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SYNTHETIC APPLICATIONS OF IRIDIUM-CATALYZED
AROMATIC C–H BORYLATION

presented by

FENG SHI

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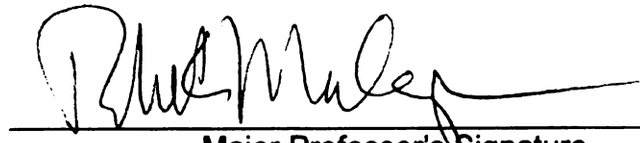

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SYNTHETIC APPLICATIONS OF IRIDIUM-CATALYZED AROMATIC C–H BORYLATION

By

Feng Shi

A DISSERTATION

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ABSTRACT

SYNTHETIC APPLICATIONS OF
IRIDIUM-CATALYZED AROMATIC C–H BORYLATION

By

Feng Shi

The Ir-catalyzed aromatic C–H borylation discovered by our group has been demonstrated as a powerful tool for direct functionalization of unactivated arenes. This reaction provides a method for preparation of aryl boronic esters directly from arenes and bypasses the need for aryl halides precursor. It also comes with a unique sterics-directed regioselectivity, thus is complementary to traditional chemistry and able to provide aromatic building blocks with substitution patterns difficult to access via other routes. The cleanliness of this reaction allows succeeding reactions performed without isolation and purification of the boronic ester intermediates.

Through the years, we have successfully demonstrated the utility of this C–H borylation by combining it with subsequent chemical events in the one-pot fashion. By doing this, we are able to not only elaborate this reaction into synthetically useful protocols toward the preparations of many functionalized aromatic motifs, but also discover new chemistries. Along these lines, we have been working on both transformating the boryl group to other functionalities and carrying on aromatic substitution with the boronic ester groups intact. We have established the borylation/oxidation protocol for the preparation of substituted phenols, the borylation/deuteration protocol for the preparation of specifically deuterated aromatics, and the borylation/amidation/oxidation protocol for the

preparation of 5-substituted 3-amidophenols. At the same time, we have also demonstrated the viability to extend the Ir-catalyzed aromatic C–H borylation chemistry from simple arenes to aromatic amino acid substrates and successfully carried out the borylation/oxidation protocol to prepare hydroxylated phenylalanine and tryptophan derivatives and analogues. Moreover, we have discovered that the proto-/deuterio-deborylation reaction of aryl boronic acids/esters is an Ir-catalyzed reaction and therefore established a thermal, acid-/base-free deborylation condition on its own. The borylation/ amidation/oxidation protocol comes with an undesired Suzuki side-reaction, and we are able to exploit it not only by utilizing its potential useful products, but also by giving preliminary success for a possible borylation/amidation/Suzuki protocol that uses the same Pd catalyst and ligand to promote both the amidation and the Suzuki reactions.

We are also applying the C–H borylation chemistry strategically to total synthesis of natural product autolytimycin. We have been able to demonstrate that autolytimycin, a new ansamycin superfamily member exhibiting antitumor, anti-inflammation, and antiviral activities, can potentially be assembled using our borylation/amidation/oxidation protocol with advanced intermediates. We have prepared the individual segments, and successfully demonstrated that the borylation/amidation/oxidation process can be successfully applied to the total synthesis in the relatively late stage. The completion of the total synthesis can be expected in the near future.

To my parents, my friends and Chunrui

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"A Ph.D. is just the beginning." That's what I have learned and have experienced during the past five and a half years here at Michigan State University. My Ph.D. study and training fulfills me with the true meaning of Ph.D. that I will have to spend my entire life to fully understand and realize. A Ph.D. is far more than a gain of knowledge and experience. It is a gain of capabilities to analyze the situation, to find problems and to solve them. It is also a gain of interest, desire, enthusiasm, and dedication that I will carry with me for my career. However, none of these could ever be possibly realized, let alone achieved, without the guildance and supervision of my advisor, Professor Robert E. Maleczka, Jr. He has been always helpful and suggestive for my research, my personal growth and my interest in chemistry. Through the years, he has led me through the murky waters of chemistry, corrected my path, taught me to face frustration and overcome it, and shaped my love of chemistry as a profession. He is strict, yet is also patient and tolerant. He allows me to explore chemistry with freedom and yet is still always ready to help me navigate the difficult area. I am very fortunate to have him as my dedicated and effective mentor, and I owe him my lifelong appreciation.

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Å	angstrom
Ac	acetyl
AD	asymmetric dihydroxylation
ADP	adenosine 5'-diphosphate
AHBA	3-amino-5-hydroxybenzoic acid
AIBN	2,2'-azobis(2-methylpropionitrile)
Anal.	analysis
aq.	aqueous
Ar	aromatic group
ATP	adenosine 5'-triphosphate
9-BBN	9-bora-bicyclo[3.3.1]nonane
Bcat	catecholboryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
4-BPA	4-boronophenylalanine
Bpin	pinacolboryl (4,4,5,5-tetramethyl-[1,3,2]dioxaborolyl)
B_2pin_2	bis(pinacolato)diboron
BPS	*tert*-butyldiphenylsilyl
br	broad
brsm	based on recovered starting material
Bu, ^{n}Bu	*n*-butyl
^{t}Bu	*tert*-butyl

Bz	benzoyl
calcd	calculated
cat.	catalyst, catalytic amount
CI	chemical ionization
cod	1,5-cyclooctadiene
coe	cyclooctene
*m*CPBA	3-chloroperbenzoic acid
CSA	camphorsulfonic acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
Davephos	2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)-biphenyl
dba	dibenzylideneacetone
d^{t}bpy	4,4'-di-*tert*-butyl-2,2'-bipyridine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
d	doublet
dec	decomposition
DIAD	di-*iso*-propyl azodicarboxylate
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
dmpe	bis(dimethylphosphino)ethane

DMSO	dimethyl sulfoxide
dppe	bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diasteromeric ratio
EDTA	ethylenediamine tetraacetic acid
EI	electron ionization
equiv	equivalent
Et	ethyl
ESI	electrospray ionization
FAB	fast atom bombardment
g	gram
GC	gas chromatography
COSY	correlation spectroscopy
h	hour
Hal, hal, X	halogen
HBpin	pinacolborane
HETCOR	heteronuclear chemical shift correlation
HMDS	bis(trimethylsilyl)amide
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethyl phosphoramide
HMQC	heteronuclear multiple quantum correlation
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry

Hz	hertz
Im_2CO	1,1'-carbonyldiimidazole
Imid	imidazole
Ind	η^5-indenyl
IR	infrared, infrared spectrum
K_{eq}	equilibrium constant
L	liter
μL	microliter
LDA	lithium di-*iso*-propylamide
lit	literature value
LRMS	low-resolution mass spectrometry
m	multiplet
μm	micrometer
M	molar
μM	micromolar
Me	methyl
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeter of mercury
mmol	millimole

mol	mole
μmol	micromole
MOM	methoxymethyl
mp	melting point
MS	mass spectrometry, mass spectrum
nm	nanometer
NMR	nuclear magnetic resonance, nuclear magnetic resonance spectrum
NMO	*N*-methylmorpholine-*N*-oxide
[O]	oxidant
oxone	triple salt of potassium hydropersulfate, potassium hydrosulfate, and potassium sulfate
P (various superscripts)	protecting group
PCC	pyridinium chlorochromate
Ph	phenyl
Piv	pivaloyl
PMB	4-methoxybenzyl
PMHS	polymethylhydrosiloxane
PPTS	pyridinium *para*-toluenesulfonate
^{i}Pr	*iso*-propyl
py	pyridine
q	quartet
quint	quintet
R (various superscripts)	substituent

R_L, R_S	substituent, large and small, respectively
RCM	ring-closing olefin metathesis
R_f	retardation factor
rt	room temperature
s	singlet
S_N2	bimolecular nucleophilic substitution
SAR	structure-activity relationship
SEM	2-(trimethylsilyl)ethoxymethyl
sext	sextet
S-phos	2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TCD	thermal conductivity detector
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Tig	tiglic (*E*-2-methyl-but-2-enoyl)
TIPS	tri-*iso*-propylsilyl
TMS	trimethylsilyl
TNT	2,4,6-trimethyltoluene
Tol	toluene

TPAP	tetrapropylammonium perruthenate
Tr	trityl (triphenylmethyl)
Ts	4-toluenesulfonyl
UV	ultraviolet
μW	microwave
W	Watt
xantphos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene

Chapter 1. Introduction: Catalytic Aromatic C–H Borylation and its Potential Synthetic Applications

1.1 C–H Activation

C–H activation, said by its name, refers to a chemical transformation that directly functionalizes an otherwise unactivated C–H bond.[1] Such a transformation, ideally, should be a process that replaces the strong, inert C–H bond with a relatively weaker, more reactive bond. More strictly, C–H activation should be a process that "activates" a C–H bond without assistance from its neighboring functional groups, and a process that avoids the generation of uncaged reactive intermediates, such as free radicals or carbocations. Therefore, processes such as acidic C–H bond deprotonation or β-hydride elimination from a carbon atom are not considered "true" C–H activations.

The importance of C–H bond activation can be well understood from a traditional chemistry point of view. The isolated C–H bond is one of the least reactive bonds in organic reactions. Having a bond dissociation energy close to 100 kcal/mol and lack of polarity, the C–H bond is very inert towards many organic transformations. In a traditional synthetic perspective, a C–H bond is not considered as a "functional group". This nature of the C–H bond makes C–H activation a highly challenging task from a basic scientific point of view. On the other hand, hydrocarbons, consisting of only C–H and C–C bonds, are the main

constituents of oil and natural gas, which is feedstock for the chemical industry, and the starting materials for most chemical products. The transformations of unactivated C–H bonds, therefore, constitute an extremely important goal for organic chemists. Discovery and development of selective, mild, and efficient transformations that utilize C–H bonds to construct other bonds will potentially not only provide the chemical industry new, more efficient, cost-friendly, and environmentally benign methods of generating more valuable chemical products directly from hydrocarbon stock, but also provide synthetic organic chemists fundamentally novel yet extremely powerful tools for retrosynthetic analysis of complex molecules as well as rapid and direct synthesis of diversely functionalized small molecules. Therefore, C–H activation represents one of the most fundamentally important reactions in organic chemistry.

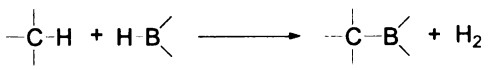
Since the 1970's, C–H activation has attracted significant attention from organic and organometallic chemists.[1,2] A variety of methods that selectively activate aliphatic, aromatic or benzylic C–H bonds to construct C–C, C–N, C–O, and C–B bonds have been reported. These methods represent great success toward this fundamentally challenging mission and have provided synthetic chemistry new and efficient methods to construct C–C or C–Heteroatom bonds that are not straightforward by other means. Mechanistically, C–H activation methods can be roughly divided into two categories: inner-sphere and

outer-sphere.[3] The inner-sphere C–H activations utilize a transition metal for direct C–H oxidative addition (or σ-bond metathesis) and have been used to construct C–C,[4] C–N,[5] C–O,[6] C–Halogen,[7] and C–B (*vide infra*) bonds. The outer-sphere mechanism, on the other hand, does not call for a direct interaction of the metal center to the C–H bond. It generally utilizes a metal-bound carbene or nitrene to directly insert into the C–H bond and completes the C–H activation. It may also involve activation of a small molecule, such as dioxygen, to form a highly reactive intermediate, which reacts with the C–H bond in a radical H abstraction/rebound manner. This type of process has also been used to construct C–C,[8] C–N,[9] and C–O[10] bonds.

1.2 C–H Borylation and Its Special Features

C–H borylation is a type of C–H activation[11] where a C–H bond is transformed into a C–B bond (Scheme 1.1). So far, C–H borylation follows an inner-sphere mechanism which calls for a transition metal, typically Pd, Re, Ir or Rh, to directly undergo oxidative addition (or σ-bond metathesis) to cleave the C–H bonds.

Scheme 1.1 General equation of C-H borylation

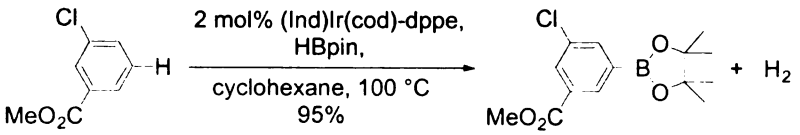


Since 1999, when Smith and coworkers demonstrated that C–H borylation could be catalyzed by some Ir species,[12,13] much work has been done to improve and further develop this reaction[14-20] in terms of substrate scope, catalyst choice

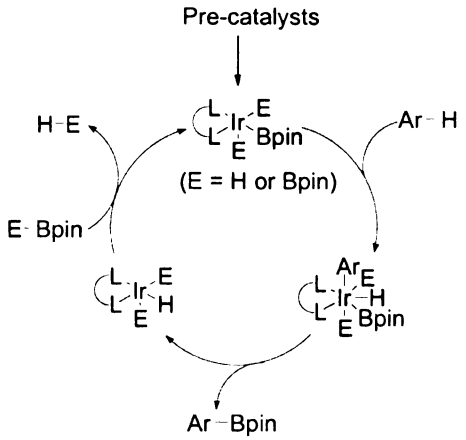
and activity, and reaction conditions. It has been realized that depending on the catalyst choices, C–H borylations can selectively take place on aromatic,[14-17] aliphatic,[18] benzylic,[19] or β-styrylic C–H bonds.[20] It has also been discovered that some of these reactions can be performed in solvents whose C–H bonds are not reactive under the reaction conditions.[14b] For the aromatic C–H borylation, the discovery of (η^5-Indenyl)Ir(cod) catalyst (abbreviated as (Ind)Ir(cod)), by Smith and coworkers, was one of the breakthroughs in terms of product cleanliness, catalyst activity and turnover.[14c] This catalyst in combination of a bidentate phosphine ligand, generally bis(dimethylphosphino)ethane (dmpe) or bis(diphenylphosphino)ethane (dppe), allows a variety of aromatic substrates to undergo clean C–H borylation with pinacolborane (HBpin) under relatively mild conditions to give aromatic boronic pinacol esters in good yields (Scheme 1.2). Further improvements by Miyaura, Ishiyama and Hartwig revealed [Ir(μ^2-OMe)(cod)]$_2$ as a more active catalyst (abbreviated as [Ir(OMe)(cod)]$_2$).[15b] This catalyst in combination with a bipyridine ligand 4,4'–di-*tert*-butyl-2,2'-bipyridine (d^{t}bpy) could allow for reactions at room temperature with bis(pinacolato)diboron (B_2pin_2) and with more functional groups tolerated. The mechanism of this C–H borylation has been studied, and an Ir(III)/Ir(V) catalytic cycle involving an oxidative addition (or σ-bond metathesis) of the aromatic C–H bond[14c,15a] followed by a reductive elimination to afford the

corresponding C–B bond (Scheme 1.3) has been supported.

Scheme 1.2 An example of (Ind)Ir(cod)-catalyzed aromatic C-H borylation



Scheme 1.3 Proposed catalytic cycle of Ir-catalyzed C-H borylation



Like other C–H activation methods, catalytic C–H borylation increases the pool of starting materials to include unactivated hydrocarbons. It also allows for improved efficiency, economy, and "greenness". One specific attraction that draws the attention of synthetic chemists is its ability to *generate a boronic ester directly from an unactivated C–H bond with sterics-directed regioselectivity.*[16d]

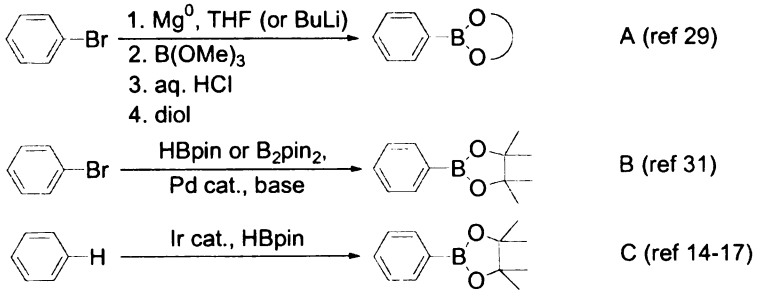
Boronic acids/esters are versatile intermediates in organic syntheses. They undergo a variety of important transformations to make C–C or C–Heteroatom bonds, and therefore are intensively used in organic syntheses. Typical examples of such important transformations include, but are certainly not limited

to, Pd-catalyzed Suzuki-Miyaura couplings,[21] Rh-catalyzed addition reactions to alkynes/olefins, CO_2, carbonyls, or α,β-unsaturated carbonyls,[22] Petasis reactions,[23] Matteson homologations,[24] and Cu-mediated cross-coupling reactions.[25] They also serve as functional molecules,[26] ^{10}B carriers for neutron capture therapy,[27] and biologically active compounds.[28] Such uses of boronic acids/esters keep urging the development of new, mild, easy, and scalable synthetic protocols for their preparations. Traditionally, boronic acids/esters are made via a metal/metal exchange step (transmetalation) from the corresponding lithium or Grignard reagents with trialkyl borate (Scheme 1.4 A).[29] Although such a protocol is commonly used, it obviously has drawbacks. For one, this approach calls for the intermediacy of highly reactive organolithium or magnesium species, resulting in relatively poor functional group compatibility and are operationally inconvenient at large scales. It also necessitates the ready availability of the corresponding halides, which may not always be the case. Hydroboration of olefins or alkynes, either catalyzed or uncatalyzed, can minimize such limitations,[30] but aromatic boronic acid/ester preparations via such an approach is obviously not viable. Recently, Miyaura and Masuda developed a clever method to couple aryl halide directly with borane or diboron reagents utilizing Pd-catalyzed dehydrohalogenative conditions and thus avoid generating the reactive organolithium or magnesium intermediates (Scheme 1.4 B).[31] Such

an improvement greatly expands the scope of aromatic boronic acid/ester preparations, especially for those with functionalized arenes, but still does not overcome the need for halogenated starting materials.

C–H borylation, on the other hand, does not require the corresponding halide as the starting material (Scheme 1.4 C). It uses a C–H bond to form the boronic ester without generating a highly reactive intermediate. Thus, it has considerable functional group tolerance. Considering that halides are ultimately made from the hydrocarbon feedstock, C–H borylation serves as a much more direct and concise route to prepare boronic esters. Moreover, C–H borylation not only bypasses the aryl halide precursors, but also tolerates halides as a functional group. Therefore, the product of the C–H borylation can still possess a halide for further manipulation, which further expands the utility of this process.

Scheme 1.4 Comparison of different methods for boronic ester preparation

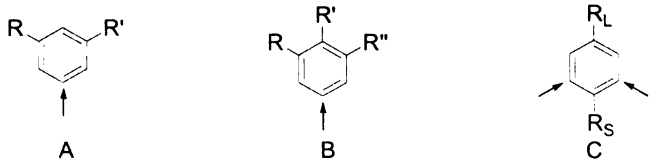


In addition, C–H borylation has a very unique sterics-directed regioselectivity. Such selectivity allows for the activation of the C–H bonds that are viewed as "less reactive" in the traditional chemistry standpoint. For example, C–H

borylation on aliphatic substrates can lead to selective borylation on primary C–H bonds, leaving secondary and tertiary C–H bonds intact, which is complementary to traditional electrophilic substitution chemistry.[18-19] This trend is also followed for aromatic substrates. Traditional aromatic substitution is generally dictated by electronics. Thus, electron-releasing groups direct the incoming electrophilic substituent to their *ortho*/*para* positions, and electron-withdrawing groups direct the incoming electrophilic substituent to their *meta* positions. Under such guidelines, it is predictable that functionalization of aromatics at positions that are not favored by existing substituents will be difficult. For example (Figure 1.1 A), selective substitution of the 5-position of a 1,3-disubstituted benzene is notoriously hard by traditional chemistry methods, because in order to achieve such a directing effect, both the existing substitution groups need to be electron-withdrawing. However, in that case, the aromatic ring is too deactivated to undergo electrophilic substitution.[32] Similarly, substitution of the 5-position of a 1,2,3-trisubstituted benzene (Figure 1.1 B) would require R and R" to be electron-withdrawing groups. Although in this case R' could be an electron-releasing group, restoring the reactivity of the aromatic ring towards electrophilic substitution may not be guaranteed. For another example (Figure 1.1 C), traditional functionalization of 1,4-disubstituted benzenes generally occur at the *ortho* positions of the stronger electron-releasing group and it is very hard to

twist. This leads to difficulties in functionalizing the *ortho* positions of sterically small but electron-withdrawing groups, such as cyano and fluoride. One method that deviates from this electronics-governed regioselectivity is the chelation-directed *ortho*-metallation.[33] Under such reaction conditions, a chelating substitutent, regardless of its electronic nature, will direct the incoming group to its *ortho* positions, and therefore be able to potentially turn some traditional *meta* directors into *ortho* directors. This complements the traditional substitution chemistry in some cases, yet still does not provide for access to other problematic substitution patterns, such as the one shown in Figure 1.1 A.

Figure 1.1 Difficult aromatic substitution tasks for traditional chemistry



C–H borylation, on the other hand, operates largely with a sterics-directed regioselectivity. While the electronic effects of the substituents will affect the rate of the borylation,[14-15,34] borylation of aromatic substrates generally occurs at the least hindered positions, regardless of the electronic nature of the existing substitution groups. Therefore, this unique regioselectivity complements both the traditional substitution chemistry and the *ortho*-metallation methods, and is particularly suitable for substitution at the difficult *meta*/*para* positions. Taking

the same example into consideration (*vide supra*), selective substitution of the 5-position of a 1,3-disubstituted benzene is now straightforward (Figure 1.1 A), because the 5-position is the most sterically accessible position. Selective functionalization at the 2-position of 4-substituted fluorobenzenes or benzonitriles is also straightforward (Figure 1.1 C),[14d] because such positions are relatively less sterically demanding compared with the other positions. Thus, C–H borylation can be used to synthesize aromatic chemical products whose substitution patterns prohibit their traditional syntheses.

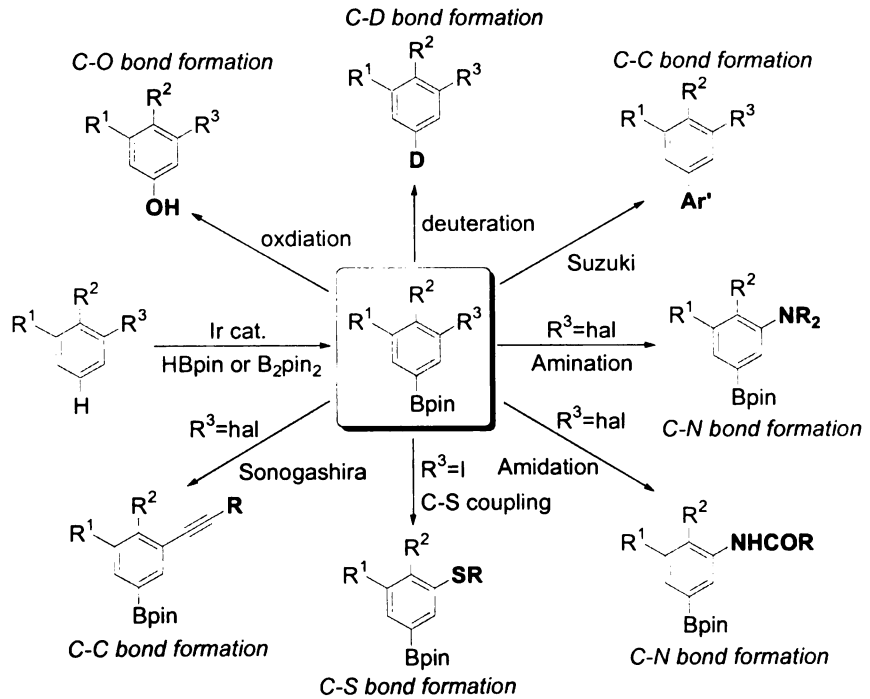
1.3 Potential Synthetic Applications of Catalytic Aromatic C–H Borylation

Synthetically, the activation of aromatic C–H bonds, if used in combination with subsequent chemical events, may serve as efficient methods for rapid preparation of diversely functionalized, pharmaceutically important aromatic building blocks with substitution patterns difficult to achieve by other means. The synthetic utility of this method is highlighted by the functional group compatibility of the catalytic aromatic C–H borylation.[14c,d,15b] In fact, ethers, esters, amides, amines, cyanos, and halides are all well tolerated in the borylation step, allowing densely functionalized products to be quickly assembled. Moreover, this Ir-catalyzed aromatic C–H borylation is generally clean and the only byproduct is hydrogen gas, which allows the subsequent reactions to be performed on crude materials without isolation and purification of the boronic ester intermediates.

This telescoping-reaction technique can further improve the throughput and the overall efficiency of the reaction combinations.

There are two ways of applying this catalytic aromatic C–H borylation to the construction of aromatic building blocks (Scheme 1.5). One way is to borylate a substituted aromatic substrate, and transform the boronic ester into other functional groups, thus achieving an overall C–H functionalization. The other way is to utilize the halide tolerance of this C–H borylation and transform the pre-existing halide on the aromatic substrates to other groups after the borylation step. Should the boryl group stay intact in the second elaboration, this method

Scheme 1.5 Possible synthetic applications of Ir-catalyzed aromatic C-H borylation



would allow the rapid formation of highly functionalized aromatic boronic esters with substitution patterns not straightforward to achieve by traditional chemistry.

Chapter 2. The C–H Borylation/Oxidation Approach for the Preparation of *meta*-Substituted Phenols

2.1 Phenols and Their Preparations

Phenols and phenolic derivatives, both synthetic and natural, are ubiquitous.[35] Phenols serve as resin monomers, surfactants, and antioxidants.[36] They have also gained significant attention for their toxicity, radical scavenging activity, metal binding activity, and physical organic properties.[37] Combinatorial libraries have been built around them,[38] synthetic methods use them as starting materials,[39] and the construction of many macromolecules, natural products, and pharmaceuticals use phenols as synthetic intermediates.[40] For these reasons, phenol preparations have evolved over decades.[41,42]

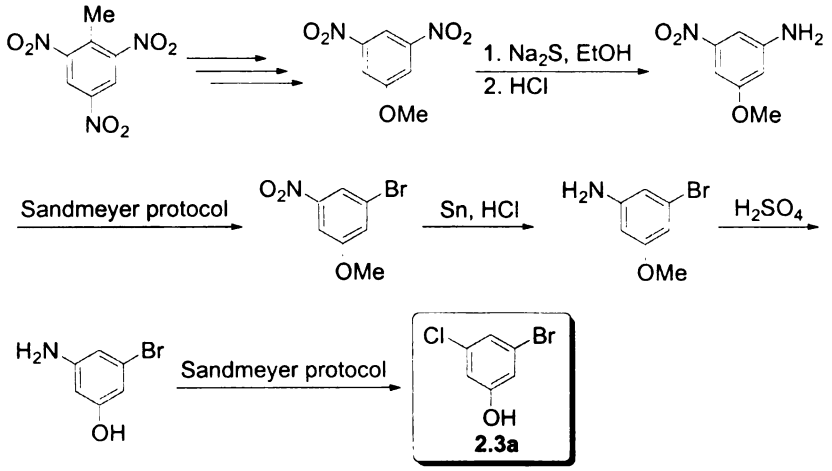
Traditional phenol preparation methods are vast, ranging from oxidations to substitutions, from rearrangements to annulations. Oxidation methods use aryl metallic species, such as aryl silanes, lithiums, or boronic acids/esters as substrates for oxidation.[43] These methods necessitate the preparation of corresponding precursors ultimately from aryl halides. Thus they are lengthy and may be limited by the availability of such halides, as well as the problems associated with the preparation of these precursors such as reactive intermediate generation and functional group tolerance. Substitution methods use either diazonium salts or halides for formal hydrolysis.[44] Obviously, the former case

deals with hazardous materials, and the latter case deals with harsh reaction conditions. Rearrangement methods include classic examples of benzylic hydroperoxide rearrangements and Bayer-Villiger rearrangements (followed by hydrolysis in this case),[45] as well as newer cyclodienone rearrangements.[46] These methods do not need halides as precursors but certainly need the presence of other groups. In fact, except for very few examples,[47] all the methods mentioned above only transform an existing group to the hydroxyl group of phenols. Therefore, using these traditional methods, a substituted phenol must come from a precursor with an equally difficult (or simple) substitution pattern. Hence, they are limited to the availability of such corresponding starting materials. As a result, the preparation of some phenols, even those with seemingly simple structures, can be unimaginably hard. This is illustrated by the preparation of 3-bromo-5-chlorophenol (**2.3a**), a structurally simple molecule. The only literature preparations traced back about 80 years and called for a 10-step route starting from TNT (Scheme 2.1)![48]

Understanding these limitations, another class of phenol preparations has been developed. They start with acyclic molecules and through different cyclization-aromatization methods, build up the benzene rings. Such examples include classic cyclization of polyketones or polyketo-esters,[41] the Wulff-Dotz benzannulation[49] and other [m+n+p] annulation methods, as well as

electrocyclization methods.[50] These methods are exceptionally good at preparing highly substituted phenols and are not confined by the directing effects of traditional aromatic substitutions. Unfortunately however, they generally require multiple steps to prepare the precursors and thus are low in overall throughput and efficiency. Therefore, the demand for a rapid, efficient, scalable, and operation-friendly method to prepare phenols with difficult substitution patterns is still high.

Scheme 2.1 A traditional preparation of 3-bromo-5-chlorophenol

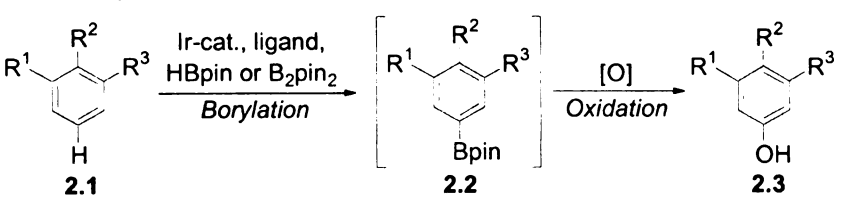


2.2 Applications of Catalytic Aromatic C–H Borylation in Phenol Synthesis and Initial Studies

As mentioned in Chapter 1, the catalytic aromatic C–H borylation is particularly good at making aromatic building blocks having otherwise difficult substitution patterns, especially all *meta*-substituted benzenes. In addition, the

C–H borylation generates a boronic ester group, which are known to be oxidized to phenols.[43d,e] Therefore, it could be envisioned that treatment of the C–H borylation product with an appropriate oxidant should be able to afford a hydroxyl group at a position where the C–H borylation occurs (Scheme 2.2). Furthermore, since the borylation step is clean enough to allow subsequent reactions to occur on crude reaction mixtures, it might be possible to telescope the C–H borylation with the oxidation step in the same reaction vessel. This overall process would constitute a one-pot, highly efficient protocol to convert a substituted benzene to a substituted phenol with a net hydroxyl group installation at the most sterically open position. The good functional group tolerance of C–H borylation and the efficiency to eliminate the intermediate isolation might allow this method to be extended to high-throughput screening and large-scale processes. Therefore, this protocol would represent a most direct route to numerous structurally simple phenols, especially *meta*-substituted, densely functionalized phenols, whose practical use may be currently limited by their accessibility.

Scheme 2.2 Proposed one-pot C-H borylation/oxidation protocol for preparation of phenols



2.1 **2.2** **2.3**

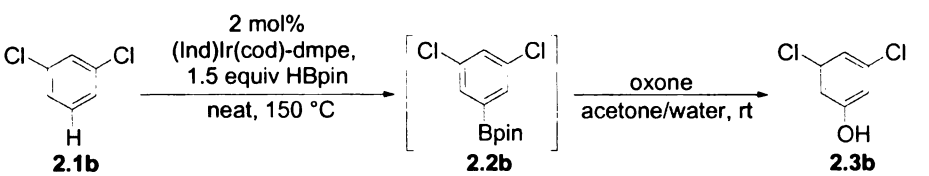
Literature reveals two practical methods to oxidize aryl boronic acids/esters.

One uses hydrogen peroxide as the oxidant[43e] while the other calls for oxone.[43d] We favored the oxone oxidation for a number of reasons. First, the reported conditions for hydrogen peroxide oxidation do not cover boronic esters, whereas the oxone oxidation does. Secondly, the reaction time can be shortened from hours for hydrogen peroxide to minutes for oxone. Lastly, unlike hydrogen peroxide, oxone is a solid that is easy to handle and poses no storage issues. However, the reported oxone oxidation conditions were far from being considered friendly. They use 0.9 equiv oxone in a 0.4 mmol/L EDTA aqueous solution with 10~15% acetone, 1.5 equiv NaOH, and ~42 equiv $NaHCO_3$ as buffer, at 2 °C for 5 min. The details of this operationally complicated procedure suggest the involvement of the highly reactive transient oxidant dimethyldioxirane[51] (DMDO) in this process. DMDO, normally generated *in situ* from the reaction of oxone and acetone, is a strong oxidant and has been demonstrated as a versatile reagent for oxidation chemistry. Yet its generation has to be controlled rigorously at low temperature within a narrow pH range. The oxone oxidation conditions mentioned above may possibly be needed to insure the generation of DMDO.

As we first demonstrated that the oxidation could be carried out on crude borylation mixtures and no isolation and purification of the aryl boronic esters were needed, the literature procedure gave reproducible yields in our hands. This problem, as well as the complicated procedure and the elaborate oxidation

system, triggered us to simplify the reported conditions. EDTA was first found to be dispensable, and more work was targeted at identifying the necessity for other additives and controlling factors. As listed in Table 2.1, we found that almost everything in the reported reaction conditions was unnecessary. The oxidation did not require EDTA, did not require NaOH, and did not need $NaHCO_3$ as buffer. Temperature control was also unnecessary.[52] Interestingly enough, however, contrary to the literature report, the acetone/water ratio was a critical parameter in

Table 2.1 Initial study of reaction conditions for oxone oxidation



Entry	Base used[a]	Buffer used[b]	Temperature[c]	Acetone/water ratio *V/V*	% Yield[d]
1	Yes	Yes	0 °C	0	(0)
2	Yes	Yes	0 °C	0.2:1	(43)
3	Yes	Yes	0 °C	0.4:1	(98)
4	Yes	Yes	0 °C	0.6:1	(100)
5	Yes	Yes	0 °C	1:1	(100)
6	Yes	No	0 °C	0.2:1	(57)
7	Yes	No	0 °C	0.4:1	(94)
8	Yes	No	0 °C	1:1	(100)
9	Yes	Yes	0 °C	1:1	81
10	Yes	No	0 °C	1:1	78
11	No	No	0 °C	1:1	78
12	No	No	rt	1:1	81

All reactions were run in 1 mmol scale. [a] 1.5 equiv NaOH. [b] ~42 equiv $NaHCO_3$. [c] 15 min for 0 °C reaction, and 7 min for room temperature reaction. [d] Isolated yields; GC yields (internal standard) listed in parenthesis.

our reactions. In order to reproducibly obtain full conversions, a ratio of at least 0.4:1 of acetone/water is needed. We chose 1:1 as our standard conditions.

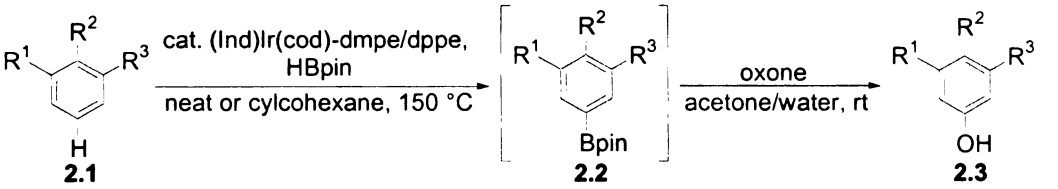
In summary, this modified oxidation protocol was greatly simplified and easy to operate. However, it raised an elementary question regarding to the mechanism of the oxidation, namely, whether DMDO is indeed generated and participating in the oxidation. This question will be addressed in Section 2.4.

2.3 Substrate Study[53]

Having developed the optimized oxidation conditions, we next screened a variety of substituted arenes in the one-pot C–H borylation/oxidation protocol (Table 2.2). Our standard procedure involves simply heating the arene and HBpin with (Ind)Ir(cod) catalyst and dmpe to 150 °C (or dppe at 100 °C) to achieve a complete borylation, and treating the cooled crude mixture with acetone and an aqueous solution of oxone. Such a procedure is easy and timesaving. In fact, compound **2.3a**, previously made from TNT in 10 steps (Scheme 2.1), could be quickly prepared via our method from 3-chlorobromobenzene **2.1a** in 83% yield in a single day (Entry 1). Moreover, a variety of functional groups were tolerated in this process, including ethers, esters, amines and halides. Thus a variety of diversely functionalized phenols could be rapidly prepared. In terms of substitution patterns, our protocol is amendable to 1,3-disubstituted and 1,2,3-trisubstituted benzene substrates, where hydroxyls are installed selectively

at the 5-positions. Compound **2.1g**, a pyridine derivative, could also undergo the same reaction sequence with similar regioselectivity (Entry 6). This protocol, therefore, constitutes a general and unified route for preparation of these *meta*-substituted phenols. In fact, quite a few phenols such as **2.3h** and **2.3q** (Entries 7, 17) had not been reported in the literature.

Table 2.2 C-H Borylation/oxidation protocol for phenol synthesis



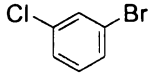
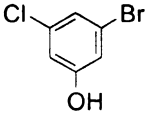
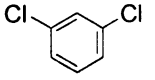
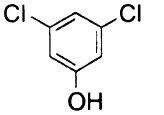
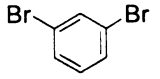
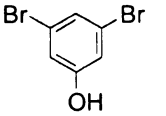
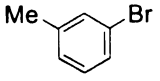
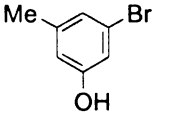
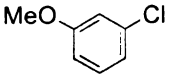
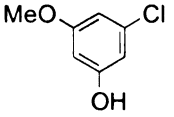
Entry	Starting arene	Borylation conditions[a]	Phenol	% Yield[b]
1	 **2.1a**	2 equiv HBpin, 3.5 h, 150 °C	 **2.3a**	83
2	 **2.1b**	1.5 equiv HBpin, 3.5 h, 150 °C	 **2.3b**	80
2	 **2.1c**	2 equiv HBpin, 18 h, 100 °C	 **2.3c**	87
3	 **2.1d**	1.5 equiv HBpin, 12 h, 150 °C	 **2.3d**	81
4	 **2.1e**	2 equiv HBpin, 18 h, 150 °C	 **2.3e**	79

Table 2.2 Continued

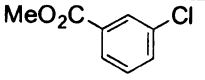
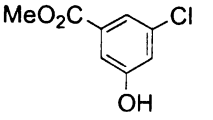
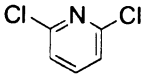
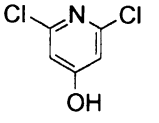
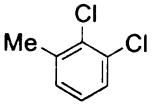
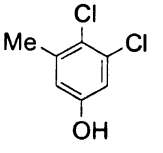
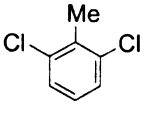
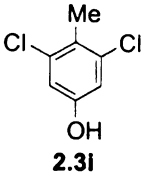
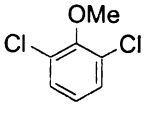
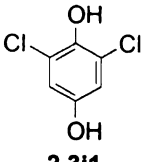
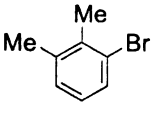
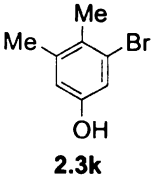
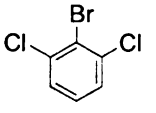
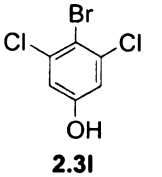
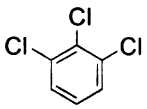
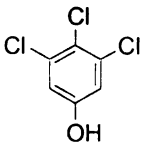
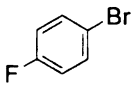
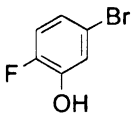
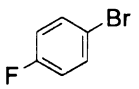
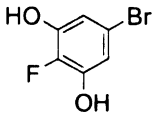
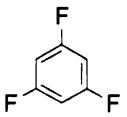
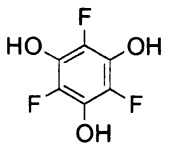
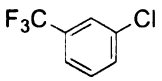
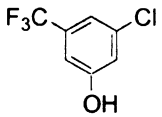
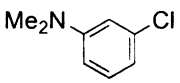
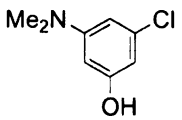
Entry	Starting arene	Borylation conditions[a]	Phenol	% Yield[b]
5	 **2.1f**	1.5 equiv HBpin, 3 h, 150 °C	 **2.3f**	70
6	 **2.1g**	1.5 equiv HBpin, 3 h, 150 °C	 **2.3g**	64
7	 **2.1h**	2 equiv HBpin, 12 h, 150 °C	 **2.3h**	85
8	 **2.1i**	1.5 equiv HBpin, 12 h, 150 °C	 **2.3i**	88
9	 **2.1j**	2.5 equiv HBpin, 16 h, 150 °C	 **2.3j1**	68
10	 **2.1k**	2.5 equiv HBpin, 50 h, 100 °C	 **2.3k**	72
11	 **2.1l**	2 equiv HBpin, 3.5 h, 150 °C	 **2.3l**	80

Table 2.2 Continued

Entry	Starting arene	Borylation conditions[a]	Phenol	% Yield[b]
12	 **2.1m**	1.8 equiv HBpin, 3 h, 150 °C	 **2.3m**	89
13	 **2.1n**	0.25 equiv HBpin, 3.5 h, 150 °C	 **2.3n**	68 (based on HBpin)
14[c]	 **2.1n**	4.5 equiv HBpin, 53 h, 110 °C	 **2.3n1**	74
15[d]	 **2.1o**	5 equiv HBpin, 63 h, 150 °C	 **2.3o**	51
16	 **2.1p**	1.5 equiv HBpin, 3.5 h, 150 °C	 **2.3p**	80
17	 **2.1q**	2 equiv HBpin, 18 h, 150 °C	 **2.3q**	79

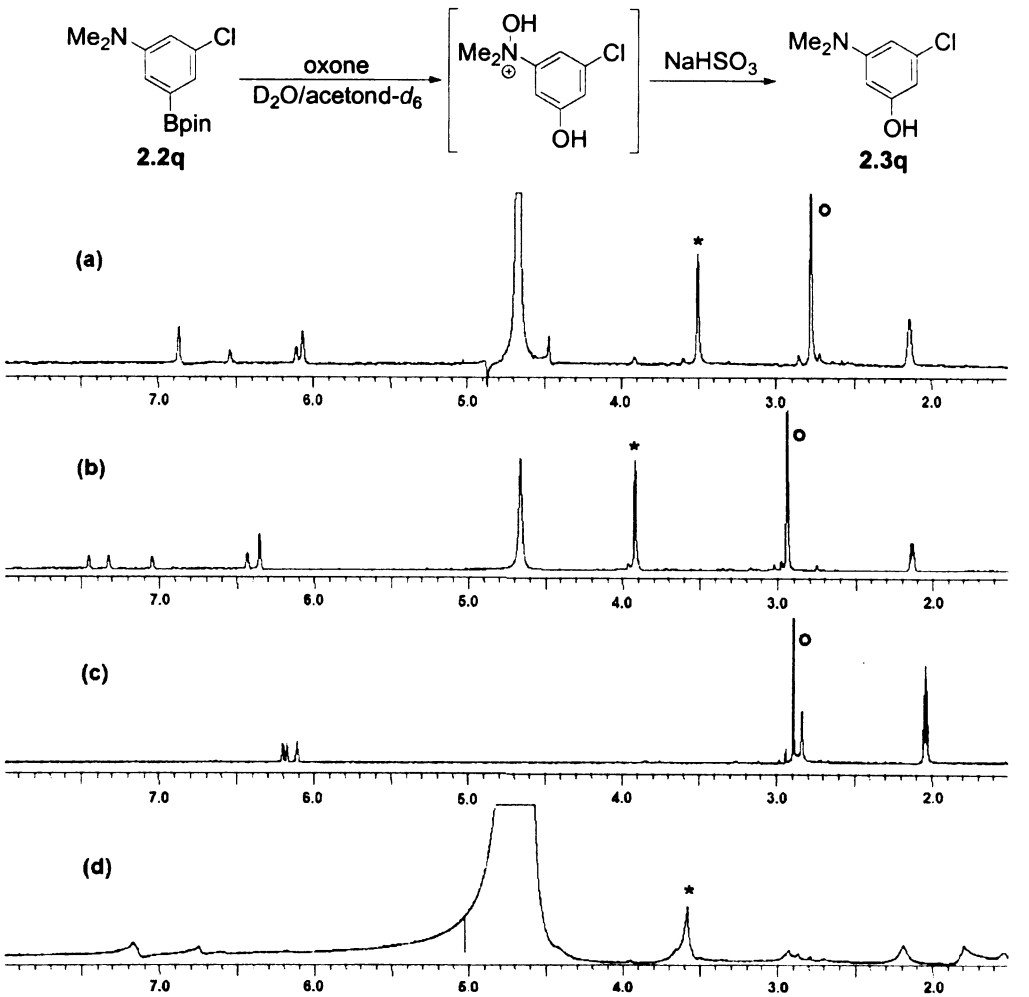
All reactions were run in 1 mmol scale. [a] Borylation used 2 mol% Ir and ligand. The time can be HBpin-batch dependent. See experimental section for full details. [b] Isolated yields, average of two runs. (Note: Most phenols were isolated with contamination of solvents, such as acetone or ether. However, due to the volatility of these phenols, forcing evaporation led to significant products loss. Thus in that case, yields were calculated by the total weight of the phenols with contaminants, and the ^{1}H NMR ratio thereof.) [c] 5 mol% Ir and ligand. [d] 3 mol% Ir and ligand.

Other substitution patterns were also possible. Since the borylation is largely sterically directed, the small size of fluorine could be exploited to achieve a

C–H borylation on its *ortho* position(s).[54] This could be further manipulated with stoichiometry adjustment to achieve a mono hydroxylated phenol or a multiple hydroxylated phenol from the same starting material (Entries 13-14). It should be noted that phenols such as **2.3n1** and **2.3o** were also prepared here for the first time.

The one-pot borylation/oxidation approach is generally clean and gives the desired phenol as the only aromatic product, with no protodeborylation or overoxidation[55] detected. That being said, this one-pot protocol still came with surprises. For example, the oxidizable nitrogens survived the oxidation and no *N*-oxides were detected (Entries 6 and 17). Surprisingly enough, it is known that both DMDO and oxone can oxidize amines or pyridines to their corresponding *N*-oxides.[56] It is hardly imaginable that such an oxidation did not occur under our reaction conditions. However, since the oxone oxidation was quenched by $NaHSO_3$ before workup, it is possible that such a quenching step reduced the *N*-oxide back to the corresponding amine. In order to test this hypothesis, we performed the oxidation of **2.2q** in deuterated solvents and then analyzed the reaction by ^1H NMR before and after the quench (Figure 2.1). The methyl protons in *N*,*N*-dimethylaniline and its oxide and hydroxide have been characterized and reported.[57] Thus by comparison with the literature, it might be clear whether the *N*-oxide is generated transiently or not.

*Figure 2.1 ^1H NMR analysis of the crude oxidation of **2.2q** before and after quench*



(a) Before quench, pH = 10. * = methyl protons in the *N*-oxide, o = methyl protons in aniline.

(b) Before quench, pH < 4. * = methyl protons in *N*-hydroxide, o = methyl protons in protonated (or hydrogen-bonded) aniline.

(c) After quench, organic layer. o = methyl protons in aniline.

(d) After quench, aqueous layer. * = methyl protons in *N*-hydroxide.

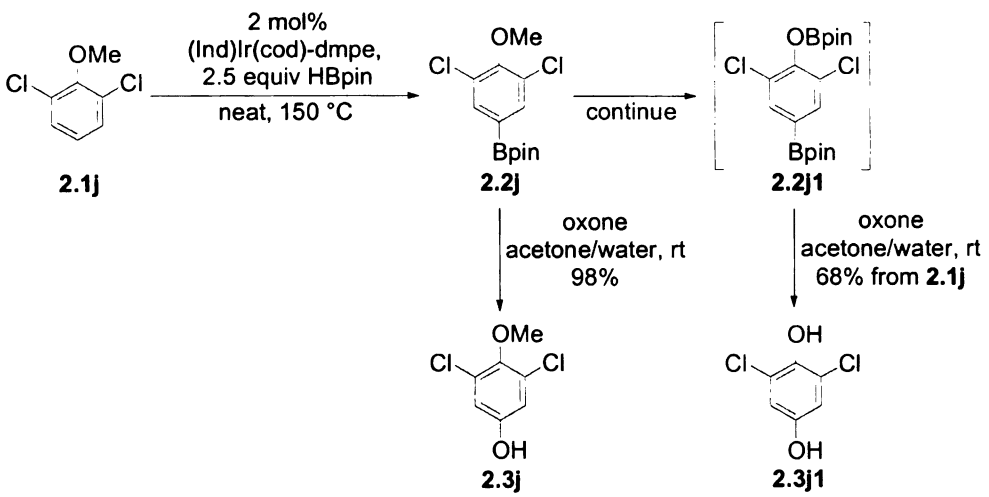
Shown in Figure 2.1 (a) and (b), the crude oxidation mixture, before being quenched, clearly had two sets of signals with approximately equal amounts. One of them (labeled as "o") corresponded to the free amine by the chemical shift

of the *N*-methyl protons. The other set (labeled as "*") showed a significant pH dependency. In a basic environment (pH 10), the chemical shift of the *N*-methyl protons occurred at 3.50, while in an acidic environment (pH 3-4), these proton signals shifted to 3.93. The exact chemical shifts are consistent with the literature values for the methyl protons of *N*,*N*-dimethylaniline *N*-oxide and its *N*-hydroxide.[57] Moreover, the pKa of a tertiary amine *N*-hydroxide is ~5,[58] which can also explain the migration of this signal with the change of pH. After quenching the oxidation with $NaHSO_3$, the signal for the *N*-oxide or the *N*-hydroxide disappeared. Thus, it would appear that the reaction conditions oxidized the nitrogen to its corresponding *N*-oxide, and the *N*-oxide was reduced back to the amine upon quenching the oxidation with $NaHSO_3$. Nonetheless, it is unlikely that the *N*-oxide intermediate can serve as a competing oxidant to convert the boronic ester into a hydroxyl. A control experiment using an *N*-oxide (NMO) as the oxidant failed in this task. In addition, literature precedence clearly indicates that amine *N*-oxide oxidation of boronic esters only occurs slowly at elevated temperatures.[59]

Another interesting observation was the demethylation of **2.1j** (Entry 9, Table 2.2). As previously mentioned, ethers are well-tolerated functional groups in both the borylation and the oxidation steps.[14,15] In fact, the same methyl ether group in **2.1e** survived the borylation/oxidation protocol quite well (Entry 4, Table

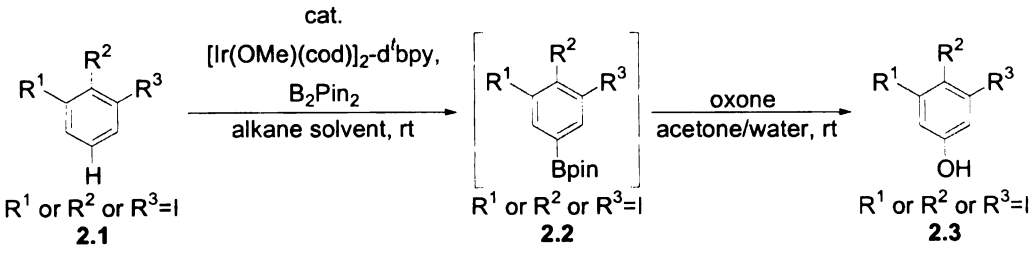
2.2). That contrast led us to investigate this specific demethylation. As the borylation step was carefully monitored by GC and GC-MS, it was realized that the demethylation occurred only after the borylation (Scheme 2.3). Therefore, isolation of the normal borylation product **2.2j** could be achieved by stopping the reaction at an early stage (less than 1 h at 150 °C, see experimental section for details). Subsequent studies confirmed that the demethylation needed both HBpin and the Ir catalyst. This is indicative of a demethylation via an S_N2 attack of the methyl group by some Ir-bound nucleophile, such as a hydride.[60] The presence of two chlorine atoms as well as the boryl group may help to stabilize the negative charge of the oxyanion and make it a better leaving group. Further studies ruled out the possibility that the demethylation occurred during the oxidation step, as **2.2j** could be oxidized to afford the 4-methoxyphenol **2.3j** in 98% yield.

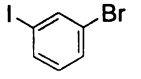
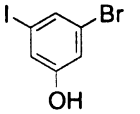
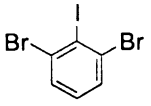
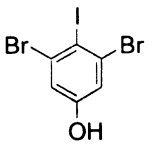
*Scheme 2.3 Investigation of the demethylation of **2.1j***



While the borylation has good functional group tolerance, Smith's original catalyst (Ind)Ir(cod) does not work well with iodobenzenes.[14c] By virtue of the higher reactivity of Miyaura, Ishiyama and Hartwig's $[Ir(OMe)(cod)]_2$ catalytic system, borylation could be achieved at room temperature and iodide tolerance became attainable. Under such conditions, the borylation/oxidation protocol could be successfully extended to iodobenzene substrates (Table 2.3). It is noteworthy that **2.3s** (Entry 2) was a starting material in the total syntheses of the anticancer natural products duocarmycin and yatakemycin. In these cases, the literature preparation of **2.3s** consists of a 6-step process from 4-nitrophenol.[40,61]

Table 2.3 C-H Borylation/oxidation protocol for iodinated substrates



Entry	Starting arene	Borylation conditions[a]	Phenol	% Yield[b]
1	 **2.1r**	0.6 equiv B_2pin_2, 11 h, rt	 **2.3r**	76
2	 **2.1s**	1.0 equiv B_2pin_2, 3 h, rt	 **2.3s**	93

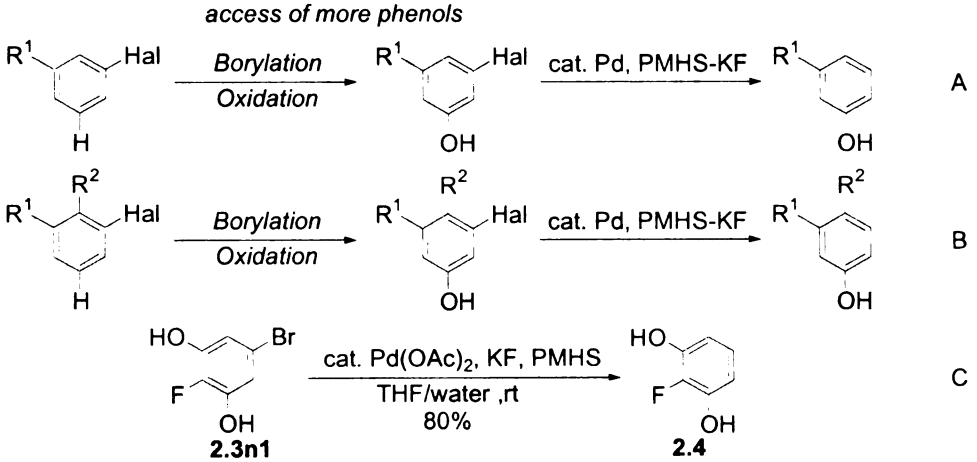
All reactions were run in 1 mmol scale. [a] Borylation used 3 mol% Ir. See experimental section for full details. [b] Isolated yields, average of two runs.

Although such a process could afford **2.3s** in a satisfactory 65% overall yield, our one-pot procedure is much more concise and high-yielding.

While our one-pot C–H borylation/oxidation protocol is efficient at preparing *meta*-substituted phenols or phenols with an *ortho* fluoride, phenols with different substitution patterns remain elusive. Since the C–H borylation is directed to the sterically open sites, substrates with more than one sterically open position could not be functionalized regioselectively. For example, monosubstituted benzenes generally afford a statistic mixture of *meta* and *para* borylated products. 1,2-Disubstituted benzenes bearing different groups also undergo nonselective borylation at the 4- and 5-positions. Achieving regioselective monoborylation of these substrates is not straightforward. Therefore, preparing mono-substituted phenols with a single *meta*-substituent or 3,4-disubstituted phenols with different groups at the 3- and 4-positions is not straightforward. Since the C–H borylation tolerates halides, it is possible to utilize halides as protecting groups to block certain positions from being borylated. Such halides could be removed by subsequent Pd-catalyzed hydrodehalogenation reaction with polymethylhydrosiloxane (PMHS)[62]. In this manner, preparing mono-substituted phenols with a single *meta*-substituent could start from a *meta*-substituted halobenzene (Scheme 2.4 A) and reduce the halide after borylation/oxidation. Similarly, preparing 3,4-disubstituted phenols with different groups at the 3- and 4-positions

could start from a 2,3-disubstituted halobenzene (Scheme 2.4 B) and reduce the halide after borylation/oxidation. Such a combination could further extend the utility of the borylation/oxidation protocol. By virtue of the extremely low cost of PMHS (< $8 per mole hydride), these preparations would still remain economical. For example (Scheme 2.4 C), compound **2.4** cannot be obtained via simple borylation/oxidation because borylation of fluorobenzene is not regioselective. However, PMHS-reduction of the bromide in **2.3n1**, previously prepared from **2.1n** (Entry 14, Table 2.2), was easy and successful, affording **2.4** in good yield.

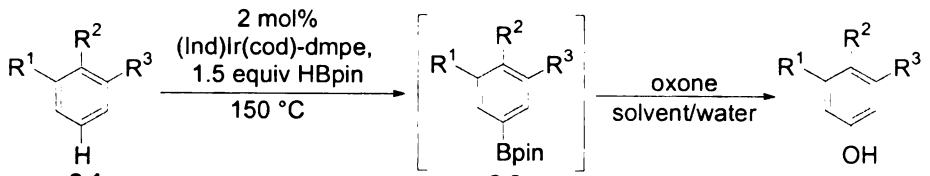
Scheme 2.4 Combining borylation/oxidation with Pd-catalyzed PMHS reduction: access of more phenols



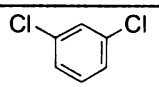
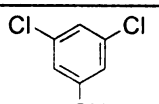
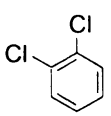
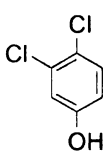
2.4 Mechanistic Investigation of Aryl Boronic Ester Oxidation with Oxone

Mentioned previously in Section 2.2, our oxidation conditions questioned the literature suggestion[43d] that the oxone oxidation of an aryl boronic ester involves the *in situ* formation of DMDO. In order to examine this question, the oxidation was performed in solvents other than acetone (Table 2.4). These solvents

Table 2.4 Solvent study in the oxidation step



certainly **2.1** **2.2** **2.3**

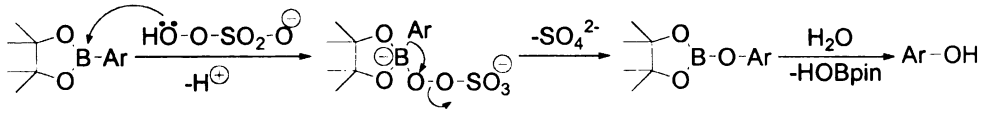
Entry	Substrate	Solvent[a]	Product	Temperature[b]	% Yield[c]
1		THF		0 °C	74
2		CH_3CN		0 °C	82
3	**2.1b**	Dioxane	**2.3b**	rt	79
4		Diglyme		rt	80
5		$CHCl_3$		0 °C	0
6		CH_2Cl_2		rt	0
7[d]		CH_2Cl_2		rt	44
8		DMF		rt	85
	2.1t		**2.3t**		

All reactions were run in 1 mmol scale. [a] 1:1 to water (*V/V*). [b] 15 min for 0 °C reaction, and 7 min for room temperature reaction. [c] Isolated yields. [d] 25 mol% Bu_4NI was added as phase transfer catalyst.

could not be used to make DMDO and a successful oxidation in these solvents would strongly support our hypothesis that DMDO was not the real oxidant. Indeed, the results indicated that the oxidation did not have to be run in acetone, as solvents such as THF, dioxane, and DMF proved well suited for this oxidation. This result argues against the participation of DMDO in the oxidation. On the other hand, CH_2Cl_2 and $CHCl_3$ were not good solvents (Entries 5-7), as the oxidation failed in these two solvents. Interestingly, it seemed that all the suitable solvents are polar and water-miscible, whereas the unsuitable solvents are less polar and not water-miscible. As the aryl boronic esters are sparingly

soluble in water, particularly in the highly salted aqueous oxone solution, while at the same time oxone is insoluble in less polar organic solvents such as $CHCl_3$ and CH_2Cl_2, it is reasonable to imagine that the role of the organic solvent is simply to bring the two reagents into the same phase. To test this hypothesis, the oxidation in CH_2Cl_2 was repeated with a phase transfer catalyst (Entry 7). This time, considerable conversion was observed within the same period of time to afford the phenol in 44% yield. Therefore, it is very possible that in the oxidation, the need for a polar, water-miscible organic solvent is simply a solubility issue. Thus, the oxidation mechanism probably does not involve DMDO. Instead, the traditional mechanism involving a nucleophilic attack of the peroxy nucleophile to the boron atom, followed by an aryl transfer (Scheme 2.5) is very likely at work, which resembles the hydrogen peroxide oxidation of trialkylborane.

Scheme 2.5 The revised mechanism for the oxone oxidation of an aryl boronic ester



To further probe this hypothesis, the reaction was performed with *m*CPBA as the oxidant in THF. Like oxone, *m*CPBA is another nucleophilic oxidant with an internal leaving group. As expected, we found that *m*CPBA could oxidize the boronic ester intermediate to the corresponding phenol in 69% yield. That again supports the hypothesized mechanism shown in Scheme 2.5. It should also be

noted that distilled DMDO (acetone solution) was unable to perform the oxidation, which strongly disfavors the involvement of DMDO in the oxidation step.

2.5 Conclusions

In conclusion, we have developed an efficient one-pot C–H borylation/oxidation protocol to prepare *meta*-substituted phenols directly from arenes without isolation of the boronic ester intermediates. This protocol is complementary to traditional methods, and is particularly suitable for preparation of phenols with substitution patterns hard to access through traditional methods. The oxidation does not involve the formation of DMDO.

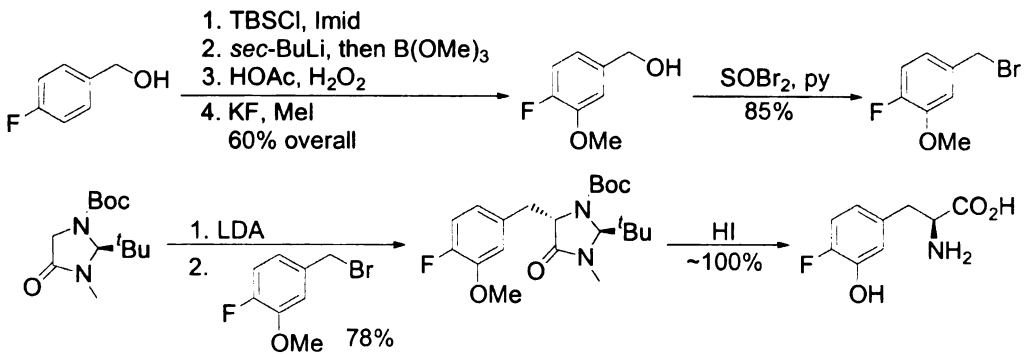
Chapter 3. The C–H Borylation/Oxidation Study of Aromatic Amino Acids Derivatives and Analogues

3.1 Aromatic Amino Acids and the Potential C–H Borylation Investigation

Aromatic amino acids, including phenylalanine, tyrosine, histidine and tryptophan, are important building blocks for peptides, natural products and pharmaceuticals.[63] Although bearing different aromatic rings, these molecules can be viewed as substituted arenes. Therefore, they are interesting substrates for the C–H borylation chemistry. In fact, certain boronic acids derived from these amino acids, such as 4-boronophenylalanine (4-BPA), are very important radiotherapeutical agents[64] due to the neutron capture nature of ^{10}B. In addition, certain hydroxylated amino acids, such as 5-hydroxytryptophan and *meta*-tyrosine, are important bioactive compounds.[65] Access to these compounds may be straightforward via our C–H borylation (or borylation/oxidation), even though their efficient preparation with traditional chemistry may be difficult. In fact, the most efficient preparation of 4-BPA is a multiple-step process from tyrosine.[66] The synthesis involves triflation of the phenol hydroxyl group followed by Pd-catalyzed borylation of the triflate[31] as key steps. The direct preparations of hydroxylated tryptophans and phenylalanines are also limited.[67] Most of the existing methods, ironically, start from an aromatic precursor and construct the amino acid moiety later,[66c-e] instead of modifying an aromatic moiety with the amino acid functionality

pre-installed.[68,69b] For example, 4-fluoro-*meta*-tyrosine is a biochemical probe of striatal dopaminergic function and has attracted significant attention,[69a] yet its current synthesis requires arduous multiple-step processes[69b-e] (Scheme 3.1).

Scheme 3.1 Literature preparation of 4-fluoro-meta-tyrosine



Due to this limitation, direct and rapid synthesis of those biologically interesting hydroxylated amino acids for SAR or combinatorial studies is hard to realize. Therefore, development of a method that can directly functionalize the aromatic moiety of the amino acids is needed. We proposed that the catalytic borylation would serve this purpose. Putting this chemistry into practice, we should gain easy and rapid access to not only the borono/boryl and hydroxyl aromatic amino acids, but also other diverse functionalized derivatives.

On the other hand, although the C–H borylation has been studied extensively for simple substituted arenes with various substitution groups and patterns, this reaction has not been well developed with more complicated substrates such as these aromatic amino acids. Exactly how the functionalized side chain of the

amino acids would respond to the borylation was not known. Should the borylation of the aromatic amino acids be successful, the scope of C–H borylation would be significantly expanded and further information on reaction condition modifications and catalyst designs could be obtained.

3.2 Study of Substituted Phenylalanine Derivatives and Analogues

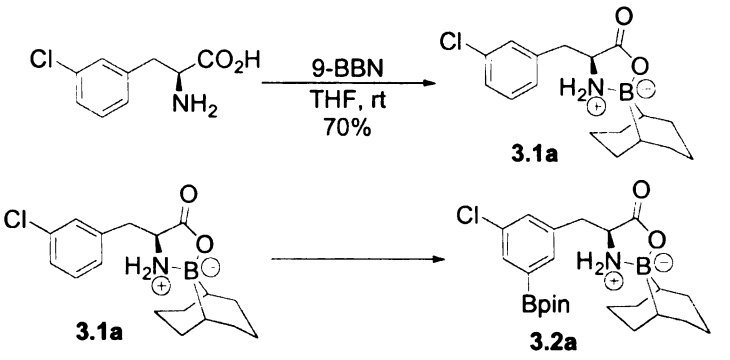
Since the catalytic borylation has been studied most extensively on substituted benzenes, our initial plan was to use substituted phenylalanines as substrates. 3-Chlorophenylalanine was chosen as the test substrate due to its commercial availability and the presence of an electron-withdrawing group, which would hopefully accelerate the borylation. We first investigated the protecting group choice of the amine and carboxylate.

The protection of amino acids has been extensively studied,[70a] and two main methods of protection are available. Joint protection of both the amine and the acid with a single protecting group is one option, and individual protection with two different protecting groups is another common strategy. An operationally easy joint protection uses 9-BBN,[70b,c] the presence of which is also reported to increase the solubility of amino acids in organic solvents. Thus, the 9-BBN-derived 3-chlorophenylalanine **3.1a** was prepared and subjected to the C–H borylation conditions using the more reactive $[Ir(OMe)(cod)]_2$ catalytic system (Scheme 3.2). Two problems were quickly realized. First, **3.1a** was still not soluble in standard

C–H borylation solvents, namely alkanes or cycloalkanes, thus a more polar solvent such as THF had to be used. Second, the reaction of **3.1a** was extremely sluggish. Mild heating at 45 °C for 14 h did not lead to any observable borylation with 3 mol% Ir catalyst. Compared with simple arene substrates,[15b] this behavior could be evaluated as "unreactive". Since microwave irradiation can be a much more effective heating method,[71] borylation of **3.1a** was then studied under microwave conditions. Still, only low conversion (37%[72]) was observed with 6 mol% Ir catalyst after 20 min of irradiation at 120 °C.

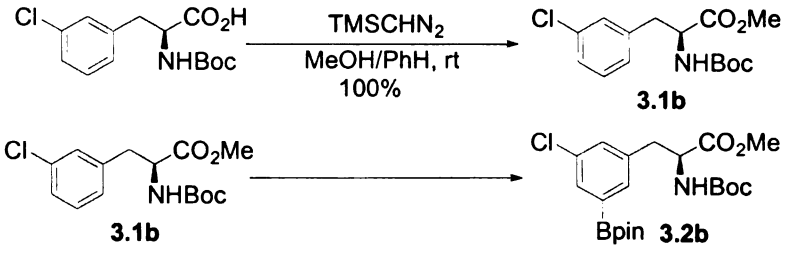
Given these poor results, a different protection strategy was pursued. The individual protection method provided an *N*-Boc amino acid methyl ester **3.1b**. This substrate was soluble in cyclohexane, the standard solvent for catalytic borylation. Gratefully, **3.1b** reacted much faster than **3.1a**, giving full conversion under the same microwave conditions (Scheme 3.3). The reaction conditions could be further improved in terms of catalyst loading and reaction times without impairment of conversion. Thus, conditions with half of the Ir loading (3 mol%) and half of the microwave irradiation time (10 min) allowed a virtually complete borylation of **3.1b.** Upon isolation, the product was identified as the desired 5-borylated **3.2b**. Control experiments demonstrated that the borylation failed with the unprotected acid, and gave complex mixtures with the unprotected amine.

Scheme 3.2 9-BBN-derived 3-chlorophenylalaine and its borylation



1	1.5 mol% $[Ir(OMe)(cod)]_2$, 3 mol% d^{t}bpy, 1.5 equiv B_2pin_2, THF, 45 °C, 14 h	No conversion
2	3 mol% $[Ir(OMe)(cod)]_2$, 6 mol% d^{t}bpy, 1.5 equiv B_2pin_2, THF, μW, 120 °C, 20 min	37% conversion (see ref 72)

Scheme 3.3 N-Boc 3-chlorophenylalaine methyl ester and its borylation



1	3 mol% $[Ir(OMe)(cod)]_2$, 6 mol% d^{t}bpy, 1.5 equiv B_2pin_2, CyH, μW, 120 °C, 20 min	100% conversion
2	1.5 mol% $[Ir(OMe)(cod)]_2$, 3 mol% d^{t}bpy, 1.2 equiv B_2pin_2, CyH, μW, 120 °C, 10 min	97% conversion (see ref 72) 80% isolated

The successful borylation of **3.1b** demonstrated the viability of the borylation on amino acid derivatives. It also demonstrated the importance of the protecting group choice on such borylations. On the basis of this success, we investigated other substituted phenylalanine substrates in the form of *N*-Boc amino acid methyl esters.

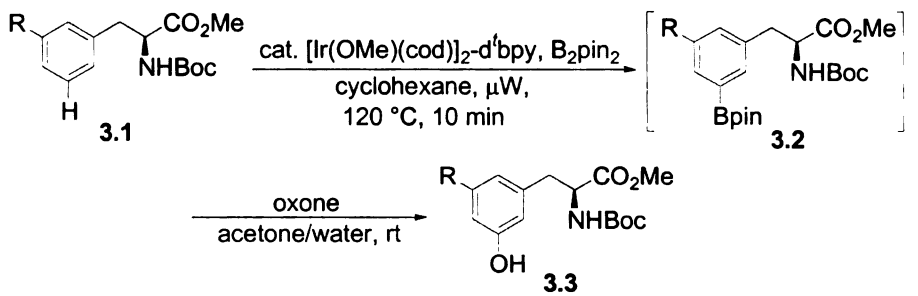
Surprisingly enough, it was quickly realized that the successful borylation conditions for **3.1b** (Entry 2, Scheme 3.3) worked only for **3.1b** itself. Other substrates such as the 3-trifluoromethyl analogue **3.1c** and 3-cyano analogue **3.1d** (see Table 3.1 for structures) could not be completely borylated under the same conditions. It was also found that in order to achieve higher conversions, it was better to increase the loading of Ir catalyst rather than increase the reaction time. This may be indicative of the catalytic species undergoing some type of decomposition under the reaction conditions. Unfortunately, when the catalyst loading, as well as the loading of B_2pin_2, increased, isolation and purification of the corresponding boronic ester products became very difficult. The product tails significantly on silica gel chromatography, making removal of the B_2pin_2 byproducts and the d^{t}bpy ligand hard to achieve. Reverse phase HPLC was also unsuccessful at this task. However, since the boronic pinacol ester can be transformed in its crude form to the corresponding, but isolable (by reverse phase HPLC), boronic acid in the same pot,[68a,c] we believe that this problem of separation is not without a solution.

Having developed successful borylation conditions, we attempted to further utilize this reaction, as well as the boronic ester intermediates, toward preparation of more amino acids derivatives. Our attention then shifted to applying the one-pot C–H borylation/oxidation, discussed in Chapter 2, to these phenylalanine

derivatives to obtain tyrosine derivatives and analogues. Thus the crude borylation mixture was treated with acetone and oxone. To our pleasure, the corresponding hydroxyl phenylalanine derivatives could be generated and isolated in satisfactory yields for a scope of substrates (Table 3.1).

