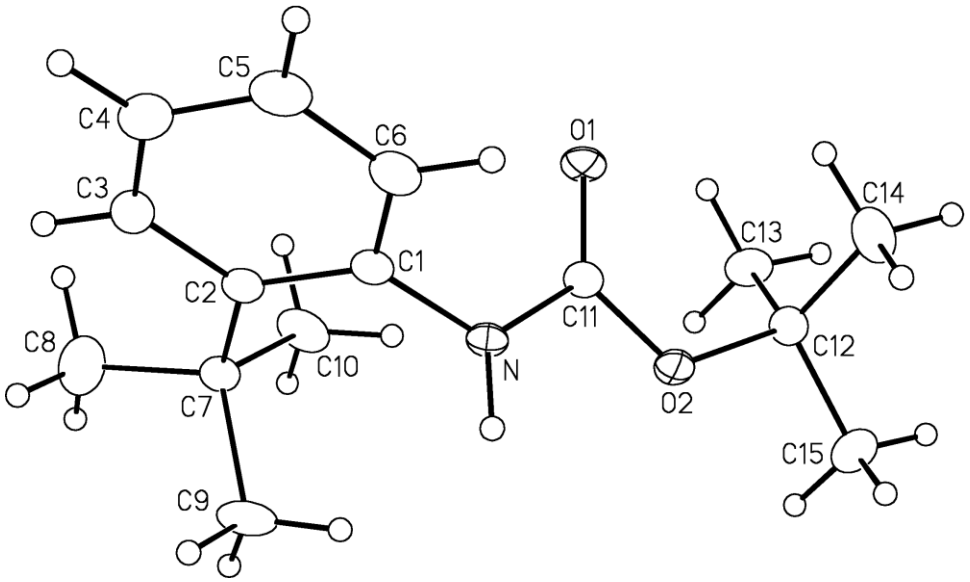
UNIVERSITY OF ALBERTA
X-Ray Crystallography Laboratory
Department of Chemistry • University of Alberta
Edmonton, Alberta T6G 2G2 Canada

Phone: +1 780 492 2485
Fax: +1 780 492 8231
Bob.McDonald@ualberta.ca • Michael.Ferguson@ualberta.ca
http://xray.chem.ualberta.ca/

XCL Code: DGH0816 **Date:** 18 July 2008

Compound: *t*-butyl (2-*t*-butylphenyl)carbamate
Formula: $C_{15}H_{23}NO_2$

Supervisor: D. G. Hall **Crystallographer:** M. J. Ferguson



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta

12. X-Ray Crystallography Report of 1-*tert*-Butyl-2,3 diiodo-5-methylbenzene

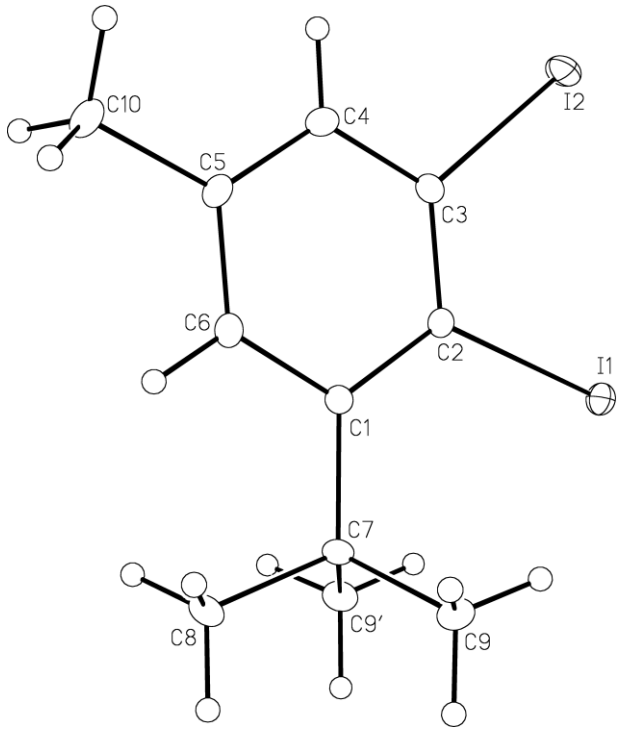
UNIVERSITY OF ALBERTA
X-Ray Crystallography Laboratory
Department of Chemistry • University of Alberta
Edmonton, Alberta T6G 2G2 Canada

Phone: +1 780 492 2485
Fax: +1 780 492 8231
Bob.McDonald@ualberta.ca • Michael.Ferguson@ualberta.ca
http://xray.chem.ualberta.ca/

XCL Code: DGH0824 **Date:** 11 September 2008

Compound: 1-*tert*-butyl-2,3-diiodo-5-methylbenzene
Formula: $C_{11}H_{14}I_2$

Supervisor: D. G. Hall **Crystallographer:** M. J. Ferguson



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta

13. X-Ray Crystallography Report of *tert*-Butyl biphenyl-2-ylcarbamate

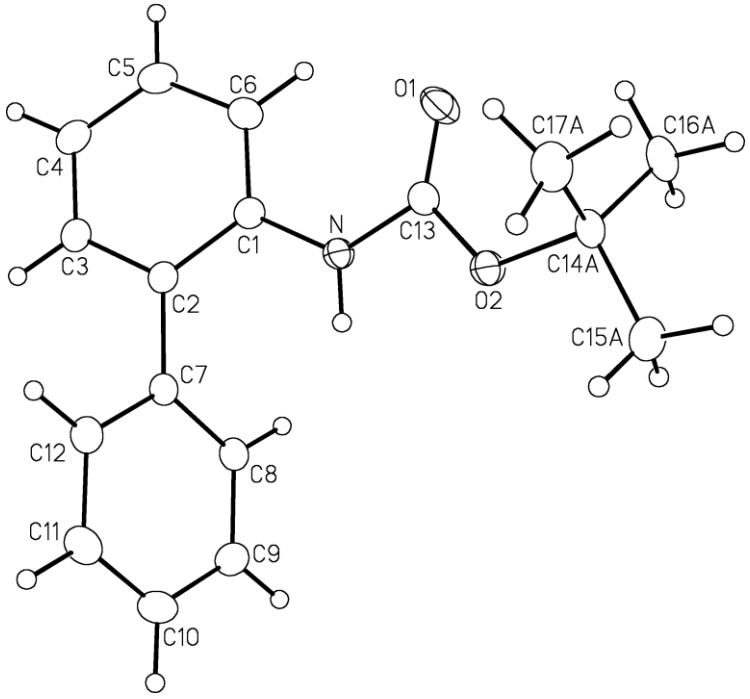
UNIVERSITY OF ALBERTA
X-Ray Crystallography Laboratory
Department of Chemistry • University of Alberta
Edmonton, Alberta T6G 2G2 Canada

Phone: +1 780 492 2485
Fax: +1 780 492 8231
Bob.McDonald@ualberta.ca • Michael.Ferguson@ualberta.ca
http://xray.chem.ualberta.ca/

XCL Code: DGH0815 **Date:** 16 July 2008

Compound: *tert*-butyl biphenyl-2-ylcarbamate
Formula: $C_{17}H_{19}NO_2$

Supervisor: D. G. Hall **Crystallographer:** M. J. Ferguson



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta

14. X-Ray Crystallography Report of 2,6-Anhydro-5-deoxy-1-*C*-(4-nitrophenyl) hexitol

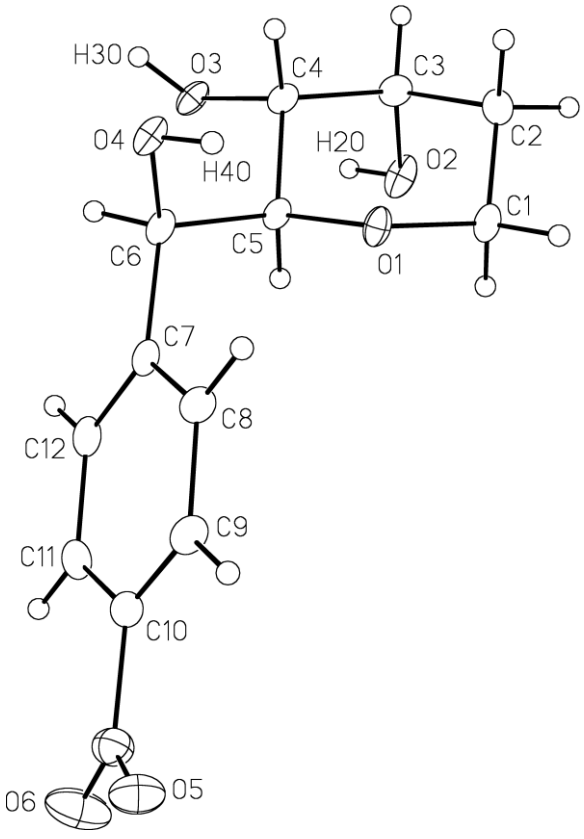
UNIVERSITY OF ALBERTA
X-Ray Crystallography Laboratory
Department of Chemistry • University of Alberta
Edmonton, Alberta T6G 2G2 Canada

Phone: +1 780 492 2485
Fax: +1 780 492 8231
Bob.McDonald@ualberta.ca • Michael.Ferguson@ualberta.ca
http://xray.chem.ualberta.ca/

XCL Code: DGH0913 **Date:** 25 September 2009

Compound: 2,6-Anhydro-5-deoxy-1-*C*-(4-nitrophenyl)hexitol
Formula: $C_{12}H_{15}NO_6$

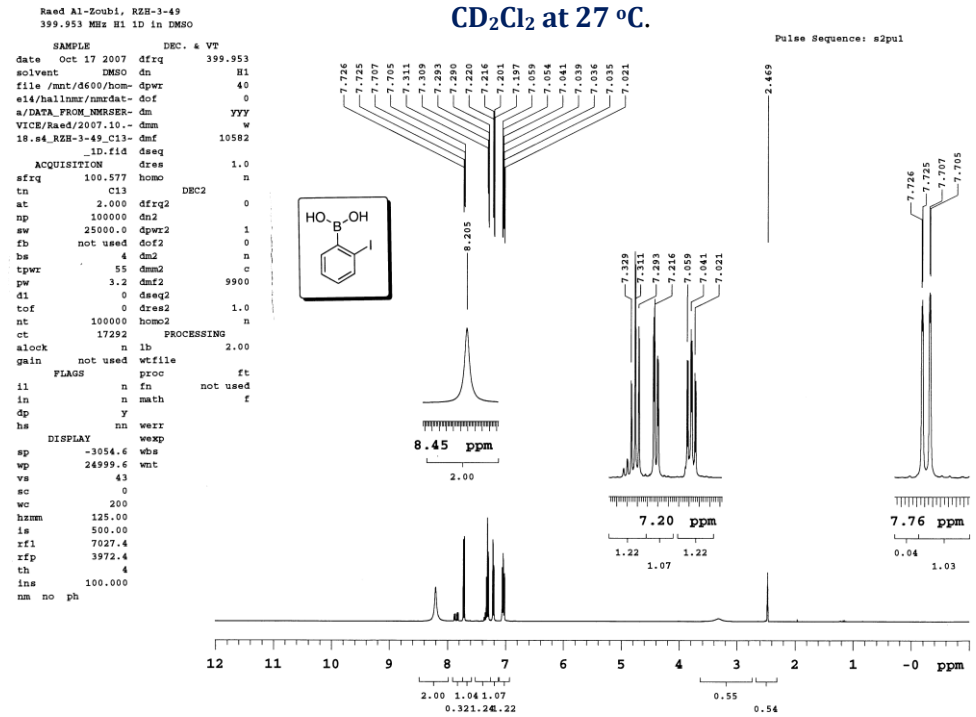
Supervisor: D. G. Hall **Crystallographer:** R. McDonald

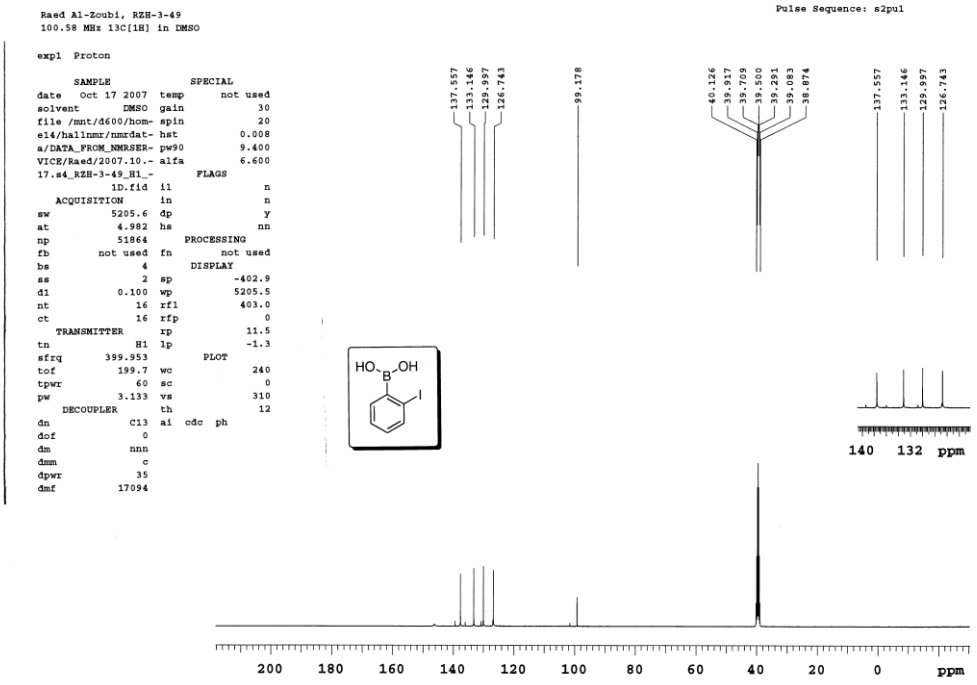


For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta

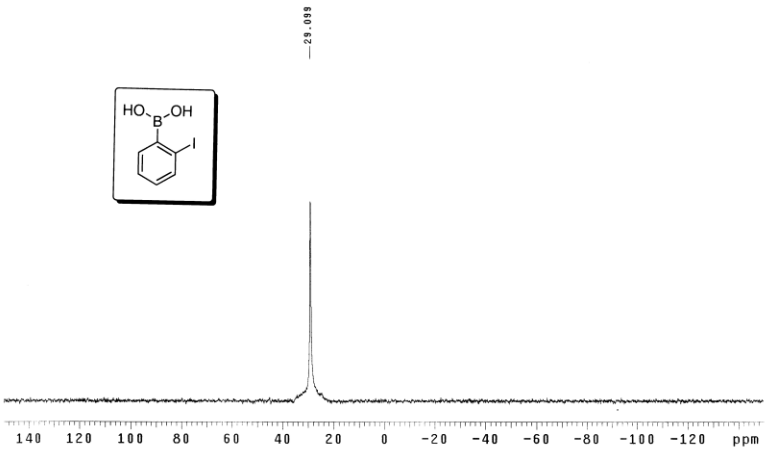
^{1}H & ^{13}C NMR Spectra of Important Compounds

1. ^{1}H- ^{13}C & ^{11}B-NMR of 2-iodophenylboronic acid (IBA) in DMSO-d_6 and CD_2Cl_2 at 27 ^{o}C.



