Functionalization of Strong Sigma Bonds by Nickel and Tungsten Catalysis

Raúl Martín Montero

UNIVERSITAT ROVIRA i VIRGILI

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DOCTORAL THESIS
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DOCTORAL THESIS

Supervised by Prof. Rubén F. Martín Romo

Institut Català d'Investigació Química (ICIQ)

Universitat Rovira i Virgili (URV)

Department of Analytical Chemistry & Organic Chemistry

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Prof. Rubén Martín Romo, Group Leader at the Institute of Chemical Research of Catalonia (ICIQ) and Research Professor of the Catalan Institution for Research and Advanced Studies (ICREA),

STATES that the present study, entitled "Functionalization of Strong Sigma Bonds by Nickel and Tungsten Catalysis", presented by Raúl Martín Montero for the award of the degree of Doctor, has been carried out under his supervision at the Institute of Chemical Research of Catalonia (ICIQ).

Tarragona, November 2020

Doctoral Thesis Supervisor

Prof. Rubén Martín Romo

List of Publications

At the time of printing, the results reported herein have been published as:

1. **Martin-Montero, R.**; Reddy V.; Yin, H.; Davies, J.; Martin, R. Ni-catalyzed Reductive Deaminative Arylation at sp^3 Carbon Centers. *Org. Lett.* **2019**, *21*, 2947-2951, DOI: 10.1021/acs.orglett.9b01016.

2. **Martin-Montero, R.**; Krolikowski, T.; Zarate, C.; Manzano R.; Martín R. Stereospecific Nickel-Catalyzed Borylation of Secondary Benzyl Pivalates. *Synlett,* **2017**, *28*, 2604-2608, DOI: 10.1055/s-0036-1590962.

The author has also contributed to the following:

3. Rand, A. W.; Yin, H.; Xu, L.; Giacoboni, J.; **Martin-Montero, R**.; Romano, C.; Montgomery, J.; Martin, R. Dual Catalytic Platform for Enabling sp3 a C–H Arylation & Alkylation of Benzamides *ACS Catal.* **2020**, *10*, 4671-4676. DOI: 0.1021/acscatal.0c01318.

4. Sun, S-Z.; Borjesson M.; **Martin-Montero R.**; Martin R. Site-Selective Ni-Catalyzed Reductive Coupling of alpha-Haloboranes with Unactivated Olefins. *J. Am. Chem. Soc.* **2018**, *140*, 12765–12769, DOI: 10.1021/jacs.8b09425.

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Abbreviations & Acronyms

acac =acetylacetonate

BDE = bond dissociation enthalpy

BINAP = Bis(diphenylphosphino)-1,1'-binaphthalene

COD = 1,5-cyclooctadiene

Cy = cyclohexyl

Conv = conversion

DMA = *N,N*-dimethylacetamide

DME = 1,2-dimethoxyethane

DMF = *N,N*-dimethylformamide

dcpe = 1,2-Bis(dicyclohexylphosphino)ethane

dppe = 1,2-bis(diphenylphosphino)ethane

ee = enantiomeric excess

equiv = equivalents

FID = Flame Ionization Detector

GC = gas chomatrography

h = hour(s)

HPLC = High Pressure Liquid Chromatography

IPr = 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene

L = ligand

Mes = mesityl

nep = neopentyl glycolate

NMP = N-methyl-2-pyrrolidone

NMR = Nuclear Magnetic Resonance

OA = oxidative addition

PDA = Photodiode Array Detector

phen = 1,10-phenanthroline

pin = pinacolate

piv = pivalate

PMT = Photomultiplier tube

ppm = parts per million

rac = racemic

rt = room temperature

SET = single-electron transfer

SM = starting material

S_N = nucleophilic substitution

T = temperature

TEMPO = 2,2,6,6-Tetramethyl-1-piperidinyloxy

THF = tetrahydrofuran

TMS = tetramethylsilane

Tol = tolyl

UPC2 = UltraPerformance Convergence Chromatography

UV = Ultraviolet

DAD = diode array detector

Abstract

In recent years, the functionalization of strong sigma bonds has received considerable attention as demonstrated by numerous investigations into the efficiency of transition metals in this process.[1–3] Among them, nickel has been considered one of the leaders due to its earth-abundance, nucleophilicity, and capacity to participate in one- or two-electron redox pathways.[4,5] On the other hand, the ability of tungsten to functionalize strong sigma bonds has only been hinted at by a small selection of promising W-catalysed reactions, which have opened the door for further studies.

In line with the Martin group's interest in developing catalytic methods for the activation of inert bonds, this Doctoral Thesis is focused on the nickel-catalyzed scission of C–O bonds to achieve the stereospecific formation of C-B bonds (*Chapter 2*), the cleavage of unactivated C–N bonds for the assembly of C–C bonds by nickel catalysis (*Chapter 3*), and the functionalization of strong sigma bonds by a site-selective C–H activation protocol utilizing tungsten catalysis (*Chapter 4*).

Despite all the advances recently performed in the scission of C–O bonds by the derivatization of unactivated phenol derivatives,[6] such as benzyl esters or ethers, no stereospecific C–Heteroatom bond formations had been reported. In the *Chapter 2* of this dissertation, the first stereospecific borylation of secondary benzyl alcohol derivatives catalyzed by a cooperative Ni/Cu-catalysis is presented (Scheme 1, *left*). The final formation of an enantioenriched borylated product paves the way for further functionalizations.
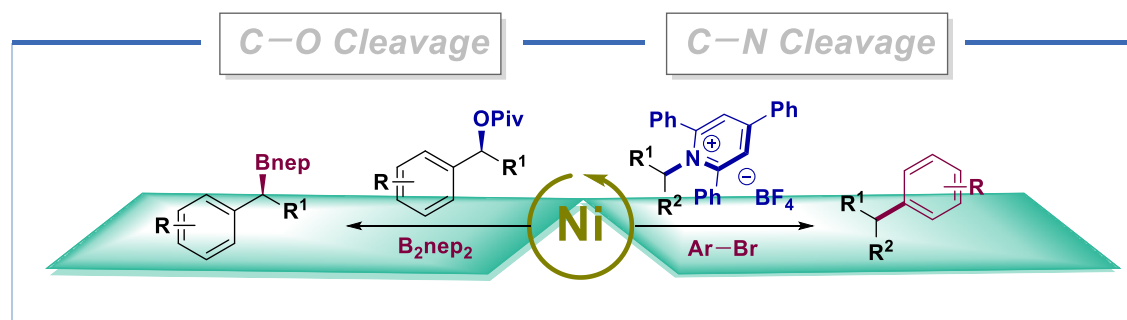
Scheme 1. Ni-Catalyzed C–O and C–N cleavages.

Subsequently, studies moved toward the functionalization of unactivated alkyl amines. In spite of the vast literature for the utilization of activated sp^3 C–N bonds in cross-coupling reactions,[7] unactivated alkyl amine coupling partners did not initially attract the attention of chemists due to their high C–N bond dissociation energies. Nevertheless, the formation of $C(sp^3)$–$C(sp^2)$ bonds was accomplished via the utilization of organometallic species or biased heteroarenes as coupling partners with pyridinium salts.[8,9] In such a way, *Chapter 3* of this Thesis is based on a reductive deaminative arylation at sp^3 carbon centers catalyzed by nickel (Scheme 1, *right*). This strategy establishes a user-friendly and unbiased coupling partner that allows with the arylation of

unactivated alkyl amines. The work performed in this chapter also includes experimental results that clarify the mechanistic aspects of the transformation.

Driven by our interest in the functionalization of strong sigma bonds, remote C–H activation caught our attention. Despite the advances performed by many transition metals in this field,[3] the final functionalized sites are commonly the terminal position of an alkyl chain or the α-carbon geminal to a functional group. Motivated by unique reactivity[10–12] of tungsten and its abundance, *Chapter 4* reports a site-selective β-hydroboration of terminal alkenes catalyzed by tungsten complexes (Scheme 2). This protocol is complementary to that shown with Pd-, Ni- or Co-catalyzed chain-walking reactions offering a new strategy for promoting the functionalization at unactivated sp^3 C–H sites of alkyl chains. A series of applications have also been described, thus opening a gateway for investigations into further functionalizations that would otherwise be beyond reach.
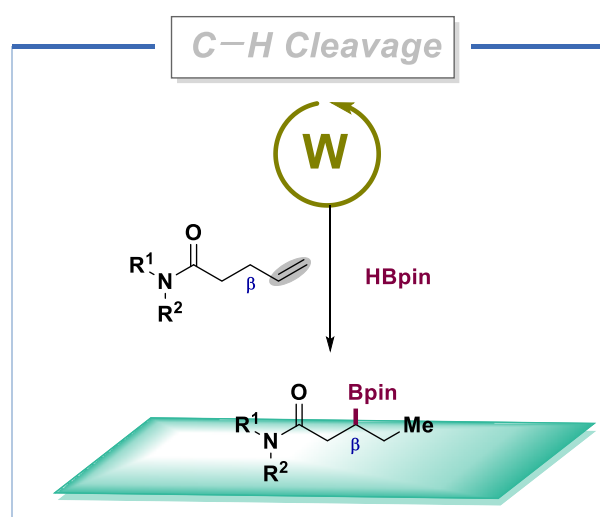
Scheme 2. W-catalyzed remote functionalization of C–H bonds.

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Chapter 1.

General Introduction

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1.1 General Introduction

Metal-catalyzed cross-coupling reactions have become one of the pillars of modern organic chemistry since their exponential growth 50 years ago.[1–3] These technologies have offered synthetic chemists in both academic and industrial laboratories a reliable new technique to rapidly build up molecular complexity when forging C–C and C–heteroatom bonds. Not surprisingly, the relevance of these technologies was recognized with the 2010 Noble Prize in Chemistry awarded to Heck, Negishi and Suzuki for their developments in Pd-catalyzed cross-coupling reactions.

Traditionally, C–C bond-formation by means of transition metal-catalyzed cross-coupling reactions rely on the combination of an organometallic nucleophile and an appropriately substituted electrophilic counterpart (Scheme 1.1). While a wide variety of transition metals can be employed for such purposes, Pd catalysts have been well-adopted by the Community due to their versatility, modularity and wide substrate scope across an array of differently substituted counterparts.
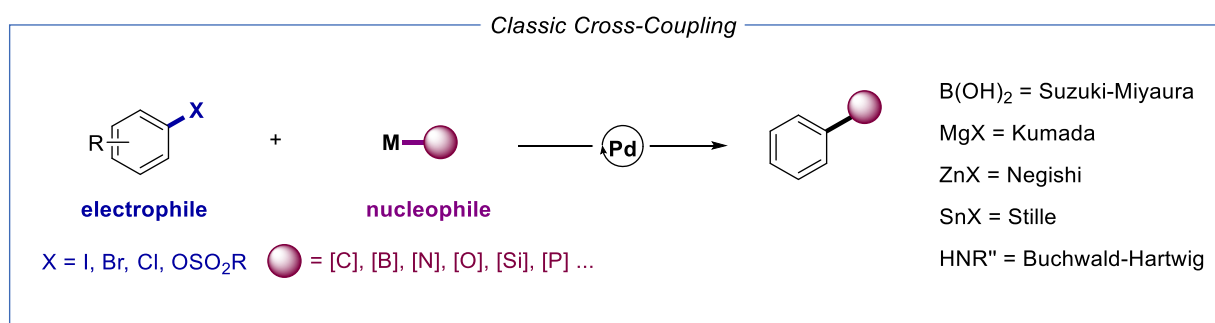
Scheme 1.1. Pd-catalyzed cross-coupling reactions.

Although organic halides are probably the most common electrophiles employed in metal-catalyzed cross-coupling reactions, their toxicity and difficult accessibility have prompted chemists to look for cheaper alternatives with improved flexibility, practicality and modularity. In recent years, particular attention has been devoted to the utilization of alcohols, amines, esters or carboxylic acid derivatives as surrogated of organic halides. In addition, the direct functionalization of alkanes and alkenes has also served as an alternative for forging C–C and C–heteroatom bonds without the need for prefunctionalization at the electrophilic site.[3,4] Among different alternatives, the means to promote C–O and C–N cleavage in simple alcohols and amine as electrophilic partners have attracted considerable attention.[5–10] These compounds are commonly found in nature, pharma, agrochemicals and material science, making them particularly useful for late-stage functionalization in densely functionalized substrates.

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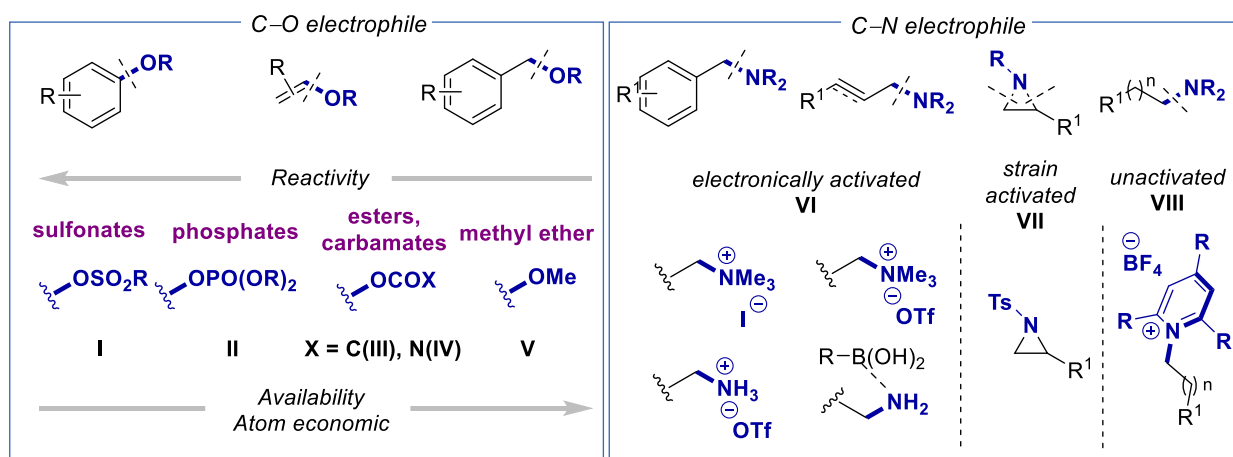
Figure 1.1. C–O and C–N electrophiles in metal-catalyzed cross-coupling reactions.

Despite the advances realized, the utilization of simple alcohols and amines in metal-catalyzed cross-coupling reactions is particularly challenging due to the high activation barrier required for effecting C–OH and C–NH$_2$ scissions. To this end, early research efforts have been devoted to the utilization of aryl triflates (Figure 1.1 **I**, R = CF$_3$) due to the low dissociation energy required for effecting C–O bond-cleavage in a canonical oxidative addition pathway. These conceptions served as a starting point for exploring less reactive aryl phenol derivatives such as aryl mesylates, (Figure 1.1, **I**, R = CH$_3$), tosylates, (**I**, R = *p*-C$_6$H$_4$CH$_3$), nonaflates (**I**, R = C$_4$F$_9$), and phosphates (**II**).[11] Although better alternatives than triflates, these derivatives do not represent an added value in terms of availability, stability and atom economy, thus limiting the potential application profile of these protocols. These challenges could partially be alleviated by the utilization of nickel catalysts and the employment of phenol derivatives possessing higher bond-dissociation energies such as aryl esters (**III**), carbamates (**IV**), or even aryl ethers (**V**), as nicely illustrated by the pioneering work of Dankwardt and Wenkert in 2004.[12,13]

In 1988, Wenkert and co-workers reported that even trialkylammonium salts derived from aryl amines can be used as organic halide surrogates within the context of a Kumada-Corriu reaction, thus showing the viability of nickel complexes to promote a *sp^2* C–N scission.[14–16] It was not until 2003 when MacMillan demonstrated that these technologies could be applied with less basic organometallic reagents, resulting in the development of a Suzuki-Miyaura coupling of aryl trimethylammonium salts and Grignard reagents catalyzed by nickel complexes.[17] These findings served as an entry point for extending the scope of these reactions beyond aryl amine electrophiles. Indeed, it was possible to promote similar cross-coupling reactions with activated benzyl alkyl ammonium salts (Figure 1.1, **VI**),[9] propargylic ammonium salts,[18,19] or strained aziridine counterparts.[20–24] Few years later, the generality of these reactions was illustrated by the successful cross-coupling reactions of unactivated alkyl amine congeners (**VIII**) thus showing the potential that C–N electrophiles might offer within the context of metal-catalyzed cross-coupling reactions.[25,26]

Chapter 1
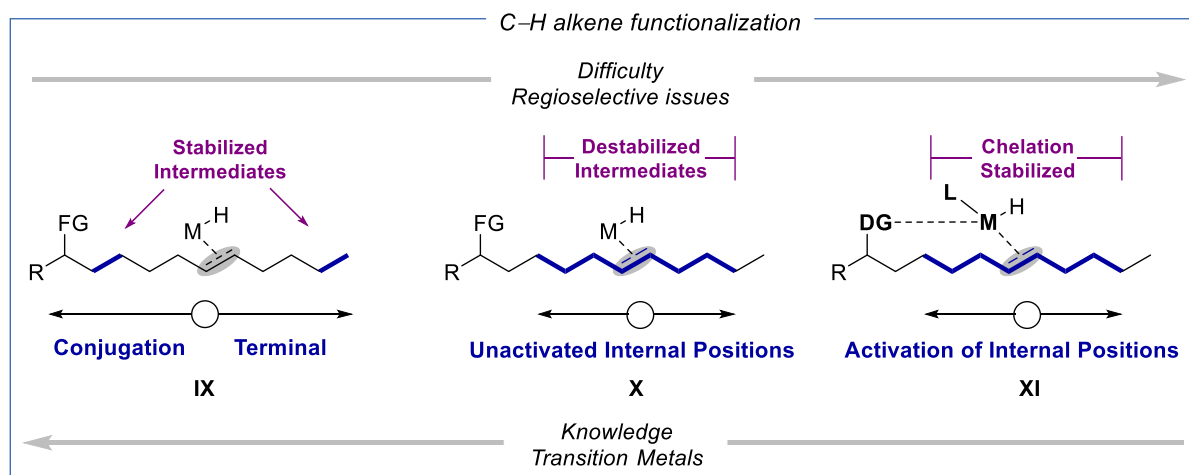
Figure 1.2. C–H alkene functionalization.

The desire to build complex architectures from simple, yet less-functionalized precursors, has turned the attention of chemists to alkenes, which rank amongst the most abundant building blocks in organic chemistry endeavors. Alkenes can be activated by some unique transition metal catalysts leading to elegant transformations[27] – some of these being particularly attractive in industrial settings – such as the Wacker process,[28] olefin metathesis,[29] olefin hydroformylation,[30] Heck reaction[31] or hydroboration of olefins, undoubtedly one of the most important transformations in organic settings due to the versatility and applicability of organoboron compounds.[32–35] While the vast majority of transformations of alkenes rely on the functionalization across the double C=C bond or at the allylic *sp³* C–H motif, the recent years have witnessed the development of catalytic techniques aimed at promoting the functionalization of alkenes at remote *sp³* C–H sites (Figure 1.2, **IX**).[36] However, site-selectivity has been a difficult challenge to tackle due to the intrinsic reactivity of non-particularly stabilized alkyl-metal intermediates, thus leading to mixtures of different regioisomers (**X**). Despite these drawbacks, the development of new catalysts and ligands have allowed to tackle these challenges by promoting a wide variety of transformations that enable bond-formation at remote, yet previously unfunctionalized, *sp³* C–H sites (**XI**).[37–44]

1.2   Cleavage of strong sigma bonds

1.2.1   Nickel-catalyzed C–Heteroatom bond formation *via* C–O bond cleavage

1.2.1.1   Introduction to nickel-catalyzed C–O bond cleavage

The inherent interest about the utilization of aryl C–O electrophiles in metal-catalyzed cross-coupling reactions arises from the abundance and ready availability of phenols compared to organic halides, and the prevalence of these motifs in a myriad of natural products, agrochemicals or pharmaceutically-relevant molecules.[5,45] Not surprisingly, the higher bond-dissociation energy of *sp³*

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C–O bonds (BDE ~96 kcal/mol)[48] make them particularly problematic for the utilization of aliphatic alcohol derivatives in cross-coupling reactions (Figure 1.2.1, *bottom*).
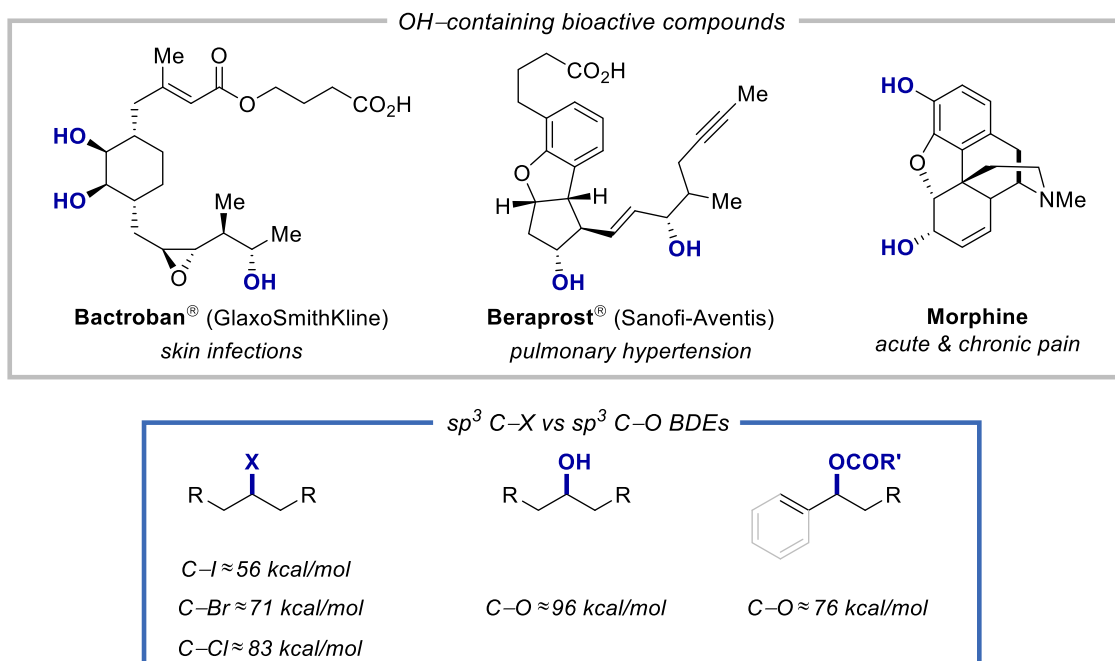
Figure 1.2.1. Importance and BDEs of alcohols.

Driven by these observations, chemists have devoted considerable attention to the development of Ni-catalyzed cross-coupling reactions of allylic C–O electrophiles due to the weak bond-dissociation energy of the corresponding sp^3 allylic C–O bond (Figure 1.2.2).[49–52] Despite the advances realized in C–C bond forgings by C–O scission, C–Heteroatom bond formation protocols were not investigated only after the inspirational work of Shi in 2008 (Figure 1.2.2, *right*).[53]
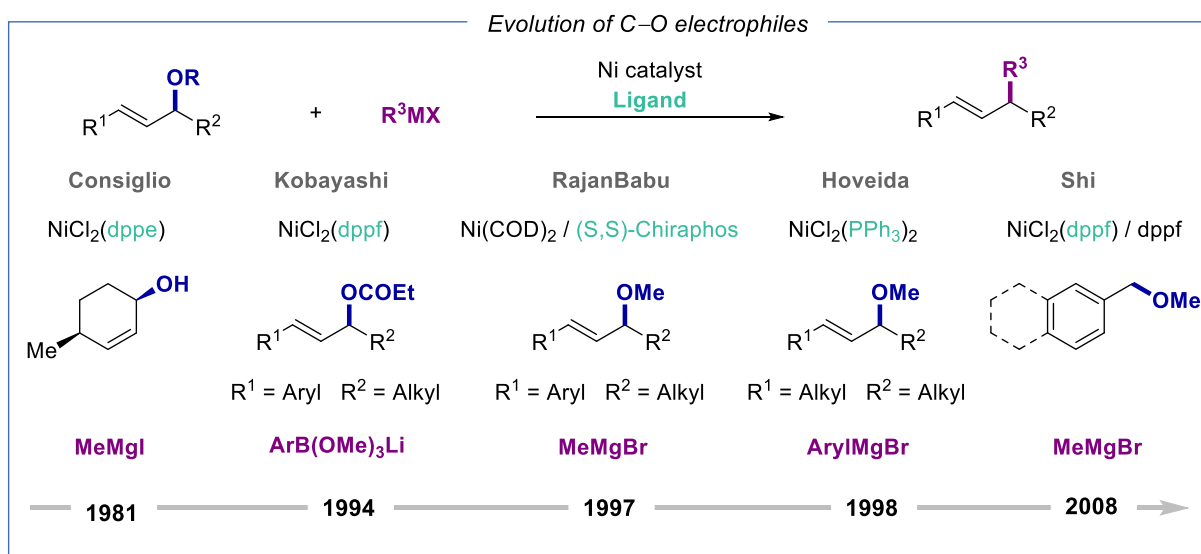
Figure 1.2.2. Evolution of C–O electrophiles in time.

Chapter 1

1.2.1.2   C–N bond formation

In 2009, Chatani and co-workers reported a direct amination of anisoles involving the cleavage of C(sp^2)–OMe by means of nickel catalysis (Scheme 1.2.1, *left*).[54] This transformation is particularly interesting as it demonstrated, for the first time, the means to promote a C–N bond-formation at a particularly strong C(sp^2)–OMe bond with simple Ni catalysts bearing NHC-carbene ligands. Unfortunately, however, this reaction was limited to π-extended anisoles, invariably requiring high temperatures and a limited set of amine counterparts. This reaction could subsequently be applied to the coupling of *N*-heteroaryl methyl ethers (Scheme 1.2.1, *right*).[55] While a step-forward, the functional group tolerance could not be fully demonstrated, and low yields were generally achieved when promoting the reaction with non-π-extended anisoles.
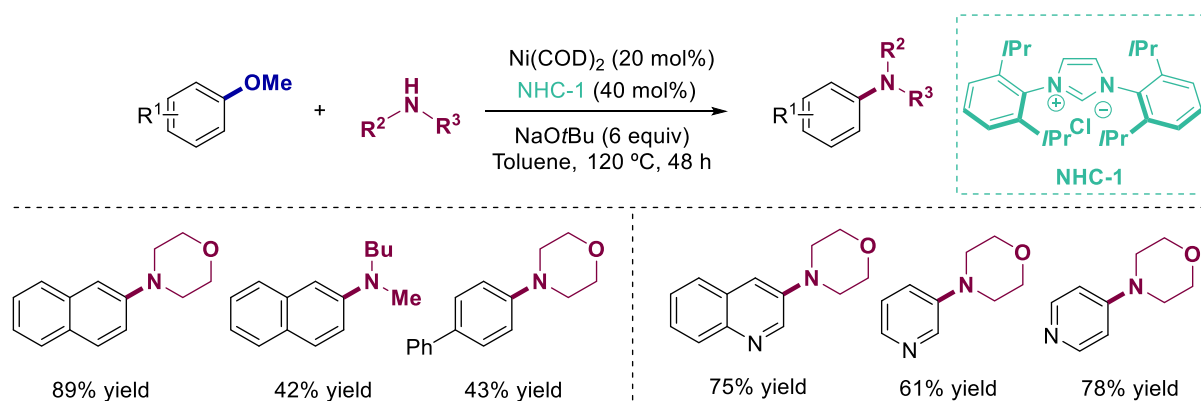
Scheme 1.2.1. Ni-catalyzed amination of anisoles derivatives *via* C–O cleavage.