The substrate screening revealed valuable information. As seen in Table 3.1, the borylation has a reasonable substrate scope for these phenylalanine derivatives and analogues. That said, substrates having electron-withdrawing

Table 3.1 C-H Borylation/oxidation protocol to phenylalanine derivatives and analogues



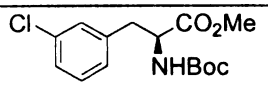
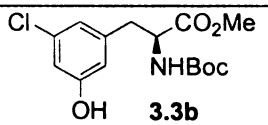
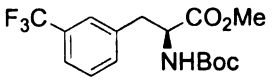
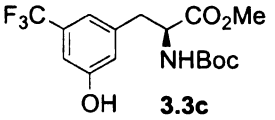
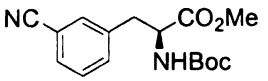
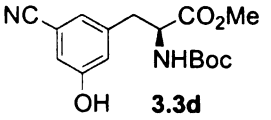
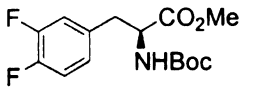
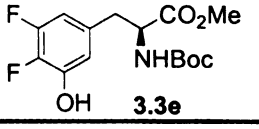
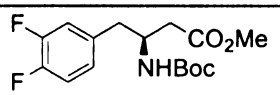
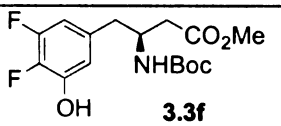
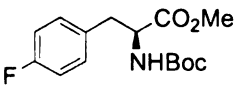
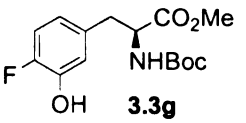
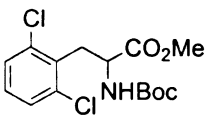
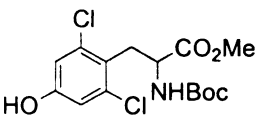
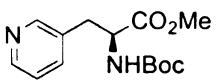
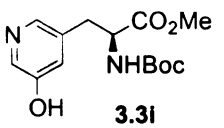
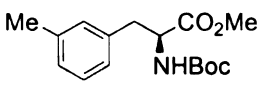
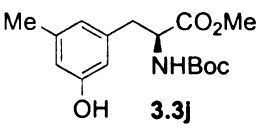
Entry	Starting material	Borylation conditions[a]	Product[b]	% Yield[c]
1	 **3.1b**	3 mol% Ir 1.2 equiv B_2pin_2	 **3.3b**	70
2	 **3.1c**	9 mol% Ir 2.0 equiv B_2pin_2	 **3.3c**	66
3	 **3.1d**	7 mol% Ir 1.75 equiv B_2pin_2	 **3.3d**	77
4	 **3.1e**	8 mol% Ir 1.75 equiv B_2pin_2	 **3.3e**	79

Table 3.1 Continued

Entry	Starting material	Borylation conditions[a]	Product[b]	% Yield[c]
5	 **3.1f**	3 mol% Ir 1.5 equiv B_2pin_2	 **3.3f**	48[d]
6	 **3.1g**	6 mol% Ir 1.25 equiv B_2pin_2	 **3.3g**	44[e]
7	 **3.1h**	3 mol% Ir 1.5 equiv B_2pin_2	 **3.3h**	71
8	 **3.1i**	15 mol% Ir 2.0 equiv B_2pin_2	 **3.3i**	36[f]
9	 **3.1j**	15 mol% Ir 2.0 equiv B_2pin_2	 **3.3j**	0[g]

All reactions were run in 0.5 mmol scale. [a] All borylations gave > 90% conversion under the specific conditions, unless otherwise indicated in experimental section. [b] The stereochemistry of products were not determined. [c] Isolated yields. [e] 20% starting material recovered. [d] 9% 3,5-dihydroxyl product was also isolated. Attempt to obtain this dihydroxyl compound as major product experienced unsuccessful oxidation. [f] Reaction was run in THF and product was isolated as a TFA salt. [g] Borylation of this substrate gave 43% conversion at 140 °C, but oxidation on crude material failed to give any phenolic product.

groups seem to have higher reactivity and likelihood for successful borylation/oxidation. An electron-releasing group on the aromatic ring, such as in **3.1j**, significantly slowed the reaction (Entry 9). Notably, although the reactions were performed at 120 °C, functional group tolerance was still

maintained. Not only did the protected amino acid side chains survive the reaction, other groups on the aromatic ring, such as the cyano group (Entry 3) also survived quite well. Regretfully, we did not examine the stereochemistry of the products, and therefore, the response of the stereogenic centers on the amino acid side chains to the borylation remains unknown.

The small size of fluorine, again, can be exploited to allow borylation to occur at its *ortho* position (Entries 4-6). This reaction could also be applicable to a β-amino acid derivative such as **3.1f** (Entry 5). While most substrates are 3-substituted phenylalanines, a 2,6-disubstituted phenylalanine can be selectively functionalized at 4-position (Entry 7). Heterocyclic substrates, such as **3.1i** (Entry 8) can also react, albeit under more forcing borylation conditions. Compound **3.3g**, a protected version of 4-fluoro-*meta*-tyrosine (see Scheme 3.1), can be readily prepared in acceptable yield directly from commercially available 4-fluorophenylalanine.

In terms of solvents for the borylation, it was found that substrates that are insoluble in cyclohexane could be successfully borylated in THF (Entry 8). Although control experiments showed that the same borylation occurs more slowly in ethereal solvents than in alkane solvents, the introduction of ethereal solvents to borylation is still beneficial, because our previous solution to the insoluble substrates was to use fairly expensive HBpin as the solvent.

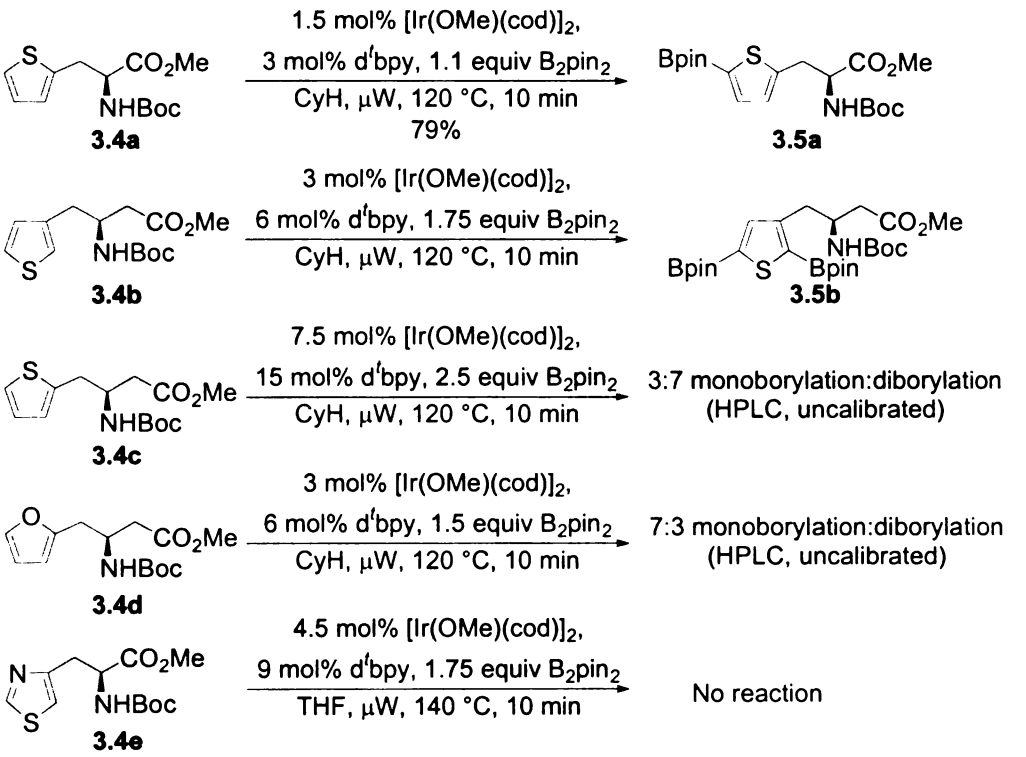
3.3 Study of 5-Membered Phenylalanine Analogues

While phenylalanine derivatives and its 6-membered heterocyclic analogue work well under the C–H borylation conditions, the reactivity of the 5-membered analogues remained unexplored. Previous literature and experience suggested that the 5-membered heteroaromatics react faster toward the borylation and are generally borylated at the α-positions.[17] Thus, a brief survey was conducted to include various thiophenylalanine, furylalanine derivatives, and etc (Scheme 3.4).

Although the results are very preliminary, the data are interesting. A thiophene substituted by an α-amino acid side chain at the α-position (**3.4a**) could be smoothly monoborylated at the other α-position to afford **3.5a**, whereas a thiophene substituted by a β-amino acid side chain at the β-position (**3.4b**) could be smoothly diborylated at both α-positions to afford **3.5b**. Somewhat surprisingly, although crude **3.5a** was accompanied with ~10% diborylation byproduct, pushing the reaction conditions to achieve full diborylation of **3.4a** was not achieved. On the contrary, attempts to stop the borylation of **3.4b** at the monoborylation stage also failed, resulting in the formation of a mixture of starting material, two monoborylation products, and **3.5b**. This difference is more likely due to the higher reactivity of the α-position of thiophene toward the borylation, rather than the difference in the amino acid side chains, because **3.4c**, having a β-amino acid side chain at the α-position, could not be fully diborylated either.

That being said, for these 5-membered substrates, the significant conversion to the second borylation, especially on the *ortho* position of a sterically demanding alkyl chain, was considerably different from the behavior of the 6-membered aromatic substrates. The elevated reactivity of thiophene toward the borylation, as well as the difference in ring sizes,[73] may be possible explanations of this observation that is not seen in 6-membered rings.

Scheme 3.4 Borylation of 5-membered phenylalanine analogues

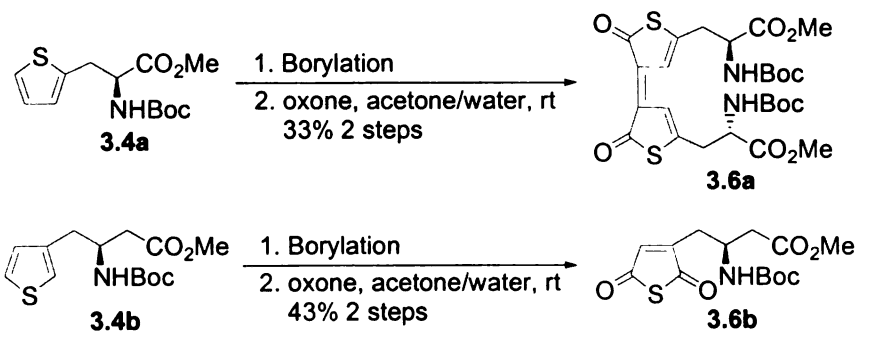


Nonetheless, it was found that different aromatic structures resulted in different reactivity. The furan ring in **3.4d** was not borylated as selectively as **3.4a** and **3.4c**. In fact, under the specific conditions shown in Scheme 3.4, **3.4d**

afforded two isomeric monoborylation products (ca. 1.8:1), as well as a diborylation product. Such a difference in reactivities between furan and thiophene had not previously been observed to this extent in simple substrates. In addition, a thiazole substrate **3.4e** did not give any observable product.

The one-pot C–H borylation/oxidation of these heteroaromatic substrates was even more unexpected (Scheme 3.5). First of all, complete oxidation of **3.5a** and **3.5b** required more oxone than the oxidation of simple arenes. Using 1 equiv of oxone simply led to incomplete consumption of **3.5a** and **3.5b**. Secondly, neither of these substrates afforded the expected hydroxylated product or its keto tautomer. Oxidation of crude **3.5a** revealed the dimerized **3.6a** as the only observed product by HPLC, while oxidation of crude **3.5b** afforded the overoxidized **3.6b** with only small amount of dimer (ca. 8%). We reasoned that the formation of **3.6a** might involve the transient generation of the hydroxyl intermediate, since 2-boronothiophene was known to be oxidized by hydrogen peroxide to afford the 2-hydroxythiophene product,[74a] and at the same time 5-

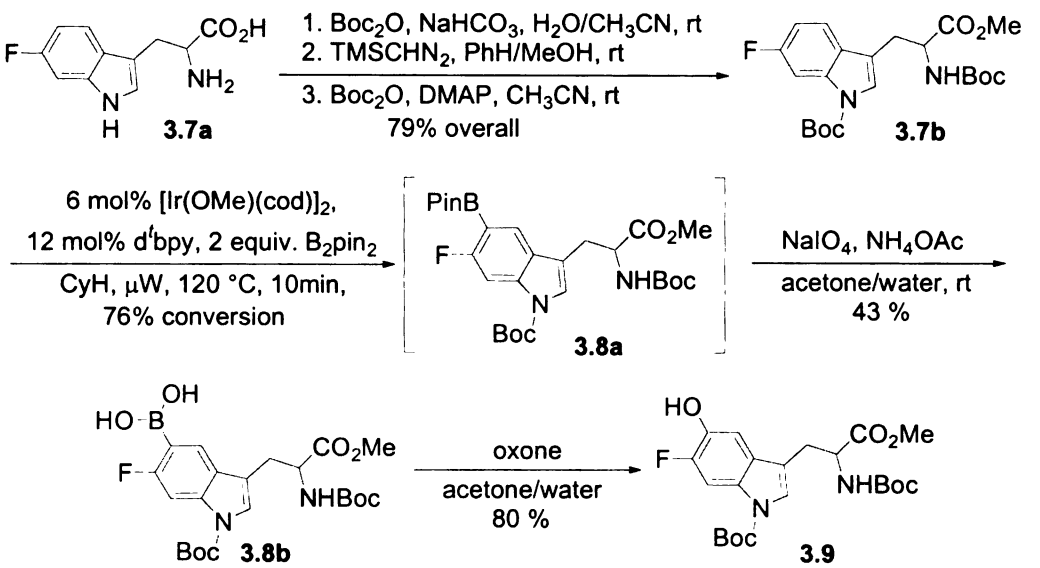
Scheme 3.5 Borylation/oxidation of 5-membered phenylalanine analogues



alkyl-2-hydroxythiophene is also known to undergo the same oxidative dimerization to generate products resembling **3.6a**.[74b,c]

3.4 Study of a Tryptophan Derivative

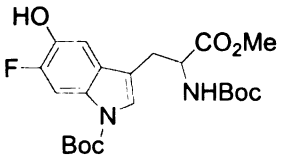
Scheme 3.6 Boylation/oxidation of a tryptophan derivative

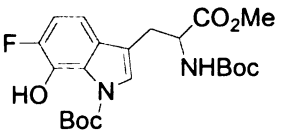


Our attention was then turned to a tryptophan derivative (Scheme 3.6). To our delight, after global protection of commercially available 6-fluorotryptophan **3.7a**, **3.7b** could be smoothly borylated, albeit in lowered 76% conversion. Isolation of **3.8a** from the crude reaction mixture was not successful, but **3.8a** could be converted into the corresponding isolable boronic acid **3.8b**. Oxidation of pure **3.8b** successfully afforded the corresponding hydroxyl product **3.9** in good yield. However, as the 7-position in unprotected indole is also available for borylation,[17e,f] the borylation of **3.7b** would possibly occur at either the 5-position

or the 7-position. Therefore, the unambiguous assignment of regioselectivity of this borylation remains elusive.[75-76] A temporary assignment as the 5-borylated product has been proposed based on the absence of two doublets of doublets in ^{1}H NMR (due to J_{H-F} coupling), as well as the empirical calculation of ^{13}C NMR chemical shifts (Figure 3.1). Clearly, more work needs to be done with regards to the structural assignment.

Figure 3.1 Empirical calculation of the ^{13}C NMR chemical shifts and structural assignment





			Observed
C5	138	110	141
C6	140	140	150
C7	99	127	103

3.5 Conclusions

In conclusion, we have demonstrated that the C–H borylation chemistry can be extended to aromatic amino acid derivatives, especially phenylalanine and tryptophan derivatives and analogues, under microwave irradiation conditions. The one-pot C–H borylation/oxidation protocol is also viable to certain phenylalanine derivatives and analogues. However, 5-membered phenylalanine analogues undergo overborylation and overoxidation. As these results are only preliminary, more work in this area is certainly needed to further understand the

chemistry and the behavior of questionable substrates.

Chapter 4. The C–H Borylation/Deuteration Approach for the Preparation of Specifically Deuterated Aromatics

4.1 Specifically Deuterated Aromatics and Their Preparations

Isotopically labeled compounds,[77] including those labeled at specific positions, are widely used as probes for spectroscopy,[78] reaction mechanisms,[79] pharmacokinetics, and enzymology.[80] Deuterated or tritiated compounds are of particular interest since they are easier to prepare and relatively less expensive than the corresponding ^{13}C or ^{14}C-labeled compounds. Deuterium also has a larger kinetic isotope effect versus hydrogen, compared with ^{13}C versus ^{12}C.[81] As the need for specifically labeled compounds grows, ready incorporation of deuterium atoms at specific positions, on aromatic rings for instance, in good yield and with high incorporation becomes increasingly important. Ideally, isotopic incorporation methods would be more attractive if they can be applied at the late stage of a synthesis. In such cases, however, functional group compatibility and good regioselectivity become important factors.

Traditional deuteration methods such as acid-, base- or transition metal-promoted direct H/D exchange methods[77,82] often suffer from harsh conditions, incomplete deuterium incorporation and relatively poor regioselectivity, and are therefore more useful for global deuteration of insensitive substrates.[82d-e] Deuteriolysis of organometallic[78c,79,83] compounds and reduction of

organohalogen compounds[84] by deuteride or its equivalents are among the most important and most used methods to generate site-specifically deuterated compounds. However, the necessary preparation of the halide precursors and functional group compatibility retard their use. This is particularly true if the halide precursor is either equipped with sensitive functional groups or, in case of an aromatic halide precursor, bearing substitution patterns contrary to the electronic directing effects. Another drawback of Grignard deuteriolysis is the lowered deuterium incorporation (~80% is not uncommon), attributed to the partial H radical abstraction from the solvent by the Grignard reagent.[79,83] Consequently, direct H/D exchanges or one-pot deuteration methods without these drawbacks would be attractive. In this regard, transition metal catalysts, such as the Felkin-Crabtree catalyst ($[Ir(PCy_3)(py)(cod)][PF_6]$) are known to catalyze the direct H/D exchange of a variety of substrates at the positions that are accessible to the metal center via an internal coordination.[85] Such chelation-directed metalation methods can be regioselective toward the *ortho* positions of the chelating group on the aromatic substrates and also tend to be tolerant of functional groups. However, the level of deuterium incorporation is widespread against different substrates and varies significantly from one to another and can be unpredictable. Deuterated acids and Lewis acidic $BF_3{\cdot}Et_2O$ with D_2O can promote H/D exchange on aromatic substrates at the *ortho/para*

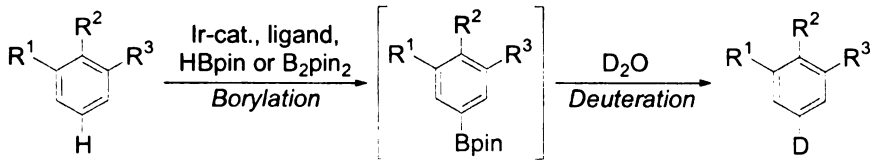
positions with respect to strong electron-donating groups.[86] However, a simple method to install deuterium atoms at sites that are neither close to a chelating group nor activated by electronic effects is still lacking. As a result, preparation of certain deuterated aromatics can be arduous.[78c]

4.2 Applications of Catalytic Aromatic C–H Borylation in the Synthesis of Specifically Deuterated Aromatics and the Discovery of Ir-catalyzed Deuteration of Arylboronic Acids/Esters

Regiochemically, catalytic aromatic C–H borylation, previously mentioned in Chapters 1 and 2, is shown to be dominated by a sterics-directing effect. Thus it is complementary in regioselectivity to the existing metal-catalyzed direct H/D exchange methods and acid-promoted H/D exchanges of electron-rich arenes. In addition, the C–H borylation generates a boronic ester group, which upon subsequent deuteriolysis, presumably, would afford the corresponding deuterium-labeled compounds (*vide infra*) without suffering the hydrogen atom abstraction problems of Grignard reagents. The particular capability of the borylations to tolerate halogens would minimize the problems of regio- or chemoselectivity of Grignard formation or deuterio-reduction from polyhaloarenes, and therefore would be beneficial for preparing deuterated arenes with halide substituents. Thus, a one-pot C–H borylation/deuteration strategy should constitute a general method to prepare specifically labeled aromatics with

deuterium, which could possibly be extended to tritium labeling (Scheme 4.1).

Scheme 4.1 Proposed one-pot C-H borylation/deuteration protocol for preparation of specifically deuterated aromatics



2.1 **2.2** **4.3**

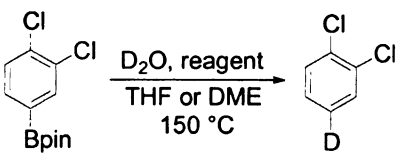
Although the protonolysis/deuteriolysis of organoboron compounds is a well-known process,[87] most investigations have employed trialkyl and triaryl boranes as starting materials.[88] Surprisingly, utilization of boronic acids/esters as starting substrates in this reaction has only been performed as mechanistic studies or other physical organic investigations.[89] Synthetically useful reaction conditions and the development thereof are still lacking.[90]

Presented with such a situation, we first sought reaction conditions that would provide a reliable method for the protonolysis/deuteriolysis of the aryl boronic esters generated in the borylation reactions. A variety of conditions were tested on commercially available 3,4-dichlorophenylboronic acid pinacol ester **2.2t** (Table 4.1). In this study, water-soluble solvents, such as THF or DME, were chosen in order to make the reaction homogeneous.

Much to our disappointment, the desired deuteration reaction proved unexpectedly difficult. At temperatures as high as 150 °C (sealed tube), the reaction with pure **2.2t** in D_2O failed to give the deuterated arene when promoted

by either an acid (Entry 1) or a tertiary amine base (Entry 7). Although an oxygen base (Entries 2-5) or cesium fluoride (Entry 6) could promote the reaction, full conversion was not obtained even after extended periods. This low reactivity of the boronic acids/esters toward protonolysis/deuteriolysis was obviously an obstacle that needed to be overcome.

Table 4.1 Acid and base-promoted conditions



2.2t **4.3a**

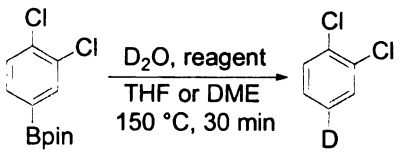
Entry	Reagent (equiv)	Time /h	% Conversion[a]
1	AcOD (1.0)[b]	2	trace
2	NaOH (0.11)	2	26%
3	NaOH (1.1)	2	59%
4	NaOMe (2.2)	1	61%
5	NaOMe (2.2)	5	76%
6	CsF (1.1)	4[c]	55%
7	DABCO (1.1)	5	trace

All reactions were run in 0.5 mmol scale in 0.25 mL D_2O (~23 equiv) and 2 mL DME. [a] GC area ratio calibrated with corresponding non-deuterated compound. [b] 0.5 equiv Ac_2O was actually used. [c] 1 h at 150 °C followed by 3 h at 160 °C

Fortunately, but unexpectedly, a control experiment using crude **2.2t** generated from the borylation of 1,2-dichlorobenzene (**2.1t**) gave full conversion to the corresponding deuterium-labeled product **4.3a** within 1 h at 150 °C. This reaction was performed without acid or base, and the only "extra additive" in the reaction mixture was the residual Ir catalyst and phosphine ligand that were used

during the borylation. This surprising result triggered the thought that the Ir residue might serve as a catalyst for the deuteriolysis of aryl boronic esters. Of course, the phosphine residue could also be playing a role. However, it is not known that phosphine can catalyze such a process.

Table 4.2 Ir-catalyzed conditions



2.2t **4.3a**

Entry	Ir species[b]	Other species	Solvent	Conversion[c]
1	None	None	THF	<1%
2	None	None	DME	<1%
3	None	dmpe	THF	<1%
4	Crude borylation mixture	None	THF	100%
5	(Ind)Ir(cod)	None	THF	95%
6	(Ind)Ir(cod)	None	DME	97%
7	$[Ir(OMe)(cod)]_2$	None	THF	98%
8	$[Ir(PCy_3)(py)(cod)][PF_6]$	None	DME	100%
10	$[IrCl(cod)]_2$	None	THF	33%
11	$IrCl_3 \cdot 3H_2O$	None	THF	<1%
12	$(C_6H_6)Ir(Bcat)_3$	None	THF	<1%
13	$(d^tbpy)Ir(coe)(Bpin)_3$	None	DME	47%
14	None	$Pd(P^tBu_3)_2$	THF	trace

All reactions were run in 1 mmol scale in 0.5 mL D_2O (~23 equiv) and 3-4 mL solvent, arbitrarily for 30 min. [b] 2 mol% Ir in every case. [c] GC area ratio calibrated with corresponding non-deuterated compound.

This hypothesis was then tested. Pure **2.2t**, obtained Ir-free either from the commercial source or prepared from the corresponding boronic acid and pinacol, was subjected to the deuteration conditions, but this time with an added Ir species

(Table 4.2) and without any added acid or base. The reaction proceeded smoothly when certain Ir species were introduced, while the phosphine ligand was ruled out as a catalyst (Entry 3). Clearly, the reaction is promoted by some Ir-derived species.

Not all Ir species are able to catalyze this reaction. The two Ir catalysts that were known to promote C–H borylation served quite well as the active catalysts, or possibly pre-catalysts, in this deuteration reaction (Entries 5-7). The Ir residue in the crude borylation mixture was also an active promoter (Entry 4). Surprisingly, however, (d^tbpy)Ir(coe)$(Bpin)_3$, the catalyst resting state during the borylation,[15a] was found to be a poor promoter for the deborylation (Entry 13), although significant conversion of 47% was observed. Crabtree's catalyst, previously known to promote H/D exchanges, was also capable of affecting this deuteration specifically at the boronic ester site (Entry 8). It should also be included that the protodeborylation reaction can be performed in alcohols, such as 1-butanol, instead of water and DME (or THF).

Mechanistically, it should be noted that every reaction here used the Ir species without any added ligand. Therefore, an active catalytic species different from the catalytic C–H borylation is possibly in play, so is a catalytic cycle different from the C–H borylation. However, an in-depth mechanistic study to identify the active catalytic species and the mechanism has not been performed.

Some mechanistic discussion will be presented in Section 4.3.

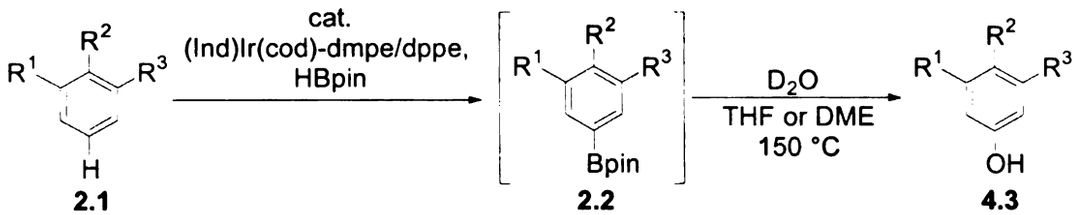
4.3 Substrate Study[91]

On the basis of the above study, we noticed that the crude borylation product could be simply treated with D_2O in a suitable solvent, and then heated to 150 °C in a sealed tube, to obtain the desired deuterated arene. This process is very easy and quick to execute. However, for safety concerns, we looked to lower the reaction temperature. In practice, running the reaction at 100 °C or lower can still lead to full conversion of the boronic ester, albeit in a longer period of time.[92] The Ir catalyst loading could also be lowered to 0.6 mol% while still achieving 97% conversion of **2.2t**.[92] We then screened several substrates against this one-pot C–H borylation/deuteration protocol (Table 4.3).

The overall reactions were very clean, producing the deuterated arenes as the only aromatic products. High yields were easily achieved for non-volatile products. More importantly, the level of the deuterium incorporation obtained via this method was generally more than 95%, which is much higher than the Grignard deuteriolysis, provided the borylation went to completion and no atmospheric moisture was introduced into the system during the deuteration reaction. Of course in cases where the borylations cannot be pushed to completion, it should be possible to simply isolate the boronic ester intermediate and then run the deuteration with this pure material plus Ir to achieve a high level

of deuterium incorporation. ^2H and ^1H NMR analysis of these reactions indicated that deuteration occurred selectively at the boron-bearing carbon. Due to the absence of acid or base in the deuteration step, functional groups such as cyano group (Entry 6) survived the reaction conditions. Note that **4.3f** is not a straightforward product from Grignard deuteriolysis, because of the incompatibility of Grignard reagent with the cyano group. On the other hand, this protocol can also be used in the opposite direction, namely to start from a perdeuterioarene to a monoprotioarene (Entry 2).

Table 4.3 C-H Borylation/deuteration protocol for synthesis of deuterated aromatics



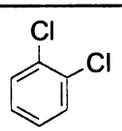
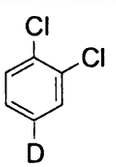
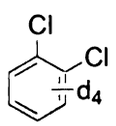
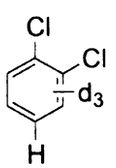
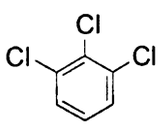
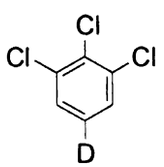
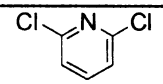
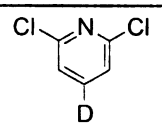
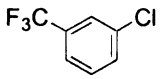
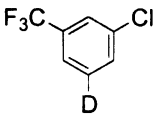
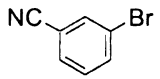
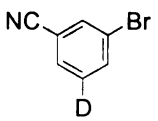
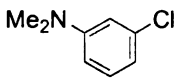
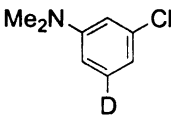
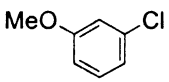
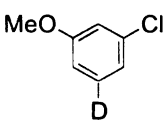
Entry	Starting arene	Borylation conditions[a]	Deuteration time[b]	Product	% Yield[c]	% D[d]
1	 **2.1t**	1.4 equiv HBpin, 3.5 h	0.5 h	 **4.3a**	75	98
2[e]	 **2.1u**	1.5 equiv HBpin, 3 h	1 h	 **4.3b**	82	N/A[f]
3	 **2.1m**	1.8 equiv HBpin, 3.25 h	1 h	 **4.3c**	95	98

Table 4.3 Continued

Entry	Starting arene	Borylation conditions	Deuteration time[b]	Product	% Yield[c]	% D[d]
4	 **2.1g**	1.8 equiv HBpin, 3.25 h	1 h	 **4.3d**	89	96
5	 **2.1p**	1.8 equiv HBpin, 3 h	1.5 h	 **4.3e**	67	100
6	 **2.1v**	1.5 equiv HBpin, 6 h	2 h	 **4.3f**	69	99
7	 **2.1q**	2 equiv HBpin, 18 h	2 h[g]	 **4.3g**	92	92
8	 **2.1e**	1.5 equiv HBpin, 12 h	1 h	 **4.3h**	88	96

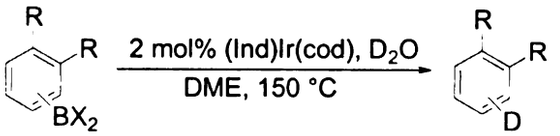
All reactions were run in 2 mmol scale. [a] 2 mol % (Ind)Ir(cod)-dmpe at 150 °C for all entries except 6, for which 1.5 mol% $[Ir(OMe)(cod)]_2$ and 3 mol% d'bpy at room temperature instead. [b] On the crude borylation mixture with 0.5 mL D_2O (~11 equiv) and 3-4 mL solvent. [c] Isolated yields, average of two runs. [d] Determined by MS intensities; see experimental section for method of calculation. [e] The second step was carried out with H_2O, not D_2O, and this reaction was not duplicated. [f] Not measured. [g] Deuteration was carried out with 0.5 equiv Ac_2O; see further discussion for details.

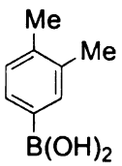
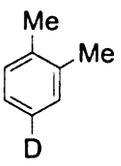
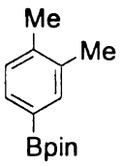
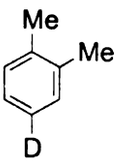
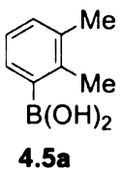
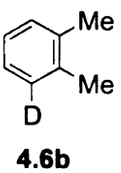
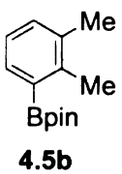
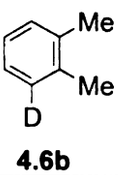
In these reactions, it is not obvious how the electronic nature of the aromatic ring affects the rate of the deuteration. Considering that all the deuterations were typically complete in 2 h or less (except Entry 7), it would seem that the arene electronics have little effect on the deuteration time. However, this is

complicated by the dramatically distinct behavior of **2.2q** (Entry 7), whose deuteration took over 15 h and was not reproducible from run to run. Nonetheless, adding 0.5 equiv Ac_2O, which should generate 1 equiv AcOD under the reaction conditions, significantly accelerated that reaction to the point where it was also complete in about 2 h with good reproducibility. It remains unclear whether this acceleration is due to the "protonation" of the basic nitrogen, or due to the introduction of free acetate, or other effects, such as possible acid catalysis. Nonetheless, this observation piqued our curiosity to further investigate the electronic and steric perturbations of the rate of the deuteration step.

Two xylylboronic acids were obtained from their commercial sources and the corresponding boronic esters were prepared (Table 4.4). Compound **4.4b** has the same substitution pattern as **2.2t** (Table 4.2). However, by replacing the two chlorides with more electron-releasing methyl groups, the aromatic ring of **4.4b** is more electron-rich. Boronic esters **4.4b** and **4.5b** have a similar electronic nature. However, by moving the *para*-methyl group to the *ortho*-position, **4.5b** is more sterically demanding. Upon subjecting these boronic acids and esters to the deuteration conditions, we observed the following: 1) deuterations of **4.4b** and **4.5b** took approximately the same time to complete (although monitoring the reaction before full conversion suggested that **4.4b** was somewhat faster than **4.5b**); 2) deuterations of **4.4b** and **4.5b** were slower than that of **2.2t**, but not by

Table 4.4 Electronic and steric perturbations



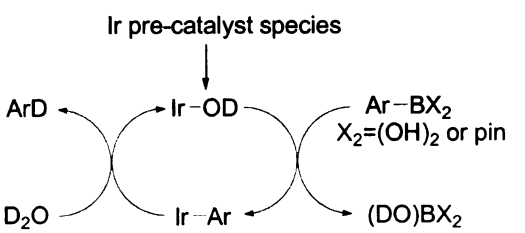
Entry	Starting arene	Deuteration time[a]	Product	% Yield[b]
1	 **4.4a**	0.5 h	 **4.6a**	100
2	 **4.4b**	2 h	 **4.6a**	91
3	 **4.5a**	1 h	 **4.6b**	94
4	 **4.5b**	2 h	 **4.6b**	93

All reactions were run in 1 mmol scale. [a] The time for full conversion, checked at 30 min intervals. [b] GC yields calibrated with corresponding non-deuterated compound.

much; 3) deuterations of the corresponding boronic acids **4.4a** and **4.5a** took comparable periods of time compared to **2.2t**. These observations, together with the data in Table 4.3 (except Entry 7), suggested that the electronics and sterics of the aromatic ring do not have a significant effect on the rate of the deuteration reaction. Therefore, the behavior of Entry 7 in Table 4.3 remains mysterious.

In terms of the reaction mechanism, although we have not performed an in-depth investigation, a putative catalytic cycle is given in Scheme 4.2. It calls for an Ir(I) hydroxide (or alkoxide if the reaction is performed in alcoholic solvents) as the active catalytic species. A subsequent transmetalation step is responsible for the cleavage of the C–B bond to generate the aryl Ir species. Protonolysis/deuteriolysis of this Ir-Ar bond affords the arene and regenerates the Ir hydroxide. Our major explanations that Ir(I), rather than Ir(III), is the catalytically active species is based on two reasons. For one, according to Table 4.2, Ir(I) species are better catalysts than Ir(III). For the other, this transmetalation is known for Rh-catalyzed reactions and Rh(I) species are generally recognized as the active catalysts in these reactions.[22] Since Ir is one row lower in the periodic table than Rh, it is logical to consider that Ir may have a similar reactivity.[93] In addition, we think that those catalytically active Ir(III) species (Entry 13, Table 4.2) would probably be first reduced to Ir(I) prior to entering the reaction cycle. However, since this mechanistic hypothesis has not been studied in full details, other possibilities are still open for discussion and

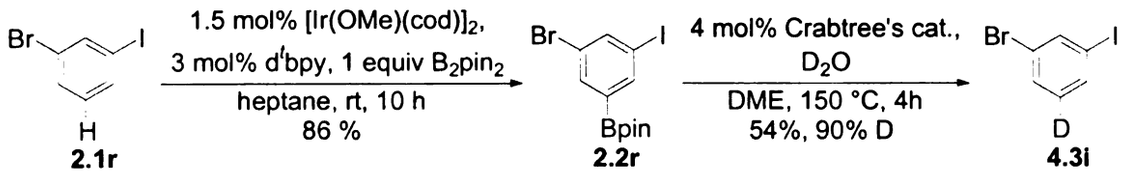
Scheme 4.2 A putative mechanism for Ir-catalyzed deuteriodeboronation



clearly more work needs to be done to address the related questions.

Although both (Ind)Ir(cod) and $[Ir(OMe)(cod)]_2$ are good catalysts for the deuteration, neither of them was found to be able to promote the deuteration for iodinated substrates. The reaction was much slower and was accompanied with significant deiodination, even if the deuteration was carried out on isolated iodoaryl boronic esters. However, Felkin-Crabtree's catalyst provided satisfactory results (Scheme 4.3). Compound **4.3i** could be isolated in 54% yield for the deuteration step and 47% yield over 2 steps with no detectible deiodination by ^1H NMR. This success allows for the preparation of iodine-containing aromatics that are specifically deuterated, which is not always straightforward for traditional Grignard deuteriolysis. It also allows the potential preparation of ^2H and ^{131}I (or ^{125}I) doubly labeled aromatics for related studies.

Scheme 4.3 An iodinated substrate for C-H borylation and deuteration

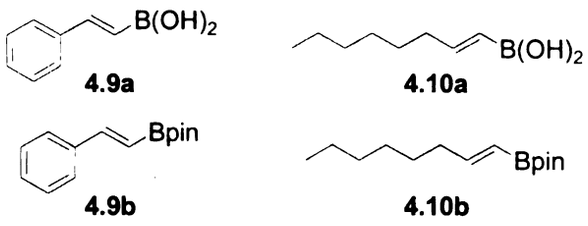


4.4 Attempts to Deuterate Vinyl Boronic Acids/Esters

The success in deuteration of aromatic boronic acids/esters led us to study the possible extension of this method to vinyl boronic acids/esters. Two sets of substrates were considered for this study, *trans*-styrylboronic acid/ester and

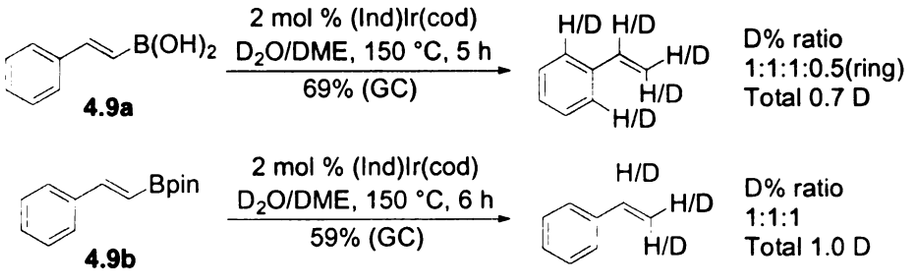
trans-1-octenylboronic acid/ester (Figure 4.1).

Figure 4.1 Vinyl boronic acids/esters as potential substrates



Although still in the very preliminary stage, surprisingly enough, under the same reaction conditions (150 °C, 2 mol% (Ind)Ir(cod)), those vinyl boronic acids/esters behave very differently from the aromatic substrates. For compounds **4.10a** and **4.10b**, the olefin transposition was a serious competing reaction. Both 1-octene and 2-octenes (*cis* and *trans*) were observed by GC and GC-MS, together with isomerized starting material. At the same time, deuterium was observed to be incorporated not only into the vinyl positions, but also significantly into the aliphatic positions. Therefore, fairly complex mixtures were generated.

Scheme 4.4 Styryl boronic acid/ester in the deuteration reaction



On the other hand, for compounds **4.9a** and **4.9b**, such olefin transposition

cannot occur and the reaction mixture was easier to analyze. However, it was observed that deuterium completely scrambled throughout all the possible vinyl positions (Scheme 4.4).

First, for the products of the deuteration of **4.9a** and **4.9b**, the three vinyl positions were equally deuterated. This was clearly indicated by both ^{1}H NMR and ^{2}H NMR, as all the residual vinyl ^{1}H's signals integrated at 1:1:1, and all the newly formed vinyl ^{2}H's signals also integrated at 1:1:1. Secondly, using **4.9a** as the starting material also resulted in the introduction of deuterium to the aromatic ring, albeit to a lesser extent. In contrast, **4.9b** did not undergo arene deuteration. This introduction of deuterium to the aromatic ring is regioselective, as ^{2}H NMR only showed one single signal for aromatic deuterium. The chemical shift of this aromatic ^{2}H in ^{2}H NMR, as well as the decrease of the proton integration in ^{1}H NMR indicated an *ortho* position deuteration. Thirdly, ^{1}H NMR analysis revealed a deuterium incorporation of 0.7 D per molecule for deuteration of **4.9a** and 1.0 D per molecule for deuteration of **4.9b**. The exact ratio of d_0, d_1, and d_2 compounds remained elusive,[94] although they are all present in significant amounts.

4.5 Conclusions

In conclusion, some Ir species, including the Ir precatalysts for the C–H borylation, can promote fast protonolysis or deuteriolysis of aryl boronic acids or

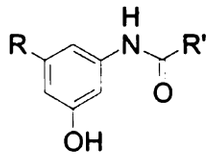
esters. The reaction is high yielding, clean, facile, and able to incorporate an extraordinarily high level of deuterium regioselectively on the boron-bearing carbon. The absence of any need for acids, bases, strong nucleophiles, or reducing agents in this process affords good functional group tolerance. In combination with the catalytic C–H borylation, this method can be used to perform H/D exchanges on specific positions of arenes, with regioselectivity complementary to the conventional means. Further mechanistic studies and an investigation of the reactivity of vinyl substrates are also warranted.

Chapter 5. The C–H Borylation/Amidation/Oxidation Protocol for the Preparation of 5-Substituted 3-Amidophenols

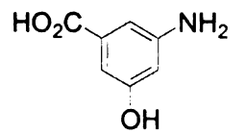
5.1 5-Substituted 3-Amidophenols and Their Preparations

5-Substituted 3-amidophenols, with the amido group including ureas and carbamates (Figure 5.1), are useful structural motifs for pharmaceuticals and other biologically important compounds.[95] Many molecules bearing this structural motif are recognized as kinase inhibitors, growth regulators,[96] etc. There are also a number of biologically active natural products that can structurally fall into this category (e.g. the ansamycin family, see Chapter 6 for details). Such natural products, containing 5-substituted 3-amidophenols or further elaborated aromatic cores within macrolactams, have been reported to be antitumor agents and antibacterial agents (see Chapter 6 for details). Biosynthetically, these natural products are derived from 3-amino-5-hydroxybenzoic acid (AHBA, Figure 5.1),[97] itself a 5-substituted 3-amidophenol derivative. Due to the interesting biological activities of these natural products, as well as the vast number of small molecule derivatives of 5-substituted 3-amidophenols,[94-96] this moiety is a valuable, versatile building block that can be potentially further elaborated into pharmaceutically interesting libraries.

Figure 5.1 5-Substituted-3-amidophenol and AHBA



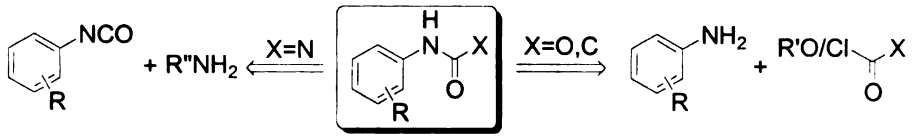
General structure



AHBA

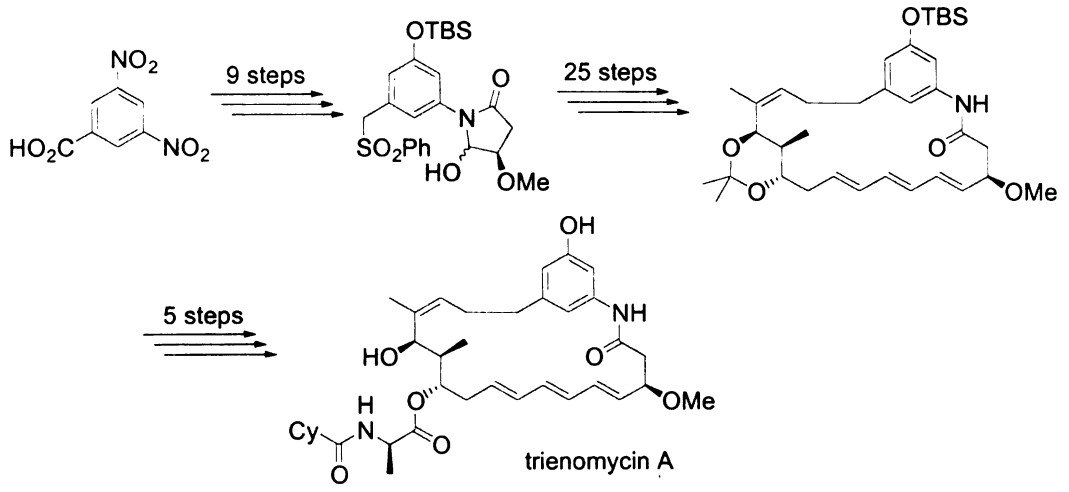
However, synthetic paths to such useful structures are quite narrow. Due to the limitations of traditional aromatic substitution chemistry, generating these 1,3,5-trisubstituted benzene rings having at least two *ortho*/*para* directing groups is very difficult. Reported methods for making AHBA are typified by long routes and harsh conditions.[98] Methods for constructing more complicated structures generally involve an acylation step as the key reaction (Scheme 5.1),[99] namely the acylation of aromatic amines with acyl chlorides or esters[100] (for syntheses of carboxyamides and carbamates) or the acylation of amines with aromatic isocyanates[101] (for syntheses of ureas). Although such acylations are straightforward, the overall route lacks versatility. They often involve multiple-step processes and are heavily dependent on the availability of suitable aromatic components. In fact, due to the limited availability of related aromatic starting materials, syntheses of the small molecules bearing 5-substituted 3-amidophenol moieties have been limited to molecules bearing only few different groups at the 5-position.[102]

Scheme 5.1 Acylation strategy for preparation of amidobenzenes



Likewise, syntheses of more complicated 5-substituted 3-amidophenol-containing natural products often count a considerable number of steps in assembling the aromatic moiety. An illustrative example is the Smith total synthesis of trienomycin A.[103] While the total synthesis of such a complicated natural product took only 39 steps, 9 out of those 39 steps were dedicated to generating the aromatic core (Scheme 5.2). With these facts in mind, we viewed it attractive to establish a new, versatile, and efficient route to build around this aromatic core, especially if this route could provide a variety of substituents at the 5-position.

Scheme 5.2 Smith total synthesis of trienomycin A



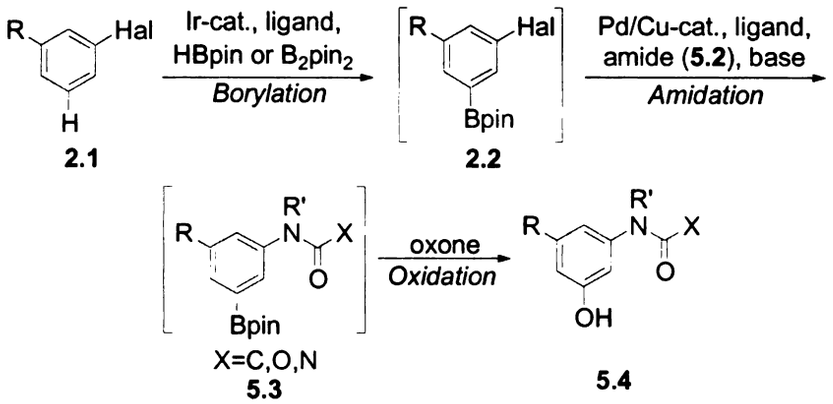
5.2 Applications of Catalytic Aromatic C–H Borylation in the Synthesis of

5-Substituted 3-Amidophenols

We envisioned that some of the obstacles in traditional syntheses of 5-substituted 3-amidophenols could be overcome by our discovery and development of the sterics-directed C–H borylation and the one-pot protocols developed thereof. This C–H borylation event, working outside the electronics-dominated aromatic substitution, is able to position a boronic ester group at the 5-position of a 1,3-disubstituted benzene, giving us the exact substitution pattern in question.

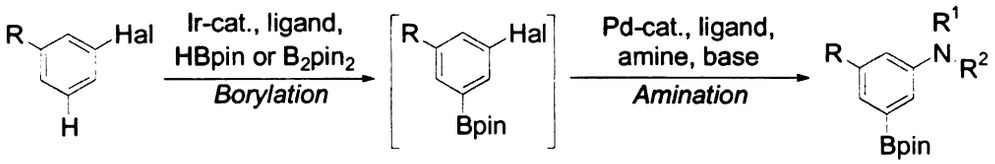
A hallmark of the C–H borylation is its compatibility with halides. As demonstrated by Buchwald and co-workers, aromatic halides can participate in Cu- or Pd-catalyzed C–N coupling reactions with corresponding amides to form amidobenzene derivatives.[104-105] By incorporating this chemistry with catalytic C–H borylation, a different strategy to synthesize these 5-substituted 3-amidophenols can be envisaged. Borylation of a 3-substituted halobenzene, followed by Buchwald amide coupling, would in theory provide us a 5-substituted 3-amidophenyl boronic ester intermediate. Subsequent oxidation, as discussed in Chapter 2, should reveal the hydroxyl group in the target molecule (Scheme 5.3). This method would be uniquely efficient for the rapid preparation of these types of densely functionalized aromatic building blocks, especially if all reactions could be telescoped into a single reaction vessel.

Scheme 5.3 Proposed C-H borylation/amidation/oxidation protocol



The viability of such a protocol was further supported by the success in the establishment of the related borylation/*amination* protocol, demonstrated by Mr. G. A. Chotana and Dr. D. Holmes in the group.[106] In their process, a crude borylation mixture of a 3-substituted halobenzene could be subjected to Pd-mediated *amination* conditions to afford the 5-substituted 3-*amino*phenyl boronic ester (Scheme 5.4). Thus, the related borylation/*amidation*/oxidation approach looked very promising.

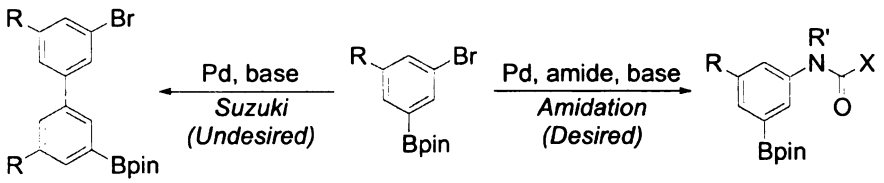
Scheme 5.4 A related C-H borylation/amination protocol



That said, while Buchwald and co-workers have demonstrated the utility and versatility of the amidation reaction with a wide range of functional groups, reaction conditions, and coupling partners, to the best of our knowledge, no examples of aryl halides that bear boronic ester groups have been reported in

such a coupling reaction. The absence of this type of substrates led us to be concerned that the amidation conditions might instead promote an undesired Suzuki coupling between the boronic ester group and the halide (Scheme 5.5). In fact, we had previously demonstrated that polyphenylenes could be generated by such a Suzuki event.[14c] Thus, the proposed borylation/amidation method must deal with the competition between the C–N coupling and the Suzuki reaction during the second step. Luckily, our related borylation/*amination* work showed that this Suzuki coupling could be suppressed if the *amination* was run under dry conditions.[106] We hoped that suppression of the undesired Suzuki could also be achieved for the borylation/*amidation* sequence.

Scheme 5.5 Desired amidation versus undesired Suzuki

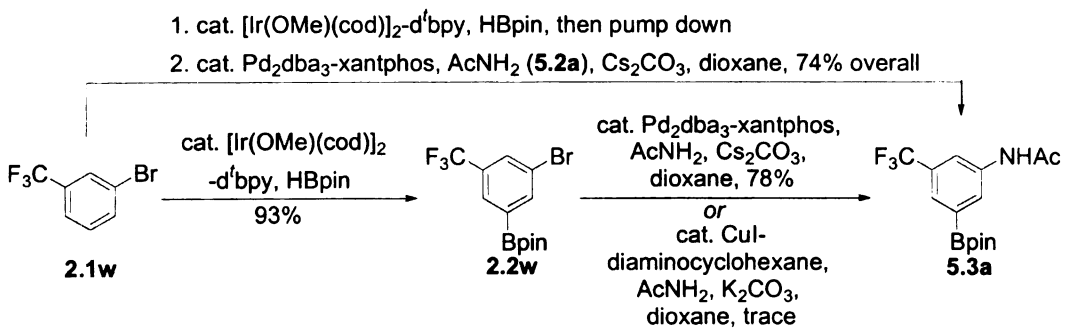


Initial experiments targeted exclusively on the amidation step using acetamide as the amide coupling partner. 3-Bromobenzotrifluoride (**2.1w**) was chosen to be the standard halide partner for this preliminary study. Due to our concern over potential Suzuki couplings, our first thought was to avoid the use of the Pd catalysis for the amidation. Thus, after borylation of **2.1w**, the amidation was attempted using Buchwald's CuI-catalyzed conditions (Scheme 5.6).

Unfortunately, those conditions[104] netted little success. Although we were able to repeat Buchwald's reported result with simple aryl halide bearing no boronic ester group, these conditions failed to amidate **2.2w**. Instead, we observed high levels of protodeborylation under these Cu-catalyzed amidation conditions. Even using purified boronic ester or increasing the Cu loading from 1 mol% to 10 mol% met no success.

To our pleasure, the amidation step could be achieved under Buchwald's Pd-catalyzed conditions (Scheme 5.6).[105a-c] Protodeborylation was not observed and Suzuki coupling was observed in no more than trace amounts (see Section 5.4 for details). We also increased the catalyst loading so that the amidation step could be complete in a few hours instead of overnight. It was also delightful to find that the Pd-catalyzed amidation could be performed on the crude borylation mixture without isolation of the boronic ester intermediate.

Scheme 5.6 Stepwise borylation and amidation reactions



Having combined the borylation with a subsequent amidation, we next

attempted to convert the crude amidation mixture to the amidophenol via the oxone oxidation conditions. We expected the oxidation of this crude amidophenylboronic ester to be uneventful, given the results from Chapter 2.

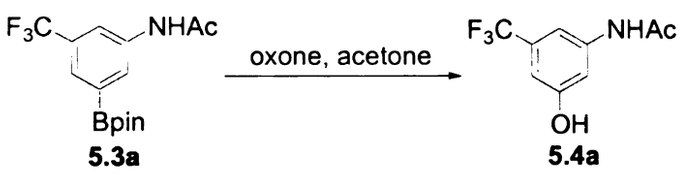
Specifically, although our standard oxidation solvent is acetone, we have demonstrated that water-miscible ethereal solvents, such as THF and dioxane, could also be used for successful oxidation. As the amidation was carried out in THF or DME, oxidation of the crude amidation mixture should not have a problem with solvent incompatibility. Secondly, although our standard oxidation does not require base or buffer, we have also demonstrated that the presence of base and buffer did not hamper the oxidation. As the amidation was carried out in presence of Cs_2CO_3, it could be expected that the excessive Cs_2CO_3, and its byproducts $CsHCO_3$ and CsBr generated in the amidation, would simply be viewed as bases or buffer. Thus, we reasoned that the oxidation should not have a problem with the presence of these inorganic salts, either.

Unfortunately, this hypothesis proved incorrect as all attempts at a strictly one-pot borylation/amidation/oxidation failed to give any desired phenol. The only detectable product (GC-MS and ^{1}H NMR) was pinacol. Adding HCl into the crude mixture to neutralize Cs_2CO_3 thus making the system homogenous did not help. We were able to determine that this failure stemmed from the catalytic milieu and not the amidation intermediate, as isolated **5.3a** could be uneventfully

oxidized to the phenol with oxone in 95% yield (Scheme 5.7). While a one-pot borylation/amidation followed by purification and then an oxidation would make for a fairly efficient route to 5-substituted 3-amidophenols, the poor behavior of the amidophenyl boronic ester on silica gel chromatography makes the purification of this intermediate unfavorable.

Seeking a compromise between a two-step process with a purification step and a true one-pot procedure, we filtered the crude amidation mixture through a pad of silica gel to remove the offending residue. Gratefully this filtration was able to "clean" up the crude intermediate to a sufficient level that the filtrate, after evaporation, could be successfully oxidized with ease.

Scheme 5.7 The oxdiation of the amidophenyl boronic ester



Status of **5.3a**	yield
crude	0%
purified	95% (69% from **2.1w**)
filtered (silica pad)	(63% from **2.1w**)

In order to identify the destructive agent that was removed by this filtration, we repeated the oxidations on filtered amidation mixtures with different reaction species added into the oxidation. It was found that the Pd catalyst, the phosphine ligand, and Cs_2CO_3 that are used in the amidation step were all harmless to the oxidation. Unexpectedly, adding $[Ir(OMe)(cod)]_2$, the pre-catalyst that promoted the borylation, into the oxidation led to the lowest yield

for the oxidation step. The qualitative features of this Ir-containing reaction, such as the black color, were identical to those failed reactions that were performed without such filtration, and were distinctively different from the successful oxidations with a brownish color. Certainly, this $[Ir(OMe)(cod)]_2$ species should be different from the residual Ir species that was present in the crude amidation mixture, thus it is still not conclusive that it is this Ir species that caused the problems of the unfiltered oxidation. However, Ir-retardation of the oxidation was observed in the study of amino acid borylation/oxidations (see Chapter 3, Entries 6 and 9, Table 3.1), especially when the Ir loadings needed to be extraordinarily high (> 10 mol%) for successful borylations. The understanding of such behavior will need more detailed investigations.

Although the filtration solved the problems of oxidizing crude amidation mixtures, we quickly realized another problem. The oxidation produces a stoichiometric amount of pinacol. As the desired amidophenol products are polar, the separation of the desired product from pinacol was sometimes difficult. To solve this problem, the crude oxidation mixture was stirred over $NaIO_4$ for a period of time (ca. 1 h) to remove pinacol. Thus, the final amidophenol could be isolated clean without contamination.

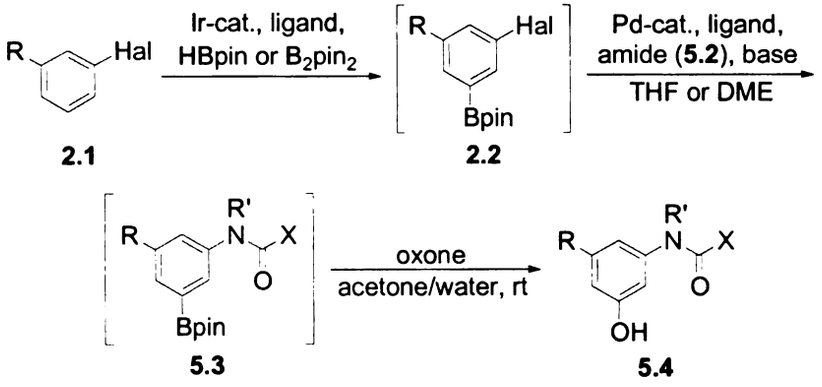
Thus our final borylation/amidation/oxidation protocol consists of a catalytic borylation, subsequent Pd-catalyzed amidation of the crude borylation mixture, a

filtration, oxidation of the evaporated filtrate, and finally a $NaIO_4$ workup before extraction and chromatographic purification. Although requiring a number of operations, this protocol is still very efficient, as there is only one chromatography step after three different chemical events. Indeed, the whole procedure can be finished within two days and is reproducible.

5.3 Substrate Study[107]

With optimized reaction conditions in hand, we screened a series of substrates, both halobenzenes and amides, to test the scope of this 3-step sequence (Table 5.1).

Table 5.1 C-H Borylation/amidation/oxidation protocol



2.1 2.2 5.3 5.4

Entry	Substrate	Amide	Product	% Yield[a,b]
1	F_3C, Br **2.1w**	$AcNH_2$ **5.2a**	F_3C, NHAc, OH **5.4a**	63
2	NC, Br **2.1v**	$AcNH_2$ **5.2a**	NC, NHAc, OH **5.4b**	68

Table 5.1 Continued

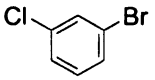
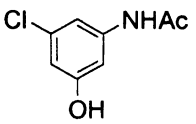
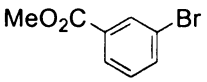
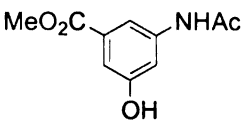
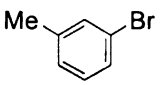
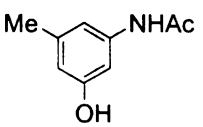
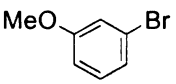
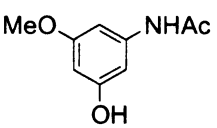
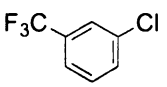
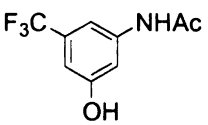
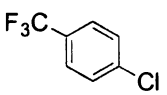
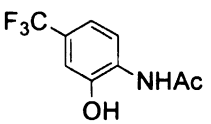
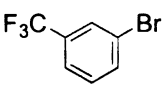
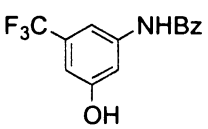
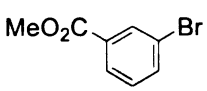
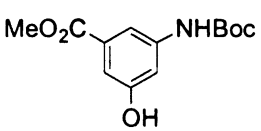
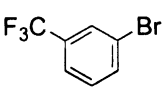
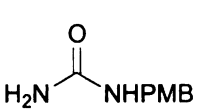
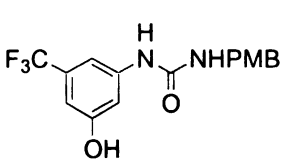
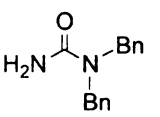
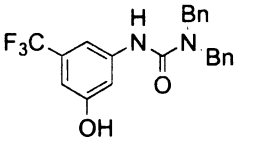
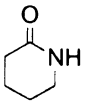
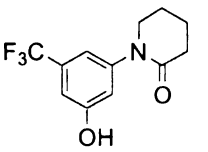
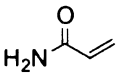
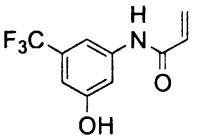
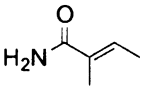
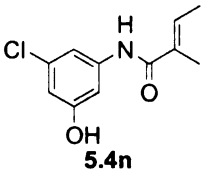
Entry	Substrate	Amide	Product	% Yield[a,b]
3	 **2.1a**	$AcNH_2$ **5.2a**	 **5.4c**	75
4	 **2.1x**	$AcNH_2$ **5.2a**	 **5.4d**	60
5	 **2.1d**	$AcNH_2$ **5.2a**	 **5.4e**	43[c,d]
6	 **2.1y**	$AcNH_2$ **5.2a**	 **5.4f**	33[c,d]
7	 **2.1p**	$AcNH_2$ **5.2a**	 **5.4a**	40[e]
8	 **2.1z**	$AcNH_2$ **5.2a**	 **5.4g**	(0)[e,f]
9	 **2.1w**	$BzNH_2$ **5.2b**	 **5.4h**	82
10	 **2.1x**	$BocNH_2$ **5.2c**	 **5.4i**	46[g]
11[e]	 **2.1w**	 **5.2d**	 **5.4j**	12[g] (19)[c,g]

Table 5.1 Continued

Entry	Substrate	Amide	Product	% Yield[a,b]
12	**2.1w**	 **5.2e**	 **5.4k**	55
13	**2.1w**	 **5.2f**	 **5.4l**	46[g]
14	**2.1w**	 **5.2g**	 **5.4m**	37
15	**2.1a**	 **5.2h**	 **5.4n**	66

All reactions were run in 2 mmol scale. [a] See experimental section for details. [b] Isolated yields over three steps with $NaIO_4$ workup, average for two runs. Yields not duplicated are listed in parentheses. [c] No $NaIO_4$ workup was performed. [d] Significant protodeborylation and phenyl transfer products were observed. [e] Significant protodeborylation side-products were observed. [f] Only product isolated was 45% protodeborylation. [g] Significant Suzuki side-products were observed (see Section 5.4 and Table 5.2).

As can be seen in Table 5.1, this 3-step protocol was able to tolerate a range of functional groups, such as chlorides, cyanos, ethers, and esters. However, due to the presence of the boronic ester group, side-reactions were present during the Pd-catalyzed amidation step. Therefore, the substrate scope for a successful borylation/amidation/oxidation process is narrower than the

corresponding substrate scope for the amidation alone demonstrated by Buchwald.

In general, this 3-step protocol worked best on electron-deficient aromatic bromides with primary amides (free NH_2). In this case, the desired amidophenols (**5.4**) could be obtained in high yields. Side-products such as protodeboylation and Suzuki dimerization (see Section 5.4 for details) were not observed in significant amounts (Entries 1-4, 9). In contrast, electron-rich aromatic bromides did not work well in the borylation/amidation/oxidation process (Entries 5 and 6), although they are a class of "no-problem" substrates in the Buchwald amidations alone. In that case, while the 3-step protocol produced the desired products in moderate yields (33-43%), side-reactions took place, including Suzuki dimerization, protodeborylation and phenyl transfer from the xantphos ligand. Furthermore, due to the electron-rich nature of the aromatic rings, the products could not stand the $NaIO_4$ workup utilized to destroy pinacol. Thus pinacol contamination was observed without a recrystallization or HPLC separation.

The amidation reaction became very sluggish when a chloride was used instead of a bromide (Entries 1 and 7). Higher temperature and much longer reaction times were needed and severe protodeborylation byproduct was observed. Suzuki dimerization, however, was suppressed, presumably due to

the lowered reactivity of the chlorides.

Another observation was the effect of *ortho* substituents on the amidation step. Arene **2.1z** could be borylated *ortho* to the chloride, but the subsequent amidation only afforded the protodeborylation product (Entry 8). Therefore, by comparing entries 7 and 8, it can be seen that sterics indeed have an adverse effect on the amidation step of our borylation/amidation/oxidation protocol, although Buchwald demonstrated that certain substrates with *ortho* substituents but without boronic ester could be amidated. Therefore, achieving substituted aminophenols with other substitution patterns unfortunately seems less viable.

On the other hand, the scope of the amide partners proved to be relatively broad. In addition to carboxyamides, carbamates and ureas (Entries 10-15) could be used in the borylation/amidation/oxidation process. For example, $BocNH_2$ (**5.2c**), a carbamate, could be used as a protected form of "NH_3" and product **5.4i**, a doubly protected version of AHBA, could be synthesized quickly from commercially available starting materials in 46% overall yield (Entry 10). Likewise, 1,1-dibenzylurea (**5.2e**) could be used as a protected form of urea to synthesize the urea-analogue of the amidophenol **5.4k** (Entry 12). This work provides an alternative route for the preparation of such molecules without using isocyanates. Unfortunately, coupling with a guanidine derivative (1,3-bis(*t*-butoxycarbonyl)guanidine) was not successful.

Lactams and α,β-unsaturated carboxyamides were also useful coupling partners (Entries 13-15). The use of α,β-unsaturated carboxyamides further demonstrated the functional group compatibility for this protocol. However, with acrylic amide itself the overall yield was only 37% (Entry 14). This yield could be increased to a synthetically useful 66% when the olefin was further substituted in a form of tiglic amide (Entry 15). For a lactam and secondary amide (Entry 13), the competing Suzuki dimerization during the amidation step became intrusive (see Section 5.4 for details) and the overall yield for the desired product dropped accordingly to 46% (Entry 13). Disappointingly, this Suzuki dimerization could not be suppressed by using 3 equiv amide instead of 1.1 equiv (Entry 13).

5.4 Competing Suzuki Side-Reaction during the Amidation Step and Its Potential Utility

As discussed previously, the Pd-catalyzed amidation conditions occasionally promote an undesired Suzuki coupling, leading to the dimerization or further oligomerization of the borylated halobenzene intermediate (Scheme 5.5). We originally expected that such a Suzuki coupling could be suppressed given the anhydrous reaction conditions and the absence of reports using xantphos as a ligand for Suzuki coupling.[108] However, this proved incorrect, as several examples in Table 5.1 indicated that the amidation reaction was accompanied by significant Suzuki dimerization side-products. The dimerization products could

continue to undergo amidation and oxidation to afford 5,5'-disubstituted 3-amido-3'-hydroxy biphenyls **5.5** (Scheme 5.8), which could be isolated together with the desired amidophenol product **5.4** at the end of the 3-step borylation/amidation/oxidation protocol.

Scheme 5.8 Undesired Suzuki side-product formation

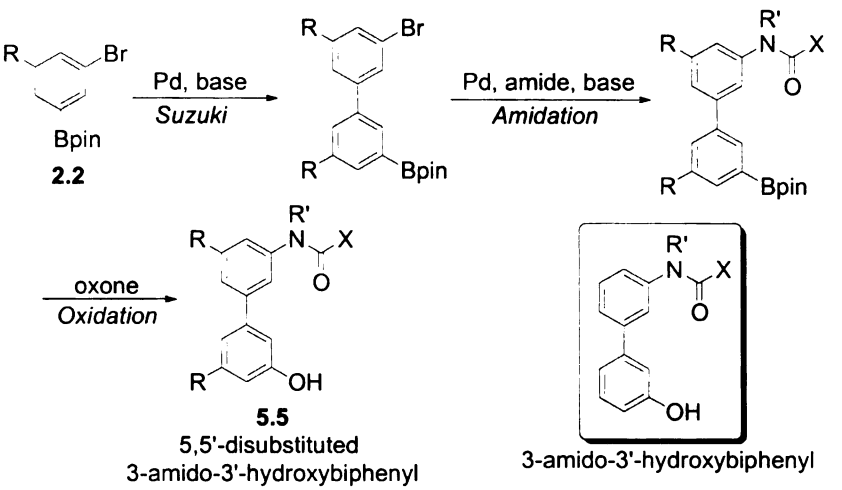
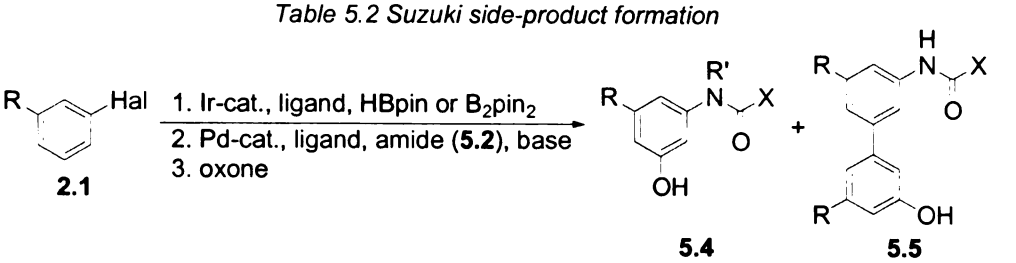
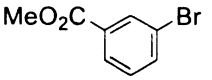
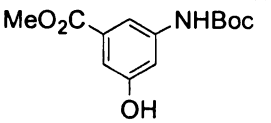
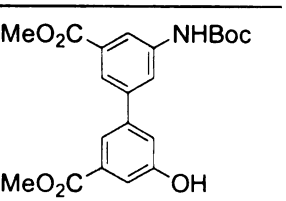
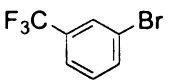
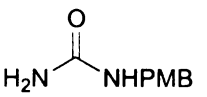
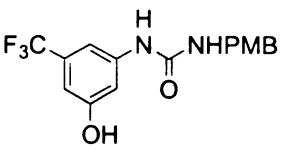
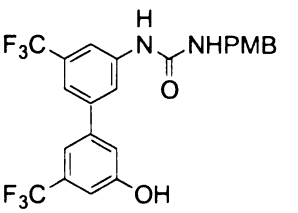
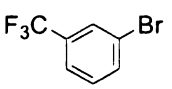
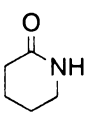
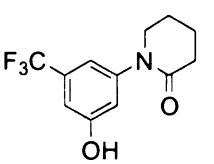
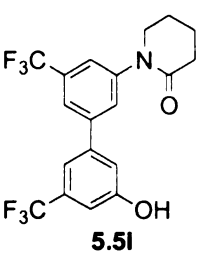


Table 5.2 lists the formation of **5.5** for several examples. The yields of **5.5** here are just reflective of however much was obtained under the conditions specified in Table 5.1. In other words, they are by no means optimized for **5.5**. Interestingly, however, this Suzuki side-reaction can be potentially useful. 3-Amido-3'-hydroxybiphenyl (see Scheme 5.8) is a structural motif for bioactive compounds recognized as vanilloid VR1 receptor antagonists, antiviral agents, etc.[109] However, the corresponding 5,5'-disubstituted variants **5.5** are not known, presumably because of the difficulty in synthesis. Therefore, this Suzuki event

Table 5.2 Suzuki side-product formation



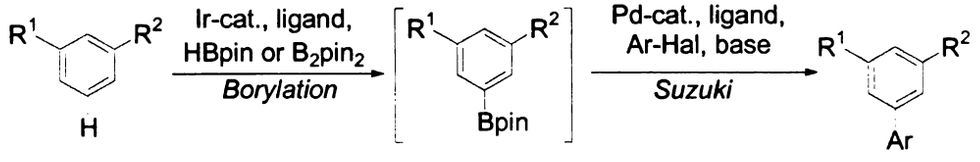
Entry	Substrate	Amide	Product **5.4** (% yield)[a]	Side-product **5.5** (% yield)[a]
1	 **2.1x**	$BocNH_2$ **5.2c**	 **5.4i** (46)	 **5.5i** (18)
2[b]	 **2.1w**	 **5.2d**	 **5.4j** (19)	 **5.5j** (24)
3	 **2.1w**	 **5.2f**	 **5.4l** (46)	 **5.5l** (23)

All reactions were run in 2 mmol scale, in the same conditions shown in Table 5.1. [a] Isolated yields over three steps with $NaIO_4$ workup, average for two runs. [b] No $NaIO_4$ workup was performed, not duplicated.

may provide a quick preparation of **5.5**-type small molecules for further manipulation into biologically interesting compounds.