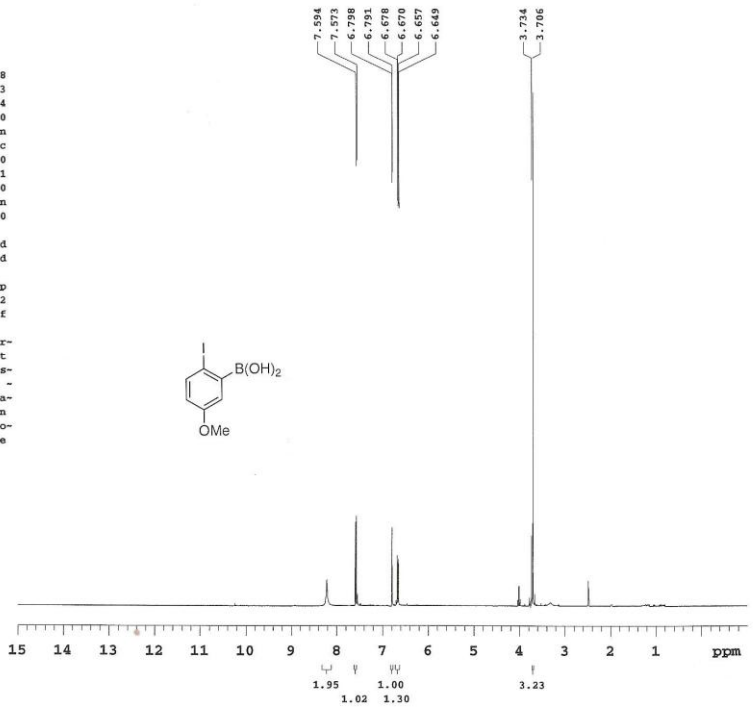


```
Oliver Marion, OMH4-81
128.269 MHz B11[H1] 1D in CD2Cl2

exp5  Boron

      SAMPLE              SPECIAL
date   Oct 10 2007  temp       not used
solvent     cd2cl2  gain         40
file /mnt/d600/hom~ spin       not used
e12/gennmr/nmrdata~ hst          0.008
/HALL/Olivier/2007~ pw90        29.125
.10/2007_10.10.14_~ alfa        10.000
OMH4-81_B11_1D.fid        FLAGS
   ACQUISITION          il             n
sw          38461.5     in             n
at            2.012     dp             y
np           154798     hs            nn
fb        not used      PROCESSING
bs               4      lb         10.00
ss               2      fn       not used
d1           0.100       DISPLAY
nt           1e+06      sp        -19230.5
ct             120      wp         38461.2
   TRANSMITTER          rfl        19230.8
tn             B11      rfp              0
sfrq        128.270     rp           -23.3
tof          2852.8     lp               0
tpwr             60         PLOT
pw            9.708     wc             180
    DECOUPLER          sc               0
dn               H1     vs              47
dof               0     th              17
dm              yyy     nm  cdc  ph
dmm               w
dpwr             40
dmf           11441
```

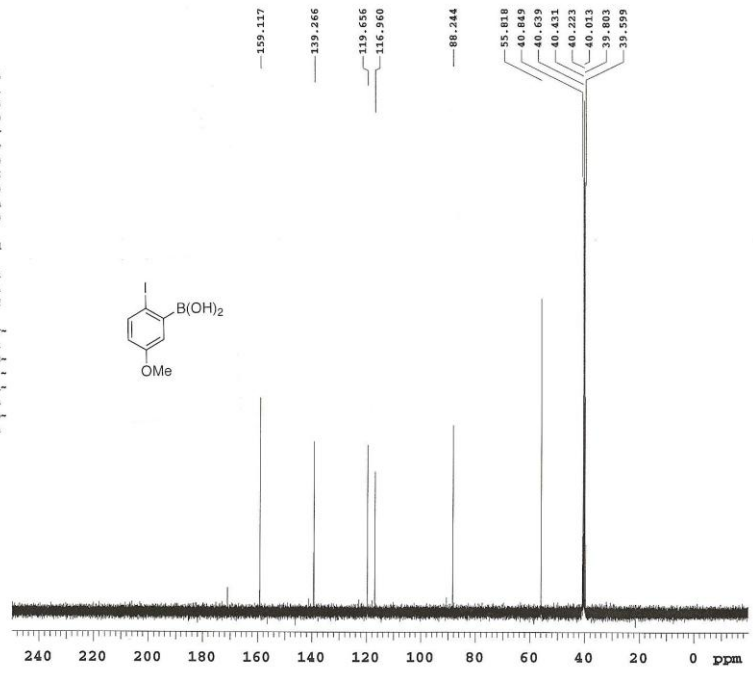


2. ^{1}H- & ^{13}C -NMR of 5-methoxy-2-iodophenylboronic acid (MIBA) in DMSO-d_6 at 27 °C.

```
Raed, RZH-6-84-1
400.395 MHz H1 1D in dmso (ref. to DMSO
@ 2.49 ppm), temp 27.0 C -> actual temp
= 27.0 C, m400gz probe

exp2  H1_1D

      SAMPLE            DEC. & VT
date   Jul 20 2009  dfrq       100.688
solvent       dmso  dn             C13
file /mnt/d600/hom-  dpwr            44
e14/hallnmr/nmrdat-  dof            0.0
a/DATA_FROM_NMRSER-  dm             nnn
VICE/Raed/2009.07/-  dmm              c
2009.07.20.m4_RZH--  dmf          15900
6-84-1_16:22_H1_1D-  dseq         garp1
              .fid   dres           1.0
   ACQUISITION       homo             n
sfrq       400.395  temp          27.0
tn              H1      PROCESSING
at           4.998  gf         not used
np           64030  gfs        not used
sw          6406.1  wtfile
fb            3600  proc             lp
bs               8  fn           131072
ss               2  math              f
tpwr            60
pw             4.5  werr ao_txt restor-
d1           0.100       enode xmreact
tof          776.7  wexp abortoff flus-
nt              32  h procplot ao_txt ~
ct              32  MM_auto_autosave a-
alock            y            borton
gain            22  wbs ao_txt procplo-
     FLAGS          t MM_auto_autosave
il               n  wnt
in               n
dp               y
hs              nn
    DISPLAY
sp          -400.2
wp          6406.1
vs              69
sc               0
wc             180
hzmm         35.59
is          992.06
rfl          400.3
rfp              0
th               8
ins          1.000
ai    ph
```

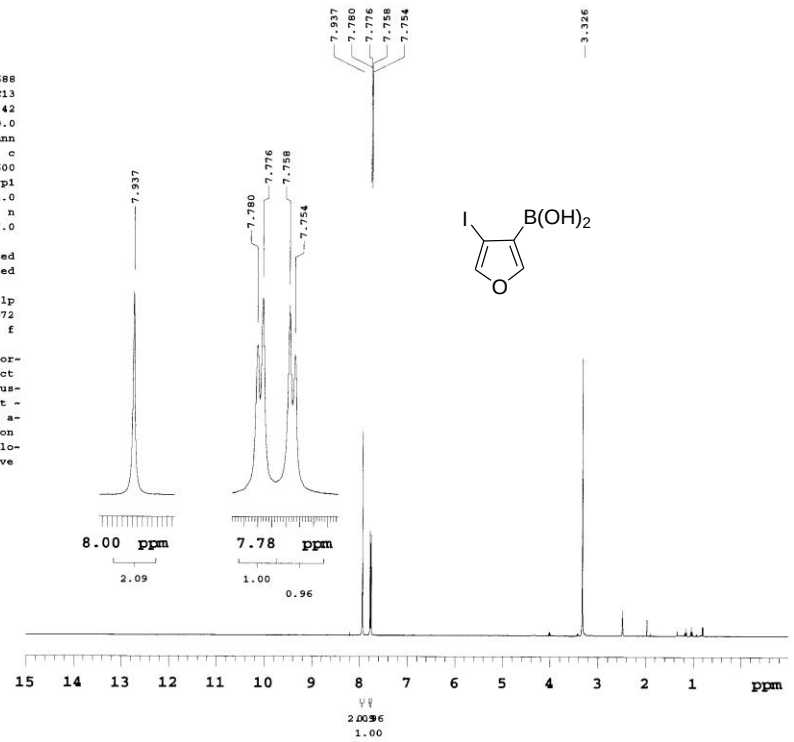



```
Raed, RZH-6-84-1
100.690 MHz C13{H1} 1D in dmso (ref. to
DMSO @ 39.5 ppm), temp 27.0 C -> actual
temp = 27.0 C, m400gz probe

exp3  C13_1D

      SAMPLE            DEC. & VT
date   Jul 20 2009  dfrq       400.394
solvent       dmso  dn              H1
file /mnt/d600/hom-  dpwr            45
e14/hallnmr/nmrdat-  dof            0.0
a/DATA_FROM_NMRSER-  dm             yyy
VICE/Raed/2009.07/-  dmm              w
2009.07.20.m4_RZH--  dmf          11500
6-84-1_16:25_C13_1-  dseq       waltz16
              D.fid  dres           90.0
   ACQUISITION       homo             n
sfrq       100.690  temp          27.0
tn              C13     PROCESSING
at           2.000  lb         not used
np          108696  wtfile
sw         27173.9  proc             ft
fb           15000  fn           262144
bs              32  math              f
ss               2
tpwr            60  werr ao_txt restor-
pw             2.7       enode xmreact
d1           0.100  wexp abortoff flus-
tof         2045.0  h procplot ao_txt ~
nt            1000  MM_auto_autosave a-
ct            1000            borton
alock            y  wbs ao_txt procplo-
gain            30  t MM_auto_autosave
     FLAGS          wnt
il               n
in               n
dp               y
hs              nn
    DISPLAY
sp         -2008.7
wp         27173.7
vs              81
sc               0
wc             180
hzmm        150.97
is         5000.00
rf1         2008.9
rfp              0
th              16
ins         100.000
```

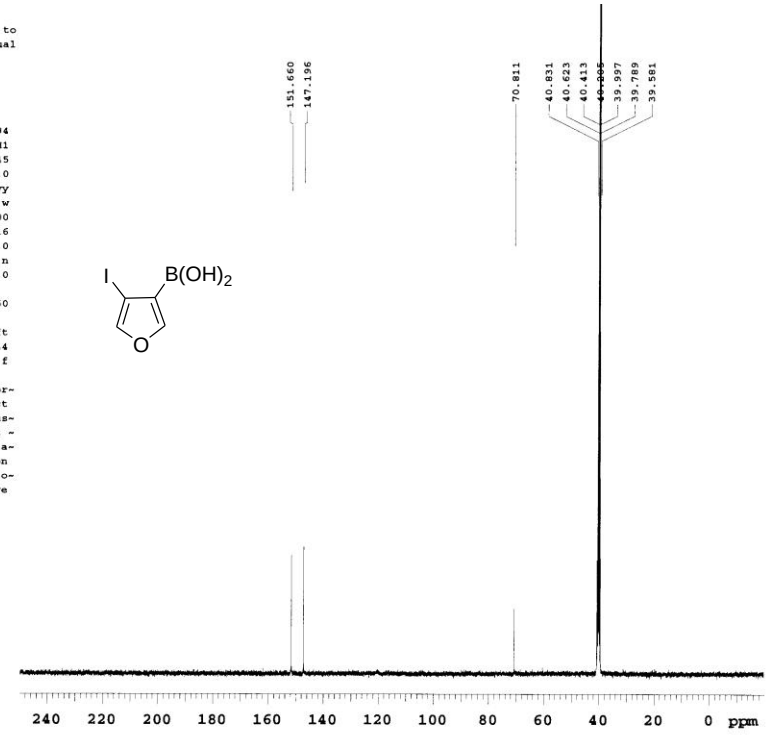


3. ^{1}H- & ^{13}C -NMR of 4-iodo-3-furanboronic acid (FIBA) in DMSO-d_6 at 27 °C.

```
Raed, RZH-6-146-pure
400.395 MHz H1 1D in dmso (ref. to DMSO
@ 2.49 ppm), temp 27.0 C -> actual temp
= 27.0 C, m400gz probe

exp1  H1_1D

      SAMPLE            DEC. & VT
date   Nov 18 2009  dfrq        100.688
solvent       dmso  dn              C13
file /mnt/d600/hom-  dpwr             42
e14/hallnmr/nmrdat-  dof             0.0
a/DATA_FROM_NMRSER-  dm              nnn
VICE/Raed/2009.11/-  dmm               c
2009.11.18.m4_RZH--  dmf           19600
6-146-pure_20.03_H-  dseq          garp1
          1_1D.fid   dres            1.0
   ACQUISITION       homo              n
sfrq       400.395  temp           27.0
tn              H1       PROCESSING
at           4.998  gf         not used
np           64030  gfs        not used
sw          6406.1  wtfile
fb            3600  proc             lp
bs               8  fn           131072
ss               2  math              f
tpwr            60
pw             4.5  werr ao_txt restor-
d1           0.100       enode xmreact
tof          776.7  wexp abortoff flus-
nt              32  h procplot ao_txt -
ct              32  MM_auto_autosave a-
alock            y                borton
gain            22  wbs ao_txt procplo-
      FLAGS         t MM_auto_autosave
il               n  wnt
in               n
dp               y
hs              nn
     DISPLAY
sp          -400.2
wp          6406.1
vs              81
sc               0
wc             180
hzmm         35.59
is         1719.75
rfl         400.3
rfp              0
th              11
ins          1.000
ai    ph
```

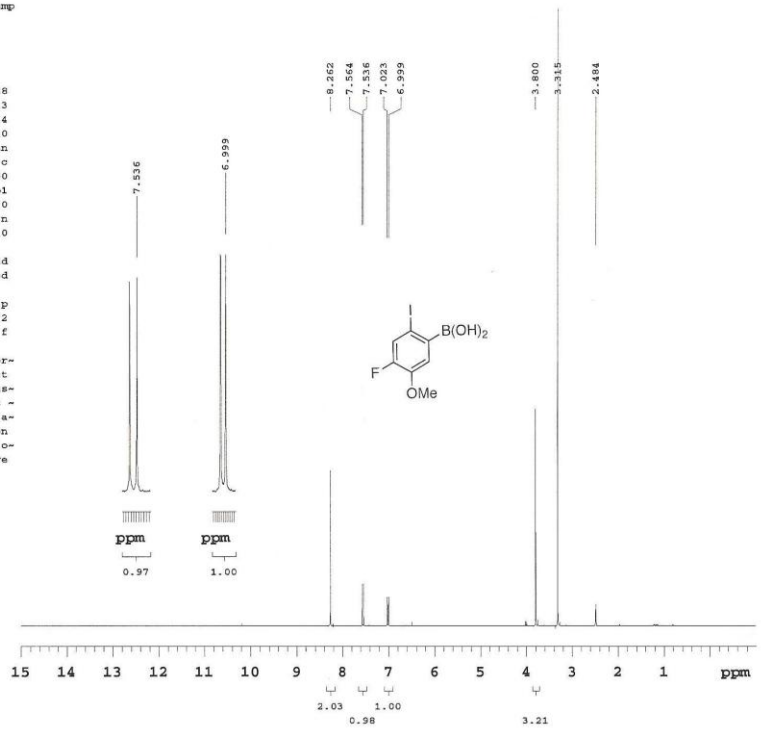



```
Raed, RZH-6-146-pure
100.690 MHz C13{H1} 1D in dmso (ref. to
DMSO @ 39.5 ppm), temp 27.0 C -> actual
temp = 27.0 C, m400gz probe

exp1  C13_1D

      SAMPLE            DEC. & VT
date   Nov 18 2009  dfrq        400.394
solvent       dmso  dn               H1
file /mnt/d600/hom-  dpwr             45
e14/hallnmr/nmrdat-  dof             0.0
a/DATA_FROM_NMRSER-  dm              yyy
VICE/Raed/2009.11/-  dmm               w
2009.11.18.m4_RZH--  dmf           11500
6-146-pure_20.06_C-  dseq        waltz16
         13_1D.fid   dres            90.0
   ACQUISITION       homo              n
sfrq       100.690  temp           27.0
tn              C13      PROCESSING
at           2.000  lb             1.50
np          108696  wtfile
sw         27173.9  proc             ft
fb           15000  fn           262144
bs              32  math              f
ss               2
tpwr            57  werr ao_txt restor-
pw             3.0       enode xmreact
d1           0.100  wexp abortoff flus-
tof         2045.0  h procplot ao_txt -
nt            1000  MM_auto_autosave a-
ct            1000                borton
alock            y  wbs ao_txt procplo-
gain            30  t MM_auto_autosave
      FLAGS         wnt
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp         -2008.7
wp         27173.7
vs             174
sc               0
wc             180
hzmm        150.97
is         5000.00
rfl         2008.9
rfp              0
th              12
ins         100.000
ai    ph
```

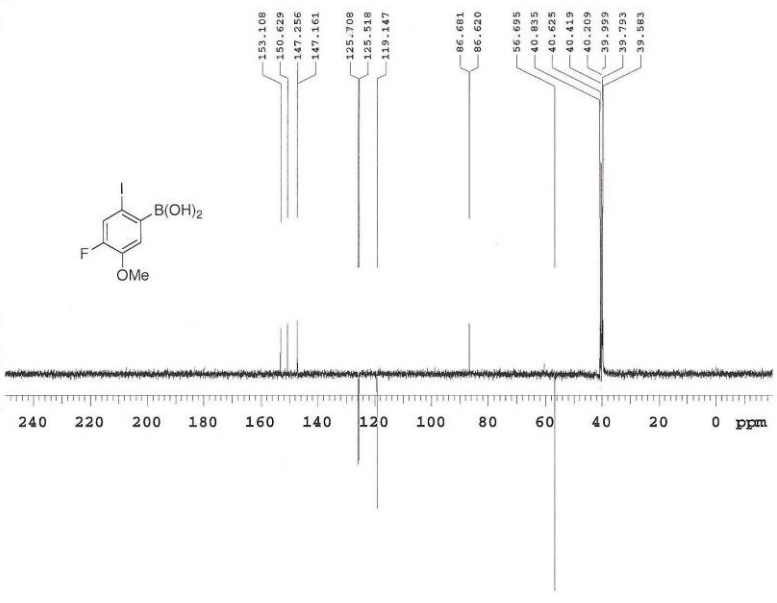


4. ^{1}H- & ^{13}C -NMR of 4-fluoro-2-iodo-5-methoxyphenylboronic acid in DMSO-d_6 at 27 °C.