In 2012, Garg and co-workers demonstrated that the combination of an air-stable NiCl$_2$·DME precatalyst with Ph–BPin as reducing agent could promote the amination of aryl carbamates and sulfonates.[56] Interestingly, the transformation tolerated a wide range of functionalities and sterically hindered *ortho*-substituted substrates, including non-π-extended systems and heteroaromatic rings. In 2010, Chatani's group addressed the limitations of the amination of aryl methyl ethers beyond activated π-extended systems by using aryl esters as counterparts (Scheme 1.2.2).[57] These substrates still required the utilization of strong basic conditions, but offered a mild protocol for promoting C–N bond-formation *via* C–O scission.

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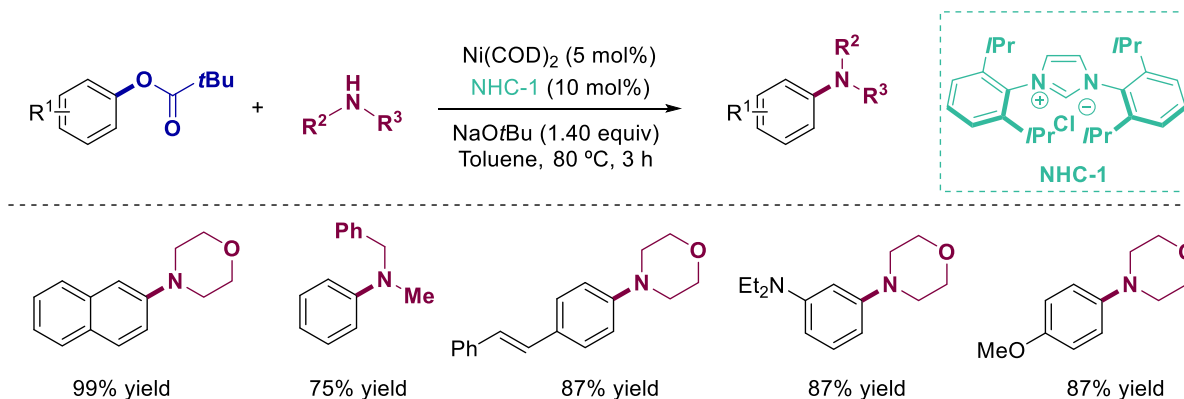
Scheme 1.2.2. Ni-catalyzed amination of aryl pivalates *via* C–O cleavage.

In 2017, Rueping and co-workers reported a nickel-catalyzed decarbonylative amination of esters and amides by means of C–O and C–C bond functionalization (Scheme 1.2.3).[58] Unfortunately, the utilization of heteroaromatic substrates or non-π-extended systems resulted in lower yields of the targeted products. The mechanism of the reaction is proposed to start with an oxidative addition of the C(acyl)–O bond of the aryl ester to Ni(0) complex (**XII**). The corresponding acyl nickel(II) intermediate (**XIII**) triggers a CO extrusion and ligand exchange with the benzophenone imine (**XIV**). Reductive elimination delivers the targeted aminated product prior to acid hydrolysis and a Ni(0) bound to CO that ultimately recovers back the propagating **XII** by loss of CO.
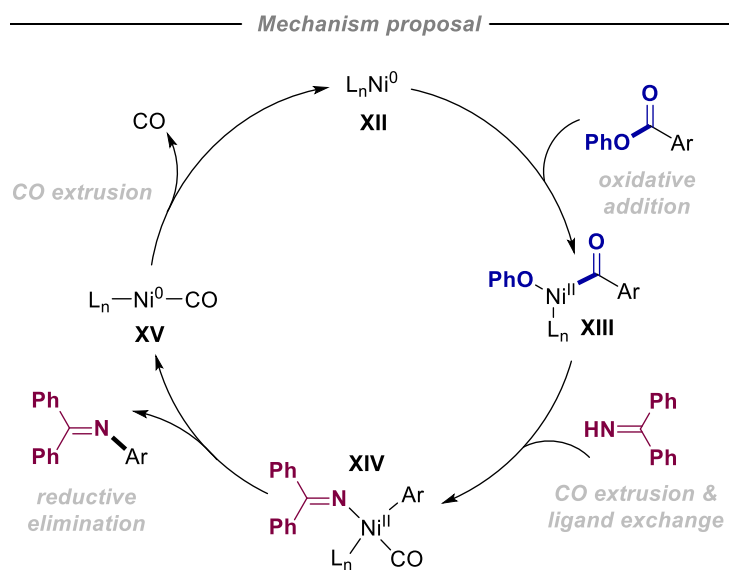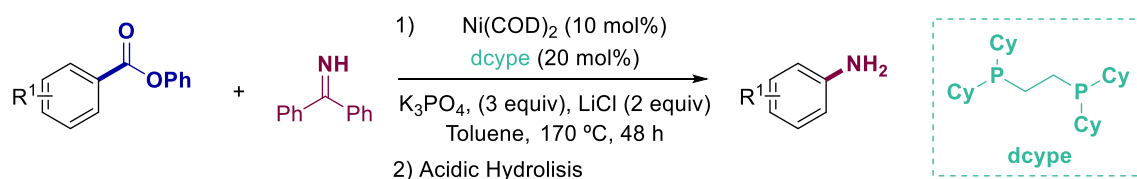
Scheme 1.2.3. Decarbonylative amination of esters and proposed mechanism.

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1.2.1.3   C–Si bond formation

Prompted by the synthetic applicability of organosilanes in a myriad of different transformations, chemists have been challenged to come up with new catalytic technologies aimed at forging C–Si bonds.[59–65] In 2014, our group reported the first C–O silylation of aryl esters with silylboronate reagents (Scheme 1.2.4).[66] This work could be executed with aryl esters possessing multiple functional groups, and the technology could be applied to both π-extended and non-π-extended systems. Moreover, benzylic substrates could be used, holding promise to design stereospecific or even enantioselective C–Si bond-forming reactions. Although initially a mechanism consisting of a Ni/Cu cooperative effect was proposed, later on the authors demonstrated that CuF$_2$ could be replaced by exogenous fluoride sources, an assumption that was corroborated by in depth mechanistic studies, DFT calculations and the isolation of some putative reaction intermediates that involved Ni(I) bimetallic intermediates as off-cycle reservoirs (Scheme 1.2.5).[67]
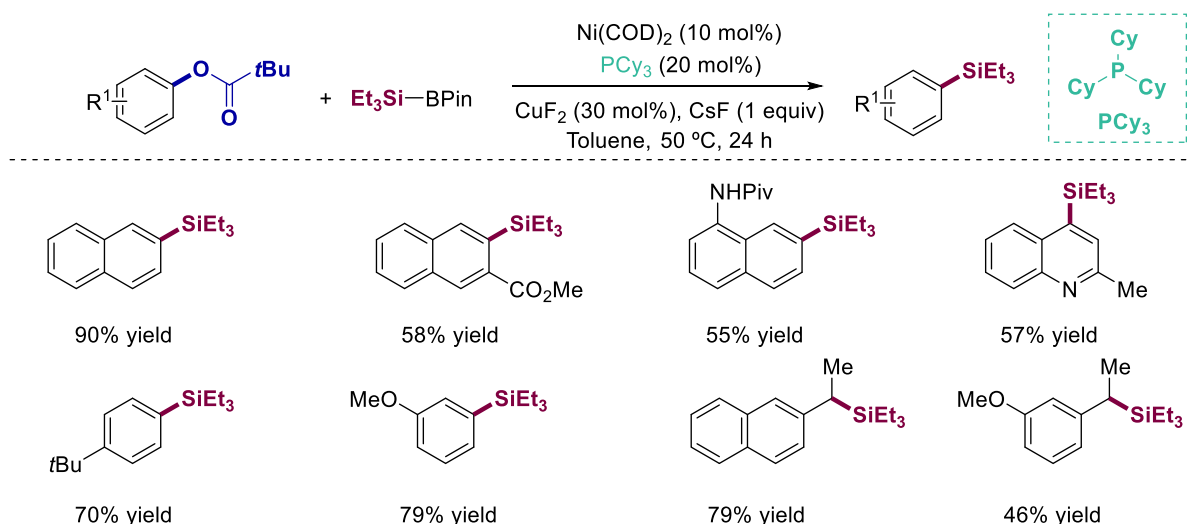
Scheme 1.2.4. Ni-catalyzed silylation of aryl- and benzyl pivalates.
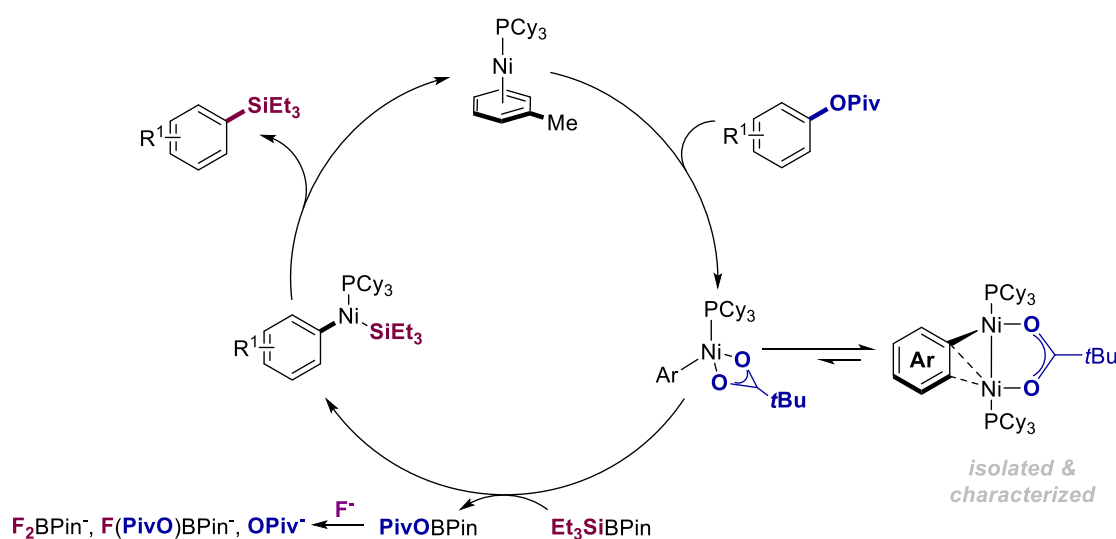
Scheme 1.2.5. Mechanistic proposal for the nickel-catalyzed silylation of C–O bonds.

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Subsequently, our group developed a new Ni-catalyzed protocol for the silylation of anisoles under remarkably mild reaction conditions and in the absence of external ancillary ligands (Scheme 1.2.6).[68] Importantly, the reaction could be extended to both π-extended and non-π-extended aryl methyl ethers. Among all different alternatives, it was proposed that the reaction might operate *via* [Ni(COD)SiEt$_3$]K complexes (**XVI**) that might trigger either an internal nucleophilic aromatic substitution assisted by complexation of the K$^+$ counterion with the lone pair of the ethereal oxygen (Scheme 1.2.6, complex **XVII**) or a "*non-classical*" oxidative addition of the C(sp^2)–OMe bond to Ni(0)-ate complexes assisted by K$^+$ counterions (Scheme 1.2.6, complex **XVIII**).
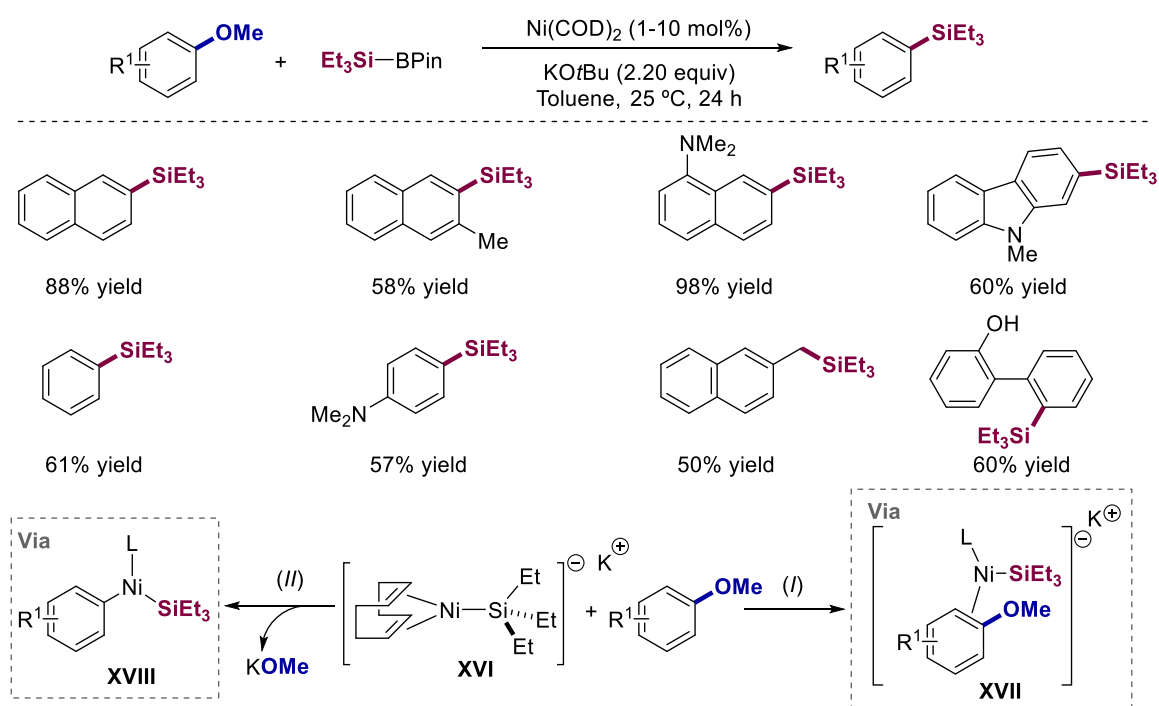
Scheme 1.2.6. Ni-catalyzed silylation *via* C–OMe cleavage and mechanistic proposal.

1.2.1.4   C–P bond formation

Usually, C–P bond-forming reactions are prepared *via* the reaction of Grignard reagents or organolithium species with the corresponding electrophilic phosphorous sources. However, these methods could not be applied in densely functionalized backbones due to chemoselectivity issues, lack of functional group tolerance or the need for special techniques due to the air-sensitivity of the corresponding organometallic reagents. Aimed at meeting these challenges, Chen and Han groups reported the first phosphoarylation of non-π-extended aryl and benzyl pivalates catalyzed by nickel complexes (Scheme 1.2.7).[69,70] The reaction was proposed to operate *via* classical oxidative addition of the aryl ester to Ni(0) followed by transmetallation and reduction elimination forming the C–P bond.

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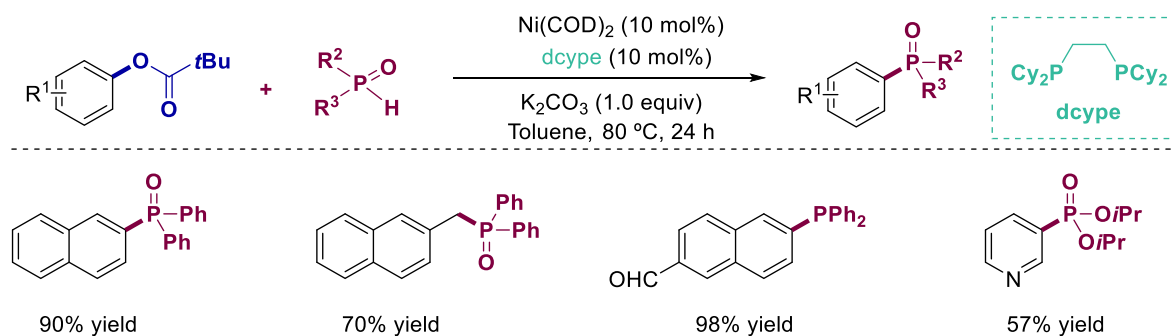
Scheme 1.2.7. Ni-catalyzed phosphoarylation of aryl and benzyl pivalates.

1.2.1.5 C–Sn bond formation

Aiming at extending the generality of C–heteroatom bond-forming reactions *via* C–O bond-cleavage, our group reported a Ni-catalyzed stannylation of aryl esters en route to the corresponding organotin reagents (Scheme 1.2.8).[71] Notably, even heterocyclic cores or non-π-extended arenes can be employed as substrates, thus allowing to access densely functionalized organotin reagents that can be used as linchpins for preparing a wide variety of compounds *via* C–Sn cleavage.[72–74]
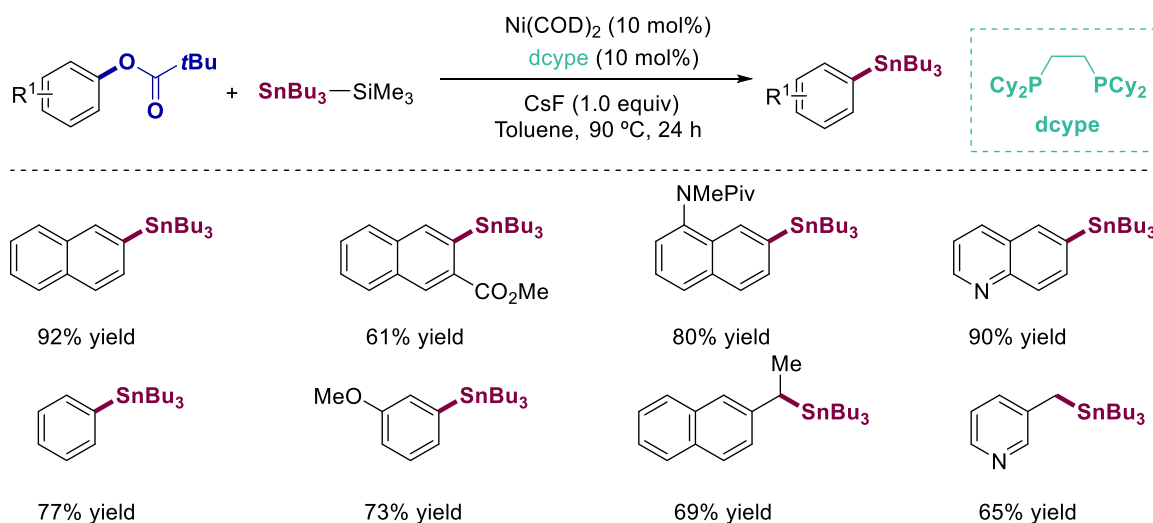
Scheme 1.2.8. Ni-catalyzed stannylation of aryl and benzyl esters.

1.2.1.6 C–B bond formation

Among all organometallic reagents, organoboron intermediates probably are the most versatile compounds to build up molecular complexity, allowing to enable a wide variety of C–C and C–heteroatom bond-forming reactions.[75] Traditionally, the preparation of aryl and benzoyl boronic acids involves the utilization of Grignard reagents or organolithium species.[76] Not surprisingly, chemists have been challenged to design catalytic C–H borylation techniques, thus avoiding the need for preformed organometallic reagents for the preparation of organoboron compounds.[77–81] However, controlling the regioselectivity of these processes might not be particularly trivial in densely

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functionalized backbones. Therefore, the catalytic borylation of organic (pseudo)halides still constitute a powerful and reliable technique for preparing organoboron compounds. Prompted by these limitations, the cleavage of sp^2 or sp^3 C–O bonds emerged over last years as an alternative method to forge C–B bonds.[82,83]

In 2011, Shi and co-workers published the first borylation of (hetero)aryl-carbamates *via* Ni-catalyzed C(sp^2)–O bond cleavage with B_2nep_2 as coupling partner (Scheme 1.2.9).[84] The scope included *N*–containing heterocycles and non-π-extended arenes, but the presence of electron-donating groups and *ortho*-substituents eroded the yield in a significant manner. Mechanistically, a canonical Ni(0)/Ni(II) pathway was proposed followed by a transmetallation and a final C–B bond reductive elimination.
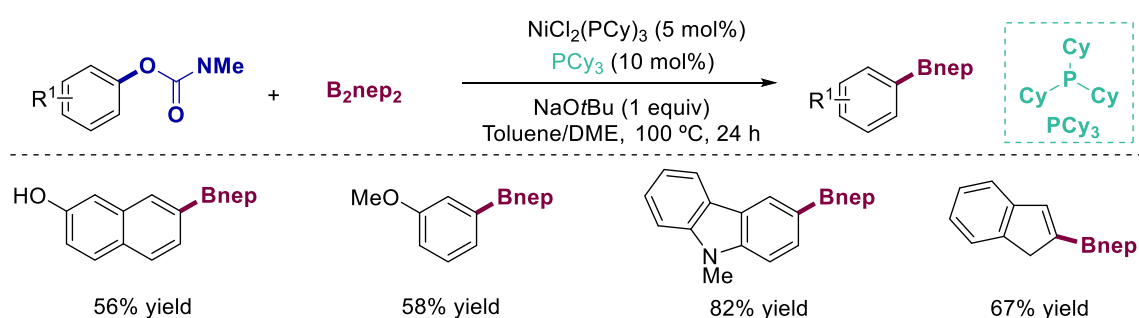
Scheme 1.2.9. Ni-Catalyzed borylation of aryl carbamates.

In 2015, our group developed the first catalytic *ipso*-borylation of aryl methyl ethers *via* C–OMe bond cleavage using a Ni/PCy$_3$ regime (Scheme 1.2.10).[85] As expected, π-extended arenes resulted in high yields, but the coupling of non-π-extended substrates required the presence of electron-withdrawing groups. Notably, two sets of conditions allowed the authors to promote a site-selective borylation of at either C(sp^3)–O or C(sp^2)–O linkages based on the *in situ* generation of nucleophilic boron reagents with different electronic and steric properties. Strategically, this protocol represented an alternative to conventional *ortho*-, *meta*-, and *para*-borylative protocols of anisole derivatives, where the methoxy entity is used as a mere regiocontrol element.[86,87]

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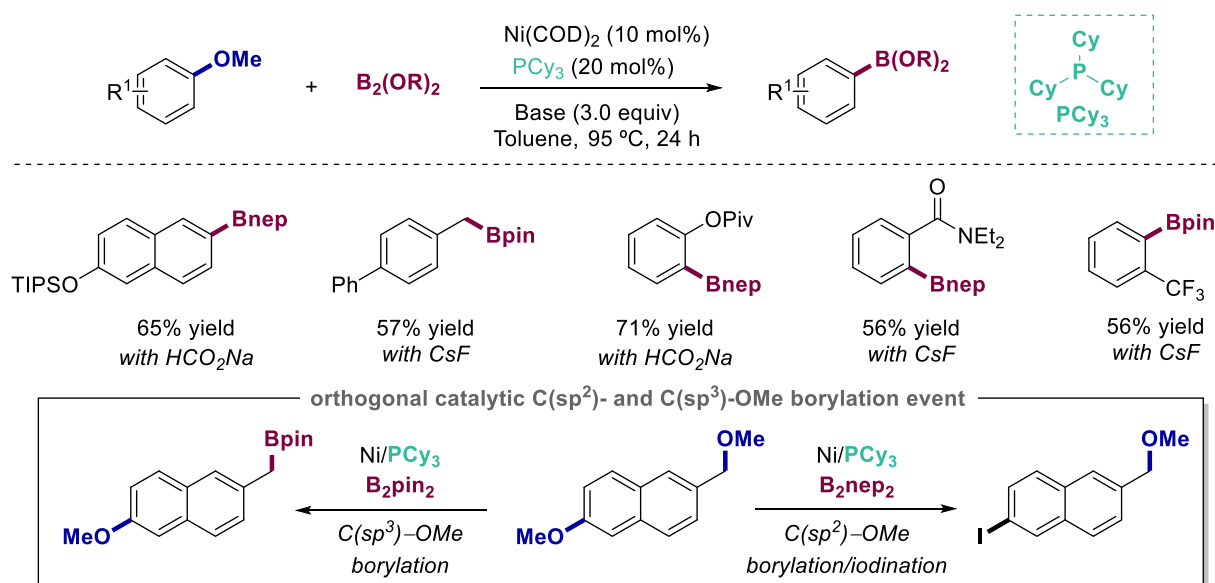
Scheme 1.2.10. Ni-catalyzed borylation of aryl and benzyl methyl ethers *via* C–OMe cleavage.

In summary, the utilization of benzyl or phenyl C–O electrophiles has received considerable attention as alternatives to commonly employed organic halide counterparts in a myriad of cross-coupling reactions.[45] While not as well-adopted as the latter, C–O electrophiles offer new opportunities for synthetic design given the ready availability and lack of toxicity of the corresponding alcohol or phenol counterparts. In this line, such advances developed a series of stereospecific reactions opening a worthy gateway to obtain enantioenriched scaffolds (see *Chapter 2*).

1.2.2 Nickel-catalyzed the cleavage of activated C(*sp³*)–N bonds

1.2.2.1 Importance of alkyl C–N bond as electrophiles

Over the recent years, the prevalence of alkyl amines in a myriad of bioactive molecules, agrochemicals or natural products have prompted chemists to design catalytic cross-coupling reactions with the latter being electrophilic partners (Figure 1.2.3, *top*). However, the considerable high bond strength of the C(sp³)–NH$_2$ linkage (BDE ~88 kcal/mol,) makes alkyl amines not particularly suited as electrophiles in cross-coupling reactions unless these motifs are functionalized at the nitrogen terminus (Figure 1.2.3, *bottom*).[48]

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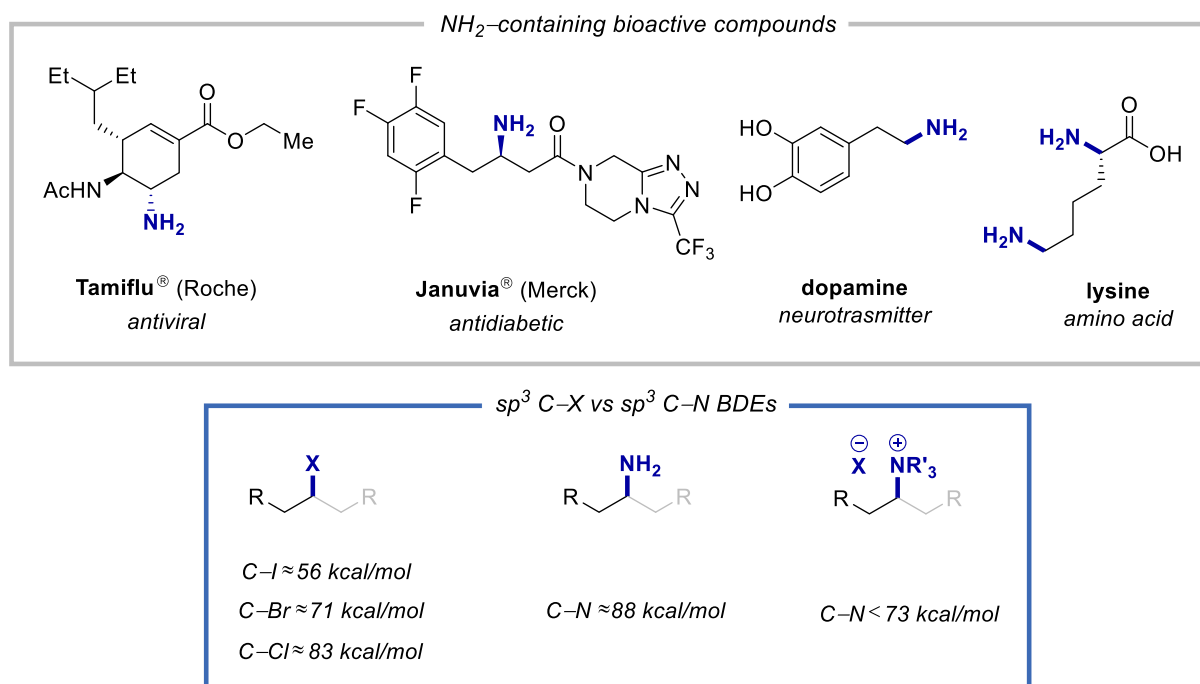
Figure 1.2.3. Importance and BDEs of alkyl amines.