At the same time, the observation of biaryl formation led us to consider the possible use of the Pd_2dba_3-xantphos-Cs_2CO_3 combination to promote a Suzuki coupling. It should be noted that Dr. D. Holmes in our group has previously demonstrated the viability of combining the C–H borylation with subsequent Pd-catalyzed Suzuki couplings of the aryl boronic ester intermediates with different organohalides (Scheme 5.9)[14c,110] and has established a one-pot borylation/Suzuki protocol. Such a protocol allows for quick preparations of a variety of substituted biaryls. However, in the context of telescoping another reaction, amidation for example, between the C–H borylation step and the Suzuki coupling has not been sought.

Scheme 5.9 The established C-H borylation/Suzuki protocol

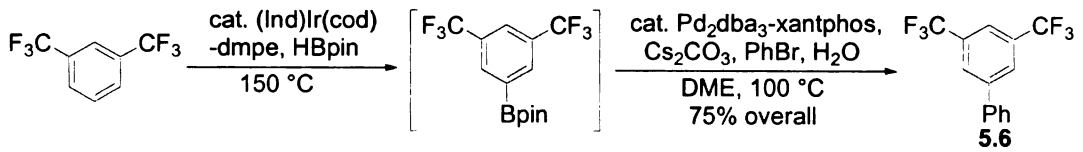


Along these lines, we were specifically interested in developing a one-pot borylation/amidation/Suzuki protocol to prepare diversely functionalized amidobiphenyls with structures more versatile than **5.5**. Unlike the original borylation/Suzuki protocol that requires charging the catalytic system (Pd, ligand and base) in between the two steps, we wanted to use the same catalytic system, namely the Pd_2dba_3-xantphos-Cs_2CO_3 combination, to promote both the

amidation and the Suzuki coupling without additional loading of any Pd catalyst, ligand, or base after the amidation step. If successful, this protocol would have a simple overall operation, high throughput and would be more economical with respect to the fairly expensive metal catalysts and ligands.

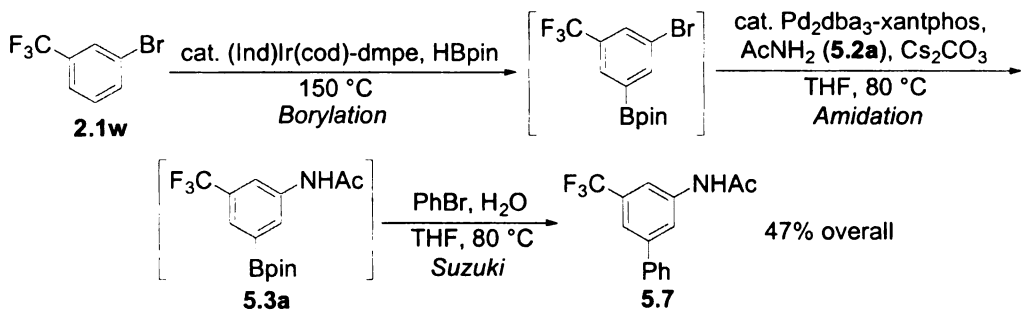
To test this proposal, we first executed a simplified borylation/Suzuki sequence using bis(trifluoromethyl)benzene as the substrate (Scheme 5.10). After borylation, the crude reaction mixture was treated with Pd_2dba_3-xantphos-Cs_2CO_3 combination and phenyl bromide was introduced as an electrophile. Since our borylation/amination study indicated that Suzuki reaction could be dramatically facilitated by added water,[107] water was also charged at this point to assist the Suzuki reaction. As no amide was present in this reaction, the only expected chemical event would be the desired Suzuki coupling, or the undesired protodeborylation. To our pleasure, the Suzuki coupling was the favored event and the desired biphenyl product **5.6** was isolated in 75% yield over 2 steps without optimization. Therefore, the Pd_2dba_3-xantphos-Cs_2CO_3 combination proved to be a good reagent combination for Suzuki coupling, and luckily enough, the Ir-catalyzed, water-promoted deborylation of the boronic ester intermediate (see Chapter 4) did not occur. A control experiment showed that the Suzuki coupling could also take place in the absence of added water, albeit at a much lowered rate (overnight instead of 2 h).

Scheme 5.10 The C-H borylation/Suzuki under standard Buchwald amidation conditions



Having obtained this result, the one-pot borylation/amidation/Suzuki protocol was tested (Scheme 5.11). Compound **2.1w** was first subjected to the standard borylation/amidation conditions. Since both the amidation and the Suzuki required a stoichiometric amounts of base, we doubled the load of Cs_2CO_3, but we kept the load of Pd catalyst and ligand the same. After completion of the amidation, the crude mixture was directly treated with phenyl bromide and water.

Scheme 5.11 One-pot borylation/amidation/Suzuki protocol



We noted that this Suzuki could be much more complicated by side-reactions than that in Scheme 5.10. First, the excessive amide **5.2a** might react with phenyl bromide (amidation). Secondly, **5.3a** might also react with phenyl bromide at the amide nitrogen (amidation). Thirdly, it would still be possible for the protodeboylation to take place. Despite these potential pitfalls, the desired product **5.7** was isolated in 47% unoptimized overall yield. However, the

reaction also produced the deboylation side-product in about 15% yield.

5.5 Conclusions

In conclusion, we have successfully developed a 3-step sequence of C–H borylation/amidation/oxidation of 3-substituted halobenzenes to afford 5-substituted 3-amidophenols in acceptable yields without intermediate isolation. This development further expands the utility of the C–H borylation chemistry and provides an alternative route for preparing these important compounds. The catalyst combination is also found to be capable of promoting Suzuki couplings and a borylation/amidation/Suzuki protocol can be expected. Applying this borylation/amidation/oxidation process in the total synthesis of a natural product will be discussed in Chapter 6.

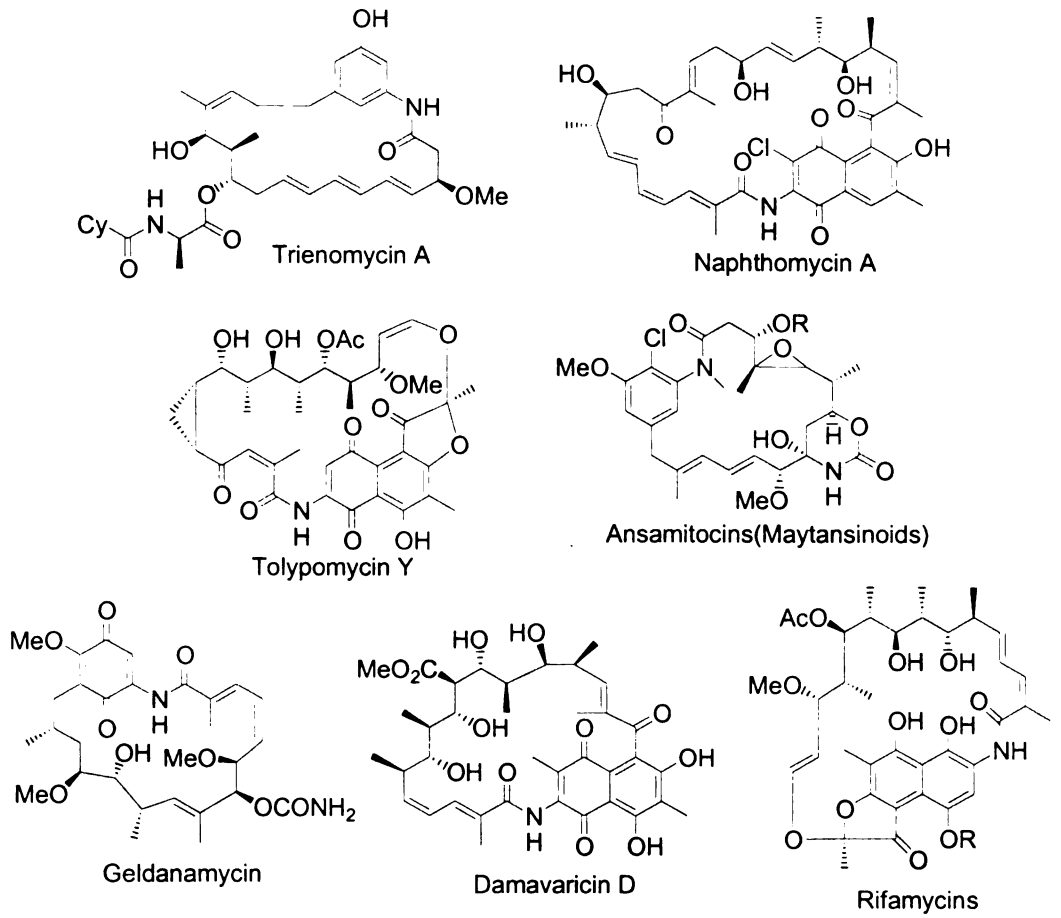
Chapter 6. Attempted Total Synthesis of Autolytimycin Utilizing the C–H Borylation/Amidation/Oxidation Protocol

6.1 Autolytimycin and Ansamycin Family Natural Products

Over the past few decades, a series of natural products called the ansamycin superfamily has been isolated (Figure 6.1).[111] Structurally, these natural products share a similar aromatic moiety called the *m*C_7N unit, which consists of a benzene core with a carbon, a nitrogen, and an oxygen substituents in an all-*meta* relationship. A macrocyclic ring bridges the nitrogen and the carbon through a macrolactam functionality. The benzene core may be further functionalized, oxidized, or fused to form a naphthalene or naphthoquinone. The benzenic ansamycins, such as trienomycins,[103,112] geldanamycin,[113] and ansamytocins,[114] whose aromatic cores are benzenes or benzoquinones, show significant cytotoxicity and anticancer activity. The naphthlenic ansamycins, such as naphthomycin,[115] rifamycins,[116] tolypomycin[117] and damavaricin,[118] whose aromatic cores are naphthalenes or naphthoquinones, show antibacterial activity, especially towards Gram-positive bacteria.[111a,d,f] The *m*C_7N unit of these natural products is believed to be biosynthetically derived from 3-amino-5-hydroxybenzoic acid (AHBA), as mentioned in Chapter 5.[97] Due to the interesting biological activities and structural features, ansamycin natural products have attracted significant attention from biological chemists as well as

synthetic chemists. Intensive total synthesis work on these natural products has been performed and a number of reports have been published.[112-121]

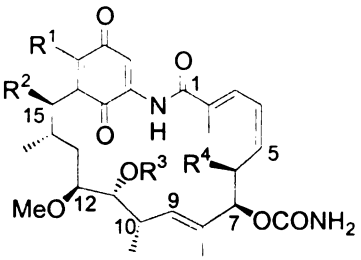
Figure 6.1 Some ansamycin natural products



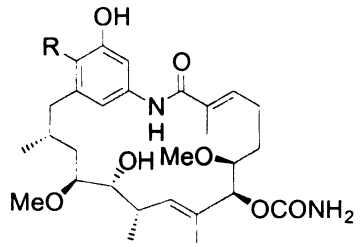
Geldanamycin family is a subfamily of ansamycin natural products (Figure 6.2). These compounds all have a 19-membered lactam ansa bridge connecting the C-substituent and the N-substitutent of the benzenic core. This ansa bridge is densely functionalized with multiple stereogenic centers, oxygen substituents, and stereochemically defined olefins. Among these structures, geldanamycin,[113]

herbimycins,[119] and macbecins[120] have benzoquinone cores, whereas a newer family member reblastatin[121] has a phenolic core. In addition to the difference in the oxidation state of the benzene moiety, reblastatin also possesses the absence of the C4,C5-unsaturation of the ansa bridge.

Figure 6.2 Geldanamycin family members



	R^1	R^2	R^3	R^4
Herbimycin A	H	OMe	Me	OMe
Herbimycin B	H	OMe	H	OMe
Herbimycin C	H	H	H	OMe
Macbecin I	H	OMe	Me	Me
Geldanamycin	OMe	H	H	OMe



Reblastatin R=OMe
Autolytimycin **6.1** R=H

Geldanamycin demonstrates its antitumor activity through binding to the *N*-terminal ATP/ADP binding domain of Hsp90, a protein responsible of folding other "client proteins" for conformational maturation. Such a binding leads to the inhibition of the inherent ATPase activity of Hsp90, which in turn inhibits its capability to fold its client proteins to their mature form and ultimately disrupts the cell cycle.[122] Reblastatin, in addition, is also reported to exhibit potent inhibitory activity in the cell-based oncostatin M signaling pathway. Oncostatin M is a pleiotropic cytokine with pro-inflammatory activity, which upregulates adhesion

molecule expression in endothelial cells and synergizes with IL-1 to promote cartilage degradation. It is present in the synovium and synovial fluid of patients with rheumatoid arthritis. Therefore, inhibition of oncostatin M can be potentially important from an anti-inflammation point of view.[123a]

Autolytimycin (**6.1**), a new geldanamycin analogue, was first isolated in 2000 and 2001 independently by Stead and Jiang groups through fermentation with *Streptomyces*.[123a,b] A third isolation[123d] was achieved in 2005 by Rascher group. Autolytimycin also appeared as a hit structure in a patent.[123e] The structure of autolytimycin shares an identical ansa bridge with reblastatin and the two natural products only differ by a methoxy group on the benzene ring. Autolytimycin, like geldanamycin and reblastatin, also interrupts Hsp90 protein and therefore has potential to control tumor growth and angiogenesis.[123e] In addition, like reblastatin, autolytimycin also demonstrates potent inhibition of oncostatin M and IL-6-driven sPAP production with IC_{50} of 0.7 μM in HepG2B6 cells and therefore has potential to serve as an anti-inflammation agent.[123a] Moreover, autolytimycin also exhibits quite interesting antiviral activity against HSV-1, HSV-2, vesicular stomatitis virus, andcoxakie virus B3, etc.[123b,c] This spectrum of interesting biological activity makes autolytimycin highly attractive as a target for total synthesis and further SAR studies on its structural analogues.

Although geldanamycin, herbimycin A, macbecin I, and reblastatin have all

succumbed total synthesis, to the best of our knowledge, autolytimycin has not been accessed via total synthesis. Total synthesis is unlikely to provide more material than that which is available from fermentation, which could provide up to 59 mg autolytimycin in a single batch.[123d] Nonetheless, a synthetic route toward this interesting molecule would help to confirm its absolute stereochemical assignment, which is currently based on analogy with other natural products in the family. Moreover, a total synthesis that lends itself to analogue production could be used to develop the biological properties of this molecule.

6.2 Reported Total Syntheses of Geldanamycin Family Natural Products

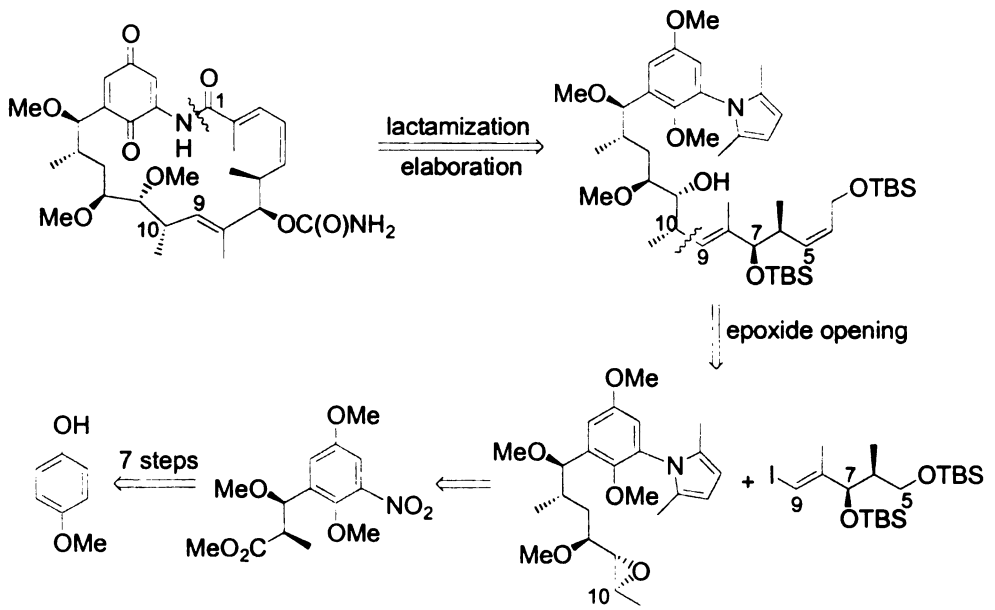
Most of the synthetic strategies for the construction of the geldanamycin family natural products involve the preparation of the aromatic precursor, followed by construction of the side chain from the C15 substituent toward C1. Macrolactamization at the late stage furnishes the macrocyclic ring.

Pioneering work in this area traces back to 1989, when Baker and co-workers achieved the first asymmetric total synthesis of macbecin I.[120c] In their synthetic strategy, a key epoxide opening was used for construction of the C9–C10 bond (Scheme 6.1).

Evans and co-workers later achieved a more convergent route for the asymmetric total synthesis of macbecin I (Scheme 6.2).[120b] Although utilizing the same aromatic starting material as well as the same macrolactamization method,

Evans' total synthesis is highlighted by the strategic disconnection of the C12–C13 bond, which was constructed via an aldol reaction. This disconnection allows the union of the two segment pieces with similar sizes and complexity, and therefore makes the overall total synthesis more convergent and favorable.

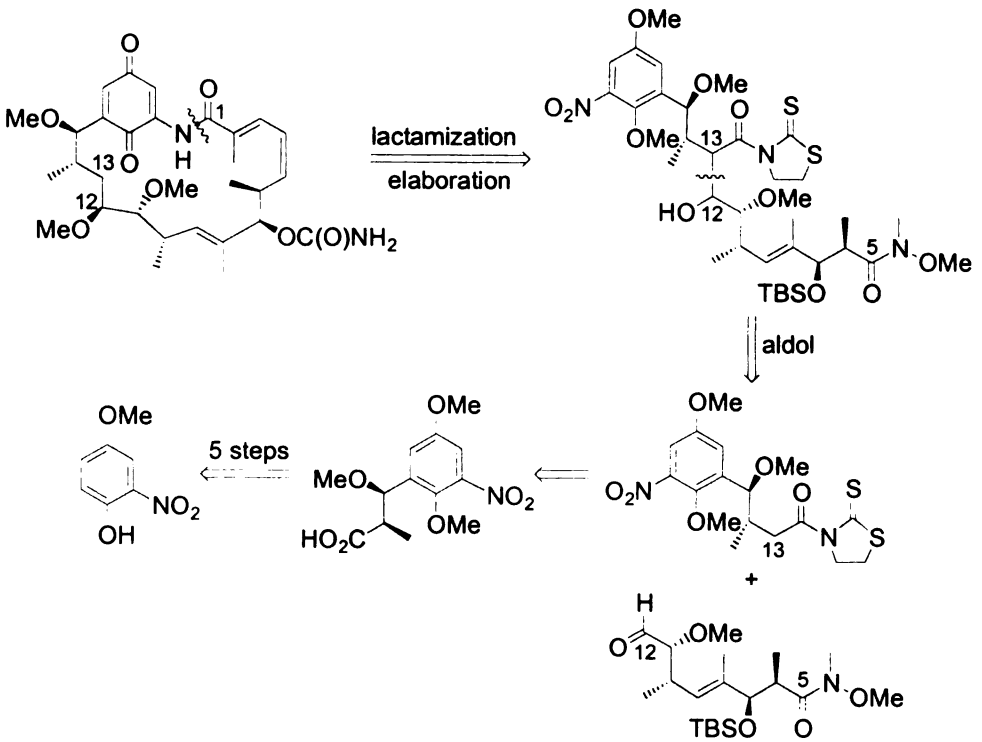
Scheme 6.1 Baker's syntheis of macbecin I



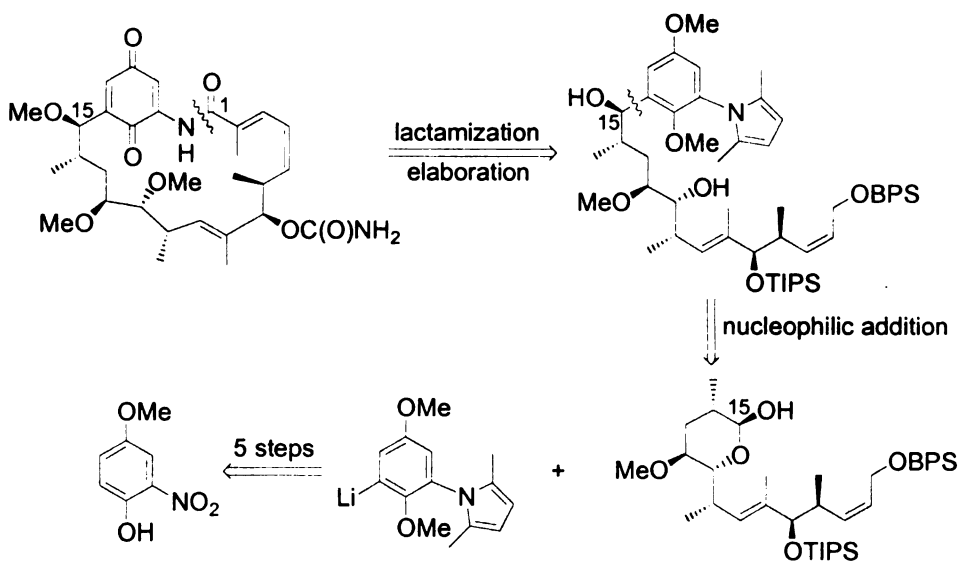
Another strategy involves disconnecting the aromatic segment from C15 in a nucleophilic addition manner. Such a strategy has been used independently by Martin and co-workers[119c] (Scheme 6.3) as well as Tatsuta and co-workers[119d] in their syntheses of herbimycin A and formal synthesis of macbecin I. Although these routes required a lengthy linear route to prepare the corresponding ansa chain, their syntheses demonstrated the viability of preparing the aromatic segment independently from the side chain and the late-stage coupling of the two

subunits.

Scheme 6.2 Evans' syntheis of macbecin I



Scheme 6.3 Martin's syntheis of macbecin I



The recent decade has witnessed extensive work on the total syntheses of

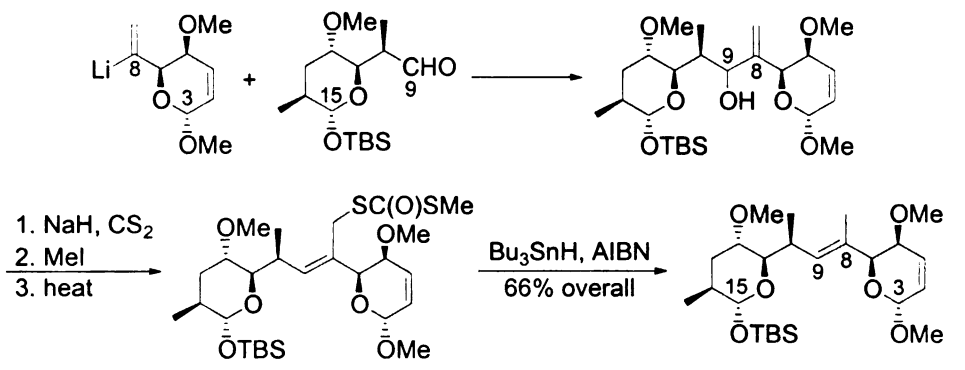
these natural products. Panek and Andrus have both been heavily involved in this area.[113,119b,120a] Somewhat surprisingly, these more recent efforts have not brought more novel or convergent disconnection strategies. For example, both Panek's and Andrus' synthetic strategies employed a rather lengthy and linear construction from C15 to C1. Linearity in the total synthesis of complex molecules tends to be inefficient and suffers from low overall yields. It also retards the synthesis of analogous structures. Nonetheless, such total syntheses can serve to test new synthetic tactics in a challenging environment.

Other retrosynthetic analyses have been put forward,[124] such as a ring-closing metathesis to construct the C4–C5 olefin in the late stage of the synthesis. However, the successful applications of these strategies to the total synthesis of these natural products are still pending.

Several bond construction approaches are common among all the reported syntheses. For example, the amide linkage of the ansa chain to the aromatic core was almost universally constructed late in the syntheses via C1–N amide bond formation. In addition, except very few examples,[120c,121a,124b] C8–C9 olefin was almost universally constructed with a Wittig-typed olefination. Establishing other alternative methods for the assembly of these units would be instructional and potentially beneficial. For instance, disconnection of the C8–C9 olefin breaks the ansa chain into two pieces with similar sizes and complexity without

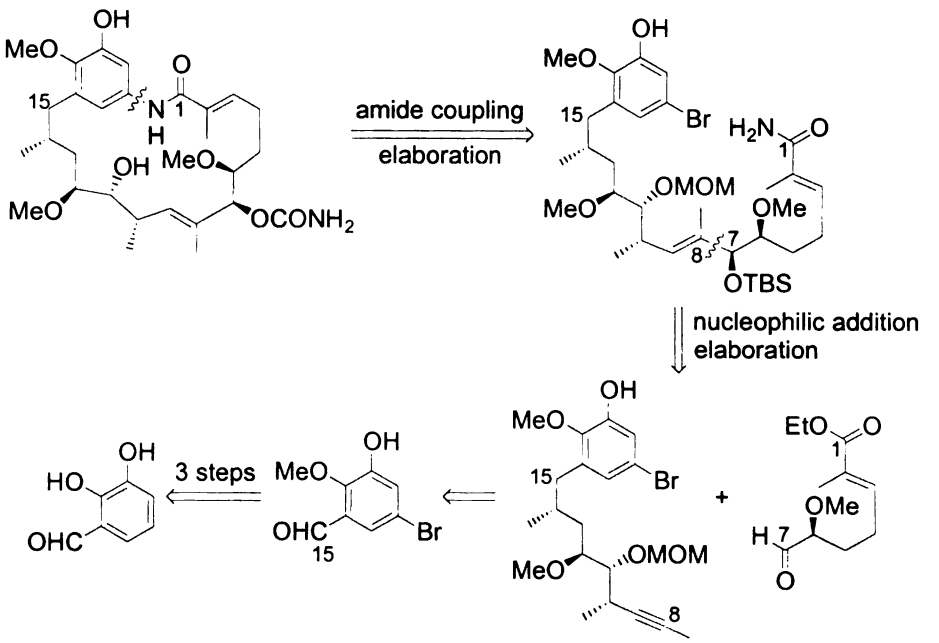
disruption of the stereogenic centers and the heteroatom substituents along the ansa chain. In this regard, Martin has reported an alternative strategy for construction of C8–C9 olefin through a [2,3]-sigmatropic rearrangement.[125] In his report, two advanced intermediates with multiple stereogenic centers could be successfully coupled to give the trisubstituted olefin with the desired *E* geometry in excellent yield (Scheme 6.4). This provides a useful alternative to Julia-typed olefination methods, which could be often problematic with methyl ketones.[126]

Scheme 6.4 Martin's C8-C9 olefination approach



In 2005, Panek and co-workers reported the total synthesis of reblastatin with a much more novel disconnection strategy.[121a] Not only did they avoid the C8–C9 Wittig olefination, but they also introduced the amide N–C_{Ar} bond to the benzene ring via a Buchwald amidation (Scheme 6.5). In addition to their application of novel chemistry to total synthesis, their overall route is more convergent and concise than Panek's original synthesis of herbimycin.[119b]

Scheme 6.5 Panek's syntheis of reblastatin



6.3 Our Strategic Disconnection and Retrosynthetic Analysis for Autolytimycin

Autolytimycin **6.1**, as discussed previously, has a different structure from all its cousins (Figure 6.2). Thus a different synthesis strategy is needed to allow a convergent coupling of highly elaborated segments in the late-stage synthesis and avoid the linear construction from one end to the other. Another specific goal of our synthesis is to establish a different and improved synthesis of the aromatic structure of autolytimycin, which may shed light on the synthesis of related natural products sharing the same or similar aromatic core structures.

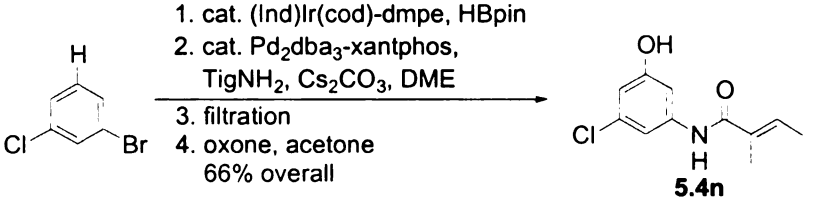
As can be seen, the aromatic core of autolytimycin is a 5-substituted 3-amidophenol structure with three functionalized *ortho*/*para* directing groups all

in a *meta* relationship. Such a substitution pattern is different from all other geldanamycin family members, and therefore many methods used to prepare the aromatic cores of these other natural products are not easily applied to autolytimycin. Additionally, this 1,3,5-trisubstitution pattern also poses its own synthetic challenge, as traditional aromatic substitution is not able to provide such a structure efficiently. Although preparations of similar 5-substituted 3-amidophenol structures of other natural products, such as trienomycin,[103,112] have been achieved, they tend to be lengthy and laborious (see Chapter 5, Scheme 5.2).

As discussed in Chapter 5, we have established a very attractive, highly efficient aromatic C–H borylation/amidation/oxidation protocol for the preparation of 5-substituted 3-amidophenols from simple 3-substituted halobenzenes. Since the aromatic segment of autolytimycin is a 5-substituted 3-amidophenol, utilization of this C–H borylation/amidation/oxidation protocol to the total synthesis of autolytimycin is attractive. Furthermore, we have demonstrated good functional group tolerance of that protocol, especially the tolerance of the α,β-unsaturation of the amide partner that resembles the C1–C4 portion of autolytimycin (Scheme 6.6). Therefore, it is very appealing to test the feasibility of applying this borylation/amidation/oxidation protocol to total synthesis. Should this protocol succeed, the preparation of the aromatic region of this type of natural products

would be dramatically simplified over the existing methods, and the power of C–H borylation in bringing efficiency and speed of assembly to synthetic chemistry would be highlighted.

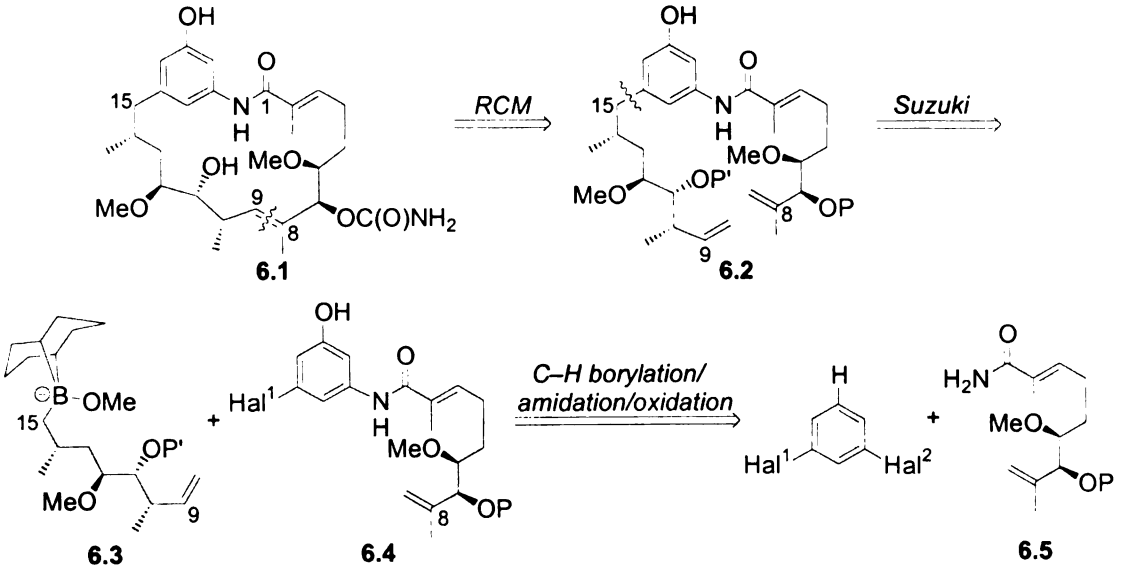
Scheme 6.6 Success in the borylation/amidation/oxidation with unsaturated amide



5.4n

However, as mentioned in Chapter 5, the borylation/amidation/oxidation protocol works best if the aromatic bromide is electron-poor. Therefore, although preparation of **5.4n** (Scheme 6.6) is straightforward, this protocol could be problematic on a phenyl bromide bearing the C15 alkyl chain of the target molecule. Therefore, our plan was to apply this borylation/amidation/oxidation

Scheme 6.7 Retrosynthetic analysis for autolytimycin



6.1 **6.2** **6.3** **6.4** **6.5**

strategy prior to the installation of the C15 alkyl substituent, as illustrated in Scheme 6.7.

According to this plan, a late-stage ring-closing metathesis will be used to construct the C8–C9 olefin from the acyclic precursor **6.2**. Such a ring-closing metathesis has been attempted in the total synthesis of geldanamycin and resulted in a failure.[113a] However, although Andrus reported that his attempts included different solvents, concentrations, temperatures, etc., the only catalyst attempted was the Grubbs' second generation catalyst. Since olefin metathesis has been dramatically developed in recent years including the discovery of microwave-assisted conditions[127a] as well as the emergence of new catalysts with much higher reactivity, such as Hoveyda-Grubbs' catalyst[127b] and Grubb's fluorinated catalyst,[127c] the scope of successful metathesis has been considerably increased. Given this situation, in addition to the higher flexibility of precursor **6.2** compared to Andrus' precursor of geldanamycin due to the absence of C4–C5 olefin and a less crowded aromatic segment, we viewed our proposed ring-closing metathesis as a challenge worth pursuing.

Compound **6.2** would arise from the union of the C15 substitutent and the halobenzene segment **6.4**, which would be assembled via our borylation/amidation/oxidation protocol first. This should avoid the aforementioned incompatibility of the electron-releasing group with the

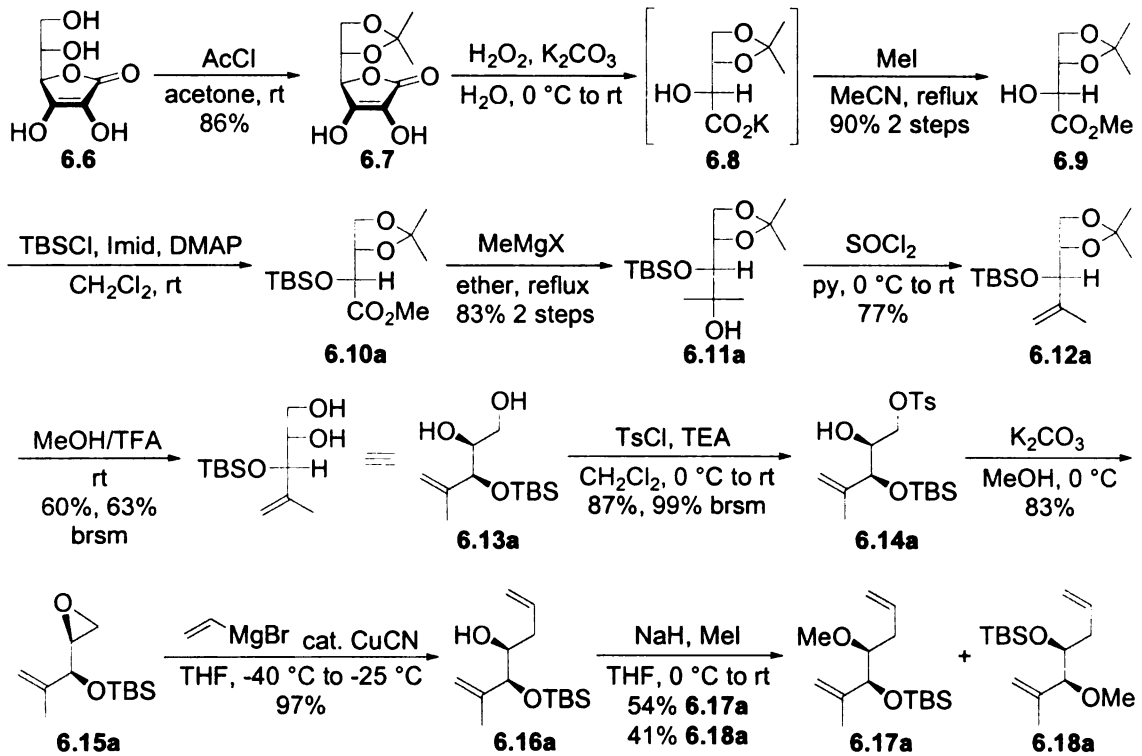
borylation/amidation/oxidation protocol. In this context, a modified Suzuki coupling between the corresponding aryl halide **6.4** and a corresponding *B*-alkyl-BBN nucleophile **6.3** carrying the C15 alkyl chain was planned. Such Suzuki couplings have been developed in quite a few laboratories over recent years, and has proved a versatile strategy for late-stage construction of $C(sp^3)$–$C(sp^2)$ bonds.[128] As mentioned previously, halide **6.4** would be prepared from a dihalobenzene and a fully elaborated amide segment **6.5** via the C–H borylation/amidation/oxidation protocol. Although our study in Chapter 5 demonstrates the versatility and functional group tolerance of this protocol, application of this method to a system with such complexity has not been attempted. Thus, the validation of the borylation/amidation/oxidation for complex, functionalized substrates would be an important advance in this chemistry.

6.4 Synthesis of the Right-hand Segment

Our synthetic journey began with the construction of the right-hand segment **6.5** (Scheme 6.8). While previous syntheses used different methods to generate the two stereogenic centers with oxygen substituents,[113,119-121] we decided to build this moiety from the chiral pool. (L)-Threonic acid, which structurally resembles the C5-C8 moiety of **6.5**, caught our attention. The literature preparations of a (L)-threonic acid derivative start from vitamin C (**6.6**). Thus, following literature procedures,[129] the diol of **6.6** was first protected as an acetonide, followed by an

oxidative cleavage of the endiol to generate a four-carbon unit, 3,4-isopropylidene (L)-threonic acid potassium salt **6.8**. This salt, without purification, was alkylated to afford a methyl ester (**6.9**). Subsequent TBS protection of the free alcohol followed by a two-fold Grignard attack of the ester yielded the tertiary carbinol **6.11a**. Dehydration provided the desired methyl olefin moiety in **6.12a**.[129c,d]

Scheme 6.8 First-generation synthesis en route to the right-hand segment ***6.5***

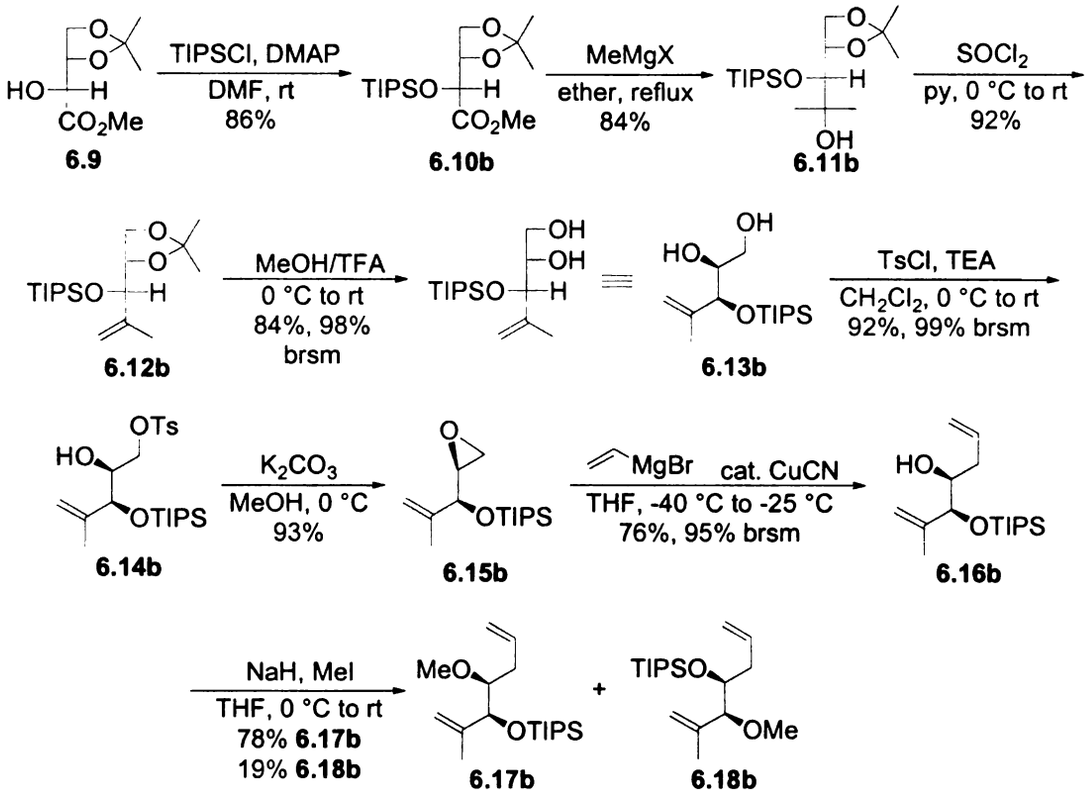


The acetonide protecting group was removed under acidic conditions to give diol **6.13a**.[129c,d] Although the isolated material from this step clearly indicated the survival of the TBS group under this reaction condition, the 60% yield was only moderate, suggesting a significant loss of material. The primary alcohol of **6.13a**

was tosylated, followed by an intramolecular displacement of the tosylate under basic conditions to afford epoxide **6.15a**. Epoxide opening was achieved with vinyl Grignard using CuCN as the catalyst,[130] generating a secondary alcohol **6.16a**. Using other cupper sources such as CuBr and CuI gave inferior results. Surprisingly, methylation of **6.16a** came with significant silyl migration, giving the desired methyl ether **6.17a** and undesired methyl ether **6.18a** in a 1.3:1 ratio. Although methylation using MeOTf and 4-methyl-2,6-di-*tert*-butylpyridine gave isomerially pure **6.17a** without silyl migration, the reaction was very slow. In fact, 1.5 days of such methylation only afforded ~50% conversion. We then reconsidered the choice of TBS as a protecting group. The lack of steric bulk around the silicon may contribute to the ease of transfer to the neighboring oxyanion during the methylation. Moreover, the low yield during the acetonide removal (**6.12a** to **6.13a**) may be partially due to methanolysis of the TBS group and formation of water-soluble triol. On the basis of these uncertainties, recourse to the sterically more crowded tri-*iso*-propylsilyl group (TIPS) was made.

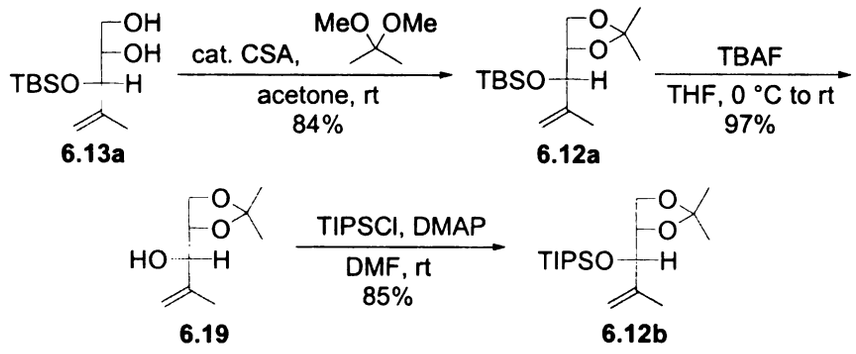
We obtained the TIPS-protected acetonide **6.12b** from two routes (Schemes 6.9 and 6.10). One route (Scheme 6.9) mimicked the chemistry shown in Scheme 6.8, while the other "recycled" the TBS-protected **6.12a** and **6.13a** to the desired TIPS variants (Scheme 6.10). Subjecting TIPS-protected **6.12b** to the acidic acetonide removal conditions afforded 84% yield of **6.13b** along with 14%

Scheme 6.9 Second-generation synthesis en route to the right-hand segment ***6.5***



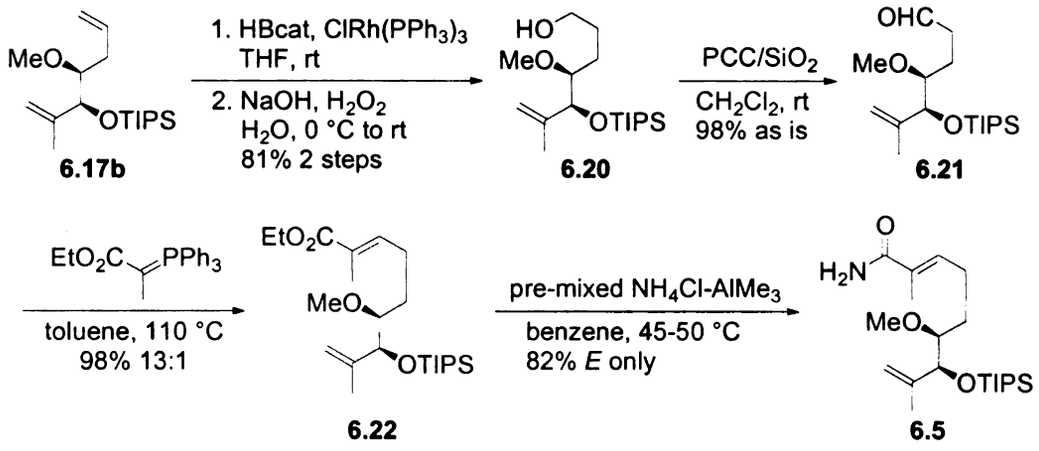
recovered starting material. This represented a much improved result compared with **6.12a**, indicating that the use of the TIPS protecting group was beneficial. The same steps of tosylation, epoxide formation, and Cu-catalyzed epoxide ring opening led to the secondary alcohol **6.16b**. Gratefully, under the same methylation conditions, **6.16b** afforded the desired product **6.17b** and the undesired silyl migration product **6.18b** in a much improved 4.2:1 ratio. Although the amount of side-reaction was still significant, the yield of the desired product **6.17b** was sufficient enough to carry out further elaborations (Scheme 6.11).

Scheme 6.10 Recycling of undesired TBS diol



The two olefins in compound **6.17b** were successfully discriminated via an Rh-catalyzed hydroboration with catecholborane (HBcat). Under those conditions, the mono-substituted olefin chemoselectively reacted, leaving the disubstituted olefin intact. This type of selectivity has been reported with similar substrates.[131] A subsequent oxidation with basic hydrogen peroxide furnished primary alcohol **6.20** in good yield. PCC oxidation of **6.20** generated the desired aldehyde **6.21**, which, without purification, was subjected to a Wittig olefination to give the α,β-unsaturated ester **6.22** in a 13:1 *E*/*Z* ratio. Unfortunately, the *E* and *Z* isomers were not separable at this stage. Conversion of the ester group to the amide group was achieved with a standard Weinreb procedure using NH_4Cl and $AlMe_3$,[132] which presumably generates an aluminum amide typed nitrogen nucleophile. Luckily, after this transformation, the *E* and *Z* isomers of the α,β-unsaturated amide could be separated by chromatography, with the desired *E* isomer **6.5** obtained in 82% yield.

Scheme 6.11 Completion of the synthesis of the right-hand segment ***6.5***

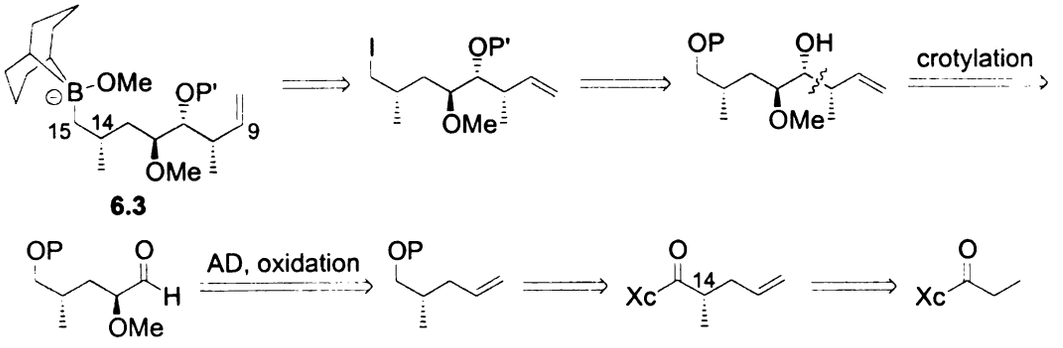


Thus, the synthesis of the right-hand segment **6.5** was completed in 14 steps from vitamin C in 22% overall yield. The overall process is efficient and high yielding, and does not require any asymmetric induction.

6.5 Synthesis of the Left-hand Segment

Having obtained the right-hand segment **6.5**, we turned our attention to the preparation of the left-hand segment **6.3**. Its synthesis would require some type of asymmetric induction, at least for the stereogenic center at C14 (Scheme 6.12). An asymmetric alkylation with a chiral auxiliary was proposed for this purpose.

Scheme 6.12 Retrosynthetic analysis for segment ***6.3***



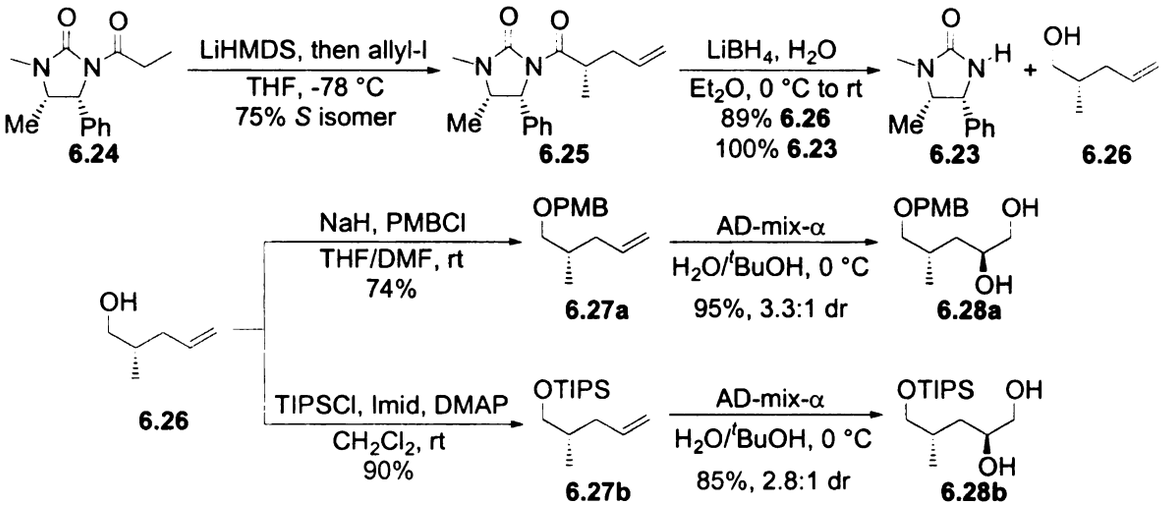
Initially we focused on use of the imidazolidinone chiral auxiliary **6.23**.[133]

This chiral auxiliary can be easily prepared from ephedrine and has been utilized in our laboratory's total synthesis of the proposed structure of amphidinolide A.[134] Thus, a large stock of **6.24** and the optimized reaction conditions are readily available.

Following that procedure,[134] the enolate of **6.24** underwent an asymmetric allylation to give the corresponding product **6.25** (Scheme 6.13). Contrary to our previous experiences, it was observed that LiHMDS worked better than NaHMDS, giving an improved diastereomeric ratio of 12-15:1 versus 7:1 for NaHMDS. However, scaling up the LiHMDS allylation (3.7 g scale) resulted in some problems such as gel formation during the reaction. Luckily, the two diastereomers were separable by careful column chromatography. The chiral auxiliary of **6.25** could be reductively removed by $LiBH_4$ to furnish the alcohol **6.26** in 89% yield with quantitative recovery of **6.23**. Our plan was to perform a Sharpless asymmetric dihydroxylation[135] on protected **6.26** to stereoselectively generate the diol functionality. To our dissapointment, such a dihydroxylation did not lead to a good stereochemical induction, with either PMB or TIPS protected alcohol. Diastereomeric ratios of about 3:1 were observed, and the two diastereomers were not separable, even after protection of the diol as an acetonide. This twist led us to consider other approaches for the diol generation. Particular interest was given to systems that could lead to the ready separation of

diastereomers, since the Sharpless asymmetric dihydroxylation can sometimes give unsatisfactory results with unhindered monosubstituted olefins.[135]

Scheme 6.13 First-generation synthesis en route to the left-hand segment ***6.3***

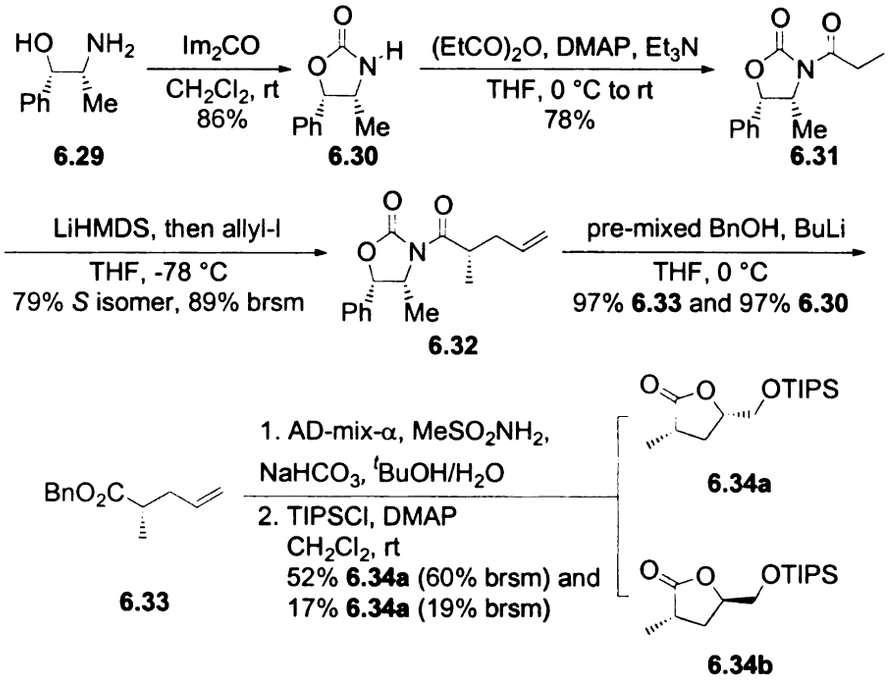


In seeking for a more facile way to separate such diastereomers, we considered the formation of a ring so as to turn the linear diastereomers into hopefully more separable *cis* and *trans* isomers. Such a strategy was used in a related system by Carter and co-workers during their attempt to synthesize azaspiracid.[136] Thus, we sought to reproduce their early-stage results.

This journey began with Evans oxazolidinone chiral auxiliary **6.30**,[137] which is conveniently prepared from norephedrine **6.29** by treatment of carbonyl diimidazole[138] (Scheme 6.14). This switch from **6.23** to **6.30** was made simply because the starting material to prepare **6.23**, ephedrine, was no longer commercially available.

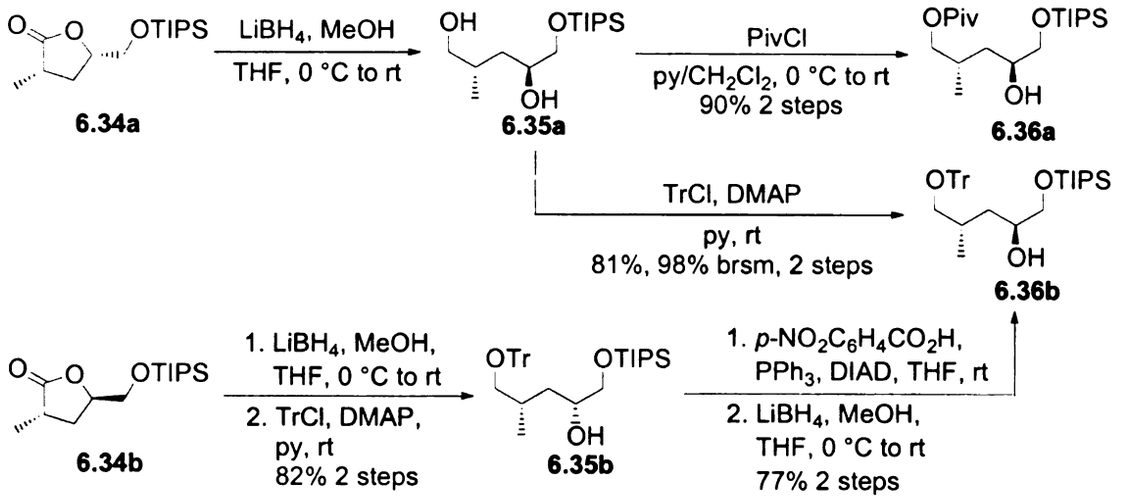
Thus, following a literature acylation procedure that gave **6.31**,[139] the same allylation was performed, furnishing **6.32** as a single diastereomer as indicated by crude ^{1}H NMR (> 95:5 dr). The chiral auxiliary was removed via a transacylation reaction to afford the benzyl ester **6.33** along with quantative recovery of the chiral auxiliary. Sharpless asymmetric dihydroxylation of **6.33** was accompanied by an *in situ* lactonization of the secondary alcohol to furnish a five-membered lactone ring. TIPSCl protection of this crude mixture gave the corresponding silyl ethers **6.34a** and **6.34b** as a pair of *cis* and *trans* isomers. These two silyl ethers were easily separable by column chromatography, giving the desired **6.34a** in 52% yield over the two steps. One drawback of the asymmetric dihydroxylation was that, due to its heterogeneous nature, a reproducible reaction rate was not achieved and the percent conversion of starting material varied from run to run. Best results were obtained by stopping the reaction at 1-1.5 days regardless of the conversion, since longer reaction times gave significantly lower yields. Irrespective of when we stopped the reaction, the stereoselectivity of this process remained unsatisfactory (3:1). Nonetheless, since Carter and co-workers reported the same ratio[136] in their synthesis, and since the two diastereomers were separable, this result was deemed acceptable. That said, it would certainly be useful if we could recycle or utilize the undesired isomer.

Scheme 6.14 Second-generation synthesis en route to the left-hand segment ***6.3***



Shown in Scheme 6.15, the lactone ring in **6.34a** was reductively opened to afford diol **6.35a**. The primary alcohol in **6.35a** could be easily and chemoselectively protected with either a pivaloyl group[140] or a trityl group.[141] Mr. L. A. Sanchez of our group demonstrated that the undesired isomer **6.34b** could undergo a similar process to afford **6.35b**. In addition, Mitsunobu inversion of the secondary alcohol in **6.35b** followed by a reduction of the resulted ester gave the same Tr ether **6.36b** as obtained from **6.34a** in reasonably good overall yield (63%). This recycling process minimized the downside of the poor asymmetric induction during the Sharpless dihydroxylation. However, given this recycling protocol, the use of a Piv protective group would not be favored due to its incompatibility with $LiBH_4$ reduction.

*Scheme 6.15 Second-generation synthesis en route to the left-hand segment **6.3** (continued)*



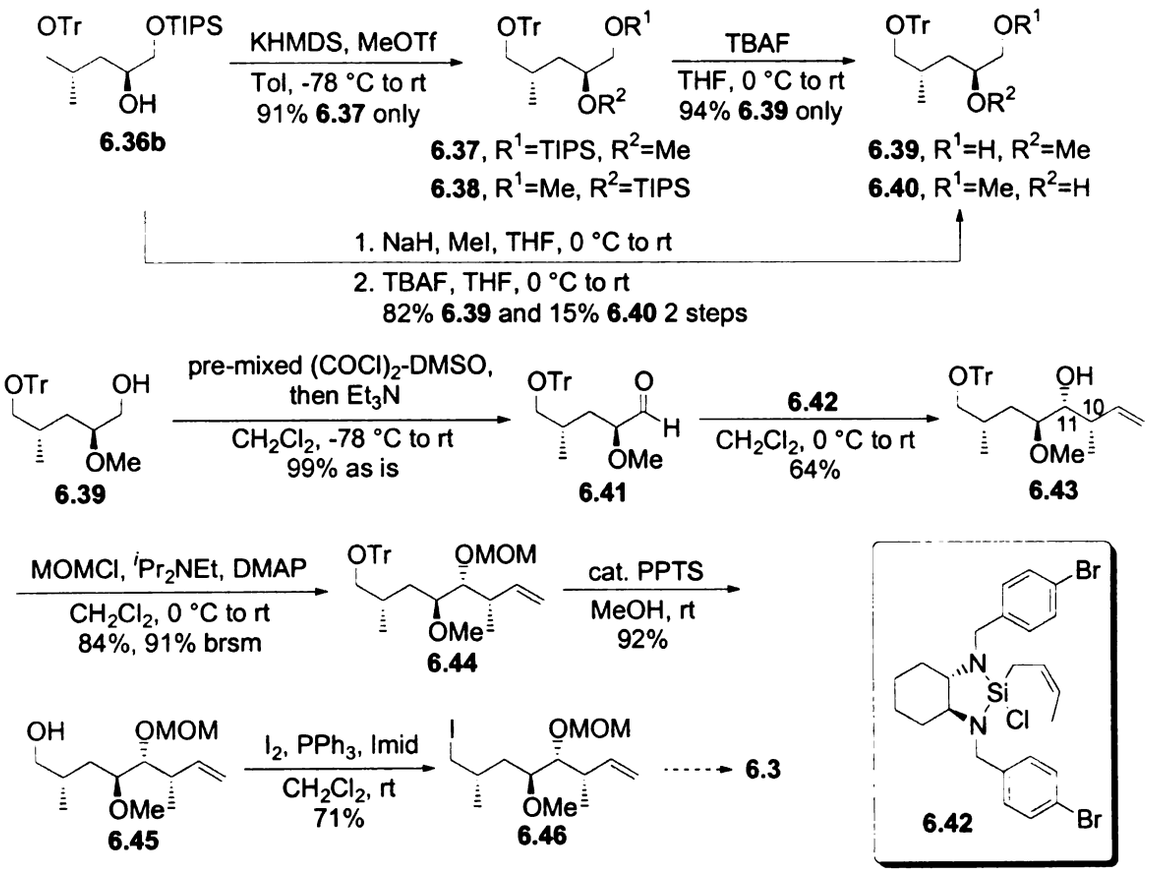
Subsequent methylation of the secondary alcohol in **6.36a/b** was performed. Under NaH-MeI conditions, methylation of **6.36a** was accompanied by multiple side-reactions. On the other side, the same methylation worked well with **6.36b** to afford 82% **6.39** after desilylation with TBAF (Scheme 6.16). This result further confirmed the choice of Tr as the protecting group. That said, as expected, this methylation step, like the methylation of **6.16b**, also resulted in a small amount of silyl migration (15% after silyl deprotection). The silyl migration problem could be eliminated by using an alternative methylation method. Treatment of **6.36b** with KHMDS in toluene followed by methylation with MeOTf[142] furnished pure **6.39** without silyl migration.[143] However, the overall yield of **6.39** after desilylation via this route (86%) was not improved.

The primary alcohol in **6.39** was then oxidized to form aldehyde **6.41**. This oxidation was less facile than the oxidation of **6.20**. Among different conditions

attempted, Swern oxidation proved the best. Other oxidants gave inferior results. For example, using PCC resulted in epimerization of the α stereocenter, while using TPAP-NMO combination led to incomplete conversion.

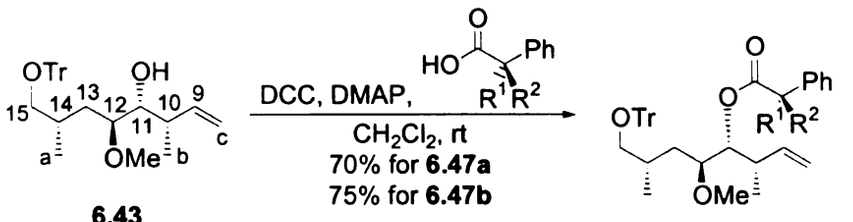
According to our retrosynthetic plan (Scheme 6.12), the aldehyde functionality in **6.41** needs to undergo an asymmetric crotylation to elongate the carbon chain and generate the two stereogenic centers at C10 and C11. This crotylation could be performed with various reagents.[144,145] Among them, we chose Leighton's crotylsilane[145] for that purpose due to its easy preparation and handling. Thus,

Scheme 6.16 Completion of the synthesis of the left-hand segment ***6.3***



crude **6.41** was treated with reagent **6.42**. To our pleasure, the desired product **6.43** was isolated in 64% yield as the only diastereomer. To the best of our knowledge, application of Leighton's asymmetric crotylation in total synthesis has only been reported once[145d] and utilization of **6.42** in total synthesis has not been reported. The absolute stereochemistry of **6.43** was confirmed by the modified Mosher ester analysis developed by Trost[146] on the *O*-methylmandelate esters. Thus, the secondary alcohol in **6.43** was esterified with both *R* and *S* isomers of *O*-methylmandelic acid. ^{1}H NMR spectra were recorded for **6.43**, **6.47a**, and **6.47b**, and each proton in the spectra was assigned by its chemical shift, splitting pattern and gCOSY experiment. The change in the ^{1}H NMR chemical shifts between **6.47a** and **6.47b** was consistent with an *R*-configuration assignment of stereochemistry at C11 in **6.43** (Table 6.1).

*Table 6.1 ^{1}H NMR analysis of the stereochemistry of **6.34** at C11*



6.43
assumed stereochemistry

6.47a (*R*), R^1=H, R^2=OMe
6.47b (*S*), R^1=OMe, R^2=H

Proton	15	14	a	13	12	10	9	b
6.43	3.03, 2.93	2.05	1.02	1.64, 1.26	3.28	2.28	5.67	1.16
6.47b	2.99, 2.91	2.01	0.93	1.61, 1.14	3.28	2.24	5.51	0.59
6.47a	2.84, 2.70	1.82	0.84	1.22, 0.92	3.19	2.39	5.63	0.91
Δδ (*S*-*R*)	0.15, 0.21	0.19	0.09	0.39, 0.22	0.09	-0.15	-0.12	-0.32

Having made the appropriate stereochemical assignments, our synthetic journey continued. MOM protection[147] of the free alcohol in **6.43** was followed by a mild acidic detritylation to give the free primary alcohol **6.45**. The free alcohol was iodinated[128c] to afford a primary iodide **6.46**, which could be simply treated with ^{t}BuLi followed by *B*-OMe-BBN to generate **6.3**. We favor storing alcohol **6.45** due to its stability, and then preparing and using **6.46** and **6.3** when needed.

In this way, alcohol **6.45**, the precursor of **6.3**, was synthesized in 14 steps from norephedrine in 16% overall yield. With recycling of **6.34b**, the overall yield increased to 19%.

6.6 Coupling of Segments in the Late Stage

Having the fully elaborated segments **6.5** and **6.3** both in hand, we next investigated the coupling of these pieces in the late stage. First, we attempted to perform the C–H borylation/amidation/oxidation protocol with fully elaborated right-hand piece **6.5** to prepare **6.4**.

6.6.1 Choice of the Halides on the Aromatic Starting Material

As discussed before, the aromatic starting material should be a dihalide (Scheme 6.7). One halide would be used for the amidation and the other for the subsequent Suzuki coupling. It should be noted that in our previous studies (Chapter 5), this type of substrate was purposefully avoided due to the uncertainty of the reactivity of the second halide during the course of the amidation. The

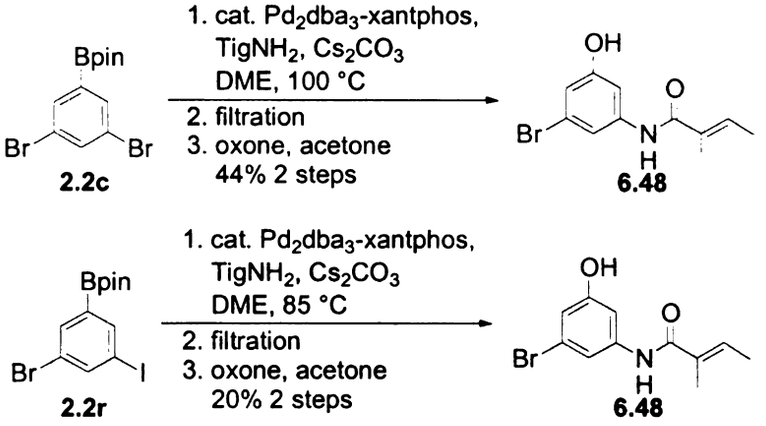
only such substrate tested was 3-bromochlorobenzene **2.1a**, which gave no significant side-reactions because of the low reactivity of chloride towards either the amidation or the Suzuki. However, this substrate might not be suitable for this total synthesis due to the questionable reactivity of the chloride in the successive Suzuki coupling. Hence, the behavior of a dihalide substrate, with neither halide being chloride, in the borylation/amidation/oxidation protocol had to be investigated.

Two related aryl dihalides, 1,3-dibromobenzene **2.1c** and 1-bromo-3-iodobenzene **2.1r**, were first investigated in the borylation/amidation/oxidation protocol. We hoped that for **2.1r**, the amidation would selectively occur on the iodide and leave the bromide for Suzuki coupling. For **2.1c**, we hoped that the first amidation would introduce enough electronic perturbation to the aromatic ring so that the second bromide would not be reactive under the amidation conditions.

Unfortunately, our expectations went unmet. Reaction conditions that were successful with **5.4n** (Scheme 6.6) led to only 40-44% yield for **6.48** from isolated **2.2c** and tiglic amide (Scheme 6.17), a much inferior result compared with the formation of **5.4n**. Analysis of the crude reaction product revealed that a major side-reaction was the Suzuki coupling of the residual bromide with the boronic ester, leading to significant dimer formation with various extent of amidation coupling. Obviously, our thought that upon amidation, the remaining bromide

would be unreactive towards the undesired Suzuki side-reaction was not correct. Stopping the amidation before consumption of its starting material, to our disappointment, proved no big improvement.

Scheme 6.17 Amidation/oxidation of dihalobenzenes with tiglic amide



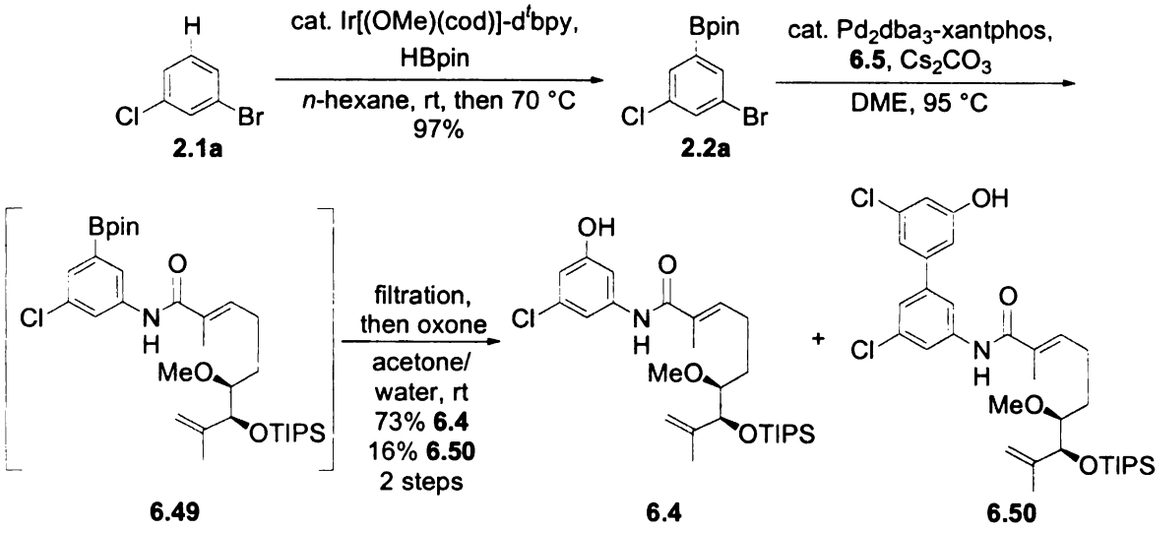
Next, we examined the use of **2.2r**, hoping that the amidation of iodide would be fast enough to discriminate against the undesired Suzuki reaction. This expectation proved incorrect as well, as the yield of **6.48** dropped further to about 20% from isolated **2.2r**. At the same time, the amount of Suzuki dimerization products actually increased, indicating the possibility that the iodide might participate in both the Suzuki and amidation competitively. The Suzuki side-reaction was certainly a much bigger obstacle than expected. As a result, we reconsidered 3-bromochlorobenzene as our starting arene. In this context, we sought for conditions that would allow the chloride to be employed in a Suzuki reaction or other equally productive transformations. Over the past several

years, Suzuki couplings of chlorides have been witnessed to dramatic advances.[148] Thus we would look to see if some of the newly published conditions would be applicable to our synthesis.