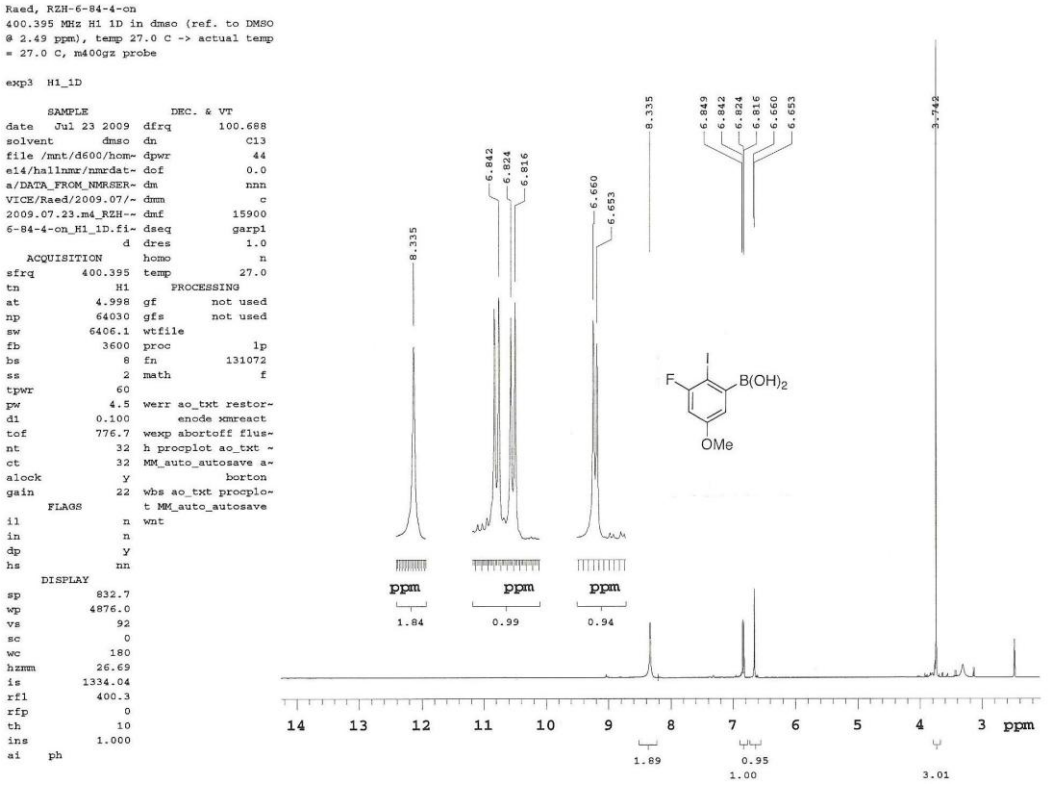
```
Raed, RZH-6-84-5-on
400.395 MHz H1 1D in dmso (ref. to DMSO
@ 2.49 ppm), temp 27.0 C -> actual temp
= 27.0 C, m400gz probe

exp3  H1_1D

      SAMPLE            DEC. & VT
date   Jul 24 2009  dfrq       100.688
solvent       dmso  dn             C13
file /mnt/d600/hom~ dpwr            44
e14/hallnmr/nmrdat~ dof            0.0
s/DATA_FROM_NMRSER~ dm             nnn
VICE/Raed/2009.07/~ dmm              c
2009.07.24.m4_RZH~~ dmf          15900
6-84-5-on_02:17_H1~ dseq         garp1
          _1D.fid   dres           1.0
   ACQUISITION      homo             n
sfrq       400.395  temp          27.0
tn              H1      PROCESSING
at           4.998  gf        not used
np           64030  gfs       not used
sw          6406.1  wtfile
fb            3600  proc             lp
bs               8  fn           131072
ss               2  math              f
tpwr            60
pw             4.5  werr ao_txt restor~
d1           0.100       enode xmreact
tof          776.7  wexp abortoff flus~
nt              16  h procplot ao_txt ~
ct              16  MM_auto_autosave a~
alock            y              borton
gain            22  wbs ao_txt procplo~
      FLAGS         t MM_auto_autosave
il               n  wnt
in               n
dp               y
hs              nn
     DISPLAY
sp          -400.2
wp          6406.1
vs              50
sc               0
wc             180
hzmm         35.59
is         1049.11
rf1          400.3
rfp              0
th               5
ins          1.000
ai    ph
```

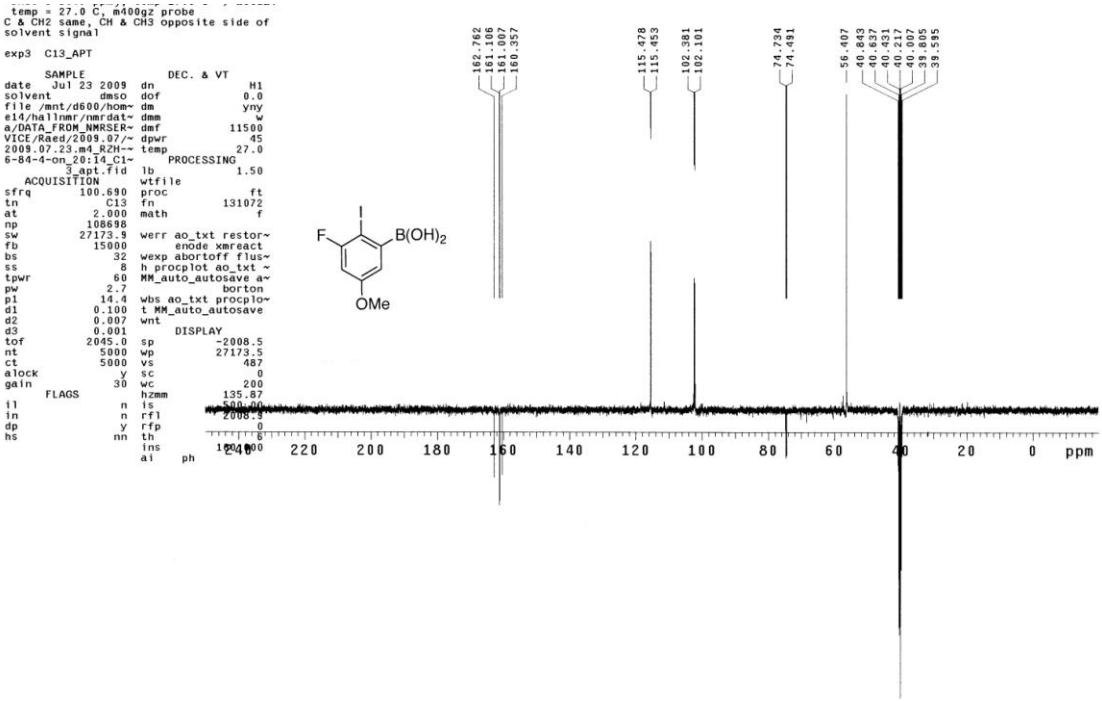



```
Raed, RZH-6-84-5-on
100.690 MHz C13[H1] apt in dmso (ref. to
 DMSO @ 39.5 ppm), temp 27.0 C -> actual
 temp = 27.0 C, m400gz probe
C & CH2 same, CH & CH3 opposite side of
solvent signal

exp3  C13_APT

      SAMPLE            DEC. & VT
date   Jul 24 2009  dn               H1
solvent       dmso  dof             0.0
file /mnt/d600/hom~ dm              yny
e14/hallnmr/nmrdat~ dmm               w
s/DATA_FROM_NMRSER~ dmf           11500
VICE/Raed/2009.07/~ dpwr             45
2009.07.24.m4_RZH~~ temp           27.0
6-84-5-on_02:18_C1~     PROCESSING
         3_apt.fid  lb             1.50
   ACQUISITION      wtfile
sfrq       100.690  proc             ft
tn              C13  fn           131072
at            2.000  math              f
np           108698
sw          27173.9  werr ao_txt restor~
fb            15000       enode xmreact
bs               32  wexp abortoff flus~
ss                8  h procplot ao_txt ~
tpwr             60  MM_auto_autosave a~
pw              2.7              borton
p1             14.4  wbs ao_txt procplo~
d1           0.100  t MM_auto_autosave
d2           0.007  wnt
d3           0.001       DISPLAY
tof         2045.0  sp          -2008.5
nt            5000  wp          27173.5
ct            5000  vs              511
alock            y  sc                0
gain            30  wc              180
      FLAGS         hzmm         150.96
il               n  is           500.00
in               n  rf1          2008.9
dp               y  rfp               0
hs              nn  th                5
                    ins          100.000
```



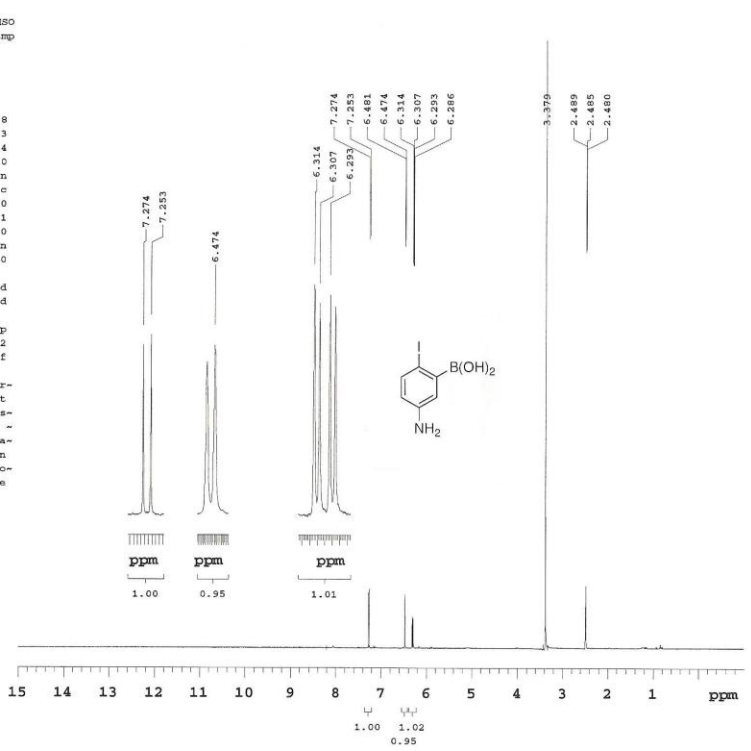
5. ^{1}H- & ^{13}C -NMR of 3-fluoro-2-iodo-5-methoxyphenylboronic acid in DMSO-d_6 at 27 ^{o}C.



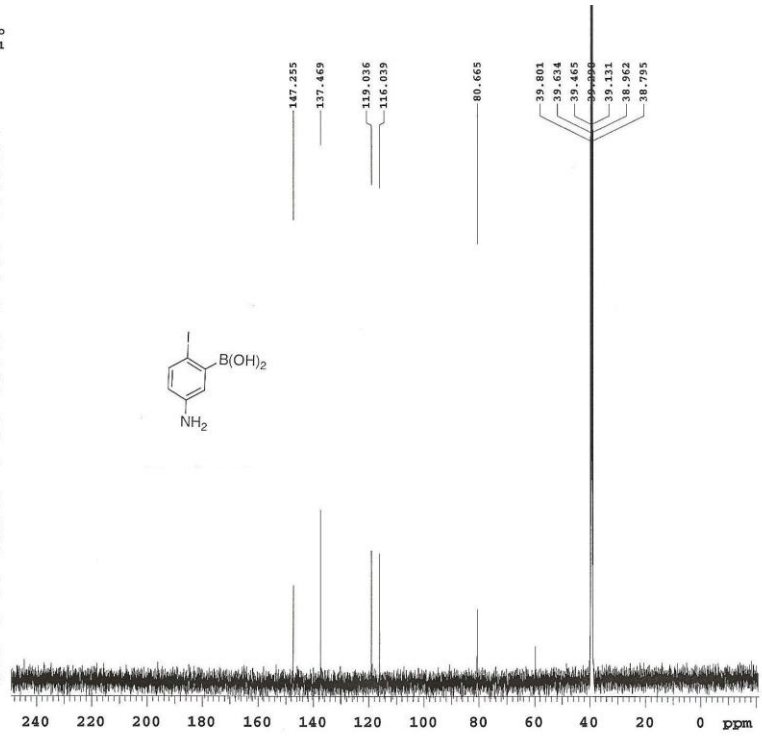


6. ^{1}H- & ^{13}C -NMR of 5-amino-2-iodophenylboronic acid in DMSO-d_6 at 27 ^{o}C.

```
Raed, RZH-6-60-3
400.395 MHz H1 1D in dmso (ref. to DMSO
@ 2.49 ppm), temp 27.0 C -> actual temp
= 27.0 C, m400gz probe

exp3  H1_1D

      SAMPLE
date   Jul  3 2009
solvent       dmso
file /mnt/d600/hom-
e14/hallnmr/nmrdat-
a/DATA_FROM_NMRSER-
VICE/Raed/2009.07/-
2009.07.3.m4_RZH-6-
   -60-3_H1_1D.fid
   ACQUISITION
sfrq       400.395
tn              H1
at           4.998
np           64030
sw          6406.1
fb            3600
bs               8
ss               2
tpwr            60
pw             4.5
d1           0.100
tof          776.7
nt              32
ct              32
alock            y
gain            22
      FLAGS
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp          -400.2
wp          6406.1
vs             143
sc               0
wc             180
hzmm         26.69
is         2452.43
rfl          400.3
rfp              0
th               6
ins          1.000
ai    ph

      DEC. & VT
dfrq       100.688
dn              C13
dpwr             44
dof             0.0
dm              nnn
dmm               c
dmf           15900
dseq          garp1
dres            1.0
homo              n
temp           27.0
     PROCESSING
gf          not used
gfs         not used
wtfile
proc              lp
fn            131072
math               f

werr ao_txt restor-
     enode xmreact
wexp abortoff flus-
h procplot ao_txt ~
MM_auto_autosave a-
               borton
wbs ao_txt procplo-
t MM_auto_autosave
wnt
```