In the early 80's, the first cleavage of C(sp^3)–N bonds was reported by utilizing tetrahydropyridinium salts bearing β-silicon groups capable of inducing the fragmentation of the targeted alkyl C–N bond by means of exogenous fluoride ions.[88] In 1987, Gumpton and co-workers derivatized allylic amines to more activated quaternary ammonium salts prior to coupling with Grignard reagents.[89] This publication paved the way for the future cross-coupling reactions using activated C(sp^3)–N bonds as a means to promote derivatization of simple alkyl amines.

Some years later, Trost and co-workers disclosed a Ni-catalyzed cross-coupling of allylic amines with boronic acids obtaining the corresponding allylic products with moderate to good yields, with site-selectivity being dictated by the nature of the ligand backbone.[15] In 1997, Mortreux and co-workers developed a Ni-catalyzed coupling reaction of allylic amines with soft nucleophiles instead.[16] Despite these precedents, it is somewhat surprising that the attention of chemists was shifted to the activation of C(sp^2)–N bonds instead of looking at the reactivity of simple unactivated alkyl amine congeners.[17] It was not until recently that the potential of nickel catalysts was assessed in benzyl C(sp^3)–N bonds and strained activated aziridines.

1.2.2.2   *Primary and secondary benzyl C(sp^3)–C bond formation via boronic acids*

In 2013, Watson and co-workers reported the first nickel-catalyzed cross-coupling of benzylic ammonium triflate salts and boronic acids by the stereospecific formation of diarylethanes via C–N bond activation (Scheme 1.2.11).[90] The choice of using ammonium triflates was not arbitrary: a) these compounds have shown their willingness to promote cross-coupling reactions with boronic acids,[14,17] b) they offer an orthogonal method to both halides and ethers, c) also remained stable to long-term

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storage, d) highly enantioenriched benzylic amines are readily available *via* common asymmetric techniques, making them particularly attractive as coupling counterparts.[91]
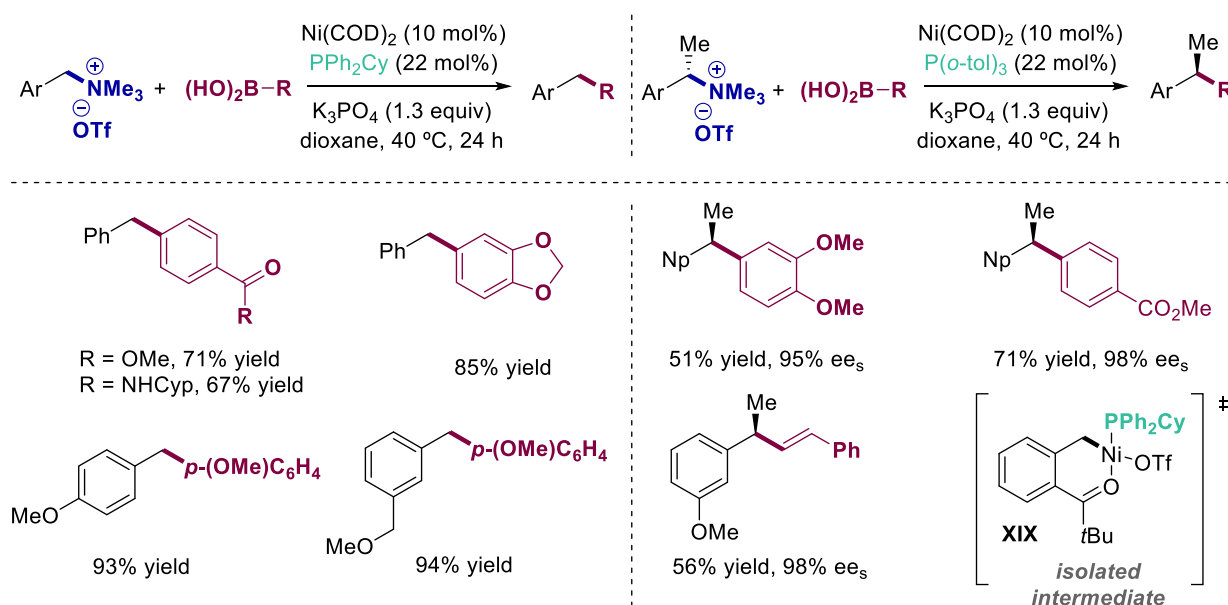
Scheme 1.2.11. Nickel-catalyzed cross-coupling of benzylic ammonium salts and boronic acids.

The transformation could accommodate a wide variety of different benzylic ammonium salts bearing electron-rich and electron-poor substituents. Moreover, the transformation was suitable for a large variety of boronic acids bearing different functional groups such as ester, amides and acetals (Scheme 1.2.11, *left*). Remarkably, the C–N bond is selectively activated over the C–O bond under these conditions. The authors were able to develop a stereospecific version of the reaction by changing the ligand to a more electron-rich phosphine (Scheme 1.2.11, *right*). The scope showed a wide variety of boronic acids and enantioenriched secondary benzyl ammonium salts, allowing to extend the application of these methods to stereospecific C–N cleavage reports.[92,93] Notably, the transformation operated with an inversion of stereochemistry *via* S_N2-type mechanisms.

One year later, Watson and co-workers reported the same stereospecific cross-coupling protocol for benzylic ammonium triflates and boronic acids where no ligand was required (Scheme 1.2.12).[94] This permitted a vast improvement of the scope in heteroaromatic boronic acids with diverse electronics.
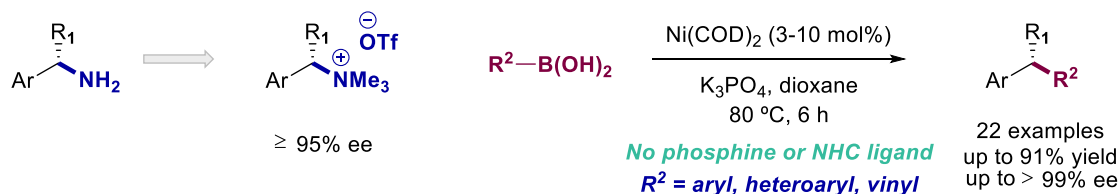
Scheme 1.2.12. Stereospecific cross-coupling of benzylic ammonium triflates and boronic acids: no phosphine ligand required.

1.2.2.3   Primary and secondary benzyl C(sp^3)–CO$_2$H bond formation *via* CO$_2$

Traditionally, ammonium salts have been exclusively employed in nucleophile/electrophile regimes using well-defined stoichiometric organometallic reagents. As part of our investigations in nickel catalysis[66,85,95] and cross-electrophile couplings with CO_2,[96–99] our group reported the first cross-electrophile coupling of benzylic C–N bonds with CO_2 as electrophilic partners (Scheme 1.2.13).[100] This study comprised the utilization of primary and secondary benzyl ammonium salts with phenanthroline ligands (**L1-L2**) being particularly useful for success (Scheme 1.2.13, *A* and *B*). Although speculative, some stoichiometric experiments pointed out at the intermediacy of benzyl Ni(I) species *via* single-electron reduction of benzyl Ni(II) complexes mediated by Mn (Scheme 1.2.13, *bottom*). In line with this notion, **XXI** was found to be competent as reaction intermediate in the presence of Mn. The inhibition of the reaction in the presence of TEMPO suggested the involvement of radical intermediates in the reaction mixture. This proposal gains credence by the complete loss of optical purity by reacting enantioenriched ammonium salt under the optimized reaction conditions. However, care must be taken when generalizing this, as racemization might occur *via* bimolecular mechanisms in which an inversion occurs *via* reaction of a low-valent Ni(0) species to *in situ* generated Ni(II) intermediates *via* oxidative addition pathways.
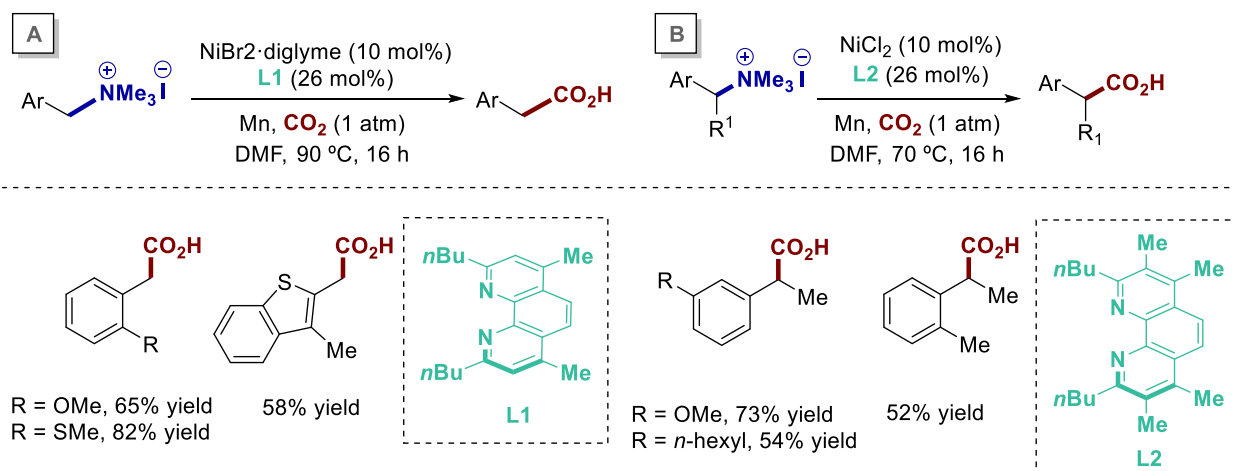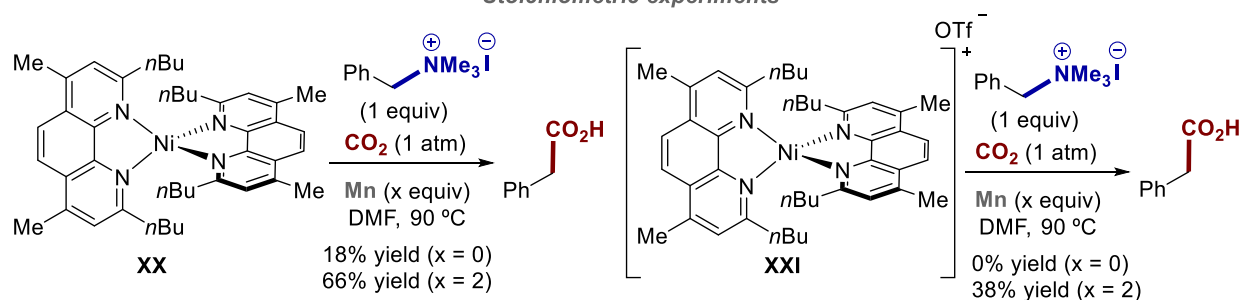
Scheme 1.2.13. Cross-electrophile coupling of benzylic C–N bonds with CO_2 catalyzed by nickel.

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1.2.2.4   C(sp^2)– and C(sp^3)–B bond formation of aromatic systems *via* B$_2$pin$_2$ reagents

In 2015, Itami and Shi independently reported the first C–N borylation of phenyl and benzyl ammonium triflates with nickel catalysts supported by either PnBu$_3$ or ICy (1,3-dicyclohexyl-1H-imidazol-3-ium chloride) (Scheme 1.2.14, *A* and *B*).[23,101] In both works, the borylation of phenyl and benzyl ammonium triflates was compatible with the presence of diverse electronic and steric substituents obtaining good yields.
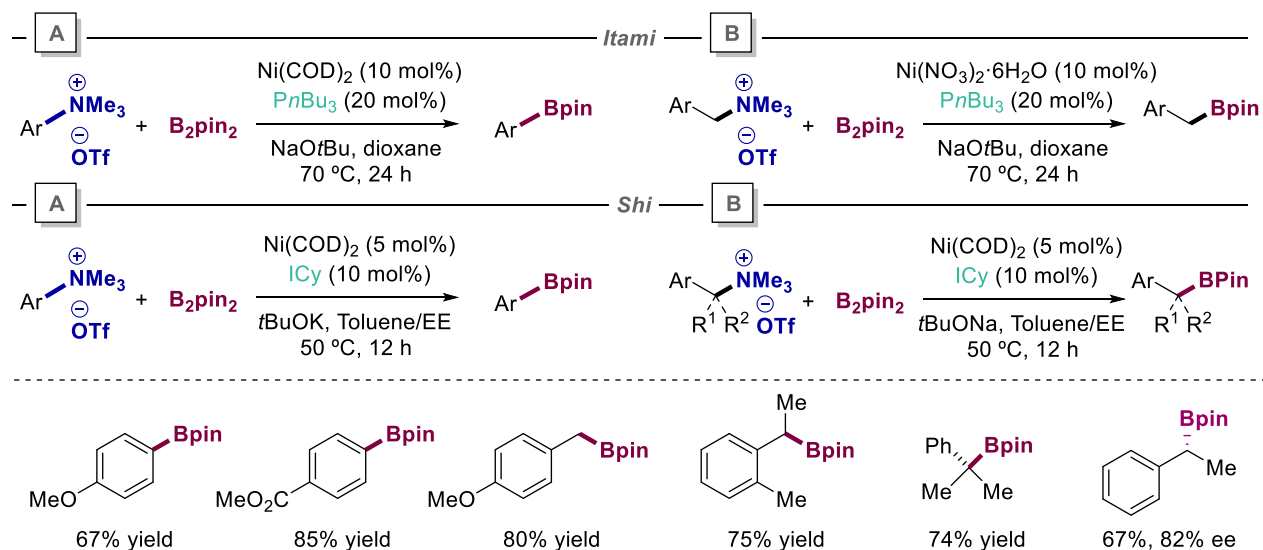
Scheme 1.2.14. Nickel-catalyzed C–N borylation of phenyl and benzyl ammonium salts.

Watson reported the "*first*" stereospecific borylation of benzylic ammonium salts catalyzed by nickel complexes (Scheme 1.2.15).[102] The procedure proved to be suited for the utilization of activated amines containing electron-rich, electron-poor and heteroaromatic rings in good yields and with an excellent chirality transfer. The attractiveness of this procedure relies on the formation of chiral benzylic boronic esters, useful intermediates for the construction of complex molecules in an enantioenriched fashion.
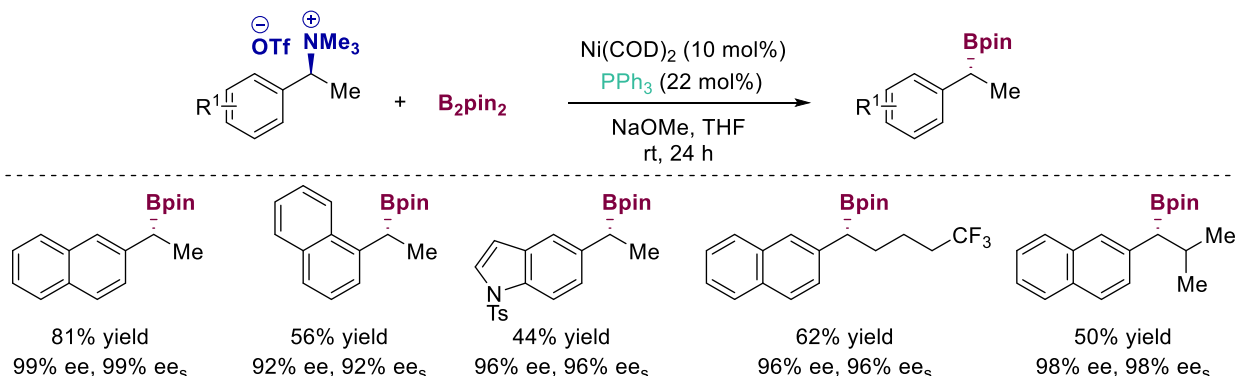
Scheme 1.2.15. Stereospecific borylation of benzylic ammonium salts catalyzed by nickel.

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1.2.2.5   Nickel-catalyzed C(sp^3)–N scission of aziridines

As part of a program aimed at the employment of aziridines in cross-coupling reactions, Doyle and co-workers reported the utilization of the latter as coupling partners for the formation of β-substituted amines *via* C(sp³)–N bond cleavage.[103] The inspiration for developing such a technique arose from the pioneering work reported by Hillhouse[104] and Wolfe,[105] where an oxidative addition of an aziridine to low-valent Ni(0) results in a four-membered azanickelacycle. In particular, Doyle reported a nickel-catalyzed Negishi alkylation of activated styrenyl aziridines in 2012 (Scheme 1.2.16, *top*).[93] Based on the available literature data,[104,105] the author proposed two alternatives for the insertion of nickel catalyst into the C–N bond (Scheme 1.2.16, *bottom*). In *path a*, a S$_N$2-type oxidative addition is accompanied by reversible homolysis at the benzylic Ni–C bond, thus furnishing **XXII**. In *path b*, an irreversible SET oxidative addition could afford the intermediate **XXIII**. Then, transmetallation with an alkylzinc reagent occurs (likely stabilized by the dimethyl fumarate ligand, **XXIV**) prior to reductive elimination en route to the targeted product.
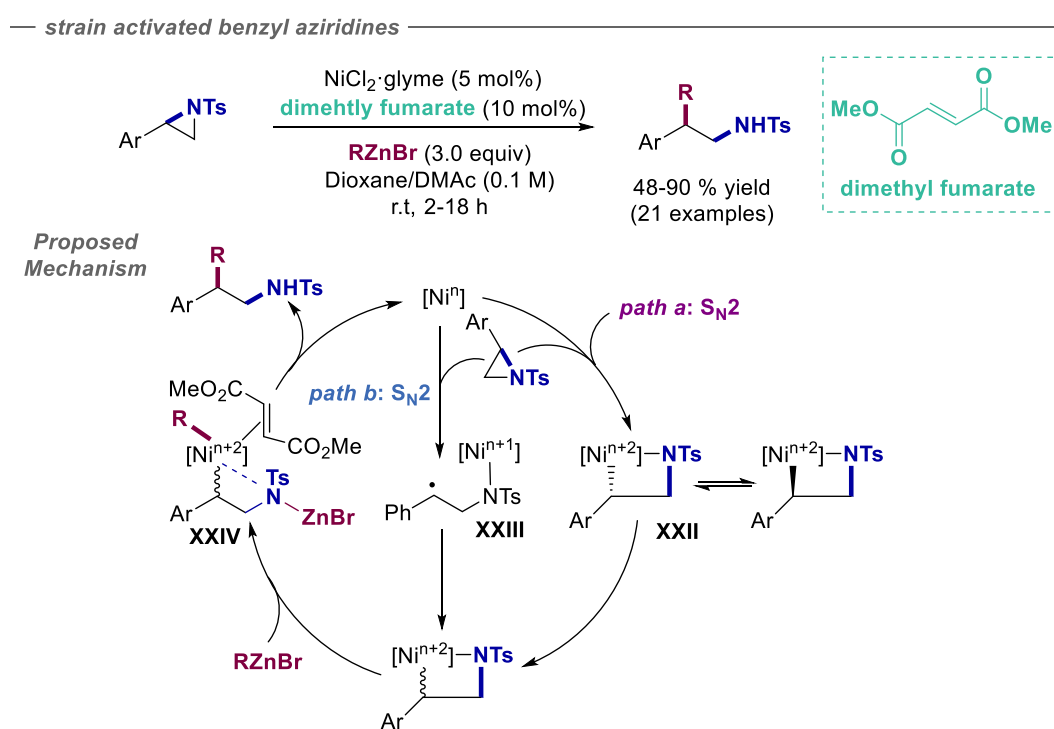
Scheme 1.2.16. Nickel-catalyzed Negishi alkylations of styrenyl aziridines & mechanism.

In 2013, the same authors reported a directed nickel-catalyzed Negishi cross-coupling of alkyl aziridines (Scheme 1.2.17, *A*)[106] possessing a protecting group that resembles a dimethyl fumarate ligand used before in the previous Negishi-type coupling reaction. The objective was to activate the C–N bond and stabilize the intermediates that are *a priori* prone to β-hydride elimination by facilitating the reductive elimination step. The methodology was applied to a wide number of aziridines bearing different functional groups and to diverse zinc reagents, albeit with low

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regioselectivities. Inspired by these results, Jamison and co-workers developed a highly regioselective nickel-catalyzed cross-coupling of *N*-tosylazyridines and alkylzinc reagents (Scheme 1.2.17, *B*).[24] This platform allowed the authors to furnish the linear amines by the utilization of nickel/phenanthroline regimes. The mechanism was believed to proceed *via* oxidative addition (**XXV**), followed by transmetallation and reductive elimination steps.
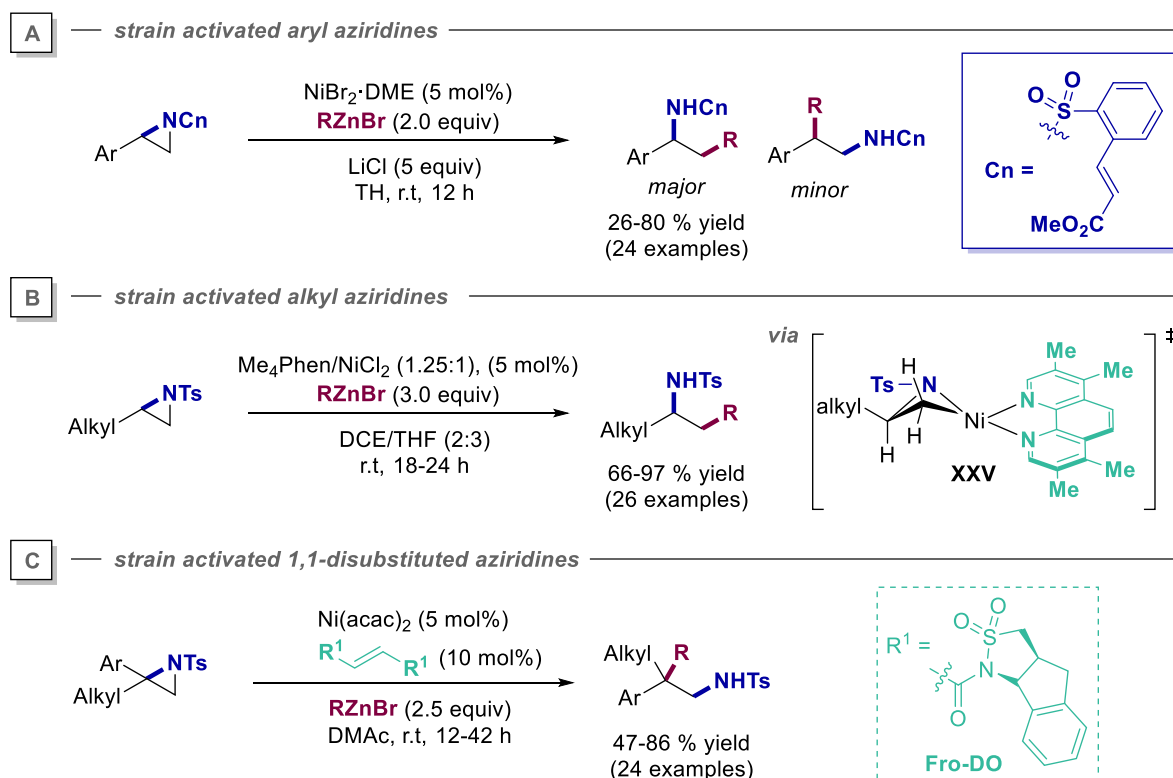
Scheme 1.2.17. Ni-catalyzed Negishi cross-coupling with aziridines.

In 2015, a Negishi cross-coupling of 1,1-disubstituted-aziridines catalyzed by nickel was reported by Doyle and co-workers (Scheme 1.2.17, *C*).[107] Interestingly, the protocol was based on the utilization of an electron-deficient olefin ligand (**Fro-DO**), likely allowing to adopt a U-shaped conformation with Ni, creating a sterically congested environment around the metal center. In this manner, reductive elimination is likely facilitated by bringing into close proximity the two fragments required for effecting C–C bond-formation. However, the substrate scope was limited to the presence of a pending aryl moiety, as the presence of a 1,1'-dialkyl motif was not tolerated.

A remarkable step-forward was reported in 2017 by Watson and co-workers, demonstrating the viability of promoting cross-coupling reactions with unactivated alkyl amines by using pyridinium salts as electrophilic partners.[108] This methodology paved the way for the discovery of deaminative cross-coupling reactions by employing pharmaceutically-important unactivated alkyl amine counterparts (see *Chapter 3*).

1.2.3   Remote functionalization of unactivated C–H bonds by walking metals

1.2.3.1   Introduction and mechanism of chain-walk events

In early 1970s,[109–111] the concept of remote functionalization consisted of an indirect activation of a site distant from an initial functional group (Figure 1.2.4, *A*).[36] The control of such selectivity profile relies on the directionality of the substrate by directing groups, present or preinstalled or through an undirected activation of particularly reactive C–H bonds (Figure 1.2.4, *B*). Although directed activation of C–H bonds has been exploited over the last decades, this strategy is rather limited to the distance between the catalyst and the targeted C–H bond.[112]
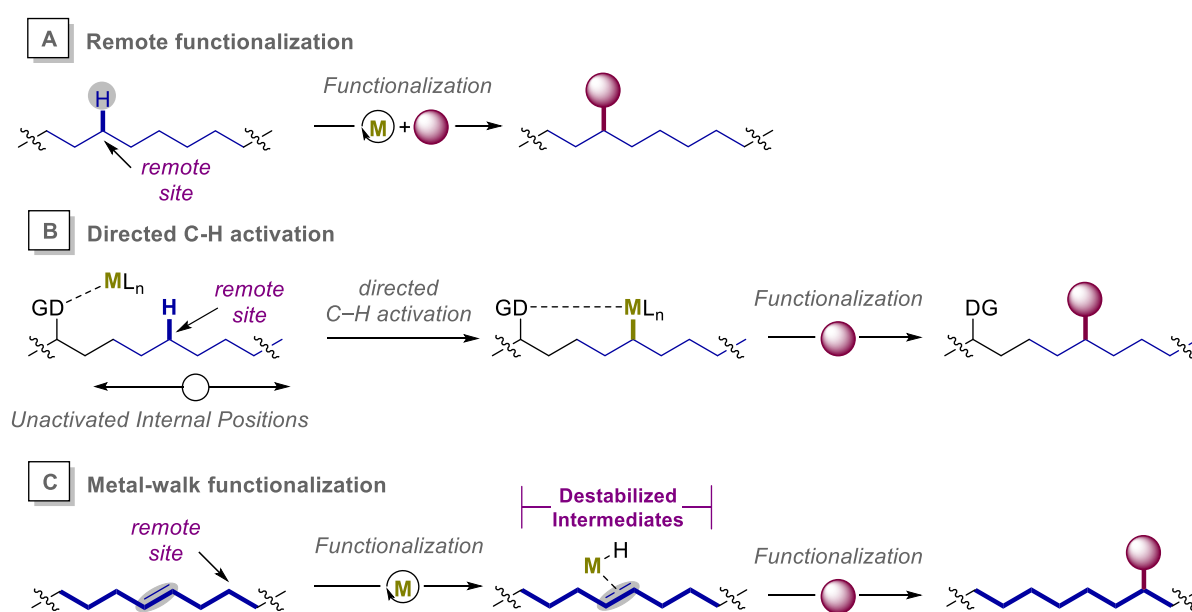
Figure 1.2.4. Metal-walk vs classical modes of activation.