6.6.2 Joining the Right-hand Segment with the Aromatic Segment Using Borylation/Amidation /Oxidation Protocol

Our initial attempts toward using 3-bromochlorobenzene **2.1a** in the borylation/amidation/oxidation protocol to couple with amide **6.5** focused on understanding the behavior of **6.5** under such conditions compared with tiglic amide. Thus, boronic ester **2.2a** was prepared in 97% yield via the borylation of **2.1a** (Scheme 6.18). The amidation was then attempted with 1 equiv amide **6.5**. Two observations were quickly made. For one, amidation of **2.2a** with **6.5** was about three times slower than with tiglic amide. Also, at the end of the reaction **2.2a** was fully consumed, but not **6.5**. This clearly indicated that there were side-reactions taking place on **2.2a**, such as Suzuki couplings. These two observations argued against the use of **2.2c** or **2.2r** as the aromatic substrate, since the undesired Suzuki would be even more prevalent against the sluggish amidation. Given that amide **6.5** was obtained via a multiple-step route and thus more valuable, the amidation was modified to use excess **2.2a** instead of excess amide as described in Chapter 5.

Scheme 6.18 Amidation/oxidation protocol for the synthesis of ***6.4***



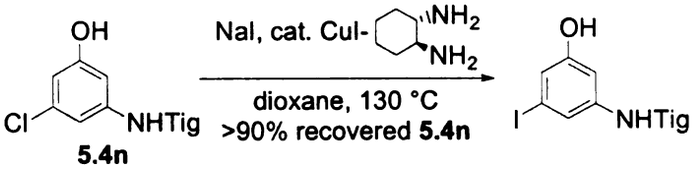
Thus, 1.5 equiv of pure bornoic ester **2.2a** became the loading of choice for the amidation/oxidation protocol. However, here a new problem emerged. Oxidation of the crude amidophenyl boronic ester **6.49** failed to go to full conversion under our standard operation conditions (1 equiv oxone per boron, 1:1 acetone/water, rt, 10 min). At the same time, the oxidation of the residual **2.2a** was complete. A reasonable explanation of this slower reaction rate of **6.49** was its poor solubility in the oxidation medium, relative to the simple aryl boronic esters in Chapter 2. Thus, modified reaction conditions using 1.5 equiv oxone per boron, in 1.5:1 acetone/water for 40 min were examined. To our delight, those conditions proved successful. Reaction between **2.2a** and **6.5** afforded the desired amidophenol **6.4** in 73% yield over the two steps. Hence, this amidation/oxidation protocol proved successful to include even highly functionalized amide coupling partners, such as **6.5**. Compound **6.4** was

accompanied by about 16% Suzuki dimerization product **6.50**, but the yield of **6.4** was high enough to continue with the synthesis. It should be noted that using 3-chlorobromobenzene (**2.1a**) in the 3-step one-pot borylation/amidation/oxidation sequence was successful, but the overall yield dropped to about 48%. For this reason, we prefer to run the borylation and the amidation/oxidation separately.

6.6.3 Attempted Suzuki Coupling of the Chloride

The success of the amidation/oxidation approach to afford 5-chloro 3-amidophenol **6.4** did not take away our worries. As mentioned previously, although this amidation/oxidation protocol is highly efficient for preparation of chloride **6.4**, utilizing the same method for preparation of the corresponding bromide or iodide is not expected. Therefore, the low reactivity of the chlorides in Suzuki couplings[148] has to be overcome. In this regard, we first looked to transform the chloride in compound **6.4** to a more reactive aryl iodide using a Finkelstein-type reaction. We tested Buchwald CuI-diamine conditions on model compound **5.4n** (Scheme 6.19).[149] To our disappointment, this reaction failed. No aryl iodide was observed, as only starting material **5.4n** was recovered.

Scheme 6.19 Attempted Finkelstein halide exchange

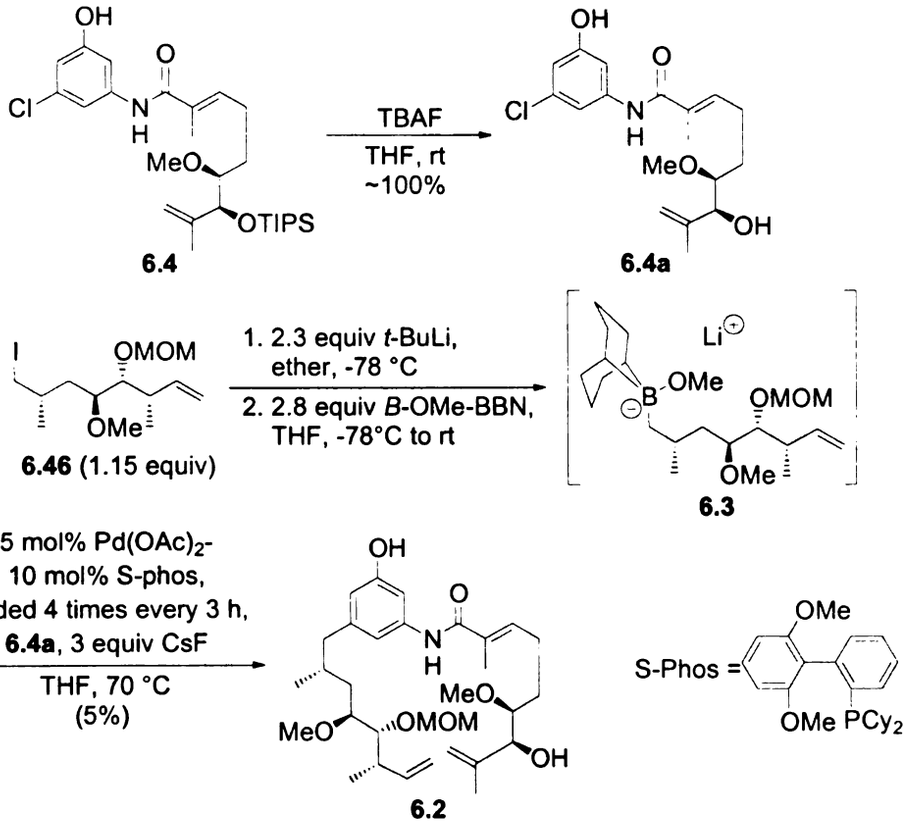


Therefore, the straightforward Suzuki reaction between the fully elaborated chloride and the BBN-derived nucleophile (**6.3**) was attempted. Among different reaction conditions that can promote Suzuki couplings from aryl chlorides,[148,150] a Buchwald report using S-phos ligand[150a] caught our attention. Buchwald has demonstrated a wide range of chlorides as suitable substrates in such Suzuki couplings, including an example of using a *B*-alkyl-BBN derivative as nucleophile, which was very similar to our *B*-OMe-*B*-alkyl-BBN coupling partner. Since these Suzuki conditions utilize CsF as a promoter, the TIPS protecting group in compound **6.4** became an issue. We worried that fluoride-promoted desilylation during the reaction might adversely affect the proposed Suzuki reaction. To avoid this potential complication, the TIPS protecting group was first removed by TBAF to afford **6.4a** as the free alcohol (Scheme 6.20). Previous Suzuki reactions tolerated free alcohols on the electrophile,[128c] thus we considered that the free alcohol in **6.4a** would not obstruct the cross-coupling.

In this manner (Scheme 6.20), iodide **6.46** was first subjected to Li/I exchange[151] conditions with ^{t}BuLi to obtain a lithium species, which was trapped with *B*-OMe-BBN to form the boron adduct **6.3**.[128] This boronate was then allowed to react with **6.4a** under Buchwald Suzuki conditions.[150a] However, during this reaction, we observed that the Pd catalyst underwent rapid decomposition to form Pd black. We attempted to compensate for this

decomposition by recharging the reaction with fresh Pd catalyst and ligand every 3 h over 9 h (total 20 mol% Pd). Careful analysis revealed that the desired Suzuki coupling product **6.2** was formed, but the yield was only ~5%. Dechlorination side-product was also observed. This result, though not satisfactory, showed promise for using chlorides, such as **6.4a**, as the Suzuki electrophiles. We thus set out to examine reaction systems in an attempt to optimize this Suzuki reaction.

Scheme 6.20 Attempted Suzuki coupling



6.6.4 Model Studies of the Suzuki Coupling of the Chloride

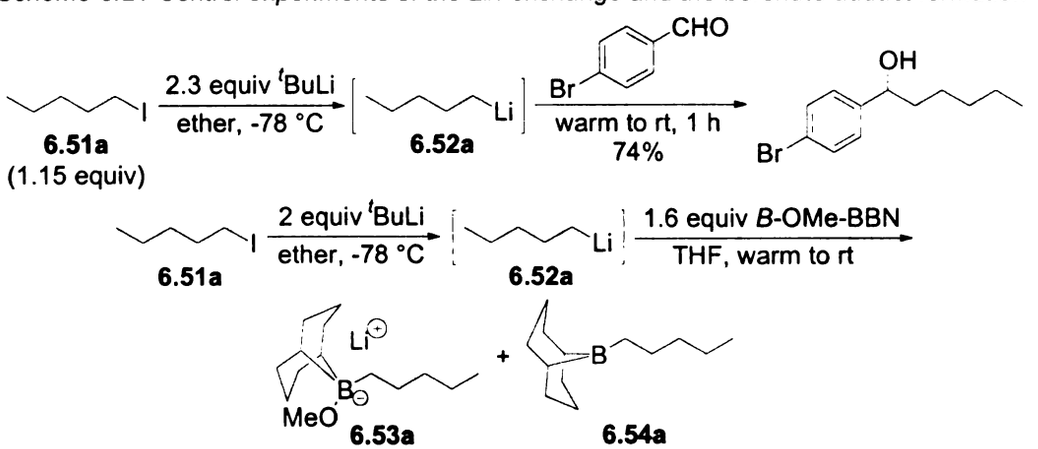
Since both of the Suzuki coupling partners were obtained in multiple steps, we

recognized that it would be synthetically challenging to perform Suzuki optimization studies using fully elaborated compounds **6.4** and **6.3**. Thus, a model Suzuki system was sought.

Before conducting even a model study, we wanted to insure that the 5% yield was truly reflective of the low reactivities of the Suzuki coupling partners, rather than other unforeseen problems. Therefore, we wanted to confirm that (a) Li/I exchange indeed took place, (b) the boron adduct **6.3** was indeed generated, and (c) literature Suzuki coupling was reproducible.

Along these lines, pentyl iodide **6.51a** was first subjected to the Li/I exchange conditions and the generated lithium species **6.52a** was trapped with an aldehyde (Scheme 6.21). Crude NMR of this reaction clearly indicated formation of the desired alcohol. Thus the Li/I exchange step was confirmed.

Scheme 6.21 Control experiments of the Li/I exchange and the boronate adduct formation

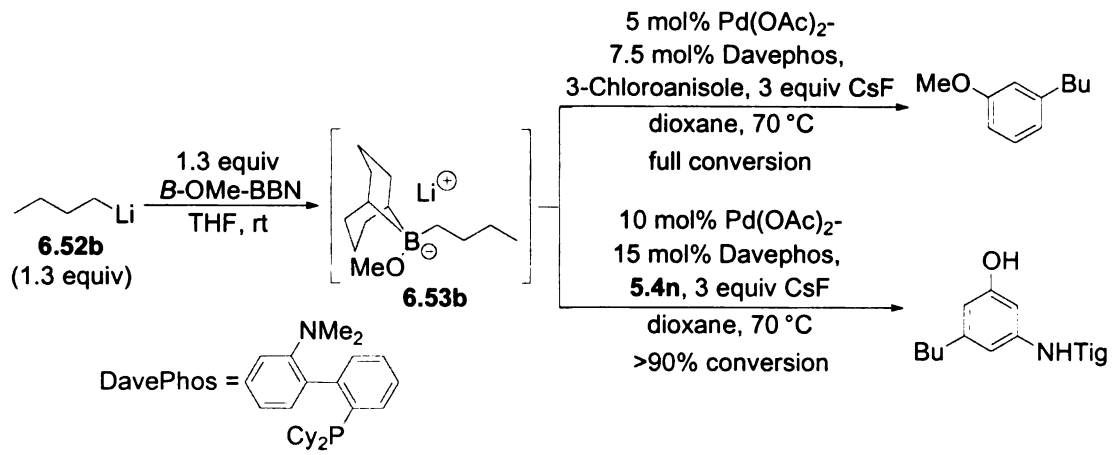


Next, **6.51a** was again subjected to the Li/I exchange condition, followed by addition of *B*-OMe-BBN to generate a model boronate **6.53a**. ^{11}B NMR of this

solution showed two characteristic signals: one signal at 86 ppm, corresponding to the neutral species **6.54a**, and another at 0 ppm, corresponding to the anionic adduct **6.53a** (Scheme 6.21).[128a,b] These two species are known to exist in an equilibrium, which lies in the direction of **6.53a** with K_{eq} ~ 100.[128b] Due to this equilibrium, isolation and quantification of **6.53a** or **6.3**-type boronate adduct would be a very tough task. Nonetheless, while not quantitative, this experiment clearly confirmed the generation of **6.3**-type boronate adduct.

Finally, a few Suzuki coupling reactions were carried out to test the reproducibility of the reported conditions as well as the operational techniques (Scheme 6.22). Commercial ^{n}BuLi **6.52b** was treated with *B*-OMe-BBN, and the generated boronate adduct **6.53b** was allowed to react with 3-chloroanisole under conditions similar to those reported by Buchwald but using Davephos ligand instead.[150b] Contrary to the reaction between **6.3** and **6.4a** (Scheme 6.20), the Pd catalyst did not decompose and only 5 mol% Pd loading was needed to smoothly carry this reaction to full completion as judged by GC and GC-MS. These reaction conditions were also found to be compatible with **5.4n** without protection of either the phenol or the amide, giving the desired coupling product in ~53% yield with only slight contamination by unreacted, inseparable starting material **5.4n** (ca 5-7%).

Scheme 6.22 Control experiments of the Suzuki coupling



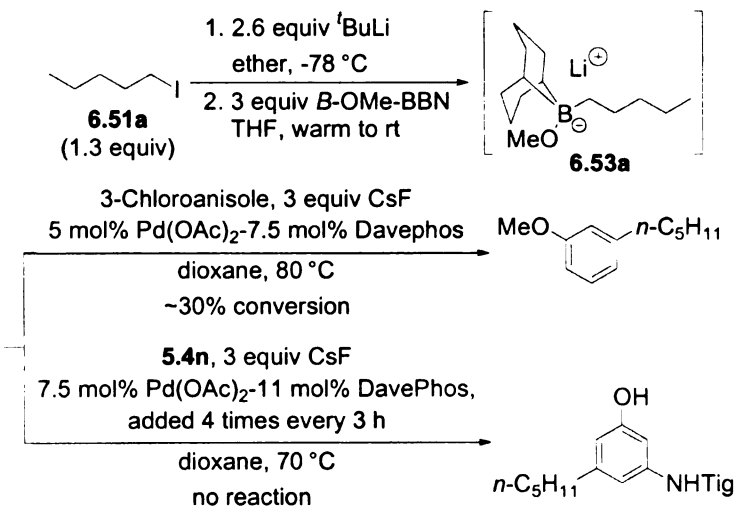
On the basis of these control experiments, we concluded that the 5% yield of **6.2** via Scheme 6.20 was reflective of the true reactivity of the two coupling partners under the reaction conditions. The question of what caused the low reactivity was next to be addressed.

In this regard, the Li/I exchange of the iodide **6.46** was scrutinized. Although we were sure that the exchange conditions indeed generated the Li species, it was possible that the Suzuki reaction was adversely affected by the different solvent system or concentration, or by the LiI by-product that came along with the Li/I exchange. To understand the effect of this Li/I exchange on the Suzuki coupling, the two control experiments in Scheme 6.22 were repeated with material prepared by a Li/I exchange from an iodide **6.51a** (Scheme 6.23).

As seen in Scheme 6.22, the Suzuki coupling between 3-chloroanisole and **6.53b**, prepared from **6.52b** via a single B/Li exchange, was successful with a full consumption of the chloride starting material. Yet the Suzuki coupling between

3-chloroanisole and **6.53a**, prepared from **6.51a** via a sequential Li/I and B/Li exchange, gave only ~30% conversion (GC, uncorrected) of the chloride (Scheme 6.23). The same trend was observed in the Suzuki coupling with **5.4n**. With a single B/Li exchange, **6.53b** successfully coupled with **5.4n** to give > 90% conversion, whereas providing the boron adduct **6.53a** via a Li/I exchange from iodide **6.51a** completely shut down the Suzuki reaction. In addition to the low conversion, it was also observed that Pd-catalyst decomposition to Pd black was severe in these reactions. This failure clearly demonstrated the offensive effect of the Li/I exchange step on the Suzuki coupling.

Scheme 6.23 Suzuki coupling with added Li/I exchange step



Although we were not sure exactly why such Li/I exchange step would cause the Suzuki coupling to fail, we attempted to further manipulate the Suzuki conditions to be compatible with this exchange step. Along these lines, the

Suzuki coupling of 3-chloroanisole with **6.53a**, obtained from **6.51a** after two exchanges, was repeated with several different Pd catalysts ($Pd(dppf)Cl_2$ and $Pd(OAc)_2$), ligands (Davephos, S-phos, (2-biphenyl)P^tBu_2,[150c] (2-biphenyl)PCy_2,[150c] and $AsPh_3$), and promoters (CsF, KF, $K_3PO_4 \cdot nH_2O$, and Cs_2CO_3). Both conventional heating and microwave irradiation were examined. Among all combinations attempted, the best reaction system consisted of $Pd(OAc)_2$, in conjunction with Davephos or S-phos ligand, promoted by CsF or $K_3PO_4 \cdot nH_2O$ under conventional heating conditions. Although those combinations were found to tolerate the Li/I exchange step, Pd decomposition remained severe and required recharging of the Pd catalyst and ligand to compensate for this decomposition. Nonetheless, these combinations all pushed the Suzuki coupling of 3-chloroanisole to > 90% conversion, with the fastest reaction (total 9 h) observed with the $Pd(OAc)_2$-S-phos-$K_3PO_4 \cdot nH_2O$ combination (Scheme 6.24).

Scheme 6.24 Improved Suzuki coupling with added Li/I exchange step

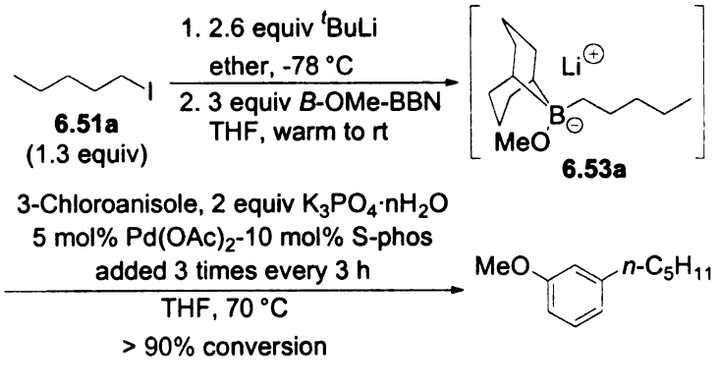
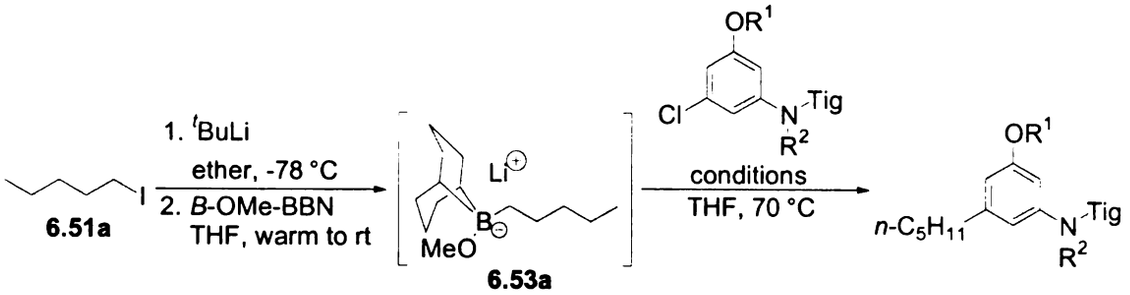


Table 6.2 Protecting group study



Entry	R^1	R^2	Reaction condition	Results[a]
1	H	H	$Pd(OAc)_2$-S-phos-CsF	no reaction
2	H	H	$Pd(OAc)_2$-Davephos-CsF	no reaction
3	Bn	H	$Pd(OAc)_2$-S-phos-CsF	no reaction
4	Bn	H	$Pd(OAc)_2$-S-phos-$K_3PO_4 \cdot nH_2O$	no reaction
5	TIPS	H	$Pd(OAc)_2$-S-phos-$K_3PO_4 \cdot nH_2O$	~30% conversion
6	TIPS	H	Pd_2dba_3-S-phos-$K_3PO_4 \cdot nH_2O$	trace conversion
7[b]	TIPS	H	$Pd(OAc)_2$-S-phos-TlOEt	no Suzuki, loss of TIPS
8	TIPS	H	$Pd(OAc)_2$-S-phos-Tl_2CO_3	no reaction
9[c]	TIPS	H	$Pd(OAc)_2$-S-phos-$K_3PO_4 \cdot nH_2O$ Ag_2O	trace conversion
10[c]	TIPS	H	$Pd(OAc)_2$-S-phos-$K_3PO_4 \cdot nH_2O$ Ag_2CO_3	no reaction
11[c]	TIPS	H	$Pd(OAc)_2$-S-phos-$K_3PO_4 \cdot nH_2O$ $AgNO_3$	no reaction
12	Ac	H	$Pd(OAc)_2$-S-phos-$K_3PO_4 \cdot nH_2O$	no Suzuki, loss of Ac
13	Ac	H	Pd_2dba_3-S-phos-$K_3PO_4 \cdot nH_2O$	no Suzuki, loss of Ac
14	Ac	H	$Pd(OAc)_2$-S-phos-CsF	no Suzuki, loss of Ac
15	TIPS	Boc	$Pd(OAc)_2$-S-phos-$K_3PO_4 \cdot nH_2O$	Suzuki occurred, complex mixture
16	TIPS	SEM	$Pd(OAc)_2$-S-phos-$K_3PO_4 \cdot nH_2O$	~30% conversion
17	Ac	Boc	$Pd(OAc)_2$-S-phos-CsF	no Suzuki, loss of Tig

All reactions were run in 0.15-0.25 mmol scale, with 4 times of periodical addition of 5 mol% Pd catalyst and 10 mol% ligand (7.5 mol% in case of Davephos). 3 equiv bases were used, except $K_3PO_4 \cdot nH_2O$ (2 equiv). See experimental section for a general procedure. [a] Judged by crude ^1H NMR. [b] Reaction was run in THF/water 3:1. [c] 1 equiv Ag per halide.

To our great disappointment and surprise, use of S-phos did not work at the coupling of **5.4n** with **6.53a** (Entry 1, Table 6.2). No reaction took place as **5.4n** was left unreacted, as observed by NMR. Up to this point, the failure of the Suzuki coupling probably should not be attributed *solely* to the Li/I exchange, because such an exchange could be tolerated by the reaction with 3-chloroanisole, yet could not be tolerated by the reaction with **5.4n**. Thus the failure of using **5.4n** in the Suzuki coupling is more likely due to a *combination* of the Li/I exchange and the intrinsic nature of **5.4n**, which might be linked to the presence of the phenol and the amide functionalities. Such functional groups in **5.4n**, in the Li/I exchange milieu, might either destabilize the boron nucleophile, or destabilize the Pd catalyst, ultimately leading to a failed reaction. Understanding this problem, the next task was to protect these groups and test the Suzuki coupling thereafter (Table 6.2).

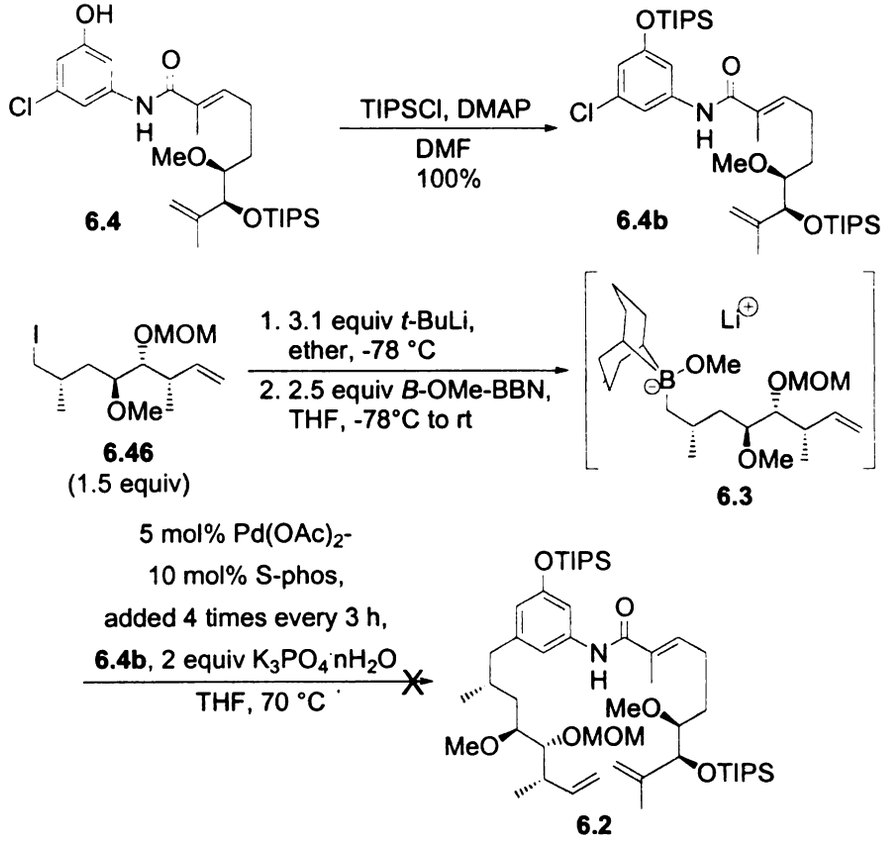
Disappointedly, protecting the phenol and the amide did not lead to an improved Suzuki coupling. Protection of the phenol functionality as a benzyl ether showed no reactivity toward the Suzuki reaction (Entries 3-4). Protection as an acetate led to exclusive hydrolysis of the protecting group (Entries 12-14). Only TIPS-protected phenol, under the $Pd(OAc)_2$-S-phos-$K_3PO_4 \cdot nH_2O$ conditions, gave ~30% conversion (Entry 5). Tl bases have previously been shown to dramatically improve the reactivity of Suzuki reactions.[152] Unfortunately,

experiments employing Tl bases afforded no success (Entries 7-8). Adding silver salts, such as $AgNO_3$, Ag_2CO_3, and Ag_2O, into the reaction system to sequester the halide also had little positive effect (Entries 9-11). Protection of the amide nitrogen also failed to improve the reactivity. An SEM-protected amide, for instance, did not couple more effectively than the unprotected amide (Entries 5 and 16). Protecting the amide nitrogen as an imide only led to significant hydrolysis during the Suzuki reaction. ^{11}B NMR of these failed Suzuki couplings showed the absence of the neutral *B*-alkyl BBN species (86 ppm) as well as the absence of the anionic *B*-OMe-*B*-alkyl BBN adduct (0 ppm). A signal at 33 ppm did emerge, which was attributed to the decomposition of these two reactive species.[128a] Finally, although the TIPS-protected phenol gave ~30% conversion in this model coupling (Entry 5), it did not work in the real system, as protection of the free phenol in **6.4** as a TIPS ether resulted in a complete failure in the coupling with **6.3** (Scheme 6.25).

Due to these negative results and the difficulties in isolating and handling the *B*-alkyl BBN species, an approach to the Suzuki coupling that would obviate the Li/I exchange milieu had to be considered. One option was to use the trifluoroborate as the Suzuki coupling partner instead of the 9-BBN adduct. Alkyl trifluoroborates have been developed in recent years as excellent Suzuki coupling partners.[153] Several advantages, such as no protodeborylation, ease for

isolation and purification, no handling and storage issues, and reasonably good reactivity have been identified for these substrates. Unlike 9-BBN adducts, which are always in equilibrium with their neutral species following loss of the methoxide and are therefore difficult to isolate, alkyl trifluoroborates are crystalline solids and can be purified very easily by crystalization. Therefore, it is possible to subject a pure boron species to the Suzuki conditions without problems from the solvent, concentration or LiI contamination.

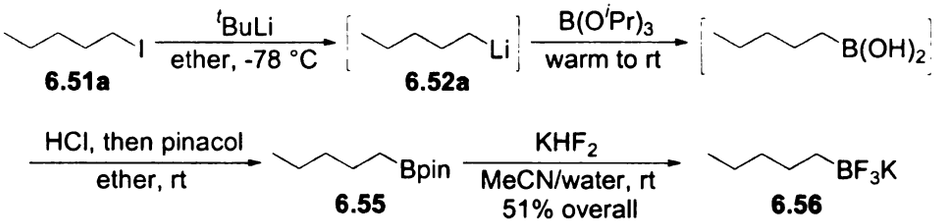
Scheme 6.25 Application of the TIPS-protected phenol in the Suzuki coupling to the real system



Thus (Scheme 6.26), the lithium species **6.52a**, obtained from **6.51a** via Li/I

exchange, was treated with triisopropyl borate followed by acid hydrolysis. The intermediacy of the boronic acid was confirmed by formation of the pinacolate **6.55**. Compound **6.55** was then allowed to react with KHF_2 under literature conditions[153] to give the desired trifluoroborate **6.56** as a crystalline solid, which gave clean ^{1}H, ^{13}C and ^{11}B NMR spectra. Pure **6.56** was then subjected to the Suzuki conditions with **5.4n** and its derivatives.

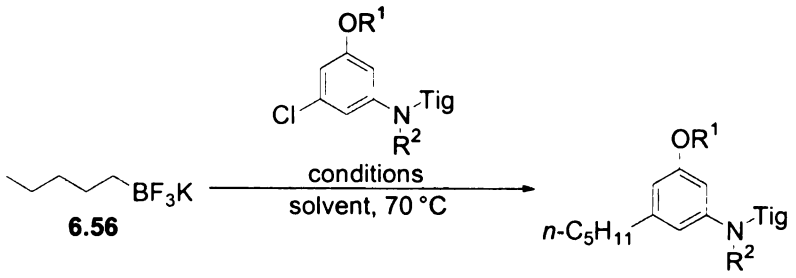
Scheme 6.26 Preparation of the trifluoroborate



To our great frustration, **6.56** turned out to be an even worse coupling partner than **6.53a**. The Pd catalyst decomposed even faster than the reactions in Table 6.2 and no Suzuki couplings were observed (Table 6.3).

To make the situation worse, the loss of the chloride in Entry 1 might suggest that the problem of the Suzuki coupling is more complicated than we had expected. Such a dechlorination would likely occur with a successful oxidative addition followed by a β-H elimination from Pd-bound methoxide. This can be further supported by the absence of such dechlorination product once the solvent is switched from methanol to THF/water (Entry 2). Thus the failure of the Suzuki coupling might lie not in the oxidative addition step, but rather in a later step in the

Table 6.3 Use of trifluoroborate in Suzuki coupling



Entry	R^1	R^2	Reaction condition	Result[a]
1	Bn	H	$Pd(OAc)_2$-S-phos-K_2CO_3, MeOH[b]	trace Suzuki 82% dechlorination
2	Bn	H	$Pd(OAc)_2$-S-phos-Cs_2CO_3, THF/water 10:1[b]	no reaction
3	TIPS	H	$Pd(OAc)_2$-S-phos-$K_3PO_4 \cdot nH_2O$ THF[c]	no reaction

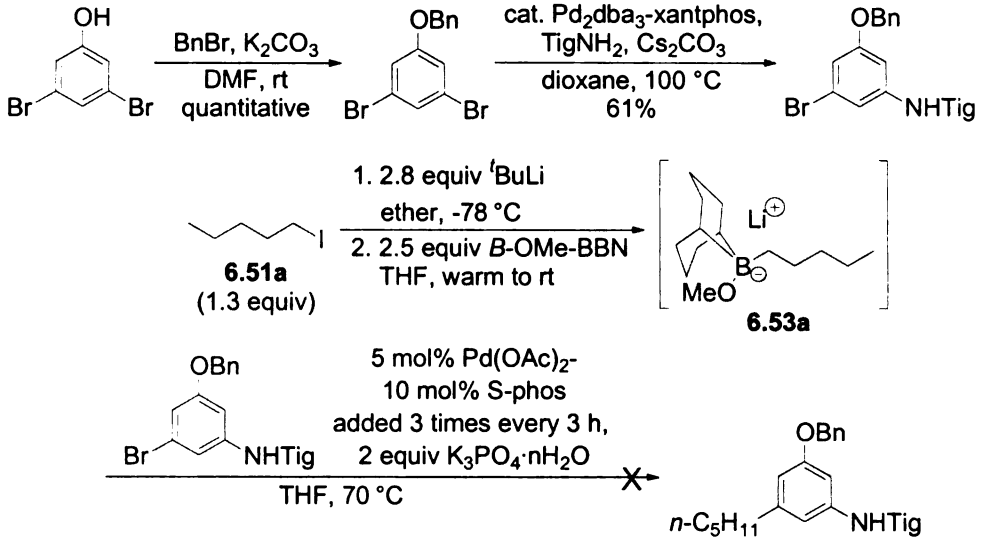
All reactions were run in 0.12 mmol scale. [a] Judged by crude ^1H NMR. [b] 10 mol% Pd and 20 mol% ligand, 4.5 h, then additional 10 mol% Pd and 20 mol% ligand, 4.5 h. 3 equiv base. [c] 5 mol% Pd and 10 mol% ligand added 4 times every 3 h, then overnight. 2 equiv base.

catalytic cycle.

A bromo version of the Bn-protected phenol was prepared and subjected to the Suzuki coupling conditions using boron adduct **6.53a** as the nucleophile (Scheme 6.27). Again, the conditions gave no Suzuki coupling. Although this result may not directly suggest a successful oxidative addition, it is consistent with our hypothesis that the Suzuki coupling has other problems, and simply changing the reactivity of the halide may not be sufficient to achieve a success.

We considered that other possibilities leading to a problematic Suzuki coupling might include (a) a relatively rapid decomposition of the boron coupling partner, (b) a kinetically sluggish transmetalation, or (c) a relatively rapid Pd

Scheme 6.27 Coupling with a bromide



decomposition. Among these factors, the intrinsic sluggish nature of the transmetalation seems the least likely, since we were able to couple **6.53b** and **5.4n**, as shown in Scheme 6.22. The Pd decomposition is also not very probable, as Mr. L. A. Sanchez in the group demonstrated that the Pd decomposition issue is more likely caused by air or moisture intrusion, since running the reaction with extreme care could eliminate the Pd black formation. Even these dry anaerobic conditions did not lead to a successful Suzuki coupling. Therefore, the remaining issue, namely the rapid decomposition of the boron coupling partner, which was supported by ^{11}B NMR, becomes our most likely explanation. Compared with the success of the coupling between **6.53b** and **5.4n** (Scheme 6.22), it is possible that organoboron coupling partner decomposition may be the major harmful effect of the Li/I exchange milieu. That

said, this may be only one of several reasons for the failed Suzuki reactions (Table 6.2 and Table 6.3). Recent results from Mr. L. A. Sanchez in the group demonstrated the feasibility of utilizing an isolated alkyl boronic acid in the coupling with the chloride in the model system.[154] The application of such conditions to the real system is expected.

6.7 Conclusions

While the total synthesis of autolytimycin remains elusive, our efforts successfully demonstrated the viability of utilizing the C–H borylation/amidation/oxidation protocol on a fully elaborated amide segment to synthesize the aromatic core of autolytimycin. However, we have not been able to use the planned Suzuki coupling to further elaborate the synthesis and couple the left-hand piece to the aromatic ring. Problems for this Suzuki coupling point to the Li/I exchange milieu as well as the presence of the amidophenol functionality in the electrophile. Although we have not been able to gain enough understanding to overcome these problems, it appears that the instability of the organoboron species under the Suzuki conditions may be one of the reasons for the failed coupling.

Summary

Through our work, we have demonstrated that catalytic C–H borylation has a wide potential to be utilized in organic synthesis. It can not only be used to prepare aryl boronic esters, but also be used to directly functionalize complicated substrates, such as amino acid derivatives. In combination with subsequent oxidation, deuteration, and amidation reactions, it allows for rapid construction of uncommon but potentially useful synthetic intermediates and building blocks. We have also demonstrated in the area of total synthesis that a borylation/amidation/oxidation protocol can be used to include highly functionalized amide substrates, which could lead to the efficient construction of the aromatic core structure of autolytimycin.

Chapter 7. Experimental Details and Compound Characterization Data for C–H Borylation and Related Reactions

7.1 Materials and Methods

7.1.1 Materials and Methods For C–H Borylation of Simple Aromatics

Unless otherwise noted, for C–H borylation and the one-pot reactions thereof, all arene substrates were purified before use. Solid substrates were sublimed under vacuum. Liquid substrates were refluxed (or stirred if the boiling points are too high) over Na, CaH_2, or molecular sieves (4 Å) overnight, and then distilled and degassed. Pinacolborane (HBpin) was stirred over PPh_3, vacuum transferred into an air-free flask and brought into the glove box. A simple distillation was also sufficient. Bis(pinacolato)diboron (B_2pin_2) was used without purification. Solvents for the C–H borylation were purified and rigorously dried. Cyclohexane was washed with concentrated H_2SO_4 until the acid layer was colorless, followed by washes with water and saturated $NaHCO_3$, then dried over $MgSO_4$, refluxed over Na, distilled, and degassed. *n*-Hexane, and other alkane solvents, such as pentane, heptane and octane, were refluxed over Na, distilled, and degassed. *All solvents should pass the Na-benzophenone test inside the glove box.* Ir catalysts for C–H borylation were prepared according to literature procedures.[155,156] Ligands for C–H borylation were obtained from the commercial sources and used without purification.

For the oxidation protocol, oxone was purchased as $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ and used as a ~0.3 mol/L aqueous solution. Reagent grade acetone was used without purification, and technical grade acetone also worked well.

For the deuteration protocol, D_2O (99.9% D) and acetic anhydride were used without purification. Commercial boronic acids were used as received and the corresponding boronic esters were prepared from these boronic acids and unpurified pinacol (see Section 7.2.3 for details). Crabtree catalyst was used as received. Ethereal solvents such as THF and DME were distilled over Na.

For the amidation protocol, the amides coupling partners were obtained from their commercial sources and were used as received. Non-commercial amides were prepared and used without purification (see Section 7.2.4 for details). Pd_2dba_3 (Strem) and xantphos ligand were used as received. Cs_2CO_3 was dried by heating at 130-150 °C under high vacuum for 1-2 days before use. Ethereal solvents such as THF and DME were distilled over Na. Dioxane, obtained as anhydrous grade (99.8%), could be used directly without purification.

All small-scale borylation reactions were set up under nitrogen atmosphere inside the glove box, and carried out in oven- or flame-dried thick-walled sealed air-free flasks, magnetically stirred, and monitored by GC-FID and GC-MS (standard GC temperature program: 70 °C for 2 min, followed by a 20 °C/min ramp to 250 °C, and stay at 250 °C). Large-scale borylation reactions were also set up in the glove box but were carried out in oven- or flame-dried round-bottom flasks with vent to nitrogen balloon or nitrogen manifold, and high-temperature reaction conditions were avoided. Yields refer to isolated, clean materials. In case of volatile products that could not stand forcing evaporation, yields were corrected to discount the added weight of the residual solvents. All spectral data reported were obtained from solvent-free materials, unless specifically noted.

Thin-layer chromatography was performed with 0.25 mm pre-coated silica-gel plates on aluminum. Silica gel was supplied as 60 Å (230-400 Mesh). GC-FID spectra were recorded on a Varian CP-3800 instrument with capillary WCOT fused silica column (30 m*0.25 mm ID coating CP-SIL 8 CB). GC-MS spectra were recorded on either a Varian 2200 GC-MS instrument, or a HP 5890 Series II GC in tandem with a Trio-1 MS instrument. The latter instrument was also used to record MS spectra with direct-probe inlet. Infrared spectra were obtained on a Nicolet IR/42 spectrometer. Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Gemini-300, Varian Inova-300, Varian VXR-500, and Varian Unity-plus 500 spectrometers (300, 500 MHz for ^{1}H, respectively, and 75, 125 MHz for ^{13}C, respectively). Chemical shifts for ^{1}H and ^{13}C were reported in part-per-million (ppm) values relative to the residue peaks of solvent $CDCl_3$ (δ 7.24 for ^{1}H and 77.0 for ^{13}C) or acetone-d_6 (δ 2.04 for ^{1}H and 29.8 for ^{13}C). ^{2}H NMR spectra were recorded on Varian Unity-plus 500 spectrometers (500 MHz for ^{1}H, 76.75 MHz for ^{2}H), with chemical shift relative to acetone-d_6 internal standard (δ 2.04 for ^{2}H). ^{11}B NMR spectra were recorded on Varian Inova-300, Varian VXR-500 and Varian Unity-plus 500 spectrometers (500 MHz for ^{1}H, 160 MHz for ^{11}B), with chemical shift relative to $BF_3 \cdot OEt_2$ as external standard (δ 0.0 for ^{11}B). High-resolution mass spectra were obtained at Michigan State University Mass Spectrometry Service Center with a JOEL-AX505 mass spectrometer (resolution 7000), or at the Mass Spectrometry Laboratory of University of South Carolina. Preparative GC was performed with a Varian 920

GC-TCD with packed C18 column. Combustion analyses were performed on a Perkin Elmer Series II 2400 CHNS/O analyzer.

7.1.2 Materials and Methods For C–H Borylation of Aromatic Amino Acid Substrates

This part of work was performed at Johnson & Johnson Pharmaceutical Research and Development, LLC. Due to the differences in laboratory equipments and requirements, differences in materials, methods and operations from Section 7.1.1 may exist. The following descriptions only depict what was performed and may not be the optimal operations.

For this part, all amino acid starting materials were purchased from PepTech as *N*-Boc amino acids and methylated using commercial (trimethylsilyl)-diazomethane reagent (see Section 7.2.2 for detail). Non-commercial amino acid starting materials were prepared according to literature procedures[157] (see Section 7.2.2 for detail). The substrates were *not* purified before use. Bis(pinacolato)diboron (B_2pin_2) and ligand d^{t}bpy were used without purification. Solvents for borylation, including cyclohexane and THF, were obtained as anhydrous grade and used as received. Other solvents, such as acetone for oxidation, benzene and methanol for methyl ester formation, were all obtained as reagent grade and used as received. Ir catalyst for C–H borylation was prepared according to literature procedures.[156]

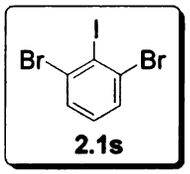
All borylation reactions were set up in air using think-walled microwave-adaptive vials that were *not* dried. Reactions were performed in a CEM Discover microwave synthesizer (75 W maximum power) equipped with

CEM Explorer automated workstation and magnetically stirred. Reactions were monitored by HP 1100 reverse phase analytical HPLC (water/acetonitrile as mobile phase) with SUPELCO column (33*4.6 mm, 3 μm) and 214/254 nm dual UV detectors, and/or Agilent 1100 reverse phase LC-MS (water/acetonitrile as mobile phase) with SUPELCO column (50*2.1 mm, 3 μm), the latter of which was also used for mass spectra recording (positive ESI). Column chromatography was performed on silica gel 60 Å (230~400 mesh). Preparative HPLC was performed on Gilson 215 liquid handler reverse phase HPLC, with YMC HPLC column (ODS-A, 100*30 mm, S-5 μ, 12 nm) and 214/254 nm dual UV detectors using 0.1% TFA-containing water/acetonitrile as the mobile phase, which was evaporated by Virtis lyophilizer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance-300 or Bruker Avance-500 spectrometers with chemical shifts reported relative to TMS (δ 0.00 ppm). Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected (Note: Lyophilized sample do not give reliable melting points. All lyophilized samples were dissolved in a solvent and then slowly evaporated before measuring the melting point). IR spectra were recorded on Nicolet 670 FT-IR spectrometer. Elemental analysis results were obtained from Robertson Microlit Laboratory. High-resolution mass spectra were obtained at Johnson and Johnson Pharmaceutical Research and Development, LLC with FAB ionization.

7.2 Preparation of Non-commercial Starting Materials

7.2.1 Preparation of Non-commercial Arenes

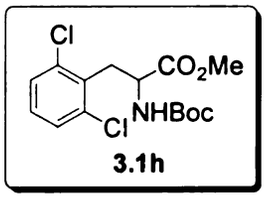
1,3-Dibromo-2-iodobenzene (2.1s): To 4.0 g 2,6-dibromoaniline (16 mmol)



2.1s

in a round bottom flask (not dried) was added 6.7 mL concentrated HCl (80 mmol, 5 equiv) followed by 30 mL water and ~30 g ice. The whole mixture was cooled by an ice bath and a suspension was generated. In a separate beaker, 1.3 g $NaNO_2$ (19 mmol, 1.2 equiv) was dissolved in 10 mL water and also cooled by an ice bath. The cold $NaNO_2$ solution was then introduced dropwise to the vigorously stirred suspension containing 2,6-dibromoaniline, and the temperature was controlled below 5 °C by addition of ice. Upon complete addition, the mixture was stirred for another 25 min until a homogenous light greenish-yellow solution was formed. This solution was filtered through glass fiber to crushed ice. Upon stirring, urea was added by small portions until gas evolution ceased. To this solution was added dropwise a solution of 5.3 g KI (32 mmol, 2 equiv) in 30 mL water. The mixture turned brown with gas evolution and quickly became a slurry. It was stirred at room temperature for 1 h and then 45 °C for 45 min, until there appeared a homogeneous brown solution on the bottom with foams and slurries on top. This mixture was filtered through glass fiber and cotton to collect the insolubles, which was further dissolved in ether. The ether layer was washed successively with $NaHSO_3$, 3 M NaOH, and water, dried over $MgSO_4$ and evaporated. 5.45 g dark brown crystals (94%) were obtained and sublimation under 0.1 mmHg vacuum at 85 °C afforded slightly orange crystals; mp 97 °C (lit[158] 99-99.5 °C). ^1H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.0 Hz, 2 H), 7.05 (t, *J* = 8.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.3, 131.1, 130.3, 109.4; IR (neat): 3054, 1547, 1418, 1387, 772 cm^{-1}; LRMS *m/e* 360 (M^+), 232, 153, 127, 74.

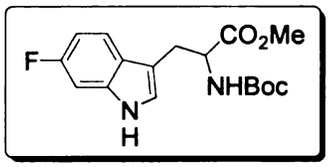
7.2.2 Preparation of Non-commercial Aromatic Amino Acid Starting Materials



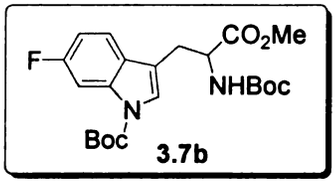
3.1h

2-*tert*-Butoxycarbonylamino-3-(2,6-dichlorophenyl)-propionic acid methyl ester (3.1h): 6.2 mL commercial LDA solution (1.8 M in heptane/THF/ethylbenzene, 11 mmol, 2.2 eq) was further diluted with 16 mL THF and cooled to 0 °C by ice bath. To this solution was added dropwise a solution of 740 μL *N*-Boc glycine methyl ester (5 mmol) in 5 mL THF over 5 min, followed by another 4 mL THF. The mixture was stirred at 0 °C for 15 min, and charged with a solution of 2.4 g 2,6-dichlorobenzyl bromide (10 mmol, 2 equiv) in 3 mL THF. The reaction mixture turned light yellow. The ice bath was then removed and the reaction was allowed to warm up to room temperature and kept for 1.5 h. Water was then added and the mixture was stirred upon slow addition of 1 M HCl until pH ~ 5. Layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layer was dried over $MgSO_4$ and evaporated. The crude material was purified by preparative HPLC (50/50 → 30/70 water/acetonitrile). After lyophilization, 595 mg of **3.1h** (34%) was obtained as a yellow oil, which solidified upon storage at room temperature; mp 69-72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, J = 8.0 Hz, 2 H), 7.12 (t, J = 8.0 Hz, 1 H), 5.18 (d, J = 8.8 Hz, 1 H), 4.7-4.8 (m, 1 H), 3.74 (s, 3 H), 3.28-3.44 (m, 2 H), 1.33 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 155.3, 136.6, 133.4, 129.0, 128.7, 80.2, 52.9, 52.7, 34.6, 28.6; LRMS (ESI): *m/e* 292, 248 ($[M\text{-}Boc+2H]^+$).

2-*tert*-Butoxycarbonylamino-3-(6-fluoro-1*H*-indol-3-yl)-propionic acid



methyl ester: 880 mg 6-fluorotryptophan (4 mmol) and 673 mg $NaHCO_3$ (8 mmol, 2 equiv) were suspended in 20 mL water and 15 mL acetonitrile To this suspension was added a solution of 1.08 g Boc_2O (5 mmol, 1.25 equiv) in 5 mL acetonitrile. The suspension turned to a clear solution upon stirring at room temperature. After the reaction was judged complete by HPLC, it was treated with 1 M HCl until pH ~ 4 and directly lyophilized. The crude residue was then dissolved in 21 mL benzene and 6 mL MeOH. With vigorous stirring, (TMS)diazomethane solution (2 M in hexanes) was slowly added and the reaction medium was kept slightly acidic by introduction of 1 M HCl dropwise. After the mixture became sustained yellow, the solution was evaporated. The residual was extracted with CH_2Cl_2, washed with saturated $NaHCO_3$, water and dried over $MgSO_4$. Chromatography purification (1:1 heptane/EtOAc) afforded 1.1 g desired product (86% 2 steps) as a white solid; mp 170-172 °C (dec); ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (br, 1 H), 7.45 (dd, *J* = 5.3, 8.6 Hz, 1 H), 6.85-7.05 (m, 3 H), 5.05 (br, 1 H), 4.65 (m, 1 H), 3.67 (s, 3 H), 3.25 (br, 2 H), 1.43 (s, 9 H); LRMS (ESI): *m/e* 695 ($[2M+Na]^+$), 359 ($[M+Na]^+$), 281, 237 ($[M-Boc+2H]^+$).



3.7b

3-(2-*tert*-Butoxycarbonylamino-2-methoxycarbonyl-ethyl)-6-fluoro-indole-1-carboxylic acid *tert*-butyl ester (3.7b): 537 mg (1.6 mmol) *N*-Boc-6-fluorotryptophan methyl ester, obtained from the previous reaction, and 21.5 mg DMAP (0.176 mmol, 11 mol%) were suspended in 20 mL acetonitrile. To this suspension was added a solution of 460 mg Boc_2O (2.1 mmol, 1.3 equiv)

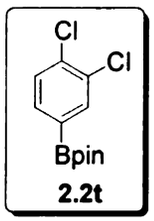
in 5 mL acetonitrile. The suspension gradually turned to a clear solution and the mixture was kept at room temperature. After being judged complete by HPLC, the reaction mixture was diluted with EtOAc and washed with brine followed by water, dried over $MgSO_4$, and evaporated. Chromatography purification (2:1 heptane/EtOAc) yielded 643 mg of **3.7b** (92%) as a gel-like material. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.9 Hz, 1 H), 7.36-7.43 (m, 2 H), 6.98 (dt, *J* = 2.1, 8.9 Hz, 1 H), 5.15 (d, *J* = 7.6 Hz, 1 H), 4.6-4.7 (m, 1 H), 3.69 (s, 3 H), 3.1-3.3 (m, 2 H), 1.66 (s, 9 H), 1.43 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 161.4 (d, *J* = 239 Hz), 155.4, 149.7, 136.0, 127.2, 124.6, 119.9 (d, *J* = 9.9 Hz), 115.4, 111.1 (d, *J* = 24.2 Hz), 103.0 (d, *J* = 28.3 Hz), 84.5, 80.4, 54.0, 52.7, 32.2, 28.7, 28.5; LRMS (ESI): *m/e* 895 ($[2M+Na]^+$), 459 ($[M+Na]^+$), 337 ($[M-Boc+2H]^+$), 281, 237; Anal. Calcd for $C_{22}H_{29}FN_2O_6$: C, 60.54; H, 6.70; N, 6.42. Found C, 60.81; H, 7.00; N, 6.21.

General Procedure for methylation of Other *N*-Boc-amino Acids: Commercially available *N*-Boc-amino acid was dissolved (or suspended if not soluble) in 3:1 ~ 4:1 benzene/MeOH to make a solution (or suspension) at the concentration of ~ 0.2 M. (TMS)diazomethane (2 M hexanes) was added via a syringe dropwise until gas evolution ceased and the yellow color sustained. The complete methylation could be confirmed by HPLC. The solution was then evaporated and dried over high vacuum overnight to afford a crude product. This product normally contained a small amount of MeOH and some TMS residue but no further purification was necessary as long as no residual benzene was detected (^{1}H NMR 7.36 ppm). In that case, further purification could be

performed by dissolving the material in CH_2Cl_2, washing with saturated $NaHCO_3$ and water, drying over $MgSO_4$, evaporating and drying over high vacuum overnight.

7.2.3 Preparation of Aryl Boronic Pinacol Esters from the Corresponding Boronic Acids

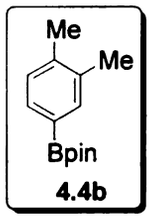
General Procedure: Aryl boronic acid and 1 equiv pinacol were dissolved in anhydrous ether and the mixture was stirred at room temperature. The crude mixture was dried over $MgSO_4$ (not necessary) before being evaporated. The residue was passed through a silica plug (CH_2Cl_2 or hexanes/CH_2Cl_2) to afford the desired pinacol ester.



2.2t

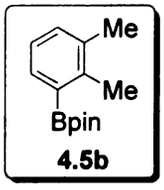
3,4-Dichlorophenylboronic acid pinacol ester (2.2t): Following the general procedure, 1.91 g dichlorophenyl boronic acid (10 mmol) and 1.2 g pinacol (10 mmol, 1.0 equiv) were dissolved in 50 mL ether and stirred at room temperature for 1 h. $MgSO_4$ was added and the mixture was filtered. The filtrate was evaporated and passed through a silica plug (CH_2Cl_2). Evaporation afforded 2.66 g of **2.2t** as colorless oil (97%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, J = 1.3 Hz, 1 H), 7.57 (dd, J = 1.5, 7.9 Hz, 1 H), 7.42 (d, J = 7.9 Hz, 1 H), 1.32 (s, 12 H); ^{11}B NMR (160 MHz, $CDCl_3$): δ 30.6; ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.6, 135.5, 133.7, 132.3, 130.0, 84.3, 24.8; IR (neat): 2980, 1591, 1383, 1354, 1144, 1096, 845, 666 cm^{-1}; LRMS (EI) *m/e* 272 (M^+), 257, 186, 83.

3,4-Dimethylphenylboronic acid pinacol ester (4.4b): Following the general procedure, 1.25 g of boronic acid **4.4a** (8.3 mmol) and 1.0 g pinacol (8.3



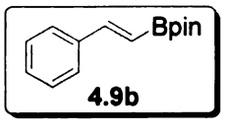
4.4b

mmol, 1.0 equiv) were suspended in 20 mL ether and stirred at room temperature for 1 h. The mixture quickly turned to a homogeneous solution. $MgSO_4$ was added and the mixture was filtered. The filtrate was evaporated and passed through a silica plug (CH_2Cl_2). Evaporation afforded 1.66 g of **4.4b** as colorless oil (86%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.57 (s, 1 H), 7.53 (d, *J* = 7.4 Hz, 1 H), 7.13 (d, *J* = 7.4 Hz, 1 H), 2.26 (s, 3 H), 2.25 (s, 3 H), 1.32 (s, 12 H); ^{11}B NMR (160 MHz, $CDCl_3$): δ 31.4; ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.0, 135.92, 135.86, 132.4, 129.1, 83.6, 24.8, 20.0, 19.4; IR (neat): 2978, 1615, 1399, 1356, 1148, 1132, 1094, 857, 669 cm^{-1}; LRMS (EI) *m/e* 232 (M^+), 217, 146, 132.



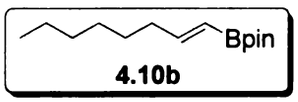
4.5b

2,3-Dimethylphenylboronic acid pinacol ester (4.5b): Following the general procedure, 1.23 g of boronic acid **4.5a** (8.2 mmol) and 0.97 g pinacol (8.2 mmol, 1.0 equiv) were suspended in 20 mL ether and stirred at room temperature for 1 h. The mixture quickly turned into a homogeneous solution. $MgSO_4$ was added and the mixture was filtered. The filtrate was evaporated and passed through a silica plug (CH_2Cl_2). Evaporation afforded 1.56 g of **4.5b** as colorless oil (82%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.4 Hz, 1 H), 7.19 (d, *J* = 7.4 Hz, 1 H), 7.07 (t, *J* = 7.4 Hz, 1 H), 2.45 (s, 3 H), 2.25 (s, 3 H), 1.33 (s, 12 H); ^{11}B NMR (160 MHz, $CDCl_3$); δ 32.0; ^{13}C NMR (125 MHz, $CDCl_3$); δ 143.0, 136.5, 133.5, 132.3, 124.8, 83.4, 24.8, 20.4, 18.4; IR (neat): 2978, 1590, 1379, 1350, 1306, 1140, 1034, 851, 727, 669 cm^{-1}; LRMS (EI) *m/e* 232 (M^+), 217, 175, 132.



4.9b

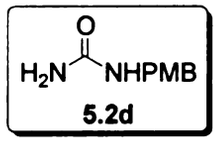
***trans*-2-Styreneboronic acid pinacol ester (4.9b)**: Following the general procedure, 1.48 g of boronic acid **4.9a** (10 mmol) and 1.18 g pinacol (10 mmol, 1.0 equiv) were dissolved in 20 mL ether and stirred at room temperature for 1 h. The reaction was directly evaporated and the residue was passed through a silica plug (1:1 CH_2Cl_2/hexanes). Evaporation afforded 2.18 g of **4.9b** as colorless oil (95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46-7.48 (m, 2 H), 7.38 (d, *J* = 18.4 Hz, 1 H), 7.25-7.33 (m, 3 H), 6.15 (d, *J* = 18.4 Hz, 1 H), 1.30 (s, 12 H); ^{11}B NMR (160 MHz, $CDCl_3$): δ 30.5; ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.5, 137.5, 128.9, 128.6, 127.1, 83.3, 24.8; IR (neat): 2978, 1624, 1387, 1352, 1325, 1211, 1144, 970, 853, 748 cm^{-1}; LRMS (EI) *m/e* 230 (M^+), 215, 187, 173, 157, 144, 130, 105, 77.



4.10b

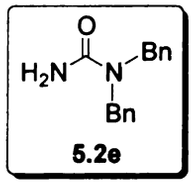
***trans*-1-Octeneboronic acid pinacol ester (4.10b)**: Following the general procedure, 1.01 g of boronic acid **4.10a** (6.5 mmol) and 0.77 g pinacol (6.5 mmol, 1.0 equiv) were dissolved in 20 mL ether and stirred at room temperature for 1 h. The reaction was directly evaporated and the residue was passed through a silica plug (1:2 CH_2Cl_2/hexanes). Evaporation afforded 1.17 g of **4.10b** as colorless oil (76%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 (dt, *J* = 17.9, 6.5 Hz, 1 H), 5.40 (dt, *J* = 17.9, 1.6 Hz, 1 H), 2.10-2.15 (m, 2 H), 1.35-1.40 (m, 2 H), 1.22-1.29 (m, 18 H), 0.85 (t, *J* = 7.0 Hz, 3 H); ^{11}B NMR (160 MHz, $CDCl_3$): δ 30.1; ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9, 83.0, 35.8, 31.7, 28.9, 28.2, 24.8, 22.6, 14.1; IR (neat): 2978, 2959, 2928, 2857, 1640, 1399, 1364, 1319, 1148, 972, 851 cm^{-1}; LRMS (EI) *m/e* 239 ($[M+H]^+$), 223, 181, 153, 139, 111, 95, 81, 67, 55, 41.

7.2.4 Preparation of Non-commercial Amides



5.2d

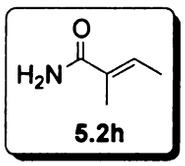
***N*-(4-Methoxybenzyl)urea (5.2d)**: 2.74 g 4-methoxybenzylamine (20 mmol) was dissolved in 60 mL water containing 1.7 mL concentrated HCl (~20 mmol, 1 equiv). Upon stirring, a solution of 2.43 g KOCN (30 mmol, 1.5 equiv) in 20 mL water was added and the mixture was stirred at room temperature for 18 h, and precipitate formed. The precipitate was collected by filtration and the cake was dissolved in 40 mL hot absolute EtOH and recrylstalized. After drying under high vacuum, 1.97 g of white needle-like crystals (55%) were obtained; mp 159-161 °C (lit[159] 163 °C). ^{1}H NMR (300 MHz, acetone-d_6): δ 7.19-7.22 (m, 2 H), 6.82-6.87 (m, 2 H), 5.93 (br, 1 H), 5.12 (br, 2 H), 4.21 (d, J = 5.8 Hz, 2 H), 3.75 (s, 3 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 159.5, 159.3, 133.8, 129.4, 114.4, 55.4, 43.7; IR (neat): 3426, 3337, 1645, 1601, 1560, 1516, 1248, 1034, 826, 812 cm^{-1}; LRMS: *m/e* 180 (M^+), 136, 121, 106, 77. Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found C, 59.61; H, 6.55; N, 15.43.



5.2e

***N,N*-Dibenzylurea (5.2e)**: 9.85 g (50 mmol) *N,N*-dibenzylamine was suspended in 200 mL water containing 4.2 mL concentrated HCl (50 mmol, 1 equiv). Upon stirring, a solution of 6.1 g KOCN (75 mmol, 1.5 equiv) in 200 mL water was added. The mixture was stirred at room temperature for 36 h (open flask), during which time a large amount of white precipitate was formed. The precipitate was collected by filtration and the cake was dissolved in minimum amount of hot absolute EtOH and recrystallized. After being dried over high vacuum, 8.5 g of a white

needle-like crystalline solid (71%) was obtained, mp 122.5-124 °C (lit[160] 125-126 °C). ^{1}H NMR (300 MHz, acetone-d_6): δ 7.22-7.36 (m, 10 H), 5.58 (br, 2 H), 4.46 (s, 4 H); ^{13}C NMR (75 MHz, acetone-d_6): δ 159.7, 139.5, 129.3, 128.2, 127.8, 50.0; IR (neat): 3410, 3337, 1636, 1595, 1495, 696 cm^{-1}; LRMS: *m/e* 240 (M^+), 149, 106, 91, 79, 65. Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found C, 75.05; H, 6.42; N, 11.51.



5.2h

Tiglic amide (5.2h): In an oven-dried 100 mL round-bottom flask (no stirrer bar) topped with a dried air condenser and flushed with nitrogen, 3 g (30 mmol) tiglic acid was heated to 50 °C neat in an oil bath. 2.5 mL (34 mmol, 1.14 equiv) $SOCl_2$ was slowly added followed by 1.5 mL (20 mmol, 0.67 equiv) DMF. The reaction mixture quickly turned into a liquid. It was kept at this temperature for 30 min and cooled to room temperature. The residue was slowly added to 150 mL cold (0 °C), concentrated aqueous ammonia. During the addition, the temperature was kept at 0 °C by addition of ice. The round-bottom flask containing tiglic acid chloride was rinsed with aqueous ammonia. Upon complete addition, the resulting aqueous mixture was extracted three times with EtOAc. Combined organics were dried over $MgSO_4$ and evaporated. 2.1 g of **5.2h** (70%) was obtained as a white crystalline solid, mp 71.5-73.5 °C (lit.[161] 77 °C). ^{1}H NMR (300 MHz, acetone-d_6): δ 6.1-7.0 (br, 2 H), 6.46 (qq, J = 7.1, 1.4 Hz, 1 H), 1.79 (apparent t, J = 1.4 Hz, 3 H), 1.70 (dq, J = 6.9, 1.1 Hz, 3 H); ^{13}C NMR (75 MHz, acetone-d_6): δ 171.2, 132.8, 130.7, 13.9, 12.4; IR (neat): 3339, 3177, 1667, 1603, 1420, 1123, 625 cm^{-1}; LRMS: *m/e* 99 (M^+), 82, 55, 44. HRMS (EI): *m/e* calcd for $[C_5H_9NO]^+$ 99.0683, found 99.0684.

7.3 General Procedures for C–H Borylation and Related One-pot Protocols

General Procedure A (C–H Borylation for Isolation of the Boronic Esters): Small scale: in the glove box, arene, HBpin (1.5-2.5 equiv), (Ind)Ir(cod) (2 mol%), and dmpe/dppe (2 mol%) (or $[Ir(OMe)(cod)]_2$ (1.5 mol%) and d^{t}bpy (3 mol%)) were transferred into an air-free flask equipped with a stirrer bar in the following order: HBpin with Ir calatyst, followed by ligand, followed by arene. 0.5-2 mL (per mmol of arene) solvent (cyclohexane, *n*-hexane, heptane, or octane) could be used to help dissolution and transfer. The flask was sealed and brought out of the glove box and placed in an oil bath heated to 150 °C (for (Ind)Ir(cod)-dmpe) or 100 °C (for (Ind)Ir(cod)-dppe), or stirred at room temperature (for $[Ir(OMe)(cod)]_2$-d^{t}bpy) until the reaction was judged complete by GC-FID. (*Note: in the cases of multiple borylations and borylations of sluggish substrates, periodic cooling and purging of the H_2 gas help to maintain an effective rate of reaction.*) At that time the reaction was allowed to cool to room temperature. Upon stirring, the residue was quenched by dropwise addition of MeOH until gas evolution ceased. The mixture was concentrated by a gentle nitrogen flow and the resultant syrup was passed through a silica plug (10-15 cm long, 2 cm wide for 1-2 mmol scale, CH_2Cl_2 or hexanes/CH_2Cl_2) to give the desired boronic ester.

Large scale: in the glove box, arene, HBpin (1.2-2.5 equiv), $[Ir(OMe)(cod)]_2$ (0.25-1 mol%) and d^{t}bpy (1 equiv per Ir) were transferred into a round-bottom flask equipped with a stirrer bar in the same order (*CAUTION! Mixing HBpin with large amount $[Ir(OMe)(cod)]_2$ may cause significant gas evolution!*). 0.5-1 mL (per mmol of arene) solvent (cyclohexane, *n*-hexane, heptane, or octane) could

be used to help dissolution and transfer. The flask was sealed by a septum and brought out of the glove box. It was topped with a nitrogen balloon or a nitrogen line connected to the manifold, and the reaction was stirred at room temperature until the reaction was judged complete by GC-FID. In case a full conversion was not achieved and the reaction had indication of slowing down, the flask could be topped with a dried condenser and heated to 70 °C. Upon completion, the reaction was allowed to cool to room temperature and quenched by dropwise addition of cold MeOH (*CAUTION! Quenching a large-scale borylation with large amount of residual HBpin may cause significant gas evolution and heat buildup!*) until gas evolution ceased. The mixture was concentrated by rotary evaporation or a gentle nitrogen flow and the syrup was passed through a silica plug (CH_2Cl_2 or hexanes/CH_2Cl_2) to give the desired boronic ester.

General Procedure B (C–H Borylation/Oxidation for Preparation of Phenols): A borylation reaction with 1 mmol arene was set up according to the general procedure A and judged complete by GC-FID. Solvent for this borylation, if any, was removed by a gentle nitrogen flow. To this residue was added 3.2 mL acetone, and the mixture was stirred to produce a homogeneous solution. An aqueous solution of 0.615 g oxone (1.0 mmol, 1.0 equiv) in 3.2 mL water was introduced dropwise over 2-4 min. Upon complete addition, the reaction mixture was vigorously stirred for an additional 7 min. At that time the reaction was quenched with aqueous $NaHSO_3$ (solid $NaHSO_3$ also worked). A layer of dark orange oil was typically observed. The reaction mixture was then extracted three times with ether or CH_2Cl_2. Combined organics were washed with brine

followed by water, and concentrated. The crude material was dissolved in minimum amount of CH_2Cl_2 or pentane/ether and passed through a plug of silica gel. Evaporation afforded the phenol.

General Procedure C (C–H Borylation/Oxidation for Amino Acid Substrates): A thick-walled microwave vessel was charged with a stirrer bar, 0.5 mmol starting *N*-Boc-amino acid methyl ester and desired amount of B_2pin_2, $[Ir(OMe)(cod)]_2$, and d^{t}bpy in open atmosphere. 2 mL solvent (normally cyclohexane, some cases THF) was added to the vessel and the system was flushed by nitrogen before the vessel was sealed. It was then irradiated by microwave and held at 120 °C for 10 min (It normally took 5-10 min for the temperature to increase to 120 °C and this period was not counted in those 10 min). After cooling down to ambient temperature, the solvent was removed by a gentle nitrogen flow.

If the boronic ester was to be isolated, the reaction was quenched with a few drops of MeOH, concentrated and passed through a silica plug (ether/CH_2Cl_2). If oxidation was to be performed, to this sticky residue was added 3 mL acetone and 1 mL water. The mixture was stirrer until no gas was evolving. An aqueous solution of 400 mg oxone (0.65 mmol, 1.3 equiv) in 2.5 mL water was added to the above mixture dropwise, and the mixture was stirrer at room temperature for 12 min before quenched with $NaHSO_3$. It was extracted three times with ether, washed with water, dried over $MgSO_4$, filtered, and evaporated. The crude product could be purified by column chromatography (CH_2Cl_2/ether) followed by evaporation and drying over high vacuum. Alternatively, preparative HPLC could

also be used for purification. In that case, the combined ether extraction was directly evaporated and re-dissolved in acetonitrile or THF and the product was purified by Gilson HPLC followed by lyophilization.

General Procedure D (C–H Borylation/Deuteration for Preparation of Deuterated Aromatics): A borylation reaction with 2 mmol arene was set up according to the general procedure A and judged complete by GC-FID. Solvent for this borylation, if any, was removed by a gentle nitrogen flow. The residue was placed under high vacuum for a few hours and the flask was back filled with nitrogen. To the reaction were added 0.5 mL D_2O and 3-4 mL dry THF or DME. The flask was resealed and heated in an oil bath to 150 °C until the reaction was judged complete by GC-FID. Upon completion, the mixture was poured into water and extracted with pentane (or CH_2Cl_2 if the product has low solubility in pentane), dried over $MgSO_4$, filtered, and evaporated. Column chromatography (pentane or CH_2Cl_2) afforded the product.

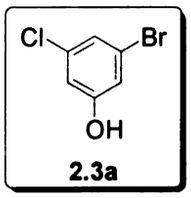
For standing-alone deuteration, 2 mmol aryl boronic acid/ester and the Ir catalyst (0.02 mmol, 2 mol %) were dissolved in 3-4 mL THF or DME in the glove box and transferred into an air-free flask equipped with a stirrer bar. The flask was sealed and brought out of the dry box and charged with 0.5 mL D_2O. It was resealed and heated in an oil bath to 150 °C until the reaction was judged complete by GC-FID, and worked up as described in the general procedure.

General Procedure E (C–H Borylation/Amidation/Oxidation for Preparation of Amidophenols): A borylation reaction with 2 mmol arene was set up according to the general procedure A and judged complete by GC-FID.