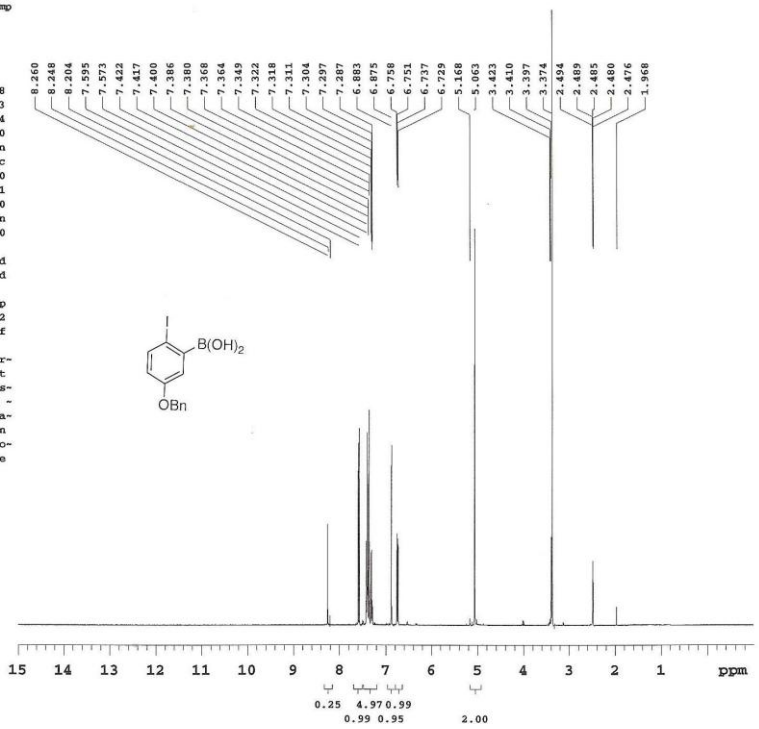



```
RZH-6-60-3-13C-DMSO
125.265 MHz C13{H1} 1D in dmso (ref. to
DMSO @ 39.5 ppm), temp 27.2 C -> actual
temp = 27.0 C, autoxdb probe

exp2  s2pul

      SAMPLE
date   Jun 22 2009
solvent       dmso
file           exp
   ACQUISITION
sfrq       125.267
tn              C13
at           2.495
np          168776
sw         33826.6
fb        not used
bs               4
ss               2
tpwr            53
pw             3.4
d1           0.100
tof         2500.0
nt          100000
ct             508
alock            n
gain            48
      FLAGS
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp         -2618.0
wp         33826.4
vs             949
sc               0
wc             180
hzmm        187.92
is         5000.00
rfl         7566.3
rfp         4948.1
th              12
ins        100.000
nm    ph

      DEC. & VT
dfrq       498.124
dn              H1
dpwr             40
dof               0
dm              yyy
dmm               w
dmf            8500
dseq
dres            1.0
homo              n
temp           26.1
      DEC2
dfrq2             0
dn2
dpwr2             1
dof2              0
dm2               n
dmm2              c
dmf2            200
dseq2
dres2           1.0
homo2             n
      DEC3
dfrq3             0
dn3
dpwr3             1
dof3              0
dm3               n
dmm3              c
dmf3          12500
dseq3
dres3           1.0
homo3             n
     PROCESSING
lb             1.50
wtfile
proc             ft
fn           262144
math              f

werr
wexp
wbs
```

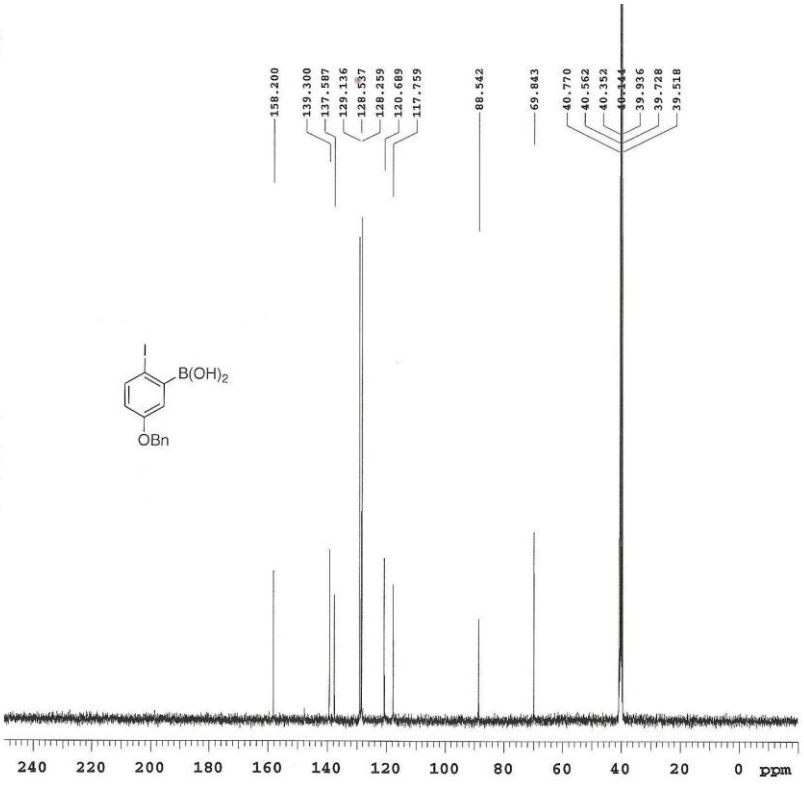


7. ^{1}H- & ^{13}C -NMR of 4-fluoro-5-(benzyloxy)-2-iodophenylboronic acid in DMSO-d_6 at 27 °C.

```
Raed, RZH-6-60-2
400.395 MHz H1 1D in dmso (ref. to DMSO
@ 2.49 ppm), temp 27.0 C -> actual temp
= 27.0 C, m400gz probe

exp1  H1_1D

      SAMPLE              DEC. & VT
date   Jul  3 2009  dfrq        100.688
solvent       dmso  dn              C13
file /mnt/d600/hom-  dpwr             44
e14/hallnmr/nmrdat-  dof             0.0
a/DATA_FROM_NMRSER-  dm              nnn
VICE/Raed/2009.07/-  dmm               c
2009.07.3.m4_RZH-6-  dmf           15900
-60-2_12:32_H1_1D.-  dseq          garp1
                fid  dres            1.0
   ACQUISITION       homo              n
sfrq        400.395  temp           27.0
tn               H1      PROCESSING
at             4.998  gf         not used
np             64030  gfs        not used
sw            6406.1  wtfile
fb              3600  proc             lp
bs                 8  fn           131072
ss                 2  math              f
tpwr              60
pw               4.5  werr ao_txt restor-
d1             0.100       enode xmreact
tof            776.7  wexp abortoff flus-
nt                32  h procplot ao_txt -
ct                32  MM_auto_autosave a-
alock              y                borton
gain              22  wbs ao_txt procplo-
      FLAGS           t MM_auto_autosave
il                 n  wnt
in                 n
dp                 y
hs                nn
     DISPLAY
sp            -400.2
wp            6406.1
vs               162
sc                 0
wc               180
hzmm           35.59
is            977.61
rf1            400.3
rfp                0
th                 2
ins            2.000
ai    ph
```




```
Raed, RZH-6-60-2
100.690 MHz C13[H1] 1D in dmso (ref. to
DMSO @ 39.5 ppm), temp 27.0 C -> actual
temp = 27.0 C, m400gz probe

exp1  C13_1D

      SAMPLE              DEC. & VT
date   Jul  3 2009  dfrq        400.394
solvent       dmso  dn               H1
file /mnt/d600/hom-  dpwr             45
e14/hallnmr/nmrdat-  dof             0.0
a/DATA_FROM_NMRSER-  dm              yyy
VICE/Raed/2009.07/-  dmm               w
2009.07.3.m4_RZH-6-  dmf           11500
-60-2_12:35_C13_1D-  dseq       waltz16
             .fid    dres           90.0
   ACQUISITION       homo              n
sfrq        100.690  temp           27.0
tn               C13      PROCESSING
at             2.000  lb             1.50
np            108696  wtfile
sw           27173.9  proc             ft
fb             15000  fn           262144
bs                32  math              f
ss                 2
tpwr              60  werr ao_txt restor-
pw               2.7       enode xmreact
d1             0.100  wexp abortoff flus-
tof           2040.0  h procplot ao_txt -
nt              1000  MM_auto_autosave a-
ct              1000                borton
alock              y  wbs ao_txt procplo-
gain              30  t MM_auto_autosave
      FLAGS           wnt
il                 n
in                 n
dp                 y
hs                nn
     DISPLAY
sp           -2013.7
wp           27173.7
vs               285
sc                 0
wc               180
hzmm          150.97
is           5000.00
rf1           2013.9
rfp                0
th                11
ins          100.000
```

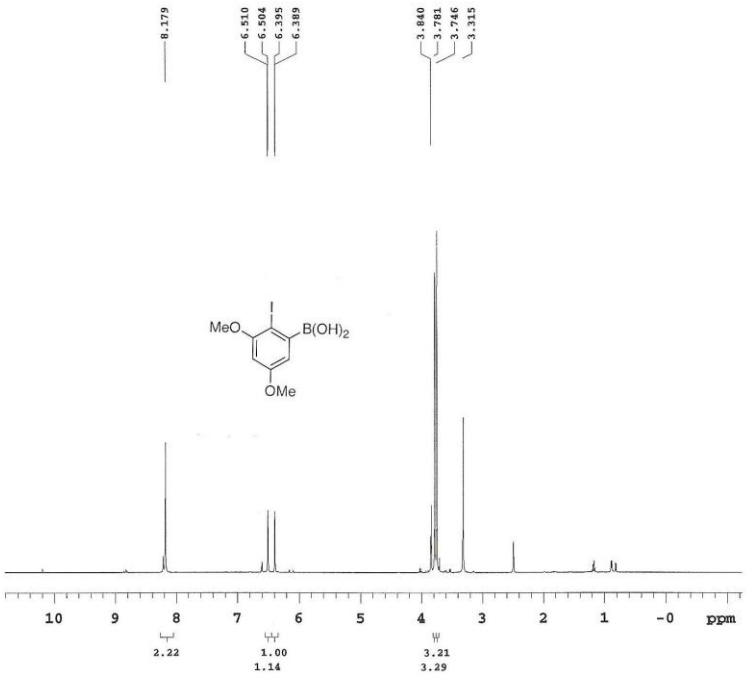


8. ^{1}H- & ^{13}C -NMR of 2-iodo-3,5-dimethoxyphenylboronic acid in DMSO-d_6 at 27 °C.

RZH-6-84-2-1H-DMSO
498.124 MHz H1 1D in dmso (ref. to DMSO @ 2.49 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

exp2 s2pul

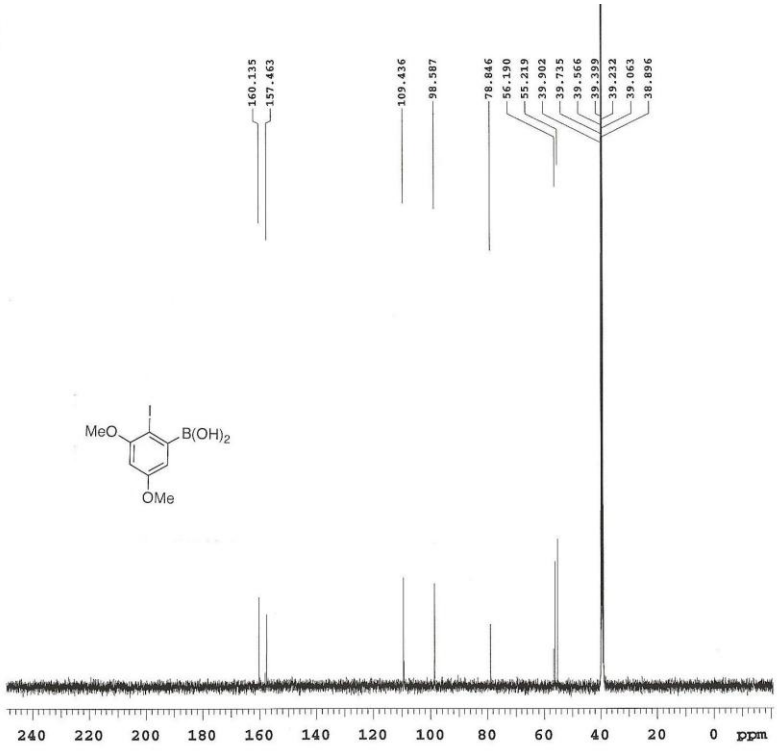
SAMPLE		DEC. & VT	
date	Jul 21 2009	dfrq	498.124
solvent	dmso	dn	H1
file	exp	dpwr	not used
ACQUISITION		dof	0
sfrq	498.124	dm	nnn
tn	H1	dmm	c
at	5.000	dmf	200
np	60002	dseq	
sw	6000.6	dres	1.0
fb	not used	homo	y
bs	4	temp	26.1
ss	2	DEC2	
tpwr	60	dfrq2	0
pw	5.9	dn2	
d1	0.100	dpwr2	1
tof	-100.0	dof2	0
nt	16	dm2	n
ct	16	dmm2	c
alock	n	dmf2	200
gain	32	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	DEC3	
dp	y	dfrq3	0
hs	nn	dn3	
DISPLAY		dpwr3	1
sp	-616.9	dof3	0
wp	6000.5	dm3	n
vs	84	dmm3	c
sc	0	dmf3	200
wc	180	dseq3	
hzmm	33.34	dres3	1.0
is	629.21	homo3	n
rf1	1857.3	PROCESSING	
rfp	1240.3	gf	not used
th	10	gfs	not used
ins	1.000	wtfile	
nm	ph	proc	lp
		fn	131072
		math	f
		werr	
		wexp	
		wbs	
		wnt	wft



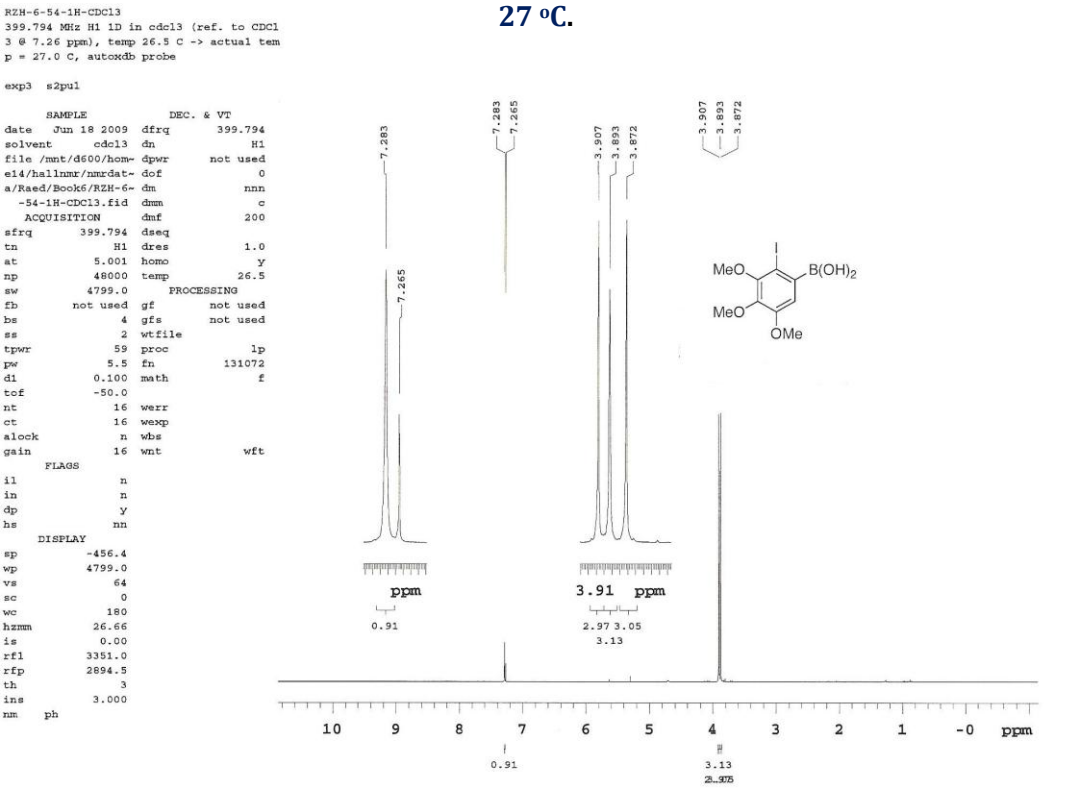
RZH-6-84-2-13C-DMSO
125.265 MHz C13[H1] 1D in dmso (ref. to DMSO @ 39.5 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