In recent years, "metal-walking" or "chain-walking" processes have attracted the interest of chemists due to the possibility of performing undirected remote functionalization at distal sp^3 C–H bonds (Figure 1.2.4, *C*). This protocol consists of an iterative series of consecutive 1,2- or 1,3-hydride shifts of a metal complex along a hydrocarbon side-chain, allowing to formally translocate the metal at a different location within the hydrocarbon prior to C–C bond-forming reaction. One of the most important characteristics of the transition metal to carry out chain-walking processes is the ability to rapidly promote an insertion across the olefin followed by a β-hydride elimination in an iterative manner (Figure 1.2.5).

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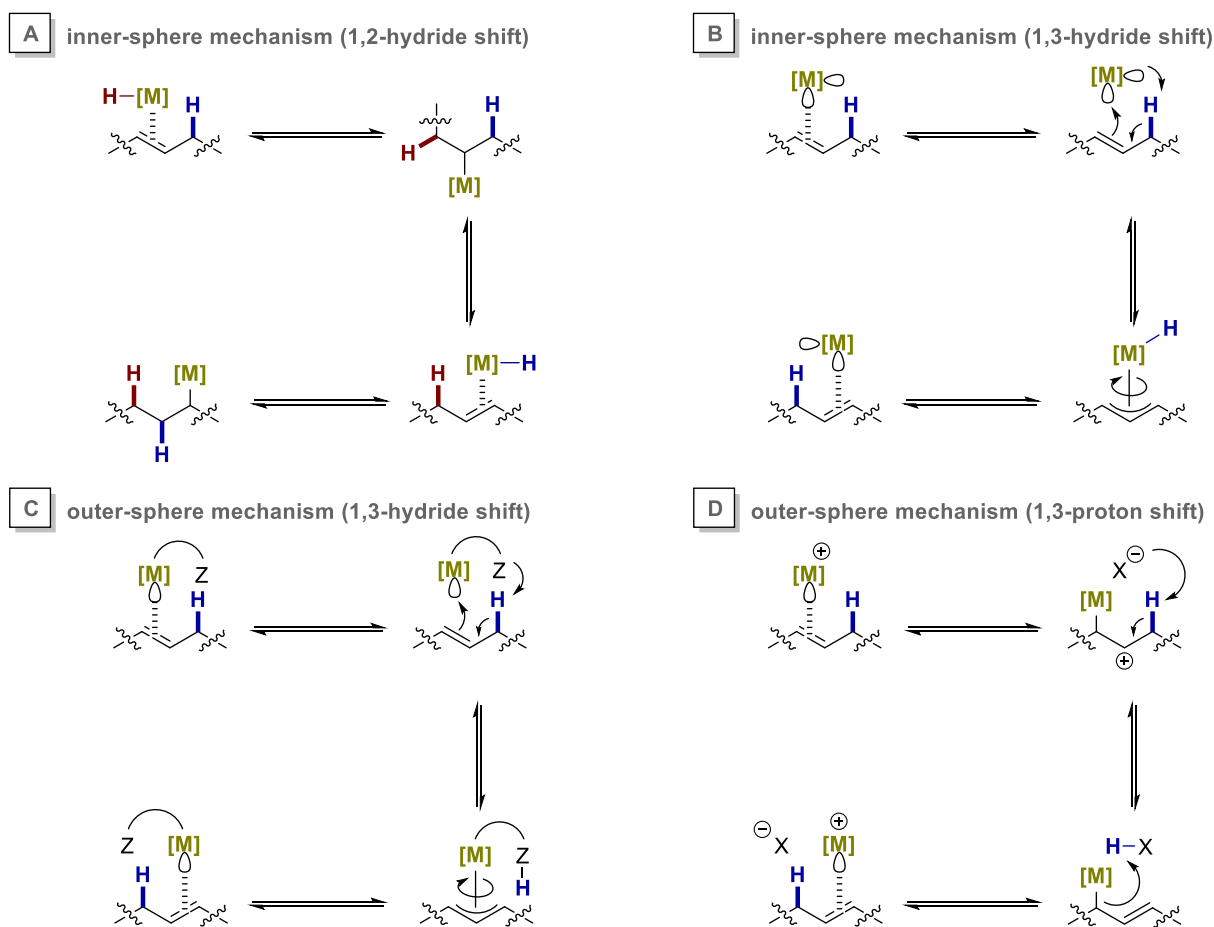
Figure 1.2.5. Mechanistic intricacies of olefin isomerization.

Four mechanistic scenarios can be envisioned for chain walking processes. Depending on the nature of the metal, olefin isomerization may occur *via* either 1,2- or 1,3-hydride shift (Figure 1.2.5):[113,114] A) In a 1,2-hydride shift inner-sphere mechanism, the metal-hydride undergoes migratory insertion into an olefin, obtaining a well-defined alkyl-metal species. Subsequent β-hydride elimination furnishes the isomerized olefin π-complex, which undergoes rotation or hydrometalation (Figure 1.2.5, *A*). B) Alternatively, an olefin isomerization can take place *via* 1,3-hydride shift inner-sphere mechanism. In this context, the metal should possess two vacant orbitals, one for the olefin coordination and the other for the C–H allylic activation. Once the η³-allyl complex has been formed, a reductive elimination provides the isomerized olefin-metal complex (Figure 1.2.5, *B*). C) In an outer-sphere mechanism, one of the two vacant orbitals of the metal is filled by a base added to the system. Upon olefin coordination and allylic activation, the base can abstract the allylic proton generating an allylic metal-complex (Figure 1.2.5, *C*). Finally, an outer-sphere 1,3-proton shift mechanism can be proposed with π-acidic transition metals such as cationic silver and palladium complexes that can acidify the allylic position upon olefin coordination. Intermolecular deprotonation gives rise to the η³-allyl complex, obtaining rapidly the olefin isomerization by protodemetalation (Figure 1.2.5, *D*). A variety of metal-catalytic protocols have been developed depending on the final termination event (Figure 1.2.6).

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Figure 1.2.6. Metals capable of chain-walking events.

1.2.3.2 *Zirconium walking metal*

In 1961, Finkbeiner reported the first isomerization event where, under Ti or Zr catalysis, branched alkene Grignard reagents afforded linear compounds *via* olefin intermediates.[115,116] It was not until 20 years later when Marek and co-workers made use of Schwartz's reagent (Cp$_2$Zr(H)Cl)[117,118] and Negishi reagent (Cp$_2$Zr(C$_4$H$_8$))[119] for the isomerization of fatty alcohols prior to electrophilic trapping in the presence of organozinc intermediates (scheme 1.2.18, *A*).[120]

Subsequently, Fletcher showed that simple internal olefins served as vehicles to obtain terminal alkylzirconium species in the presence of Schwartz's reagent, setting the basis for promoting an asymmetric conjugate addition with α,β-unsaturated cyclic ketones catalyzed by copper (Scheme 1.2.18, *B*).[121]

More recently, Marek reported a bisfunctionalization of olefins by isomerization events with zirconium species. This protocol strategically positioned cyclopropanes along the chain, leading to double electrophilic coupling by C–C bond cleavage (Scheme 1.2.18, *C*).[122,123] This methodology was based on the formation of an allyl zirconacyclobutane (**XXVII**) which react with carbonyl electrophiles at the allylic position (**XXIX**) followed by subsequent activation of the remaining zirconium species to promote a second electrophilic trapping (**XXX**). Although in all examples shown until today stoichiometric amounts of zirconium reagents are required, these transformations open a gateway to develop new catalytic methods by means of olefin isomerization.

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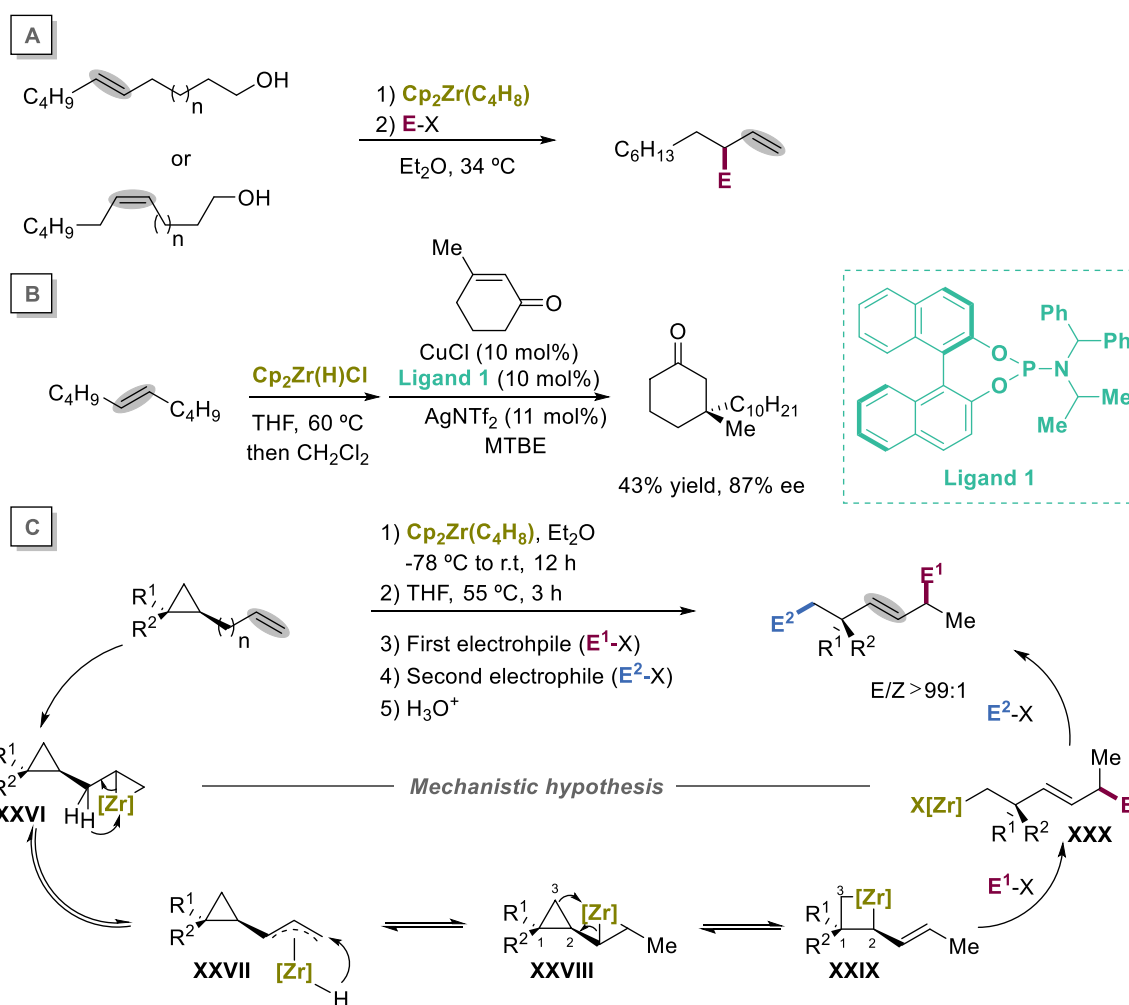
Scheme 1.2.18. Zr complexes in chain-walking events.

1.2.3.3   *Ruthenium, Rhodium, and Iridium walking metals*

In 1974, Wells and co-workers discovered the isomerization of 1-pentene to 2-pentene promoted by homogeneous ruthenium catalysis.[124] In 2007 Sharma and co-workers corroborated the robustness of olefin isomerization events by a ruthenium "alkene-zipper" catalyst. The protocol exhibited an olefin isomerization over more than 30 positions *via* an outer-sphere 1,3-hydride shift mechanism (Scheme 1.2.19, *A*).[125] One year later, Schrock published a combination of the "alkene-zipper" catalyst and an olefin metathesis catalyst (**W-1**) which were able to accomplish a tandem olefin isomerization/metathesis affording long-chain olefins (Scheme 1.2.19, *B*).[126]

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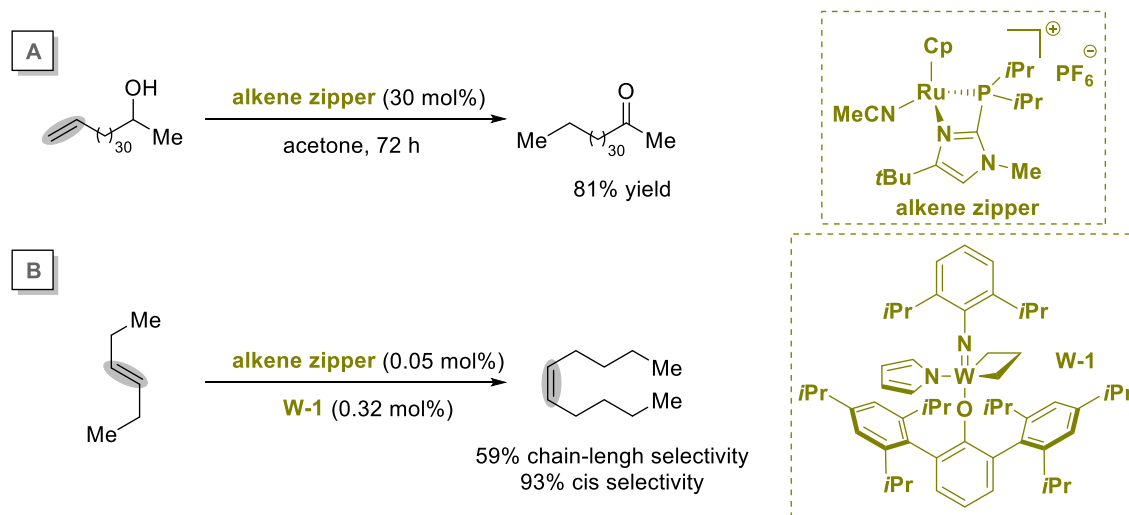
Scheme 1.2.19. Ru chain-walking reactions of olefins.

More than 50 years have passed since Wilkinson and Osborn discovered that PPh$_3$ ligands assist rhodium catalysts to perform hydroformylation reactions of terminal olefins.[127,128] In the last 20 years novel rhodium catalytic systems have been discovered,[129] with the delivery of linear aldehydes or derivatives by isomerization of mixture of alkenes (Scheme 1.2.20).[130–132]
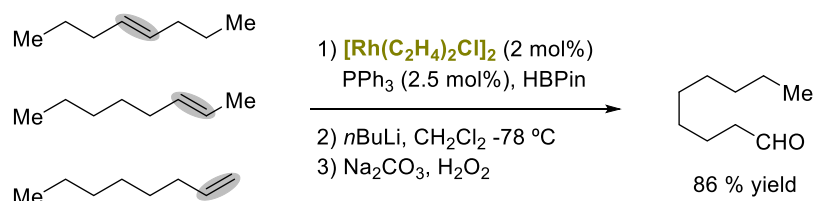
Scheme 1.2.20. Rh chain-walking reactions of olefins.

In 2011, a rhodium-catalyzed olefin isomerization/Michael addition sequence was achieved by Gooßen and co-workers (Scheme 1.2.21).[133] The authors proposed a combination of two cooperating catalytic cycles: one for the double-bond isomerization and the other one for the conjugative addition. Initiated by the isomerization cycle (Scheme 1.2.21, *cycle A*), the rhodium species sits on the olefin (**XXXI**) and undergoes a C–H insertion at the metal center to give π-allyl rhodium species (**XXXII**) that enable isomerization *via* migratory insertion/β-hydride elimination (**XXXIII**) pathways. Although all the steps are *a priori* reversible, only the isomer at the α,β-position to the carboxy group can enter into the second catalytic cycle (Scheme 1.2.21, *cycle B*), thus ultimately leading to functionalization at this end.

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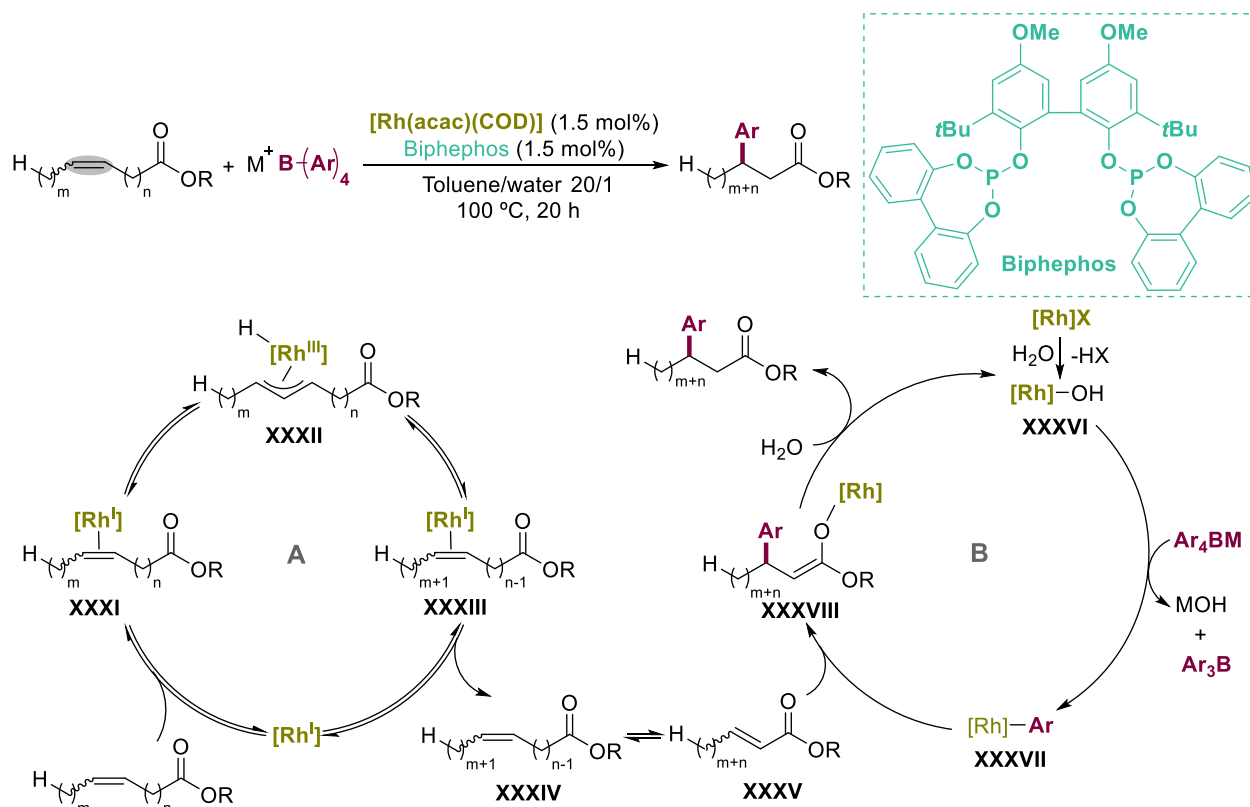
Scheme 1.2.21. Postulated mechanism of the isomerizing conjugate addition.

In the late 90's Miyaura and co-workers discovered that cationic iridium complexes in the presence of hydrogen readily promote olefin isomerization with exceptional ease.[134] By the utilization of similar cationic iridium complexes, Murakami developed a tandem isomerization/enantioselective allylation sequence in high yields and excellent enantioselectivities (Scheme 1.2.22, *A*).[135] Angelici and co-workers showed that terminal hydroboration of the fatty methyl oleate can be accomplished in the presence of an iridium catalyst (Scheme 1.2.22, *B*).[136]
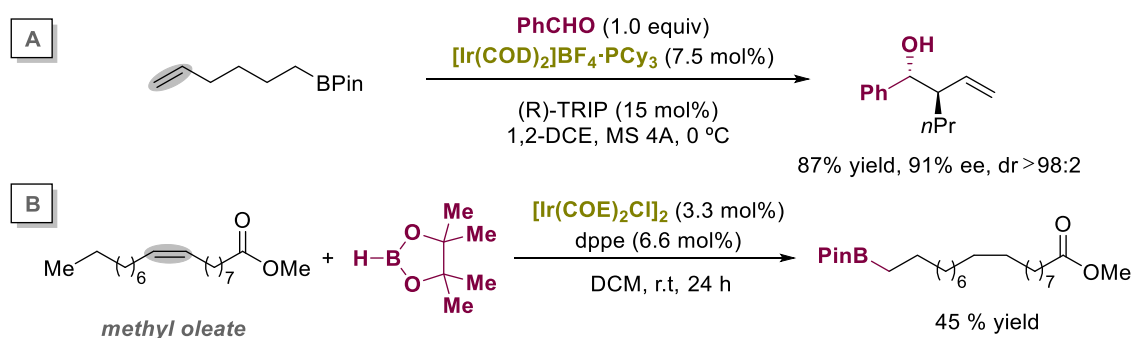
Scheme 1.2.22. Ir chain-walking reactions of olefins.

1.2.3.4   *Iron walking metals*

The ability of iron complexes to promote isomerization events was already discovered in the 60's.[137] However, it not was until the last decade that chemists revisited this concept as a means to

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trigger C–C and C–heteroatom bond-forming reactions.[138,139] Although only few examples of iron-catalyzed chain-walking processes have been reported so far, it is evident that the utilization of green metal catalysts will likely attract considerable interest in the next years to come. Particularly interesting is a methodology developed by Chirik that developed independently an iron-catalyzed isomerization/hydroboration sequence (Scheme 1.2.23, *A*).[140,141] While a significant step forward, these reactions required the utilization of particularly air- and moisture-sensitive iron complexes. An interesting solution utilized by Huang and co-workers was the employment of iron (II) precursors that generated the active catalysts *in situ via* a tandem dehydrogenation/isomerization/hydrosilylation sequence (Scheme 1.2.23, *B*).[142]
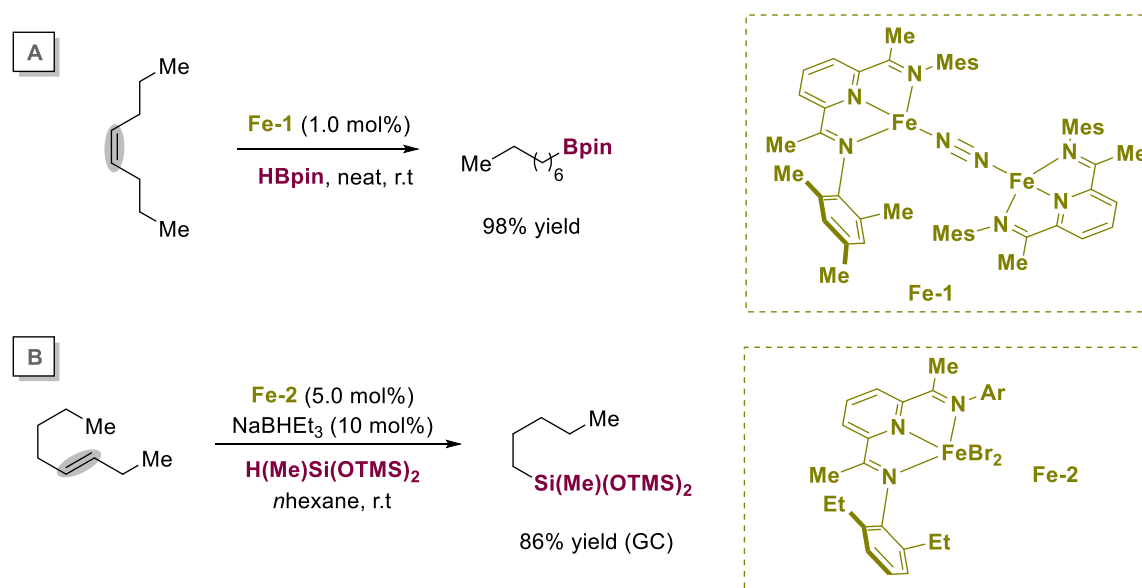
Scheme 1.2.23. Fe chain-walking hydroboration/hydrosilylation of internal olefins.