Solvent for this borylation, if any, was removed by a gentle nitrogen flow. The residue was placed under high vacuum for a few hours and the flask was backfilled with nitrogen. Upon returning to the glove box, it was charged with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), amide (~2.2 mmol, ~1.1 equiv), 900 mg Cs_2CO_3 (2.8 mmol, 1.4 equiv), and 6 mL THF or DME. The flask was sealed, taken out of the box, and heated to 80-100 °C until the reaction was judged complete by GC-FID. At this time, the reaction mixture (typically a yellow suspension) was cooled to room temperature and filtered through a silica pad (1-2 cm thick, 4.5 cm wide; ~12 g silica gel) eluting with acetone until the filtrate showed no UV activity on TLC (ca. 150-200 mL acetone was used). The acetone was evaporated and the residue was dissolved back in 6 mL acetone (or more if needed to obtain a homogenous solution). To that stirred solution was added dropwise a solution of 1.33 g oxone (2 mmol, 1 equiv) in 6 mL water and the reaction was stirred for 10 min at room temperature. An aqueous suspension of 430 mg $NaIO_4$ (1.0 equiv per pinacol) in 2 mL water was added in a single portion followed by 2 mL acetone. The mixture was further stirred for 1-2 h before being twice extracted with EtOAc. The aqueous layer was charged with solid $NaHSO_3$, and the mixture was swirled until color appeared and then diminished. The aqueous phase was then back extracted once or twice with EtOAc. The combined organics were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified on silica gel chromatography (CH_2Cl_2/EtOAc or CH_2Cl_2/acetone). Evaporation followed by drying under high vacuum afforded the final product.

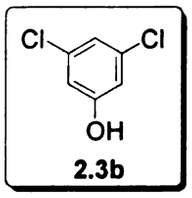
7.4 Experimental Details and Spectroscopy Data

7.4.1 Simple Phenols



2.3a

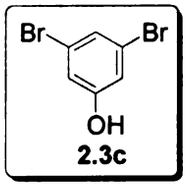
3-Bromo-5-chlorophenol (2.3a): General procedure B (page 150) was applied to 192 mg 3-bromochlorobenzene (1.0 mmol). The borylation step was carried out neat with 250 mg HBpin (1.95 mmol, ~2 equiv), 8.3 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 3.0 mg dmpe (0.02 mmol, 2 mol %) at 150 °C for 3.5 h. The oxidation step was then carried out as described in the general procedure, after which the crude material was purified with a plug of silica gel (CH_2Cl_2). Evaporation of solvent gave 183 mg of a white solid containing 171 mg of **2.3a** (82%) and 12 mg acetone. Compound **2.3a** could be obtained pure by preparative GC at 160 °C as a white solid; mp 66-68 °C (lit.[48a] 70 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (t, *J* = 1.65 Hz, 1 H), 6.89 (dd, *J* = 2.2, 1.65 Hz, 1 H), 6.78 (t, *J* = 2.1 Hz, 1 H), 5.0-5.1 (br, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 135.6, 124.0, 122.9, 117.9, 115.0; IR (neat): 3293, 1578, 1435, 914, 775 cm^{-1}; LRMS *m/e* 206 (M^+), 127, 99. Anal. Calcd for C_6H_4BrClO: C, 34.74; H, 1.94. Found C, 34.87; H 2.03.



2.3b

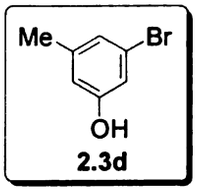
1,3-Dichlorophenol (2.3b): General procedure B (page 150) was applied to 147 mg 1,3-dichlorobenzene (1.0 mmol). The borylation step was carried out neat with 200 mg HBpin (1.55 mmol, 1.55 equiv), 8.3 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 3.0 mg dmpe (0.02 mmol, 2 mol %) at 150 °C for 3.5 h. The oxidation step was then carried out as described in the general procedure, after which the crude material was purified with a plug of silica gel (CH_2Cl_2). Evaporation of solvent gave 137 mg of

a white solid containing 127 mg of **2.3b** (78%) and 10 mg acetone. Compound **2.3b** could be obtained pure by putting under high vacuum (loss of product) as a white solid; mp 64-66 °C (Aldrich catalogue 65-68 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.93 (t, *J* = 1.65 Hz, 1 H), 6.73 (d, *J* = 1.65 Hz, 2 H), 5.32 (br, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.6, 135.4, 121.3, 114.5.



2.3c

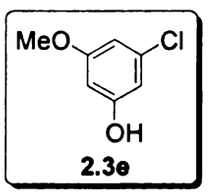
3,5-Dibromophenol (2.3c): General procedure B (page 150) was applied to 236 mg 1,3-dibromobenzene (1.0 mmol). The borylation step was carried out with 256 mg HBpin (2.0 mmol, 2 equiv), 8.3 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 8.0 mg dppe (0.02 mmol, 2 mol %) in 1.0 mL cyclohexane at 100 °C for 18 h. After removal of cyclohexane, the oxidation step was then carried out as described in the general procedure, after which the crude material was purified with a plug of silica gel (CH_2Cl_2). Evaporation of solvent gave 250 mg of a white solid containing 227 mg of **2.3c** (90%), 12 mg water, and 11 mg acetone. Compound **2.3c** could be obtained pure by sublimation at 55 °C under 0.08 mmHg as a white solid; mp 78-80 °C (Aldrich catalogue 79-83 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (t, *J* = 1.4 Hz, 1 H), 6.94 (d, *J* = 1.4 Hz, 2 H), 4.82 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 126.7, 123.1, 117.8; IR (neat): 3233, 1576, 1421, 841, 752 cm^{-1}; LRMS: *m/e* 250 (M^+), 171, 143. Anal. Calcd for $C_6H_4Br_2O$: C, 28.61; H, 1.60. Found C, 28.98; H, 1.52.



2.3d

3-Bromo-5-methylphenol (2.3d): General procedure B (page 150) was applied to 171 mg 3-bromotoluene (1.0 mmol). The

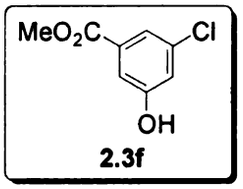
borylation step was carried out neat with 200 mg HBpin (1.55 mmol, 1.55 equiv), 8.3 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 3.0 mg dmpe (0.02 mmol, 2 mol %) at 150 °C for 12 h. The oxidation step was then carried out as described in the general procedure, after which the crude material was purified with a plug of silica gel (CH_2Cl_2). Evaporation of solvent gave 174 mg material containing 146 mg of **2.3d** (78%), 17 mg acetone, and 11 mg CH_2Cl_2. Compound **2.3d** could be obtained pure by preparative GC at 150 °C as a white solid; mp 55-57 °C (lit.[162] 52 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89 (s, 1 H), 6.80 (s, 1 H), 6.56 (s, 1 H), 4.67 (s, 1 H), 2.26 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0, 141.4, 124.7, 122.4, 115.8, 115.0, 21.1; IR (neat): 3297, 1579, 1366, 1273, 822 cm^{-1}; LRMS: *m/e* 186 (M^+), 107, 77. Anal. Calcd for C_7H_7BrO: C, 44.95; H, 3.77. Found C, 45.21; H, 3.93.



2.3e

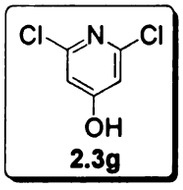
3-Chloro-5-methoxyphenol (2.3e): General procedure B (page 150) was applied to 143 mg 3-chloroanisole (1.0 mmol). The borylation step was carried out neat with 256 mg HBpin (2.0 mmol, 2 equiv), 8.3 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 3.0 mg dmpe (0.02 mmol, 2 mol %) at 150 °C for 18 h. The oxidation step was then carried out as described in the general procedure, after which the crude material was purified with a plug of silica gel (CH_2Cl_2). Evaporation of solvent gave 148 mg material containing 121 mg of **2.3e** (76%), 20 mg acetone, and 7 mg CH_2Cl_2. Compound **2.3e** could be obtained pure by preparative GC at 170 °C as a white solid; mp 94-96 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.48 (t, *J* = 2.2 Hz, 1 H), 6.43 (t, *J* = 2.2 Hz, 1 H), 6.27 (t, *J* = 2.2 Hz, 1 H), 4.81 (s, 1 H), 3.75 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3, 157.0, 135.4, 108.6, 107.3, 100.4, 55.5; IR (neat): 3378, 1597,

1159 cm^{-1}; LRMS: *m/e* 158 (M^+), 128. Anal. Calcd for $C_7H_7ClO_2$: C, 53.02; H, 4.45. Found C, 52.88; H, 4.81.



2.3f

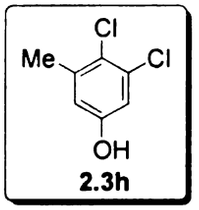
Methyl 3-chloro-5-hydroxybenzoate (2.3f): General procedure B (page 150) was applied to 171 mg 3-chlorobenzoate (1.0 mmol). The borylation step was carried out neat with 200 mg HBpin (1.55 mmol, 1.55 equiv), 8.3 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 3.0 mg dmpe (0.02 mmol, 2 mol %) at 150 °C for 3 h. The oxidation step was then carried out as described in the general procedure, after which the crude material was purified with a plug of silica gel (pentane/ether 2:1). Evaporation of solvent gave 134 mg clean material (72%). Compound **2.3f** could be obtained pure by sublimation at 85 °C under 0.06 mmHg as a white solid; mp 133-135 °C (lit.[163] 138-139 °C). ^{1}H NMR (300 MHz, acetone-d_6): δ 9.2 (brs, 1 H), 7.43 (t, *J* = 1.7 Hz, 1 H), 7.40 (dd, *J* = 2.2, 1.7 Hz, 1 H), 7.10 (t, *J* = 2.2 Hz, 1 H), 3.87 (s, 3 H); ^{13}C NMR (75 MHz, acetone-d_6): δ 165.9, 159.3, 135.3, 133.8, 121.0, 120.6, 115.7, 52.7; IR (neat): 3335, 1690, 1591, 1431, 1350, 1242, 768 cm^{-1}; LRMS: *m/e* 186 (M^+), 155, 127, 99. Anal. Calcd for $C_8H_7ClO_3$: C, 51.50; H, 3.78. Found C, 51.78; H, 3.73.



2.3g

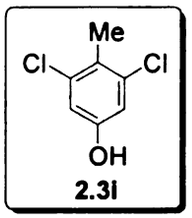
2,6-Dichloro-4-pyridinol (2.3g): General procedure B (page 150) was applied to 148 mg 2,6-dichloropyridine (1.0 mmol). The borylation step was carried out with 200 mg HBpin (1.55 mmol, 1.55 equiv), 8.3 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 3.0 mg dmpe (0.02 mmol, 2 mol %) in 1 mL cyclohexane at 150 °C for 3 h. After removal of cyclohexane, the oxidation step was then carried out as described in the general

procedure, after which the crude material was purified with a plug of silica gel (pentane/ether 2:1). Evaporation of solvent gave 145 mg material containing 108 mg of **2.3g** (66%) and 37 mg water. Compound **2.3g** could be obtained pure by sublimation at 110 °C under 0.1 mmHg as a white solid; mp 201-202 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ 10.48 (brs, 1 H), 6.88 (s, 2 H); ^{13}C NMR (75 MHz, acetone-d_6): δ 168.3, 151.5, 111.5; IR (KBr): 3200~2500 (br), 1597, 1576, 1554, 1427, 1294, 1211, 1157, 1092, 993, 966, 847 cm^{-1}; LRMS: *m/e* 163 (M^+), 128, 100. Anal. Calcd for $C_5H_3Cl_2NO$: C, 36.62; H, 1.84; N, 8.54. Found C, 36.63; H, 1.98, N, 8.52.



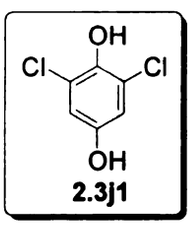
2.3h

3,4-Dichloro-5-methylphenol (2.3h): General procedure B (page 150) was applied to 161 mg 2,3-dichlorotoluene (1.0 mmol). The borylation step was carried out neat with 256 mg HBpin (2.0 mmol, 2 equiv), 8.3 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 3.0 mg dmpe (0.02 mmol, 2 mol %) in at 150 °C for 12 h. The oxidation step was then carried out as described in the general procedure, after which the crude material was purified with a plug of silica gel (CH_2Cl_2). Evaporation of solvent gave 154 mg material containing 147 mg of **2.3h** (83%) and 7 mg water. Compound **2.3h** could be obtained pure by sublimation at 70 °C under 0.07 mmHg as a white solid; mp 98-100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.81 (d, J = 2.2 Hz, 1 H), 6.63 (t, J = 2.2 Hz, 1 H), 4.61 (s, 1 H), 2.34 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.7, 139.1, 133.0, 124.3, 116.4, 115.0, 21.3; IR (neat): 3285, 1580, 1449, 1285, 1151, 886, 646 cm^{-1}; LRMS: *m/e* 176 (M^+), 141, 77. Anal. Calcd for $C_7H_6Cl_2O$: C, 47.49; H, 3.42. Found C, 47.72; H, 3.61.



2.3i

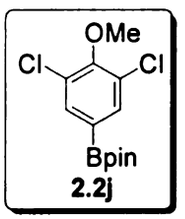
3,5-Dichloro-4-methylphenol (2.3i): General procedure B was applied to 161 mg 2,6-dichlorotoluene (1.0 mmol). The borylation step was carried out neat with 200 mg HBpin (1.55 mmol, 1.55 equiv), 8.3 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 3.0 mg dmpe (0.02 mmol, 2 mol %) in at 150 °C for 12 h. The oxidation step was then carried out as described in the general procedure, after which the crude material was purified with a plug of silica gel (CH_2Cl_2). Evaporation of solvent gave 176 mg material containing 156 mg of **2.3i** (88%), 14 mg water, and 6 mg acetone. Compound **2.3i** could be obtained pure by sublimation at 70 °C under 0.08 mmHg as a white solid; mp 92-93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.79 (s, 2 H), 4.67 (s, 1 H), 2.34 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.5, 135.6, 126.6, 115.2, 16.4; IR (neat): 3333, 1608, 1578, 1238, 947, 839 cm^{-1}; LRMS: *m/e* 176 (M^+), 141, 105, 84, 77. Anal. Calcd for $C_7H_6Cl_2O$: C, 47.49; H, 3.42. Found C, 47.65; H, 3.45.



2.3j1

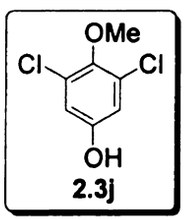
2,6-Dichloro-1,4-hydroquinone (2.3j1): General procedure B (page 150) was applied to 177 mg 2,6-dichloroanisole (1.0 mmol). The borylation step was carried out neat with 320 mg HBpin (2.5 mmol, 2.5 equiv), 8.3 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 3.0 mg dmpe (0.02 mmol, 2 mol %) in at 150 °C for 16 h. The oxidation step was then carried out as described in the general procedure, after which the crude material was purified with a plug of silica gel (pentane/ether 2:1). Evaporation of solvent gave 140 mg material containing 120 mg of **2.3j1** (67%) and 20 mg water. Compound **2.3j1** could be obtained pure by sublimation at 90 °C under 0.08 mmHg, or recrystalization from CH_2Cl_2, as a white solid; mp 160-161 °C (lit[164] 164

°C). ^{1}H NMR (300 MHz, acetone-d_6): δ 8.43 (brs, 1 H), 8.24 (brs, 1 H), 6.83 (s, 2 H); ^{13}C NMR (75 MHz, acetone-d_6): δ 150.7, 142.3, 122.3, 115.5; IR (KBr): 349, 1591, 1482, 1213, 953, 791 cm^{-1}; LRMS: *m/e* 178 (M^+), 142, 114, 86. Anal. Calcd for $C_6H_4Cl_2O_2$: C, 40.26; H, 2.25. Found C, 40.58; H, 2.17.



2.2j

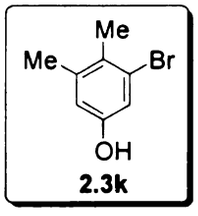
3,5-Dichloro-4-methoxyphenylboronic acid pinacol ester (2.2j): Following the same procedure mentioned above, the borylation of 3 mmol 2,6-dichloroanisole was stopped after heating at 150 °C for 20 min. Silica gel chromatography (3:1 hexanes/CH_2Cl_2) afforded 273 mg material containing the desired borylation product **2.2j** with unreacted starting material **2.1j** (clean otherwise; molar ratio of **2.2j/2.1j** ~ 8:1, corresponding to ~28% yield of **2.2j**). Another round of chromatography afforded pure **2.2j** as a white solid; mp 79-81 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (s, 2 H), 3.89 (s, 3 H), 1.31 (s, 12 H); ^{11}B NMR (160 MHz, $CDCl_3$): δ 29.8; ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.6, 135.1, 129.1, 84.4, 60.7, 24.8; IR (neat): 2980, 1588, 1381, 1350, 1146, 1129, 999, 965, 889, 851, 810, 689 cm^{-1}; LRMS *m/e* 302 (M^+), 287, 216, 202, 85, 41. Anal. Calcd for $C_{13}H_{17}BCl_2O_3$: C, 51.53; H, 5.66. Found C, 51.74; H, 5.64.



2.3j

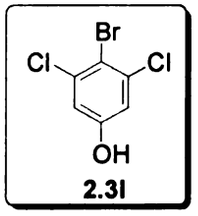
3,5-Dichloro-4-methoxyphenol (2.3j): 303 mg **2.2j** (1 mmol) was dissolved in 3 mL acetone. This solution was treated with 615 mg (1 mmol, 1 equiv) oxone in 3 mL water. The workup was performed as described in the general procedure B. Silica gel chromatography (CH_2Cl_2) afforded 190 mg of **2.3j** (98%) as a white solid, mp 121-122 °C. ^{1}H NMR

(300 MHz, $CDCl_3$): δ 6.79 (s, 2 H), 4.79 (s, 1 H), 3.82 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.9, 146.2, 129.5, 116.0, 60.9; IR (neat): 3297, 1603, 1580, 1482, 1447, 1428, 1223, 1186, 986, 953, 878, 849, 804, 768 cm^{-1}; LRMS *m/e* 192 (M^+), 177, 149, 85, 53. Anal. Calcd for $C_7H_6Cl_2O_2$: C, 43.56; H, 3.13. Found C, 43.67; H, 3.14.



2.3k

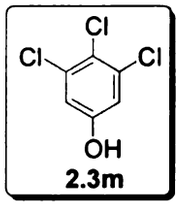
3-Bromo-4,5-dimethylphenol (2.3k): General procedure B (page 150) was applied to 185 mg 3-bromo-*o*-xylene (1.0 mmol). The borylation step was carried out with 320 mg HBpin (2.5 mmol, 2.5 equiv), 8.3 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 8.0 mg dppe (0.02 mmol, 2 mol %) in 1 mL cyclohexane at 100 °C for 50 h. After removal of cyclohexane, the oxidation step was then carried out as described in the general procedure, after which the crude material was purified with a plug of silica gel (CH_2Cl_2). Evaporation of solvent gave 148 mg pure **2.3k** (74%) as a white solid; mp 98-99 °C (lit[165] 101-102 °C). ^1H NMR (300 MHz, $CDCl_3$): δ 6.91 (d, *J* = 2.5 Hz, 1 H), 6.59 (d, *J* = 2.7 Hz, 1 H), 2.25 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.2, 139.3, 128.3, 125.2, 116.9, 116.2, 21.4, 18.3; IR (neat): 3252, 2919, 1606, 1576, 1477, 1451, 1279, 1119, 839 cm^{-1}; LRMS: *m/e* 200 (M^+), 185, 121, 91; HRMS (EI): *m/e* calcd for $[C_8H_9BrO]^+$ 199.9837, found 199.9839.



2.3l

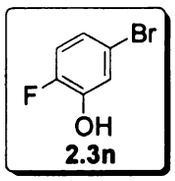
4-Bromo-3,5-dichlorophenol (2.3l): General procedure B (page 150) was applied to 226 mg 1-bromo-2,6-dichlorobenzene (1.0 mmol). The borylation step was carried out with 256 mg HBpin (2.0 mmol, 2 equiv), 8.3 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 3.0 mg dmpe (0.02 mmol, 2 mol %) in 1 mL cyclohexane at 150 °C for 3.5 h. After

removal of cyclohexane, the oxidation step was then carried out as described in the general procedure, after which the crude material was purified with a plug of silica gel (CH_2Cl_2). Evaporation of solvent gave 260 mg material containing 197 mg of **2.3l** (81%), 31 mg CH_2Cl_2, and 32 mg acetone. Compound **2.3l** could be obtained pure by sublimation at 90 °C under 0.3 mmHg as a white solid; mp 117-119 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90 (s, 2 H), 4.86 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.8, 136.5, 116.2, 114.4; IR (neat): 3366, 1570, 1412, 1129, 845 cm^{-1}. LRMS: *m/e* 240 (M^+), 162; HRMS (EI): *m/e* calcd for $[C_6H_3Cl_2BrO]^+$ 239.8744, found 239.8751.



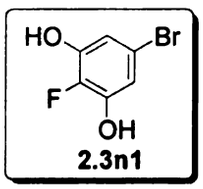
2.3m

3,4,5-Trichlorophenol (2.3m): General procedure B (page 150) was applied to 182 mg 1,2,3-trichlorobenzene (1.0 mmol). The borylation step was carried out with 226 mg HBpin (1.8 mmol, 1.8 equiv), 8.3 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 3.0 mg dmpe (0.02 mmol, 2 mol %) in 1 mL cyclohexane at 150 °C for 3 h. After removal of cyclohexane, the oxidation step was then carried out as described in the general procedure, after which the crude material was purified with a plug of silica gel (CH_2Cl_2). Evaporation of solvent gave 212 mg material containing 176 mg of **2.3m** (89%), 4 mg CH_2Cl_2, and 32 mg acetone. Compound **2.3m** could be obtained pure by sublimation at 70 °C under 0.06 mmHg as a white solid; mp 97-99 °C (lit[166] 101 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89 (s, 2 H), 5.04 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 134.4, 123.3, 116.3; IR (neat): 3312, 1574, 1420, 1144, 947, 818 cm^{-1}; LRMS: *m/e* 196 (M^+), 160, 133, 97. Anal. Calcd for $C_6H_3Cl_3O$: C, 36.50; H, 1.53. Found C, 36.73; H, 1.64.



2.3n

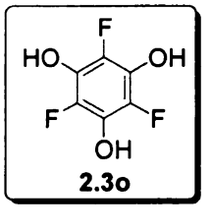
5-Bromo-2-fluorophenol (2.3n): General procedure B (page 150) was applied to 700 mg 1-bromo-4-fluorobenzene (4.0 mmol, 4 equiv). The borylation step was carried out neat with 128 mg HBpin (1.0 mmol), 8.3 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 3.0 mg dmpe (0.02 mmol, 2 mol %) at 150 °C for 3.5 h. The oxidation step was then carried out as described in the general procedure, after which the crude material was purified on silica gel chromatography (CH_2Cl_2). The first fraction (~ 500 mg) was unreacted starting material. Evaporation of the second fraction gave 165 mg material containing 134 mg of **2.3n** (70%, based on HBpin), 14 mg acetone, and 17 mg CH_2Cl_2. Compound **2.3n** could be obtained pure by preparative GC at 110 °C as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12-7.16 (m, 1 H), 6.90-6.96 (m, 2 H), 5.29 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.3 (d, J = 239 Hz), 144.4 (d, J = 15 Hz), 123.7 (d, J = 6 Hz), 120.6, 116.8 (d, J = 19 Hz), 116.8 (d, J = 3 Hz); IR (neat): 3412, 1611, 1495, 1267 cm^{-1}; LRMS: *m/e* 190 (M^+), 161, 111, 83. Anal. Calcd for C_6H_4BrFO: C, 37.73; H, 2.11. Found C, 37.58; H, 2.32.



2.3n1

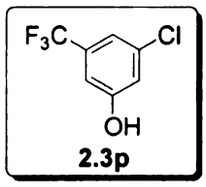
5-Bromo-2-fluororesorcinol (2.3n1): General procedure B (page 150) was applied to 175 mg 1-bromo-4-fluorobenzene (1.0 mmol). The borylation step was carried out with 580 mg HBpin (4.5 mmol, 4.5 equiv), 20.6 mg (Ind)Ir(cod) (0.05 mmol, 5 mol %) and 20.0 mg dppe (0.05 mmol, 5 mol %) in 1 mL cyclohexane at 110 °C for 53 h. After removal of cyclohexane, the oxidation step was carried out as described in the general procedure with 6.5 mL acetone, 6.5 mL aqueous solution of 1.24 g oxone (2 mmol, 1 equiv per boron) at room temperature for 11 min. The crude material,

after workup, was purified with a plug of silica gel (pentane/ether 1.5:1) followed by recrystallization from CH_2Cl_2, giving 165 mg of **2.3n1** (76%) as a white solid; mp 83-86 °C; R_f 0.31 (pentane/ether 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.72 (d, *J* = 7.1 Hz, 2 H), 5.10 (s, 2 H); ^{13}C NMR (75 MHz, acetone-d_6): δ 147.5 (d, *J* = 11 Hz), 141.4 (d, *J* = 237 Hz), 115.8 (d, *J* = 5 Hz), 112.3; IR (KBr): 3128, 1617, 1501, 1431, 1331, 1159, 1047 cm^{-1}. LRMS: *m/e* 206 (M^+), 127, 109, 79. HRMS (EI): *m/e* calcd for $[C_6H_4FBrO_2]^+$ 205.9379, found 205.9378.



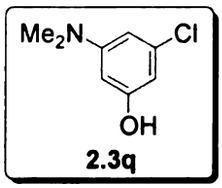
2.3o

2,4,6-Trifluoroglucinol (2.3o): General procedure B (page 150) was applied to 132 mg 1,3,5-trifluorobenzene (1.0 mmol). The borylation step was carried out with 640 mg HBpin (5 mmol, 5 equiv), 12.5 mg (Ind)Ir(cod) (0.03 mmol, 3 mol %) and 4.5 mg dmpe (0.03 mmol, 3 mol %) in 1 mL cyclohexane at 150 °C for 63 h. The borylation gave a 1:6 mixture of diborylated and triborylated products. After removal of cyclohexane, the oxidation step was carried out as described in the general procedure with 9 mL acetone, 8.5 mL aqueous solution of 1.74 g oxone (2.8 mmol) at room temperature for 13 min. The crude material, after workup, was purified with silica gel chromatography (pentane/ether 1:1.5) followed by washing with boiling CH_2Cl_2, and sublimation at 130 °C under 0.1 mmHg, giving 88 mg of **2.3o** (49%) as a slightly yellow solid; mp 260 °C (dec); R_f 0.43 (pentane/ether 1:1.5). ^{1}H NMR (300 MHz, acetone-d_6): δ 8.66 (br, 3 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 137.3 (dt, *J* = 230, 6 Hz) 131.9 (dt, *J* = 14, 5 Hz); IR (KBr): 3324, 1510, 1400-1200 (br), 1132, 980 cm^{-1}; LRMS: *m/e* 180 (M^+), 151, 104; HRMS (EI): *m/e* calcd for $[C_6H_3F_3O_3]^+$ 180.0034, found 180.0030



2.3p

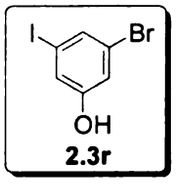
3-Chloro-5-trifluoromethylphenol (2.3p): General procedure B (page 150) was applied to 181 mg 3-chlorobenzotrifluoride (1.0 mmol). The borylation step was carried out with 200 mg HBpin (1.55 mmol, 1.55 equiv), 8.3 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 3.0 mg dmpe (0.02 mmol, 2 mol %) in 1 mL cyclohexane at 150 °C for 3.5 h. After removal of cyclohexane, the oxidation step was then carried out as described in the general procedure, after which the crude material was purified with a plug of silica gel (CH_2Cl_2). Evaporation of solvent gave 185 mg material containing 160 mg of **2.3p** (81%) and 25 mg acetone. Compound **2.3p** could be obtained pure by preparative GC at 120 °C as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (brs, 1 H), 7.01 (brs, 1 H), 6.96 (brs, 1 H), 5.03 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.5, 135.7, 133.1 (q, *J* = 33 Hz), 123.0 (q, *J* = 273 Hz), 119.2, 118.5 (q, *J* = 4 Hz), 111.0 (q, *J* = 4 Hz); IR (KBr): 3384, 1597, 1455, 1335, 1175, 1134, 936, 704, 693 cm^{-1}; LRMS: *m/e* 196 (M^+), 177, 161, 146; HRMS (EI): *m/e* calcd for $[C_7H_4ClF_3O]^+$ 195.9903, found 195.9902.



2.3q

3-Chloro-5-(dimethylamino)phenol (2.3q): General procedure B (page 150) was applied to 156 mg 3-chloro-*N,N*-dimethylaniline (1.0 mmol). The borylation step was carried out neat with 256 mg HBpin (2.0 mmol, 2 equiv), 8.3 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 3.0 mg dmpe (0.02 mmol, 2 mol %) at 150 °C for 18 h. The oxidation step was then carried out as described in the general procedure, after which the crude material was purified with a plug of silica gel (pentane/ether 2:1). Evaporation of solvent gave 155 mg material containing 146 mg of **2.3q**

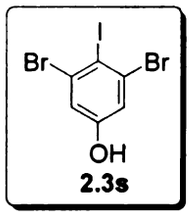
(85%) and 9 mg ether. Compound **2.3q** could be obtained pure by sublimation at 60 °C under 0.10 mmHg as a slightly colored solid; mp 86-88 °C; R_f 0.30 (pentane/ether, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.28 (brs, 1 H), 6.19 (t, J = 1.6 Hz, 1 H), 6.03 (t, J = 2.2 Hz, 1 H), 5.0-5.3 (brs, 1 H), 2.88 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 152.3, 135.4, 105.6, 104.2, 97.8, 40.4; IR (neat): 3349, 2901, 2812, 1603, 1506, 1443, 1156, 1233, 1019, 916 cm^{-1}; LRMS: *m/e* 171 (M^+), 170, 128, 99. Anal. Calcd for $C_8H_{10}ClNO$: C, 55.99; H, 5.87; N, 8.16. Found C, 56.12; H, 5.81; N, 8.11.



2.3r

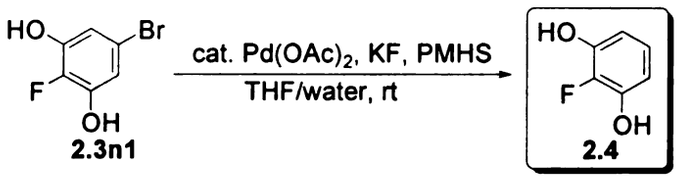
3-Bromo-5-iodophenol (2.3r): General procedure B (page 150) was applied to 283 mg 1-bromo-3-iodobenzene (1.0 mmol). The borylation step was carried out with 154 mg B_2pin_2 (0.6 mmol, 1.2 equiv boron), 10.0 mg $[Ir(OMe)(cod)]_2$ (0.015 mmol, 1.5 mol %), and 8.0 mg d^{t}bpy (0.03 mol, 3 mol %) in 5 mL *n*-hexane in dark environment at room temperature for 11 h. After removal of cyclohexane, the oxidation step was then carried out as described in the general procedure, except that ether, instead of CH_2Cl_2, was used for the extraction. The crude material was purified with a plug of silica gel (CH_2Cl_2). Evaporation of solvent gave 244 mg material containing 236 mg of **2.3r** (79%), 5 mg ether, and 3 mg acetone. Compound **2.3r** could be obtained pure by sublimation at 50 °C under 0.09 mmHg as a white solid; mp 83-84 °C (lit[48a] 82.5 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (t, J = 1.4 Hz, 1 H), 7.13 (dd, J = 1.4, 2.2 Hz, 1 H), 6.96 (dd, J = 1.9, 2.2 Hz, 1 H), 4.77 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 132.4, 123.6, 123.2, 118.6, 94.2; IR (neat): 3268, 3071, 1586, 1566, 893, 885, 664 cm^{-1}; LRMS: *m/e* 298 (M^+), 171, 143. Anal. Calcd for

C_6H_4BrIO: C, 24.11; H, 1.35. Found C, 24.26; H, 1.30.



2.3s

3,5-Dibromo-4-iodophenol (2.3s): General procedure B (page 150) was applied to 362 mg 1,3-dibromo-2-iodobenzene (1.0 mmol). The borylation step was carried out with 254 mg B_2pin_2 (1.0 mmol, 2 equiv boron), 10.0 mg $[Ir(OMe)(cod)]_2$ (0.015 mmol, 1.5 mol %), and 8.0 mg d^{t}bpy (0.03 mol, 3 mol %) in 5 mL *n*-hexane in dark environment at room temperature for 3 h. After removal of cyclohexane, the oxidation step was then carried out as described in the general procedure, except that ether, instead of CH_2Cl_2, was used for the extraction. The crude material was purified with a plug of silica gel (pentane/ether 2:1). Evaporation of solvent gave 352 mg pure **2.3s** (93%) as a white solid; mp 149-152 °C (lit[40] 153.5-153.9 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (s, 2 H), 4.92 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6): δ 159.6, 131.4, 120.0, 96.3; IR (neat): 3289, 3069, 1584, 1561, 1399, 1246, 1219, 853, 748 cm^{-1}; LRMS (EI): *m/e* 376 (M^+), 249, 143, 127, 91, 62. Anal. Calcd for $C_6H_3Br_2IO$: C, 19.08; H, 0.80. Found C, 19.62; H, 0.79.



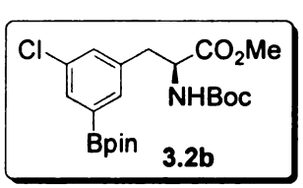
2.3n1 **2.4**

2-Fluororesorcinol (2.4): To a solution of 9.0 mg $Pd(OAc)_2$ (0.04 mmol, 5 mol%) in 4 mL degassed THF was added 166 mg of **2.3n1** (0.8 mmol). Upon stirring, a solution of 93 mg KF (1.6 mmol, 2 equiv) in 1.6 mL degassed water was added. 240 μL PMHS (240 mg, 3.2 mmol, 4 equiv) was introduced dropwise and

the reaction mixture turned black. After 30 min, TLC indicated full conversion. The reaction was quenched by addition of 4 mL 3 M NaOH, stirred for 6 h, and diluted with water and washed with ether (discarded). The aqueous layer was then acidified with concentrated HCl, and then extracted with ether. Combined ether was dried over $MgSO_4$ and evaporated. Column chromatography (1.5:1 pentane/ether) followed by sublimation at 70 °C, 0.1 mmHg afforded 82 mg of **2.4** (80%) as a white solid; mp 111-114 °C (lit[167] 114-116 °C). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.44 (s, 2 H), 6.76 (dt, J = 2.0, 8.3 Hz, 1 H), 6.45 (dd, J = 7.6, 8.1 Hz, 2 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 146.8 (d, J = 10.6 Hz), 142.2 (d, J = 235 Hz), 124.3 (d, J = 4.6 Hz), 109.3; IR (neat): 3368, 1615, 1524, 1512, 1478, 1383, 1329, 1210, 1013 cm^{-1}; LRMS *m/e* 128 (M^+), 57, 43.

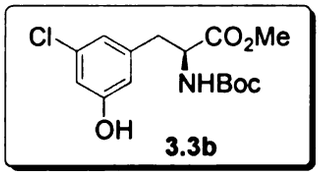
7.4.2 Hydroxylated and Borylated Aromatic Amino Acid Derivatives and Miscellaneous Products

Experiments were following general procedure C (page 151) in this section.



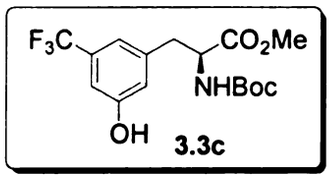
2-*tert*-Butoxycarbonylamino-3-[3-chloro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-propionic acid methyl ester (3.2b): Slightly yellow solid; mp 83-86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (s, 1 H), 7.43 (s, 1 H), 7.20 (s, 1 H), 5.01 (d, J = 7.7 Hz, 1 H), 4.5-4.6 (m, 1 H), 3.73 (s, 3 H), 2.9-3.2 (m, 2 H), 1.43 (s, 9 H), 1.33 (s, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 155.3, 137.9, 134.4, 134.2, 133.5, 132.4, 84.9, 84.5, 80.4, 54.8, 52.6, 38.2, 28.6, 25.3, 25.2; IR (neat): 3365, 2978, 1746, 1717, 1356, 1167, 1144 cm^{-1}; LRMS (ESI): *m/e* 462 ($[M+Na]^+$), 340 ($[M-Boc+2H]^+$). Anal. Calcd for $C_{21}H_{31}BClNO_6$: C, 57.36; H, 7.11; N, 3.19. Found C,

57.78; H, 7.40; N, 2.98.



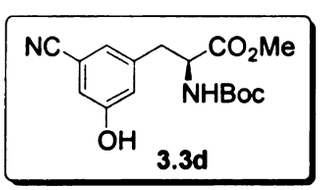
3.3b

2-*tert*-Butoxycarbonylamino-3-(3-chloro-5-hydroxy-phenyl)-propionic acid methyl ester (3.3b): A colorless thick gel. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.75 (s, 1 H), 6.67 (s, 1 H), 6.54 (s, 1 H), 6.05 (brs, 1 H), 5.06 (d, *J* = 7.9 Hz, 1 H), 4.55 (m, 1 H), 3.74 (s, 3 H), 2.8-3.1 (m, 2 H,), 1.43 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 157.5, 155.9, 139.2, 135.2, 121.8, 115.2, 115.0, 81.1, 54.7, 52.9, 38.5, 28.6; IR (neat): 3355, 2978, 2931, 1684, 1162 cm^{-1}; LRMS (ESI): *m/e* 681 ([2M+Na]$^+$), 352 ([M+Na]$^+$), 274 ([M-^{t}Bu+2H]$^+$), 230 ([M-Boc+2H]$^+$). Anal. Calcd for $C_{15}H_{20}ClNO_5 \cdot 0.5H_2O$: C, 53.18; H, 6.25; N, 4.13. Found C, 53.04; H, 5.95; N, 4.11.



3.3c

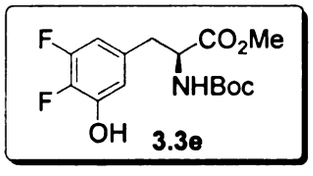
2-*tert*-Butoxycarbonylamino-3-(3-trifluoromethyl-5-hydroxy-phenyl)-propionic acid methyl ester (3.3c): White solid; mp 94-96.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.97 (s, 1 H), 6.91 (s, 1 H), 6.83 (s, 1 H), 6.01 (brs, 1 H), 5.08 (brs, 1 H), 4.57 (m, 1 H), 3.73 (s, 3 H), 3.0-3.2 (m, 2 H), 1.42 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 156.7, 155.5, 138.6, 131.9 (q, *J* = 32.5 Hz), 123.8 (q, *J* = 271 Hz), 119.5, 117.9, 111.3, 80.8, 54.3, 52.5, 38.3, 28.2; IR (neat): 3354, 2981, 1684, 1368, 1171, 1125 cm^{-1}; LRMS (ESI): *m/e* 386 ([M+Na]$^+$), 308 ([M-^{t}Bu+2H]$^+$), 264 ([M-Boc+2H]$^+$). Anal. Calcd for $C_{16}H_{20}F_3NO_5$: C, 52.89; H, 5.55; N, 3.86. Found C, 52.67; H, 5.53; N, 3.85.



3.3d

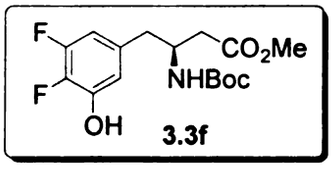
2-*tert*-Butoxycarbonylamino-3-(3-cyano-5-hydroxy-phenyl)-propionic acid methyl ester (3.3d): White

solid; mp 104-106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.00 (s, 1 H), 6.97 (s, 1 H), 6.91 (s, 1 H), 6.25 (s, 1 H), 5.08 (brs, 1 H), 4.56 (m, 1 H), 3.75 (s, 3 H), 2.9-3.2 (m, 2 H), 1.42 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 157.3, 155.8, 139.7, 125.1, 121.7, 118.9, 118.0, 113.4, 81.3, 54.6, 53.0, 38.6, 28.6; IR (neat): 3355, 2979, 2231, 1742, 1684, 1368, 1165 cm^{-1}; LRMS (ESI): *m/e* 663 ([2M+Na]$^+$), 343 ([M+Na]$^+$), 265 ([M-^{t}Bu+2H]$^+$), 221 ([M-Boc+2H]$^+$). Anal. Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.74. Found C, 60.07; H, 6.50; N, 8.92.



3.3e

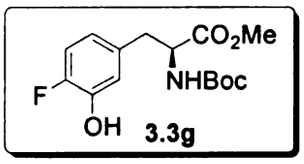
2-*tert*-Butoxycarbonylamino-3-(3,4-difluoro-5-hydroxy-phenyl)-propionic acid methyl ester (3.3e): Colorless thick oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.45-6.58 (m, 2 H), 5.53 (brs, 1 H), 5.09 (d, *J* = 8.0 Hz, 1 H), 4.5 (m, 1 H), 3.74 (s, 3 H), 2.8-3.1 (m, 2 H), 1.43 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 155.7, 151.2 (dd, *J* = 246 Hz, the other *J* value not clear due to overlapping signal), 145.9 (d, *J* = 10 Hz), 139.7 (dd, *J* = 240, 15 Hz), 132.5, 114.0, 109.4 (d, *J* = 18 Hz), 81.0, 54.7, 52.8, 38.2, 28.6; IR (neat): 3356, 2980, 1690, 1523, 1368, 1165, 1055 cm^{-1}; LRMS (ESI): *m/e* 685 ([2M+Na]$^+$), 354 ([M+Na]$^+$), 276 ([M-^{t}Bu+2H]$^+$), 232 ([M-Boc+2H]$^+$). HRMS (FAB): *m/e* calcd for [$C_{15}H_{18}F_2NO_5$-H]$^+$ 330.1153, found 330.1151.



3.3f

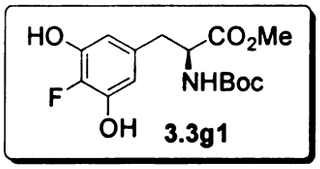
3-*tert*-Butoxycarbonylamino-4-(3,4-difluoro-5-hydroxy-phenyl)-butyric acid methyl ester (3.3f): *The borylation went to 80% conversion.* Slightly yellow solid; mp 126-129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.50-6.65 (m, 2 H), 5.70 (brs, 1 H), 5.1 (br, 1 H), 4.08 (m, 1 H), 3.70 (s, 3 H), 2.66-2.80 (m, 2 H), 2.42-2.58 (m, 2 H),

1.41 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 155.8, ~151.9 (dd, overlapped), 145.8 (d, *J* = 13 Hz), ~140.2 (dd, overlapped), 134.3, 113.9, 109.5 (d, *J* = 29 Hz), 80.3, 52.5, 49.0, 40.3, 38.0, 28.7; IR (neat): 3355, 2979, 1719, 1685, 1521, 1368, 1164, 1056 cm^{-1}; LRMS (ESI): *m/e* 713 ($[2M+Na]^+$), 368 ($[M+Na]^+$), 290 ($[M-^tBu+2H]^+$), 246 ($[M-Boc+2H]^+$). Anal. Calcd for $C_{16}H_{21}F_2N_2O_5$: C, 55.65; H, 6.13; N, 4.06. Found C, 55.94; H, 6.28; N, 4.10.



3.3g

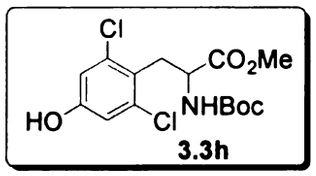
2-*tert*-Butoxycarbonylamino-3-(4-fluoro-3-hydroxy -phenyl)-propionic acid methyl ester (3.3g): Colorless thick oil. ^1H NMR (300 MHz, $CDCl_3$): δ 6.96 (dd, *J* = 8.3, 10.5 Hz, 1 H), 6.78 (dd, *J* = 8.3, 1.5 Hz, 1 H), 6.6 (m, 1 H), 5.38 (brs, 1 H), 5.07 (d, *J* = 7.8 Hz, 1 H), 4.55 (m, 1 H), 3.72 (s, 3 H), 2.9-3.1 (m, 2 H), 1.42 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 155.7, 150.8 (d, *J* = 236 Hz), 144.0 (d, *J* = 15 Hz), 133.2, 121.7 (d, *J* = 6.4 Hz), 118.6, (d, *J* = 1.7 Hz), 115.9 (d, *J* = 18 Hz), 80.7, 54.8, 52.7, 38.1, 28.6; IR (neat): 3365, 2979, 1692, 1512, 1165 cm^{-1}; LRMS (ESI): *m/e* 649 ($[2M+Na]^+$), 336 ($[M+Na]^+$), 258 ($[M-^tBu+2H]^+$), 214 ($[M-Boc+2H]^+$). HRMS (FAB): *m/e* calcd for $[C_{15}H_{19}FNO_5-H]^+$ 312.1247, found 312.1233;



3.3g1

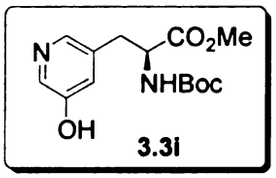
2-*tert*-Butoxycarbonylamino-3-(4-fluoro-3,5-dihy-droxy-phenyl)-propionic acid methyl ester (3.3g1, byproduct of borylation/oxidation of **3.1g** due to double borylation): ^1H NMR (300 MHz, acetone-d_6): δ 6.38 (d, *J* = 7.3 Hz, 2 H), 4.34 (m, 1 H), 3.68 (s, 3 H), 2.8-3.0 (m, 2 H), 1.38 (s, 9 H), OH and NH protons were not observed; LRMS (ESI): *m/e* 681 ($[2M+Na]^+$), 393 ($[M+Na+CH_3CN]^+$), 352 ($[M+Na]^+$), 274 ($[M-^tBu+2H]^+$), 230 ($[M-Boc+2H]^+$). HRMS (FAB): *m/e* calcd for

$[C_{15}H_{19}FNO_6\text{-}H]^+$ 328.1196, found 328.1201.



3.3h

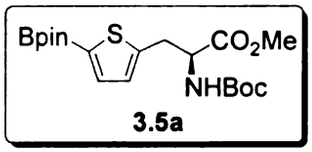
2-*tert*-Butoxycarbonylamino-3-(2,6-dichloro-4-hydroxy-phenyl)-propionic acid methyl ester (3.3h): White crystal; mp 164-165 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (s, 2 H), 5.30 (d, *J* = 9.3 Hz, 1H), 4.6-4.7 (m, 1 H), 3.78 (s, 3 H), 3.1-3.5 (m, 2 H), 1.38 (s, 9 H), OH proton was not observed; ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 156.5, 155.9, 136.4, 124.0, 116.2, 81.0, 53.3, 53.0, 34.0, 28.6; IR (neat): 3347, 2979, 1685, 1164 cm^{-1}; LRMS (ESI): *m/e* 749 ($[2M+Na]^+$), 427 ($[M+Na+CH_3CN]^+$), 386 ($[M+Na]^+$), 308 ($[M-^tBu+2H]^+$), 264 ($[M-Boc+2H]^+$). Anal. Calcd for $C_{15}H_{19}Cl_2NO_5 \cdot 0.5H_2O$: C, 48.27; H, 5.40; N, 3.75; Cl, 19.00. Found C, 48.35; H, 5.27; N, 3.64; Cl, 18.62.



3.3i

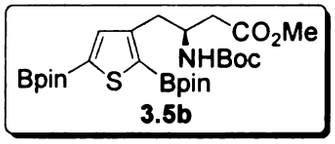
2-*tert*-Butoxycarbonylamino-3-(5-hydroxy-pyridin-3-yl)-propionic acid methyl ester (3.3i, isolated as TFA salt): *The borylation went to 84% conversion.* The workup procedure was slightly different for this compound. Following general procedure C (page 151), the oxidation step was quenched with $NaHSO_3$. The resultant solution was directly lyophilized. The residual solid was extracted with MeOH and concentrated. Preparative HPLC followed by lyophilization afforded **3.3i** as a slightly yellow gel. ^{1}H NMR (300 MHz, CD_3OD): δ 8.22 (s, 2 H), 7.84 (s, 1 H), 4.45-4.50 (m, 1 H), 3.76 (s, 3 H), 3.0-3.1 (m, 2 H), 1.36 (s, 9 H), OH and NH protons were not observed; ^{13}C NMR (75 MHz, CD_3OD): δ 173.2, 158.5, 158.1, 140.9, 135.2, 134.4, 129.9, 81.4, 55.5, 53.4, 36.0, 29.0; IR (neat): 3600-2400 (br), 3307, 2979, 1683, 1202, 1182 cm^{-1}; LRMS (ESI): *m/e* 297 (M+H). Anal. Calcd for

$C_{16}H_{21}F_3N_2O_7$ (TFA salt): C, 46.83; H, 5.16; N, 6.83. Found C, 47.22; H, 5.07; N, 7.14.



3.5a

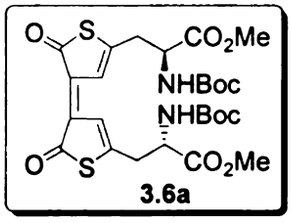
2-*tert*-Butoxycarbonylamino-3-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-thiophen-2-yl]-propionic acid methyl ester (3.5a): Slightly yellow gel. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, *J* = 3.4 Hz, 1 H), 6.87 (d, *J* = 3.4 Hz, 1 H), 5.14 (d, *J* = 7.8 Hz, 1 H), 4.6 (m, 1 H), 3.75 (s, 3 H), 3.38 (d, *J* = 4.9 Hz, 2 H), 1.44 (s, 9 H), 1.33 (s, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 155.5, 145.4, 137.8, 128.6, 84.4, 80.5, 54.6, 52.8, 33.0, 28.7, 25.1, 25.1; IR (neat): 3363, 2978, 1747, 1717, 1472, 1358, 1165, 1144 cm^{-1}; LRMS (ESI): *m/e* 434 ([M+Na]$^+$), 356 ([M-^{t}Bu+2H]$^+$), 312 ([M-Boc+2H]$^+$). Anal. Calcd for $C_{19}H_{30}BSNO_6$: C, 55.48; H, 7.35; N, 3.41. Found C, 55.70; H, 7.00; N, 3.21.



3.5b

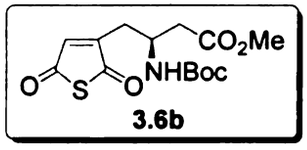
4-[2,5-Bis-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-thiophen-3-yl]-3-*tert*-butoxycarbonylamino-butyric acid methyl ester (3.5b): Slightly yellow gel. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (s, 1 H), 5.52 (d, *J* = 7.7 Hz, 1 H), 4.0-4.2 (m, 1 H), 3.69 (s, 3 H), 3.0-3.2 (m, 2 H), 2.4-2.7 (m, 2 H), 1.32-1.36 (three overlapping s, 33 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 155.6, 150.0, 140.7, 84.5, 84.5, 79.3, 51.9, 50.0, 40.1, 34.6, 28.7, 25.3, 25.2, 25.1, 25.0; IR (neat): 3383, 2978, 1738, 1715, 1386, 1333, 1167, 1140 cm^{-1}; LRMS (ESI): *m/e* 496 ([M-Boc+2H]$^+$), 452 ([M-Boc+2H]$^+$), 352. HRMS (FAB): *m/e* calcd for [$C_{26}H_{44}B_2SNO_8$+H]$^+$ 552.2974, found 552.2986.

2-*tert*-Butoxycarbonylamino-3-[5'-(2-*tert*-butoxycarbonylamino-2-methoxycarbonyl-ethyl)-2,2'-dioxo-[3,3']-bithiophenyliden-5-yl]-propionic acid



3.6a

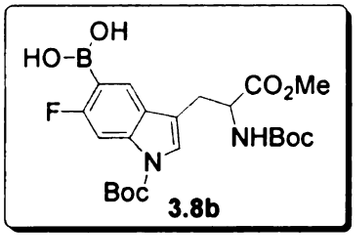
methyl ester (3.6a): Dark purple solid; mp 136 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (s, 2 H), 5.25 (d, *J* = 7.5 Hz, 2 H), 4.6 (m, 2 H), 3.79 (s, 6 H), 3.1-3.3 (m, 4 H), 1.45 (s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) and DEPT: δ 195.3 (C), 171.4 (C), 155.2 (C), 150.7 (C), 135.2 (C), 120.7 (CH), 80.9 (C), 53.3 (CH), 53.2 (CH_3), 36.8 (CH_2), 28.6 (CH_3); COSY (300 MHz with respect to ^{1}H, $CDCl_3$): 7.48-3.1, 5.25-4.6, 4.6-3.1, 4.6-3.3, 3.1-3.3; HETCOR (500 MHz with respect to ^{1}H, $CDCl_3$): H7.48-C120.7, H4.6-C53.3, H3.79-C53.2, H3.1-C36.8, H1.45-C28.6; HMBC (500 MHz with respect to ^{1}H, $CDCl_3$): H7.48-C36.8, H7.48-C53.3, H7.48-C135.2, H7.48-C150.7, H7.48-C195.3, H5.25-C53.3, H5.25-C171.4, H4.6-C36.8, H4.6-C150.7, H4.6-C171.4, H3.79-C171.4, H3.1-C53.3, H3.1-C120.7, H3.1-C135.2, H3.1-C150.7, H3.1-C171.4, H1.45-C80.9; IR (neat): 3340, 2957, 2925, 2855, 1738, 1726, 1678, 1513, 1272, 1155, 1028 cm^{-1}; LRMS (ESI): *m/e* 621 ([M+Na]$^+$), 487 ([M-2^{t}Bu+3H]$^+$), 443 ([M-Boc-^{t}Bu+3H]$^+$). HRMS (FAB): *m/e* calcd for [$C_{26}H_{33}N_2O_{10}S_2$-H]$^+$ 597.1577, found 597.1586.



3.6b

3-*tert*-Butoxycarbonylamino-4-(2,5-dioxo-2,5-dihydro-thiophen-3-yl)-butyric acid methyl ester (3.6b): Yellow thick oil which solidified upon storage, mp 95-98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84 (s, 1 H), 5.26 (d, *J* = 8.8 Hz, 1 H), 4.2 (m, 1 H), 3.73 (s, 3 H), 2.6-2.9 (m, 4 H), 1.39 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) and DEPT: δ 193.1 (C), 190.6 (C), 171.6 (C), 156.4 (C), 155.3 (C), 139.0 (CH), 80.1 (C), 52.0 (CH_3), 46.0 (CH), 38.5 (CH_2), 32.0 (CH_2), 28.2 (CH_3); HETCOR (500 MHz with respect to ^{1}H, $CDCl_3$): H6.84-C139.0, H4.2-C46.0, H3.73-C52.0,

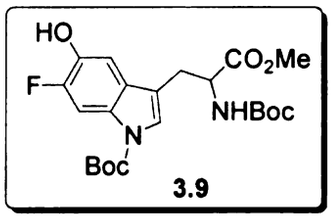
H2.9-C32.0, H2.6-C38.5, H1.39-C28.2; HMBC (500 MHz with respect to ^1H, $CDCl_3$): H6.84-C32.0, H6.84-C155.3/156.4, H6.84-C190.6, H6.84-C193.1, H3.73-C171.6, H2.9-C46.0, H2.9-C139.0, H2.9-C155.3/156.4, H2.9-C193.1, H2.6-C32.0, H2.6-C46.0, H2.6-171.6, H1.39-C80.1; IR (neat): 3367, 2957, 2928, 1734, 1690, 1164 cm^{-1}; LC-MS (ESI): *m/e* 352 ($[M+Na]^+$), 274 ($[M-^tBu+2H]^+$), 230 ($[M-Boc+2H]^+$). HRMS (FAB): *m/e* calcd for $[C_{14}H_{19}NO_6S]^+$ 329.0933, found 329.0943.



3.8b

3-(2-*tert*-Butoxycarbonylamino-2-methoxycarbonyl-ethyl)-5-borono-6-fluoroindole-1-carboxylic acid *tert*-butyl ester (3.8b): General procedure C (page 151) was applied to 210 mg of **3.7b** (0.5 mmol). The borylation step was carried out with 254 mg B_2pin_2 (1.0 mmol, 2 equiv), 20 mg $[Ir(OMe)(cod)]_2$ (0.03 mmol, 6 mol%) and 16 mg d^tbpy (0.06 mmol, 12 mol %) in 2 mL cyclohexane. After removal of cyclohexane, 15 mL acetone and 15 mL aqueous solution of 90 mg NH_4OAc (1.2 mmol, 2.4 equiv) and 1.07 g $NaIO_4$ (5 mmol, 2.5 equiv per Bpin) were added. The reaction mixture turned dark green with a white precipitation formed. It was stirred at room temperature until reaction judged complete by HPLC. The reaction was filtered to remove the precipitate and extracted with CH_2Cl_2. The combined organic layer was evaporated and the residue was dissolved in acetonitrile and purified by preparative HPLC (50/50 → 70/30 acetonitrile/water) to afford 102 mg (43 %) of **3.8b** as a pale yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, J = 6.3 Hz, 1 H), 7.74 (d, J = 12.1 Hz, 1 H), 7.31 (s, 1 H), 5.8 (br, 2 H), 5.17 (d, J = 7.6 Hz, 1 H),

4.58 (br, 1 H), 3.66 (s, 3 H), 3.16 (m, 2 H), 1.59 (s, 9 H), 1.35 (s, 9 H) (Note: $CDCl_3$ signal was observed at 7.19); LRMS (ESI): *m/e* 503 ($[M+Na]^+$), 381 ($[M-Boc+2H]^+$), 325 ($[M-Boc-^tBu+3H]^+$), 281 ($[M-2Boc+3H]^+$).

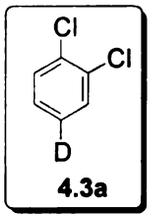


3.9

3-(2-*tert*-Butoxycarbonylamino-2-methoxycarbonyl-ethyl)-5-hydroxy-6-fluoroindole-1-carboxylic acid *tert*-butyl ester (3.9): To a solution of 21 mg of **3.8b** (44 μmol) in 400 μL acetone was added a solution of 30 mg oxone (49 μmol, 1.1 equiv) in 400 μL water. The mixture was stirred at room temperature for 12 min and quenched with $NaHSO_3$. The reaction mixture was extracted with EtOAc and evaporated. It was further dissolved in acetonitrile and purified by preparative HPLC (50/50 → 70/30 acetonitrile/water) to afford 16 mg of **3.9** (80%) as a pale white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (br, 1 H), 7.24 (s, 1 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 5.08 (d, *J* = 7.4 Hz, 1 H), 4.53 (m, 1 H), 3.64 (s, 3 H), 2.9-3.2 (m, 2 H), 1.56 (s, 9 H), 1.36 (s, 9 H) (Note: $CDCl_3$ signal was observed at 7.18); ^{13}C NMR: (125 MHz, $CDCl_3$): δ 172.7, 155.6, 150.3 (d, *J* = 233 Hz), 149.6, 140.8 (d, *J* = 15.6 Hz), 129.1, 127.2, 124.9, 115.1, 105.9, 103.3 (d, *J* = 26 Hz), 84.3, 80.7, 54.0, 52.9, 28.7, 28.6, 28.3; IR (neat): 3373, 2980, 2934, 1733, 1472, 1395, 1160, 1074 cm^{-1}; LRMS (ESI): *m/e* 475 ($[M+Na]^+$), 353 ($[M-Boc+2H]^+$), 297 ($[M-Boc-^tBu+3H]^+$), 253 ($[M-2Boc+3H]^+$).

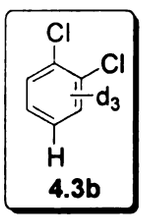
7.4.3 Deuterated Aromatics

1,2-Dichlorobenzene-4-*d* (4.3a): General procedure D (page 152) was applied to 295 mg 1,2-dichlorobenzene (2 mmol). The borylation step was



4.3a

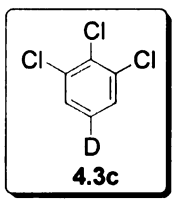
carried out neat with 365 mg HBpin (2.85 mmol, 1.4 equiv), 16.6 mg (Ind)Ir(cod) (0.04 mmol, 2 mol%) and 6.0 mg dmpe (0.04 mmol, 2 mol%) at 150 °C for 3.5 h. The crude borylation mixture was pumped down under high vacuum and charged with 0.5 mL D_2O and 3 mL THF. The deuteration step was then carried out at 150 °C for 30 min and worked up as described in the general procedure, after which the crude material was purified with a silica gel chromatography (pentane) to afford 220 mg of **4.3a** (74%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.44 (m, 2 H), 7.16-7.20 (m, 1 H); ^{2}H NMR (76.75 MHz, pentane): δ 7.21; ^{13}C NMR (125 MHz, $CDCl_3$): δ 132.6, 130.5, 130.4, 127.6, 127.4 (t, $J_{C\text{-}D}$ = 25 Hz); IR (neat): 3063, 1564, 1455, 1385, 1125, 1034, 901, 835, 731, 648 cm^{-1}; LRMS (EI): *m/e* 147 (M^+), 112, 76. HRMS (EI) *m/e* calcd for $[C_6H_3DCl_2]^+$ 146.9753, found 146.9759.



4.3b

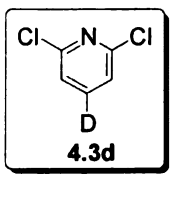
1,2-Dichlorobenzene-3,4,6-d_3 (4.3b): General procedure D (page 152) was applied to 303 mg *unpurified* 1,2-dichlorobenzene-d_4 (2 mmol). The borylation step was carried out neat with 402 mg HBpin (3.1 mmol, 1.55 equiv), 16.6 mg (Ind)Ir(cod) (0.04 mmol, 2 mol%) and 6.0 mg dmpe (0.04 mmol, 2 mol%) at 150 °C for 3 h. The crude borylation mixture was pumped down under high vacuum and charged with 0.5 mL H_2O and 3 mL THF. The protonation step was then carried out at 150 °C for 60 min and worked up as described in the general procedure, after which the crude material was purified with a silica gel chromatography (pentane) to afford 246 mg of **4.3b** (82%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (s), a small peak (ca. 10%) at 7.42-7.44 (m) was also present (^{1}H at *ortho* positions of the chlorides, presumably

because i) the starting material was 98% deuterated, and ii) some borylation occurred to such positions); ^{2}H NMR (76.75 MHz, pentane): δ 7.49 (s, 2 D), 7.21 (s, 1 D); ^{13}C NMR (125 MHz, $CDCl_3$): δ 132.5, 130.2 (t, $J_{C\text{-}D}$ = 25 Hz), 130.1 (t, $J_{C\text{-}D}$ = 25 Hz), 127.5, 127.3 (t, $J_{C\text{-}D}$ = 26 Hz); IR (pentane solution film): 1557, 1418, 1393, 1352, 1157, 1069, 1026, 626 cm^{-1}; LRMS (EI): *m/e* 149 (M^+), 114, 77. HRMS (EI): *m/e* calcd for $[C_6HD_3Cl_2]^+$ 148.9878, found 148.9879.



4.3c

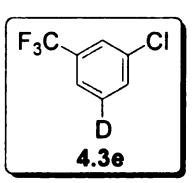
1,2,3-Trichlorobenzene-5-*d* (4.3c): General procedure D (page 152) was applied to 364 mg 1,2,3-trichlorobenzene (2 mmol). The borylation step was carried out neat with 450 mg HBpin (3.6 mmol, 1.8 equiv), 16.6 mg (Ind)Ir(cod) (0.04 mmol, 2 mol%) and 6.0 mg dmpe (0.04 mmol, 2 mol%) at 150 °C for 3.25 h. The crude borylation mixture was pumped down under high vacuum and charged with 0.5 mL D_2O and 3 mL THF. The deuteration step was then carried out at 150 °C for 60 min and worked up as described in the general procedure, after which the crude material was purified with a silica gel chromatography (pentane) to afford 343 mg of **4.3c** (94%) as a white solid; mp 52-53 °C (53-55 °C for commercial non-deuterated compound). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (t, $J_{H\text{-}D}$ = 1.1 Hz); ^{2}H NMR (76.75 MHz, pentane): δ 7.14; ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.3, 131.6, 128.6, 127.2 (t, $J_{C\text{-}D}$ = 25 Hz); IR (neat): 3071, 1553, 1412, 1385, 1196, 1159, 899, 768, 666 cm^{-1}; LRMS (EI): *m/e* 181 (M^+), 146, 110. Anal. Calcd for $C_6H_2DCl_3$: C, 39.50. Found C, 39.06.



4.3d

2,6-Dichloropyridene-4-*d* (4.3d): General procedure D (page 152) was applied to 300 mg 2,6-dichloropyridene (2 mmol). The

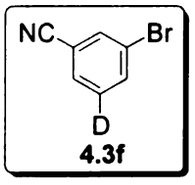
borylation step was carried out with 450 mg HBpin (3.6 mmol, 1.8 equiv), 16.6 mg (Ind)Ir(cod) (0.04 mmol, 2 mol%) and 6.0 mg dmpe (0.04 mmol, 2 mol%) in 1 mL heptane at 150 °C for 3.25 h. After removal of heptane by a gentle nitrogen flow, the crude borylation mixture was pumped down under high vacuum and charged with 0.5 mL D_2O and 3 mL THF. The deuteration step was then carried out at 150 °C for 60 min and worked up as described in the general procedure, after which the crude material was purified with a silica gel chromatography (CH_2Cl_2) to afford 273 mg of **4.3d** (92%) as a white solid; 84-86 °C (86-88.5 °C for commercial non-deuterated compound). ^1H NMR (500 MHz, $CDCl_3$): δ 7.25 (t, $J_{H\text{-}D}$ = 1.1 Hz); ^2H NMR (76.75 MHz, CH_2Cl_2): δ 7.65; ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.6, 140.4 (t, $J_{C\text{-}D}$ = 25 Hz), 122.7; IR (neat): 3050, 2269, 1559, 1547, 1373, 1136, 986, 901, 739, 702 cm^{-1}; LRMS (EI): *m/e* 148 (M^+), 113. Anal. Calcd for $C_5H_2DNCl_2$: C, 40.31; N, 9.40. Found C, 40.34; N, 8.80.



4.3e

3-Chlorobenzotrifluoride-5-*d* (4.3d): General procedure D (page 152) was applied to 363 mg 3-chlorobenzotrifluoride (2 mmol). The borylation step was carried out with 450 mg HBpin (3.6 mmol, 1.8 equiv), 16.7 mg (Ind)Ir(cod) (0.04 mmol, 2 mol%) and 6.0 mg dmpe (0.04 mmol, 2 mol%) in 2 mL cyclohexane at 150 °C for 3 h. After removal of cyclohexane by a gentle nitrogen flow, the crude borylation mixture was pumped down under high vacuum and charged with 0.5 mL D_2O and 3 mL THF. The deuteration step was then carried out at 150 °C for 90 min and worked up as described in the general procedure, after which the crude material was purified with a silica gel chromatography (pentane) to afford 244 mg material containing

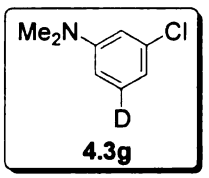
239 mg of **4.3e** (66%) and 5 mg pentane. Continuing evaporation afforded pure **4.3e** (some loss of product occurred) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (br, 1 H), 7.50-7.51 (br, 2 H); ^{2}H NMR (76.75 MHz, pentane): δ 7.45; ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.0, 132.3 (q, $J_{C\text{-}F}$ = 34 Hz), 131.9, 129.9 (t, $J_{C\text{-}D}$ = 25 Hz), 125.7 (q, $J_{C\text{-}F}$ = 4 Hz), 123.3 (q, $J_{C\text{-}F}$ = 4 Hz), 123.3 (q, $J_{C\text{-}F}$ = 272 Hz); IR (pentane solution film): 3087, 1576, 1426, 1310, 1175, 1134, 1103, 1161, 887, 708, 677 cm^{-1}; LRMS (EI): *m/e* 181 (M^+), 162, 146. HRMS (EI): *m/e* calcd for $[C_7H_3DClF_3\text{-}Cl]^+$ 146.0328, found 146.0330.



4.3f

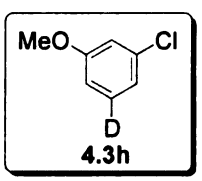
3-Bromobenzonitrile-5-*d* (4.3f): General procedure D (page 152) was applied to 364 mg 3-bromobenzonitrile (2 mmol). The borylation step was carried out with 400 mg HBpin (3.1 mmol, 1.55 equiv), 20.0 mg $[Ir(OMe)(cod)]_2$ (0.03 mmol, 1.5 mol%) and 16.0 mg d^{t}bpy (0.06 mmol, 3 mol%) in 2 mL heptane at room temperature for 6 h. After removal of heptane by a gentle nitrogen flow, the crude borylation mixture was pumped down under high vacuum and charged with 0.5 mL D_2O and 3 mL THF. The deuteration step was then carried out at 150 °C for 2 h and worked up as described in the general procedure, after which the crude material was purified with a silica gel chromatography (CH_2Cl_2), followed by a sublimation at 45-50 °C under 0.1 mmHg to afford 257 mg of **4.3f** (70%) as a white solid; mp 37-39 °C (38-40 °C for commercial non-deuterated compound). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (apparent t, *J* = 1.6 Hz, 1 H), 7.73 (br, 1 H), 7.59 (br, 1 H); ^{2}H NMR (76.75 MHz, CH_2Cl_2): δ 7.39; ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.0, 134.7, 130.5, 130.3 (t, $J_{C\text{-}D}$ = 25 Hz), 122.8, 117.2, 114.2; IR (neat): 3075, 2234, 1553, 1429, 1406, 1186,

909, 882, 785, 675 cm^{-1}; LRMS (EI): *m/e* 182 (M^+), 103. Anal. Calcd for C_7H_3DNBr: C, 45.94; N, 7.65. Found C, 45.70; N, 7.53.



4.3g

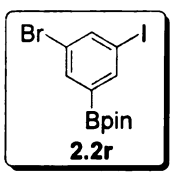
3-Chloro-*N,N*-dimethylaniline-5-*d* (4.3g): General procedure D (page 152) was applied to 312 mg 3-chloro-*N,N*-dimethylaniline (2 mmol). The borylation step was carried out neat with 512 mg HBpin (4 mmol, 2 equiv), 16.6 mg (Ind)Ir(cod) (0.04 mmol, 2 mol%) and 6.0 mg dmpe (0.04 mmol, 2 mol%) at 150 °C for 18 h. The crude borylation mixture was pumped down under high vacuum and charged with 0.5 mL D_2O and 3 mL DME. 102 mg Ac_2O (1 mmol, 0.5 equiv) was also added at this time. The deuteration step was then carried out at 150 °C for 2 h and cooled to room temperature. It was basified with 5% NaOH to pH > 10 before being extracted with CH_2Cl_2. After drying and concentration, the crude material was purified with a silica gel chromatography (pentane/CH_2Cl_2 3:1) to afford 292 mg of **4.3g** (93%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 6.68 (br, 2 H), 6.58 (br, 1 H), 2.93 (s, 6 H); ^2H NMR (76.75 MHz, pentane): δ 7.14; ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.5, 134.9, 129.6 (t, J_{C-D} = 24 Hz), 116.1, 112.2, 110.4, 40.3; IR (neat): 3085, 2892, 2807, 2272, 1593, 154, 1491, 1439, 1227, 1113, 986, 972, 675 cm^{-1}; LRMS (EI): *m/e* 155 ($[M-H]^+$). Anal. Calcd for C_8H_9DNCl: C, 61.35; N, 8.94. Found C, 61.09; N, 8.86.



4.3h

3-Chloroanisole-5-*d* (4.3h): General procedure D (page 152) was applied to 288 mg 3-chloroanisole (2 mmol). The borylation step was carried out neat with 400 mg HBpin (3.1 mmol, 1.55 equiv), 16.6 mg (Ind)Ir(cod) (0.04 mmol, 2 mol%) and 6.0 mg dmpe (0.04 mmol, 2

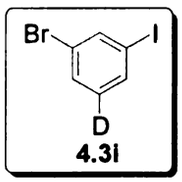
mol%) at 150 °C for 12 h. The crude borylation mixture was pumped down under high vacuum and charged with 0.5 mL D_2O and 3 mL THF. The deuteration step was then carried out at 150 °C for 1 h and worked up as described in the general procedure, after which the crude material was purified with a silica gel chromatography (CH_2Cl_2), to afford 258 mg of **4.3h** (90%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 6.91 (br, 1 H), 6.88 (t, J = 2.2 Hz, 1 H), 6.77 (br, 1 H), 3.78 (s, 3 H); ^2H NMR (76.75 MHz, pentane): δ 7.20; ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 134.9, 129.9 (t, J_{C-D} = 24 Hz), 120.7, 114.3, 112.4, 55.3; IR (neat): 3083, 3007, 2963, 2940, 2834, 1593, 1574, 1458, 1258, 1237, 1044, 679 cm^{-1}; LRMS (EI): *m/e* 143 (M^+). Anal. Calcd for C_7H_6DClO: C, 58.55. Found C, 58.61.