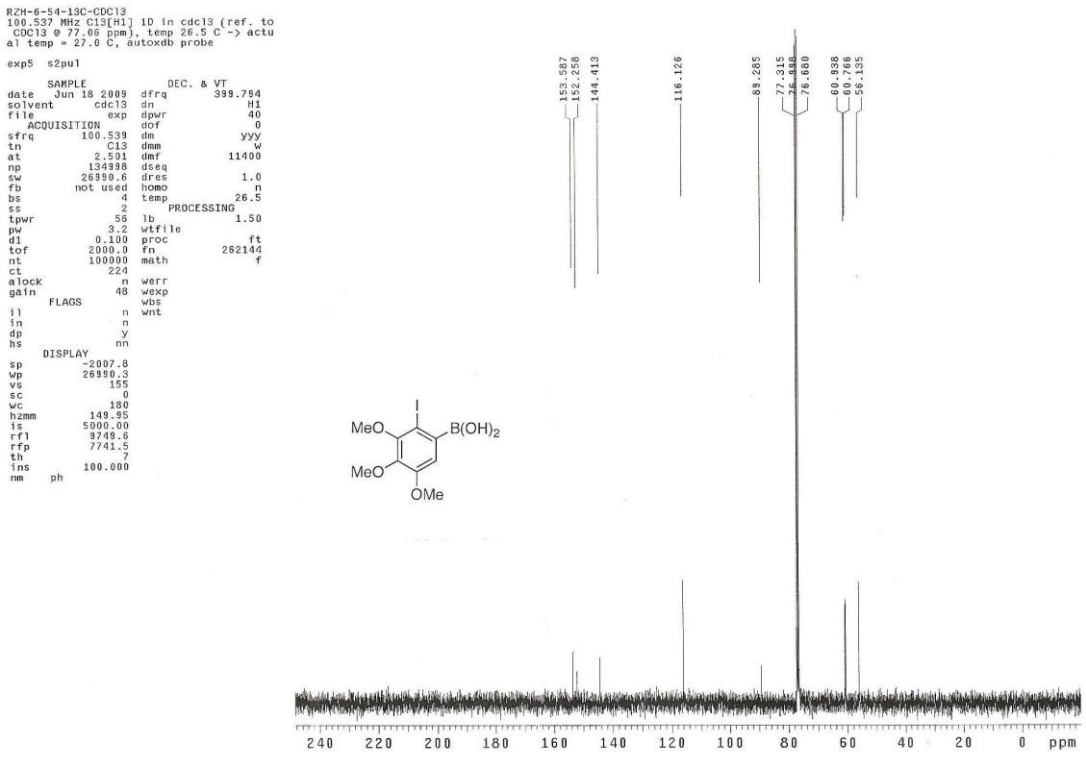
exp3 s2pul

SAMPLE		DEC. & VT	
date	Jul 21 2009	dfrq	498.124
solvent	dmso	dn	H1
file	exp	dpwr	40
ACQUISITION		dof	0
sfrq	125.267	dm	yyy
tn	C13	dmm	w
at	2.495	dmf	8500
np	168776	dseq	
sw	33826.6	dres	1.0
fb	not used	homo	n
bs	4	temp	26.1
ss	2	DEC2	
tpwr	53	dfrq2	0
pw	3.4	dn2	
d1	0.100	dpwr2	1
tof	2500.0	dof2	0
nt	100000	dm2	n
ct	212	dmm2	c
alock	n	dmf2	200
gain	48	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	DEC3	
dp	y	dfrq3	0
hs	nn	dn3	
DISPLAY		dpwr3	1
sp	-2618.0	dof3	0
wp	33826.4	dm3	n
vs	302	dmm3	c
sc	0	dmf3	12500
wc	180	dseq3	
hzmm	187.92	dres3	1.0
is	5000.00	homo3	n
rf1	7566.3	PROCESSING	
rfp	4948.1	lb	1.50
th	12	wtfile	
ins	100.000	proc	ft
nm	ph	fn	262144
		math	f
		werr	
		wexp	
		wbs	



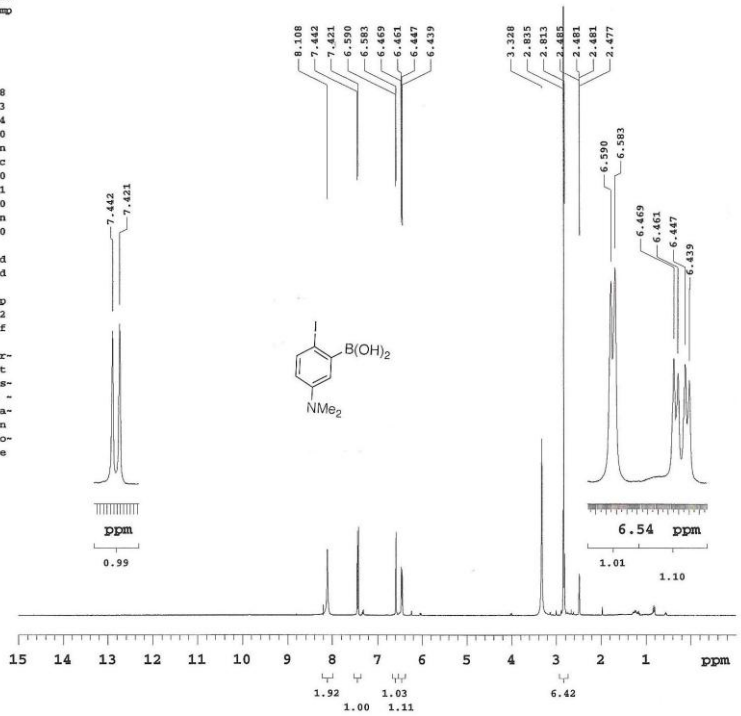
9. ^{1}H-& ^{13}C -NMR of 2-iodo-3,4,5-trimethoxyphenylboronic acid in DMSO-d_6 at 27 ^{o}C.



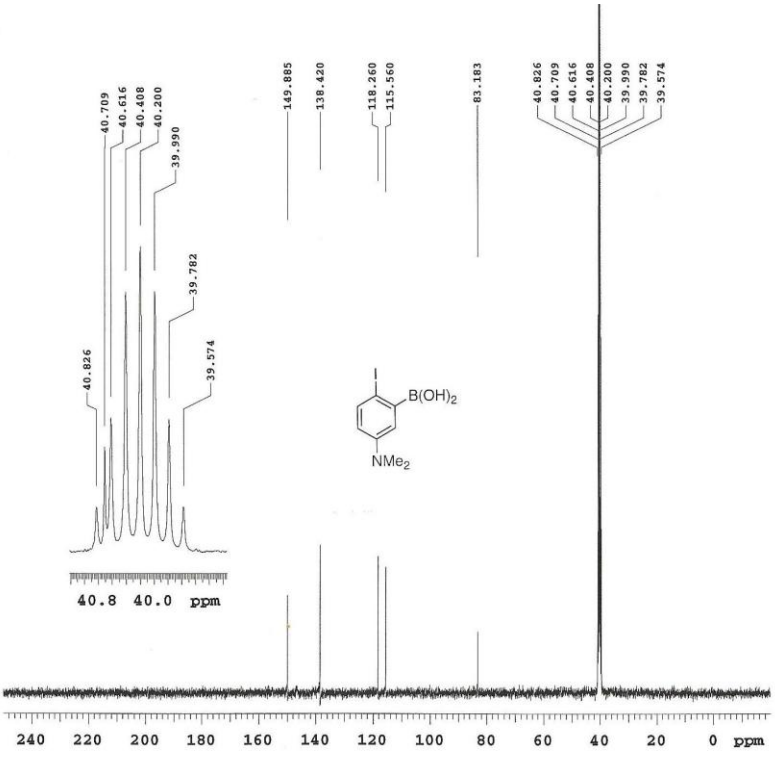


10. ^{1}H- & ^{13}C -NMR of 5-(dimethylamino)-2-iodophenylboronic acid in DMSO-d_6 at 27 ^{o}C.

```
Raed, RZH-6-86
400.395 MHz H1 1D in dmso (ref. to DMSO
@ 2.49 ppm), temp 27.0 C -> actual temp
= 27.0 C, m400gz probe

exp2  H1_1D

      SAMPLE            DEC. & VT
date    Jul 22 2009  dfrq       100.688
solvent       dmso   dn             C13
file /mnt/d600/hom-  dpwr            44
e14/hallnmr/nmrdat-  dof            0.0
a/DATA_FROM_NMRSER-  dm             nnn
VICE/Raed/2009.07/-  dmm              c
2009.07.22.m4_RZH--  dmf          15900
6-86_14:26_H1_1D.f-  dseq         garp1
               id    dres           1.0
   ACQUISITION      homo             n
sfrq       400.395  temp          27.0
tn              H1      PROCESSING
at           4.998  gf         not used
np           64030  gfs        not used
sw          6406.1  wtfile
fb            3600  proc             lp
bs               8  fn           131072
ss               2  math              f
tpwr            60
pw             4.5  werr ao_txt restor-
d1           0.100       enode xmreact
tof          776.7  wexp abortoff flus-
nt              32  h procplot ao_txt -
ct              32  MM_auto_autosave a-
alock            y               borton
gain            22  wbs ao_txt procplo-
      FLAGS         t MM_auto_autosave
il               n  wnt
in               n
dp               y
hs              nn
     DISPLAY
sp          -400.2
wp          6406.1
vs             152
sc               0
wc             180
hzmm         35.59
is          710.06
rfl          400.3
rfp              0
th               7
ins          1.000
ai    ph
```

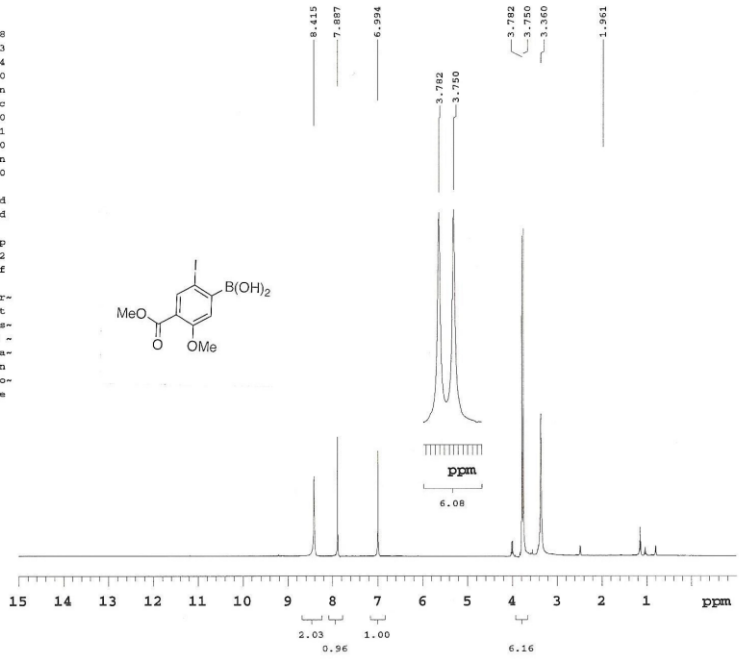



```
Raed, RZH-6-86
100.690 MHz C13[H1] 1D in dmso (ref. to
DMSO @ 39.5 ppm), temp 27.0 C -> actual
temp = 27.0 C, m400gz probe

exp2  C13_1D

      SAMPLE            DEC. & VT
date    Jul 22 2009  dfrq       400.394
solvent       dmso   dn              H1
file /mnt/d600/hom-  dpwr            45
e14/hallnmr/nmrdat-  dof            0.0
a/DATA_FROM_NMRSER-  dm             yyy
VICE/Raed/2009.07/-  dmm              w
2009.07.22.m4_RZH--  dmf          11500
6-86_14:29_C13_1D.-  dseq       waltz16
               fid   dres           90.0
   ACQUISITION      homo             n
sfrq       100.690  temp          27.0
tn              C13     PROCESSING
at           2.000  lb            1.50
np          108696  wtfile
sw         27173.9  proc             ft
fb           15000  fn           262144
bs              32  math              f
ss               2
tpwr            60  werr ao_txt restor-
pw             2.7       enode xmreact
d1           0.100  wexp abortoff flus-
tof         2045.0  h procplot ao_txt -
nt            1000  MM_auto_autosave a-
ct            1000               borton
alock            y  wbs ao_txt procplo-
gain            30  t MM_auto_autosave
      FLAGS         wnt
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp          -2008.7
wp         27173.7
vs             270
sc               0
wc             180
hzmm        150.97
is         5000.00
rfl         2008.9
rfp              0
th               6
ins        100.000
ai    ph
```

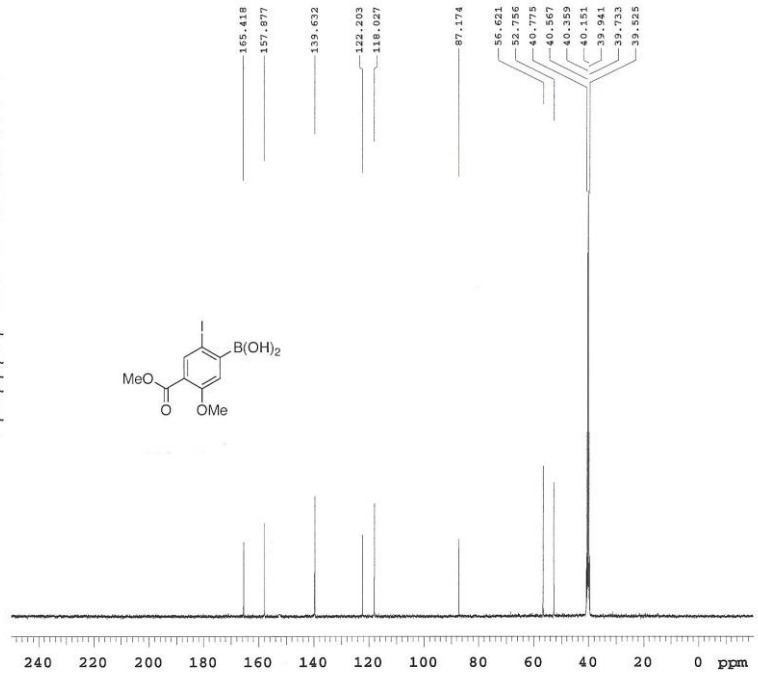


11. ^{1}H- & ^{13}C -NMR of 4-(methoxycarbonyl)-2-iodo-methoxyphenyl boronic acid in DMSO-d_6 at 27 ^{o}C.

```
Raed, RZH-6-71
400.395 MHz H1 1D in dmso (ref. to DMSO
@ 2.49 ppm), temp 27.0 C -> actual temp
= 27.0 C, m400gz probe

exp3  H1_1D

      SAMPLE            DEC. & VT
date   Jul  7 2009  dfrq       100.688
solvent       dmso  dn             C13
file /mnt/d600/hom~ dpwr            44
e14/hallnmr/nmrdat~ dof            0.0
a/DATA_FROM_NMRSER~ dm             nnn
VICE/Raed/2009.07/~ dmm              c
2009.07.7.m4_RZH-6~ dmf          15900
     ~71_H1_1D.fid  dseq         garp1
   ACQUISITION      dres           1.0
sfrq       400.395  homo             n
tn              H1  temp          27.0
at           4.998      PROCESSING
np           64030  gf         not used
sw          6406.1  gfs        not used
fb            3600  wtfile
bs               8  proc             lp
ss               2  fn           131072
tpwr            60  math              f
pw             4.5
d1           0.100  werr ao_txt restor~
tof          776.7       enode xmreact
nt              32  wexp abortoff flus~
ct              32  h procplot ao_txt ~
alock            y  MM_auto_autosave a~
gain            22                borton
      FLAGS         wbs ao_txt procplo~
il               n  t MM_auto_autosave
in               n  wnt
dp               y
hs              nn
    DISPLAY
sp          -400.2
wp          6406.1
vs              60
sc               0
wc             180
hzmm         35.59
is          404.87
rfl          400.3
rfp              0
th               9
ins          1.000
ai    ph
```




```
Raed, RZH-6-71
100.690 MHz C13[H1] 1D in dmso (ref. to
DMSO @ 39.5 ppm), temp 27.0 C -> actual
temp = 27.0 C, m400gz probe

exp3  C13_1D

      SAMPLE            DEC. & VT
date   Jul  7 2009  dfrq       400.394
solvent       dmso  dn              H1
file /mnt/d600/hom~ dpwr            45
e14/hallnmr/nmrdat~ dof            0.0
a/DATA_FROM_NMRSER~ dm             YYY
VICE/Raed/2009.07/~ dmm              w
2009.07.7.m4_RZH-6~ dmf          11500
    ~71_C13_1D.fid  dseq       waltz16
   ACQUISITION      dres          90.0
sfrq       100.690  homo             n
tn              C13  temp          27.0
at            2.000      PROCESSING
np           108696  lb            1.50
sw          27173.9  wtfile
fb            15000  proc             ft
bs               32  fn           262144
ss               2  math              f
tpwr            60
pw             2.7  werr ao_txt restor~
d1           0.100       enode xmreact
tof         2045.0  wexp abortoff flus~
nt            1000  h procplot ao_txt ~
ct            1000  MM_auto_autosave a~
alock            y                borton
gain            30  wbs ao_txt procplo~
      FLAGS         t MM_auto_autosave
il               n  wnt
in               n
dp               y
hs              nn
    DISPLAY
sp          -2008.7
wp          27173.7
vs              105
sc                0
wc              180
hzmm         150.97
is          5000.00
rfl          2008.9
rfp               0
th               10
ins          100.000
ai    ph
```