1.2.3.5 Cobalt walking metals

Since 2013, cobalt catalysts have been studied extensively for non-directed remote functionalization events *via* isomerization/hydroborations, hydrosilylations and C–C bond formations. For example, **Co-1** catalysts have been employed by Chirik in an isomerization/hydroboration of internal alkenes using pinacolborane (HBpin) with bis(imino)pyridine ligands, allowing to incorporate a Bpin residue at the terminal position (Scheme 1.2.24, *A*).[143] Subsequently, the same group discovered that the inclusion of electron-donating amino groups at *para* position of the pyridine moiety ligand afforded better reactivity (**Co-2**).[144] Some years later, Chirik reported a site-selective isomerization/hydroboration of terminal olefins decorated with pending arenes. The authors discovered that the reaction outcome can be controlled by tuning the ligand backbone obtaining either terminal or benzylic hydroboration products (Scheme 1.2.24, *B*).[145] The use of *N*-phosphinoamidinate ligands was shown to be crucial when expanding the source of boron utilized. In this line, Stradiotto and co-workers could extend the isomerization/hydroboration

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transformation to 1,3-dimethyl-1,3-diaza-2-boracyclopentane or benzo-1,3,2-diazaborolane with equal ease than HBpin (Scheme 1.2.24, *C*).[146,147]
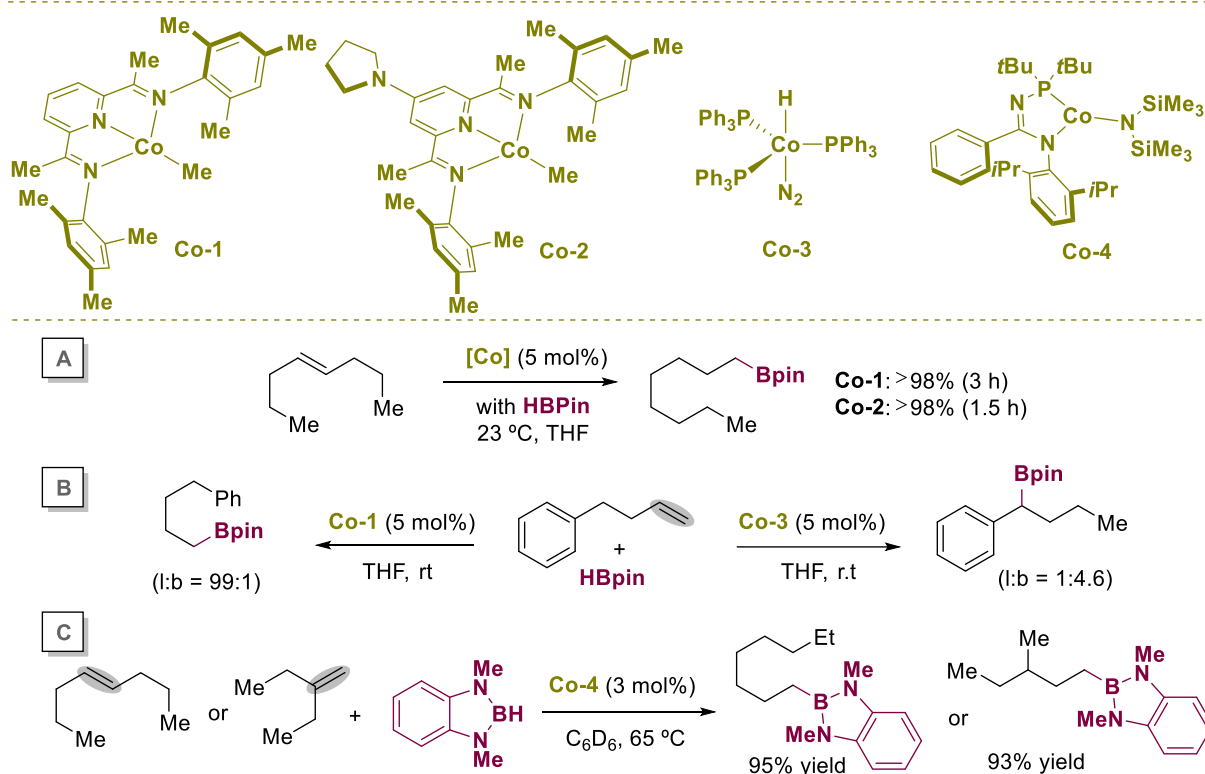
Scheme 1.2.24. Cobalt-catalyzed chain walking hydroboration events.

Superior performance has been found in cobalt complexes in terms of isomerization/hydrosilylation when compared to precious metals used for similar purposes.[148,149] In 2014, Chirik presented a dehydrogenative silylation of internal alkenes promoted by **Co-1**, affording exclusively silylated products at the terminal position (Scheme 1.2.25, *top*). Indeed, this dehydrogenative event offers the opportunity to engage multiple C–Si bonds from simple precursors.[150]

As indicated before, cobalt catalysts are able to forge C–C bonds through isomerization by remote C–H activation *via* cobalt hydride species.[151] In 2014, Yoshikai and co-workers published a site-selective transformation involving unactivated olefins bearing pending arenes, with C–H acidic indoles (Scheme 1.2.25, *bottom*).[152] On one hand, branched products were afforded with the use of *N*-heterocyclic carbenes at 60 °C and CyMgBr whereas linear products were assembled with the addition of *t*BuCH₂MgBr rather than the CyMgBr and in the absence of ligand. The latter selectivity is attributed to the formation of cobalt-hydride species by β-hydrogen elimination of the alkyl magnesium salt. Still, however, the role of the ligand is rather unclear and subject of considerable speculation.

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Scheme 1.2.25. Cobalt-catalyzed chain walking of hydrosilylation and C–C bond formation.
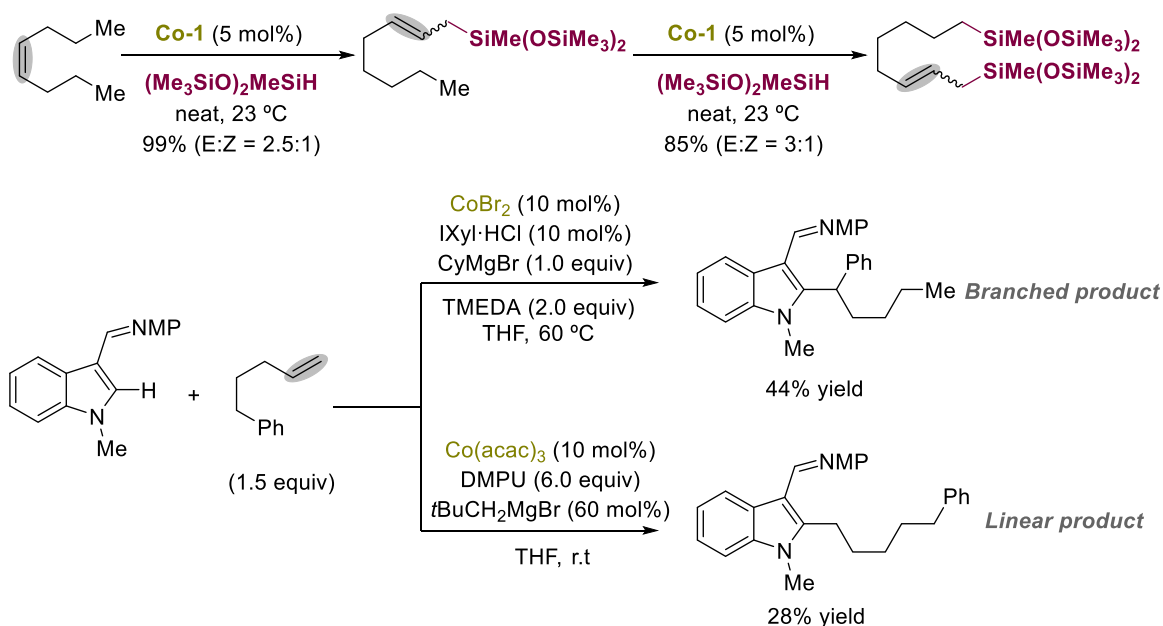
1.2.3.6   *Palladium walking metals*

The utilization of Pd catalysts in chain-walking can be traced back from the work of Magennis and Heck by combining Heck reactions and chain-walking events, obtaining the corresponding products in low yields as mixtures.[153–155] Subsequently, Larock reported that remote functionalization of aliphatic alcohols decorated with a pending alkene results in the corresponding carbonyl products by means of olefin isomerization (Scheme 1.2.26, *A*).[156] A considerable step forward was made by Sigman in 2012, describing an enantioselective remote functionalization of alcohols possessing a pending alkene with Pd catalysts bearing PyrOx ligands (Scheme 1.2.26, *B*).[157] Notably, the authors were able to achieve the formation of quaternary stereocenters in high enantioselectivity from trisubstituted olefins with a broad substrate scope.[185–196] As for zirconium-catalyzed strategies, Marek demonstrated that the utilization of Pd catalysts can be employed with cyclopropanes decorated with pending olefins and appropriately substituted alcohol motifs, resulting in the corresponding carbonyl compound (Scheme 1.2.26, *C*).[170] Optionally, chain walking can be accomplished starting from α,β-unsaturated carbonyls *via in situ* formation of palladium hydride species that ultimately afford an isomerization event (Scheme 1.2.26, *D*).[171,172]

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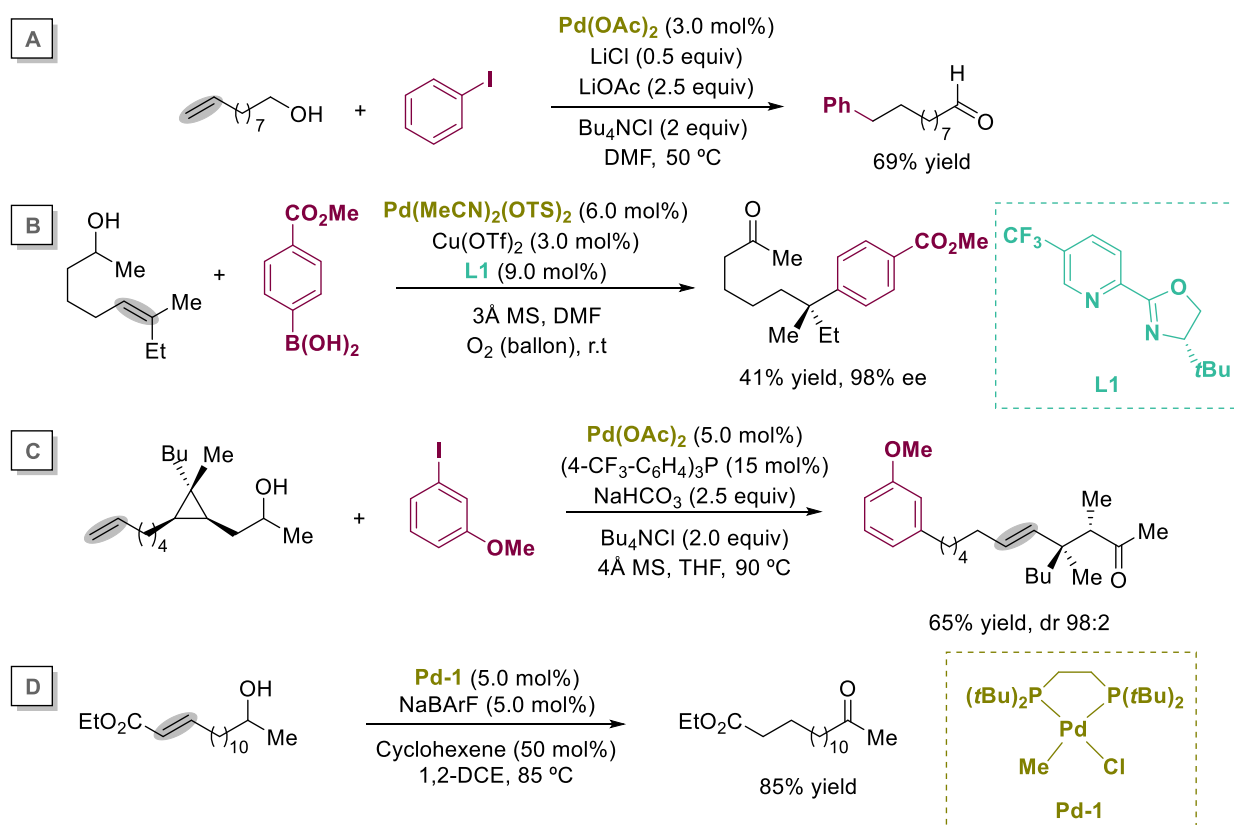
Scheme 1.2.26. Pd-catalyzed chain-walking events *via* C–C bond formations terminated by carbonyl formation.

Although these reactions are terminated by the formation of a carbonyl group, these processes are by no means confined to these compounds. Indeed, Larock and Espinet reported a series of nucleophilic trapping processes with a variety of carbon and heteroatoms nucleophiles obtaining bisfunctionalized products (Scheme 1.2.27, *A*).[173–176] In 2012, Kakiuchi and co-workers described a tandem sequence of chain-walking/cyclization with substrates possessing a strategically positioned olefin (Scheme 1.2.27, *B*).[177,178] More recently, Baudoin and co-workers described that palladium-(II) species generated from oxidative addition can undergo chain-walking prior to reductive elimination. Therefore, this strategy was applied to the remote functionalization of amino acid derivatives (Scheme 1.2.27, *C*).[179] In 2016, the same group presented a selective linear Negishi type cross-coupling using mixtures of branched alkyl bromides.[180]

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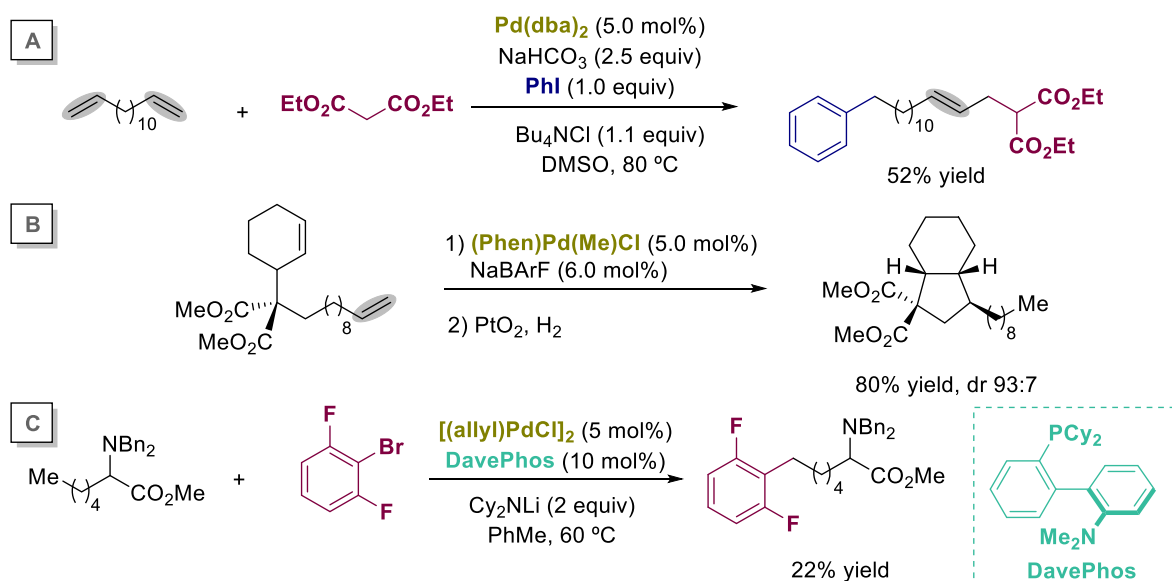
Scheme 1.2.27. Pd-catalyzed chain-walking events *via* C–C bond formation by non-terminating carbonyl formation.

1.2.3.7   *Nickel walking metals*

The utilization of nickel catalysts in chain-walking reactions can be traced back from their use in polymerization events.[181,182] Significant applications of this chemistry can be found in the Shell higher olefin process (SHOP) and Dupont process. More recently, Hu and co-workers established in 2015 a selective alkene isomerization/hydrosilylation by nickel pincer complexes, in which the nickel hydride was generated upon exposure to both metal alkoxides and silanes (Scheme 1.2.28, *A*).[183,184] A significant improvement was obtained when nickel nanoparticles were utilized, extending the scope to tertiary silanes (Scheme 1.2.28, *B*).[185]
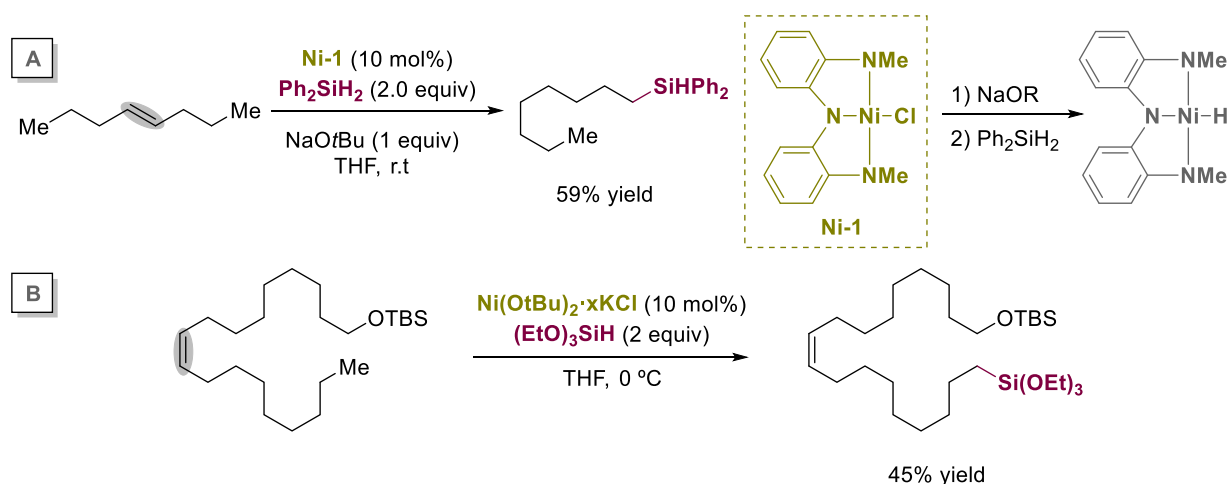
Scheme 1.2.28. Ni-catalyzed chain-walking hydrosilylations of internal olefins.

In 2013, Ong described a nickel-catalyzed olefin isomerization/hydroarylation of alkenes *via* initial C–H functionalization of (hetero)arenes with *N*-heterocyclic carbene ligand and Ni(COD)₂, enabling

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bond-formation at the benzylic position. Interestingly, the presence of AlMe$_3$ inhibits olefin isomerization, resulting in the formation of linear products (Scheme 1.2.29, *A-top*).[185] Theoretical calculations supported an initial oxidative oxidation into the C–H bond (Scheme 1.2.29, *A-bottom*).[185] In 2017, Zhu and co-workers reported a site-selective catalytic hydroarylation of alkenes occurring exclusively at benzylic C(sp^3)–H sites where the utilization of polymethylhydrosiloxane (PHMS) was crucial for success (Scheme 1.2.29, *B-top*).[186] Later, the same group described a follow-up where they were able to avoid the utilization of PHMS by utilizing light alkyl bromides as hydride sources[187] *via* β-hydride elimination (Scheme 1.2.29, *B-bottom*).[188,189]
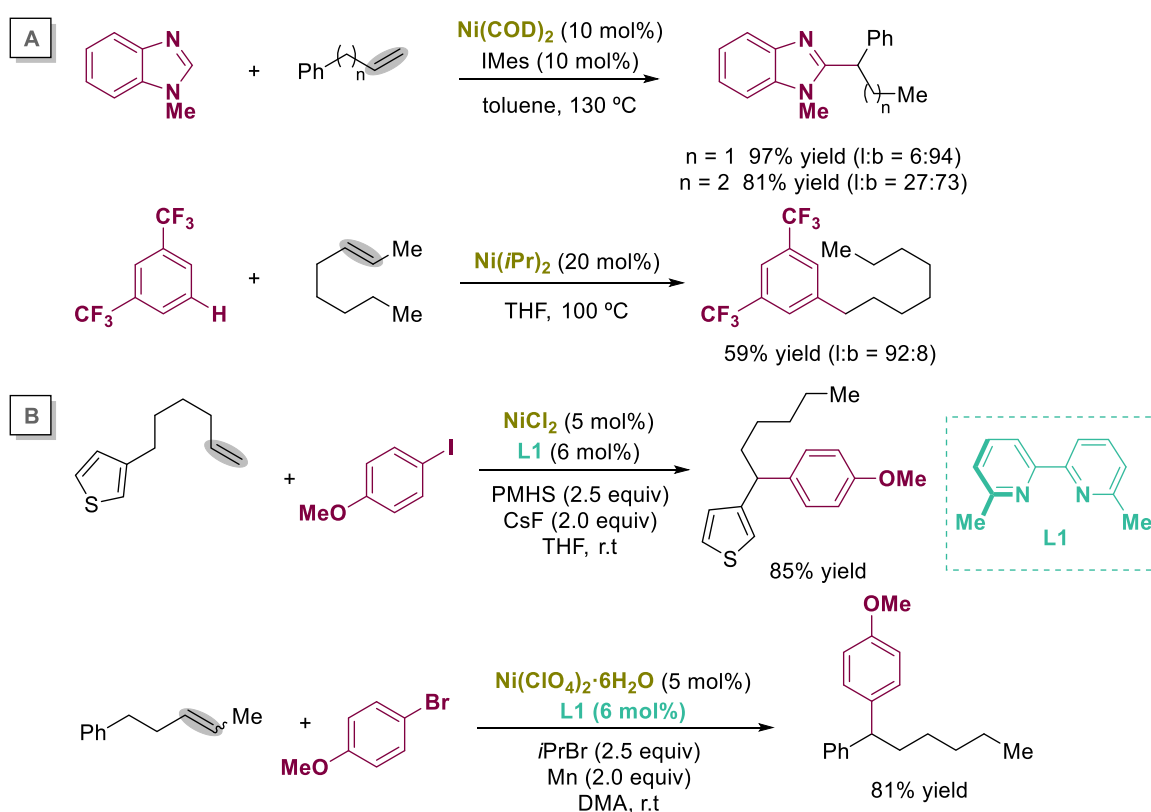
Scheme 1.2.29. Ni-catalyzed chain-walking hydroarylations.

Driven by knowledge of our group in Ni catalysts, a remote and site-selective C(sp^3)–H carboxylation of unactivated alkyl bromides with CO$_2$ (Scheme 1.2.30, *A*) was reported recently.[190] Importantly, this transformation occurs exclusively at the terminal C(sp^3)–H bond, even with alkyl bromides possessing an arene on the side chain. In addition, this study showed the possibility of controlling site-selectivity by a subtle control of the temperature, allowing to trigger bond-formation at either branched or linear positions. In 2019, our group reported that a similar strategy can be implemented by means of photoredox catalysis in the absence of inorganic reductants.[191] Moreover, Martin and co-workers demonstrated that a remote carboxylation of olefins can be implemented with water as formal hydride source (Scheme 1.2.30, *B*).[192] Interestingly, statistical mixtures of olefins can promote a carboxylation even within the context of chain-walking reactions with an exquisite site-selectivity profile.
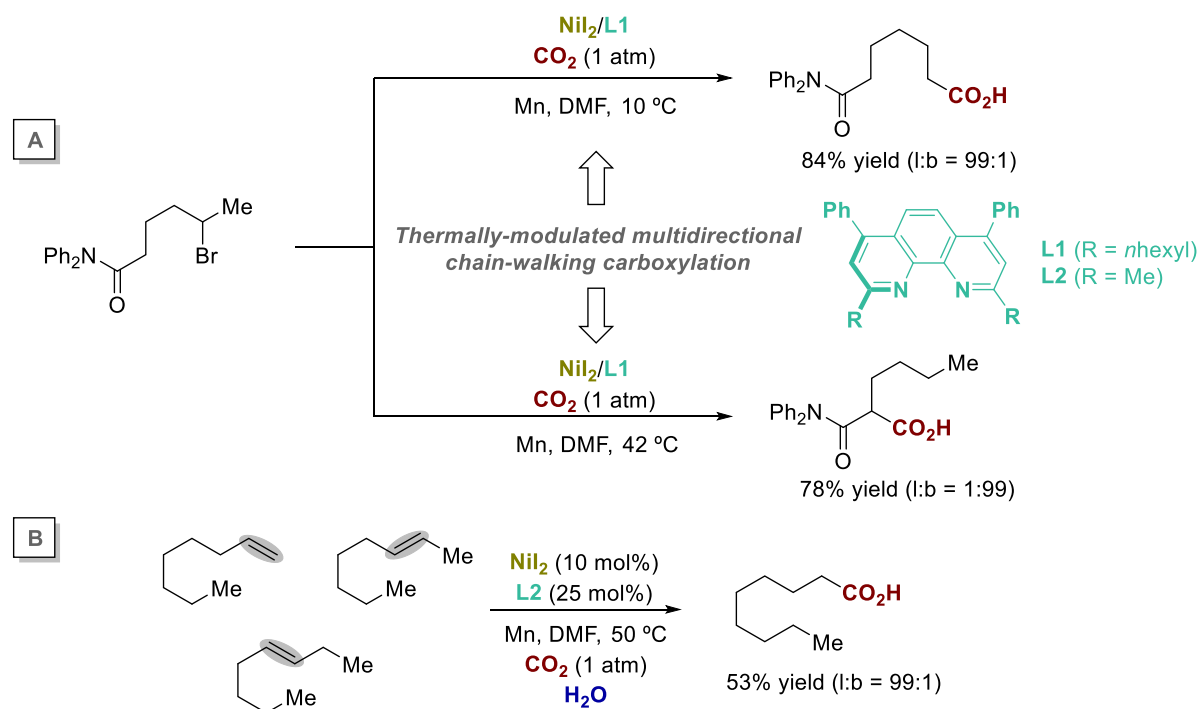
Scheme 1.2.30. Ni-catalyzed chain-walking for remote carboxylation.

Another example was reported by our group in 2018 when describing a Ni-catalyzed site-selective reductive coupling of α-haloboranes with unactivated olefins (Scheme 1.2.31, *A*),[193] thus resulting in the formation of densely functionalized organoboron reagents. More recently, Martin group described the development of a catalytic deaminative cross-electrophile coupling *via* remote functionalization of unactivated olefins (Scheme 1.2.31, *B*).[194] This method combined the C(sp^3)–N cleavage with the remote functionalization of C–H bonds using unactivated olefins. Such protocol allowed us to promote this reaction within the context of late-stage functionalization of densely functionalized compounds possessing alkyl amines in their structures.

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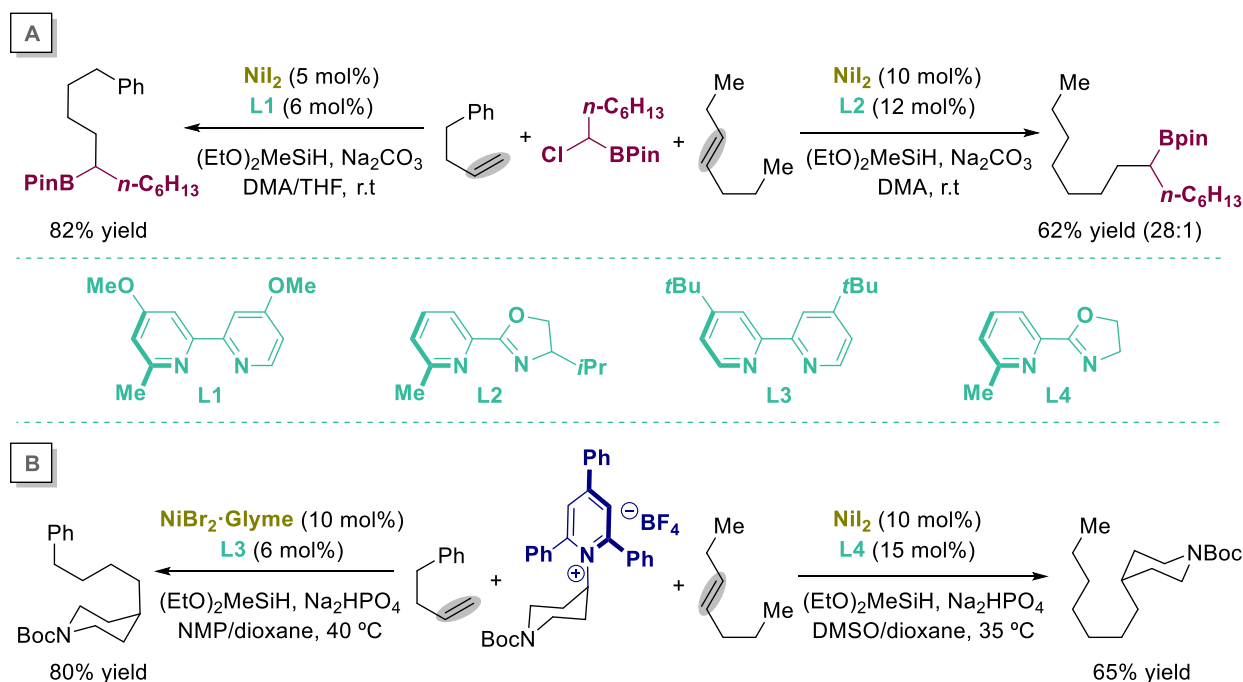
Scheme 1.2.31. Ni-catalyzed chain-walking for remote C–C bond formation of olefins.