2.2r

3-Bromo-5-iodophenyl boronic acid pinacol ester (2.2r): General procedure A (page 149) was applied to 566 mg 1-bromo-3-iodobenzene (2.0 mmol). The borylation step was carried out with 510 mg B_2pin_2 (2.0 mmol, 2.0 equiv boron), 20.0 mg $[Ir(OMe)(cod)]_2$ (0.03 mmol, 1.5 mol %), and 16.0 mg d^{t}bpy (0.06 mol, 3 mol %) in 4 mL heptane in dark environment at room temperature for 12 h. (Note: use 2.0 equiv high-quality HBpin could also be effective) The reaction was carefully quenched by addition of EtOH and concentrated. The syrup was passed through a silica plug (CH_2Cl_2) to afford 700 mg of **2.2r** (86%) as a white solid; mp 88-92 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (brs, 1 H), 7.91 (t, J = 1.5 Hz, 1 H), 7.85 (brs, 1 H), 1.31 (s, 12 H); ^{11}B NMR (96 MHz, $CDCl_3$): δ 29.5; ^{13}C NMR (75

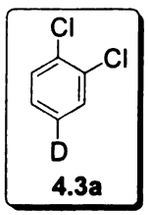
MHz, $CDCl_3$): δ 142.0, 141.8, 136.6, 122.9, 94.6, 84.5, 24.8; IR (neat): 3058, 2980, 2930, 1537, 1429, 1399, 1372, 1337, 1269, 1167, 1142, 1113, 962, 862, 723, 698 cm^{-1}; LRMS (EI): *m/e* 408 (M^+), 393, 322, 309, 181, 133, 116, 101, 83, 58, 41. Anal. Calcd for $C_{12}H_{15}BrIBO_2$: C, 35.25; H, 3.70. Found C, 35.39; H, 3.69.



4.3i

1-Bromo-3-iodobenzene-5-*d* (4.3i): In an air-free flask, 700 mg of **2.2r** (1.7 mmol) was charged with 55 mg Crabtree's catalyst (0.068 mmol, 4 mol%) 0.5 mL D_2O and 3 mL DME. The deuteration was carried out at 150 °C for 4.5 h and worked up as described in the general procedure, after which the crude material was purified with a silica gel chromatography (pentane), to afford 267 mg of **4.3i** (55%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.85 (t, J = 1.8 Hz, 1 H), 7.61 (br, 1 H), 7.45 (br, 1 H), a small peak at 6.95 (t, J = 8.0 Hz) was also present due to non-deuterated 5-position; ^2H NMR (76.75 MHz, pentane): δ 6.97; ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.8, 136.0, 131.0 (t, $J_{C\text{-}D}$ = 25 Hz), 130.7, 123.1, 94.5; IR (neat): 3063, 1549, 1416, 1391, 1105, 864, 700, 673 cm^{-1}; LRMS (EI): *m/e* 283 (M^+), 156, 77. HRMS (EI) *m/e* calcd for $[C_7H_6DClO]^+$ 282.8604, found 282.8612.

Example of Calculating D% Incorporation.



4.3a

A GC-MS spectrum for the non-deuterated 1,2-dichlorobenzene was first recorded. The peak intensities for [M-H], M, and [M+H] were observed as such: 145 (M-H), 4.43%; 146 (M), 100%; 147 (M+H), 12.8%. Therefore, a ratio of [M-H]:M:[M+H] = 4.43:100:12.8 was obtained. We *assume* that this ratio also applies for 1,2-dichlorobenzene-d_1 (This assumption is true unless the M-H signal in the d_0 compound is due to the

loss of the specific H that has been replaced by D). Thus, for 1,2-dichlorobenzene-d_1, we should expect a ratio of peak intensities for 146:147:148 to be also 4.43:100:12.8.

Next, a GC-MS spectrum of **4.3a** (a mixture of d_0 and d_1 compounds) was recorded. The peak intensities were observed as such: 146 (M-H), 6.44%; 147 (M), 100%. If **4.3a** is a mixture of x% d_0 compound and y% d_1 compound, then

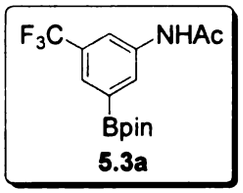
$$x + y = 100$$

At the same time, consider that the peak 146 in the mass spectrum of **4.3a** consists of two parts: the contributions from the d_0 and d_1 compounds, respectively. We assume that the peak intensities for [M-H]:M:[M+H] as 4.43:100:12.8 hold for both d_0 and d_1 compounds. Thus, for x% d_0 (M = 146), the contribution to the peak 146 (M) in mass spectrum of **4.3a** is 100x, where the number 100 is the relative peak intensity for [M]. Likewise, for y% d_1 (M = 147), the contribution to the peak 146 (M-H) in mass spectrum of **4.3a** is 4.43y, where the number 4.43 is the relative peak intensity for [M-H]. Therefore, the intensity of 146 for **4.3a** can be viewed as (100x+4.43y). Similarly, the intensity of 147 for **4.3a** can be viewed as (12.8x+100y). Thus, the ratio of 146:147 can be re-written as (100x+4.43y)/(12.8x+100y), which is 6.44:100 by experiment. So,

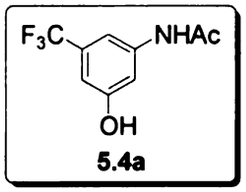
$$\frac{100x+4.43y}{12.8x+100y} = 0.0644$$

On the basis of these two equations, one can obtain the values of x = 2, and y = 98. Therefore, **4.3a** is 98% d_1 compound.

7.4.4 Amidophenols and Miscellaneous Compounds



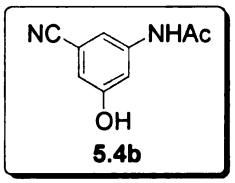
3-Acetylamido-5-trifluoromethylphenyl boronic acid pinacol ester (5.3a): General procedure E (page 152) was applied to 450 mg 3-bromobenzotrifluoride (2 mmol). The borylation step was carried out with 440 mg HBpin (3.44 mmol, 1.75 equiv), 20.0 mg $[Ir(OMe)(cod)]_2$ (0.03 mmol, 1.5 mol%) and 16.0 mg d^{t}bpy (0.06 mmol, 3 mol%) in 2 mL *n*-hexane at room temperature for 4 h. After evaporation of hexane, the crude borylation mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), 130 mg acetamide (2.2 mmol, 1.1 equiv), and 900 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv) in 6 mL THF at 80 °C for 3-4 h, resulting in a yellow suspension. The suspension was filtered to remove the insolubles and then concentrated. Silica gel chromatography (6:1 → 3:1 CH_2Cl_2/Et_2O, **5.3a** significantly tails on silica gel) afforded 507 mg of **5.3a** as a pale yellow gummy solid (~74%) that was contaminated by trace amount of pinacol. Recrystallization from acetone/hexanes gave pure **5.3a** as a cream-colored solid; mp 175–176 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ 9.41 (brs, 1 H), 8.32 (s, 1 H), 8.07 (brs, 1 H), 7.64 (apparent t, J = 0.9 Hz, 1 H), 2.14 (s, 3 H), 1.34 (s, 12 H); ^{13}C NMR (75 MHz, acetone-d_6): δ 169.4, 140.8, 130.9 (q, J = 32 Hz), 129.1, 125.8 (q, J = 4.1 Hz), 125.0 (q, J = 272 Hz), 118.7 (q, J = 3.6 Hz), 85.2, 25.1, 24.3; ^{11}B NMR (96 MHz, acetone-d_6): δ 31.8; IR (neat): 3306, 2928, 1674, 1566, 1391, 1300, 1167, 1144, 1127, 889, 846, 708, 687 cm^{-1}; LRMS (EI): *m/e* 329 (M^+), 314, 287, 272, 230, 201, 187, 43.



5.4a

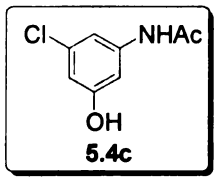
***N*-(3-Hydroxy-5-trifluoromethylphenyl)acetamide (5.4a)** (*from bromoarene*): General procedure E (page 152) was applied to 450 mg 3-bromobenzotrifluoride (2 mmol). The borylation step was carried out neat with 440 mg HBpin (3.44 mmol, 1.75 equiv), 16.6 mg (Ind)Ir(cod) (0.04 mmol, 2 mol%) and 6.0 mg dmpe (0.04 mmol, 2 mol%) at 150 °C for 4 h (these conditions pose no difference from the conditions above). The crude borylation mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), 130 mg acetamide (2.2 mmol, 1.1 equiv), and 900 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv) in 6 mL THF at 80 °C for 4 h, resulting in a yellow suspension. After filtration through a pad of silica, the oxidation and workup were performed as described in the general procedure. The crude product was purified on silica gel chromatography (2:1 → 1.5:1 CH_2Cl_2/EtOAc) to afford 282 mg of **5.4a** (64%) as a pale orange solid; mp 154.5-155.5 °C. R_f~0.38 (2:1 CH_2Cl_2/EtOAc). ^{1}H NMR (300 MHz, acetone-d_6): δ 9.33 (brs, 1 H), 8.97 (s, 1 H), 7.50 (s, 1 H), 7.46 (s, 1 H), 6.79 (s, 1 H), 2.08 (s, 3 H); ^{13}C NMR (75 MHz, acetone-d_6): δ 169.8, 159.2, 142.2, 132.1 (q, J = 32 Hz), 125.0 (q, J = 271 Hz), 110.2 (overlapped peak), 107.6 (q, apparent d, J = 3.4 Hz), 24.2; IR (neat): 3345, 3400-2800 (br), 1709, 1671, 1615, 1574, 1364, 1256, 1175, 1156, 1119, 1038, 855, 735 cm^{-1}; LRMS (EI): *m/e* 219 (M^+), 177, 43. Anal. Calcd for $C_9H_8F_3NO_2 \cdot H_2O$: C, 45.58; H, 4.25; N, 5.91. Found C, 45.62; H, 4.48; N, 5.82.

***N*-(3-Cyano-5-hydroxyphenyl)acetamide (5.4b)**: General procedure E (page 152) was applied to 364 mg 3-bromobenzonitrile (2 mmol). The borylation



5.4b

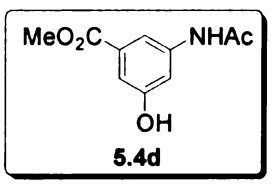
step was carried out with 400 mg HBpin (3.1 mmol, 1.55 equiv), 20.0 mg $[Ir(OMe)(cod)]_2$ (0.03 mmol, 1.5 mol%) and 16.0 mg d^{t}bpy (0.06 mmol, 3 mol%) in 2 mL *n*-hexane at room temperature for 3 h. After evaporation of hexane, the crude borylation mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), 130 mg acetamide (2.2 mmol, 1.1 equiv), and 900 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv) in 6 mL THF at 80 °C for 3 h, resulting in a yellow suspension. After filtration through a pad of silica, the oxidation and workup were performed as described in the general procedure. The crude product was purified on silica gel chromatography (4.5:1 → 2.5:1 CH_2Cl_2/acetone) to afford 222 mg of **5.4b** (63%) as a pale yellow solid; mp 264.5-266.5 °C. R_f~0.34 (1.5:1 CH_2Cl_2/EtOAc). ^{1}H NMR (300 MHz, acetone-d_6): δ 9.35 (brs, 1 H), 9.09 (s, 1 H), 7.52 (t, J = 2.1 Hz, 1 H), 7.49 (t, J = 1.6 Hz, 1 H), 6.84 (dd, J = 2.2, 1.4 Hz, 1 H), 2.07 (s, 3 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 169.4, 159.1, 142.6, 119.2, 114.3, 113.9, 113.8, 111.3, 24.3; IR (neat): 3353, 3200-2800 (br), 2226, 1671, 1599, 1572, 1426, 1331, 885, 858, 822, 770, 694 cm^{-1}; LRMS (EI): *m/e* 176 (M^+), 134, 43. HRMS (EI): *m/e* calcd for $[C_9H_8N_2O_2]^+$ 176.0586, found 176.0586.



5.4c

***N*-(3-Chloro-5-hydroxyphenyl)acetamide (5.4c)**: General procedure E (page 152) was applied to 383 mg 3-bromochlorobenzene (2 mmol). The borylation step was carried out neat with 480 mg HBpin (3.75 mmol, 1.9 equiv), 16.6 mg (Ind)Ir(cod) (0.04 mmol, 2 mol%) and 6.0 mg dmpe (0.04 mmol, 2 mol%) at 150 °C for 4 h.

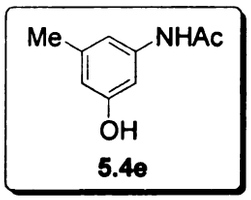
The crude borylation mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), 126 mg acetamide (2.14 mmol, 1.07 equiv), and 900 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv) in 6 mL THF at 80 °C for 3 h, resulting in a yellow suspension. After filtration through a pad of silica, the oxidation and workup were performed as described in the general procedure. The crude product was purified on silica gel chromatography (2:1 → 1.5:1 CH_2Cl_2/EtOAc) to afford 284 mg of **5.4c** (77%) as a white solid; mp 161-162 °C. R_f~0.31 (1.75:1 CH_2Cl_2/EtOAc). ^{1}H NMR (300 MHz, acetone-d_6): δ 9.17 (brs, 1 H), 8.75 (s, 1 H), 7.23 (t, J = 1.8 Hz, 1 H), 7.16 (t, J = 1.9 Hz, 1 H), 6.55 (t, J = 2.1 Hz, 1 H), 2.05 (s, 3 H); ^{13}C NMR (75 MHz, acetone-d_6): δ 169.3, 159.4, 142.4, 134.9, 111.1, 111.0, 105.4, 24.3; IR (neat): 3413, 3400-2800 (br), 1663, 1605, 1553, 1426, 1165, 866 cm^{-1}; LRMS (EI): *m/e* 185 (M^+), 143, 80, 43. Anal. Calcd for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; N, 7.55. Found C, 51.59; H, 4.46; N, 7.28.



5.4d

Methyl 3-acetylamido-5-hydroxybenzoate (5.4d): General procedure E (page 152) was applied to 430 mg methyl 3-bromobenzoate (2 mmol). The borylation step was carried out with 515 mg HBpin (4 mmol, 2 equiv), 20.0 mg $[Ir(OMe)(cod)]_2$ (0.03 mmol, 1.5 mol%) and 16.0 mg d^{t}bpy (0.06 mmol, 3 mol%) in 2 mL *n*-hexane at room temperature for 18 h, during which time the flask was open to a nitrogen manifold. After evaporation of hexane, the crude borylation mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), 133 mg

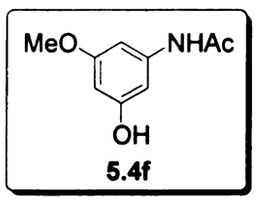
acetamide (2.25 mmol, 1.13 equiv), and 900 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv) in 6 mL THF at 100 °C for 2 h, resulting in a yellow suspension. After filtration through a pad of silica, the oxidation and workup were performed as described in the general procedure. The crude product was purified on silica gel chromatography (2.5:1 → 2:1 CH_2Cl_2/acetone) to afford 262 mg (contaminated by ~2% pinacol) of **5.4d** (~56%) as a pale yellow solid; mp 230-232 °C. R_f~0.53 (2:1 CH_2Cl_2/acetone). ^1H NMR (300 MHz, acetone-d_6): δ 9.21 (brs, 1 H), 8.66 (s, 1 H), 7.66 (t, J = 1.7 Hz, 1 H), 7.62 (t, J = 2.2 Hz, 1 H), 7.15 (dd, J = 1.5, 2.2 Hz, 1 H), 3.83 (s, 3 H), 2.07 (s, 3 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 169.1, 167.0, 158.6, 141.8, 132.4, 112.1, 111.6, 111.3, 52.3, 24.3; IR (neat): 3343, 3300-2900 (br), 1713, 1669, 1655, 1605, 1568, 1433, 1329, 1252, 874, 766 cm^{-1}; LRMS (EI): *m/e* 209 (M^+), 178, 167, 136, 109, 68, 43. Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found C, 57.11; H, 5.54; N, 6.38.



5.4e

***N*-(3-Hydroxy-5-methylphenyl)acetamide (5.4e)**: General procedure E (page 152) was applied to 342 mg 3-bromotoluene (2 mmol). The borylation step was carried out neat with 510 mg HBpin (4 mmol, 2 equiv), 16.6 mg (Ind)Ir(cod) (0.04 mmol, 2 mol%) and 6.0 mg dmpe (0.04 mmol, 2 mol%) at 150 °C for 12 h. The crude borylation mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), 134 mg acetamide (2.27 mmol, 1.14 equiv), and 900 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv) in 6 mL DME at 120 °C for 3.5 h, resulting in a yellow suspension. After filtration through a pad of silica, the oxidation and

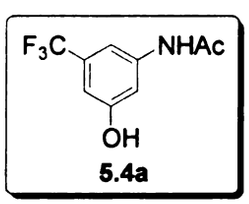
workup were performed as described in the general procedure but without the $NaIO_4$ workup. The crude product was purified on silica gel chromatography (1.25:1 → 0.75:1 CH_2Cl_2/EtOAc). Two fractions were isolated. The first fraction (69 mg) at R_f~0.5 (2:1 CH_2Cl_2/EtOAc) was an inseparable ~2:1 mixture of 3-methylacetanilide (protodeborylation) and acetanilide (phenyl transfer from phosphine ligand). The second fraction (292 mg) at R_f~0.23 (2:1 CH_2Cl_2/EtOAc) contained desired **5.4e** and substantial amount of pinacol (molar ratio of **5.4e** to pinacol ~1:1.5). Pinacol was removed by stirring the crude material in 2 mL CCl_4 for ~3 h and then decanting off the liquid (repeat if needed). The remaining orange solid was dried under vacuum to afford 150 mg of **5.4e** (46%); mp 135.5-136.5 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ 8.96 (brs, 1 H), 8.19 (s, 1 H), 7.16 (s, 1 H), 6.81 (s, 1 H), 6.35 (s, 1 H), 2.18 (s, 3 H), 2.02 (s, 3 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 168.7, 158.5, 141.3, 139.9, 111.7, 111.6, 104.4, 24.3, 21.5; IR (neat): 3306, 3400-3000 (br), 1665, 1626, 1605, 1559, 1426, 1373, 1281, 1156, 837, 687 cm^{-1}; LRMS (EI): *m/e* 165 (M^+), 123, 43. HRMS (EI): *m/e* calcd for $[C_9H_{11}NO_2]^+$ 165.0790, found 165.1787.



5.4f

***N*-(3-Hydroxy-5-methoxyphenyl)acetamide (5.4f)**: General procedure E (page 152) was applied to 375 mg 3-bromoanisole (2 mmol). The borylation step was carried out neat with 510 mg HBpin (4 mmol, 2 equiv), 16.6 mg (Ind)Ir(cod) (0.04 mmol, 2 mol%) and 6.0 mg dmpe (0.04 mmol, 2 mol%) at 150 °C for 10 h. The crude borylation mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg

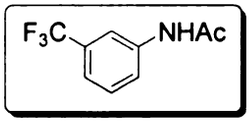
xantphos (0.06 mmol, 3 mol%), 136 mg acetamide (2.3 mmol, 1.15 equiv), and 900 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv) in 6 mL DME at 120 °C for 4 h, resulting in a yellow suspension. After filtration through a pad of silica, the oxidation and workup were performed as described in the general procedure but without the $NaIO_4$ workup. The crude product was purified on silica gel chromatography (1:1 → 0.7:1 CH_2Cl_2/EtOAc). Two fractions were isolated. The first fraction (62 mg) at R_f~0.59 (1:1 CH_2Cl_2/EtOAc) was an inseparable ~1:1 mixture of 3-methoxyacetanilide (protodeborylation) and acetanilide (phenyl transfer from phosphine ligand). The second fraction (274 mg) at R_f~0.37 (1:1 CH_2Cl_2/EtOAc) contained desired **5.4f** and substantial amount of pinacol (molar ratio of **5.4f** to pinacol ~1:0.4, corresponding to ~36% **5.4f**). Pinacol was removed by recrystallization from hexanes/acetone. Drying over high vacuum afforded pure **5.4f** as a white solid, mp 139.5-143 °C (dec). ^{1}H NMR (300 MHz, acetone-d_6): δ 9.08 (brs, 1 H), 8.44 (s, 1 H), 6.93 (t, J = 1.8 Hz, 1 H), 6.72 (t, J = 1.9 Hz, 1 H), 6.12 (t, J = 2.2 Hz, 1 H), 3.68 (s, 3 H), 2.05 (s, 3 H); ^{13}C NMR (75 MHz, acetone-d_6): δ 169.2, 161.9, 159.5, 141.9, 99.8, 97.25, 97.22, 55.3, 24.3; IR (neat): 3316, 3400-3000 (br), 1669, 1611,1559, 1505, 1428, 1281, 1196, 1154, 837, 683 cm^{-1}; LRMS (EI): *m/e* 181 (M^+), 139, 110, 43. HRMS (EI): *m/e* calcd for $[C_9H_{11}NO_3]^+$ 181.0739, found 181.0730.



5.4a

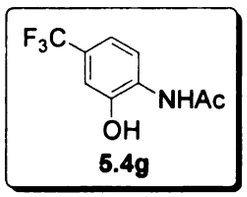
***N*-(3-Hydroxy-5-trifluoromethylphenyl)acetamide (5.4a)** (*from chloroarene*): General procedure E (page 152) was applied to 360 mg 3-chlorobenzotrifluoride (2 mmol). The borylation step was carried out with 400 mg HBpin (3.1 mmol, 1.55 equiv), 16.6

mg (Ind)Ir(cod) (0.04 mmol, 2 mol%) and 6.0 mg dmpe (0.04 mmol, 2 mol%) in 2 mL *n*-hexane at 150 °C for 4 h. After removal of hexane, the crude borylation mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), 132 mg acetamide (2.2 mmol, 1.1 equiv), and 900 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv) in 6 mL THF at 100 °C for 27 h, resulting in a yellow suspension. After filtration through a pad of silica, the oxidation and workup were performed as described in the general procedure. The crude product was purified on silica gel chromatography (2:1 CH_2Cl_2/EtOAc) to afford first a fraction of 172 mg (42%) protodeborylation product at R_f~0.63, followed by a trace amount of the presumed Suzuki byproduct, and then a fraction of 175 mg of **5.4a** (40%) at R_f~0.38.



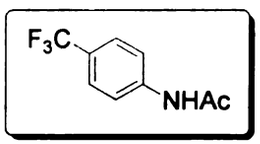
Protodeboylation product: pale yellow solid, mp 100-102 °C (commercial sample 103-104 °C), R_f~0.63 (2:1 CH_2Cl_2/EtOAc). ^{1}H NMR (300 MHz, acetone-d_6): δ 9.43 (brs, 1 H), 8.15 (s, 1 H), 7.78 (d, J = 7.7 Hz, 1 H), 7.50 (t, J = 8.0 Hz, 1 H), 7.36 (d, J = 7.7 Hz, 1 H), 2.11 (s, 3 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 169.5, 141.2, 131.2 (q, apparent d, J = 32 Hz), 130.5, 125.2 (q, apparent d, J = 272 Hz), 123.1, 120.2 (q, apparent d, J = 3.6 Hz), 116.2 (q, apparent d, J = 4.1 Hz), 24.2; LRMS (EI): *m/e* 203 (M^+), 161, 43. Anal. Calcd for $C_9H_8F_3NO$: C, 53.21; H, 3.97; N, 6.89. Found C, 53.34; H, 3.89; N, 6.69.

***N*-(2-Hydroxy-4-trifluoromethylphenyl)acetamide (5.4g)**: General procedure E (page 152) was applied to 722 mg 4-chlorobenzotrifluoride (4 mmol,

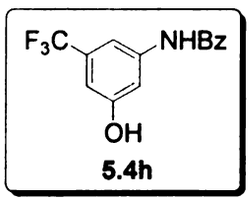


5.4g

2 equiv). The borylation step was carried out with 256 mg HBpin (2 mmol), 16.6 mg (Ind)Ir(cod) (0.04 mmol, 2 mol%) and 6.0 mg dmpe (0.04 mmol, 2 mol%) in 2 mL *n*-hexane at 150 °C for 4 h. After removal of hexane, the crude borylation mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), 132 mg acetamide (2.2 mmol, 1.1 equiv), and 900 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv) in 6 mL DME at 110 °C for 12 h, resulting in a yellow suspension. After filtration through a pad of silica, the oxidation and workup were performed as described in the general procedure. The crude product was purified on silica gel chromatography (2:1 CH_2Cl_2/EtOAc), which afforded 184 mg protodeborylation product (45%). No **5.4g** was detected.



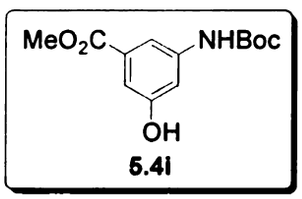
Protodeboylation product: pale solid, mp 148.5-150 °C (commercial sample 151-152 °C), R_f~0.54 (2:1 CH_2Cl_2/EtOAc). ^{1}H NMR (300 MHz, acetone-d_6): δ 9.47 (brs, 1 H), 7.84 (apparent d, J = 8.5 Hz, 2 H), 7.61 (apparent d, J = 8.5 Hz, 2 H), 2.11 (s, 3 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 169.5, 143.9, 126.7 (q, J = 4.0 Hz), 125.4 (q, apparent d, J = 271 Hz), 125.0 (q, J =33 Hz), 119.7, 24.3; LRMS (EI): *m/e* 203 (M^+), 161, 43. Anal. Calcd for $C_9H_8F_3NO$: C, 53.21; H, 3.97; N, 6.89. Found C, 53.09; H, 3.76; N, 6.78.



5.4h

***N*-(3-Hydroxy-5-trifluoromethylphenyl)benzamide (5.4h)**: General procedure E (page 152) was applied to 450 mg 3-bromobenzotrifluoride (2 mmol). The borylation step was carried out neat with 440 mg HBpin (3.44 mmol, 1.75 equiv), 16.6 mg

(Ind)Ir(cod) (0.04 mmol, 2 mol%) and 6.0 mg dmpe (0.04 mmol, 2 mol%) at 150 °C for 4 h. The crude borylation mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), 281 mg benzamide (2.32 mmol, 1.16 equiv), and 900 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv) in 6 mL THF at 80 °C for 4 h, resulting in a yellow suspension. After filtration through a pad of silica, the oxidation and workup were performed as described in the general procedure. The crude product was purified on silica gel chromatography (10:1 CH_2Cl_2/EtOAc) to afford 382 mg of **5.4h** (80%) as a pale yellow solid; mp 154-156 °C. R_f~0.36 (12:1 CH_2Cl_2/EtOAc). ^{1}H NMR (300 MHz, acetone-d_6): δ 9.69 (brs, 1 H), 9.02 (s, 1 H), 7.97-8.01 (m, 2 H), 7.77 (s, 1 H), 7.70 (s, 1 H), 7.48-7.62 (m, 3 H), 6.88 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6): δ 166.7, 159.1, 142.3, 135.8, 132.6, 132.2 (q, J = 32 Hz), 129.3, 128.4, 125.1 (q, J = 271 Hz), 111.1, 108.7 (q, J = 4.6 Hz), 108.0 (q, J = 3.4 Hz); IR (neat): 3310, 3400-2800 (br), 1655, 1615, 1557, 1451, 1439, 1354, 1254, 1175, 1127, 696 cm^{-1}; LRMS (EI): *m/e* 281 (M^+), 105, 77. Anal. Calcd for $C_{14}H_{10}F_3NO_2$: C, 59.79; H, 3.58; N, 4.98. Found C, 59.70; H, 3.81; N, 4.85.

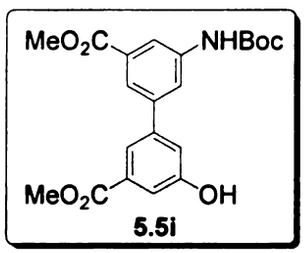


5.4i

Methyl 3-*tert*-butoxycarbonylamino-5-hydroxy-benzoate (5.4i): General procedure E (page 152) was applied to 430 mg methyl 3-bromobenzoate (2 mmol). The borylation step was carried out with 510 mg HBpin (4 mmol, 2 equiv), 20.0 mg $[Ir(OMe)(cod)]_2$ (0.03 mmol, 1.5 mol%) and 16.0 mg d^{t}bpy (0.06 mmol, 3 mol%) in 2 mL *n*-hexane at room temperature for 18 h, during which time the flask was open to a nitrogen manifold. After evaporation of hexane, the crude borylation

mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), 260 mg *tert*-butylcarbamate (2.22 mmol, 1.11 equiv), and 900 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv) in 6 mL THF at 100 °C for 2.5 h, resulting in a yellow suspension. After filtration through a pad of silica, the oxidation and workup were performed as described in the general procedure. The crude product was first passed through a silica gel column (8:1 → 4.5:1 CH_2Cl_2/EtOAc), and then purified by a second round of chromatography (1.6:1 → 1.2:1 hexanes/EtOAc). The first fraction at R_f~0.33 (2:1 hexanes/EtOAc) contained 246 mg of **5.4i** (46%), and the second fraction at R_f~0.23 (2:1 hexanes/EtOAc) contained 76 mg of impure Suzuki product **5.5i** (~19%).

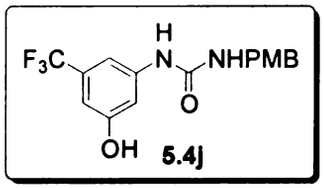
Desired product **5.4i**: White solid; mp 149-150.5 °C (dec). ^{1}H NMR (300 MHz, acetone-d_6): δ 8.61 (s, 1 H), 8.51 (brs, 1 H), 7.72 (t, J = 1.6 Hz, 1 H), 7.39 (t, J = 2.2 Hz, 1 H), 7.12 (dd, J = 1.6, 2.2 Hz, 1 H), 3.83 (s, 3 H), 1.48 (s, 9 H); ^{13}C NMR (75 MHz, acetone-d_6): δ 167.1, 158.6, 153.6, 142.0, 132.5, 111.4, 110.9, 110.4, 80.2, 52.2, 28.4; IR (neat): 3349 (br), 2982, 1700 (with a shoulder 1726), 1605, 1547, 1435, 1368, 1329, 1248, 1159, 872, 772 cm^{-1}; LRMS (EI): *m/e* 267 (M^+), 211, 167, 136, 109, 57. HRMS (EI): *m/e* calcd for $[C_{13}H_{17}NO_5]^+$ 267.1107, found 267.1100.



5.5i

Suzuki product 5.5i: White solid (recrystallized from acetone/hexanes) mp 179-181 °C (dec). ^{1}H NMR (300 MHz, acetone-d_6): δ 8.92 (s, 1 H), 8.75 (brs, 1 H), 8.30 (m,

1 H), 8.12 (t, J = 1.8 Hz, 1 H), 7.89 (t, J = 1.65 Hz, 1 H), 7.78 (t, J = 1.5 Hz, 1 H), 7.51 (dd, J = 1,4, 2.5 Hz, 1 H), 7.38 (dd, J = 1.8, 2.3 Hz, 1 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 1.51 (s, 9 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 166.95, 166.90, 158.9, 153.7, 142.6, 141.7, 141.6, 133.2, 132.4, 122.2, 121.5, 119.8, 119.05, 119.02, 116.3, 80.6, 52.49, 52.46, 28.4; IR (neat): 3353 (br), 2980, 1701 (with a shoulder 1725), 1597, 1547, 1439, 1367, 1294, 1233, 1159, 1005, 872, 770 cm^{-1}; LRMS (EI): *m/e* 401 (M^+), 345, 327, 301, 296, 270, 120, 105, 77, 59, 57. HRMS (EI): *m/e* calcd for $[C_{21}H_{23}NO_7]^+$ 401.1475, found 401.1473.

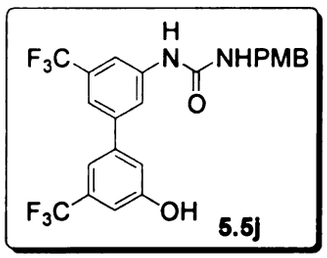


5.4j

1-(3-Hydroxy-5-trifluoromethylphenyl)-3-(4-methoxybenzyl)-urea (5.4j): General procedure E (page 152) was applied to 450 mg 3-bromobenzotrifluoride (2 mmol). The borylation step was carried out neat with 436 mg HBpin (3.44 mmol, 1.75 equiv), 17.5 mg (Ind)Ir(cod) (0.042 mmol, 2.1 mol%) and 6.4 mg dmpe (0.042 mmol, 2.1 mol%) at 150 °C for 3 h. The crude borylation mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), 398 mg 4-methoxybenzylurea (2.24 mmol, 1.12 equiv), and 900 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv) in 6 mL THF at 100 °C for 2 h, resulting in a yellow suspension. After filtration through a pad of silica, the oxidation and workup were performed as described in the general procedure, but without $NaIO_4$ workup. The crude product was purified on silica gel chromatography (6.5:1 → 1.5:1 CH_2Cl_2/EtOAc). The first fraction at R_f~0.69 (4:1 CH_2Cl_2/EtOAc) contained 115 mg of Suzuki product **5.5j** (24%) and the second fraction at R_f~0.35 (4:1 CH_2Cl_2/EtOAc)

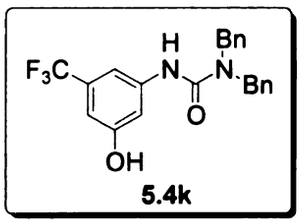
contained 130 mg of desired product **5.4j** (19%).

Desired product 5.4j: White solid; mp 194-196.5 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ 8.80 (s, 1 H), 8.18 (brs, 1 H), 7.37 (s, 1 H), 7.31 (s, 1 H), 7.24-7.27 (m, 2 H), 6.85-6.89 (m, 2 H), 6.67 (s, 1 H), 6.19 (br, 1 H), 4.32 (d, *J* = 6.0 Hz, 2 H), 3.76 (s, 3 H); ^{13}C NMR (75 MHz, acetone-d_6): δ 159.7, 159.1, 155.8, 143.6, 132.9, 132.1 (q, *J* = 32 Hz), 129.5, 125.2 (q, *J* = 271 Hz), 114.5, 108.8, 106.5 (q, *J* = 4.0 Hz), 105.7 (q, *J* = 4.0 Hz), 55.4, 43.6; IR (neat): 3341 (br), 1657, 1613, 1584, 1514, 1441, 1375, 1250, 1175, 1125, 696 cm^{-1}; LRMS (EI): *m/e* 340 (M^+), 203, 177, 136, 121, 78. Anal. Calcd for $C_{16}H_{15}F_3N_2O_3$: C, 56.47; H, 4.44; N, 8.23. Found C, 56.61; H, 4.40; N, 8.20.



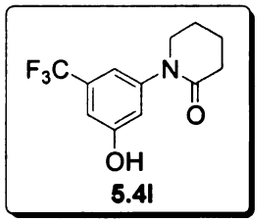
5.5j

Suzuki product 5.5j: White solid (recrystallized from acetone/hexanes) mp 185 °C (dec). ^{1}H NMR (300 MHz, acetone-d_6): δ 9.21 (s, 1 H), 8.42 (brs, 1 H), 8.01 (s, 2 H), 7.52 (s, 1 H), 7.45 (s, 1 H), 7.38 (s, 1 H), 7.26-7.30 (m, 2 H), 7.16 (s, 1 H), 6.85-6.90 (m, 2 H), 6.37 (br, 1 H), 4.36 (d, *J* = 6.0 Hz, 2 H), 3.76 (s, 3 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 159.8, 159.3, 155.9, 143.2, 143.1, 141.8, 132.84, 132.80 (q, *J* = 28 Hz), 132.0 (q, *J* = 32 Hz), 129.5, 125.2 (q apparent d, *J* = 272 Hz), 125.0 (q apparent d, *J* = 272 Hz), 120.6 (apparent d, *J* = 1.2 Hz), 118.5, 117.0 (q, *J* = 3.6 Hz), 115.5 (q, *J* = 4.0 Hz), 114.8 (q, *J* = 4.0 Hz), 114.5, 112.4 (q, *J* = 4.0 Hz), 55.4, 43.7; IR (neat): 3341 (br), 1655, 1607, 1564, 1514, 1387, 1335, 1264, 1244, 1171, 1125, 864, 702 cm^{-1}; LRMS (EI): *m/e* 484 (M^+), 347, 328, 321, 250, 163, 136, 121. Anal. Calcd for $C_{23}H_{18}F_6N_2O_3$: C, 57.03; H, 3.75; N, 5.78. Found C, 56.96; H, 4.11; N, 5.41.



5.4k

1,1-Dibenzyl-3-(3-hydroxy-5-trifluoromethylphenyl) urea (5.4k): General procedure E (page 152) was applied to 450 mg 3-bromobenzotrifluoride (2 mmol). The borylation step was carried out neat with 440 mg HBpin (3.44 mmol, 1.75 equiv), 17.5 mg (Ind)Ir(cod) (0.042 mmol, 2.1 mol%) and 6.3 mg dmpe (0.042 mmol, 2.1 mol%) at 150 °C for 4 h. The crude borylation mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), 529 mg *N,N*-(dibenzyl)urea (2.2 mmol, 1.1 equiv), and 900 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv) in 6 mL THF at 100 °C for 1.5 h, resulting in a yellow suspension. After filtration through a pad of silica, the oxidation and workup were performed as described in the general procedure. The crude product was purified on silica gel chromatography (15:1 → 7.5:1 CH_2Cl_2/EtOAc) to afford 420 mg of **5.4d** (53%) as an orange solid; mp 146.5-148.5 °C. R_f~0.38 (15:1 CH_2Cl_2/EtOAc). ^{1}H NMR (300 MHz, acetone-d_6): δ 8.81 (s, 1 H), 8.16 (s, 1 H), 7.45 (apparent t, J = 1.9 Hz, 1 H), 7.41 (s, 1 H), 7.24-7.39 (m, 10 H), 6.72 (s, 1 H), 4.63 (s, 4 H); ^{13}C NMR (75 MHz, acetone-d_6): δ 158.9, 156.2, 143.5, 138.8, 131.8 (q, apparent d, J = 32 Hz), 129.4, 128.2, 128.1, 125.2 (q, apparent d, J = 271 Hz), 110.1, 108.1 (q, apparent d, J = 4.6 Hz), 106.3 (q, apparent d, J = 4.6 Hz), 50.1; IR (neat): 3283, 3400-2900 (br), 1647, 1612, 1547, 1453, 1362, 1240, 1169, 1125, 696 cm^{-1}; LRMS (EI): *m/e* 400 (M^+), 309, 132, 106, 91, 77; HRMS (EI): *m/e* calcd for $[C_{22}H_{19}F_3N_2O_2]^+$ 400.1399, found 400.1403.

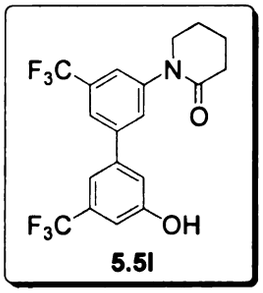


5.4l

1-(3-Hydroxy-5-trifluoromethylphenyl)piperidin-2-one (5.4l): General procedure E (page 152) was applied to 450 mg 3-bromobenzotrifluoride (2 mmol). The borylation step was carried out neat with 440 mg HBpin (3.44 mmol, 1.75 equiv), 17.5 mg (Ind)Ir(cod) (0.042 mmol, 2.1 mol%) and 6.3 mg dmpe (0.042 mmol, 2.1 mol%) at 150 °C for 4 h. The crude borylation mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), 220 mg δ-valerolactam (2.2 mmol, 1.1 equiv), and 900 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv) in 6 mL THF at 100 °C for 2 h, resulting in a yellow suspension. After filtration through a pad of silica, the oxidation and workup were performed as described in the general procedure. The crude product was purified on silica gel chromatography (1.75:1 → 0.75:1 CH_2Cl_2/EtOAc) to afford two fractions. The first fraction at R_f~0.52 (2:1 CH_2Cl_2/EtOAc) contained 94 mg of Suzuki product **5.5l** (23%), and the second fraction at R_f~0.22 (2:1 CH_2Cl_2/EtOAc) contained 247 mg of desired product **5.4l** (48%).

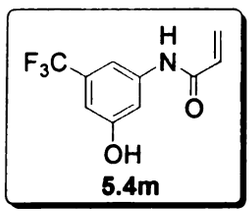
Desired product 5.4l: Pale gray solid, mp 167.5-169.5 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ 9.14 (s, 1 H), 7.13 (brs, 1 H), 7.04 (t, J = 1.8 Hz, 1 H), 6.94 (brs, 1 H), 3.71 (t, J = 6.0 Hz, 2 H), 2.44 (t, J = 6.3 Hz, 2 H), 1.86-2.00 (m, 4 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 170.5, 159.1, 146.6, 132.0 (q, J = 32 Hz), 124.9 (q, J = 271 Hz), 118.1 (q, overlapped), 114.6 (q, J = 4 Hz), 110.6 (q, J = 3.8 Hz), 51.8, 33.5, 24.0, 21.8; IR (neat): 3171, 2955, 3400-2800 (br), 1632, 1605, 1458, 1366, 1258, 1167, 1125, 702 cm^{-1}; LRMS (EI): *m/e* 259 (M^+), 202, 190, 55. Anal. Calcd

for $C_{12}H_{12}F_3NO_3$: C, 55.60; H, 4.67; N, 5.40. Found C, 55.74; H, 4.70; N, 5.34.



5.5l

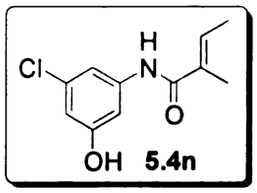
Suzuki product 5.5l: White solid (recrystallized from hexanes/acetone) mp > 205 °C (dec). ^{1}H NMR (300 MHz, acetone-d_6): δ 9.26 (s, 1 H), 7.94 (s, 1 H), 7.82 (s, 1 H), 7.74 (s, 1 H), 7.49 (s, 1 H), 7.38 (t, J = 1.8 Hz, 1 H), 7.15 (s, 1H), 3.86 (t, J = 5.9 Hz, 2 H), 2.50 (t, J = 6.6 Hz, 2 H), 1.92-2.03 (m, 4 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 170.4, 159.3, 146.2, 142.5, 142.0, 132.8 (q, J = 32 Hz), 131.9 (q, J = 32 Hz), 129.4, 125.0 (q, J = 272 Hz), 124.95 (q, J = 272 Hz), 123.5 (q, J = 3.9 Hz), 121.8 (q, J = 3.9 Hz), 118.7, 115.7 (q, J = 3.9 Hz), 112.5 (q, J = 3.7 Hz), 51.7, 33.6, 24.1, 22.0; IR (neat): 3189, 2955, 3400-2900 (br), 1632, 1601, 1455, 1385, 1331, 1264, 1167, 1125, 866, 704 cm^{-1}; LRMS (EI): *m/e* 403 (M^+), 374, 334, 236, 188, 82, 70, 55. Anal. Calcd for $C_{19}H_{15}F_6NO_2$: C, 56.58; H, 3.75; N, 3.47. Found C, 56.61; H, 4.04; N, 3.61.



5.4m

***N*-(3-Hydroxy-5-trifluoromethylphenyl)acrylamide (5.4 m)**: General procedure E (page 152) was applied to 450 mg 3-bromobenzotrifluoride (2 mmol). The borylation step was carried out neat with 440 mg HBpin (3.44 mmol, 1.75 equiv), 17.5 mg (Ind)Ir(cod) (0.042 mmol, 2.1 mol%) and 6.3 mg dmpe (0.042 mmol, 2.1 mol%) at 150 °C for 4 h. The crude borylation mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), 258 mg acrylic amide (2.23 mmol, 1.11 equiv), and 900 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv) in 6 mL THF at 80 °C for 3.5 h, resulting in a yellow suspension. After filtration through a pad of silica, the

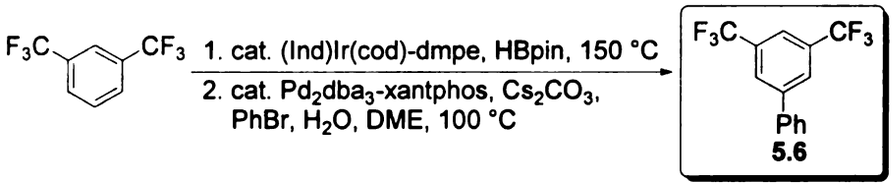
oxidation and workup were performed as described in the general procedure. The crude product was purified on silica gel chromatography (2:1 CH_2Cl_2/EtOAc) to afford 171 mg of **5.4m** (37%) as a pale-white solid; mp 118-120 °C. R_f~0.60 (2.5:1 CH_2Cl_2/EtOAc). ^{1}H NMR (300 MHz, acetone-d_6): δ 9.50 (brs, 1 H), 9.01 (s, 1 H), 7.57 (s, 2 H), 6.84 (s, 1 H), 6.31-6.48 (m, 2 H), 5.74 (dd, J = 3.3, 9.1 Hz, 1 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 164.4, 159.2, 142.1, 132.4, 132.2 (q, J = 32 Hz), 127.9, 125.0 (q, J = 272 Hz), 110.4, 108.0 (q, J = 4.4 Hz), 107.9 (q, J = 3.5 Hz); IR (neat): 3293, 3400-2900 (br), 1671, 1615, 1561, 1445, 1370, 1354, 1223, 1173, 1127, 860, 696 cm^{-1}; LRMS (EI): *m/e* 231 (M^+), 177, 55. Anal. Calcd for $C_{10}H_8F_3NO_2$: C, 51.96; H, 3.49; N, 6.06. Found C, 51.58; H, 3.54; N, 5.70.



5.4n

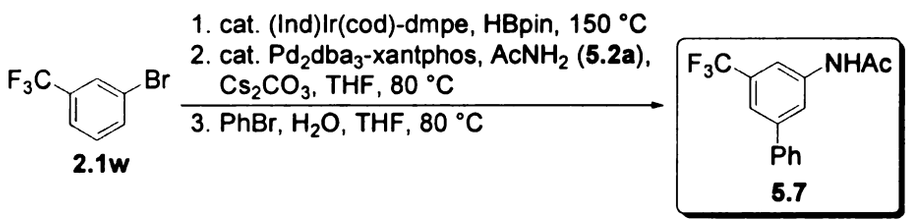
(*E*)-2-Methyl-but-2-enoic acid (3-chloro-5-hydroxy phenyl) amide (5.4n): General procedure E (page 152) was applied to 385 mg 3-bromochlorobenzene (2 mmol). The borylation step was carried out with 430 mg HBpin (3.4 mmol, 1.7 equiv), 16.6 mg (Ind)Ir(cod) (0.04 mmol, 2 mol%) and 6.0 mg dmpe (0.04 mmol, 2 mol%) in 0.5 mL *n*-hexane at 150 °C for 3.5 h. After removal of hexane, the crude borylation mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), 216 mg tiglic amide (2.18 mmol, 1.1 equiv), and 900 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv) in 6 mL THF at 100 °C for 1.5 h (or at 80 °C for 8 h), resulting in a yellow suspension. After filtration through a pad of silica, the oxidation and workup were performed as described in the general procedure. The crude product was purified on silica gel chromatography (7:1 → 3:1

CH_2Cl_2/EtOAc) to afford 298 mg of **5.4m** (65%) as a pale yellow solid; mp 131.5-133.5 °C. R_f~0.41 (7:1 CH_2Cl_2/EtOAc). ^{1}H NMR (300 MHz, acetone-d_6): δ 8.97 (brs, 1 H), 8.73 (s, 1 H), 7.32 (t, J = 1.8 Hz, 1 H), 7.30 (t, J = 2.1 Hz, 1 H), 6.56 (t, J = 2.1 Hz, 1 H), 6.47 (qq, J = 1.4, 6.9 Hz, 1 H), 1.86 (apparent t, J = 1.4 Hz, 3 H), 1.75 (dq, J = 6.9, 1.1 Hz, 3 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 168.6, 159.3, 142.6, 134.8, 133.9, 131.4, 111.7, 111.2, 106.1, 14.0, 12.5; IR (neat): 3299, 3500-2900 (br), 1663, 1599, 1536, 1429, 1289, 1179, 839, 675 cm^{-1}; LRMS (EI): *m/e* 225 (M^+), 143, 136, 105, 83, 77, 55. Anal. Calcd for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.36; N, 6.21. Found C, 58.44; H, 5.38; N, 6.04.



3,5-Bis(trifluoromethyl)biphenyl (5.6): Following general procedure E (page 152), 215 mg 1,3-bis(trifluoromethyl)benzene (1 mmol) was borylated with 217 mg HBpin (1.7 mmol, 1.7 equiv), 8.4 mg (Ind)Ir(cod) (0.02 mmol, 2 mol%) and 3.0 mg dmpe (0.02 mmol, 2 mol%) in 0.5 mL *n*-hexane at 150 °C for 3.5 h. After removal of hexane, the crude borylation mixture was pumped down under high vacuum. The flask was returned to the glove box and charged with 9.2 mg Pd_2dba_3 (0.01 mmol, 1 mol%), 17.4 mg xantphos (0.03 mmol, 3 mol%), 234 mg phenyl bromide (1.5 mmol, 1.5 equiv), 450 mg Cs_2CO_3 (2.76 mmol, 1.4 equiv), and 3 mL DME. After being taken out of the glove box, the reaction mixture was charged with 27 μL water (1.5 mmol, 1.5 equiv) and heated at 100 °C for 2 h

(control experiment showed a much slower reaction in the absence of water). After concentration, the crude product was purified on silica gel chromatography (hexanes) to afford 217 mg of **5.6** (75%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (s, 2 H), 7.84 (s, 1 H), 7.58-7.61 (m, 2 H), 7.42-7.52 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.4, 138.3, 132.1 (q, J = 33 Hz), 129.3, 128.9, 127.24, 127.21 (m), 123.4 (q, J = 273 Hz), 120.9 (sept, apparent quint, J = 3.7 Hz); IR (neat): 3071, 1466, 1383, 1280, 1177, 1132, 1063, 897, 764, 706, 683 cm^{-1}; LRMS *m/e* 290 (M^+), 220, 200, 151, 134, 56, 43. Anal. Calcd for $C_{14}H_8F_6$: C, 57.94; H, 2.78. Found C, 58.12; H, 2.71.



***N*-(5-Trifluoromethyl-biphenyl-3-yl)-acetamide (5.7)**: General procedure E (page 152) was applied to 450 mg 3-bromobenzotrifluoride (2 mmol). The borylation step was carried out neat with 432 mg HBpin (3.4 mmol, 1.7 equiv), 17.6 mg (Ind)Ir(cod) (0.042 mmol, 2.1 mol%) and 6.3 mg dmpe (0.042 mmol, 2.1 mol%) at 150 °C for 3 h. The crude borylation mixture was pumped down under high vacuum. The amidation step was then carried out with 18.4 mg Pd_2dba_3 (0.02 mmol, 1 mol%), 34.8 mg xantphos (0.06 mmol, 3 mol%), 130 mg acetamide (2.2 mmol, 1.1 equiv), and 1.6 g Cs_2CO_3 (5 mmol, 2.5 equiv) in 6 mL THF at 80 °C for 3.75 h, resulting in a yellow suspension. To this suspension was added 470 mg phenyl bromide (3 mmol, 1.5 equiv) and 40 μL water (2.2 mmol, 1.1 equiv)

and the mixture was heated at 80 °C for 2 h, turning into a pale gray suspension. The resulting mixture was concentrated and purified by chromatography (1.4:1 → 1:1 hexanes/EtOAc). The first fraction (~46 mg) at R_f~0.51 (1.5:1 hexanes/EtOAc) contained what was assigned as a *m*-terphenyl structure: *N*-(5,5'-bis-trifluoromethyl-[1,1';3',1"]terphenyl-3-yl)-acetamide. The second fraction (260 mg) at R_f~0.41 (1.5:1 hexanes/EtOAc) contained the desired product **5.7** (47%). The third fraction (61 mg) at R_f~0.34 (1.5:1 hexanes/EtOAc) contained the deborylation product *N*-(3-trifluoromethylphenyl) acetamide.

Desired product 5.7: Yellow solid; mp 84.5-87 °C. ^{1}H NMR (500 MHz, acetone-d_6): δ 9.51 (br, 1 H), 8.12 (s, 2 H), 7.66-7.69 (m, 2 H), 7.61 (s, 1 H), 7.48-7.51 (m, 2 H), 7.40-7.43 (m, 1 H), 2.14 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5, 143.6, 141.8, 140.2, 131.9 (q, J = 32 Hz), 129.9, 129.1, 127.8, 125.2 (q, apparent d, J = 272 Hz), 121.5, 118.7 (q, J = 4.1 Hz), 115.1 (q, apparent d, J = 4.1 Hz), 24.3; IR (neat): 3287, 1673, 1617, 1566, 1466, 1451, 1364, 1282, 1167, 1125, 878, 764, 700 cm^{-1}; LRMS *m/e* 279 (M^+), 237, 43. HRMS (EI) *m/e* calcd for $[C_{15}H_{12}F_3NO]^+$ 279.0871, found 279.0868.

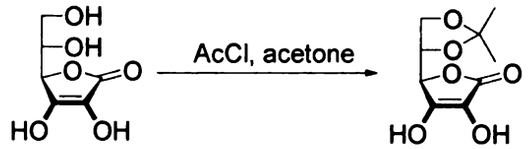
Chapter 8. Experimental Details and Compound Characterization Data for Attempted Total Synthesis of Autolytimycin

8.1 Materials and Methods

Unless otherwise noted, all commercial compounds were used as received. Solvents for the reactions were purified as indicated in Chapter 7, unless otherwise noted. All reactions, except those performed in aqueous conditions and/or in unpurified solvents, were performed in oven- or flame-dried glassware and monitored by TLC. Visualization was achieved by UV lamp or phosphomolybdic acid stain.

Optical rotation was measured with Perkin-Elmer 341 polarimeter. Other instrumental analysis was performed as indicated in Chapter 7 (page 137).

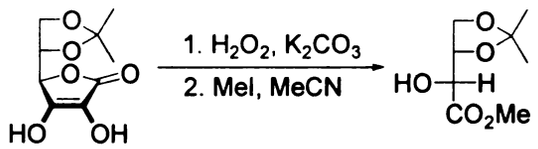
8.2 Experimental Details and Characterization Data for the Compounds Related to the Total Synthesis



6.6 **6.7**

To a stirred solution of 105 g vitamin C (0.6 mol) in 600 mL acetone (no purification or drying needed) was added 10 mL acetyl chloride (11 g, 0.14 mol, ~23 mol%). The reaction was sealed with a septum and stirred overnight. A precipitate formed and was collected by suction filtration and washed with cold

acetone to remove the yellow color. The combined mother liquor was concentrated to about 200 mL and a second crop of precipitate was collected and washed. The combined mother liquor was again concentrated to about 100 mL and a third crop of precipitate was collected and washed. The combined solid was dried over high vacuum to afford 110.5 g of crude **6.7** (~86%) as a white solid, mp (crude) 204 °C (dec) (lit[168] 217-222 °C, dec); $[\alpha]^{20}_{D}$ +16.3 (*c* 0.96, EtOH); ^{1}H NMR (500 MHz, acetone-d_6): δ ~9.6 (br, 1 H), ~7.6 (br, 1 H), 4.71 (d, J = 3.3 Hz, 1 H), 4.35 (dt, J = 3.3, 6.7 Hz, 1 H), 4.17 and 4.00 (d of ABq, ^{3}J = 6.8 Hz, J_{AB} = 8.5 Hz, 2 H), 1.29 (s, 3 H), 1.28 (s, 3 H), some impurities at 4.71 and 3.7; ^{13}C NMR (125 MHz, acetone-d_6): δ 171.1, 151.1, 120.0, 110.2, 75.4, 75.0, 66.0, 26.2, 25.8; LRMS (EI): *m/e* 216 (M^+), 201, 141, 101, 85, 73, 60, 44. This crude product was used directly in the next step without further purification.



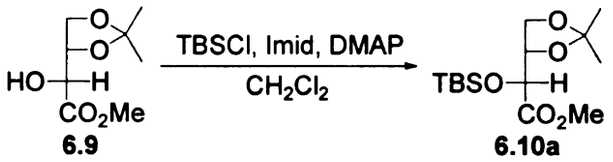
6.7 **6.9**

To a solution of 110 g of **6.7** (0.51 mol) in 750 mL water was added 138 g K_2CO_3 (1 mmol, 2 equiv) and the resultant solution was cooled by an ice-water bath. To this solution was added 200 mL cold (by ice bath) 30% H_2O_2 (~1.94 mol, ~4 equiv) slowly. Ice was also added so that the internal temperature did not exceed 30 °C. Upon complete addition, the ice-water bath was removed and the

reaction was stirred at room temperature in the open flask for about 15 h. Water was removed by rotary evaporation in a 60-65 °C water bath. The remaining water was removed by co-evaporation with EtOH and then drying under high vacuum. The residual solid was suspended in 500 mL EtOH at refluxing temperature to extract the organic salt. The insoluble inorganic salt was removed by careful filtration of the hot supernatant through cotton. This extraction was repeated 3 times, and the combined EtOH was evaporated.

This crude solid was then suspended in 600 mL acetonitrile (no purification or drying needed). To that suspension was added 45 mL MeI (103 g, 0.72 mol, 1.45 equiv, purified by passing through neutral alumina). With vigorous stirring, the whole mixture was heated to reflux for 1 day, during which time the reaction mixture became a slightly yellow-brown solution. After being cooled to room temperature, it was evaporated to ~ 200 mL and 300 mL CH_2Cl_2 was added to precipitate KI. The KI was filtered off and washed with CH_2Cl_2 and the combined filtrate was evaporated. Column chromatography (1:1 → 1:1.5 hexanes/EtOAc) afforded 87 g of **6.9** (90% over 2 steps) as a colorless oil; R_f~0.5 (1:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +20.0 (*c* 1.14, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.37 (dt, *J* = 1.8, 6.7 Hz, 1 H), 4.10 (d, *J* = 2.8 Hz, 1 H), 4.07 and 3.99 (d of ABq, ^3J = 6.7 Hz, J_{AB} = 8.4 Hz, 2 H), 3.80 (s, 3 H), ~2.9 (br, 1 H), 1.40 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 110.0, 76.2, 70.3, 65.6, 52.7, 26.1, 25.3;

LRMS (EI): *m/e* 175 ([M-Me]$^+$), 133, 115, 101, 43.

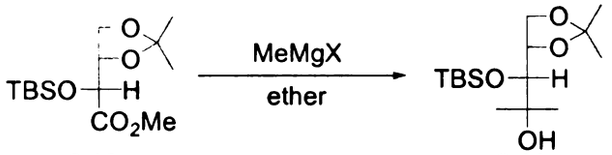


6.9 **6.10a**

Small scale: to a solution of 1.9 g of **6.9** (10 mmol) in 25 mL CH_2Cl_2 were added 122 mg DMAP (1 mmol, 10 mol%) and 0.88 g imidazole (13 mmol, 1.3 equiv). Upon stirring, 1.8 g TBSCl (12 mmol, 1.2 equiv) was added in one portion. The reaction was sealed with a septum and topped with a nitrogen balloon and stirred at room temperature overnight. Upon completion, the reaction mixture was poured into half saturated (by mixing saturated solution with equal volume of water) $NaHCO_3$, and extracted with CH_2Cl_2. After drying over $MgSO_4$ and evaporation, the crude product was purified by column chromatography (4:1 hexanes/ether) to yield 2.92 g of **6.10a** (96%) as colorless oil; R_f~0.41 (4:1 hexanes/ether); $[\alpha]^{20}_D$ +33.2 (*c* 1.26, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.29-4.33 (m, 1 H), 4.21 (d, J = 5.1 Hz, 1 H), 4.02 and 3.95 (d of ABq, ^3J = 6.6 and 6.1 Hz, J_{AB} = 8.5 Hz, 2 H), 3.73 (s, 3 H), 1.38 (s, 3 H), 1.32 (s, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 109.8, 77.1, 73.1, 65.5, 51.9, 26.2, 25.7, 25.3, 18.3, -5.0, -5.3; IR (neat): 2988, 2955, 2932, 2892, 2859, 1761, 1474, 1381, 1372, 1256, 1215, 1157, 1074, 839, 781 cm^{-1}; LRMS (EI): *m/e* 289 ([M-Me]$^+$), 247, 204, 189, 161, 101, 89, 73, 59, 43;

HRMS (CI, methane) *m/e* calcd for $[C_{14}H_{28}O_5Si+H]^+$ 305.1784, found 305.1785.

Large scale: to a solution of 32.5 g of **6.9** (0.17 mol) in 350 mL CH_2Cl_2 were added 2.1 g DMAP (17 mmol, 10 mol%) and 14.0 g imidazole (0.205 mol, 1.2 equiv). Upon stirring, 28.4 g TBSCl (0.19 mol, 1.1 equiv) was added in one portion. The reaction was sealed with a septum, topped with a nitrogen balloon, and stirred at room temperature overnight. Precipitate formed. Upon completion, the precipitate was filtered off and washed with CH_2Cl_2. The combined filtrate was washed with half saturated NH_4Cl and then half saturated NaCl, dried over $MgSO_4$ and evaporated. The resultant crude oil (55 g) was obtained and used directly in next reaction without further purification.



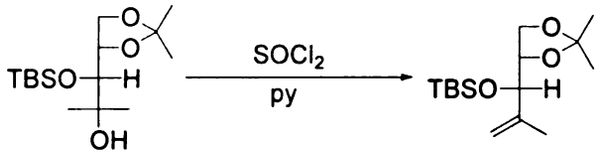
6.10a **6.11a**

Small scale: commercial MeMgCl solution (12.8 mL, 3 M in THF, 38.4 mmol, 4 equiv) was diluted with 35 mL anhydrous ether (some white precipitate was observed). To this Grignard solution was added a solution of 2.92 g of **6.10a** (9.6 mmol) in 35 mL ether via cannula. Upon complete addition, the mixture was refluxed for 1 h and then cooled to room temperature. It was then quenched with saturated NH_4Cl and poured into half saturated NH_4Cl and extracted with ether. The combined organics were dried over K_2CO_3, evaporated, and purified by

column chromatography (5:1 CH_2Cl_2/ether) to afford 1.81 g of **6.11a** (62%) as colorless oil; R_f~0.5 (5:1 CH_2Cl_2/ether); $[\alpha]^{20}_D$ -3.5 (*c* 1.06, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.02-4.07 (m, 1 H), 3.96 (dd, *J* = 6.1, 8.3 Hz, 1 H), 3.68 (t, *J* = 8.5 Hz, 1 H), 3.47 (d, *J* = 7.3 Hz, 1 H), 2.25 (s, 1 H), 1.39 (s, 3 H), 1.32 (s, 3 H), 1.18 (s, 3 H), 1.16 (s, 3 H), 0.90 (s, 9 H), 0.12 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 108.0, 80.0, 77.3, 72.4, 66.8, 27.0, 26.6, 26.2, 25.44, 25.42, 18.5, -3.6, -4.6; IR (neat): 3470, 2986, 2957, 2932, 2897, 2859, 1472, 1370, 1254, 1101, 1059, 860, 837, 775 cm^{-1}; LRMS (CI, methane): *m/e* 289 ($[M-Me]^+$), 247, 187, 171, 145, 131, 101; HRMS (CI, methane) *m/e* calcd for $[C_{15}H_{32}O_4Si+H]^+$ 305.2148, found 305.2142.

Large scale: commercial MeMgI solution (200 mL, 3 M in ether, 0.6 mol, 3.5 equiv) was placed in a round-bottom flask topped with a refluxing condenser and heated to 50 °C in an oil bath. In a separate round-bottom flask, 55 g of crude **6.10a** (0.17 mol) was dissolved in 250 mL ether. This ethereal solution was transferred into the Grignard solution over 30 min via cannula, after which the mixture was refluxed for another 30 min before being cooled to room temperature. TLC indicated full consumption of the starting material. While stirring, the reaction was carefully quenched with saturated NH_4Cl (CAUTION!) and significant precipitation occurred. The supernatant of this mixture was transferred into a separation funnel and washed with saturated NH_4Cl and water. The slurry was

diluted with ether and stirred over 200 mL saturated sodium potassium tartrate for a few hours until it was no longer milk-like. The mixture was filtered and the filtrate was extracted with ether. This ether extraction was combined with the previous ether supernatant, and dried over Na_2SO_4 and evaporated. After column chromatography, 46 g of **6.11a** was obtained (83% over 2 steps) as a slightly yellow oil.

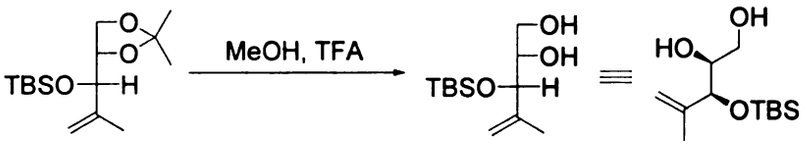


6.11a **6.12a**

Small scale: a solution of 1.8 g of **6.11a** (5.9 mmol) in 30 mL pyridine (no purification or drying needed) was cooled in an ice-water bath. To this solution was added 860 μL $SOCl_2$ (1.4 g, 11.8 mmol, 2 equiv) via syringe and the reaction mixture quickly turned yellow-orange. It was then warmed to room temperature and stirred for 1 h. Upon completion, it was quenched with half saturated Na_2CO_3 at 0 °C and diluted with ether. The layers were separated and the aqueous layer was extracted with ether. Combined organics were washed with water, followed by 5% $CuSO_4$ until the aqueous phase was no longer purple, and then again water. The organics were dried over K_2CO_3, evaporated, and purified by column chromatography (12:1 hexanes/ether or 1:1 hexanes/CH_2Cl_2) to yield 1.33 g of **6.12a** (79%) as a clear, slightly yellow oil; R_f~0.39 (1:1 hexanes/CH_2Cl_2);

$[\alpha]^{20}_D$ -2.1 (*c* 1.27, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.03 (m, 1 H), 4.93 (quint, *J* = 1.5 Hz, 1 H), 4.34 (d, *J* = 8.1 Hz, 1 H), 3.75-3.82 (m, 2 H), 3.67 (dd, *J* = 4.2, 11.2 Hz, 1 H), 1.76 (m, 3 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 0.88 (s, 9 H), 0.051 (s, 3 H), 0.046 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.1, 113.9, 108.9, 81.1, 80.0, 62.9, 27.08, 27.06, 25.9, 18.4, 17.4, -5.3, -5.5; IR (neat): 2988, 2955, 2932, 2859, 1653, 1474, 1464, 1379, 1370, 1254, 1146, 1086, 837, 777 cm^{-1}; LRMS (EI): *m/e* 271 ($[M-Me]^+$), 171, 141, 75; HRMS (CI, NH_3) *m/e* calcd for $[C_{15}H_{30}O_3Si+H]^+$ 287.2042, found 287.2045.

Large scale: a solution of 46 g of **6.11a** (0.15 mol) in 480 mL pyridine was cooled to 0 °C. To this solution was added 22 mL $SOCl_2$ (35.7 g, 0.3 mol, 2 equiv) via a pressure-equalized addition funnel over 25 min. The reaction quickly turned dark and cloudy with some precipitate formed. The ice bath was removed after complete addition and the reaction was stirred at room temperature for 1 h 20 min. Upon completion, it was cooled to 0 °C and quenched by slow addition of saturated Na_2CO_3 (CAUTION!) until gas evolution ceased. After extraction with ether, the organic layer was washed with saturated Na_2CO_3, water, followed by 5% $CuSO_4$ until the aqueous phase was no longer purple, and then half saturated NH_4Cl before being dried over K_2CO_3 and evaporated. Column chromatography afforded 33.3 g of **6.12a** (77%) as a slightly yellow oil.

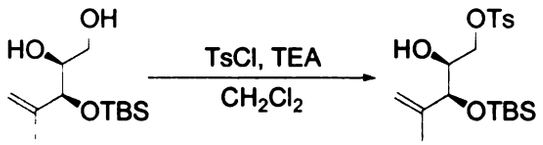


6.12a **6.13a**

To a solution of 1.43 g of **6.12a** (5 mmol) in 30 mL MeOH (no purification or drying needed) was added 8 mL TFA slowly. 20 min later, the reaction was quenched with saturated Na_2CO_3 and extracted six times with EtOAc. Combined organics were dried over Na_2SO_4 ($MgSO_4$ was avoided due to its partial solubility in the solvent) and evaporated. The crude material was purified by column chromatography (2:1 hexanes/EtOAc). Along with ~80 mg of recovered **6.12a** (~5%), 0.74 g of **6.13a** (60%) was isolated as a white solid; R_f~0.18 (3:1 hexanes/EtOAc); mp < 35 °C (it quickly melted when the vial was held in hand); $[\alpha]^{20}_D$ +19.8 (*c* 1.24, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.96 (m, 1 H), 4.91 (quint, *J* = 1.5 Hz, 1 H), 4.03 (d, *J* = 5.6 Hz, 1 H), 3.57-3.61 (m, 2 H), 3.47-3.51 (m, 1 H), 2.27 (br, 2 H), 1.70 (m, 3 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.6, 114.1, 77.1, 73.0, 63.3, 25.8, 18.2, 17.6, -4.6, -5.2; IR (neat): 3409, 2955, 2930, 2859, 1649, 1472, 1254, 1084, 837, 777 cm^{-1}; LRMS (CI, methane) : *m/e* 247 ($[M+H]^+$), 229, 213, 201, 185, 171, 159, 133, 115; HRMS (CI, methane) *m/e* calcd for $[C_{12}H_{26}O_3Si+H]^+$ 247.1729, found 247.1726.

This procedure can be performed up to 6 g scale. Beyond that scale the

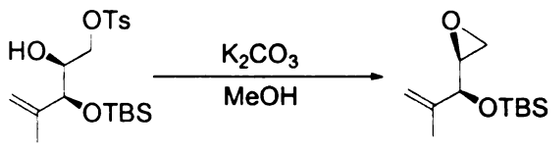
workup became problematic, although the yield remained the same.



6.13a **6.14a**

A solution of 2.99 g of **6.13a** (12.2 mmol) in 40 mL CH_2Cl_2 was cooled to 0 °C. To this solution was added 17 mL Et_3N (12.3 g, 122 mmol, 10 equiv) followed by 2.8 g TsCl (14.6 mmol, 1.2 equiv, no recrystallization needed). The reaction was stirred overnight allowing the ice bath to slowly melt. The reaction was then quenched with saturated $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4 and evaporated. Column chromatography purification (3:1 → 1:1 hexanes/ EtOAc) afforded 360 mg of recovered **6.13a** (12%) and 4.24 g of **6.14a** (87%) as oil. *This material deteriorates over time and thus should be quickly used in the next step*; R_f~0.55 (3:1 hexanes/EtOAc); $[\alpha]^{20}_D$ -8.1 (*c* 1.18, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77-7.79 (m, 2 H), 7.32 (m, 2 H), 4.94 (m, 1 H), 4.90 (quint, *J* = 1.5 Hz, 1 H), 4.04 (d, *J* = 4.9 Hz, 1 H), 3.98 and 3.92 (d of ABq, ^3J = 5.4 and 5.7 Hz, J_{AB} = 10.3 Hz, 2 H), 3.69 (dddd, *J* = 4.9, 5.6, 5.6, 5.6 Hz, 1 H), 2.43 (m, 4 H, overlapping signal), 1.67 (br, 3 H), 0.85 (s, 9 H), 0.03 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.9, 143.9, 132.9, 129.8, 128.0, 114.1, 75.5, 70.5, 69.9, 25.7, 21.6, 18.1, 18.0, -4.7, -5.3; IR (neat):

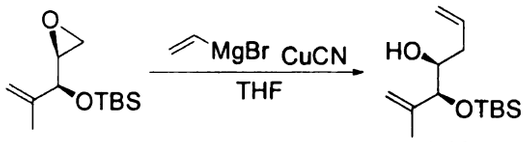
3544, 2955, 2930, 2859, 1364, 1190, 1179, 1098, 980, 837, 779, 667 cm^{-1}; LRMS (CI, methane): *m/e* 401 ($[M+H]^+$), 383, 343, 329, 313, 287, 269, 229, 213, 185, 171; HRMS (CI, methane) *m/e* calcd for $[C_{19}H_{32}O_5SSi+H]^+$ 401.1818, found 401.1818.



6.14a **6.15a**

To a stirred solution of 2.0 g of **6.14a** (5 mmol) in 25 mL MeOH (no purification or drying needed) was added 1.2 g K_2CO_3 (8.7 mmol, 1.7 equiv) at 0 °C in one portion. The suspension was stirred at 0 °C for 2 h and poured into half saturated NaCl and extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4 and evaporated. Column chromatography purification (1:1 hexanes/CH_2Cl_2) afforded 0.95 g of **6.15a** (83%) as a colorless oil; R_f~0.42 (1:1 hexanes/CH_2Cl_2); $[\alpha]^{20}_D$ -2.6 (*c* 1.00, EtOH); ^1H NMR (500 MHz, $CDCl_3$): δ 4.99 (m, 1 H), 4.86 (m, 1 H), 3.69 (d, *J* = 6.2 Hz, 1 H), 2.95 (ddd, *J* = 2.7, 4.0, 6.1 Hz, 1 H), 2.76 (dd, *J* = 4.2, 5.0 Hz, 1 H), 2.59 (dd, *J* = 2.7, 5.0 Hz, 1 H), 1.75 (m, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.6, 111.9, 78.1, 55.5, 44.9, 25.8, 18.8, 18.3, -4.9, -5.1; IR (neat): 2957, 2930, 2859, 1653, 1474, 1252, 1092, 937, 837, 777 cm^{-1}; LRMS (CI, MeOH): *m/e* 229 ($[M+H]^+$), 221, 199, 185, 171, 81; HRMS (CI, methane) *m/e* calcd for $[C_{12}H_{24}O_2Si+H]^+$ 229.1624,

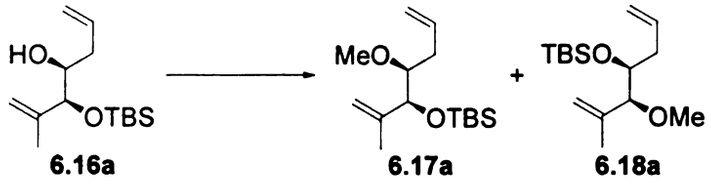
found 229.1622.