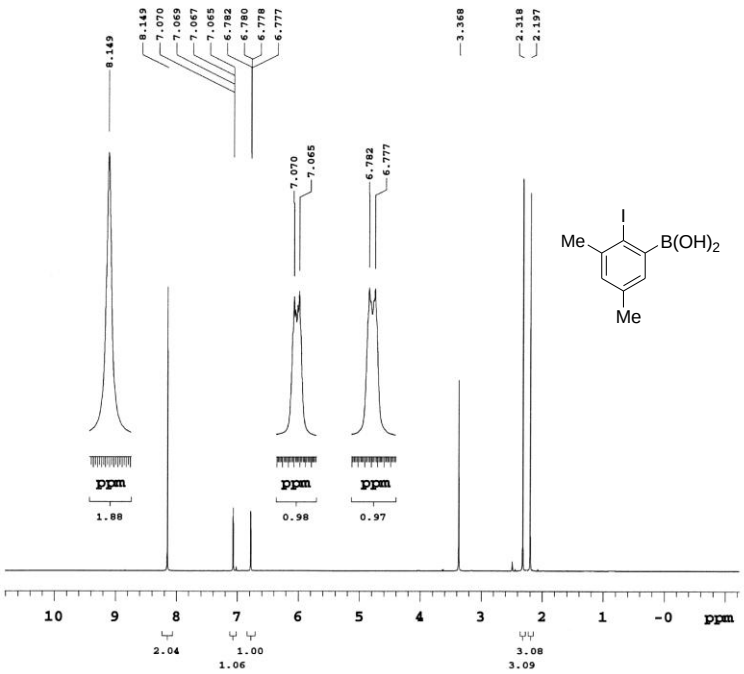


12. ^{1}H- & ^{13}C -NMR of 3,5-dimethyl-2-iodophenylboronic acid in DMSO-d_6 at 27 ^{o}C.

RZH-6-192-1H-DMSO
498.124 MHz H1 1D in dmso (ref. to DMSO @ 2.49 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

exp1 s2pul

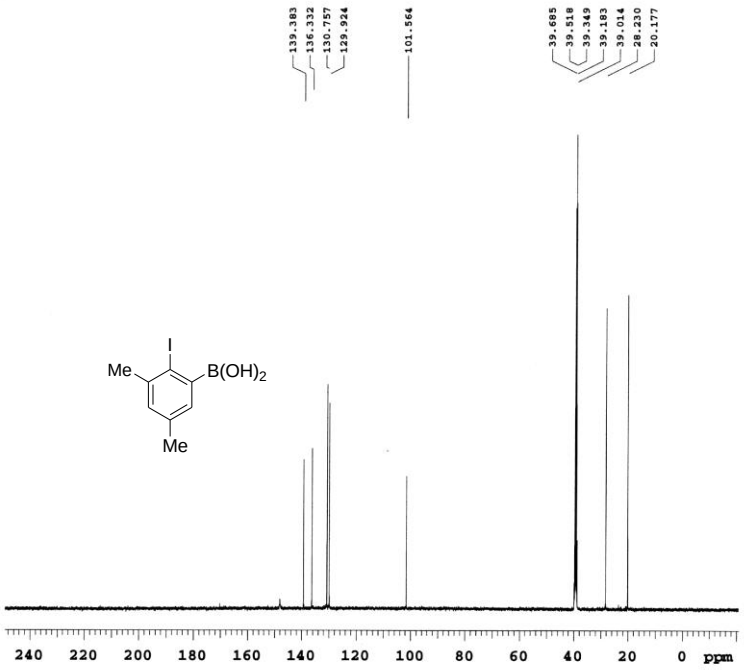
SAMPLE		DEC. & VT	
date	Apr 22 2010	dfrq	498.124
solvent	dmso	dn	H1
file	/mnt/d600/hom-	dpwr	not used
e14/hallnmr/nmrdat-		dof	0
a/Raed/Book6/RZH-6-		dm	nnn
-192-1H-DMSO.fid		dmm	c
ACQUISITION		dmf	200
sfrq	498.124	dseq	
tn	H1	dres	1.0
at	5.000	homo	y
np	60002	temp	26.1
sw	6000.6	PROCESSING	
fb	not used	gf	not used
bs	4	gfs	not used
ss	2	wtfile	
tpwr	60	proc	lp
pw	5.9	fn	131072
d1	0.100	math	f
tof	-100.0		
nt	16	werr	
ct	16	wexp	
alock	n	wbs	
gain	32	wnt	wft
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-616.9		
wp	6000.5		
vs	97		
sc	0		
wc	180		
hzmm	33.34		
is	234.32		
rfl	1857.3		
rfp	1240.3		
th	11		
ins	1.000		
nm	ph		



RZH-6-192-13C-DMSO
125.265 MHz C13[H1] 1D in dmso (ref. to DMSO @ 39.5 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

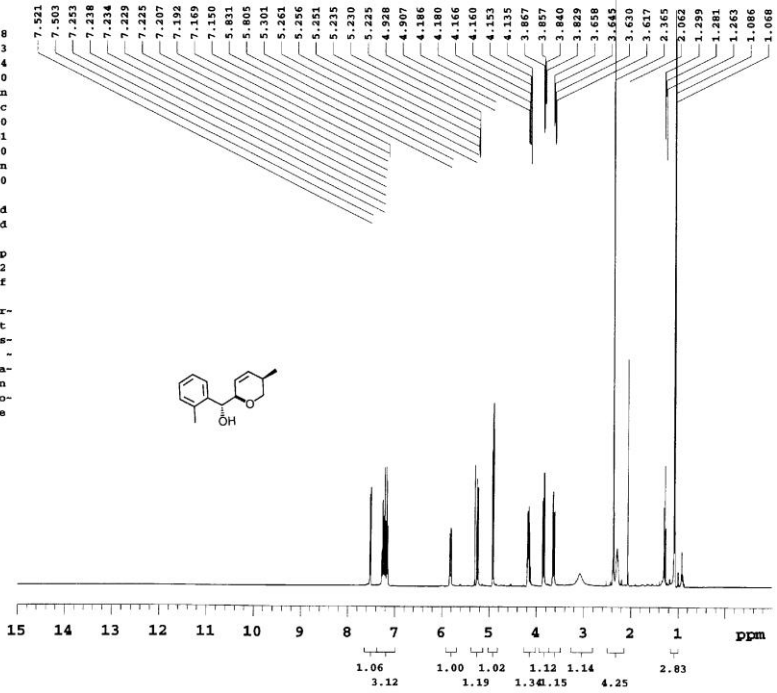
exp1 s2pul

SAMPLE		DEC. & VT	
date	Apr 22 2010	dfrq	498.124
solvent	dmso	dn	H1
file	/mnt/d600/hom-	dpwr	42
e14/hallnmr/nmrdat-		dof	0
a/Raed/Book6/RZH-6-		dm	yyy
-192-13C-DMSO.fid		dmm	w
ACQUISITION		dmf	10600
sfrq	125.267	dseq	
tn	C13	dres	1.0
at	2.495	homo	n
np	168776	temp	26.1
sw	33826.6	PROCESSING	
fb	not used	lb	1.50
bs	4	wtfile	
ss	2	proc	ft
tpwr	52	fn	262144
pw	3.5	math	f
d1	0.100		
tof	2500.0	werr	
nt	100000	wexp	
ct	316	wbs	
alock	n	wnt	
gain	48		
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-2618.0		
wp	33826.4		
vs	117		
sc	0		
wc	180		
hzmm	187.92		
is	5000.00		
rfl	7566.3		
rfp	4948.1		
th	20		
ins	100.000		
nm	ph		

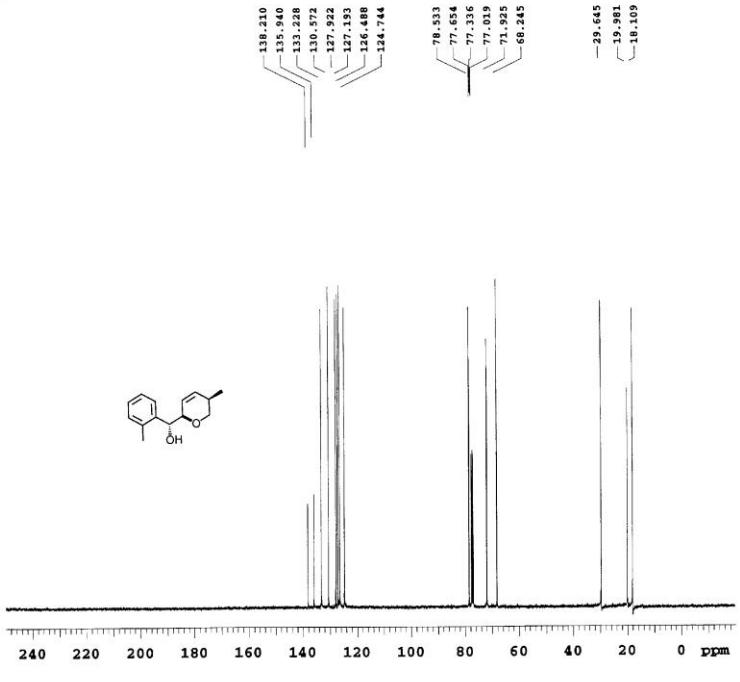


13. ^{1}H- & ^{13}C -NMR of title compound (5-81) in CD_3OD at 27 ^{o}C.

```
Raed, RZH-6-83-s2
400.393 MHz H1 1D in cdcl3 (ref. to CDCl
3 @ 7.26 ppm), temp 27.0 C -> actual tem
p = 27.0 C, m400gz probe

exp2  H1_1D

      SAMPLE              DEC. & VT
date    Jul 29 2009  dfrq        100.688
solvent       cdcl3  dn               C13
file /mnt/d600/hom-  dpwr              44
e14/hallnmr/nmrdat-  dof              0.0
a/DATA_FROM_NMRSER-  dm                nnn
VICE/Raed/2009.07/-  dmm                c
2009.07.29.m4_RZH--  dmf            15900
6-83-s2_16:22_H1_1-  dseq          garp1
             D.fid   dres             1.0
   ACQUISITION       homo               n
sfrq        400.393  temp            27.0
tn               H1      PROCESSING
at             4.998  gf         not used
np             64030  gfs        not used
sw            6406.1  wtfile
fb              3600  proc             lp
bs                 8  fn           131072
ss                 2  math              f
tpwr              60
pw               4.5  werr ao_txt restor-
d1             0.100       enode xmreact
tof            776.7  wexp abortoff flus-
nt                32  h procplot ao_txt -
ct                32  MM_auto_autosave a-
alock              y                borton
gain              22  wbs ao_txt procplo-
      FLAGS           t MM_auto_autosave
il                 n  wnt
in                 n
dp                 y
hs                nn
     DISPLAY
sp            -400.2
wp            6406.1
vs                63
sc                 0
wc               180
hzmm           35.59
is            130.75
rfl           400.3
rfp                0
th                12
ins            1.000
ai    ph
```




```
Raed, RZH-6-83-s2
100.690 MHz C13[H1] 1D in cdcl3 (ref. to
 CDCl3 @ 77.06 ppm), temp 27.0 C -> actu
al temp = 27.0 C, m400gz probe

exp2  C13_1D

      SAMPLE              DEC. & VT
date    Jul 29 2009  dfrq        400.392
solvent       cdcl3  dn                H1
file /mnt/d600/hom-  dpwr              45
e14/hallnmr/nmrdat-  dof              0.0
a/DATA_FROM_NMRSER-  dm               yyy
VICE/Raed/2009.07/-  dmm                w
2009.07.29.m4_RZH--  dmf            11500
6-83-s2_16:26_C13_-  dseq         waltz16
             1D.fid  dres             90.0
   ACQUISITION       homo               n
sfrq        100.690  temp            27.0
tn               C13     PROCESSING
at             2.000  lb               1.50
np            108696  wtfile
sw           27173.9  proc             ft
fb             15000  fn           262144
bs                32  math              f
ss                 2
tpwr              60  werr ao_txt restor-
pw               2.7       enode xmreact
d1             0.100  wexp abortoff flus-
tof           2045.0  h procplot ao_txt -
nt              1000  MM_auto_autosave a-
ct                 0                borton
alock              y  wbs ao_txt procplo-
gain              30  t MM_auto_autosave
      FLAGS           wnt
il                 n
in                 n
dp                 y
hs                nn
     DISPLAY
sp           -2008.8
wp           27173.7
vs                81
sc                 0
wc               180
hzmm          150.97
is           5000.00
rfl           2009.0
rfp                0
th                16
ins          100.000
nm    ph
```

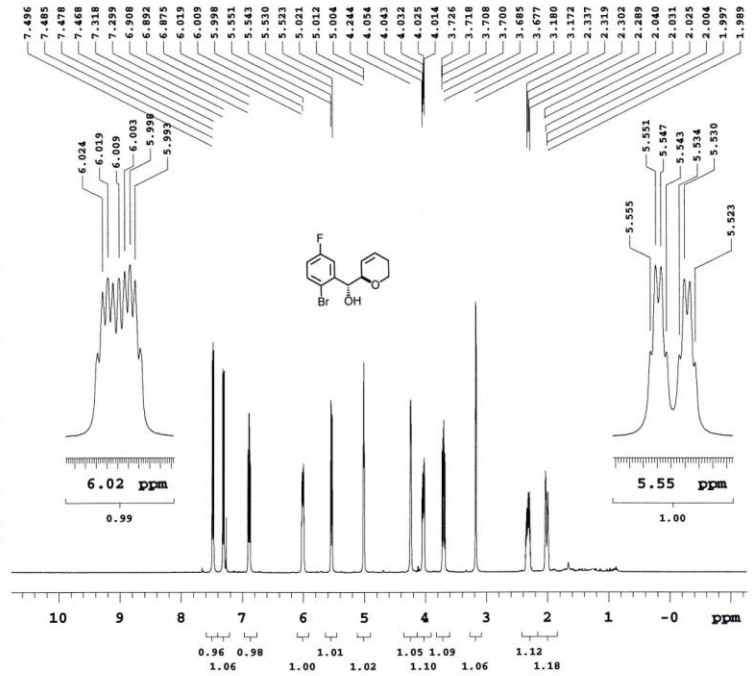


14. ^{1}H- & ^{13}C -NMR of title compound (5-69) in CD_3OD at 27 ^{o}C.