1.2.3.8 *Tungsten as a promise chain-walking catalyst*

The Szymańska-Buzar group reported the utilization of tungsten as catalyst for the hydroamination of terminal alkynes (Figure 1.2.7, *top right*).[195] In addition, tungsten catalysts have been employed within the context of olefin metathesis (*bottom right*),[196] hydrogenation/hydrodesulfurization processes (*top left*),[197] alkene(alkyne)-cyclizations, rearrangement processes (*bottom left*),[198] and in hydroisomerization/hydrocracking of alkanes for the production of high octane products in industry porpuses.[199]
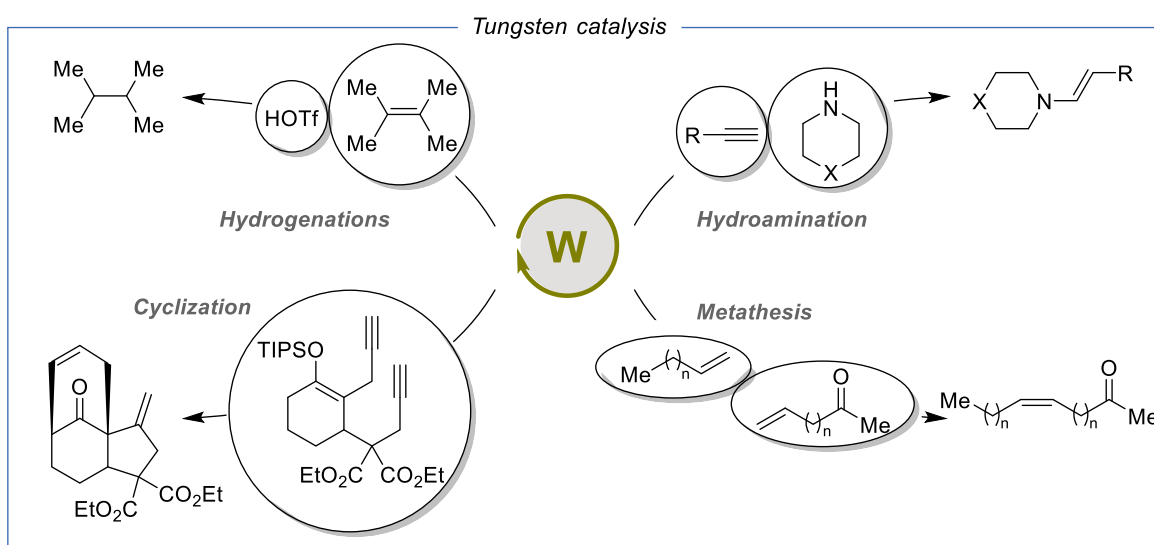
Figure 1.2.7. Basic lines of tungsten catalysis.

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During last two years, Macmillan has discovered a new utility for tungsten metal using decatungstate complexes to perform the direct arylation of strong aliphatic C–H bonds (Scheme 1.2.32).[200] Intriguingly, tungsten has a double role in this reaction acting first *via* a dual polyoxometalate HAT reagent and secondly as a reductant to recover the Ni(0) catalyst. The strongly photoactivated species formed after irradiation with blue Kessil lights can abstract protons of unactivated aliphatic C–H bonds with a high dissociation energy, thus resulting in a hydride species. Disproportionation of singly reduced decatungstate (**XLI**) regenerates the active HAT photocatalyst (**XXXIX**), concurrently forming a double reduced decatungstate (**XLIII**). Decatungstate was used later for the same group in order to afford trifluoromethylation of C(sp^3)–H aliphatic bonds by merging this technology with copper catalysis.[201]
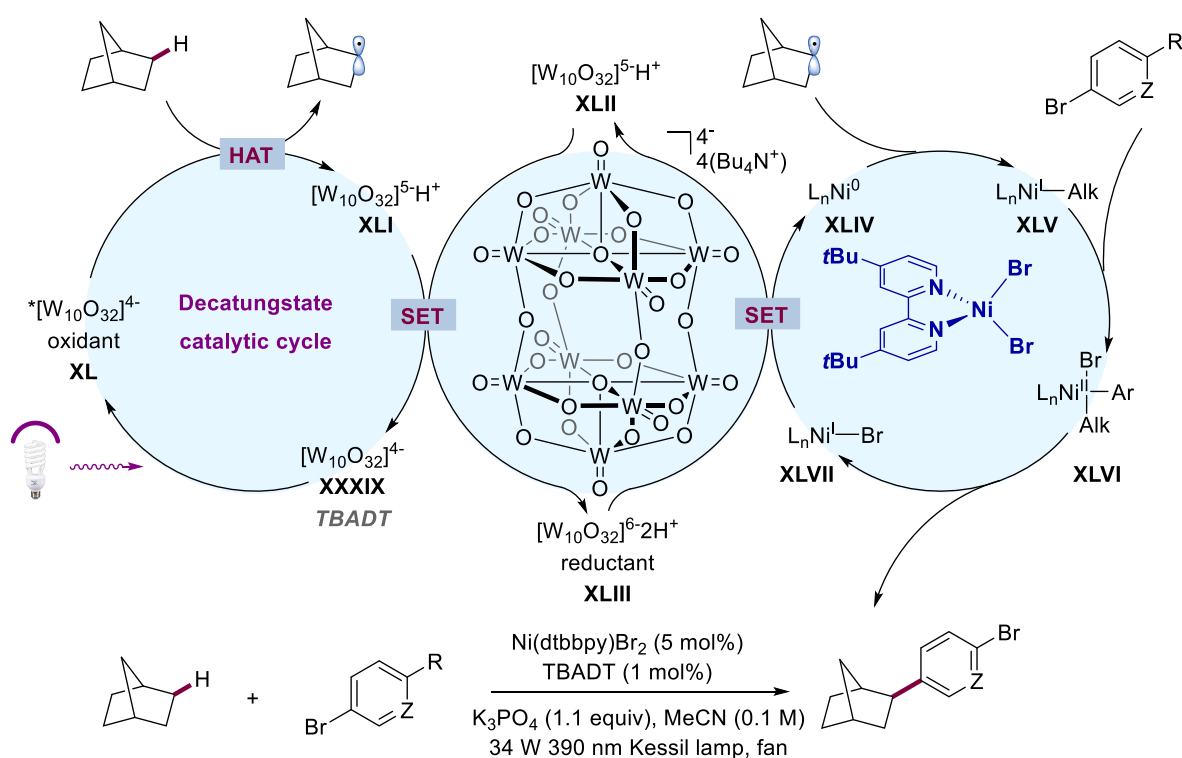
Scheme 1.2.32. C(sp^3)–H arylation *via* dual polyoxometalate HAT and nickel catalytic manifold.

Although not a single remote functionalization has been reported within the context of tungsten catalysis, the potential to carry out olefin isomerizations is known since 1974.[202] This premise will be tackle in *Chapter 4* where we tried to unravel the potential of tungsten catalysts in remote functionalization reactions.

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1.3 *General objectives of this Doctoral Thesis*

Despite the advances realized in nickel catalysis, C–O functionalization, C–N cleavage and remote functionalization, a number of challenges remain in these endeavors. In particular, we wondered whether it would be possible to enable stereospecific C–heteroatom bond-forming reactions by means of C–O cleavage, the ability to promote new deaminative technologies *via* C–N scission and the ability to promote remote functionalizations beyond the utilization of Pd, Rh, Fe or Ni catalysts. Specifically, the main objectives of this PhD thesis can be delineated in the following three objectives:

- To describe a stereospecific borylation by the utilization of π-extended secondary benzyl esters catalyzed by nickel complexes.

- To broaden the means to trigger deaminative C–C bond-forming reactions within the context of cross-electrophile coupling events.

- To discover new reactivity of tungsten catalysts for promoting the functionalization of remote sp^3 C–H sites.

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UNIVERSITAT ROVIRA I VIRGILI
Functionalization of Strong Sigma Bonds by Nickel and Tungsten Catalysis
Raúl Martín Montero

General Introduction

II: Catalysts Based on Molybdenum and Tungsten Carbides. *Catal. Ind.* **2016**, *8* (3), 224–230. https://doi.org/10.1134/S2070050416030120.

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Chapter 2.

Stereospecific Nickel-Catalyzed Borylation of Secondary Benzyl Pivalates

Research carried out in collaboration with

Tim Krolikowski, Cayetana Zarate, Rubén Manzano

Chapter 2

2.1   Introduction

Metal-catalyzed cross-coupling reactions have evolved as a mature discipline for building up molecular complexity. The vast majority of these reactions relies on the utilization of aryl and alkyl halides as coupling counterparts. Despite the advances realized, the toxicity of the latter and the difficulty of accessing advanced organic halides in densely functionalized backbones prompted the development of alternative coupling partners such as C–O electrophiles.[1–3] The paucity of these processes relies on the inherent challenges posed by these electrophiles, such as the high activation barrier of the C–O cleavage and chemoselectivity profile, among others (Chapter 1.2.1). However, in recent years, numerous C–O bond-functionalization protocols have been reported, even within the context of stereospecific reactions.[3]

2.2   Stereospecific cleavage of activated C(sp³)–O bonds by nickel catalysis

2.2.1   Introduction

In recent years, the utilization of allyl and benzyl electrophiles have received significant attention in cross-coupling reactions due to the possibility of creating enantioenriched stereocenters *via* the formation of particularly stabilized organometallic intermediates, either in a stereoconvergent (catalyst-controlled) or stereospecific manner (substrate-controlled).[4,5] Undoubtedly, the installation of a chiral stereogenic center by means of stereoconvergent reactions with an asymmetric catalyst is a particularly powerful tool, as the protocol makes use of achiral reagents. On the other hand, stereospecific reactions rely on enantioenriched precursors, and can *a priori* be triggered *via* inversion or retention of configuration, thus allowing to preserve the stereochemical information of the starting material without requiring chiral catalysts or chiral ligands.[6–10]

Attention was initially focused on the utilization of nickel as catalyst due to its propensity to undergo oxidative addition and slow down β–hydride elimination.[11–13] However, it is worth noting that nickel complexes often populate one-electron pathways instead of two-electron manifolds that operate within the realm of Pd catalysis,[14,15] thus leaving a reasonable doubt on whether nickel catalysis might be suited within the context of stereospecific reactions due to the intermediacy of open-shell intermediates (Figure 2.2.1, *top*).[16–20] In order to trigger a stereospecific reaction, the inherent radical reactivity of the nickel catalyst must be suppressed to favor a two-electron polar oxidative addition. In this line, the polar character of the electrophile is crucial for a two-electron oxidative addition reaction, and the combination of low-valent nickel complexes with benzyl ethers seemed to be particularly promising.[1,21] In addition, highly enantioenriched starting materials can be easily synthesized from secondary aliphatic alcohols by many well-known reported enantioselective methods (Figure 2.2.1, *bottom*).[22]

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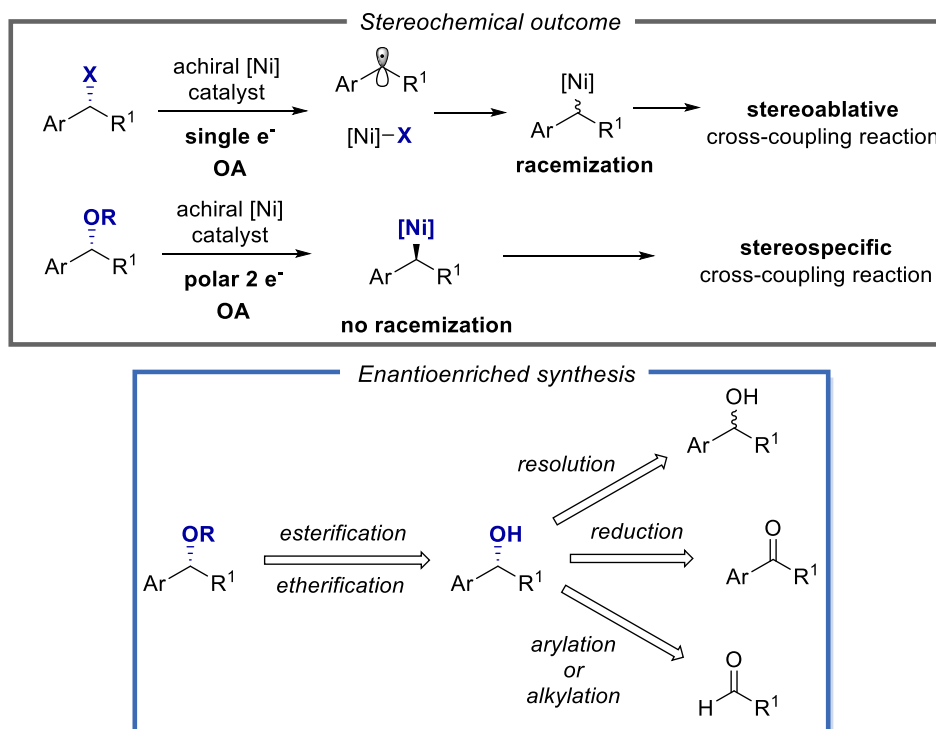
Figure 2.2.1. Stereospecific coupling and synthesis of benzyl esters or ethers.

2.2.2   Ni-catalyzed stereospecific C–O cleavage of π-extended secondary benzyl ethers

Jarvo and co-workers were able to develop Kumada-type cross-coupling reactions of enantioenriched secondary benzylic ethers with Grignard reagents as nucleophiles (Scheme 2.2.1).[23] One of the difficulties in developing the transformation was determining the optimal conditions to suppress undesired competing β–hydride elimination while accomplishing the formation of the desired product with an adequate transfer of the stereochemical information from the substrate to the product. The authors discovered that the combination of Ni(COD)₂ and rac-BINAP provided the final product in high yields and enantiospecificities. In this manner, a number of enantioenriched secondary benzyl ethers bearing π-extended arenes could be used as substrates, allowing to obtain the targeted products in good yields and excellent stereochemical fidelity. These results imply that the coordination of the nickel catalyst to the arene facilitates an oxidative addition, an assumption that was further corroborated in later a work by the authors.[24]

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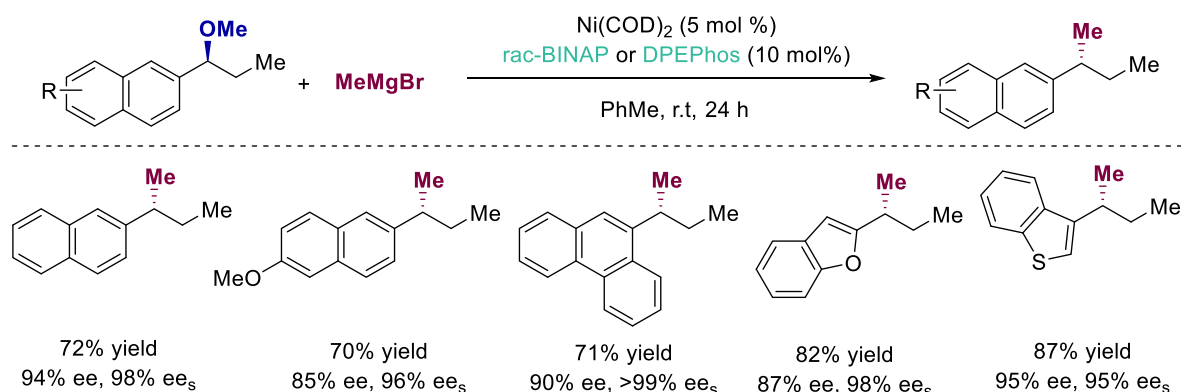
Scheme 2.2.1. Stereospecific Kumada cross-coupling of secondary benzylic ethers with alkyl Grignards.

Transmetalating agents with alkyl chains have shown to be more problematic due to their propensity to undergo competitive β–hydride elimination upon transmetalation to form alkylnickel intermediates. Therefore, a solution was required to expand the scope of the stereospecific Kumada coupling to these coupling partners. Jarvo and co-workers found that the use of dppe (1,2-bis(diphenylphosphino)ethane) ligand favored the formation of the product with the suppression of competing side reactions with alkyl Grignard reagents (Scheme 2.2.2).[25] The reaction conditions were able to accommodate a wide range of functional groups on the secondary benzyl substrate and most importantly, a diverse set of alkyl and even aryl Grignard reagents. Unfortunately, the utilization of secondary alkyl Grignard species resulted in lower yields as a result of the competitive β–hydride elimination. In general terms, the scope was broad, obtaining the targeted products with a neat inversion of configuration.
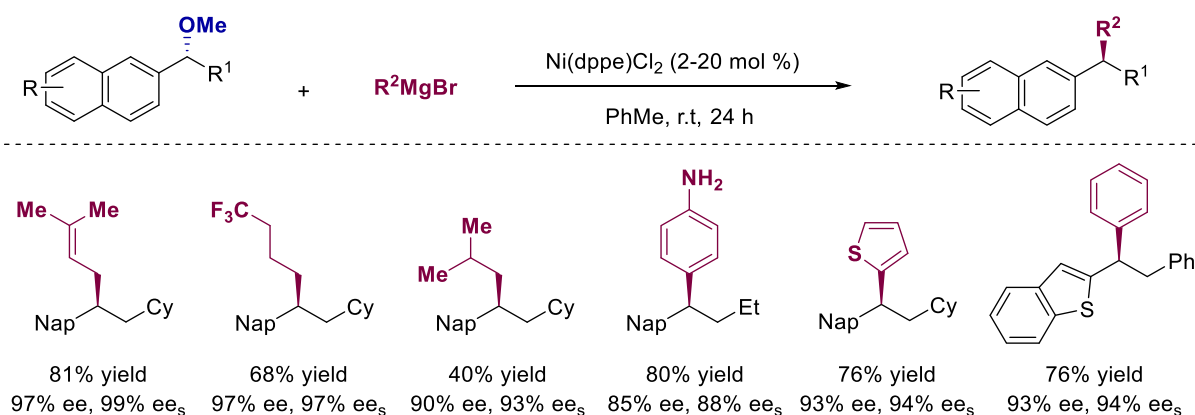
Scheme 2.2.2. Expanding the scope of C–O functionalization with Grignard reagents.

Interestingly, Jarvo and co-workers found an intriguing inverse correlation between the catalyst loading and enantioespecificity of the reaction. These findings could be interpreted on the basis of a nucleophilic attack of low-valent Ni(0) species to the *in situ* generated π-benzylnickel intermediate (**I**) under high catalyst loadings (Figure 2.2.2). To overcome the problem of low yields obtained for some

of the challenging substrates, a second portion of Ni(dppe)Cl$_2$ was added after 12 h to keep a low catalyst concentration at all time.
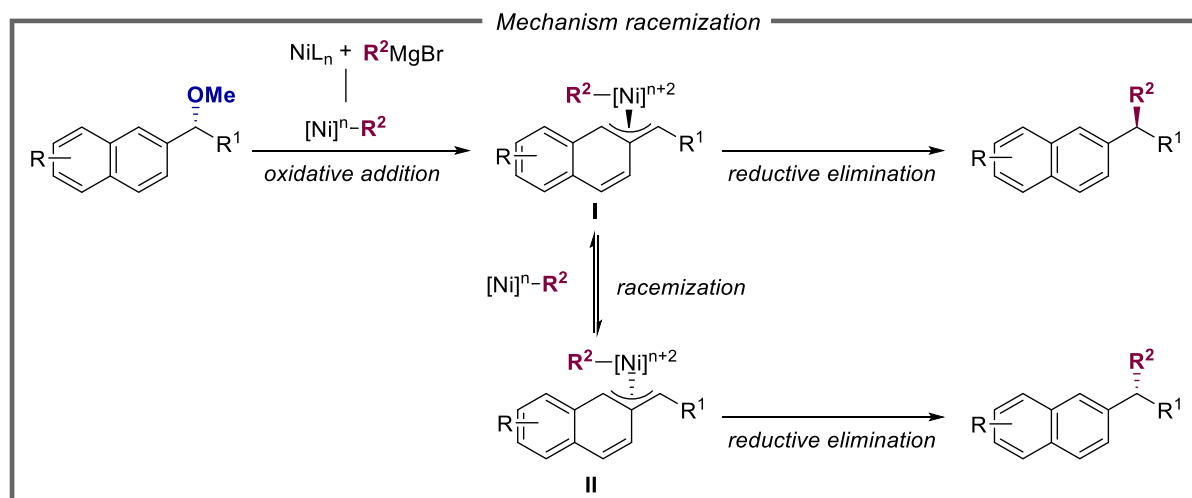
Figure 2.2.2. Rationalization for racemization at high catalyst loadings.

2.2.3 *Ni-catalyzed stereospecific reactions of benzyl C–O electrophiles by traceless directing groups*

Stereospecific nickel-catalyzed cross-coupling reactions of secondary benzylic ethers were achieved due to the inherent activation of the π-extended-systems such as naphthalene, benzothiophene or benzofuran to Ni(0). Unfortunately, regular arenes with lower aromatic stabilization energies reacted more smoothly, suggesting that the employment of non-π-extended systems might require a different strategy.[26,27] To this end, Jarvo and co-workers developed a new approach by using benzyl-2-methoxyethyl ethers as traceless directing groups (Scheme 2.2.3, *left*).[28,29] This approach likely forms five-membered ring chelates (**IV**) with the corresponding Mg salts, leading to the activation of the C–O bond towards S$_N$2-type oxidative addition with an overall inversion of configuration. This strategy employed benzhydryl alcohol derivatives that had previously resisted Kumada coupling reactions, thus expanding the scope of the electrophilic partner.

The chemoselectivity issues found by the utilization of Grignard reagents could be overcomed by the use of organozinc reagents.[30] Inspired by the traceless directing group strategy used in Scheme 2.2.3 *left*, Jarvo found that similar chelates might be formed with Zn reagents, avoiding undesirable β-hydride elimination or isomerization pathways while ultimately leading to an excellent stereospecificity through a S$_N$2-type oxidative addition (Scheme 2.2.3, *right*).[31] In this way, a large number of enantioenriched secondary benzyl alcohol derivatives bearing 2-naphthyl or benzo-fused heteroaryl substituents could be efficiently coupled with alkylzinc reagents.

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Scheme 2.2.3. Stereospecific Ni-catalyzed Negishi coupling of benzylic ester derivatives: Mechanistic rationale.
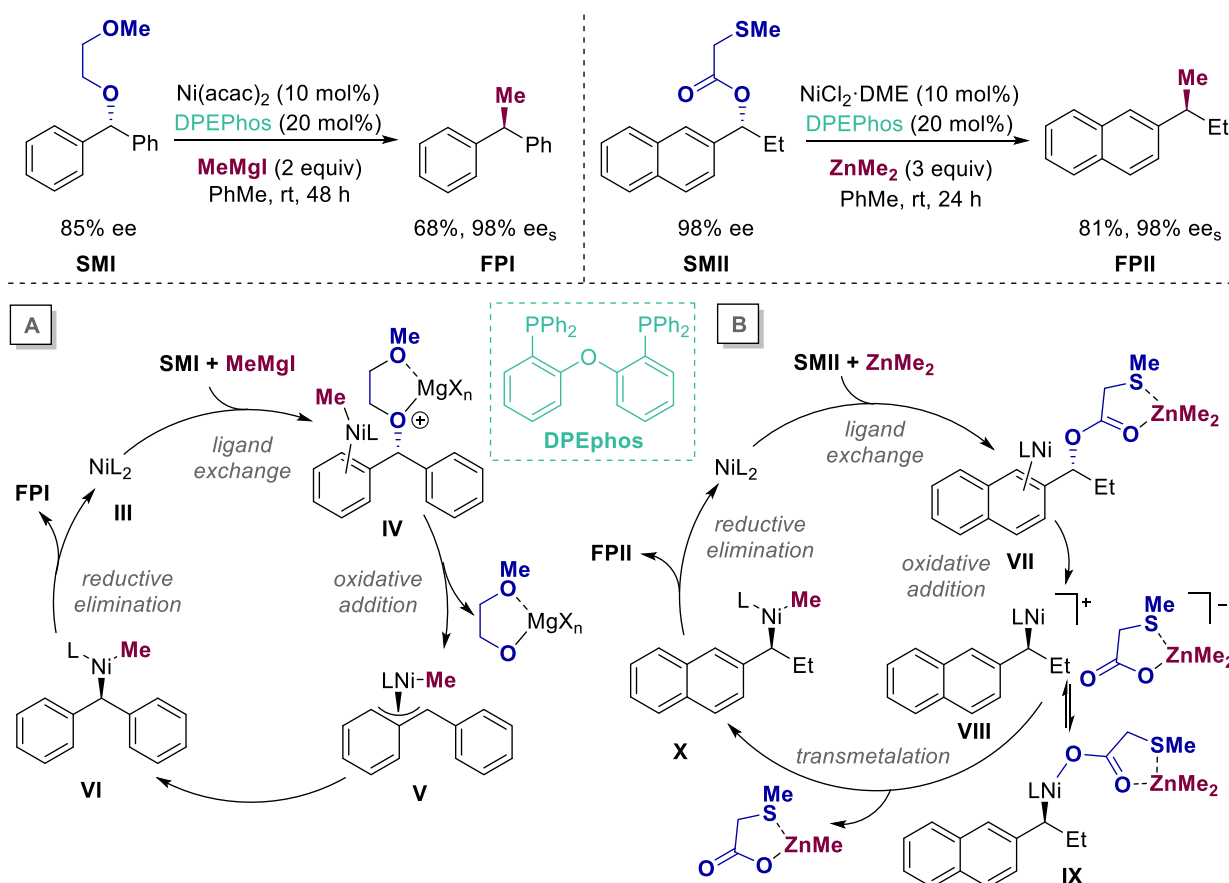
2.2.4 Nickel catalyzed stereospecific C–O cleavage of π-extended benzyl pivalates

Prompted by the successful implementation of stereospecific reactions with both Grignard reagents and organozinc compounds, a significant attention was devoted to the utilization of less-basic organoboron reagents. Inspired by the first Suzuki-Miyaura cross-coupling reaction of achiral ester derivatives in 2005 by Kuwano and Yokogi using Pd(II) precatalysts,[32] Jarvo and Watson independently developed a Suzuki-Miyaura-type coupling of secondary benzylic pivalates using aryl boronic esters or aryl boroxines (Scheme 2.2.4, *left*).[33–35] Surprisingly, the use of different electron-rich ligands, such as SIMes (1,3-bis-(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidine) and PCy$_2$R (R = Ph, Cy) provided an opposite enantiomeric outcome with high stereochemical fidelity. In analogy to the previously described Negishi and Kumada-type coupling reactions,[28,29,31] the utilization of *N*-heterocyclic carbene ligand (SIMes, **XI**) or a ligand-free catalytic system resulted in an inversion of the configuration. In contrast, Watson demonstrated that PCy$_2$R (R = Ph, Cy) ligands offered a retention of the configuration (Scheme 2.2.4, *right,* R^3 = H). This phenomenon was also observed by Jarvo in the Ni(0)/PCy$_3$-catalyzed coupling of benzylic carbamates with aryl boronic esters.[34] In 2016, Watson was able to expand the scope of the reaction leading to the arylation of tertiary enantioenriched benzylic acetates with less sterically hindered CyJohnPhos ligand.[36] The authors

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proposed a directed S$_N$2' oxidative addition *via* a seven-membered transition state in which the acetate binds to the Ni center (**XII**), an assumption further corroborated by theoretical calculations.[24]

Scheme 2.2.4. Stereospecific Ni-catalyzed Suzuki-Miyaura-type arylations of benzylic pivalates.
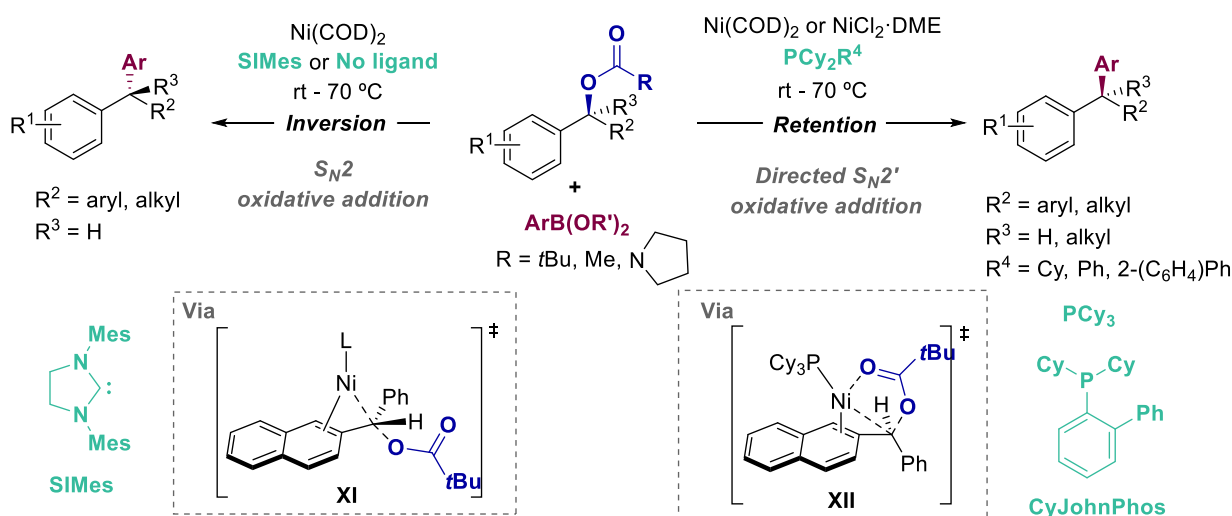
2.2.5   *Nickel catalyzed stereospecific C–O cleavage of allylic pivalates*

In 2014, the first report of stereospecific Ni-catalyzed cross-coupling of allylic pivalates and arylboroxines was published by Watson and co-workers (Scheme 2.2.5, *A*).[37] This protocol reunited the conditions commented above, avoiding the use of more expensive second row transition metal catalysts and the utilization of air sensitive coupling partners. The study produced enantioenriched 1,3-diaryl allyl products with an inversion of the stereochemical information *via* transition state **XIV**, thus avoiding the strain generated between the methyl and hydrogen at the 1,3-position.