6.15a **6.16a**

To a solution of 1.14 g of **6.15a** (5 mmol) in 25 mL THF was added 45 mg CuCN (0.5 mmol, 10 mol%). The mixture was cooled to -40 °C and 10 mL of a vinyl Grignard solution (1 M in THF, 10 mmol, 2 equiv) was added via syringe pump over 45 min. Upon complete addition, the reaction was kept at that temperature for 20 min before being warmed up to -25 °C and stirred overnight. The reaction was quenched with saturated Na_2CO_3 and detoxified with saturated $Na_2S_2O_3$ before being extracted with ether. The combined organics were dried over Na_2SO_4 and evaporated. Column chromatography (1:1 hexanes/CH_2Cl_2) afforded the 1.24 g of **6.16a** (97%) as a colorless oil; R_f~0.41 (1:1 hexanes/CH_2Cl_2); $[\alpha]^{20}_D$ +10.6 (*c* 1.08, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87 (dddd, *J* = 6.8, 6.8, 10.0, 17.1 Hz, 1 H), 5.04-5.10 (m, 2 H), 4.92 (m, 1 H), 4.89 (quint, *J* = 1.6 Hz,1 H) 3.85 (d, *J* = 6.3 Hz, 1 H), 3.55 (ddd, *J* = 4.2, 6.3, 8.1 Hz, 1 H), ~2.5 (br, 1 H), 2.06-2.24 (m, 2 H), 1.69 (m, 3 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.9, 135.1, 116.9, 114.0, 80.0, 72.3, 37.4, 25.8, 18.2, 17.6, -4.6, -5.2; IR (neat): 3582, 3077, 2955, 2930, 2859, 1643, 1473, 1254, 1067, 837, 777 cm^{-1}; LRMS (EI): *m/e* 239 ([M-OH]$^+$), 199, 185, 129,

107; HRMS (CI, methane) *m/e* calcd for $[C_{14}H_{28}O_2Si+H]^+$ 257.1937, found 257.1936.

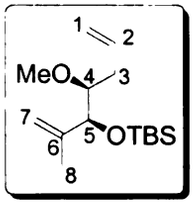


6.16a **6.17a** **6.18a**

Method 1 (NaH, MeI): in a round-bottom flask, ~58 mg NaH (60% dispersion in mineral oil, ~1.45 mmol, ~3 equiv) was suspended in 3 mL dry THF to remove the mineral oil and the supernatant was removed. The remaining slurry was dried under high vacuum. This purified NaH was suspended in 1 mL THF and the mixture was cooled to 0 °C. To this mixture was added 130 μL MeI (purified by passing through neutral alumina, 300 mg, 2.1 mmol, 4 equiv) via syringe followed by a solution of 136 mg of **6.16a** (0.53 mmol) in 1 mL THF. The ice bath was removed and the reaction was allowed to warm to room temperature and stirred for 19 h. The reaction was then quenched with saturated NH_4Cl and extracted with ether. The combined organics were dried over $MgSO_4$ and evaporated. Column chromatography (6:1 hexanes/CH_2Cl_2) afforded two fractions. The first fraction at R_f~0.40 contained 59 mg of **6.18a** (41%) as a colorless oil and the second fraction at R_f~0.23 contained 78 mg of **6.17a** (54%) as a colorless oil.

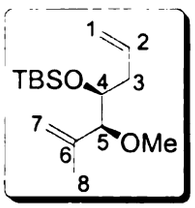
Method 2 (MeOTf, 4-methyl-2,6-di-*tert*-butylpyridine): to a solution of 128 mg

of **6.16a** (0.5 mmol) in 2 mL dry CH_2Cl_2 was added 359 mg 4-methyl-2,6-di-*tert*-butylpyridine (1.75 mmol, 3.5 equiv) in one portion followed by dropwise addition of 140 μL MeOTf (205 mg, 1.25 mmol, 2.5 equiv). The reaction was stirred at room temperature for 38 h, but was not complete. Nonetheless, it was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2. After drying over Na_2SO_4 and evaporation, the crude product was purified by column chromatography (2:1 hexanes/CH_2Cl_2) to yield 64 mg of recovered **6.16a** (50%) and 66 mg of **6.17a** (49%).

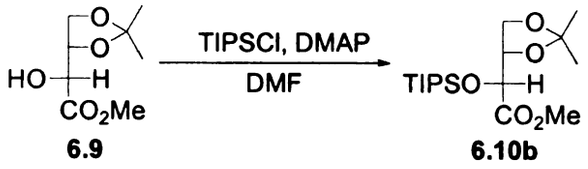


Desired product 6.17a: R_f~0.23 (6:1 hexanes/CH_2Cl_2); $[\alpha]^{20}_D$ +5.8 (*c* 1.08, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.85 (dddd, *J* = 7.1, 7.1, 10.3, 17.3 Hz, 1 H), 4.99-5.06 (m, 2 H), 4.88 (m, 1 H), 4.83 (m, 1 H), 4.01 (d, *J* = 6.6 Hz, 1 H), 3.43 (s, 3 H), 3.14 (ddd, *J* = 3.4, 6.6, 8.5 Hz, 1 H), 2.17-2.23 (m, 1 H), 1.97-2.04 (m, 1 H), 1.70 (m, 3 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.3, 135.7, 116.4, 113.1, 84.0, 78.9, 59.4, 35.4, 25.8, 18.2, 18.1, -4.9, -5.0; IR (neat): 3077, 2955, 2930, 2859, 1642, 1471, 1464, 1252, 1109, 1088, 902, 862, 837, 775 cm^{-1}; LRMS (CI, methane): *m/e* 269 ($[M-H]^+$), 255, 229, 213, 185, 159, 107; HRMS (CI, methane) *m/e* calcd for $[C_{15}H_{30}O_2Si+H]^+$ 271.2093, found 271.2087. The positions of Me and TBS were assigned by HMQC and HMBC in a selected region: *H* on C4 (ddd) had HMBC correlation to CH_3O, so had the CH_3O to *C*4. Such a correlation was

not observed between *H* on C5 (d) and *C*H_3O, or between C*H*$_3$O and *C*5. This concludes that MeO is on C4, not C5.

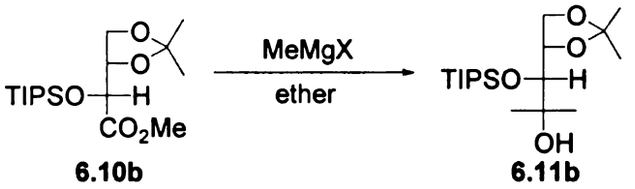


Silyl migration product 6.18a: R_f~0.40 (6:1 hexanes/CH_2Cl_2); $[\alpha]^{20}_D$ +23.6 (*c* 0.90, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.84 (dddd, *J* = 7.1, 7.1, 9.5, 16.8 Hz, 1 H), 4.96-5.01 (m, 3 H), 4.91 (m, 1 H), 3.69 (dt, *J* = 4.2, 7.1 Hz, 1 H), 3.33 (d, *J* = 7.3 Hz, 1 H), 3.17 (s, 3 H), 2.16-2.22 (m, 1 H), 2.00-2.06 (m, 1 H), 1.63 (m, 3 H), 0.87 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.2, 135.6, 116.7, 115.4, 89.4, 73.3, 56.2, 38.3, 26.0, 18.4, 17.7, -4.1, -4.8; IR (neat): 3077, 2953, 2930, 2857, 1647, 1472, 1464, 1252, 1117, 1101, 1019, 907, 835, 777 cm^{-1}; LRMS (CI, methane): 269 ([M-H]$^+$), 255, 239, 229, 213, 185, 107; HRMS (CI, methane) *m/e* calcd for [$C_{15}H_{30}O_2Si$-H]$^+$ 269.1937, found 269.1941. The positions of Me and TBS were assigned by HMQC and HMBC in a selected region: *H* on C5 (d) had HMBC correlation to *C*H_3O, so had the C*H*$_3$O to *C*5. Such a correlation was not observed between *H* on C4 (dt) and *C*H_3O, or between C*H*$_3$O and *C*4. This concludes that MeO is on C5, not C4. By comparison of ^{1}H NMR spectra of this pair of isomers, it was also noted that the H on the C bearing OTBS always had a higher chemical shift than the H on the C bearing OMe.



6.9 **6.10b**

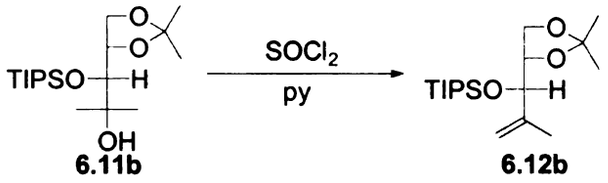
To a solution of 1.75 g of **6.9** (10.2 mmol) in 15 mL DMF (distilled over $MgSO_4$) was added 2.49 g DMAP (20.4 mmol, 2 equiv). Upon stirring, 3.27 mL TIPSCl (2.95 g, 15.3 mmol, 1.5 equiv) was added dropwise. The flask was sealed with a septum, topped with a nitrogen balloon, and stirred at room temperature for 1 day. White precipitate formed. Upon completion, the reaction mixture was poured into half saturated $NaHCO_3$ and extracted with CH_2Cl_2. Combined CH_2Cl_2 was washed with water and dried over $MgSO_4$ and evaporated. Column chromatography (1.5:1 hexanes/CH_2Cl_2) afforded 2.86 g of **6.10b** (85%) as a colorless oil; R_f~0.42 (5:1 hexanes/ether); $[\alpha]^{20}_D$ +10.7 (*c* 1.27, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.43 (d, J = 5.4 Hz, 1 H), 4.28 (q, J = 6.1 Hz, 1 H), 4.08 and 4.00 (d of ABq, ^3J = 6.1 Hz, J_{AB} = 8.8 Hz, 2 H), 3.72 (s, 3 H), 1.36 (s, 3 H), 1.32 (s, 3 H), 0.99-1.11 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 109.7, 77.1, 73.3, 65.2, 51.8, 26.2, 25.1, 17.81, 17.78, 12.2; IR (neat): 2946, 2869, 1756, 1464, 1372, 1256, 1204, 1156, 1073, 884, 826, 683 cm^{-1}; LRMS (ESI): *m/e* 410 ([M+MeCN+Na]$^+$), 385, 369, 307, 289; HRMS (ESI) *m/e* calcd for $[C_{17}H_{34}O_5Si+K]^+$ 385.1813, found 385.1822.



6.10b **6.11b**

Commercial MeMgI solution (13.4 mL 3 M in THF, 40 mmol, 3.2 equiv) was diluted with 30 mL anhydrous ether. To this Grignard solution was added a 40 mL ethereal solution of 4.33 g of **6.10b** (12.5 mmol) via cannula. Upon complete addition, the mixture was refluxed for 45 min and the allowed to cool to room temperature, after which it was quenched with water. The resultant slurry was treated with saturated sodium potassium tartrate and vigorously stirred until all the solid dissolved (ca. 30 min). After separation of the layers, the aqueous layer was extracted four times with ether. The combined organics were dried over $MgSO_4$ and evaporated. Column chromatography purification (1:1 hexanes/ether) afforded 3.64 g of **6.11b** (84%) as white wax-like solid; R_f~0.47 (1:1 hexanes/ether); mp 74-75.5 °C; $[\alpha]^{20}_D$ -5.9 (*c* 1.19, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.60-3.65 and 3.95-4.04 (m, 4 H), 2.26 (s, 1 H), 1.37 (s, 3 H), 1.31 (s, 3 H), 1.19 (s, 3 H), 1.16 (s, 3 H), 1.15-1.22 (m, 3 H), 1.06-1.08 (m, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 107.7, 80.8, 77.5, 72.3, 66.9, 26.6, 25.4, 25.3, 18.4, 13.4 (There is one overlapped signal); IR (neat): 3472, 2946, 2869, 1466, 1369, 1244, 1129, 1059, 884, 866, 814, 679 cm^{-1}; LRMS (CI, MeOH): *m/e* 329 ([M+H-H_2O]$^+$), 311, 271, 229, 115, 101; HRMS (FAB) *m/e* calcd for [$C_{18}H_{38}O_4Si$+H]$^+$ 347.2618,

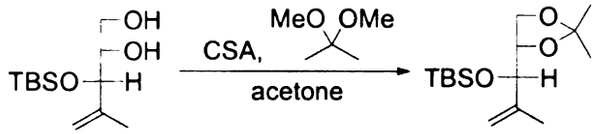
found 347.2617.



6.11b **6.12b**

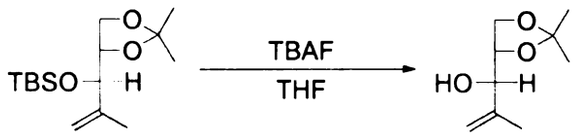
A solution of 3.54 g of **6.11b** (10.2 mmol) in 80 mL pyridine (no purification or drying needed) was cooled to 0 °C by an ice-water bath. To this solution was added 1.5 mL $SOCl_2$ (2.45 g, 20.5 mmol, 2 equiv) dropwise via syringe and the mixture quickly turned yellow-orange. The reaction was then warmed to room temperature and stirred for 1 h. Upon completion, the reaction was quenched with half saturated Na_2CO_3 at 0 °C and diluted with ether. The layers were separated and the aqueous layer was extracted with ether. The combined organics were washed with water, followed by 5% $CuSO_4$ until the aqueous phase was no longer purple, and then water before being dried over $MgSO_4$. After evaporation, the crude material was purified by column chromatography (1.1:1 hexanes/CH_2Cl_2) to yield 3.09 g of **6.12b** (92%) as a clear, slightly yellow oil; R_f~0.57 (1:1 hexanes/CH_2Cl_2); $[\alpha]^{20}_D$ -2.0 (*c* 1.12, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 (m, 1 H), 4.86 (quint, J = 1.7 Hz, 1 H), 4.10-4.21 (m, 2 H), 3.83 and 3.62 (d of ABq, ^3J = 6.4 and 7.6 Hz, J_{AB} = 8.5 Hz, 2 H), 1.73 (m, 3 H), 1.37 (s, 3 H), 1.32 (s, 3 H), 1.01-1.08 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.8, 113.3, 109.4, 78.5, 78.4, 65.9, 26.5, 25.4, 18.3, 17.99, 17.98, 12.4; IR (neat): 3075, 2944,

2869, 1647, 1464, 1379, 1370, 1252, 1211, 1159, 1108, 1067, 884, 830, 681 cm^{-1}; LRMS (EI): *m/e* 328 (M^+), 313, 285, 227, 185, 157, 101; HRMS (FAB) *m/e* calcd for $[C_{18}H_{36}O_3Si]^+$ 328.2434, found 347.2440.



6.13a **6.12a**

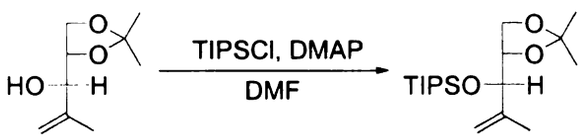
To a solution of 8.58 g of **6.13a** (34.9 mmol) and 25 mL 2,2-dimethoxypropane (21 g, 202 mmol, 5.8 equiv) in 150 mL acetone (dried over Drierite) was added 810 mg racemic camphor-10-sulphonic acid (3.5 mmol, 10 mol%). The solution was stirred at room temperature for 3 h and then quenched with saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$. Column chromatography purification (1:1 hexanes/CH_2Cl_2) afforded 8.37 g of **6.12a** (84%).



6.12a **6.19**

To a solution of 8.36 g of **6.12a** (29.2 mmol) in 150 mL THF at 0 °C was slowly added 48 mL TBAF (1 M in THF, 48 mmol, 1.64 equiv). Upon complete addition, the reaction was allowed to warm to room temperature and stir for 2.5 h. Upon completion, the reaction was quenched with water and concentrated to about half

of its original volume. The solution was partitioned between saturated $NaHCO_3$ and ether, and layers separated. The aqueous layer was extracted further with ether. Combined organics were dried over Na_2SO_4 and concentrated. Column chromatography purification (3.5:1 hexanes/EtOAc) afforded 4.88 g of **6.19** (97%) as colorless oil; R_f~0.45 (3:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +11.9 (*c* 1.50, acetone); ^1H NMR (500 MHz, $CDCl_3$): δ 5.00 (m, 1 H), 4.92 (m, 1 H), 4.14 (q, J = 6.3 Hz, 1 H), 3.94 (d, J = 6.6 Hz, 1 H), 3.95 and 3.73 (d of ABq, ^3J = 6.6 Hz, J_{AB} = 8.6 Hz, 2 H), 2.40 (br, 1 H), 1.75 (s, 3 H), 1.44 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.8, 113.8, 109.8, 77.3, 76.7, 66.3, 26.8, 25.3, 18.1; IR (neat): 3474, 3079, 2988, 1653, 1456, 1372, 1254, 1214, 1157, 1071, 905 cm^{-1}; LRMS (CI, MeOH): *m/e* 155 ($[M+H-H_2O]^+$), 101, 69, 59; HRMS (CI, NH_3) *m/e* calcd for $[C_9H_{16}O_3+H]^+$ 173.1178, found 173.1177.



6.19 **6.12b**

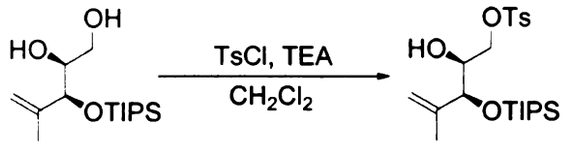
To a solution of 2.85 g of **6.19** (15 mmol) in 45 mL DMF (distilled over $MgSO_4$) was added 5.5 g DMAP (45 mmol, 3 equiv). Upon stirring, 6.5 mL TIPSCl (5.8 g, 30 mmol, 2 equiv) was added dropwise. The reaction was sealed with a septum, topped with a nitrogen balloon, and stirred at room temperature for 16 h. Upon completion, the reaction mixture was partitioned between half saturated $NaHCO_3$

and ether. The layers were separated and the aqueous layer was further extracted with ether. The combined organics were dried over $MgSO_4$ and evaporated. Column chromatography (5:1 hexanes/ether) afforded 4.45 g of **6.12b** (86%) as a colorless oil.

6.12b **6.13b**

To a solution of 10.5 g of **6.12b** (32 mmol) in 190 mL MeOH (no purification or drying needed) at 0 °C was added 64 mL TFA over a few minutes. The ice bath was removed and 35 min later, the reaction was quenched with saturated Na_2CO_3 until gas evolution ceased. This quench generated precipitate. The reaction mixture was concentrated to about half of its original volume and extracted with EtOAc (At the beginning of extraction, some water or saturated $NaHCO_3$ could be used to help separate layers). The combined organics were dried over Na_2SO_4 ($MgSO_4$ was avoided due to its partial solubility in the solvent) and evaporated. The crude material was purified by column chromatography (2.5:1 hexanes/EtOAc). Along with 1.5 g of recovered **6.12b** (14%), 8.0 g of **6.13b** (containing 0.24 g EtOAc, 84% yield discounting the added weight of EtOAc) was isolated as a very thick oil; R_f~0.47 (2.5:1 hexanes/EtOAc); $[\alpha]^{20}_D$ -9.1 (*c* 1.04, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.98 (m, 1 H), 4.92 (quint, *J* = 1.6 Hz, 1 H),

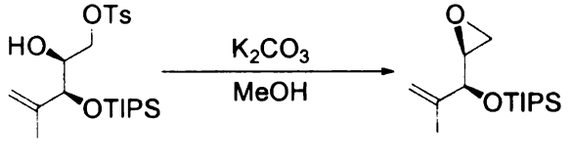
4.19 (d, J = 6.5 Hz, 1 H), 3.59-3.65 (m, 2 H), 3.46-3.51 (m, 1 H), 1.6-2.8 (br, 2 H), 1.73 (dd, J = 0.9, 1.5 Hz, 3 H), 1.04-1.10 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.7, 114.4, 77.6, 73.4, 63.0, 18.05, 18.01, 17.6, 12.4; IR (neat): 3414, 2946, 2869, 1464, 1385, 1092, 1065, 1015, 884, 681 cm^{-1}; LRMS (ESI): *m/e* 311 ([M+Na]$^+$), 289, 271, 246, 198, 115; HRMS (ESI) *m/e* calcd for [$C_{15}H_{32}O_3Si$+Na]$^+$ 311.2018, found 311.2025.



6.13b **6.14b**

To a solution of 9.44 g of **6.13b** (32.8 mmol) in 100 mL CH_2Cl_2 at 0 °C was added 45 mL Et_3N (32.7 g, 323 mmol, ~10 equiv) followed by 7.02 g TsCl (36.8 mmol, 1.12 equiv, no recrystallization needed). The reaction was stirred overnight allowing the ice bath to slowly melt. The reaction was quenched with saturated $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4 and evaporated. Column chromatography purification (4.5:1 → 1:1 hexanes/ EtOAc) afforded 0.67 g of recovered **6.13b** (7%) and 13.55 g of **6.14b** (containing 0.24 g EtOAc, 92% discounting the added weight of EtOAc) as oil. *This material deteriorates over time and thus should be quickly used in the next step*; R_f~0.53 (4:1 hexanes/ EtOAc); $[\alpha]^{20}_D$ -24.9 (*c* 1.05, EtOH); ^{1}H NMR (500

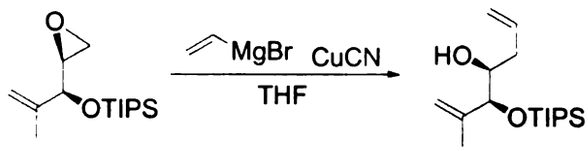
MHz, $CDCl_3$): δ 7.77 (m, 2 H), 7.32 (m, 2 H), 4.94 (m, 1 H), 4.90 (quint, J = 1.5 Hz, 1 H), 4.19 (d, J = 5.7 Hz, 1 H), 4.06 and 3.94 (d of ABq, ^3J = 4.2 and 6.1 Hz, J_{AB} = 10.3 Hz, 2 H), 3.73 (dt, J = 4.2, 5.9 Hz, 1 H), 2.43 (s, 3 H), 1.68 (m, 3 H), 0.99-1.03 (m, 21 H) (OH not ovserved); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.8, 144.0, 132.9, 129.8, 128.0, 114.5, 76.3, 71.2, 70.2, 21.6, 17.98, 17.96 (17.96 is an overlapping signal for 2 C's. HMQC confirmed its correlation to both the Me's in TIPS and the allylic Me), 12.4; IR (neat): 3540, 2946, 2869, 1599, 1464, 1366, 1190, 1179, 1098, 980, 667 cm^{-1}; LRMS (ESI): *m/e* 460 ($[M+NH_4]^+$), 443 ($[M+H]^+$), 269, 198, 97; HRMS (ESI) *m/e* calcd for $[C_{22}H_{38}O_5SSi+H]^+$ 443.2287, found 443.2281.



6.14b **6.15b**

To a stirred solution of 14.5 g of **6.14b** (containing 0.2 g EtOAc, corresponding to 14.3 g of pure **6.14b**, 32.4 mmol) in 150 mL MeOH (no purification or drying needed) at 0 °C was added 7.6 g K_2CO_3 (55 mmol, 1.7 equiv) in one portion. The suspension was stirred at 0 °C for 2 h and poured into half saturated NH_4Cl before being extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4 and evaporated. Column chromatography purification (1.5:1 hexanes/CH_2Cl_2) afforded 8.16 g of **6.15b** (93%) as a colorless oil; R_f~0.5 (1.5:1 hexanes/CH_2Cl_2); $[\alpha]^{20}_D$ -10.5 (*c* 1.01, EtOH); ^1H NMR (500 MHz, $CDCl_3$): δ

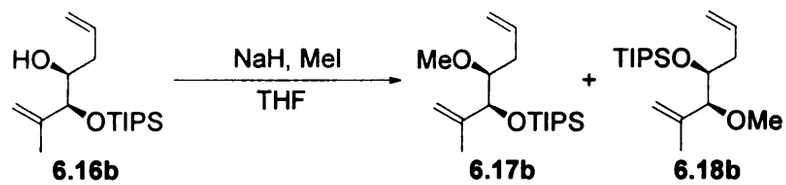
4.98 (m, 1 H), 4.86 (apparent quint, J = 1.5 Hz, 1 H), 3.79 (d, J = 6.3 Hz, 1 H), 3.00 (ddd, J = 2.7, 4.2, 6.3 Hz, 1 H), 2.76 (dd, J = 4.2, 4.9 Hz, 1 H), 2.57 (dd, J = 2.7, 4.9 Hz, 1 H), 1.77 (m, 3 H), 1.02-1.10 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.8, 112.2, 78.6, 56.0, 44.9, 18.7, 17.95, 17.90, 12.3; IR (neat): 2946, 2869, 1653, 1464, 1100, 1069, 936, 884, 832, 681 cm^{-1}; LRMS (CI, methane): *m/e* 271 ($[M+H]^+$), 253, 227, 197, 185, 157, 145; HRMS (CI, methane) *m/e* calcd for $[C_{15}H_{30}O_2Si+H]^+$ 271.2093, found 271.2091.



6.15b **6.16b**

To 3.07 g of **6.15b** (11.4 mmol) and 153 mg CuCN (1.7 mmol, 15 mol%) was added 55 mL THF. The mixture was cooled to -40 °C and 28 mL of a vinyl Grignard solution (1 M in THF, 28 mmol, 2.5 equiv) was introduced via syringe pump over 45 min. Upon complete addition, the reaction was kept at -40 °C for 20 min before being warmed to -25 °C and then stirred overnight. The reaction was quenched with saturated Na_2CO_3 and detoxified with saturated $Na_2S_2O_3$. The mixture was then extracted with ether and the combined organics were dried over $MgSO_4$ and evaporated. Column chromatography (2:1 hexanes/CH_2Cl_2) afforded 0.62 g of recovered **6.15b** (20%) and 2.58 g of **6.16b** (76%) as a colorless oil (**6.15b** and **6.16b** are not easily separable and use of large amount of

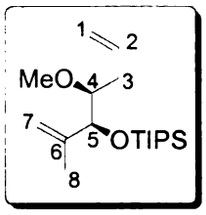
silica gel is suggested); R_f~0.4 (1.5:1 hexanes/CH_2Cl_2); $[\alpha]^{20}_D$ -18.0 (*c* 1.02, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88 (dddd, *J* = 6.6, 7.6, 10.3, 17.1 Hz, 1 H), 5.04-5.10 (m, 2 H), 4.93 (m, 1 H), 4.90 (quint, *J* = 1.6 Hz,1 H), 4.00 (d, *J* = 7.1 Hz, 1 H), 3.55 (ddd, *J* = 3.7, 7.3, 8.5 Hz, 1 H), ~2.6 (br, 1 H), 2.01-2.27 (m, 2 H), 1.71 (m, 3 H), 1.02-1.09 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.7, 135.2, 116.9, 114.5, 80.5, 72.5, 37.0, 18.08, 18.03, 17.6, 12.4; IR (neat): 3584, 3077, 2946, 2869, 1642, 1464, 1385, 1092, 1063, 905, 884, 681 cm^{-1}; LRMS (CI, methane): *m/e* 299 ($[M+H]^+$), 281, 255, 227, 213, 201, 185, 175, 157, 131, 107; HRMS (CI, methane) *m/e* calcd for $[C_{17}H_{34}O_2Si+H]^+$ 299.2406, found 299.2403.



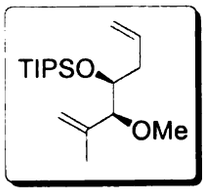
6.16b **6.17b** **6.18b**

To a suspension of 887 mg NaH (60% dispersion in mineral oil, not washed, corresponding to 532 mg pure NaH, 22.2 mmol, 1.6 equiv) in 35 mL THF was added 2.76 mL MeI (purified by passing through neutral alumina, 6.3 g, 44.4 mmol, 3.2 equiv) via syringe. A solution of 4.13 g of **6.16b** (13.86 mmol) in 35 mL THF was then added via syringe. The reaction was stirred at room temperature for 20 h. Upon completion, it was quenched with saturated NH_4Cl and extracted with ether. The combined organics were dried over $MgSO_4$ and evaporated. Column chromatography (6:1 hexanes/CH_2Cl_2) afforded two fractions. The first

fraction at R_f~0.60 contained 0.8 g of **6.18b** (18.5%) as a colorless oil and the second fraction at R_f~0.37 contained 3.37 g of **6.17b** (78%) as a colorless oil.

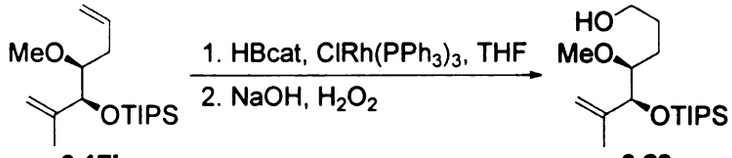


Desired product 6.17b: R_f~0.37 (6:1 hexanes/CH_2Cl_2); $[\alpha]^{20}_D$ -1.9 (*c* 0.97, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87 (dddd, *J* = 7.1, 7.1, 10.2, 17.3 Hz, 1 H), 5.04 (dq, *J* = 17.3, 1.7 Hz, 1 H), 5.00 (dddd, *J* = 1.2, 1.2, 2.2, 10.2 Hz, 1 H), 4.93 (m, 1 H), 4.89 (quint, *J* = 1.6 Hz, 1 H), 4.26 (d, *J* = 6.1 Hz, 1 H), 3.42 (s, 3 H), 3.26 (ddd, *J* = 2.9, 6.1, 8.8 Hz, 1 H), 2.06-2.32 (m, 1 H), 1.93-2.00 (m, 1 H), 1.72 (m, 3 H), 1.02-1.08 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.9, 136.0, 116.3, 113.1, 84.4, 76.8, 58.8, 34.7, 18.9, 18.06, 18.03, 12.4; IR (neat): 3077, 2946, 2869, 1642, 1464, 1111, 1067, 903, 884, 681 cm^{-1}; LRMS (CI, methane): *m/e* 311 ([M-H]$^+$), 281, 269, 227, 157, 145, 139, 107; HRMS (CI, methane) *m/e* calcd for [$C_{18}H_{36}O_2Si$-H]$^+$ 311.2406, found 311.2404. The positions of Me and TIPS were assigned by HMQC and HMBC in a selected region: *H* on C4 (ddd) had HMBC correlation to *C*H_3O, so had the C*H*$_3$O to *C*4. Such a correlation was not observed between *H* on C5 (d) and *C*H_3O, or between C*H*$_3$O and *C*5. This concludes that MeO is on C4, not C5.



Silyl migration product 6.18b: R_f~0.60 (6:1 hexanes/CH_2Cl_2); $[\alpha]^{20}_D$ +42.8 (*c* 1.12, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.90 (dddd, *J* = 6.6, 7.6, 10.5, 17.1 Hz, 1 H), 4.95-5.01 (m, 3 H), 4.92 (m, 1 H), 3.87 (ddd, *J* = 5.6, 5.6, 7.8 Hz, 1 H), 3.35 (d, *J* = 7.8 Hz, 1

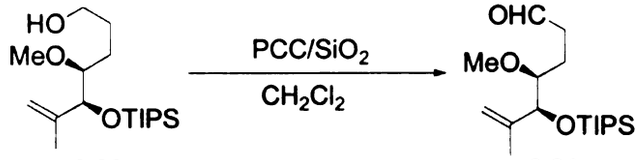
H), 3.13 (s, 3 H), 2.22-2.28 (m, 1 H), 2.02-2.09 (m, 1 H), 1.61 (m, 3 H), 1.03-1.10 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.2, 135.1, 116.8, 115.8, 89.4, 72.8, 55.8, 38.5, 18.3, 17.4, 12.8; IR (neat): 3077, 2944, 2867, 1647, 1464, 1103, 1017, 907, 884, 677 cm^{-1}; LRMS (CI, methane): *m/e* 311 ($[M-H]^+$), 281, 269, 227, 157, 145, 117, 107; HRMS (CI, methane) *m/e* calcd for $[C_{18}H_{36}O_2Si-H]^+$ 311.2406, found 311.2397.



6.17b **6.20**

To a solution of 4.94 g of **6.17b** (15.8 mmol) and 439 mg Wilkinson's catalyst (0.475 mmol, 3 mol%) in 150 mL THF was added 47.5 mL commercial catecholborane solution (1 M in THF, 47.5 mmol, 3 equiv) via syringe. The reaction mixture turned dark and was stirred for 50 min at room temperature before being cooled to 0 °C. The reaction was then quenched by the slow addition of 32 mL of 1:1 water/THF. Gas evolution was observed. A pre-cooled (via ice bath) mixture of 32 mL 2 M NaOH (64 mmol, 4 equiv) and 32 mL 30% H_2O_2 (310 mmol, ~20 equiv) was added into the reaction mixture slowly. Ice was also added to the reaction so that the internal temperature never exceeded 30 °C. Upon complete addition, the mixture was stirred for 25 min at 0 °C and another 25 min after the ice bath was removed. The reaction was then partitioned between

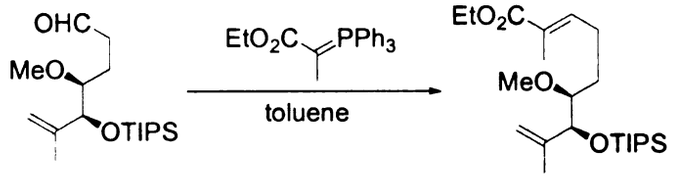
brine and ether. The layers were separated and the aqueous layer was extracted with ether. The combined organic were washed with 1 M NaOH until the wash was colorless. After being dried over $MgSO_4$ and evaporated, the crude residue was purified by column chromatography (3:1 hexanes/EtOAc) to afford 4.24 g of **6.20** (81%) as oil; R_f~0.43 (3:1 hexanes/EtOAc); $[\alpha]^{20}_D$ -12.8 (*c* 1.01, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.94 (m, 1 H), 4.87 (quint, *J* = 1.6 Hz, 1 H), 4.30 (d, *J* = 6.0 Hz, 1 H), 3.60 (t, *J* = 6.1 Hz, 2 H), 3.45 (s, 3 H), 3.18 (ddd, *J* = 2.1, 6.0, 8.5 Hz, 1 H), 1.75-1.80 (br, 1 H), 1.72 (m, 3 H), 1.62-1.68 (m, 3 H), 1.22-1.29 (m 1 H), 1.02-1.10 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.9, 113.0, 84.8, 76.6, 63.1, 58.7, 29.3, 26.6, 18.9, 18.07, 18.04, 12.4; IR (neat): 3366, 2946, 2869, 1464, 1101, 1067, 901, 884, 681, 656 cm^{-1}; LRMS (CI, NH_3): *m/e* 331 ($[M+H]^+$), 299, 255, 228, 174, 157, 125; HRMS (CI, methane) *m/e* calcd for $[C_{18}H_{38}O_3Si+H]^+$ 331.2668, found 331.2661.



6.20 **6.21**

To a solution of 4.24 g of **6.20** (12.85 mmol) in 150 mL CH_2Cl_2 was added 9.42 g solid-supported PCC (4.71 g PCC, 21.8 mmol, 1.7 equiv, ground together with 4.71 g of silica gel). The resulted purple-brown suspension was stirred at room temperature for 2.5 h and then filtered through a pad of silica gel (~2 cm thick,

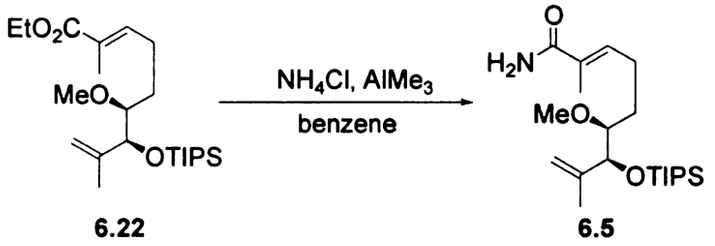
~4.5 cm wide). The silica pad was further eluted with ether. The filtrate was evaporated and 4.25 g of crude **6.21** (containing 0.1 g CH_2Cl_2, 98% as is, discounting the added weight of CH_2Cl_2) was obtained. This product was clean enough by NMR to be used in the next reaction without further purification; $[\alpha]^{20}_D$ -20.4 (crude, *c* 0.97, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.69 (t, *J* = 2.0 Hz, 1 H), 4.95 (m, 1 H), 4.89 (quint, *J* = 1.7 Hz, 1 H), 4.27 (d, *J* = 5.9 Hz, 1 H), 3.38 (s, 3 H), 3.16 (ddd, *J* = 3.0, 5.9, 9.0 Hz, 1 H), 2.43-2.47 (m, 2 H), 1.87 (dddd, *J* = 3.2, 7.1, 7.1, 14.4 Hz, 1 H), 1.73 (m, 3 H), 1.57 (dddd, *J* = 7.1, 7.1, 9.2, 14.4 Hz, 1 H), 1.03-1.06 (m, 21 H), some impurity at 3.46; ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.6, 144.8, 113.2, 83.9, 76.9, 58.7, 40.6, 23.1, 19.0, 18.06, 18.02, 12.4; IR (neat): 2946, 2869, 2720, 1728, 1464, 1098, 1067, 903, 884, 679 cm^{-1}; LRMS (EI): *m/e* 285 ([M-^{i}Pr]$^+$), 253, 227, 185, 157, 145, 117, 101, 89, 75, 59; HRMS (FAB) *m/e* calcd for $[C_{18}H_{36}O_3Si\text{-}H]^+$ 327.2356, found 327.2350.



6.21 **6.22**

To a solution of 4.25 g of crude **6.21** obtained from the previous reaction (~12.6 mmol) in 120 mL dry toluene was added 9.12 g of Wittig reagent (25.2 mmol, 2 equiv). The suspension was heated to 110 °C and stirred overnight. The Wittig reagent dissolved to give a clear, light yellow solution initially, and as

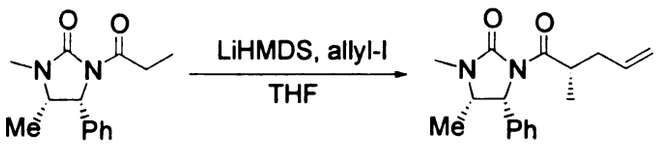
the reaction proceeded, a white precipitate formed. After cooling the reaction to room temperature, the solvent was removed by rotary evaporation, followed by co-evaporation with EtOAc (For ease of operation, the white precipitate could be filtered off before evaporation and chromatography). Chromatography purification (10:1 hexanes/EtOAc) afforded 4.80 g of a 13.8:1 *E*/*Z* mixture of **6.22** (93%) as a colorless oil. (Another run gave 98% of a 12.7:1 *E*/*Z* mixture) R_f~0.59 (10:1 hexanes/EtOAc); $[\alpha]^{20}_D$ -10.8 (12.7:1 *E*/*Z* mixture, *c* 1.04, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.72 (ddq, *J* = 7.1, 8.2, 1.5 Hz, 1 H, the β-proton of the α,β-unsaturated ester moiety in the *E* isomer. The corresponding proton for the *Z* isomer appears at 5.87), 4.94 (m, 1 H), 4.88 (quint, *J* = 1.6 Hz, 1 H), 4.30 (d, *J* = 5.6 Hz, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 3.43 (s, 3 H), 3.15 (ddd, *J* = 2.8, 5.7, 9.0 Hz, 1 H), 2.20-2.28 (m, 2 H), 1.81 (d, *J* = 1.2 Hz, 3 H), 1.72 (br, 3 H), 1.64 (dddd, *J* = 2.8, 7.6, 9.0, 14.1 Hz, 1 H), 1.34 (dddd, *J* = 5.7, 8.2, 9.2, 14.0 Hz, 1 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 1.03-1.07 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.2, 145.0, 142.1, 127.9, 112.9, 84.0, 76.3, 60.4, 58.7, 28.8, 25.0, 19.2, 18.07, 18.03, 14.3, 12.4, 12.3; IR (neat): 2946, 2869, 1713, 1464, 1275, 1260, 1113, 883, 683 cm^{-1}; LRMS (EI): *m/e* 412 (M^+), 369, 337, 227, 185, 157, 145, 75, 59; HRMS (CI, methane) *m/e* calcd for $[C_{23}H_{33}O_4Si]^+$ 412.3009, found 412.3006.



6.22 **6.5**

To a suspension of 1.13 g NH_4Cl (21.2 mmol, 3 equiv) in 20 mL dry benzene at 0 °C was slowly added 10.6 mL of $AlMe_3$ solution (2 M in toluene, 21.2 mmol, 3 equiv) via syringe. Gas evolution was observed. The cold reaction mixture was stirred for a few minutes and then warmed to room temperature. After being stirred for another 30-35 min, gas evolution ceased and all the solid NH_4Cl had dissolved (More $AlMe_3$ could be added if NH_4Cl was not completely dissolved). This clear solution was transferred via cannula to another flask containing 2.91 g of **6.22** (7.06 mmol, 12.7:1 *E/Z* mixture) in 70 mL dry benzene. Upon complete addition, the flask was topped with a condenser and the mixture was heated to 45-50 °C. After ~9.5 h, another 1.13 g NH_4Cl (21.2 mmol, 3 equiv) and 10.6 mL $AlMe_3$ solution (2 M in toluene, 21.2 mmol, 3 equiv) were mixed in the same way described above and transferred into the reaction vessel. The reaction continued overnight. After being cooled to room temperature, the reaction was quenched carefully with 1 M HCl until no more gas evolved. The mixture was then stirred over saturated sodium potassium tartrate for 30 min until a clear solution was obtained. Extraction with EtOAc was followed by drying over $MgSO_4$ and evaporation. Column chromatography separation (1:1

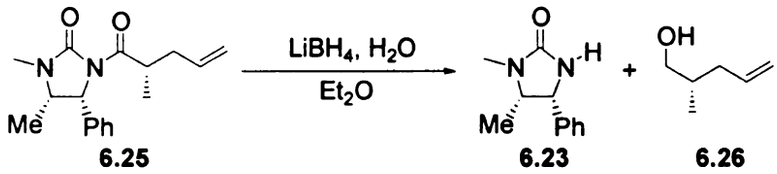
hexanes/EtOAc) afforded a small amount of *Z* isomer (R_f~0.41, 1:1 hexanes/EtOAc) and 2.21 g of the desired *E* isomer (82%) as a white solid; R_f~0.29 (1:1 hexanes/EtOAc); mp 62-65 °C; $[\alpha]^{20}_D$ -13.2 (*c* 1.14, acetone); ^{1}H NMR (300 MHz, acetone-d_6): δ 6.67 (br, 1 H), 6.39 (tq, *J* = 7.5, 1.5 Hz, 1 H), 6.18 (br, 1 H), 5.01 (m, 1 H), 4.90 (m, 1 H), 4.38 (d, *J* = 6.0 Hz, 1 H), 3.45 (s, 3 H), 3.25 (ddd, *J* = 3.1, 6.2, 8.8 Hz, 1 H), 2.20-2.28 (m, 2 H), 1.81 (m, 3 H), 1.76 (m, 3 H), 1.64 (dddd, *J* = 2.9, 7.3, 9.2, 13.9 Hz, 1 H), 1.32 (dddd, *J* = 6.6, 8.0, 8.0, 14.5 Hz, 1 H), 1.07-1.15 (m, 21 H); ^{13}C NMR (75 MHz, acetone-d_6): δ 171.0, 146.3, 136.2, 131.9, 113.1, 84.6, 77.6, 58.8, 29.9, 25.1, 19.3, 18.47, 18.44, 13.2, 12.7; IR (neat): 3350, 3196, 2946, 2889, 1667, 1636, 1603, 1377, 1111, 884, 681 cm^{-1}; LRMS (EI): *m/e* 340 ([M-^{i}Pr]$^+$), 308, 253, 227, 185, 157, 115, 89, 75, 59; Anal. Calcd for $C_{21}H_{41}NO_3Si$: C, 65.75; H, 10.77; N, 3.65. Found C, 66.00; H, 10.89; N, 3.86.



6.24 **6.25**

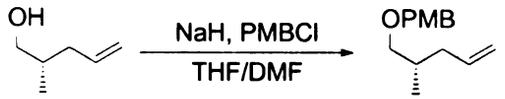
A solution of 15.7 mL commercial LiHMDS (1 M in THF, 15.7 mmol, 1.05 equiv) was further diluted with 10 mL THF and cooled to -78 °C. To this solution was added a solution of 3.69 g of **6.24** (15 mmol) in 25 mL THF via syringe pump at a rate of 0.77 mL/min. Upon complete addition, the mixture was stirred at -78 °C for 1 h. A solution of 1.65 mL (3.04 g, 18.1 mmol, 1.2 equiv) allyl iodide in 10 mL

THF was added via syringe pump at a rate of 0.77 mL/min. *This process may cause a large amount of precipitate or gel formation, so occasionally stopping the addition and warming the mixture to dissolve this precipitate may be needed.* The mixture was stirred at -78 °C overnight. Upon completion, the reaction was quenched with water and warmed to room temperature. It was partitioned between brine and ether. The layers were separated and the aqueous layer was extracted with ether. The combined organics were dried over $MgSO_4$ and evaporated. ^1H NMR of the crude material showed a diastereomeric ratio of ~12:1. Two rounds of column chromatography (2:1 hexanes/EtOAc) afforded a small amount of the undesired *R* isomer (R_f~0.51) and 3.21 g of the desired *S* isomer (75%) as a white solid; R_f~0.43 (2:1 hexanes/EtOAc); mp 71-73 °C; $[\alpha]^{20}_D$ -43.6 (*c* 1.06, acetone); ^1H NMR (500 MHz, $CDCl_3$): δ 7.23-7.30 (m, 3 H), 7.11-7.13 (m, 2 H), 5.65 (dddd, *J* = 6.5, 7.6, 10.3, 17.0 Hz, 1 H), 5.28 (d, *J* = 8.7 Hz, 1 H), 4.89-4.95 (m, 2 H), 4.00 (sext, *J* = 6.8 Hz, 1 H), 3.87 (dq, *J* = 8.7, 6.6 Hz, 1 H), 2.81 (s, 3 H), 2.42 (dtt, *J* = 13.9, 1.3, 6.3 Hz, 1 H), 2.04 (dtt, *J* = 13.9, 1.2, 7.4 Hz, 1 H), 1.09 (d, *J* = 6.7 Hz, 3 H), 0.78 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.0, 155.7, 136.8, 135.7, 128.4, 128.0, 127.1, 116.6, 59.4, 53.8, 38.1, 37.3, 28.2, 16.3, 15.0; LRMS (EI): *m/e* 286 (M^+), 189, 132, 69, 58.



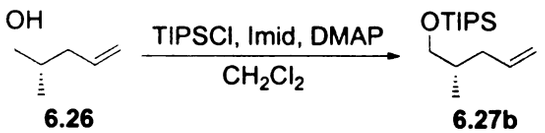
6.25 **6.23** **6.26**

To a solution of 2.86 g of **6.25** (10 mmol) in 100 mL dry ether was added 0.2 mL water (200 mg, 11.1 mmol, 1.1 equiv). The solution was cooled to 0 °C and 6 mL $LiBH_4$ solution (2 M in THF, 12 mmol, 1.2 equiv) was added via syringe. The reaction quickly turned cloudy and a white precipitate formed. The mixture was stirred for 1 h at 0 °C followed by another 2 h at room temperature before being quenched with saturated NH_4Cl. While stirring, 10 mL water and 10 mL glycerol were added and the mixture was stirred overnight. The layers were separated and the aqueous layer was extracted with ether. The combined organics were dried over Na_2SO_4 and evaporated. Column chromatography (1.5:1 hexanes/ether) afforded 895 mg of **6.26** (89%) as the first fraction. Further elution with 1:1 EtOAc/acetone afforded 1.88 of g **6.23** (quantitative). Alcohol **6.26**: R_f~0.32 (1.5:1 hexanes/ether); $[\alpha]^{20}_D$ -2.6 (*c* 1.10, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.79 (dddd, *J* = 7.3, 7.3, 10.3, 17.3 Hz, 1 H), 4.98-5.05 (m, 2 H), 3.50 and 3.44 (d of ABq, calculated ν_A at 3.494 ppm, ν_B at 3.440 ppm, ^3J = 6.1 Hz, J_{AB} = 10.7 Hz, 2 H), 2.12-2.19 (m, 1 H), 1.89-1.96 (m, 1 H), 1.72 (sext, *J* = 6.8 Hz ,1 H), 1.40-1.43 (br, 1 H), 0.90 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.0, 116.1, 67.9, 37.8, 35.6, 16.3; LRMS (EI): *m/e* 99 ($[M-H]^+$), 83, 67.



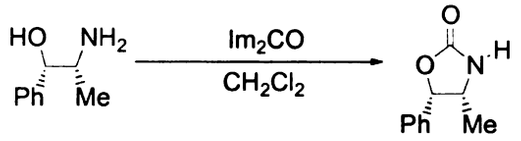
6.26 **6.27a**

To a suspension of 528 mg NaH (60% dispersion in mineral oil, not washed, corresponding to 317 mg pure NaH, 13.2 mmol, 1.5 equiv) in 9 mL DMF was added a solution of 882 mg of **6.26** (8.8 mmol) in 18 mL THF. The mixture was stirred at room temperature for 30 min before 1.44 mL PMBCl (1.67 g, 10.7 mmol, 1.2 equiv) was added via syringe. The mixture was stirred overnight and then quenched with diethylamine. After stirring the mixture for another 10 min, water was added until gas evolution ceased. The mixture was diluted with saturated NH_4Cl and extracted with ether. The combined organics were dried over K_2CO_3 and evaporated. Column chromatography (12:1 hexanes/ether) afforded 1.43 g of **6.27a** (74%) as a colorless oil; R_f~0.32 (10:1 hexanes/ether); $[\alpha]^{20}_D$ +0.9 (*c* 1.05, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (m, 2 H), 6.86 (m, 2 H), 5.76 (dddd, *J* = 6.8, 6.8, 10.5, 17.1 Hz, 1 H), 4.95-5.03 (m, 2 H), 4.41 (s, 2 H), 3.79 (s, 3 H), 3.29 and 3.22 (d of ABq, calculated ν_A at 3.282 ppm, ν_B at 3.228 ppm, ^3J = 6.1 Hz, J_{AB} = 9.0 Hz, 2 H), 2.15-2.24 (m, 1 H), 1.77-1.94 (m, 2 H), 0.90 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 137.0, 130.8, 129.1, 115.9, 113.7, 75.0, 72.6, 55.3, 38.0, 33.3, 16.8; IR (neat): 3075, 2955, 2838, 1612, 1514, 1249, 1092, 1038, 820 cm^{-1}; LRMS (CI, MeOH): *m/e* 219 ($[M-H]^+$), 121; HRMS (CI, methane) *m/e* calcd for $[C_{14}H_{20}O_2]^+$ 220.1463, found 220.1464.



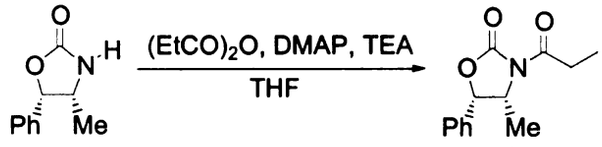
6.26 **6.27b**

To a solution of 258 mg of **6.26** (2.5 mmol) in 7.5 mL CH_2Cl_2 was added 30 mg DMAP (0.25 mmol, 10 mol%) followed by 204 mg imidazole (3 mmol, 1.2 equiv). While stirring, 640 μL TIPSCl (580 mg, 3 mmol, 1.2 equiv) was added via syringe. The reaction flask was sealed with a septum, topped with a nitrogen balloon, and stirred overnight at room temperature. Upon completion, the reaction mixture was poured into half saturated $NaHCO_3$, and extracted with CH_2Cl_2. After drying over $MgSO_4$ and evaporation, the crude product was purified by column chromatography (hexanes) to yield 600 mg of **6.27** (90%) as colorless oil; R_f~0.53 (hexanes); $[\alpha]^{20}_D$ -2.5 (*c* 1.10, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.78 (dddd, *J* = 7.1, 7.1, 10.3, 17.1 Hz, 1 H), 4.95-5.02 (m, 2 H), 3.51 and 3.48 (d of ABq, calculated ν_A at 3.509 ppm, ν_B at 3.481 ppm, ^3J = 6.1 Hz, J_{AB} = 9.5 Hz, 2 H), 2.18-2.24 (m, 1 H), 1.83-1.89 (m, 1 H), 1.68 (octet, *J* = 6.6 Hz, 1 H), 1.02-1.10 (m, 21 H), 0.88 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.5, 115.6, 68.0, 37.7, 36.0, 18.0, 16.4, 12.0; IR (neat): 3079, 2944, 2867, 1642, 1105, 993, 884, 793, 681 cm^{-1}; LRMS (EI): *m/e* 213 ($[M-^iPr]^+$), 171, 143, 131, 103, 75, 61; HRMS (CI, methane) *m/e* calcd for $[C_{15}H_{32}OSi+H]^+$ 257.3201, found 257.2304.



6.29 **6.30**

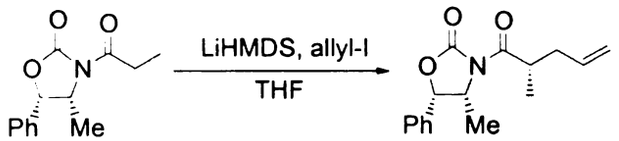
A mixture of 12.08 g norephedrine (80 mmol) and 14.6 g carbonyldiimidazole (90 mmol, 1.12 equiv) was dissolved in 300 mL dry CH_2Cl_2 and stirred at room temperature for 2 h. Upon completion, the mixture was evaporated and the residue was directly purified by column chromatography (1:4 hexanes/EtOAc) to afford 12.2 g of **6.30** (86%) as a white solid; mp 115-118 °C (commercial material 118-121 °C); $[\alpha]^{20}_D$ +163.4 (*c* 2.03, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.26-7.39 (m, 5 H), ~6.2 (br, 1 H), 5.69 (d, *J* = 8.0 Hz, 1 H), 4.16-4.22 (m, 1 H), 0.79 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5, 134.8, 128.47, 128.44, 125.9, 81.0, 52.4, 17.5; LRMS (EI): *m/e* 177 (M^+), 107, 79.



6.30 **6.31**

To a solution of 12.2 g of **6.30** (68.9 mmol) in 40 mL THF were added 210 mg DMAP (1.72 mmol, 2.5 mol%) and 11.6 mL Et_3N (8.35 g, 82.7 mmol, 1.2 equiv). The mixture was then cooled to 0 °C. 15 mL propionic anhydride (15.2 g, 117 mmol, 1.7 equiv) was added dropwise via syringe and the reaction was allowed to warm up to room temperature and stirred for 1 h 35 min. The mixture was

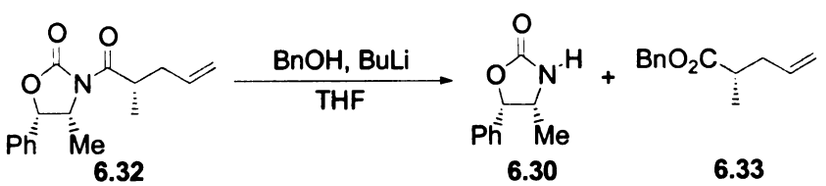
poured into half saturated $NaHCO_3$ and extracted with EtOAc. After drying over Na_2SO_4 and evaporation, the crude product was purified by column chromatography (4:1 hexanes/EtOAc) to first afford 12.59 g of **6.31** (78%) as a very thick oil. Further elution with 100% EtOAc afforded 2.70 g of recovered **6.30** (22%). Compound **6.31**: R_f~0.4 (4:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +42.9 (*c* 2.08, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27-7.41 (m, 5 H), 5.65 (d, *J* = 6.7 Hz, 1 H), 4.74 (quint, *J* = 6.7 Hz, 1 H), 2.98 and 2.90 (q of ABq, ^3J = 7.3 Hz, J_{AB} = 17.8 Hz, 2 H), 1.16 (t, *J* = 7.3 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 153.1, 133.3, 128.71, 128.67, 125.6, 79.0, 54.7, 29.3, 14.5, 8.3; LRMS (EI): *m/e* 233 (M^+), 116, 107, 91, 70, 57.



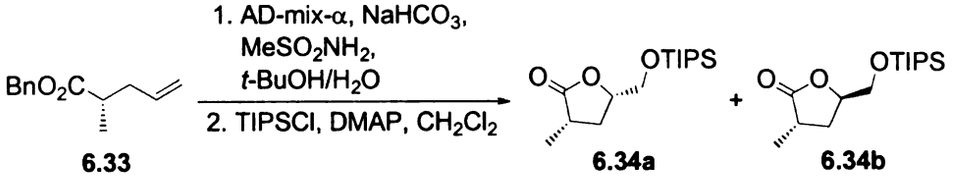
6.31 **6.32**

A solution of 50 mL commercial LiHMDS (1 M in THF, 50 mmol, 1.1 equiv, the solution in hexanes also worked) was further diluted with 40 mL THF and cooled to -78 °C. To this solution was added a solution of 10.5 g of **6.31** (45 mmol) in 90 mL THF via syringe pump at a rate of 0.67 mL/min. Upon complete addition, the mixture was stirred at -78 °C for 1 h and a solution of 6.2 mL allyl iodide (11.4 g, 67.9 mmol, 1.5 equiv) in 30 mL THF was added via syringe pump at a rate of 0.67 mL/min. *This process may cause a large amount of precipitate or gel formation*

so occasionally stopping the addition and warming the mixture to dissolve this precipitate may be needed. The mixture was stirred at -78 °C for 1 day. The reaction was quenched with half saturated NaCl and warmed up to room temperature. It was partitioned between brine and ether. The layers were separated and the aqueous layer was extracted with ether. The combined organics were dried over Na_2SO_4 and evaporated. ^{1}H NMR of the crude material showed a single diastereomer (> 95:5 dr). *Conversion of the reaction might vary from run to run.* Column chromatography (5:1 hexanes/EtOAc) afforded 9.64 g of **6.32** (79%) as a wax solid, along with 1.15 g of **6.31** (11%). Compound **6.32**: R_f~0.47 (5:1 hexanes/EtOAc); mp 64-66 °C (lit[169] 69-70 °C); $[\alpha]^{20}_D$ +46.9 (*c* 2.02, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27-7.41 (m, 5 H), 5.77 (dddd, *J* = 7.0, 7.0, 10.1, 17.1 Hz, 1 H), 5.64 (d, *J* = 7.4 Hz, 1 H), 4.98-5.05 (m, 2 H), 4.76 (quint, *J* = 6.7 Hz, 1 H), 3.86 (sext, *J* = 6.8 Hz, 1 H), 2.43-2.49 (m, 1 H), 2.16-2.22 (m, 1 H), 1.17 (d, *J* = 6.8 Hz, 3 H), 0.83 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.2, 152.7, 135.2, 133.3, 128.69, 128.64, 125.6, 117.1, 78.7, 54.8, 37.9, 37.1, 16.5, 14.6; LRMS (EI): *m/e* 273 (M^+), 258, 230, 178, 156, 134, 118, 107, 97, 70, 42.



To a solution of 6.1 mL BnOH (6.4 g, 59.2 mmol, 1.8 equiv, no purification needed) in 160 mL THF at 0 °C was added 28.5 mL of commercial BuLi solution (titrated to be 1.5 M in hexanes, 42.8 mmol, 1.3 equiv) dropwise. The mixture was stirred at 0 °C for 20 min before a solution of 9.0 g of **6.32** (32.9 mmol) in 35 mL THF was added. The mixture was stirred at 0 °C for another 40 min before being quenched with water and diluted with saturated NH_4Cl. The layers were separated and the aqueous layer was extracted with ether. The combined organics were dried over $MgSO_4$ and evaporated. Column chromatography purification (12:1 hexane/ether) afforded 6.60 g of **6.33** as oil (97%). Further elution with 100% EtOAc afforded 5.62 g of **6.30** (97%). Ester **6.33**: R_f~0.46 (10:1 hexanes/ether); $[\alpha]^{20}_D$ +2.6 (*c* 4.23, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.31-7.36 (m, 5 H), 5.73 (dddd, *J* = 7.0, 7.0, 10.3, 17.1 Hz, 1 H), 5.11 (s, 2 H), 4.98-5.07 (m, 2 H), 2.58 (sext, *J* = 7.1 Hz, 1 H), 2.38-2.48 (m, 1 H), 2.14-2.25 (m, 1 H), 1.17 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.8, 136.1, 135.3, 128.5, 128.08, 128.04, 116.9, 66.1, 39.2, 37.7, 16.5; LRMS (EI): *m/e* 204 (M^+), 130, 91, 69, 41.

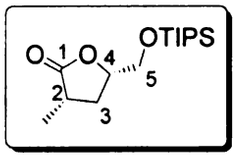


6.33 **6.34a** **6.34b**

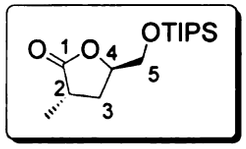
A suspension of 46.7 g commercial AD-mix-α, 13.5 g $NaHCO_3$ (160 mmol, 4.8

equiv), and 3.17 g $MeSO_2NH_2$ (33.4 mmol, 1 equiv) in 170 mL water and 170 mL *t*-BuOH was vigorously stirred at room temperature until both layers were clear. The mixture was then cooled to 5-10 °C and 6.81 g of **6.33** (33.4 mmol) was added. The reaction was then warmed to room temperature and stirred for 22 h. A batch of 12.3 mg $K_2OsO_2(OH)_4$ (~33 μmol, 0.1 mol%) was added at this time (This is not necessary if the conversion is good). The reaction continued for 16 h and was quenched with saturated Na_2SO_3. *The conversion of this dihydroxylation reaction is not very consistent. It is advised to quench the reaction at ~1.5 days even if incomplete.* After being diluted with water, the mixture was extracted with ether, dried over $MgSO_4$, and evaporated. The residue showed about 80% conversion by ^1H NMR and was taken in the next reaction without further purification.

The residue obtained from the above reaction was diluted with 70 mL dry CH_2Cl_2. To this solution was added 11.0 g DMAP (90 mmol) followed by dropwise addition of 15.2 mL TIPSCl (13.7 g, 71 mmol). The reaction was stirred at room temperature for 2.5 h before being poured into half saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and evaporated. Column chromatography purification (7:1 hexanes/EtOAc) afforded 0.89 g of recovered **6.33** (13%), 1.63 g of **6.34b** (containing 0.04 g ether, 17% discounting the added weight of ether), and 4.94 g of **6.34a** (clean, 52%).

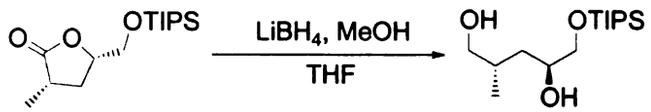


Desired *cis*-isomer 6.34a: R_f~0.38 (5:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +5.3 (*c* 3.45, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 4.41 (dddd, *J* = 3.8, 3.8, 6.1, 9.9 Hz, 1 H), 3.90 and 3.78 (d of ABq, ^3J = 3.8 Hz, J_{AB} = 11.1 Hz, 2 H), 2.62-2.70 (m, 1 H), 2.36 (ddd, *J* = 6.2, 9.0, 12.5 Hz, 1 H), 1.84 (dt, *J* = 9.9, 12.0 Hz, 1 H), 1.25 (d, *J* = 7.1 Hz, 3 H), 1.01-1.08 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.5, 78.3, 64.2, 35.4, 31.9, 17.85, 17.84, 15.4, 11.8; IR (neat): 2944, 2867, 1777, 1462, 1171, 1130, 884, 683 cm^{-1}; LRMS (EI): *m/e* 243 ($[M-^iPr]^+$), 185, 173, 131, 103; HRMS (CI, methane) *m/e* calcd for $[C_{15}H_{30}O_3Si+H]^+$ 287.2042, found 287.2040. The stereochemistry was assigned by nOe experiment: *H*4 and *H*2 showed nOe to each other.



Undesired *trans*-isomer 6.34b: R_f~0.45 (5:1 hexanes/EtOAc); $[\alpha]^{20}_D$ -15.7 (*c* 3.26, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 4.51 (dddd, *J* = 2.9, 2.9, 2.9, 8.9 Hz, 1 H), 3.91 and 3.74 (d of ABq, ^3J = 3.4 and 3.0 Hz, J_{AB} = 11.0 Hz, 2 H), 2.80 (tq, *J* = 9.4, 7.3 Hz, 1 H), 2.43 (ddd, *J* = 2.8, 9.5, 12.6 Hz, 1 H), 1.93 (dt, *J* = 12.7, 8.9 Hz, 1 H), 1.24 (d, *J* = 7.4 Hz, 3 H), 1.01-1.07 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.4, 77.7, 65.3, 34.2, 32.1, 17.87, 17.85, 16.4, 11.8; IR (neat): 2924, 2867, 1779, 1462, 1381, 1171, 1125, 884, 683 cm^{-1}; LRMS (EI): *m/e* 243 ($[M-^iPr]^+$), 185, 173, 131, 103; HRMS (CI, methane) *m/e* calcd for $[C_{15}H_{30}O_3Si+H]^+$ 287.2042, found 287.2038. The stereochemistry was assigned by nOe experiment: *H*4 and *H*2 showed no nOe to

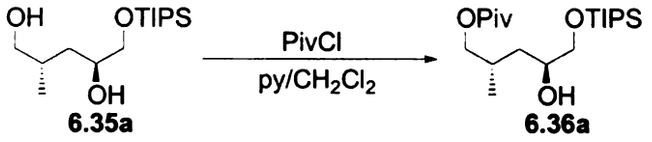
each other.



6.34a **6.35a**

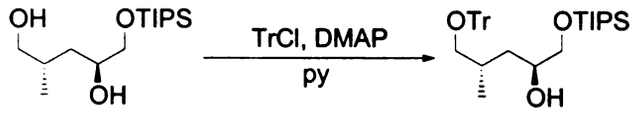
To a solution of 5.00 g of **6.34a** (17.5 mmol) in 90 mL dry THF was added 820 μL MeOH (640 mg, 20 mmol, 1.14 equiv). This solution was cooled to 0 °C and stirred for 10 min before 10.95 mL of commercial $LiBH_4$ solution (2 M in THF, 21.9 mmol, 1.25 equiv) was added dropwise. The reaction was stirred for 1 h at 0 °C followed by 2 h at room temperature before being quenched with saturated NH_4Cl (CAUTION!). To the mixture were then added 20 mL water and 15 mL glycerol. The mixture was stirred overnight before being partitioned between brine and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organics were dried over Na_2SO_4 and evaporated. The resulted 5.76 g residue was directly used in the next reaction without purification. $[\alpha]^{20}_D$ -28.6 (*c* 1.48, EtOH); ^1H NMR (500 MHz, $CDCl_3$): δ 3.73-3.78 (m, 1 H), 3.37-3.66 (2 overlapping d of ABq, can be approximated into 4 dd at 3.64 (dd, *J* = 3.8, 9.6 Hz, 1 H), 3.54 (dd, *J* = 4.3, 11.0 Hz, 1 H), 3.44 (dd, *J* = 8.3, 9.6 Hz, 1 H), and 3.39 (dd, *J* = 7.3, 11.0 Hz, 1 H)), 3.16 (s, 2 H), 1.78-1.88 (m, 1 H), 1.29-1.39 (m, 2 H), 1.02-1.08 (m, 21 H), 0.90 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 71.2, 68.7, 67.8, 38.2, 34.6, 18.1, 17.9, 11.9; LRMS (FAB): *m/e* 291

([M+H]$^+$), 247.



6.35a **6.36a**

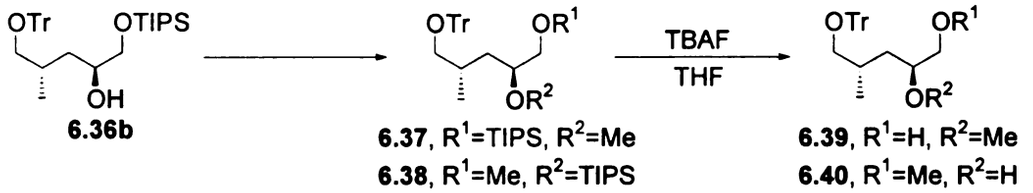
To a solution of 564 mg of **6.35a** (1.94 mmol) in 2.5 mL pyridine (no purification or drying needed) and 2.5 mL dry CH_2Cl_2 at 0 °C was added dropwise 250 μL PivCl (245 mg, 2.04 mmol, 1.05 equiv). The ice bath was removed 5 min after complete addition and the reaction was allowed to stir at room temperature overnight. The mixture was diluted with water and extracted with CH_2Cl_2. The combined organics were washed with 5% $CuSO_4$ and water before being dried over $MgSO_4$ and evaporated. Column chromatography (6:1 hexanes/EtOAc) afforded 656 mg of **6.36a** (90%) as a colorless oil; R_f~0.42 (6:1 hexanes/EtOAc); $[\alpha]^{20}_D$ -24.1 (*c* 1.08, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.96 and 3.88 (d of ABq, ^3J = 5.7 and 6.5 Hz, J_{AB} = 10.7 Hz, 2 H), 3.75 (dddd, *J* = 3.3, 3.3, 7.0, 10.4 Hz, 1 H), 3.68 (dd, *J* = 3.4, 9.6 Hz, 1 H), 3.46 (dd, *J* = 7.2, 9.6 Hz, 2 H), ~2.44 (br, 1 H), 2.06-2.12 (m, 1 H), 1.52 (ddd, *J* = 4.5, 9.8, 14.0 Hz, 1 H), 1.18 (s, 9 H), 1.03-1.09 (m, 21 H), 0.96 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.5, 69.6, 69.4, 68.0, 38.8, 36.4, 29.4, 27.2, 17.9, 16.5, 11.9; LRMS (CI, MeOH): *m/e* 375 ([M+H]$^+$), 357, 331, 229, 99, 57.



6.35a **6.36b**

To a solution of 1.23 g trityl chloride (4.4 mmol, 1.1 equiv) and 12 mg DMAP (0.1 mmol, 2.5 mol%) in 4 mL pyridine (no purification or drying needed) was added a solution of 1.19 g of **6.35a** (4 mmol) in 3 mL pyridine. The mixture was stirred at room temperature for 2.5 days and quenched with water. The mixture was partitioned between water and CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried over $MgSO_4$ and evaporated. Column chromatography (9:1 hexanes/EtOAc) afforded 1.76 g of **6.36b** (containing 0.03 g ether, 81% discounting the added weight of solvent) as an oil. Further elution with 1:1 hexanes/EtOAc afforded 192 mg of recovered **6.35a** (17%). Trityl ether **6.36b**: R_f~0.43 (9:1 hexanes/EtOAc); $[\alpha]^{20}_D$ -13.8 (*c* 1.08, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.48 (m, 6 H), 7.22-7.32 (m, 9 H), 3.72-3.78 (m, 1 H), 3.68 (dd, *J* = 3.8, 9.6 Hz, 1 H), 3.51 (dd, *J* = 7.6, 9.6 Hz, 1 H), 2.95-3.01 (m, 2 H), 2.57 (d, *J* = 3.5 Hz, 1 H), 2.03-2.10 (m, 1 H), 1.59 (ddd, *J* = 4.8, 9.4, 14.0 Hz, 1 H), 1.23 (ddd, *J* = 3.5, 9.2, 13.4 Hz, 1 H), 1.07-1.12 (m, 21 H), 1.01 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.4, 128.7, 127.7, 126.8, 86.2, 69.7, 69.0, 68.0, 37.2, 30.5, 18.0, 17.2, 11.9; IR (neat): 3476, 2976, 2928, 2867, 1448, 1383, 1121, 1074, 708 cm^{-1}; LRMS (ESI): *m/e* 555 ([M+Na]$^+$), 291, 243; HRMS (ESI) *m/e* calcd for

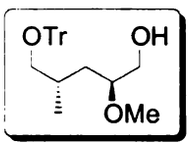
$[C_{34}H_{48}O_3Si+Na]^+$ 555.3270, found 555.3259. *This compound does not store well in $CDCl_3$.*



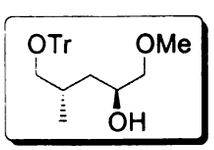
Method 1 (NaH, MeI): to a suspension of 1.16 g NaH (60% dispersion in mineral oil, not washed, corresponding to 0.70 g pure NaH, 29 mmol, 1.7 equiv) in 70 mL THF at 0 °C was added 3.2 mL MeI (purified by passing through neutral alumina, 7.28 g, 51.3 mmol, 3.0 equiv) via syringe. A solution of 9.5 g of **6.36b** (17.1 mmol) in 90 mL THF was added next via syringe. The ice bath was removed and the reaction was stirred at room temperature for 1 day. Upon completion, the reaction was quenched with half saturated NH_4Cl and briefly concentrated. The mixture was extracted with ether, dried over $MgSO_4$ and evaporated. The resultant material was a mixture of two inseparable isomers (**6.37** and **6.38**) and was used directly in the next step.

The crude residue from the previous reaction was diluted with 35 mL THF and cooled to 0 °C. To this solution was added dropwise 25.7 mL of TBAF solution (1 M in THF, 25.7 mmol, 1.5 equiv based on 100% yield of the previous reaction). Upon complete addition, the reaction was warmed to room temperature and stirred for 3 h. Water was added and the reaction was diluted with saturated

$NaHCO_3$ and extracted with ether. The combined organics were dried over $MgSO_4$ and evaporated. Column chromatography (2:1 hexanes/EtOAc) afforded 1.01 g of **6.40** (containing 0.03 g EtOAc, 15% discounting the added weight of EtOAc, 2 steps) and 5.26 g of **6.39** (containing 0.16 g EtOAc, 82% discounting the added weight of EtOAc, 2 steps) as a colorless oil.