RZH-6-46-3-1H-CDCl3
498.122 MHz H1 1D in cdcl3 (ref. to CDCl
3 @ 7.26 ppm), temp 27.2 C -> actual tem
p = 27.0 C, autoxdb probe

exp3 s2pul

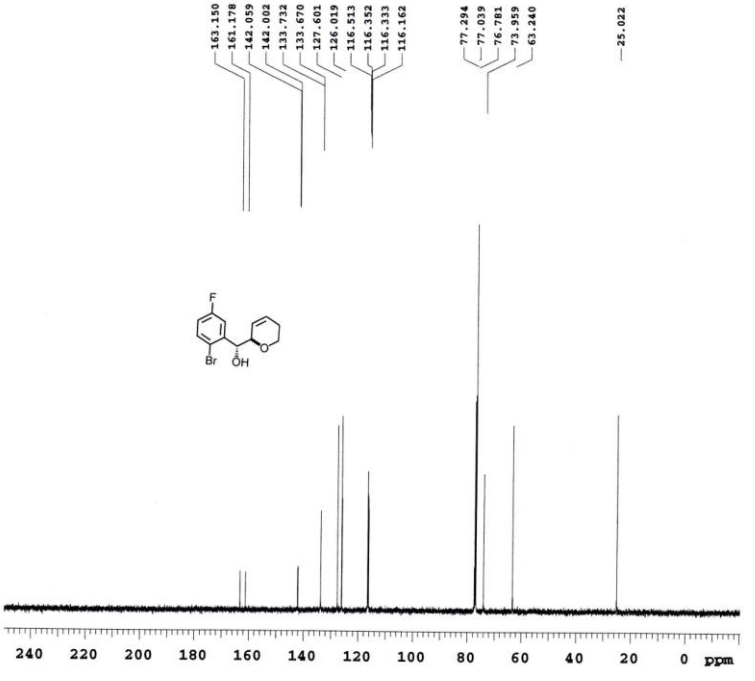
SAMPLE		DEC. & VT	
date	Jun 3 2009	dfrq	498.122
solvent	cdcl3	dn	H1
file	exp	dpwr	not used
ACQUISITION		dof	0
sfrq	498.122	dm	nnn
tn	H1	dmm	c
at	5.000	dmf	200
np	60002	dseq	
sw	6000.6	dres	1.0
fb	not used	homo	y
bs	4	temp	26.1
ss	2	DEC2	
tpwr	60	dfrq2	0
pw	5.9	dn2	
d1	0.100	dpwr2	1
tof	-100.0	dof2	0
nt	16	dm2	n
ct	16	dmm2	c
alock	n	dmf2	200
gain	32	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	DEC3	
dp	y	dfrq3	0
hs	nn	dn3	
DISPLAY		dpwr3	1
sp	-629.9	dof3	0
wp	6000.5	dm3	n
vs	66	dmm3	c
sc	0	dmf3	200
wc	180	dseq3	
hzmm	33.34	dres3	1.0
is	200.69	homo3	n
rfl	4236.4	PROCESSING	
rfp	3606.4	gf	not used
th	15	gfs	not used
ins	1.000	wtfile	
nm ph		proc	lp
		fn	131072
		math	f
		werr	
		wexp	
		wbs	
		wnt	wft



RZH-6-46-3-13C-CDCl3
125.264 MHz C13[H1] 1D in cdcl3 (ref. to
CDCl3 @ 77.06 ppm), temp 27.2 C -> actu
al temp = 27.0 C, autoxdb probe

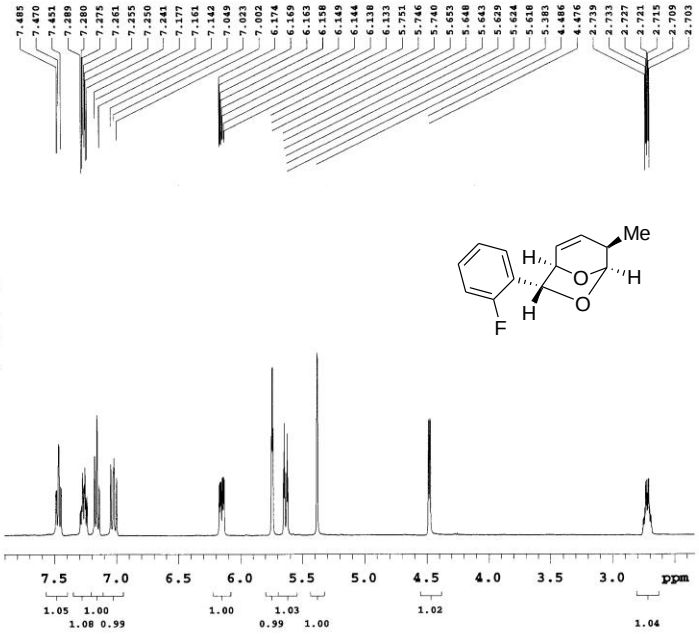
exp4 s2pul

SAMPLE		DEC. & VT	
date	Jun 3 2009	dfrq	498.122
solvent	cdcl3	dn	H1
file	exp	dpwr	40
ACQUISITION		dof	0
sfrq	125.267	dm	yyy
tn	C13	dmm	w
at	2.495	dmf	8500
np	168776	dseq	
sw	33826.6	dres	1.0
fb	not used	homo	n
bs	4	temp	26.1
ss	2	DEC2	
tpwr	53	dfrq2	0
pw	3.4	dn2	
d1	0.100	dpwr2	1
tof	2500.0	dof2	0
nt	100000	dm2	n
ct	100	dmm2	c
alock	n	dmf2	200
gain	48	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	DEC3	
dp	y	dfrq3	0
hs	nn	dn3	
DISPLAY		dpwr3	1
sp	-2545.5	dof3	0
wp	33826.4	dm3	n
vs	95	dmm3	c
sc	0	dmf3	12500
wc	180	dseq3	
hzmm	187.92	dres3	1.0
is	5000.00	homo3	n
rfl	12191.3	PROCESSING	
rfp	9645.5	lb	1.50
th	6	wtfile	
ins	100.000	proc	ft
nm ph		fn	262144
		math	f
		werr	
		wexp	
		wbs	
		wnt	

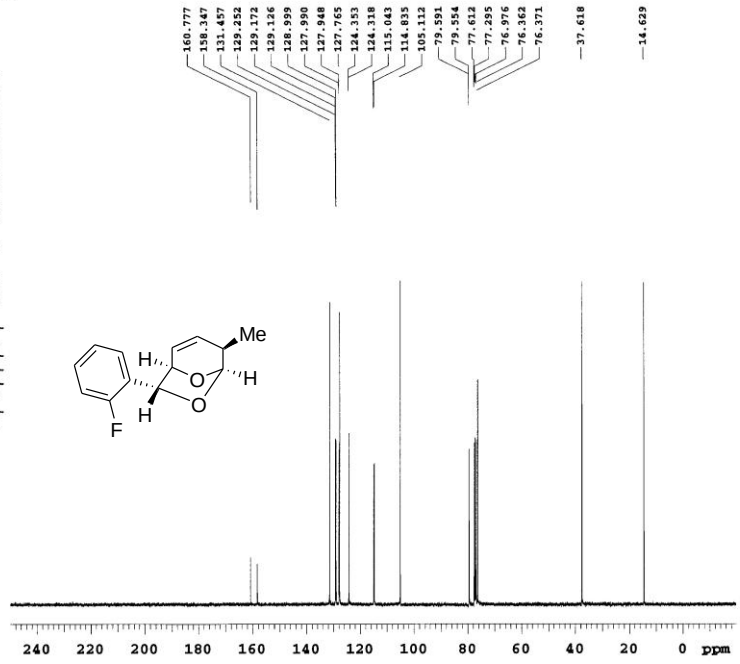


15. ^{1}H- & ^{13}C -NMR of title compound (5-55) in CD_3OD at 27 ^{o}C.

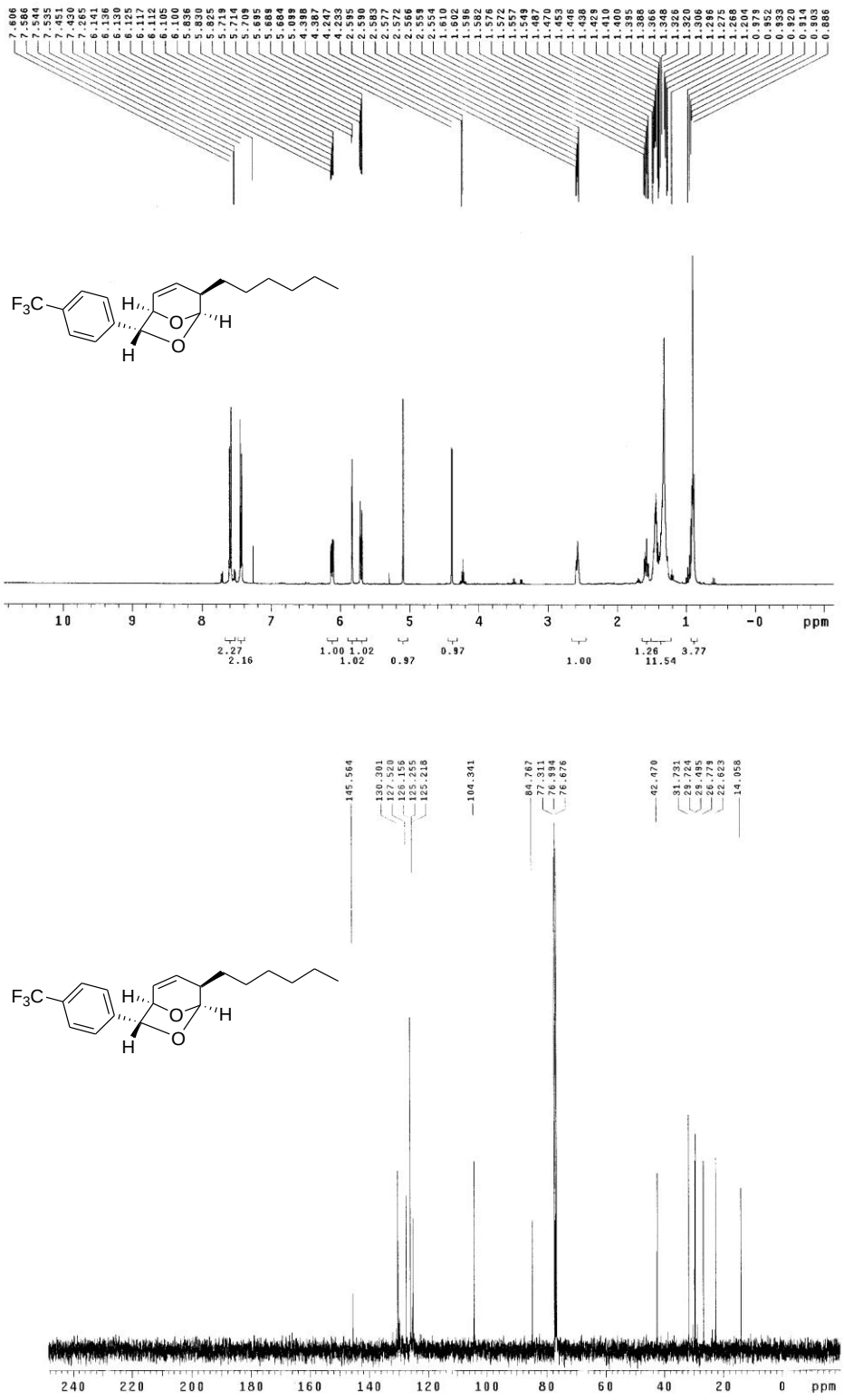
```
Raed, RZH-6-104-1-1st
400.393 MHz H1 1D in cdcl3 (ref. to CDCl
3 @ 7.26 ppm), temp 27.0 C -> actual tem
p = 27.0 C, m400gz probe

expl  H1_1D

      SAMPLE              DEC. & VT
date   Aug 26 2009  dfrq        100.688
solvent      cdcl3  dn              C13
file /mnt/d600/hom- dpwr             44
e14/hallnmr/nmrdat- dof             0.0
a/DATA_FROM_NMRSER- dm              nnn
VICE/Raed/2009.08/- dmm               c
2009.08.26.m4_RZH-- dmf           15900
6-104-1-1st_H1_1D.- dseq          garp1
              .fid  dres            1.0
   ACQUISITION      homo             n
sfrq       400.393  temp          27.0
tn              H1      PROCESSING
at            4.998  gf         not used
np            64030  gfs        not used
sw           6406.1  wtfile
fb             3600  proc             lp
bs                8  fn           131072
ss                2  math              f
tpwr             60
pw              4.5  werr ao_txt restor-
d1            0.100       enode xmreact
tof           776.7  wexp abortoff flus-
nt               16  h procplot ao_txt -
ct               16  MM_auto_autosave a-
alock             y                borton
gain             22  wbs ao_txt procplo-
      FLAGS           t MM_auto_autosave
il                n  wnt
in                n
dp                y
hs               nn
    DISPLAY
sp            936.2
wp           2227.4
vs               78
sc                0
wc              180
hzmm          12.37
is           250.83
rfl           400.3
rfp               0
th                6
ins           1.000
ai    ph
```




```
Raed, RZH-6-104-1-1st
100.690 MHz C13[H1] 1D in cdcl3 (ref. to
 CDCl3 @ 77.06 ppm), temp 27.0 C -> actu
al temp = 27.0 C, m400gz probe

expl  C13_1D

      SAMPLE              DEC. & VT
date   Aug 26 2009  dfrq        400.392
solvent      cdcl3  dn               H1
file /mnt/d600/hom- dpwr             45
e14/hallnmr/nmrdat- dof             0.0
a/DATA_FROM_NMRSER- dm              yyy
VICE/Raed/2009.08/- dmm               w
2009.08.26.m4_RZH-- dmf           11500
6-104-1-1st_C13_1D- dseq       waltz16
              .fid  dres            90.0
   ACQUISITION      homo             n
sfrq       100.690  temp          27.0
tn              C13     PROCESSING
at            2.000  lb            1.50
np           108696  wtfile
sw          27173.9  proc             ft
fb            15000  fn           262144
bs               32  math              f
ss                2
tpwr             60  werr ao_txt restor-
pw              2.7       enode xmreact
d1            0.100  wexp abortoff flus-
tof          2045.0  h procplot ao_txt -
nt             1000  MM_auto_autosave a-
ct             1000                borton
alock             y  wbs ao_txt procplo-
gain             30  t MM_auto_autosave
      FLAGS          wnt
il                n
in                n
dp                y
hs               nn
    DISPLAY
sp           -2008.8
wp          27173.7
vs               88
sc                0
wc              180
hzmm         150.97
is          5000.00
rfl          2009.0
rfp               0
th                6
ins         100.000
ai    ph
```

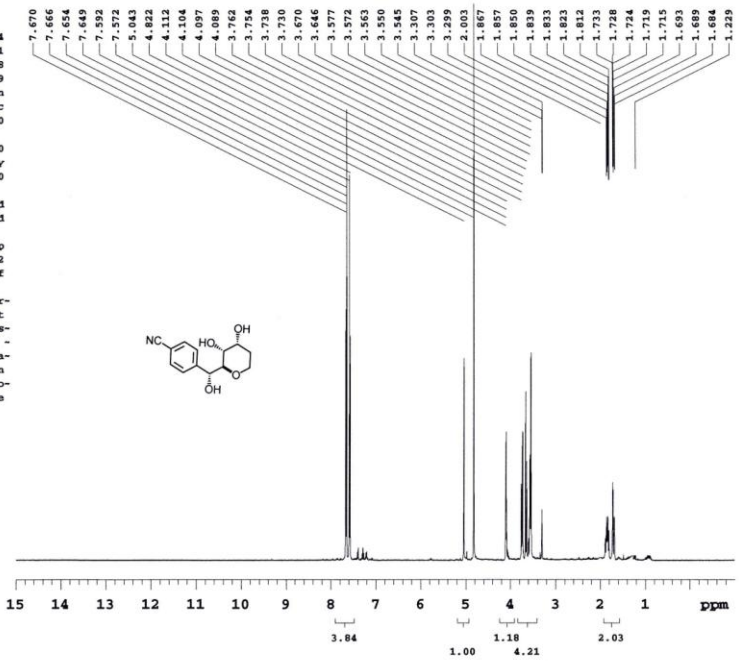


16. ^{1}H- & ^{13}C -NMR of title compound (5-58) in CD_3OD at 27 ^{o}C.