Scheme 2.2.5. Stereospecific Ni-catalyzed Suzuki-Miyaura-type arylations and borylations of allylic pivalates.
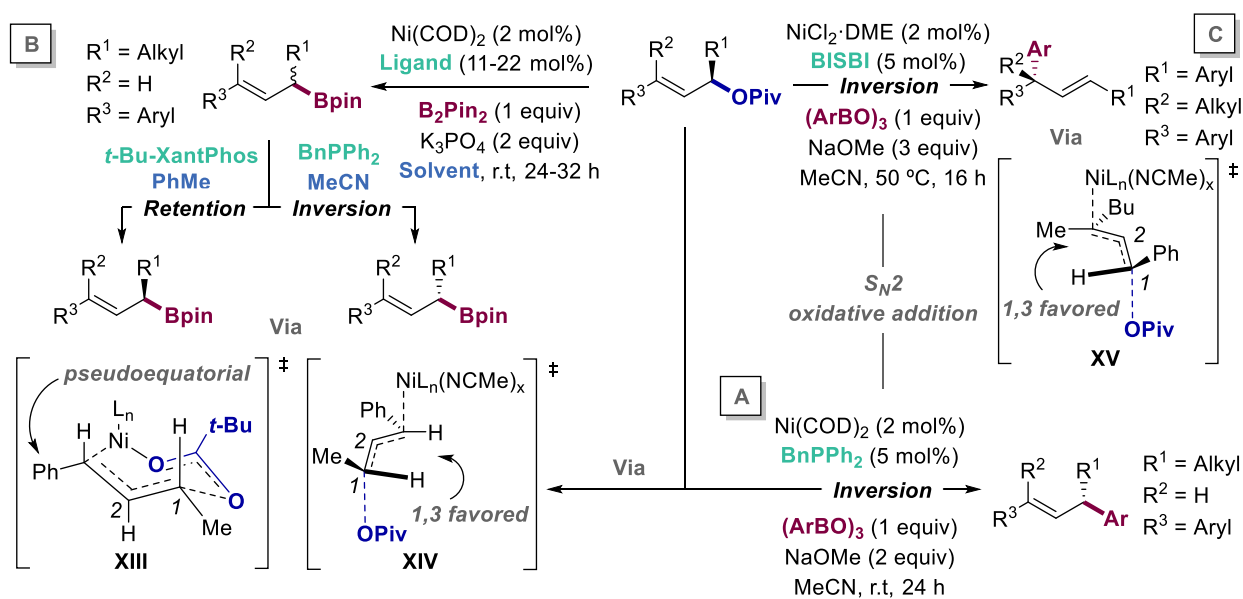
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Later, the same group reported a successful stereospecific borylation of allylic pivalates to deliver highly enantioenriched α-stereogenic γ-aryl allylic boronates (Scheme 2.2.5, *B*).[38] The transformation proceeds either with inversion or retention of configuration, with selectivity arising by judicious choice of the ligand or the solvent. On one hand, stereochemical inversion was driven by strain release between the 1,3-positions of the transition state (**XIV**) and the use of MeCN as solvent. Given the ability of MeCN to act as a ligand for transition metals,[39] the authors claimed that MeCN coordinates to nickel, preventing the subsequent oxidative addition. On the other hand, retention of configuration was driven by the pivalate leaving group, which directs the nickel catalyst in non-polar solvents as PhMe. This observation indicates that although two 7-membered chair-like compounds could be formed, only the pseudoequatorial (**XIII**) is favored, leading to overall retention of configuration.

Watson and co-workers realized that a powerful approach for the synthesis of quaternary stereocenters may be performed by an allylic substitution reaction. In this endeavor, such a reaction does not only create a quaternary center, but also includes a versatile alkene substituent that provides multiple opportunities for further functionalization. Recognizing this potential, they reported a stereospecific nickel-catalyzed Suzuki-Miyaura cross-coupling of allylic pivalates to deliver quaternary stereocenters (Scheme 2.2.5, *C*).[40] The protocol proceeds with inversion of the stereochemical outcome, allowing to couple a variety of enantioenriched allylic pivalates with arylboroxine using a combination of $NiCl_2 \cdot DME/BISBI$.

2.3   *Stereospecific Nickel-catalyzed borylation of secondary aryl benzyl pivalates*

2.3.1   *Aim of the project*

Despite the advances realized in catalytic stereospecific cross-coupling reactions *via* functionalization of benzylic and allylic C–O bonds, the majority of these processes are based on the formation of C–C bonds. In contrast, the ability to extend these processes to C–heteroatom bond-forming reactions has remained a much less-explored endeavor. Among the different scenarios, we anticipated that the possibility of triggering a stereospecific borylation *via* benzyl or allyl C–O cleavage would be a worthwhile endeavor given the versatility and modularity of the corresponding organoboranes. At the time that this PhD thesis was being developed, there were no examples of stereospecific borylations *via sp³* C–O bond-cleavage.

2.3.2   *Optimization of the reaction conditions*

We started our investigations by exposing enantioenriched 2-(1-methoxyethyl)naphthalene to our previously developed borylation of benzyl methyl ethers (Scheme 2.3.1). Unfortunately, no sign of stereospecificity was observed for this reaction, even by carefully tuning the experimental

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variables of the reaction (Ni(COD)$_2$/PCy$_3$ loadings, temperatures and reaction time), obtaining exclusively racemic mixtures.
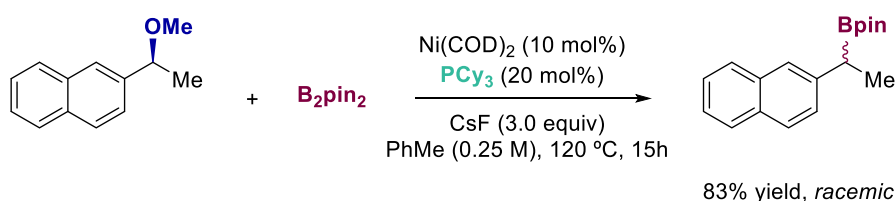
Scheme 2.3.1. Attempt of stereospecific borylation under previously optimized reaction conditions.

Despite these results, we turned our attention to study stereospecific borylations of benzyl pivalates, as these compounds have extensively been employed by both Jarvo and Watson in related cross-coupling reactions.[33,34]

Prompted by previously developed silylation of aryl and benzyl pivalates by our group,[41] we started the screening of our stereospecific borylation technique with B$_2$nep$_2$. An initial screening of the equivalents of the boron source revealed the potential of this system (Table 2.3.1). Gratefully, the desired product ((**S**)-**2a**) was obtained in moderate yields and promising stereospecificity. We observed a trend in the use of B$_2$nep$_2$ where the best results were achieved with 1.5 equivalents (entry **5**). The utilization of B$_2$pin$_2$ led to a much lower reactivity and a diminished stereospecificity, highlighting the influence of the stereoelectronic properties of the boron reagent. The conversion of the reaction was quantitative and GC analysis allowed the detection of two side-products: the linear borylated product **2X** and the reduced product **2Z**. For the former, an oxidative addition of Ni(0) species into the benzyl C(sp^3)–O bond followed by a beta hydride elimination/nickel insertion might place the catalyst at the terminal position delivering the borylation. For the latter side-product, the benzyl radical – generated from the homolytic cleavage of the nickel oxidative addition species – abstracts a proton from the solvent delivering the reduced byproduct **2Z**.

It is remarkable that an overall retention of the configuration was observed, suggesting that the pivalate group coordinates to the nickel catalyst, thus setting the stage for a directed S$_N$2'-type oxidative addition. Due to the significant difficulties encountered in separating (**S**)-**1a** and (**S**)-**2a** by HPLC techniques and the low stability of the resulting products, the latter were transformed into the corresponding benzyl alcohol in order to measure the enantiomeric excess. While one might argue that the hydrolysis of (**S**)-**1a** might lead to wrong conclusions by forming the exact same benzyl alcohol, we corroborated that this was not the case, as the benzyl pivalate (**S**)-**1a** does not hydrolyze to the corresponding alcohol under the catalytic conditions.

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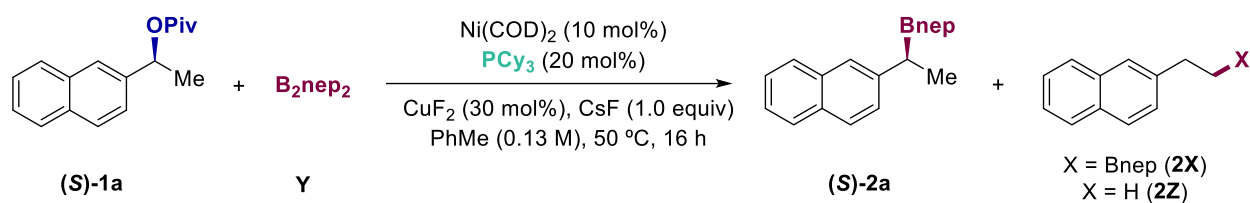
Entry	Deviation from standard conditions	Conv. (%)	2a (%)	(S)-2a ee (%)	2a/2X	2Z (%)
1	B_2nep_2 (1.1 equiv.)	95	47	70	1.9	12
2	B_2nep_2 (1.2 equiv.)	95	48	72	1.9	11
3	B_2nep_2 (1.3 equiv.)	96	54	75	2.0	12
4	B_2nep_2 (1.4 equiv.)	100	55	81	2.0	13
5	B_2nep_2 (1.5 equiv.)	100	58	85	2.1	12
6	B_2nep_2 (1.7 equiv.)	100	54	84	2.2	11
7	B_2nep_2 (2.0 equiv.)	100	39	82	1.3	12
8	B_2pin_2 (1.3 equiv.)	70	19	52	1.0	4

Reaction conditions: **(S)-1a** (0.2 mmol), **Y** (x mmol), Ni(COD)$_2$ (10 mol%), PCy$_3$ (20 mol%), CuF$_2$ (30 mol %), CsF (1.0 equiv.), PhMe (1.5 mL), 50 ºC, 16 h. GC conversion and yields using decane as internal standard. *ee* calculated by HPLC analysis

Table 2.3.1. Screening of B$_2$nep$_2$ equivalents and B$_2$pin$_2$.

With a good result in hand (Table 2.3.1, entry **5**), subsequent screening was carried out with different ligands, solvents, copper sources and fluoride derivatives (Table 2.3.2). Carbenes and acyclic phosphine ligands did not provide any reactivity (entries **1** & **4**) whereas bidentate ligands and monodentate phosphines other than PCy$_3$ provided lower results in terms of both yields and enantioselectivities (entries **2** & **3**). The utilization of THF or dioxane led to the products with similar *enantiomeric excess (ee)* albeit in lower yield (entries **5** & **6**). As shown in entries **7-9**, the utilization of different copper and fluoride sources did not result in better yields. Surprisingly, reducing the nickel and ligand loading while keeping constant the Ni/L ratio afforded a much better *ee* and a boost in the yield of **2a** (entry **10**). This avoid the formation of side-competitive reactions that might operates *via* bimolecular mechanism in which low-valent Ni(0) species react with the *in situ* generated Ni(II) intermediates losing chiral information and efficiency.
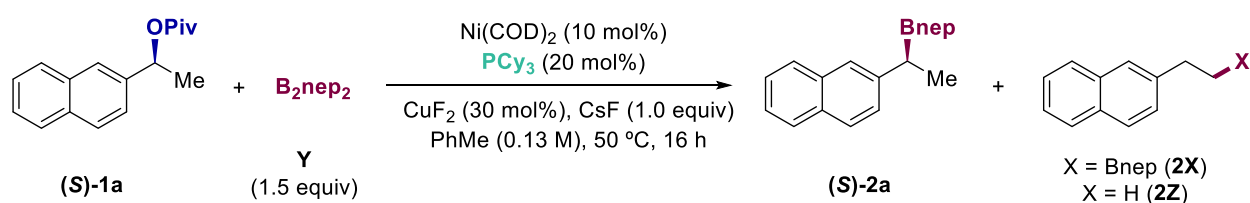
Entry	Deviation from standard conditions	Conv. (%)	2a (%)	(S)-2a ee (%)	2a/2X	2Z (%)
1	iPr·HCl (20 mol%)	4	2	-	-	0
2	PCy_2Ph (20 mol%)	100	49	79	1.8	15
3	dcpe (20 mol%)	86	36	58	2	12
4	$PiPR_3$ (20 mol%)	0	0	-	-	0
5	THF as solvent	61	29	81	2.6	9
6	Dioxane as solvent	49	28	82	4.5	8
7	AgF in lieu of CsF	25	13	81	3.3	7
8	$CuBr_2$ in lieu of CuF_2	0	0	-	-	0
9	Cu_2SO_4	91	61	81	only **2a**	10
10	$Ni(COD)_2$ (5 mol%), PCy_3 (10 mol%)	100	78	93	5.4	9

Reaction conditions: **(S)-1a** (0.2 mmol), **Y** (1.5 mmol), $Ni(COD)_2$ (10 mol%), PCy_3 (20 mol%), CuF_2 (30 mol %), CsF (1.0 equiv.), PhMe (1.5 mL), 50 ºC, 16 h. GC conversion and yields using decane as internal standard. *ee* calculated by HPLC analysis

Table 2.3.2. Screening of ligands solvents and copper source.

Next, our attention turned to studying the loading of the fluoride base and the effect of the copper salt in the reaction outcome (Table 2.3.3). As shown in entries **1** and **2**, a lower loading of these parameters resulted in a slight increase in the branched/linear ratio, albeit in lower yields. In parallel with the development of this project, mechanistic studies on the silylation of aryl and benzyl pivalates were being performed in our group.[42] These studies suggested that CuF_2 just served as a mere fluoride source, and that additional CsF could perform the same role as that of CuF_2. Interestingly, the addition of additional CsF improved the yield and the **2a/2X** ratio. However, these conditions led to substantial amounts of **2Z** and lower enantioselectivities (entries **3**-**6**). Similarly, low yields but high regioselectivities were found by conducting the reaction with CuF_2 in the absence of CsF, indicating that an optimal combination of these variables was essential for success (entry **7**).

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Reaction conditions: **(S)-1a** (0.2 mmol), **Y** (1.5 mmol), Ni(COD)$_2$ (5 mol%), PCy$_3$ (10 mol%), CuF$_2$ (30 mol %), CsF (1.0 equiv.), PhMe (1.5 mL), 50 ºC, 16 h. GC conversion and yields using decane as internal standard. *ee* calculated by HPLC analysis

Table 2.3.3. Screening of CuF$_2$ and CsF equivalents.
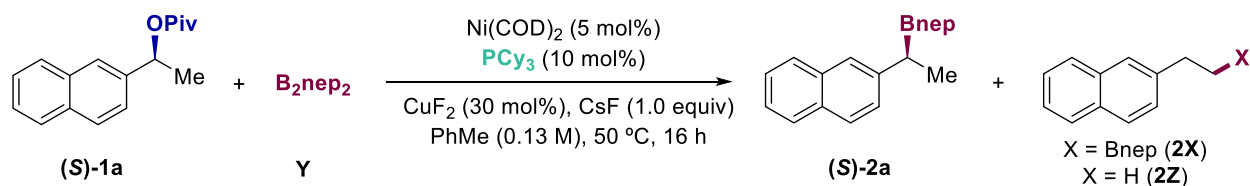
Entry	Deviation from standard conditions	Conv. (%)	2a (%)	(S)-2a ee (%)	2a/2X	2Z (%)
1	CuF$_2$ (15 mol%), CsF (0.5 equiv)	72	48	94	6.5	5
2	CuF$_2$ (7.5 mol%), CsF (0.25 equiv)	80	44	94	6.6	5
3	No CuF$_2$, CsF (0.5 equiv)	95	70	94	7.4	6
4	No CuF$_2$, CsF (2.0 equiv)	89	64	94	only **2a**	9
5	No CuF$_2$, CsF (2.5 equiv)	89	64	94	32	8.8
6	No CuF$_2$, CsF (2.0 equiv), 24 h	87	66	94	62	12
7	CuF$_2$ (15 mol%), no CsF	61	33	94	12.4	0

Surprisingly, good regioselectivities were found upon using low amounts of CuF$_2$ but with substantial amounts of CsF (Table 2.3.4, entries **1**-**2**). A subtle balance of these reagents gave rise to excellent yields and high **2a/2X** ratio, with minimum amounts of reduced products (entry **4**). Moreover, lower amounts of nickel/ligand improved the yield, but with considerable amounts of linear and reduced products (entry **3**).
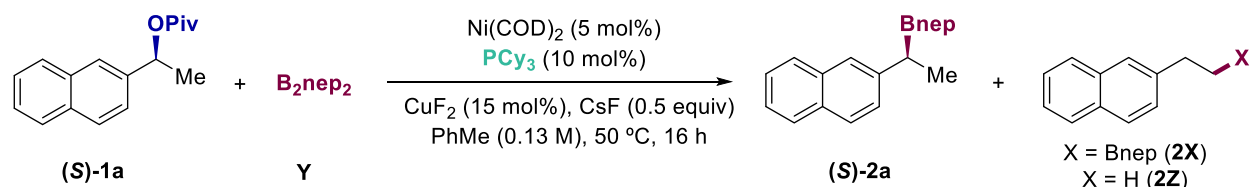
	Entry	Deviation from standard conditions	Conv. (%)	2a (%)	(S)-2a ee (%)	2a/2X	2Z (%)
Day 1	1	CuF$_2$ (10 mol%), CsF (2.0 equiv)	74	51	94	18	9
	2	CuF$_2$ (15 mol%), CsF (2.0 equiv)	75	51	94	17	10
	3	Ni(COD)$_2$ (3.5 mol%), PCy$_3$ (7 mol%)	100	83	94	9	9
	4	CuF$_2$ (10 mol%), CsF (15% mol)	89	87	94	61	3
Day 2	5	Ni(COD)$_2$ (3.5 mol%), PCy$_3$ (7 mol%)	100	80	94	5.7	9
	6	Ni(COD)$_2$ (3.5 mol%), PCy$_3$ (7 mol%)	85	69	94	11	6
	7	CuF$_2$ (10 mol%), CsF (15% mol)	96	71	93	6.9	9

Reaction conditions: **(S)-1a** (0.2 mmol), **Y** (1.5 mmol), Ni(COD)$_2$ (5 mol%), PCy$_3$ (10 mol%), CuF$_2$ (15 mol %), CsF (0.5 equiv.), PhMe (1.5 mL), 50 ºC, 16 h. GC conversion and yields using decane as internal standard. *ee* calculated by HPLC analysis

Table 2.3.4. Demonstrating reproducibility issues.

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Unfortunately, we faced notorious reproducibility issues by applying the optimized reaction conditions multiple times (entries **5** and **6**). Therefore, we invested a considerable amount of time to unravel the origin of such uncertainty.

A systematic analysis was performed by modifying all reaction parameters (Table 2.3.5). As shown in entry **11**, high yields and excellent stereospecificities were found by subjecting (*S*)-**1a** to a cocktail consisting of Ni(COD)$_2$/PCy$_3$ (7.50 mol%, 1:1 ratio) with minimum amounts of **2Z.** Unfortunately, variable results were found by repeating these reaction conditions (entries **12** and **13**).
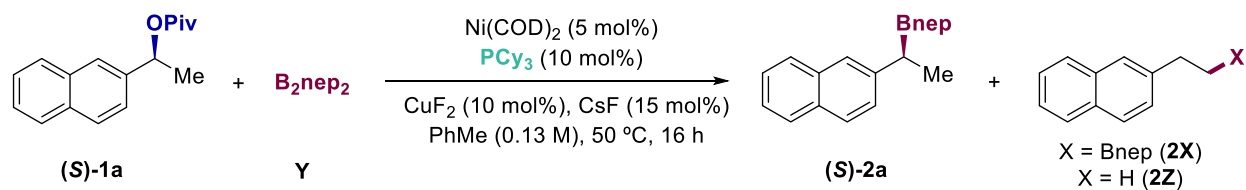
Entry	Deviation from standard conditions	Conv. (%)	2a (%)	(*S*)-2a *ee* (%)	2a/2X	2Z (%)
1	60 ºC	92	65	94	9	7
2	0.4 mmol scale	97	67	94	6	10
3	0.4 mmol scale, CsF (20 mol%)	92	69	94	7	12
4	PCy$_3$ (5 mol%)	66	63	94	32	3
5	PCy$_3$ (7.5 mol%)	81	63	94	16	5
6	PCy$_3$ (12 mol%)	100	59	94	4	10
7	PCy$_3$ (15 mol%)	100	52	93	3	10
8	CuF$_2$ (30 mol%)	92	73	94	11	7
9	CuF$_2$ (40 mol%)	82	75	94	6.8	7
10	CuF$_2$ (60 mol%)	88	67	94	6.7	7
11	Ni(COD)$_2$ (7.5 mol%), PCy$_3$ (7.5 mol%)	97	88	94	18	7
12	Ni/L (7.5 mol%), CuF$_2$/CsF (30 mol%)	96	91	94	20	7
13	Ni/L (7.5 mol%), CuF$_2$/CsF (30 mol%)	88	79	94	26	5

(Entries 12 and 13: – Day 2 –)

Reaction conditions: (*S*)-**1a** (0.2 mmol), **Y** (1.5 mmol), Ni(COD)$_2$ (5 mol%), PCy$_3$ (10 mol%), CuF$_2$ (15 mol %), CsF (15 mol%), PhMe (1.5 mL), 50 ºC, 16 h. GC conversion and yields using decane as internal standard. *ee* calculated by HPLC analysis

Table 2.3.5. Screening of temperature, scale, ligand, copper and nickel parameters.

At this point we wondered whether the reproducibility issues might be solved by operating with stock solutions of Ni/L instead of weighing out both Ni and L. As shown in Table 2.3.6, this turned out to be the case obtaining same results by applying the same conditions in different days (entries **1**-**3**).

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Reaction conditions: **(S)-1a** (0.2 mmol), **Y** (1.5 mmol), Ni(COD)$_2$ (7.5 mol%), PCy$_3$ (7.5 mol%), CuF$_2$ (30 mol %), CsF (30 mol%), PhMe (1.5 mL), 50 ºC, 16 h. GC conversion and yields using decane as internal standard. *ee* calculated by HPLC analysis

Table 2.3.6. Screening of final conditions & influence of stock solutions.
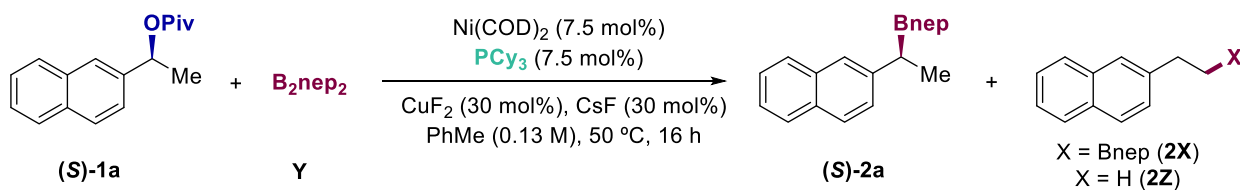
Entry	Deviation from standard conditions	Conv. (%)	2a (%)	(S)-2a ee (%)	2a/2X	2Z (%)
1	Stock solution of Ni(COD)$_2$/PCy$_3$	100	92	94	17	5
Day 2						
2	Stock solution of Ni(COD)$_2$/PCy$_3$	100	92	94	17	6
Day 3						
3	Stock solution of Ni(COD)$_2$/PCy$_3$	100	92	94	18	5

Next, we turned our attention to the influence of the electrophile used in the targeted borylation event (Table 2.3.7). As shown, the utilization of benzyl esters, carbonates or amide derivatives provided lower reactivities and enantiomeric excesses (entries **2-9**) whereas the employment of benzyl ethers did not undergo the desired C(sp^3)–O borylation reaction (entries **10** & **11**).