Desired primary alcohol 6.39: R_f~0.32 (2:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +2.9 (*c* 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.47 (m, 6 H), 7.23-7.33 (m, 9 H), 3.65-3.70 (m, 1 H), 3.43-3.47 (m, 1 H), 3.36 (s, 3 H), 3.29-3.33 (m, 1 H), 3.00 and 2.95 (d of ABq, calculated ν_A at 2.994 ppm, ν_B at 2.951 ppm, ^3J = 6.0 Hz, J_{AB} = 8.8 Hz, 2 H), 1.92 (sext, *J* = 6.8 Hz, 1 H), 1.87 (br, 1 H), 1.73 (ddd, *J* = 5.9, 7.3, 13.7 Hz, 1 H), 1.21 (ddd, *J* = 5.4, 7.8, 13.7 Hz, 1 H), 1.03 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.3, 128.7, 127.7, 126.8, 86.2, 79.4, 68.4, 64.1, 57.0, 34.9, 30.7, 17.9; IR (neat): 3389, 3059, 2928, 1491, 1449, 1090, 764, 747, 709, 633 cm^{-1}; LRMS (ESI): *m/e* 413 ($[M+Na]^+$), 243; HRMS (ESI) *m/e* calcd for $[C_{26}H_{30}O_3+Na]^+$ 413.2093, found 413.2085. The structure was assigned through HMQC and HMBC analysis: the carbon bearing OMe is a methine, not a methylene. *This compound does not store well in $CDCl_3$.*



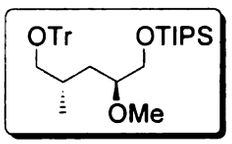
Undesired secondary alcohol 6.40 via silyl migration: R_f~0.43 (2:1 hexanes/EtOAc); $[\alpha]^{20}_D$ -1.0 (*c* 1.15, EtOH); ^{1}H NMR

(500 MHz, $CDCl_3$): δ 7.42-7.45 (m, 6 H), 7.20-7.30 (m, 9 H), 3.83-3.88 (m, 1 H), 3.36 (s, 3 H), 3.33 and 3.23 (d of ABq, can be approximated as 2 dd, 3.33 (dd, J = 3.4, 10.4 Hz, 1 H), 3.23 (dd, J = 7.6, 9.5 Hz, 1 H)), 2.98 and 2.95 (d of ABq, calculated ν_A at 2.978 ppm, ν_B at 2.954 ppm, ^3J = 6.0 Hz, J_{AB} = 8.9 Hz, 2 H), 2.51 (d, J = 2.9 Hz, 1 H), 1.98-2.08 (m, 1 H), 1.51 (ddd, J = 5.2, 9.5, 14.0 Hz, 1 H), 1.22 (ddd, J = 3.4, 8.5, 13.9 Hz, 1 H), 0.96 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.3, 128.7, 127.7, 126.8, 86.4, 77.5, 69.1, 68.2, 59.0, 37.7, 30.7, 17.4; IR (neat): 3460, 2977, 2919, 2851, 1491, 1449, 1383, 1121, 1073, 764, 747, 708, 633 cm^{-1}; LRMS (ESI): *m/e* 454 ($[M+MeCN+Na]^+$), 429 ($[M+K]^+$), 413 ($[M+Na]^+$), 243; HRMS (ESI) *m/e* calcd for $[C_{26}H_{30}O_3+Na]^+$ 413.2093, found 413.2088. The structure was assigned through HMQC and HMBC analysis: the carbon bearing OMe is a methylene, not a methine. *This compound does not store well in $CDCl_3$.*

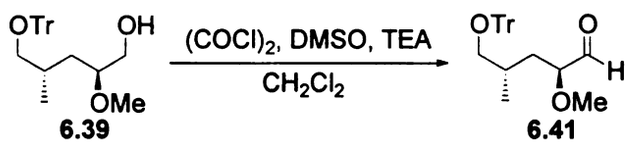
Method 2 (KHMDS, MeOTf): a solution of 7.2 g of **6.36b** (13.5 mmol) in 60 mL dry toluene was cooled to -78 °C. To this solution was added 80 mL of commercial KHMDS solution (0.5 M in toluene, 40 mmol, 3 equiv) via syringe pump at the rate of 0.77 mL/min. The reaction mixture gradually turned into a slurry. After the mixture was stirred at -78 °C for 15 min, 7.5 mL MeOTf (11 g, 67 mmol, 5 equiv) was added dropwise. The reaction mixture was stirred overnight, during which time the dry ice-acetone bath gradually warmed up, letting the

reaction warm up to room temperature. *If the slurry became hard to stir, the cold bath could be removed right away.* The reaction was quenched with saturated $NaHCO_3$ and extracted with ether. The combined organics were dried over $MgSO_4$ and evaporated. Column chromatography (3:1 → 1:1 hexanes/CH_2Cl_2) afforded 6.74 g of pure **6.37** (91%) as a colorless oil.

The TBAF desilylation was carried out via the same procedure mentioned above.



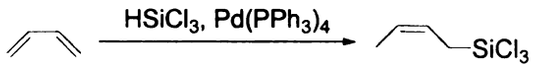
Silyl migration intermediate 6.37: R_f~0.35 (2:1 hexanes/CH_2Cl_2); $[\alpha]^{20}_D$ –10.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46-7.48 (m, 6 H), 7.22-7.32 (m, 9 H), 3.74 and 3.60 (d of ABq, ^3J = 5.5 and 5.0 Hz, J_{AB} = 10.1 Hz, 2 H), 3.42 (s, 3 H), 3.27-3.32 (m, 1 H), 3.01 and 2.92 (d of ABq, ^3J = 5.5 and 6.5 Hz, J_{AB} = 8.8 Hz, 2 H), 2.00-2.06 (m, 1 H), 1.56 (ddd, *J* = 4.6, 9.3, 13.0 Hz, 1 H), 1.36 (ddd, *J* = 3.7, 9.3, 13.2 Hz, 1 H), 1.07-1.11 (m, 21 H), 1.03 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.5, 128.8, 127.6, 126.7, 86.0, 80.0, 68.8, 66.1, 58.1, 36.2, 30.5, 18.0, 17.4, 11.9; IR (neat): 3059, 2942, 2867, 1449, 1103, 1071, 706 cm^{-1}; LRMS (ESI): *m/e* 585 ($[M+K]^+$), 569 ($[M+Na]^+$), 243; HRMS (ESI) *m/e* calcd for $[C_{35}H_{50}O_3Si+Na]^+$ 569.3427, found 569.3427. *This compound does not store well in $CDCl_3$.*



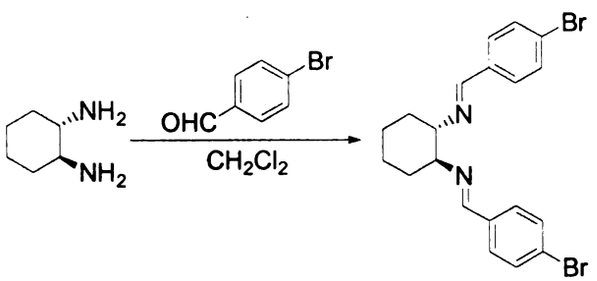
6.39 **6.41**

A solution of 0.90 mL oxalyl chloride (1.31 g, 10.3 mmol, 1.2 equiv, freshly distilled) in 30 mL dry CH_2Cl_2 was cooled to -78 °C. To this solution was added dropwise a solution of 1.46 mL DMSO (1.61 g, 20.5 mmol, 2.4 equiv, freshly distilled) in 60 mL CH_2Cl_2. The mixture was stirred for 5 min before a solution of 3.4 g of **6.39** (containing 0.1 g EtOAc, 8.5 mmol discounting the added weight of EtOAc) in 11 mL CH_2Cl_2 was added dropwise, during which time a precipitate was observed. The mixture was stirred cold for another 10 min before 5.95 mL Et_3N (4.32 g, 43 mmol, 5 equiv, freshly distilled) was added dropwise. The reaction was warmed to room temperature, and judged complete after 1.5 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4 and evaporated. The residue (3.81 g, containing 0.40 g CH_2Cl_2 and 0.13 g DMSO, ~99% as is discounting the added weight of solvents) was used in the next step without purification; $[\alpha]^{20}_D$ -42.9 (*c* 0.78, CH_2Cl_2, crude); ^1H NMR (500 MHz, $CDCl_3$): δ 9.64 (d, *J* = 2.0 Hz, 1 H), 7.45-7.47 (m, 6 H), 7.23-7.33 (m, 9 H), 3.61 (ddd, *J* = 2.2, 4.2, 9.8 Hz, 1 H), 3.41 (s, 3 H), 2.99 (d, *J* = 5.9 Hz, 2 H), 2.03-2.10 (m, 1 H), 1.79 (ddd, *J* = 4.6, 9.5, 14.2 Hz, 1 H), 1.44 (ddd, *J* = 2.4, 7.3, 12.0 Hz, 1 H), 1.02 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.9, 144.3, 128.7, 127.7, 126.9, 86.3, 84.0, 68.2, 58.2, 33.7, 30.2, 17.0; IR (neat): 3058, 2930, 2874, 1734, 1449, 1071, 764, 747, 708, 633 cm^{-1}; LRMS (ESI): *m/e* 429 ($[M+MeCN+H]^+$), 411 ($[M+Na]^+$); HRMS (ESI) *m/e*

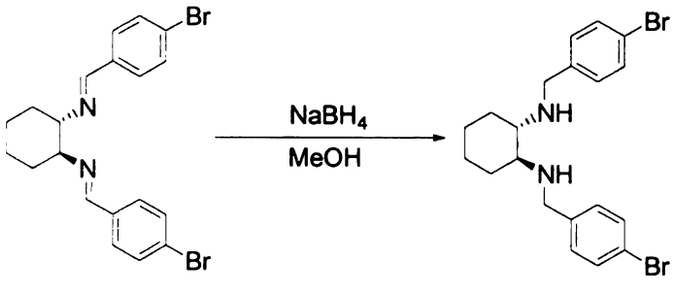
calcd for $[C_{26}H_{28}O_3+Na]^+$ 411.1936, found 411.1929. *This compound does not store well in $CDCl_3$.*



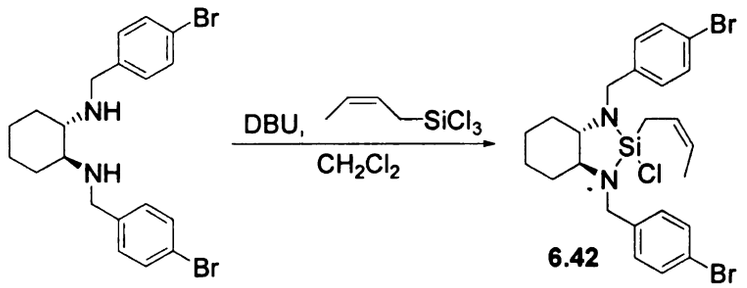
Butadiene gas was condensed into a round-bottom flask in a dry ice-acetone bath. A portion of 8.7 mL such liquid butadiene (5.39 g, 0.1 mol) was taken by a syringe and quickly injected into an air-free flask containing 350 mg $Pd(PPh_3)_4$ (0.3 mmol, 0.3 mol%) that was placed in another dry ice-acetone bath. While stirring, 10 mL trichlorosilane (13.4 g, ~0.1 mol) was added into the air-free flask via syringe and the reaction turned black. The flask was sealed with a Teflon screw cap and the cold bath was removed. The reaction was stirred at room temperature overnight. Distillation at 140-142 °C (1 atm) afforded 15.2 g of the desired product (79%) as a colorless oil. ^{1}H NMR showed a 96:4 *Z*/*E* ratio; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.67-5.74 (m, 1H), 5.38-5.42 (m, 1 H), 2.33 (ddq, *J* = 1.7, 8.0, 0.6 Hz, 2 H), 1.65 (ddt, *J* = 1.7, 6.8, 1.0 Hz, 3 H), minor *E* isomer at 2.24 and 1.70; ^{13}C NMR (125 MHz, $CDCl_3$): δ 128.3, 118.6, 24.7, 13.0.



To a flask containing 9.0 g of the diamine (78.9 mmol), 29.2 g of the aldehyde (157 mmol, 2 equiv), and 15 g freshly activated molecular sieves (4 Å) was added 200 mL CH_2Cl_2. The mixture was stirred at room temperature for 1 day before being filtered through a pad of celite. The celite pad was washed with CH_2Cl_2 and the filtrate was evaporated. This crude material contained a small amount of unreacted aldehyde. Thus it was suspended in hexanes with vigorous stirring. Solid (product) was collected by filtration and washed with minimum amount of hexanes. The mother liquor was evaporated and the residual solid was again suspended in hexanes and a second crop of solid (product) was collected. A third crop was obtained in the same manner. The combined solids were dried under high vacuum to yield 33.8 g of a white solid (96%), mp 122-123 °C (lit[170] 124-125.5 °C); $[\alpha]^{20}_D$ +263.1 (*c* 1.19, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (s, 2 H), 7.43 (br, 8 H), 3.37 (br, 2 H), 1.78-1.86 (m, 6 H), 1.43-1.49 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 135.1, 131.6, 129.3, 124.6, 73.7, 32.8, 24.4; IR (neat): 2930, 2857, 1644, 1590, 1485, 1069, 1011, 818 cm^{-1}; LRMS (EI): *m/e* 446 (M^+), 265, 184; HRMS (EI) *m/e* calcd for $[C_{20}H_{20}Br_2N_2]^+$ 445.9943, found 445.9978.



To a solution of 7.17 g of the diimine (16 mmol) in 80 mL MeOH (no purification or drying needed) and ~10 mL ether (no purification or drying needed) at 0 °C was added 1.46 g $NaBH_4$ (38.4 mmol, 2.4 equiv) delivered in small portions. Gas evolution was observed and the reaction was allowed to warm to room temperature and stir for 19 h. The reaction was quenched with water and the suspension was extracted with CH_2Cl_2. The combined organics were dried over K_2CO_3 and evaporated to afford 7.25 g of the desired product (100%) as a slightly yellow oil; $[\alpha]^{20}_D$ +38.4 (*c* 1.14, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.40-7.42 (m, 4 H), 7.16-7.18 (m, apparent d, 4 H), 3.86 and 3.62 (ABq, J_{AB} = 13.5 Hz, 4 H), ~2.31 (m, 2 H), 2.11-2.14 (m, 2 H), 1.71-1.73 (m, 2 H), 1.07-1.24 (m, 4 H) (NH protons not observed); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.9, 131.4, 129.7, 120.5, 60.8, 50.1, 31.4, 24.9; IR (neat): 2926, 2853, 1487, 1455, 1071, 1011, 799 cm^{-1}; LRMS (EI): *m/e* 450 (M^+), 281, 184, 169, 96, 90; HRMS (EI) *m/e* calcd for $[C_{20}H_{24}Br_2N_2]^+$ 450.0306, found 450.0286. This product was used directly in the next step without further purification.

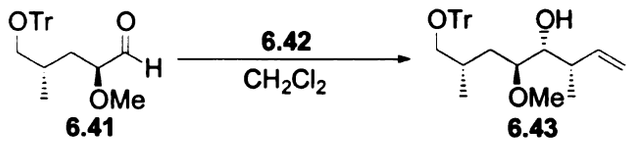


6.42

To a solution of 2.09 g trichlorocrotylsilane (weighed in a syringe, 11 mmol, 1.1 equiv) in 20 mL CH_2Cl_2 in an air-free flask was added 3.3 mL DBU (3.34 g, 22 mmol, 2.2 equiv, freshly distilled) at 0 °C. A solution of 4.5 g of the diamine in 10 mL CH_2Cl_2 was introduced via syringe pump at the rate of 0.6 mL/min. The air-free flask was sealed with a Teflon screw cap and the reaction was warmed to room temperature and stirred overnight. The reaction mixture was pumped down under high vacuum to remove the solvent, and a white syrup was obtained. It was taken into the glove box and 30 mL dry pentane was added. A large amount of precipitate was formed. The flask was sealed and this precipitate was aged with vigorous stirring overnight. The mixture was filtered and the cake was washed with pentane. The combined filtrate was concentrated to ~18 mL and stored in -20 °C freezer inside the glove box (no precipitation was formed after 2 days in freezer). This solution was used directly in the crotylation reaction without isolation of the reagent.

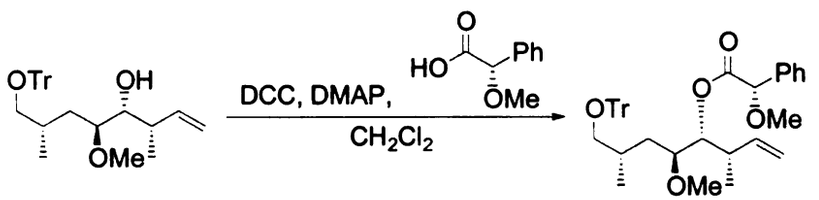
Determination of the concentration: a solution of 1.0 mL of the crotylsilane reagent was diluted with 9 mL CH_2Cl_2. To this solution was added 185 mg

4-bromobenzaldehyde (1.0 mmol) in one portion. The reaction flask was sealed with a Teflon stopper and the reaction was stirred at room temperature for 19 h, before being quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2. After drying over $MgSO_4$ and evaporation, the crude material was analyzed by ^1H NMR. The ratio of the residual aldehyde vs. crotylation product was determined to be 1:0.6. Therefore, the conversion was 37%. The concentration of the solution obtained above was 0.37 M (corresponding to ~65% yield of **6.42**).



A solution of **6.42** (9.5 mL, 0.37 M determined above, ~3.5 mmol, 1.17 equiv) was diluted with 40 mL CH_2Cl_2 and cooled to 0 °C. Upon stirring, a solution of 1.32 g of crude **6.41** (containing DMSO and CH_2Cl_2, 3.0 mmol discounting the added weight), made via a Swern oxidation of 1.17 g of **6.39** (3.0 mmol), in 7 mL CH_2Cl_2 was added dropwise. The reaction was warmed to room temperature and stirred for 1.5 days before being quenched with saturated $NaHCO_3$. After being stirred for 15 min, the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated. Column chromatography (5:1 hexanes/EtOAc) afforded 0.87 g of **6.43** as a single diastereomer (containing trace amount of EtOAc, 64% discounting the added weight of EtOAc). Further elution with

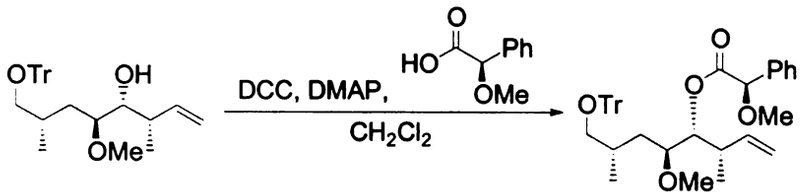
1:1:0.1 hexanes/EtOAc/Et_3N afforded 1.61 g of the chiral diamine ligand (100%). Alcohol **6.43**: R_f~0.36 (5:1 hexanes/EtOAc); $[\alpha]^{20}_D$ -13.7 (*c* 1.05, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.48-7.50 (m, 6 H), 7.24-7.34 (m, 9 H), 5.67 (ddd, *J* = 8.5, 10.3, 17.1 Hz, 1 H), 5.04-5.10 (m, 2 H), 3.63-3.65 (m, 1 H), 3.35 (s, 3 H), 3.28 (dt, *J* = 10.5, 2.7 Hz, 1 H), 3.03 and 2.93 (d of ABq, ^3J = 5.4 and 6.8 Hz, J_{AB} = 8.5 Hz, 2 H), 2.24-2.31 (m, 1 H), 2.15 (s, 1 H), 2.01-2.08 (m, 1 H), 1.64 (ddd, *J* = 3.9, 10.5, 14.2 Hz, 1 H), 1.26 (ddd, *J* = 2.4, 10.0, 14.4 Hz, 1 H), 1.16 (d, *J* = 6.6 Hz, 3 H), 1.02 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.5, 140.1, 128.8, 127.6, 126.7, 115.1, 86.1, 80.0, 73.4, 69.1, 56.9, 40.3, 31.4, 30.4, 17.2, 17.1; IR (neat): 3457, 3059, 2959, 2928, 1491, 1449, 1088, 1032, 916, 764, 741, 708, 633 cm^{-1}; LRMS (ESI): *m/e* 467 ($[M+Na]^+$), 243; HRMS (ESI) *m/e* calcd for $[C_{30}H_{36}O_3+Na]^+$ 467.2562, found 467.2551. *This compound does not store well in $CDCl_3$.*



6.43 **6.47b**

To a solution containing 34 mg of **6.43** (77 μmol), 13.1 mg of the chiral acid (77 μmol, 1.0 equiv), and 17.8 mg DCC (84 μmol, 1.1 equiv) in 1 mL CH_2Cl_2 was added one crystal of DMAP. The reaction was stirred at room temperature

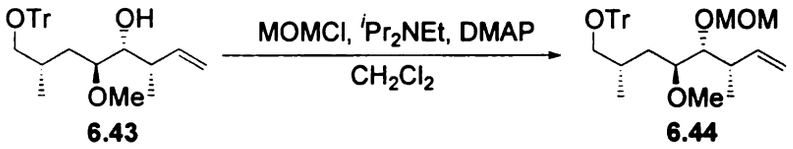
overnight, before being quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, dried over $MgSO_4$ and evaporated. Column chromatography (5:1 hexanes/EtOAc) afforded 34 mg of **6.47b** (75%, containing trace EtOAc); R_f~0.39 (5:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +14.5 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): (*Due to the large number of aromatic protons, the residual peak of $CDCl_3$ was not observed. Therefore, the chemical shift in this spectrum was referenced to the residual peak of acetyl methyl protons of EtOAc at 2.05 ppm*): δ 7.46-7.49 (m, 6 H), 7.41-7.43 (m, 2 H), 7.28-7.33 (m, 9 H), 7.23-7.26 (m, 3 H), 5.51 (ddd, *J* = 8.5, 10.3, 16.9 Hz, 1 H), 5.08 (dd, *J* = 3.2, 9.3 Hz, 1 H), 4.90-4.94 (m, 2 H), 4.75 (s, 1 H), 3.40 (s, 3 H), 3.29 (s, 3 H), 3.28 (dt, overlapped peak, 1 H), 2.99 and 2.91 (d of ABq, ^3J = 5.6 and 6.8 Hz, J_{AB} = 8.5 Hz, 2 H), 2.20-2.27 (m, 1 H), 1.98-2.03 (m, 1 H), 1.61 (ddd, *J* = 3.9, 10.7, 14.4 Hz, 1 H), 1.14 (ddd, *J* = 2.0, 10.0, 13.7 Hz, 1 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.59 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 144.4, 139.1, 136.5, 128.8, 128.6, 128.5, 127.6, 127.3, 126.8, 115.6, 86.0, 82.4, 78.3, 75.2, 68.9, 57.2, 57.0, 39.2, 32.5, 30.3, 16.7, 16.3; IR (neat): 3061, 2930, 2826, 1752, 1491, 1449, 1198, 1179, 1100, 1075, 747, 708, 698, 633 cm^{-1}; LRMS (ESI): *m/e* 615 ($[M+Na]^+$), 243, 83; HRMS (ESI) *m/e* calcd for $[C_{39}H_{44}O_5+Na]^+$ 615.3086, found 615.3073. *This compound does not store well in $CDCl_3$.*



6.43 **6.47a**

The same operation procedure was applied to 34 mg of **6.43** (77 μmol), 13.1 mg of the chiral acid (77 μmol, 1.0 equiv), and 17.8 mg DCC (84 μmol, 1.1 equiv) in 1 mL CH_2Cl_2 with one crystal of DMAP. The reaction afforded 32 mg of **6.47a** (containing 1 mg ether, ~70% discounting the added weight); R_f~0.43 (5:1 hexanes/EtOAc); $[\alpha]^{20}_D$ -19.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): (*Due to the large number of aromatic protons, the residual peak of $CDCl_3$ was not observed. Therefore, the chemical shift in this spectrum was referenced to the residual peak of acetyl methyl protons of EtOAc at 2.05 ppm*): δ 7.43-7.46 (m, 6 H), 7.38-7.40 (m, 2 H), 7.29-7.32 (m, 6 H), 7.23-7.26 (m, 3 H), 7.17-7.21 (m, 2 H), 7.09-7.12 (m, 1 H), 5.63 (ddd, *J* = 8.5, 10.3, 17.3 Hz, 1 H), 5.06 (dd, *J* = 3.2, 8.5 Hz, 1 H), 5.00-5.05 (m, 2 H), 4.74 (s, 1 H), 3.41 (s, 3 H), 3.19 (dt, *J* = 10.7, 2.7 Hz, 1 H), 3.16 (s, 3 H), 2.84 and 2.70 (d of ABq, ^3J = 5.4 and 7.3 Hz, J_{AB} = 8.8 Hz, 2 H), 2.35-2.43 (m, 1 H), 1.78-1.85 (m, 1 H), 1.22 (ddd, *J* = 3.6, 10.7, 14.1 Hz, 1 H), ~0.92 (ddd, overlapped peak, 1 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 0.84 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 144.5, 139.3, 136.3, 128.8, 128.5, 128.3, 127.6, 127.3, 126.8, 115.7, 86.0, 82.7, 78.3, 75.6, 68.9, 57.4, 56.8, 39.0, 32.4, 30.1, 16.7, 16.5; IR (neat): 3061, 2930, 2826, 1752, 1734, 1491, 1449, 1177,

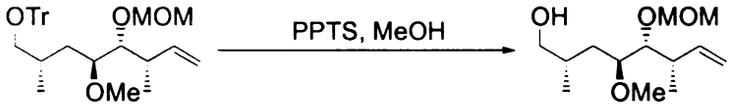
1103, 747, 708, 698, 633 cm^{-1}; LRMS (ESI): *m/e* 615 ($[M+Na]^+$), 243; HRMS (ESI) *m/e* calcd for $[C_{39}H_{44}O_5+Na]^+$ 615.3086, found 615.3088. *This compound does not store well in $CDCl_3$.*



6.43 **6.44**

To a solution of 1.71 g of **6.43** (3.84 mmol) and 50 mg DMAP (0.41 mmol, ~10 mol%) in 15 mL CH_2Cl_2 was added 2.0 mL diisopropylethylamine (1.48 g, 11.5 mmol, 3 equiv, freshly distilled). The mixture was cooled to 0 °C and dropwise charged with 580 μL MOMCl (615 mg, 7.64 mmol, 2 equiv). The reaction was allowed to warm to room temperature and stir for 1.5 days. *Conversion of this reaction varied from run to run.* The reaction was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, dried over $MgSO_4$ and evaporated. Column chromatography (8:1 hexanes/EtOAc) afforded 1.58 g of **6.44** (84%) and 135 mg of recovered **6.43** (~8%). MOM acetal **6.44**: R_f~0.30 (8:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +18.2 (*c* 1.00, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.42-7.44 (m, 6 H), 7.18-7.28 (m, 9 H), 5.67 (ddd, *J* = 8.5, 10.3, 17.1 Hz, 1 H), 4.96-5.02 (m, 2 H), 4.78 and 4.59 (ABq, J_{AB} = 6.6 Hz, 2 H), 3.57 (dd, *J* = 2.0, 8.3 Hz, 1 H), 3.37 (s, 3 H), 3.26 (s, 3 H), 3.27 (dt, overlapped peak, 1 H), 2.99 and 2.84 (d of ABq, ^3J = 5.4 and 7.3 Hz, J_{AB} = 8.7 Hz, 2 H), 2.22-2.29 (m, 1 H), 1.95-2.02 (m, 1 H), 1.59

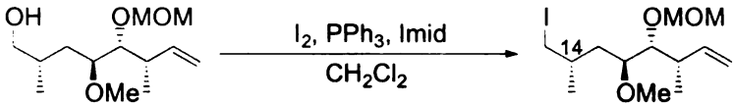
(ddd, J = 3.9, 10.5, 14.4 Hz, 1 H), 1.19 (ddd, J = 2.0, 10.0, 14.2 Hz, 1 H), 1.09 (d, J = 6.8 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.5, 141.1, 128.8, 127.6, 126.7, 114.8, 97.4, 86.1, 80.7, 79.5, 69.1, 56.9, 56.0, 40.5, 33.3, 30.7, 17.4, 17.2; IR (neat): 3058, 2919, 1449, 1096, 1032, 918, 764, 747, 708, 633 cm^{-1}; LRMS (ESI): *m/e* 511 ([M+Na]$^+$), 243; HRMS (ESI) *m/e* calcd for [$C_{32}H_{40}O_4$+Na]$^+$ 511.2824, found 511.2825. *This compound does not store well in $CDCl_3$.*



6.44 **6.45**

To a solution of 2.42 g of **6.44** (4.92 mmol) in 35 mL MeOH (no drying or purification needed) was added 617 mg PPTS (2.46 mmol, 0.5 equiv) at room temperature in one portion. The reaction was stirred for 21 h and then quenched with saturated $NaHCO_3$. Extraction with ether was followed by drying over $MgSO_4$ and evaporation. Column chromatography (1:2 hexanes/EtOAc) afforded 1.11 g of **6.45** (92%); R_f~0.50 (1:2 hexanes/EtOAc); [α]$^{20}_D$ +8.2 (*c* 1.29, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.66 (ddd, J = 8.8, 10.3, 17.1 Hz, 1 H), 4.98-5.03 (m, 2 H), 4.81 and 4.62 (ABq, J_{AB} = 6.6 Hz, 2 H), 3.63 (dd, J = 1.5, 8.8 Hz, 1 H), 3.49 and 3.39 (d of ABq, ^3J = 5.2 and 5.9 Hz, J_{AB} = 11 Hz, 2 H), 3.39 (s, 3 H), 3.33 (s, 3 H), ~3.31 (dt, overlapped peak, 1 H), 2.24-2.32 (m, 1 H), 2.23 (br,

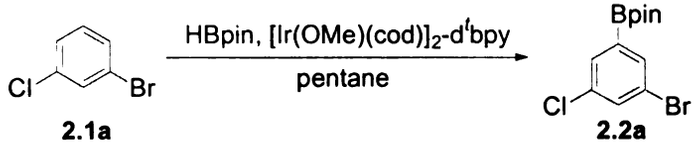
1 H), 1.74 (sext, J = 6.4 Hz, 1 H), 1.60 (ddd, J = 6.6, 10.0, 15.1 Hz, 1 H), 1.37 (ddd, J = 1.5, 7.1, 14.9 Hz, 1 H), 1.11 (d, J = 6.6 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.9, 115.1, 97.3, 82.2, 78.6, 68.5, 56.6, 56.0, 40.9, 33.8, 33.4, 17.7, 17.6; IR (neat): 3443, 2932, 1642, 1458, 1381, 1146, 1098, 1034, 918 cm^{-1}; LRMS (CI, MeOH): *m/e* 247 ([M+H]$^+$), 215, 197, 183, 153, 129; HRMS (CI, methane) *m/e* calcd for $[C_{13}H_{26}O_4+H]^+$ 247.1909, found 247.1918.



6.45 **6.46**

To a solution of 262 mg PPh_3 (1 mmol, 2 equiv) in 5 mL CH_2Cl_2 was added 82 mg imidazole (1.2 mmol, 2.4 equiv) followed by 272 mg I_2 (1.07 mmol, 2.14 equiv). The mixture turned to a yellow suspension upon stirring, which became red after a few minutes. A solution of 121 mg of **6.45** (0.5 mmol) in 2 mL CH_2Cl_2 was added to the mixture, which was then stirred in dark environment for 2 h. The reaction mixture was concentrated and purified by chromatography (6:1 hexanes/EtOAc). The fractions collected were contaminated with I_2 and therefore were stirred over solid $Na_2S_2O_3$ before evaporation to afford 125 mg of **6.46** (71%) as slightly yellow oil (This reaction unexpectedly resulted in some epimerization at C14[171] and an optical rotation value of pure sample needs to be updated.); R_f~0.48 (6:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.66 (ddd, J = 8.8, 10.3, 17.2 Hz,

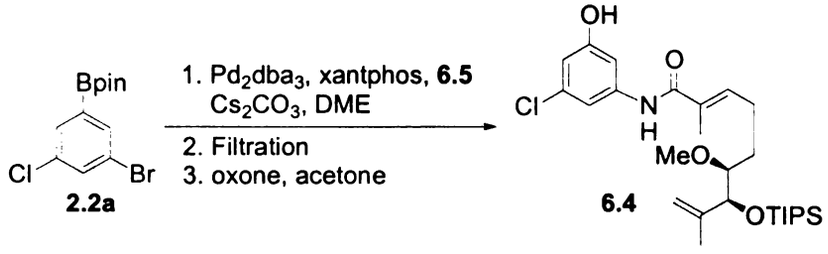
1 H), 5.03 (ddd, J = 1.0, 1.6, 17.2 Hz, 1 H), 4.98-5.01 (m, 1 H), 4.81 and 4.62 (ABq, J_{AB} = 6.7 Hz, 2 H), 3.60 (dd, J = 2.0, 8.8 Hz, 1 H), 3.40 (s, 3 H), 3.30 (s, 3 H), 3.25-3.28 (m, 2 H), 3.14 (half of d of ABq, can be viewed as dd, ^3J = 6.3 Hz, J_{AB} = 9.5 Hz, 1 H), 2.23-2.31 (m, 1 H), 1.68-1.74 (m, 1 H), 1.65 (ddd, J = 3.7, 10.4, 14.2 Hz, 1 H), 1.29 (ddd, J = 2.0, 9.4, 13.9 Hz, 1 H), 1.10 (d, J = 6.7 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.8, 115.0, 97.4, 80.9, 78.8, 57.0, 56.1, 40.7, 36.1, 31.4, 20.0, 19.0, 17.6; IR (neat): 2961, 1642, 1458, 1379, 1196, 1154, 1101, 1034, 918 cm^{-1}; LRMS (CI, MeOH): *m/e* 325 ([M-MeOH+H]$^+$), 301, 239, 227, 185, 169, 129; HRMS (CI, NH_3) *m/e* calcd for $[C_{13}H_{25}IO_3+H]^+$ 357.0927, found 357.0930.



2.1a **2.2a**

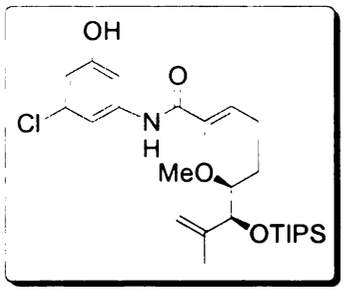
Following general procedure A outlined in Chapter 7 (page 149), 705 μL of **2.1a** (1.15 g, 6 mmol) was borylated with 1.75 mL HBpin (1.54 g, 12 mmol, 2 equiv), 20 mg $[Ir(OMe)(cod)]_2$ (0.03 mmol, 0.5 mol%) and 16.1 mg d^{t}bpy (0.06 mmol, 1.0 mol%) in 6 mL pentane at room temperature for 18 h (open to nitrogen) and then 70 °C for 2 h (sealed tube). After being cooled to room temperature, the reaction was carefully quenched with MeOH and concentrated. The residual was passed through a silica plug (CH_2Cl_2) to afford 1.85 g of **2.2a** as colorless oil

(97%), which solidified upon standing at room temperature; mp 52-54 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (dd, *J* = 0.8, 1.9 Hz, 1 H), 7.67 (dd, *J* = 0.8, 1.9 Hz, 1 H), 7.57 (t, *J* = 1.9 Hz, 1 H), 1.32 (s, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.6, 134.9, 133.8, 133.1, 122.6, 84.5, 24.8; IR (neat): 2980, 1551, 1404, 1339, 1144, 868, 770, 700 cm^{-1}; LRMS (EI): *m/e* 316 (M^+), 301, 230, 216, 85, 58, 41.

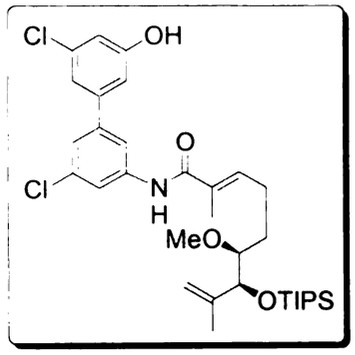


Following general procedure E outlined in Chapter 7 (page 152), the amidation was performed with 1.15 g of **2.2a** (3.6 mmol, 1.5 equiv), 920 mg of **6.5** (2.4 mmol), 44 mg Pd_2dba_3 (0.048 mmol, 2 mol%), 83 mg xantphos (0.144 mmol, 6 mol%) and 1.10 g Cs_2CO_3 (3.36 mmol, 1.4 equiv) in 9 mL DME at 95-100 °C for 5 h. After filtration through a silica pad and eluting with acetone, the oxidation was performed with a solution of 3.3 g oxone (5.36 mmol, 2.24 equiv) in 16 mL water and 24 mL acetone for 40 min, and worked up as described. Column chromatography (12:1 → 6:1 CH_2Cl_2/EtOAc) afforded 0.24 g of the Suzuki dimerization product (16%) as well as 0.90 g of the desired **6.4** (73%).

Desired product 6.4: White solid, mp 106.5-108 °C; R_f~0.42 (9:1 CH_2Cl_2/EtOAc); $[\alpha]^{20}_D$ -12.7° (*c* 1.02, acetone); ^{1}H NMR (500 MHz, acetone-d_6): δ

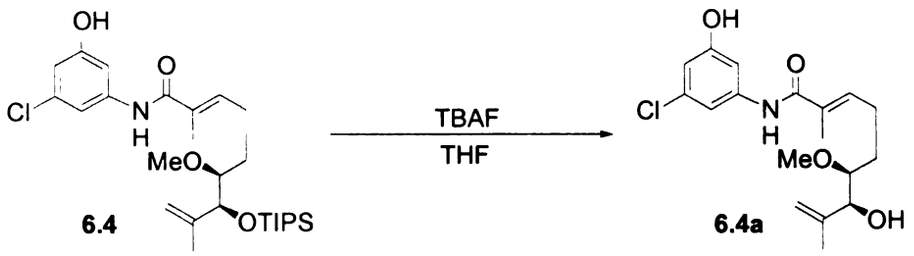


8.94 (br, 1 H), 8.69 (s, 1 H), 7.30 (t, *J* = 1.8 Hz, 1 H), 7.28 (t, *J* = 2.0 Hz, 1 H), 6.56 (t, *J* = 2.0 Hz, 1 H), 6.42 (tq, *J* = 7.6, 1.5 Hz, 1 H), 5.02-5.03 (m, 1 H), 4.91-4.92 (m, 1 H), 4.40 (d, *J* = 5.9 Hz, 1 H), 3.46 (s, 3 H), 3.27 (ddd, *J* = 3.0, 5.9, 8.5 Hz, 1 H), 2.26-2.32 (m, 2 H), 1.88 (br, 3 H), 1.77 (br, 3 H), 1.67 (dddd, *J* = 3.2, 7.3, 9.0, 14.2 Hz, 1 H), 1.33 (dddd, *J* = 6.3, 8.5, 8.5, 14.6 Hz, 1 H), 1.06-1.12 (m, 21 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 168.5, 159.3, 146.2, 142.5, 137.0, 134.8, 132.9, 113.1, 111.8, 111.2, 106.2, 84.6, 77.4, 58.8, 29.7, 25.3, 19.4, 18.47, 18.45, 13.2, 12.8; IR (neat): 3200-3300 (br), 2944, 2867, 1661, 1601, 1539, 1429, 1098, 884, 679 cm^{-1}; LRMS (EI): *m/e* 466 ([M-^{i}Pr]$^+$), 434, 253, 227, 157, 115, 89, 75, 59. Anal. Calcd for $C_{27}H_{44}ClNO_4Si$: C, 63.56; H, 8.69; N, 2.75. Found C, 63.45; H, 8.83; N, 2.64.



Suzuki dimerization product: slightly yellow solid, mp 133-136 °C; R_f~0.57 (9:1 CH_2Cl_2/EtOAc); $[\alpha]^{20}_D$ -12.2 (*c* 0.96, acetone); ^{1}H NMR (500 MHz, acetone-d_6): δ 9.17 (br, 1 H), 9.00 (s, 1 H), 7.96 (t, *J* = 1.9 Hz, 1 H), 7.89 (t, *J* = 1.9 Hz, 1 H), 7.33 (t, *J* = 1.9 Hz, 1 H), 7.13 (t, *J* = 1.7 Hz, 1 H), 7.04 (dd, *J* = 1.7, 2.2 Hz, 1 H), 6.90 (t, *J* = 2.0 Hz, 1 H), 6.51 (tq, *J* = 7.3, 1.2 Hz, 1 H), 5.02-5.03 (m, 1 H), 4.91-4.92 (m, 1 H), 4.40 (d, *J* = 5.9 Hz, 1 H), 3.47 (s, 3 H), 3.28 (ddd, *J* = 2.9, 5.9, 8.8 Hz, 1 H), 2.29-2.35 (m, 2 H), 1.92 (br,

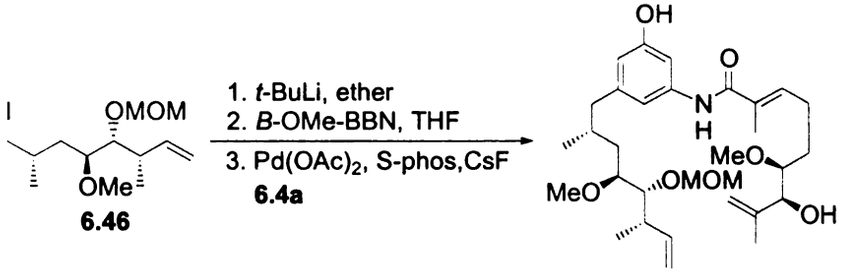
3 H), 1.77 (br, 3 H), 1.67 (dddd, J = 2.6, 7.0, 9.0, 13.7 Hz, 1 H), 1.33 (dddd, J = 6.1, 8.2, 8.2, 14.1 Hz, 1 H), 1.06-1.12 (m, 21 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 168.6, 159.7, 146.3, 143.3, 142.4, 142.3, 137.5, 135.7, 135.2, 132.8, 122.1, 119.7, 118.9, 117.5, 115.9, 113.5, 113.1, 84.7, 77.3, 58.8, 29.8, 25.3, 19.4, 18.48, 18.45, 13.2, 12.8; IR (neat): 3300 (br), 2946, 2867, 1661, 1598, 1574, 1536, 1431, 1107, 884, 843, 685 cm^{-1}; LRMS (EI): *m/e* 576 ([M-^{i}Pr]$^+$), 544, 392, 334, 253, 227, 157, 145, 115; HRMS (EI) *m/e* calcd for [$C_{33}H_{47}Cl_2NO_4Si$]$^+$ 619.2651, found 619.2678.



6.4 **6.4a**

To a solution of 0.99 g of **6.4** (1.94 mmol) in 6 mL THF at 0 °C was added dropwise 4 mL of commercial TBAF solution (1.0 M in THF, 4 mmol, ~2 equiv). After 2.5 h, 2 mL of additional TBAF solution (1.0 M in THF, 2 mmol, ~1 equiv) was added and the reaction continued overnight. The reaction was judged complete after 16.5 h. The reaction was then quenched with saturated $NaHCO_3$ and extracted with EtOAc. The combined organics were washed with 5% $CuSO_4$ followed by 1 M HCl before being dried over $MgSO_4$ and evaporated. Column chromatography (1:1.5 hexanes/EtOAc) afforded 0.69 g of **6.4a** as a glass-like material (100%); R_f~0.38 (1:1.5 hexanes/EtOAc); $[\alpha]^{20}_D$ +3.6 (*c* 1.14, acetone); ^{1}H

NMR (500 MHz, acetone-d_6): δ 8.99 (br, 1 H), 8.72 (s, 1 H), 7.31 (t, J = 1.7 Hz, 1 H), 7.28 (t, J = 2.0 Hz, 1 H), 6.56 (t, J = 2.0 Hz, 1 H), 6.41 (tq, J = 7.3, 1.5 Hz, 1 H), 4.99 (m, 1 H), 4.84 (m, 1 H), 4.04 (m, 1 H), 3.75 (d, J = 4.2 Hz, 1 H), 3.42 (s, 3 H), 3.28 (ddd, J = 4.2, 6.1, 7.8 Hz, 1 H), 2.24-2.30 (m, 2 H), 1.88 (br, 3 H), 1.73 (br, 3 H), 1.67 (dddd, J = 4.2, 6.6, 9.5, 13.9 Hz, 1 H), 1.46 (dddd, J = 6.3, 7.8, 9.0, 14.2 Hz, 1 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 168.6, 159.3, 146.8, 142.5, 136.8, 134.8, 133.0, 112.6, 111.8, 111.3, 106.2, 83.2, 77.4, 58.6, 30.2, 25.0, 18.6, 12.8; IR (neat): 3297 (br), 2932, 1661, 1597, 1539, 1429, 1289, 1169, 1098, 839, 677 cm^{-1}; LRMS (EI): *m/e* 353 ([M-^{i}Pr]$^+$), 282, 224, 143, 95; HRMS (EI) *m/e* calcd for $[C_{18}H_{24}ClNO_4]^+$ 353.1394, found 353.1392.



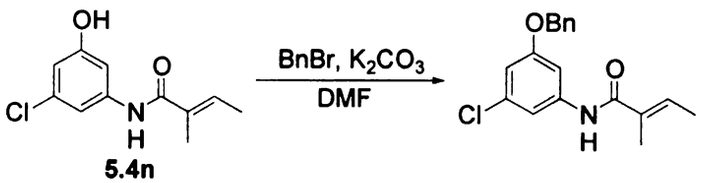
6.46 **6.4a** **6.2**

The iodide **6.46** (120 mg, 0.34 mmol, 1.15 equiv) was first dried by pumping down from benzene before being dissolved in 2 mL dry ether. After being cooled to -78 °C, the solution was charged with 0.42 mL *t*-BuLi (titrated to be 1.6 M in pentane, 0.68 mmol, 2 equiv per iodide) via syringe. After a few minutes, 0.82 mL *B*-OMe-BBN (1 M in hexanes, 0.82 mmol, 2.8 equiv) was added, followed by 2

mL THF (precipitate formation). The mixture was stirred at -78 °C for a few minutes and warmed to room temperature (precipitation dissolved). To this mixture were sequentially added ~150 mg CsF (~1 mmol, 3.4 equiv), 104 mg of **6.4a** (0.294 mmol, **6.4a** was not very soluble), ~3.5 mg $Pd(OAc)_2$ (15.6 μmol, 5.3 mol%), 12.7 mg S-Phos (31 μmol, 10.5 mol%), and 2 mL THF. The reaction was heated to 70-75 °C. Every 3 h, an additional batch of ~3.5 mg $Pd(OAc)_2$ (15.6 μmol, 5.3 mol%) and 12.7 mg S-Phos (31 μmol, 10.5 mol%) was added. This re-addition was repeated 3 times so that the total loads of Pd and ligand were 20 mol% and 40 mol%, respectively. After the last addition of Pd and ligand, the reaction was allowed to stir overnight. The reaction mixture was cooled to room temperature and diluted with saturated $NaHCO_3$ before being extracted with EtOAc. The combined organics were dried over $MgSO_4$ and evaporated. Column chromatography (1:1.5 hexanes/EtOAc) recovered ~77 mg of impure **6.4a** (estimated to be ~45-50% recovery) at R_f~0.41. A lower fraction at R_f~0.29 was re-chromatographed (1.2:1 → 1:1 hexanes/acetone) to afford ~8 mg of impure **6.2** (~5%) as a glass; R_f~0.46 (1.2:1 hexanes/acetone). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.78 (br, 1 H), 8.13 (s, 1 H), 7.28 (t, J = 2.0 Hz, 1 H), 6.90 (t, overlapping, 1 H), 6.37-6.41 (m, 2 H), 5.77 (ddd, J = 8.8, 10.3, 17.4 Hz, 1 H), 4.96-5.06 (m, 3 H), 4.84 (apparent t, J = 1.6 Hz, 1 H), 4.75 and 4.56 (ABq, J_{AB} = 6.3 Hz, 2 H), 4.04 (t, J = 5.2 Hz, 1 H), 3.75 (d, J = 4.5 Hz, 1 H), 3.62 (dd, J = 2.2,

8.6 Hz, 1 H), 3.43 (s, 3 H), 3.36 (dt, J = 10.5, 2.2 Hz, 1 H), 3.32 (s, 3 H), 3.29 (s, 3 H), 3.26-3.30 (m, 1 H), 2.53 (half of d of ABq, can be viewed as dd, ^3J = 5.9 Hz, J_{AB} = 13.2 Hz, 1 H), 2.24-2.31 (m, 4 H), 1.88 (br, 3 H), 1.73 (br, 3 H), 1.67 (ddd, J = 3.4, 10.2, 14.2 Hz, 1 H), 1.58-1.64 (m, 1 H), 1.43-1.51 (m, 1 H), 1.25-1.30 (m, 1 H), 1.23 (ddd, J = 2.5, 10.3, 14.3 Hz, 1 H), 1.08 (d, J = 6.7 Hz, 3 H), 0.80 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 168.3, 158.2, 146.9, 143.7, 142.5, 141.3, 135.9, 133.3, 114.9, 112.6, 112.5, 112.1, 105.4, 97.8, 83.2, 81.5, 79.7, 77.4, 58.6, 57.0, 56.0, 45.5, 41.5, 37.0, 32.0, 30.2, 25.0, 19.2, 18.6, 17.9, 12.9; LRMS (anionic ESI): *m/e* 1192, 1094 ([2M-H]$^-$), 644, 582 ([M+Cl]$^-$), 546 ([M-H]$^-$), 450, 352; HRMS (anionic ESI) *m/e* calcd for $[C_{31}H_{49}NO_7]^-$ 547.3509, found 547.3514.

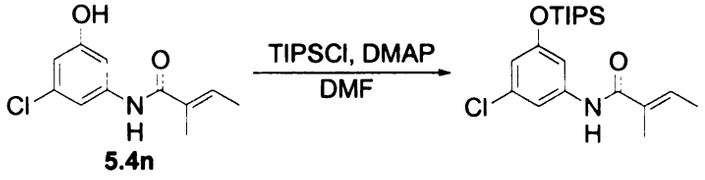
8.3 Experimental Details and Characterization Data for the Compounds Related to the Model Suzuki Coupling



5.4n

To a solution of 158 mg of **5.4n** (0.7 mmol) in 3 mL DMF (distilled over $MgSO_4$) was added 106 mg K_2CO_3 (0.77 mmol, 1.1 equiv) followed by 129 mg BnBr (0.74 mmol, 1.05 equiv). The reaction was stirred at room temperature overnight. TLC indicated incomplete consumption of **5.4n**. Thus another 50 mg K_2CO_3

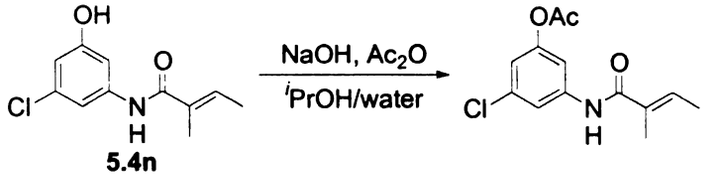
(0.36 mmol, 0.5 equiv) and 65 mg BnBr (0.38 mmol, 0.54 equiv) were added. After another 2 h at room temperature, **5.4n** was completely consumed. The reaction was quenched with saturated Na_2CO_3 and stirred for 30 min. The mixture was poured to saturated $NaHCO_3$ and extracted with EtOAc. The combined organics were dried over $MgSO_4$ and concentrated. Column chromatography (5:1 hexanes/EtOAc) afforded 210 mg of the desired product as colorless oil (93%); R_f~0.18 (5:1 hexanes/EtOAc). ^{1}H NMR (500 MHz, acetone-d_6): δ 7.31-7.41 (m, 6 H), 7.30 (t, J = 2.0 Hz, 1 H), 7.09 (t, J = 1.8 Hz, 1 H), 6.71 (t, J = 2.1 Hz, 1 H), 6.49 (qq, J = 1.5, 6.8 Hz, 1 H), 5.02 (s, 2 H), 1.91 (br, 3 H), 1.80 (dq, J = 6.8, 1.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 159.8, 140.0, 136.3, 135.0, 132.6, 131.8, 128.6, 128.1, 127.5, 112.5, 111.3, 104.7, 70.2, 14.1, 12.5; IR (neat): 3303, 1663, 1601, 1536, 1456, 1426, 1277, 1175, 844, 735, 696 cm^{-1}; LRMS (EI): *m/e* 315 (M^+), 232, 91, 83, 55.



5.4n

To a solution of 125 mg of **5.4n** (0.55 mmol) in 2 mL DMF (distilled over $MgSO_4$) was added 101 mg DMAP (0.83 mmol, 1.5 equiv). While stirring, 0.13 mL TIPSCl (117 mg, 0.61 mmol, 1.1 equiv) was added dropwise. The reaction was stirred at room temperature overnight before being partitioned between half

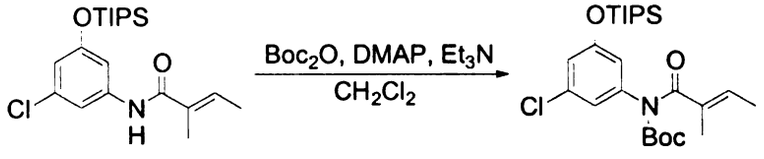
saturated $NaHCO_3$ and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organics were dried over $MgSO_4$ and evaporated. Column chromatography (8:1 hexanes/EtOAc) afforded 197 mg of the desired product (containing 4 mg acetone, corresponding to 92% discounting the added weight of acetone) as a white solid; mp 82-83 °C; R_f~0.34 (8:1 hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (brs, 1 H), 7.14 (t, J = 2.0 Hz, 1 H), 7.09 (t, J = 2.0 Hz, 1 H), 6.60 (t, J = 2.1 Hz, 1 H), 6.48 (qq, J = 1.4, 6.8 Hz, 1 H), 1.91 (quint, apparent t, J = 1.2 Hz, 3 H), 1.79 (dq, J = 6.8, 1.0 Hz, 3 H), 1.22-1.28 (m, 3 H), 1.07-1.09 (m, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 157.2, 139.8, 134.6, 132.7, 131.7, 115.9, 112.6, 109.75, 109.68, 17.9, 14.1, 12.6, 12.5; IR (neat): 3299, 2946, 2869, 1663, 1599, 1586, 1539, 1449, 1426, 1287, 1183, 1015, 884, 768, 685 cm^{-1}; LRMS (EI): *m/e* 381 (M^+), 338, 310, 83, 55. HRMS (EI): *m/e* calcd for $[C_{20}H_{32}ClNO_2Si]^+$ 381.1891, found 381.1888.



5.4n

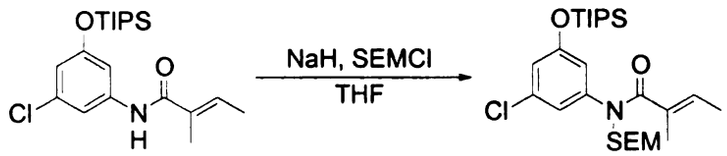
A solution of 40 mg of NaOH (1 mmol, 2 equiv) in 0.7 mL water was mixed with a solution of 115 mg of **5.4n** (0.5 mmol) in 3.4 mL *iso*-propanol (no distillation or drying needed). To this mixed solution was added dropwise 140 mg Ac_2O (1.37 mmol, 2.7 equiv). The mixture was stirred at room temperature for 30 min

before being partitioned between half saturated $NaHCO_3$ and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organics were dried over $MgSO_4$ and evaporated. Column chromatography (3:1 hexanes/EtOAc) afforded 138 mg of the desired product (containing 15 mg EtOAc, corresponding to 92% discounting the added weight of EtOAc) as oil. R_f~0.26 (3:1 hexanes/EtOAc), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (brs, 1 H), 7.40 (t, *J* = 1.8 Hz, 1 H), 7.35 (t, *J* = 2.0 Hz, 1 H), 6.83 (m, 1 H), 6.48 (qq, *J* = 1.5, 6.9 Hz, 1 H), 2.26 (s, 3 H), 1.89 (br, 3 H), 1.79 (dq, *J* = 6.8, 0.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 167.4, 151.3, 139.8, 134.8, 132.5, 132.1, 117.6, 117.2, 111.6, 21.0, 14.1, 12.4; IR (neat): 3320, 2926, 1771, 1667, 1597, 1534, 1458, 1419, 1204, 1159, 1020 cm^{-1}; LRMS (EI): *m/e* 267 (M^+), 225, 143, 83, 55. HRMS (EI): *m/e* calcd for $[C_{13}H_{14}ClNO_3]^+$ 267.0662, found 267.0663.



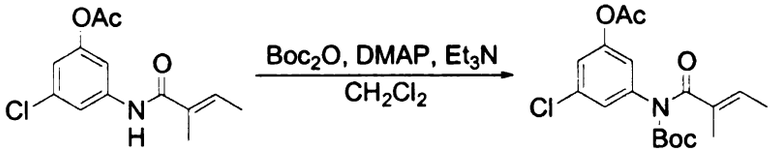
To a solution of 380 mg of starting material (1 mmol) and 120 mg DMAP (1 mmol, 1 equiv) in 23 mL CH_2Cl_2 was added 102 mg Et_3N (1 mmol, 1 equiv). While stirring, 330 mg Boc_2O (1.5 mmol, 1.5 equiv) was added in one portion. The reaction was stirred at room temperature overnight. Upon completion, the reaction was poured into water. The layers were separated and the aqueous

layer was extracted with EtOAc. The combined organics were dried over $MgSO_4$ and evaporated. Column chromatography (10:1 → 7:1 hexanes/EtOAc) afforded 400 mg of the desired product (83%) as thick oil. R_f~0.52 (7:1 hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.78 (t, J = 2.1 Hz, 1 H), 6.74 (t, J = 1.9 Hz, 1 H), 6.53 (t, J = 2.0 Hz, 1 H), 6.32 (qq, J = 1.5, 7.1 Hz, 1 H), 1.88 (quint, apparent t, J = 1.2 Hz, 3 H), 1.77 (dq, J = 7.1, 1.2 Hz, 3 H), 1.41 (s, 9 H), 1.18-1.25 (m, 3 H), 1.06-1.09 (m, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.9, 156.9, 152.9, 140.6, 134.9, 134.4, 133.1, 120.4, 119.3, 117.8, 83.1, 27.8, 17.9, 14.0, 13.1, 12.6; IR (neat): 2948, 2869, 1740, 1692, 1595, 1580, 1445, 1291, 1250, 1154, 884, 683 cm^{-1}; LRMS (EI): *m/e* 381 ([M-Boc+H]$^+$), 338, 282, 83, 57. HRMS (EI): *m/e* calcd for $[C_{25}H_{40}ClNO_4Si]^+$ 481.2415, found 481.2415.



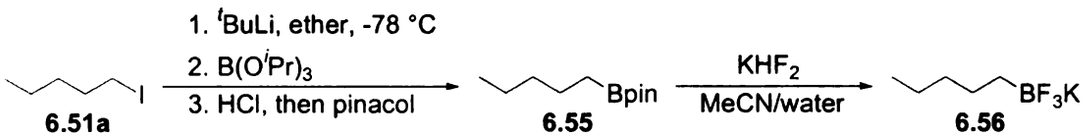
To a suspension of 30 mg NaH (95%, 1.2 mmol, 1.2 equiv) in 20 mL THF was slowly added a solution of 380 mg of starting material in 15 mL THF. Upon being cooled to 0 °C, 183 mg SEMCl (1.1 mmol, 1.1 equiv) was added dropwise. The ice bath was removed and the reaction mixture was allowed to warm to room temperature. After 5.5 h, another ~30 mg NaH (95% dry, 1.2 mmol, 1.2 equiv) and 183 mg SEMCl (1.1 mmol, 1.1 equiv) were introduced and the reaction

continued overnight. Water was added to quench the reaction, and the product was taken into EtOAc. The combined organics were dried over $MgSO_4$ and evaporated. Column chromatography (10:1 → 7:1 hexanes/EtOAc) afforded 392 mg of the desired product (77%) as thick oil along with 39 mg of impure starting material (< 10%). Product: R_f~0.45 (7:1 hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80 (t, J = 1.8 Hz, 1 H), 6.74 (dd, J = 1.8, 2.2 Hz, 1 H), 6.57 (t, J = 2.0 Hz, 1 H), 5.85 (qq, J = 1.6, 7.0 Hz, 1 H), 5.07 (s, 2 H), 3.58-3.61 (m, 2 H), 1.62 (quint, apparent t, J = 1.2 Hz, 3 H), 1.53 (dq, J = 7.0, 1.2 Hz, 3 H), 1.17-1.24 (m, 3 H), 1.05-1.08 (m, 18 H), 0.90-0.94 (m, 2 H), -0.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.4, 156.9, 145.2, 134.6, 132.3, 131.8, 119.4, 118.7, 116.9, 77.8, 66.0, 18.1, 17.8, 13.9, 13.5, 12.5, -1.4; IR (neat): 2950, 2869, 1669, 1593, 1576, 1447, 1306, 1250, 1073, 860, 837, 762, 693 cm^{-1}; LRMS (EI): *m/e* 511 (M^+), 453, 438, 410, 336, 280, 83, 73, 55. HRMS (EI): *m/e* calcd for $[C_{26}H_{46}ClNO_3Si_2]^+$ 511.2705, found 511.2696.



To a solution of 147 mg of starting material (0.55 mmol) and 81 mg DMAP (0.66 mmol, 1.2 equiv) in 10 mL CH_2Cl_2 was added 67 mg Et_3N (0.66 mmol, 1.2 equiv). While stirring, 218 mg Boc_2O (1.0 mmol, 1.8 equiv) was added in one

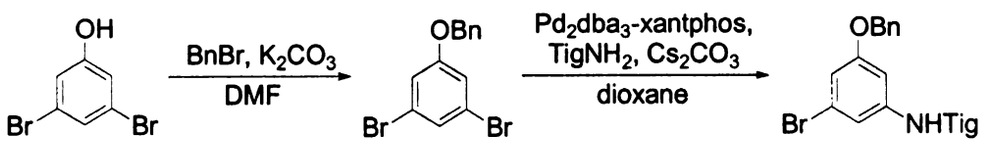
portion. The reaction was stirred at room temperature overnight before being poured into water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organics were dried over $MgSO_4$ and evaporated. Column chromatography (9:1 → 3:1 hexanes/EtOAc) afforded 130 mg of desired product (64%) as thick oil. R_f~0.50 (3:1 hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (t, J = 2.0 Hz, 1 H), 7.03 (t, J = 1.9 Hz, 1 H), 6.86 (t, J = 2.0 Hz, 1 H), 6.35 (qq, J = 1.5, 7.1 Hz, 1 H), 2.25 (s, 3 H), 1.89 (br, 3 H), 1.77-1.80 (m, 3 H), 1.42 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.9, 168.4, 152.6, 151.1, 140.5, 134.9, 134.5, 133.6, 124.9, 121.0, 119.3, 83.6, 27.8, 21.0, 14.1, 13.0; IR (neat): 2923, 1773, 1738, 1690, 1591, 1445, 1370, 1244, 1198, 1152 cm^{-1}; LRMS (EI): *m/e* 311, 267 ([M+H-Boc]$^+$), 225, 211, 169, 83, 55. HRMS (CI, NH_3): *m/e* calcd for $[C_{18}H_{22}ClNO_5+H]^+$ 368.1265, found 368.1255.



To a solution of 0.42 mL pentyl iodide (636 mg, 3.2 mmol) in 17 mL ether at -78 °C was dropwise added 4 mL ^{t}BuLi (titrated as 1.6 M in pentane, 6.4 mmol, 2 equiv). The mixture was stirred at -78 °C for 20 min before 0.74 mL $B(O^iPr)_3$ (600 mg, 3.2 mmol, 1 equiv) was added dropwise. The mixture was stirred at -78 °C for 20 min and then warmed to room temperature. To this mixture was added

20 mL 1 M HCl and the mixture was stirred for a few minutes. The layers were separated and the organic layer was charged with 380 mg pinacol (3.22 mmol, 1 equiv). After being stirred for another few minutes, the mixture was dried over $MgSO_4$ and concentrated. GC-MS analysis indicated formation of **6.55**. LRMS (EI): *m/e* 183 ([M-Me]$^+$), 129, 112, 99, 85, 57. It was used directly in the next reaction without purification.

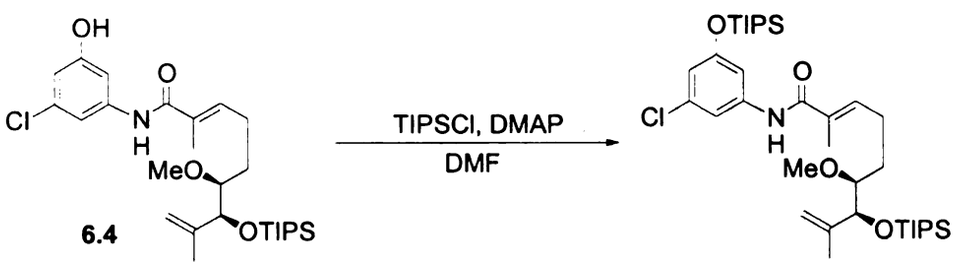
Crude **6.55** obtained from the previous reaction was dissolved in 19 mL acetonitrile (no purification or drying needed) in a Teflon vial. To this solution was added 750 mg KHF_2 (9.6 mmol) followed by 2.5 mL water. The reaction was stirred at room temperature for 1.5 h and the yellow suspension quickly turned to a bright-yellow clear solution. Solvents were evaporated and the residue was taken into hot acetone. The supernatant was decanted and charged with ether. The precipitate was collected by filtration and dried over high vacuum to afford 290 mg of **6.56** (51% overall from **6.51a**) was obtained as a white solid. ^{1}H NMR (500 MHz, acetone-d_6): δ 1.20-1.27 (m, 6 H), 0.83 (t, J = 7.0 Hz, 3 H), 0.08-0.14 (m, 2 H); ^{13}C NMR (125 MHz, acetone-d_6): δ 36.8, 26.1, 23.6, 14.6; ^{11}B NMR (160 MHz, acetone-d_6): δ 6.9 (q, apparent d, J = 58 Hz); IR (neat): 3438 (moisture), 2955, 2919, 2849, 1653, 1074, 972, 889 cm^{-1}.



To a solution of 1.21 g of 3,5-dibromophenol (4.8 mmol) in 20 mL DMF (distilled over $MgSO_4$) was added 1.66 g K_2CO_3 (12 mmol, 2.5 equiv). While stirring, 1.15 mL BnBr (1.64 g, 9.6 mmol, 2 equiv) was added via syringe. The mixture was stirred at room temperature overnight. The reaction was quenched with aqueous Na_2CO_3 and stirred to destroy excess BnBr before being extracted with CH_2Cl_2. Drying over $MgSO_4$ was followed by chromatography purification (9:1 hexanes/EtOAc) to afford 1.65 g of 3.5-dibromophenyl benzyl ether as a colorless oil (containing 0.02 g ether, quantitative); R_f~0.50 (8:1 hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.40 (m, 5 H), 7.25 (t, J = 1.6 Hz, 1 H), 7.06 (d, J = 1.5 Hz, 2 H), 5.01 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 135.7, 128.7, 128.4, 127.5, 126.7, 123.1, 117.3, 70.5; IR (neat): 3077, 3032, 1582, 1577, 1435, 1418, 1377, 1254, 1227, 1013, 873, 744, 694, 666 cm^{-1}; LRMS (EI): *m/e* 91. Anal. Calcd for $C_{13}H_{10}Br_2O$: C, 45.65; H, 2.95. Found C, 45.68; H, 3.00.

A round-bottom flask was charged with 246 mg of the benzyl ether (0.72 mmol, 1.2 equiv), 11 mg Pd_2dba_3 (0.012 mmol, 2 mol%), 21 mg xantphos (0.036 mmol, 6 mol%), 60 mg $TigNH_2$ (0.6 mmol), and 390 mg Cs_2CO_3 (1.2 mmol, 2 equiv). The mixture above was suspended in 2.5 mL dioxane and heated to 100 °C. (The reaction system developed a leak and solvents evaporated after 1.5 h. Thus an addition 2.5 mL of dioxane was added and the reaction continued for 30 min.) The reaction mixture was cooled to room temperature and poured into 1 M

HCl, before being extracted with EtOAc and dried over $MgSO_4$. Chromatography (4.5:1 hexanes/EtOAc) afforded 136 mg of the desired product (61%) as a thick oil; R_f~0.31 (4.5:1 hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30-7.41 (m, 7 H), 7.22 (t, *J* = 1.7 Hz, 1 H), 6.87 (t, *J* = 1.9 Hz, 1 H), 6.49 (qq, *J* = 1.5, 6.8 Hz, 1 H), 5.02 (s, 2 H), 1.91 (br, 3 H), 1.80 (dq, *J* = 7.1, 1.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 159.9, 140.2, 136.3, 132.6, 131.8, 128.6, 128.1, 127.5, 122.7, 115.3, 114.2, 105.3, 70.3, 14.1, 12.5; IR (neat): 3303, 1663, 1597, 1532, 1455, 1422, 1275, 1175, 1046, 845, 735, 696 cm^{-1}; LRMS (EI): *m/e* 359 (M^+), 91, 83, 55. HRMS (EI): *m/e* calcd for $[C_{18}H_{18}BrNO_2]^+$ 359.0521, found 359.0517.



To a solution of 184 mg of **6.4** (0.36 mmol) in 1.8 mL DMF (distilled over $MgSO_4$) was added 66 mg DMAP (0.55 mmol, 1.5 equiv). While stirring, 0.09 mL TIPSCl (80 mg, 0.42 mmol, 1.17 equiv) was added dropwise. The reaction was stirred at room temperature overnight, and then poured into water and extracted with EtOAc. The combined organics were dried over $MgSO_4$ and evaporated. Column chromatography (10:1 hexanes/EtOAc) afforded 247 mg of product

(containing 5 mg ether and 7 mg hexane, corresponding to 98% discounting the added weight) as an oil; R_f~0.43 (10:1 hexanes/EtOAc); $[\alpha]^{20}_D$ -10.3 (*c* 1.05, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.29 (br, 1 H), 7.14 (t, *J* = 2.0 Hz, 1 H), 7.07 (t, *J* = 1.8 Hz, 1 H), 6.60 (t, *J* = 2.0 Hz, 1 H), 6.32-6.36 (m, 1 H), 4.95 (m, 1 H), 4.89 (quint, apparent t, *J* = 1.7 Hz, 1 H), 4.31 (d, *J* = 5.6 Hz, 1 H), 3.44 (s, 3 H), 3.18 (ddd, *J* = 2.7, 5.6, 8.8 Hz, 1 H), 2.20-2.34 (m, 2 H), 1.91 (br, 3 H), 1.73 (br, 3 H), 1.67 (dddd, *J* = 2.9, 7.1, 9.5, 14.2 Hz, 1 H), 1.33 (dddd, *J* = 6.6, 9.0, 9.0, 14.4 Hz, 1 H), 1.22-1.28 (m, 3 H), 1.03-1.10 (m, 39 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 157.2, 144.9, 139.8, 136.9, 134.6, 131.9, 115.9, 112.9, 112.5, 109.7, 84.3, 76.2, 58.7, 30.0, 25.0, 19.2, 18.07, 18.04, 17.9, 12.8, 12.6, 12.4; IR (neat): 3300 (br), 2946, 2869, 1661, 1601, 1586, 1537, 1450, 1426, 1096, 884, 683 cm^{-1}; LRMS (EI): *m/e* 622 ($[M-^iPr]^+$), 590, 460, 438, 380, 253, 227, 157, 115, 75, 59. HRMS (EI): *m/e* calcd for $[C_{36}H_{64}ClNO_4Si_2]^+$ 665.4062 found 665.4064.

General Procedure for Suzuki Coupling with Li/I Exchange Step:

A solution of 0.23 mmol pentyl iodide (1.5 equiv) in 1 mL dry ether was cooled to -78 °C. ^{t}BuLi (freshly titrated, 0.46 mmol, 2 equiv per iodide) was added via syringe. After being stirred at -78 °C for 15 min, 0.37 mmol *B*-OMe-BBN (1 M in hexanes, 2.5 equiv) was added followed by 1 mL THF. The mixture was stirred at -78 °C for 15 min and warmed to room temperature. CsF (0.45 mmol, 3 equiv) or $K_3PO_4 \cdot nH_2O$ (0.3 mmol, 2 equiv) was added followed by 0.15 mmol chloride.

$Pd(OAc)_2$ (5 mol%) and S-Phos (10 mol%) were introduced next (either as solids or as a THF solution) together with 1 mL THF. The reaction was stirred at 70-75 °C. Every 3 h, additional 5 mol% $Pd(OAc)_2$ and 10 mol% S-Phos were charged. This re-addition of Pd and ligand was repeated 3 times so that the total loads of Pd and ligand were 20 mol% and 40 mol%, respectively. After the last addition of Pd and ligand, the reaction was stirred overnight before being cooled to room temperature. The mixture was then diluted with saturated $NaHCO_3$ and extracted with EtOAc. The combined organics were dried over $MgSO_4$, evaporated, and analyzed by NMR. The results of the model studies are listed in Table 6.2 (page 126).

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