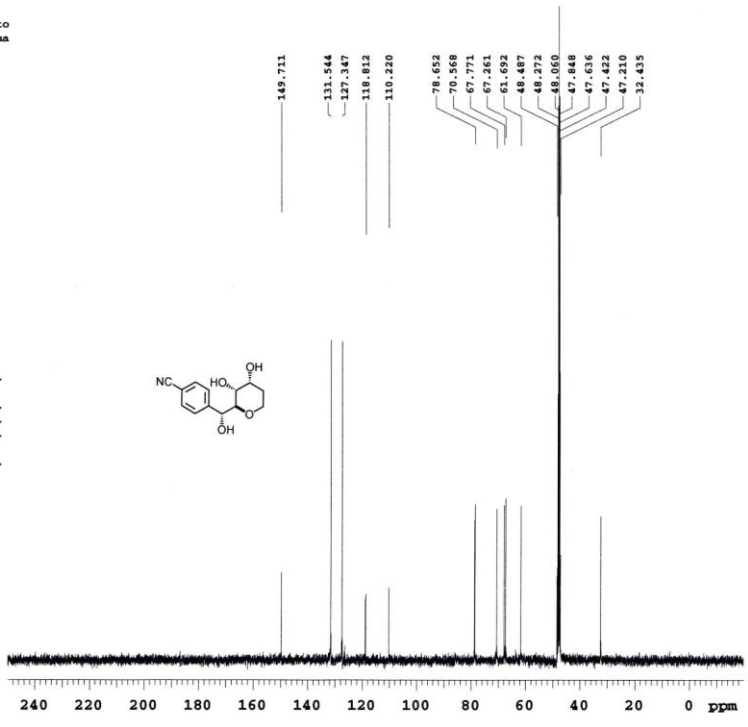


17. ^{1}H- & ^{13}C -NMR of title compound (5-103) in CD_3OD at 27 ^{o}C.

```
Raed, RZH-5-206-3
400.395 MHz H1 1D in cd3od (ref. to CD30
D @ 3.30 ppm), temp 27.0 C -> actual tem
p = 27.0 C, m400gz probe

exp2  H1_1D

      SAMPLE              DEC. & VT
date   Aug 19 2009  dfrq        400.394
solvent      cd3od  dn              H1
file /mnt/d600/hom-  dpwr             8
e14/hallnmr/nmrdat-  dof          -98.9
a/DATA_FROM_NMRSER-  dm              ynn
VICE/Raed/2009.08/-  dmm               c
2009.08.19.m4_RZH--  dmf             200
5-206-3_17:22_H1_1-  dseq
                D.fid  dres            1.0
   ACQUISITION       homo              y
sfrq        400.395  temp           27.0
tn               H1      PROCESSING
at            4.998  gf         not used
np            64030  gfs        not used
sw           6406.1  wtfile
fb             3600  proc             lp
bs                8  fn           131072
ss                2  math              f
tpwr             60
pw              4.5  werr ao_txt restor-
d1            1.500       enode xmreact
tof           776.7  wexp abortoff flus-
nt               16  h procplot ao_txt -
ct               16  MM_auto_autosave a-
alock             y                borton
gain             22  wbs ao_txt procplo-
      FLAGS          t MM_auto_autosave
il                n  wnt
in                n
dp                y
hs               nn
     DISPLAY
sp           -400.2
wp           6406.1
vs              180
sc                0
wc              180
hzmm          35.59
is           418.97
rfl           400.3
rfp               0
th                7
ins           1.000
ai    ph
```

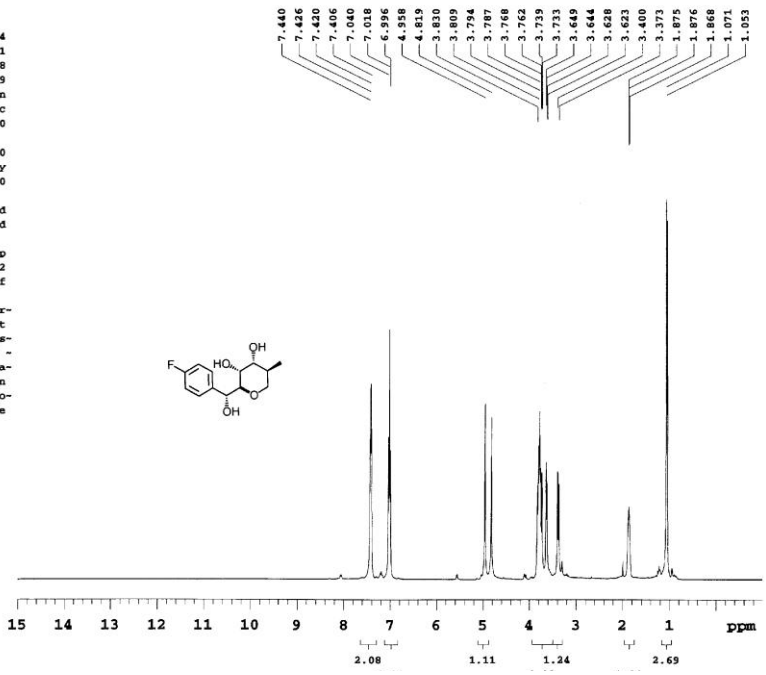



```
Raed, RZH-5-206-3
100.690 MHz C13[H1] 1D in cd3od (ref. to
 CD3OD @ 49.0 ppm), temp 27.0 C -> actua
l temp = 27.0 C, m400gz probe

exp2  C13_1D

      SAMPLE              DEC. & VT
date   Aug 19 2009  dfrq        400.394
solvent      cd3od  dn              H1
file /mnt/d600/hom-  dpwr            45
e14/hallnmr/nmrdat-  dof            0.0
a/DATA_FROM_NMRSER-  dm             yyy
VICE/Raed/2009.08/-  dmm               w
2009.08.19.m4_RZH--  dmf         11500
5-206-3_17:24_C13_-  dseq       waltz16
              1D.fid  dres           90.0
   ACQUISITION       homo              n
sfrq        100.690  temp           27.0
tn               C13     PROCESSING
at            2.000  lb             1.50
np           108696  wtfile
sw          27173.9  proc             ft
fb            15000  fn           262144
bs               32  math              f
ss                2
tpwr             60  werr ao_txt restor-
pw              2.7       enode xmreact
d1            0.100  wexp abortoff flus-
tof          2045.0  h procplot ao_txt -
nt              512  MM_auto_autosave a-
ct                0                borton
alock             y  wbs ao_txt procplo-
gain             30  t MM_auto_autosave
      FLAGS          wnt
il                n
in                n
dp                y
hs               nn
     DISPLAY
sp          -2008.8
wp          27173.7
vs              160
sc                0
wc              180
hzmm         150.97
is          5000.00
rfl          2009.0
rfp               0
th               12
ins         100.000
nm    ph
```

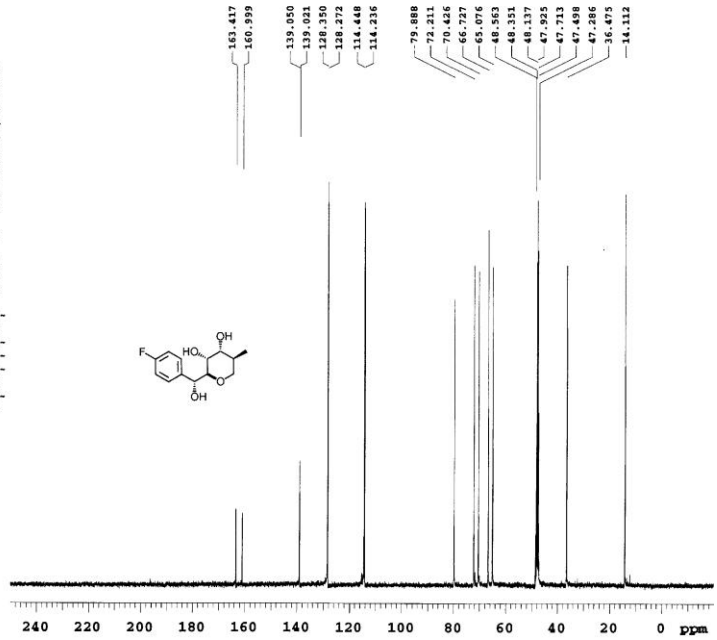


18. ^{1}H- & ^{13}C -NMR of title compound (5-107) in CD_3OD at 27 ^{o}C.

```
Raed, RZH-5-172-1
400.395 MHz H1 1D in cd3od (ref. to CD3O
D @ 3.30 ppm), temp 27.0 C -> actual tem
p = 27.0 C, m400gz probe

exp3  H1_1D

      SAMPLE            DEC. & VT
date   Aug 18 2009  dfrq       400.394
solvent      cd3od  dn              H1
file /mnt/d600/hom-  dpwr            8
e14/hallnmr/nmrdat-  dof          -98.9
a/DATA_FROM_NMRSER-  dm             ynn
VICE/Raed/2009.08/-  dmm              c
2009.08.18.m4_RZH--  dmf            200
5-172-1_15:27_H1_1-  dseq
              D.fid  dres           1.0
   ACQUISITION       homo            y
sfrq       400.395  temp         27.0
tn              H1       PROCESSING
at           4.998  gf         not used
np           64030  gfs        not used
sw          6406.1  wtfile
fb            3600  proc            lp
bs               8  fn          131072
ss               2  math             f
tpwr            60
pw             4.5  werr ao_txt restor-
d1           1.500       enode xmreact
tof          776.7  wexp abortoff flus-
nt              16  h procplot ao_txt -
ct              16  MM_auto_autosave a-
alock            y              borton
gain            22  wbs ao_txt procplo-
      FLAGS         t MM_auto_autosave
il               n  wnt
in               n
dp               y
hs              nn
     DISPLAY
sp          -400.2
wp          6406.1
vs              98
sc               0
wc             180
hzmm         35.59
is           154.51
rf1          400.3
rfp              0
th              12
ins          2.000
ai    ph
```

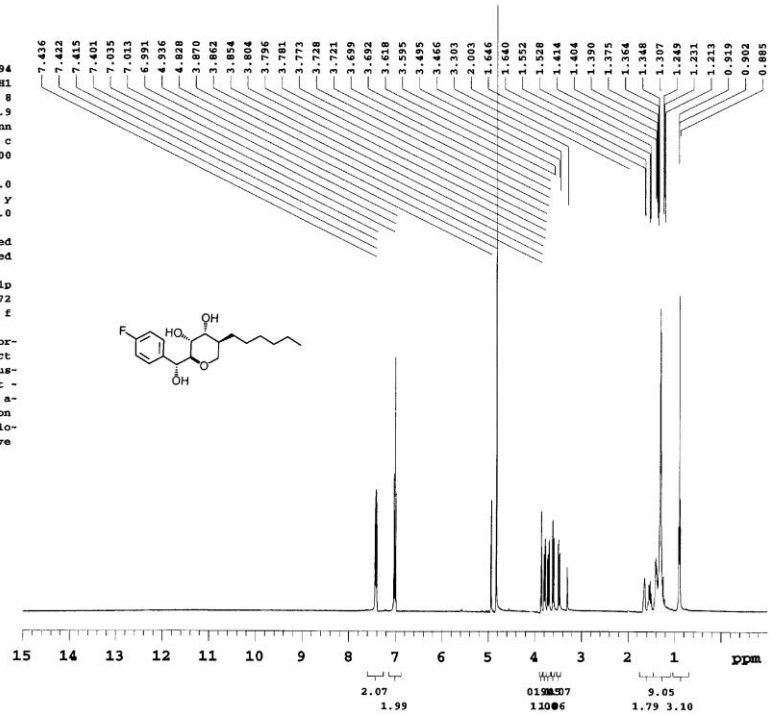



```
Raed, RZH-5-172-1
100.690 MHz C13[H1] 1D in cd3od (ref. to
 CD3OD @ 49.0 ppm), temp 27.0 C -> actua
l temp = 27.0 C, m400gz probe

exp3  C13_1D

      SAMPLE            DEC. & VT
date   Aug 18 2009  dfrq       400.394
solvent      cd3od  dn              H1
file /mnt/d600/hom-  dpwr           45
e14/hallnmr/nmrdat-  dof           0.0
a/DATA_FROM_NMRSER-  dm             yyy
VICE/Raed/2009.08/-  dmm              w
2009.08.18.m4_RZH--  dmf          11500
5-172-1_15:29_C13_-  dseq       waltz16
              1D.fid  dres          90.0
   ACQUISITION       homo            n
sfrq       100.690  temp         27.0
tn              C13      PROCESSING
at           2.000  lb            1.50
np          108696  wtfile
sw         27173.9  proc            ft
fb           15000  fn          262144
bs              32  math             f
ss               2
tpwr            60  werr ao_txt restor-
pw             2.7       enode xmreact
d1           0.100  wexp abortoff flus-
tof         2045.0  h procplot ao_txt -
nt             512  MM_auto_autosave a-
ct             512              borton
alock            y  wbs ao_txt procplo-
gain            30  t MM_auto_autosave
      FLAGS         wnt
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp         -2008.7
wp         27173.7
vs             107
sc               0
wc             180
hzmm        150.97
is         5000.00
rf1         2008.9
rfp              0
th              12
ins         100.000
ai    ph
```



19. ^{1}H- & ^{13}C -NMR of title compound (5-129) in CD_3OD at 27 ^{o}C.

```
Raed, RZH-5-188-2
400.395 MHz H1 1D in cd3od (ref. to CD3O
D @ 3.30 ppm), temp 27.0 C -> actual tem
p = 27.0 C, m400gz probe

exp5  H1_1D

      SAMPLE              DEC. & VT
date   Aug 17 2009  dfrq        400.394
solvent      cd3od  dn              H1
file /mnt/d600/hom-  dpwr             8
e14/hallnmr/nmrdat-  dof          -98.9
a/DATA_FROM_NMRSER-  dm              ynn
VICE/Raed/2009.08/-  dmm               c
2009.08.17.m4_RZH--  dmf             200
5-188-2_17:34_H1_1-  dseq
          D.fid      dres            1.0
   ACQUISITION       homo              y
sfrq       400.395  temp           27.0
tn              H1      PROCESSING
at           4.998  gf         not used
np           64030  gfs        not used
sw          6406.1  wtfile
fb            3600  proc              lp
bs               8  fn            131072
ss               2  math               f
tpwr            60
pw             4.5  werr ao_txt restor-
d1           1.500       enode xmreact
tof          776.7  wexp abortoff flus-
nt              16  h procplot ao_txt -
ct              16  MM_auto_autosave a-
alock            y                borton
gain            22  wbs ao_txt procplo-
      FLAGS         t MM_auto_autosave
i1               n  wnt
in               n
dp               y
hs              nn
     DISPLAY
sp          -400.2
wp          6406.1
vs             168
sc               0
wc             180
hzmm         35.59
is          354.26
rfl          400.3
rfp              0
th               6
ins          1.000
ai    ph
```




```
Raed, RZH-5-188-2
100.690 MHz C13{H1} 1D in cd3od (ref. to
 CD3OD @ 49.0 ppm), temp 27.0 C -> actua
l temp = 27.0 C, m400gz probe

exp5  C13_1D

      SAMPLE              DEC. & VT
date   Aug 17 2009  dfrq        400.394
solvent      cd3od  dn              H1
file /mnt/d600/hom-  dpwr            45
e14/hallnmr/nmrdat-  dof            0.0
a/DATA_FROM_NMRSER-  dm             yyy
VICE/Raed/2009.08/-  dmm               w
2009.08.17.m4_RZH--  dmf         11500
5-188-2_17:37_C13_-  dseq       waltz16
          1D.fid     dres          90.0
   ACQUISITION       homo             n
sfrq       100.690  temp           27.0
tn              C13     PROCESSING
at           2.000  lb             1.50
np          108696  wtfile
sw         27173.9  proc              ft
fb           15000  fn            262144
bs              32  math               f
ss               2
tpwr            60  werr ao_txt restor-
pw             2.7       enode xmreact
d1           0.100  wexp abortoff flus-
tof         2045.0  h procplot ao_txt -
nt             512  MM_auto_autosave a-
ct             512                borton
alock            y  wbs ao_txt procplo-
gain            30  t MM_auto_autosave
      FLAGS         wnt
i1               n
in               n
dp               y
hs              nn
     DISPLAY
sp         -2008.7
wp         27173.7
vs             146
sc               0
wc             180
hzmm        150.97
is         5000.00
rfl         2008.9
rfp              0
th               3
ins        100.000
```