Entry	Deviation from standard conditions	Conv. (%)	2a (%)	(S)-2a ee (%)	2a/2X	2Z (%)
1	OPiv	100	93	94	18	5
2	OCOMe	65	39	64	3	10
3	OCOPh	89	51	68	2	16
4	OBoc	89	65	56	15	0
5	OCOpy	4	3	94	only **2a**	0
6	OCOCH$_2$OMe	98	35	59	0.5	24
7	OCOCH$_2$SMe	30	19	90	0.3	5
8	OCOCH$_2$SCOPh	0	0	-	-	0
9	OCONMe$_2$	91	64	89	3	7
10	OMe	2	0	-	-	0
11	OCH$_2$CH$_2$OMe	10	0	-	-	8

Reaction conditions: **(S)-Xa** (0.2 mmol), **Y** (1.5 mmol), Ni(COD)$_2$ (5 mol%), PCy$_3$ (10 mol%), CuF$_2$ (15 mol %), CsF (15 mol%), PhMe (1.5 mL), 50 ºC, 16 h. GC conversion and yields using decane as internal standard. *ee* calculated by HPLC analysis

Table 2.3.7. Stereospecific borylation with different secondary benzylic C–O electrophiles.

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Stereospecific Borylation of Benzyl C(sp³)–O Bonds

As expected, the reaction did not occur in the absence of Ni(COD)$_2$ or PCy$_3$ (Table 2.3.8, entries **2** & **3**). Surprisingly, the removal of CuF$_2$ and CsF resulted in 56% yield and 93% *ee* (entry **8**). Furthermore, the use of only one of these components still furnished the product in decent yields and good *ee* (entries **4-7**), indirectly suggesting that the presence of both CuF$_2$ and CsF avoids decomposition or deactivation of the catalyst. Lastly, we observed that an increase in the loading of PCy$_3$ had a deleterious effect (entry **9**).
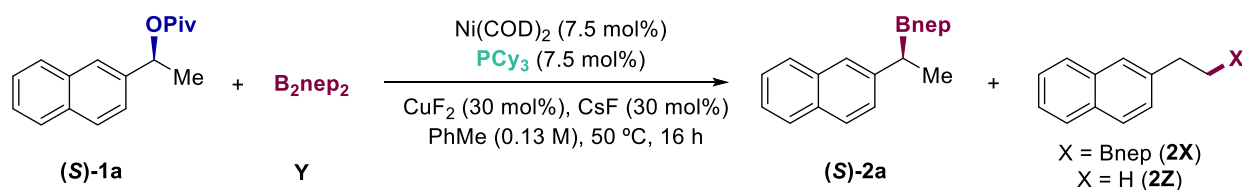
Entry	Deviation from standard conditions	Conv. (%)	2a (%)	(S)-2a ee (%)	2a/2X	2Z (%)
1	None	100	95 (87)[a]	95	18	5
2	No Ni(COD)$_2$	0	0	-	-	0
3	In the absence of PCy$_3$	0	0	-	-	0
4	In the absence of CuF$_2$	98	84	93	25	4
5	In the absence of CsF	94	75	92	16	6
6	No CsF, with CuF$_2$ (1 equiv)	99	84	86	14	6
7	No CuF$_2$, with CsF (1 equiv)	90	73	85	11	7
8	No CuF$_2$, no CsF	82	56	93	3.5	8
9	Using PCy$_3$ (20 mol%)	64	40	91	5	9

Reaction conditions: **(S)-1a** (0.2 mmol), **Y** (1.5 mmol), Ni(COD)$_2$ (7.5 mol%), PCy$_3$ (7.5 mol%), CuF$_2$ (30 mol %), CsF (30 mol%), PhMe (1.5 mL), 50 ºC, 16 h. GC conversion and yields using decane as internal standard. *ee* calculated by HPLC analysis. [a]Isolated yield after oxidation of the Bnep to the alcohol.

Table 2.3.8. Screening of critical parameters for the stereospecific borylation.

2.3.3 *Substrate scope*

Subsequently, we focused on evaluating the generality of our stereospecific borylation. As shown in Scheme 2.3.2, a series of differently substituted enantioenriched benzyl pivalates – easily synthesized from the corresponding benzyl alcohol – delivered the targeted compounds in good yields and enantioselectivities. First, we analyzed the influence of the electronic nature of the substituents on the ring, demonstrating that electron-rich (**2b**) or electron poor (**2c** & **2d**) substituents worked equally well. Unfortunately, the employment of quinolone (**2e**) afforded low yields and low enantiomeric fidelity, probably due to competitive binding of the nitrogen atom to the metal center. In the case of phenanthrene analogues (**2f**), the drop in yield and *ee* might be ascribed to racemization of the enantioenriched oxidative addition species by a bimolecular mechanism with exogenous low-valent Ni(0)L$_n$. As shown for **2g**, excellent stereospecificities and yields were found when the benzyl pivalate is placed at C1.

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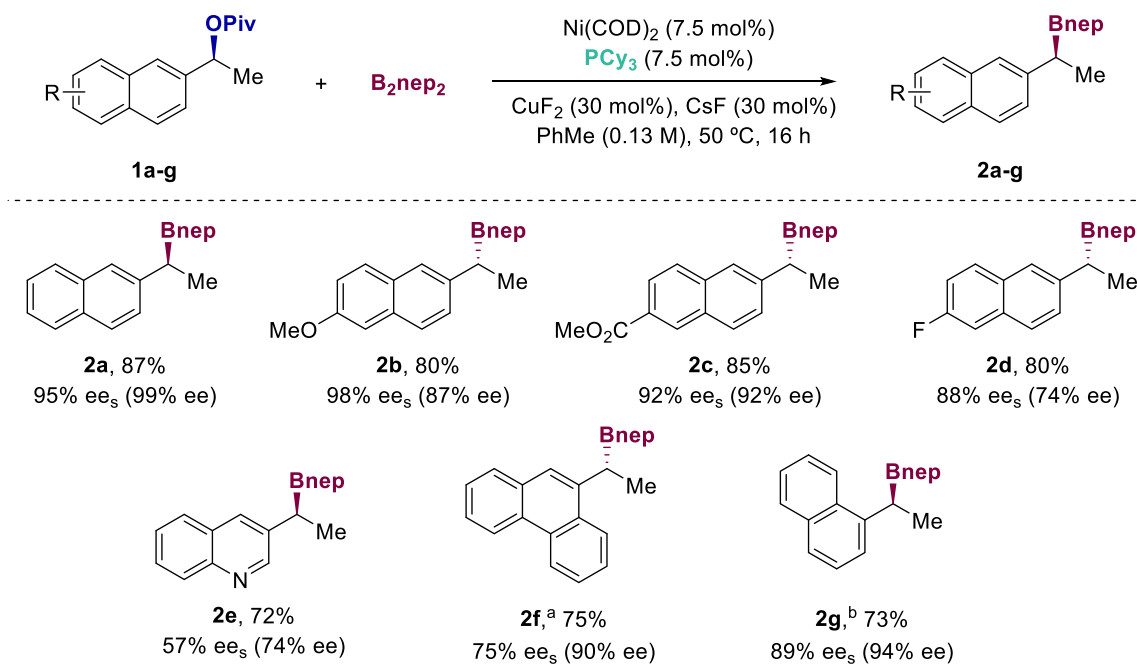
Reaction conditions: **1a-g** (0.2 mmol), B$_2$nep$_2$ (1.5 mmol), Ni(COD)$_2$ (7.5 mol%), PCy$_3$ (7.5 mol%), CuF$_2$ (30 mol %), CsF (30 mol%), PhMe (1.5 mL), 50 ºC, 16 h. Isolated yields, with enantiomeric excesses of starting precursors in parenthesis. [a]Ni(COD)$_2$ (10 mol%), PCy$_3$ (20 mol%), CsF (1 equiv). [b]Ni(COD)$_2$ (10 mol%), PCy$_3$ (10 mol%), CuF$_2$ (50 mol%), CsF (50 mol%), 55 ºC.

Scheme 2.3.2. Scope of benzyl pivalates.

Substrates possessing aliphatic side chains other than methyl groups generally resulted in lower enantioselectivities (**2h-m**), suggesting that transmetalation or oxidative addition might be hampered by the presence of larger alkyl side chains that might trigger competitive β-hydride elimination pathways (Scheme 2.3.3). In line with this notion, non-negligible amounts of homobenzylic borylation were observed in the crude reaction mixtures. Electron-rich substituents containing methoxy groups can be tolerated, obtaining the products in good enantioselectivities albeit in lower yields (**2l**). Finally, a simple comparison can be made when a longer side chain is placed at C1 of the naphthalene ring, obtaining worse yields while maintaining good levels of *ee* (**2m**). Unfortunately, the extension of this reaction to non-π-extended aryl pivalates did not afford the desired borylation.

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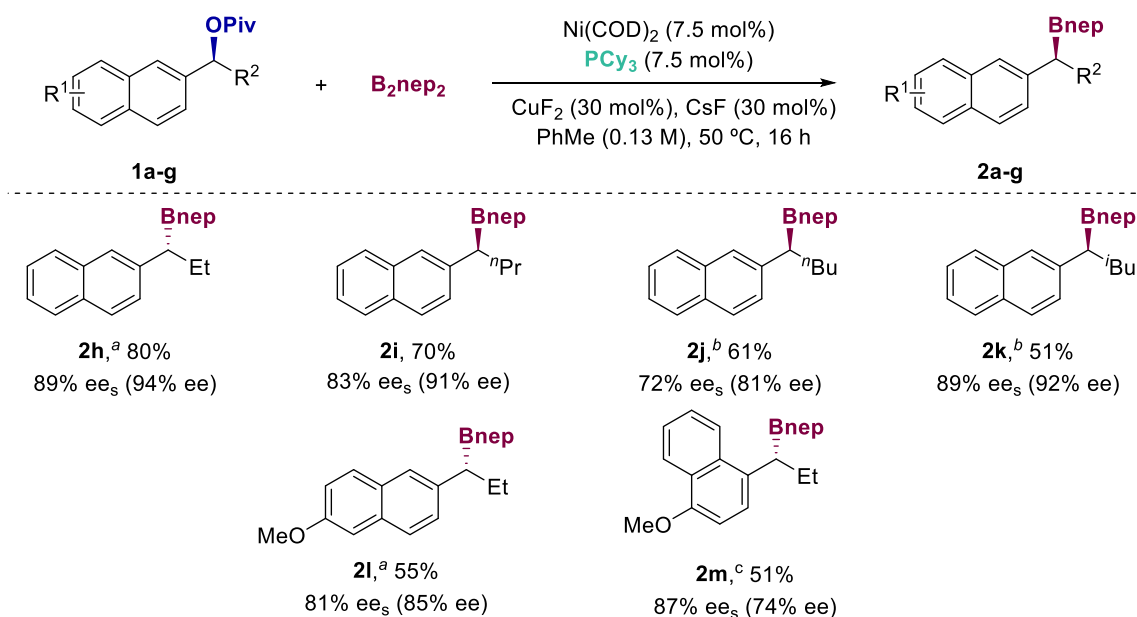*Stereospecific Borylation of Benzyl C(sp³)–O Bonds*

Reaction conditions: **1a-g** (0.2 mmol), B$_2$nep$_2$ (1.5 mmol), Ni(COD)$_2$ (7.5 mol%), PCy$_3$ (7.5 mol%), CuF$_2$ (30 mol %), CsF (30 mol%), PhMe (1.5 mL), 50 ºC, 16 h. Isolated yields, with enantiomeric excesses of starting precursors in parenthesis. [a]Ni(COD)$_2$ (5 mol%), PCy$_3$ (5 mol%), no CuF$_2$, CsF (50 mol%). [b]Ni(COD)$_2$ (10 mol%), PCy$_3$ (10 mol%). [c]Ni(COD)$_2$ (10 mol%), PCy$_3$ (10 mol%), CuF$_2$ (50 mol%), CsF (50 mol%), 55 ºC.

Scheme 2.3.3. Scope of benzyl pivalates with larger alkyl side chains.

Intriguingly, the presence of *ortho* substituents on the naphthyl ring resulted in a selectivity switch, obtaining the corresponding linear boronic esters instead (Scheme 2.3.4, **2n** & **2o**). This change in selectivity suggests that the inclusion of such substituents favour β-hydride elimination followed by a migratory insertion prior to a final C–B bond-forming reaction that avoids the clash with the proximal *ortho* group on the arene.
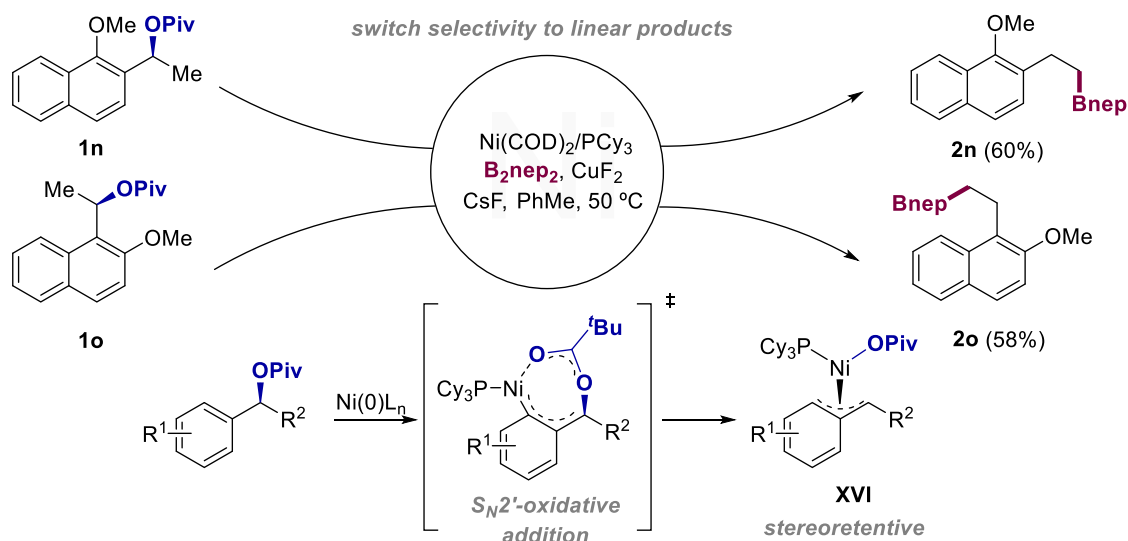
Scheme 2.3.4. Switch selectivity & stereoretentive approach.

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2.3.4   *Applications of benzyl boronates.*

Prompted by the pivotal role of the organoboron reagents as synthetic intermediates, we next explored the applicability of our protocol by utilizing the corresponding benzyl boronic ester in further synthetic applications. As shown in Scheme 2.3.5 *left*, the *in situ* generation of **2a** could be combined with a subsequent Suzuki-Miyaura reaction based on $Pd_2(dba)_3/PPh_3$, ending up in diarylethane **3** with an overall retention of configuration. In addition, exposure of **2a** to vinylmagnesium bromide followed by addition of I_2 and NaOMe/MeOH at -78 °C resulted in **4** with a good overall yield and excellent stereofidelity (Scheme 2.3.5, *right*).
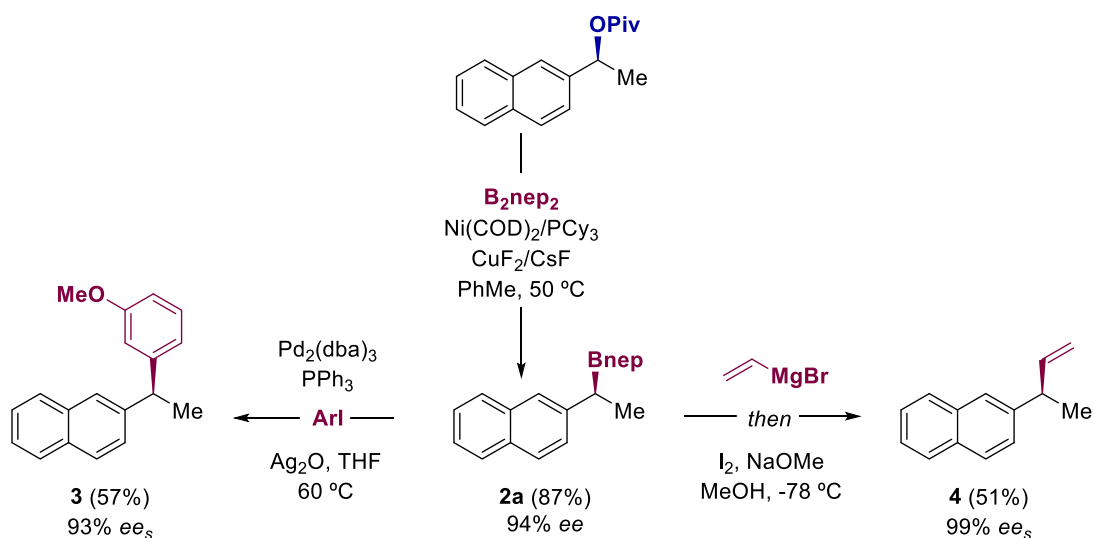
Scheme 2.3.5. Synthetic applicability.

2.3.5   *Unsuccessful substrates*

During the course of our investigations, we found some substrates that failed to provide the targeted products (Figure 2.3.1). Specifically, the substitution of the methyl substituent by a phenyl ring on the benzylic position (**A**) led to the almost quantitative reduction of the pivalate group to the alcohol. The utilization of the anthracene-derived pivalate bearing the benzylic bond at C9 (**B**) resulted in hydrogenolysis side reaction, an observation ascribed to the electron-rich benzyl C–OPiv bond prone to undergo reductive transformations.[43] The electron-rich substrate **C** bearing an isobutyl group at the benzylic carbon resulted in negligible reactivity. The reaction did not occur with π-extended heteroaromatic rings (**D** & **E**) or non-π-extended rings (**F**, **G** and **H**), resulting in recovered starting material. As mentioned during the introduction, the lack of reactivity of non- π-extended arene systems might be due to the loss of aromaticity when the nickel species undergoes the oxidative addition, being this step the barrier to overcome.[27,44]
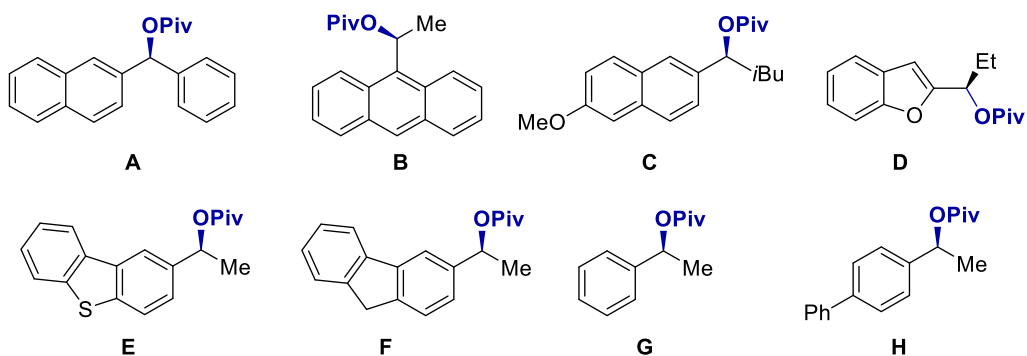
Figure 2.3.1. Unsuccessful stereospecific borylation of aryl pivalates.

2.3.6   *Mechanistic proposal*

At present, we believe that our reaction operates *via* a Ni(0)/Ni(II) regime consisting of oxidative addition, transmetalation and reductive elimination (Scheme 2.3.6, *Ni cycle*). Oxidative addition might be preceded by a η²-complexation between Ni(0) species and the aryl pivalate (**XVII**). The following transmetalation of the boron moiety might lead to a boron-containing intermediate (**XX**), that would reductively eliminate to deliver the desired borylated product while generating back the active Ni(0) species (**XXI**).
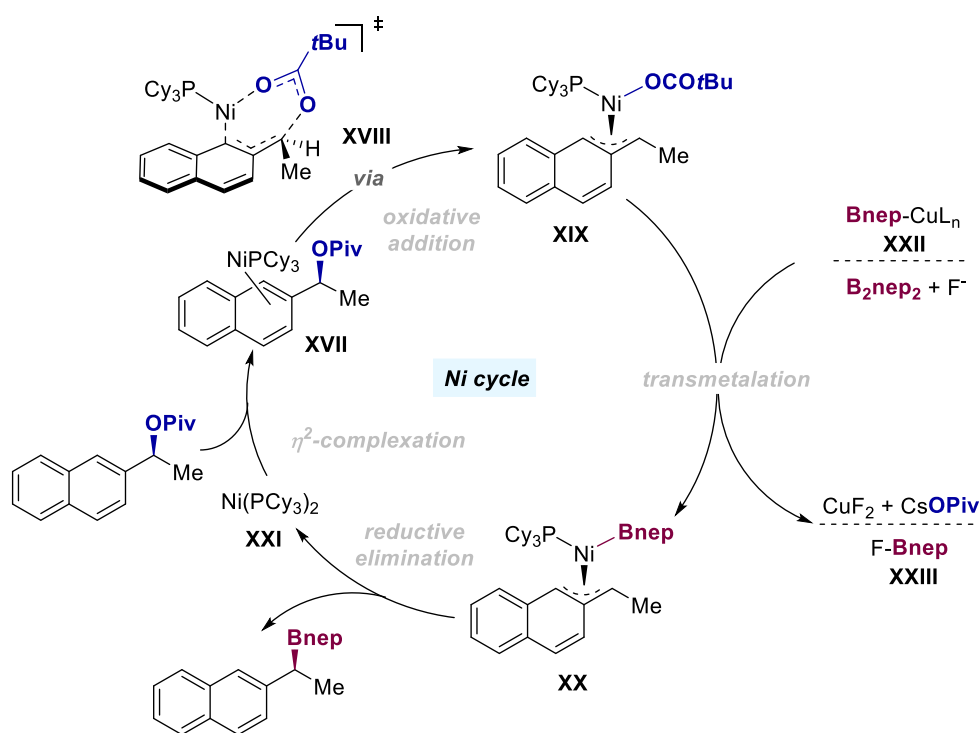
Scheme 2.3.6. Ni cycle mechanistic proposal.

After the publication of this work, Watson carried out a computational study to establish the differences of stereospecificity depending on the substrate, ligand and the conditions utilized.[24] As indicated before, a concerted oxidative addition through a cyclic transition state is likely operative

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where the nickel interacts with the pivalate carbonyl oxygen while cleaving the benzylic $C(sp^3)$–O bond (**XVIII**), thus generating a benzylnickel complex with overall retention of configuration. The key difference between the retention or inversion stereoselectivity likely depends on the substrate–nickel–ligand angle. Although in depth experimental and computational studies are needed to unravel the intricacies of this reaction, two main transmetalation scenarios might come into play 1) a transmetalation consisting of a Cu–B intermediate with two intertwined catalytic cycles, and 2) a copper-free picture that may be aided by the presence of the fluoride salts.

2.3.6.1   Ni/Cu mechanism

In 2013, our group proposed that a related silylation event occurs by a transmetalation involving copper as catalyst.[41] Therefore, it was somewhat tempted to invoke an otherwise similar pathway by activating the B–B bond by fluoride attack to generate Cu–B intermediates, which may favour the transmetalation of the boryl group to the oxidative addition complex (**XIX**) (Scheme 2.3.6).

Taking this into consideration, two plausible proposals have been suggested (Scheme 2.3.7).[41] It has been demonstrated that fluoride anions can activate related $(OR)_2$B–B$(OR)_2$ bonds forming the corresponding $B(sp^3)$ adduct that serves as a boryl anion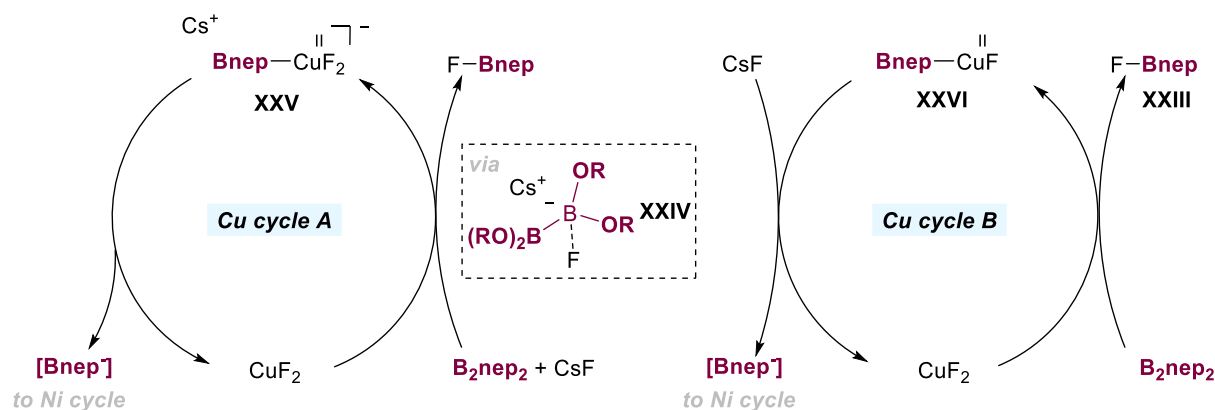 source (**XXIV**),[45] (Scheme 2.3.7, *Cu cycle A*). Such adduct can release the corresponding boryl anion, which in the presence of CuF_2 may generate a nucleophilic borylcopper species (**XXV**). This Cu–B complex should then transmetalate the boryl anion to the Ni cycle and recover the CuF_2.

Scheme 2.3.7. Plausible Cu catalytic cycles.

On the other hand, the B_2nep_2 unit might promote a transmetalation to form Cu(II)FBnep (**XXVI**) and FBnep (**XXIII**) (Scheme 2.3.7, *Cu cycle B*). **XXVI** would release the boryl anion to the Ni cycle while CsF would regenerate the active CuF_2 catalyst. This assumption is in line with previously proposed transmetalation of an aryl group from a B atom to $Cu(OAc)_2$,[46] and explains why Cu(II) sources may easily transmetalate with boron species *via* the formation of highly stable B–F or B–O bonds (Table 2.3.2). This mechanistic proposal has a number of flaws when examined more closely. First, sub-stoichiometric CsF is employed in contrast with the stoichiometric amounts required for this

mechanistic proposal to work. And more strikingly, a 60% yield of the desired product can be obtained in the absence of CuF$_2$ and CsF.

2.3.6.2   *Nickel-fluoride activation picture*

After the publication of the current project, our group investigated the mechanistic implications of the silylation of aryl pivalates.[42] Such stoichiometric and kinetic experiments demonstrated that Cu–SiEt$_3$ intermediates are not necessary for the silylation reaction to occur, thus leaving a reasonable doubt on whether the reaction operated *via* Ni/Cu co-catalysis. Indeed, the inclusion of additional amounts of CsF resulted in similar results of the targeted product. Interestingly, the silylation reaction gave a 30% yield in the absence of fluoride sources. As mentioned above, we observed a 60% yield of the desired product in the absence of the CuF$_2$ and CsF. Both results pointed out that in the first hours of the reaction the transformation takes place through a fluoride-free mechanism. Our group carried out DFT studies for both systems in order to map out the energy profile of their proposed mechanism (Figure 2.3.2).
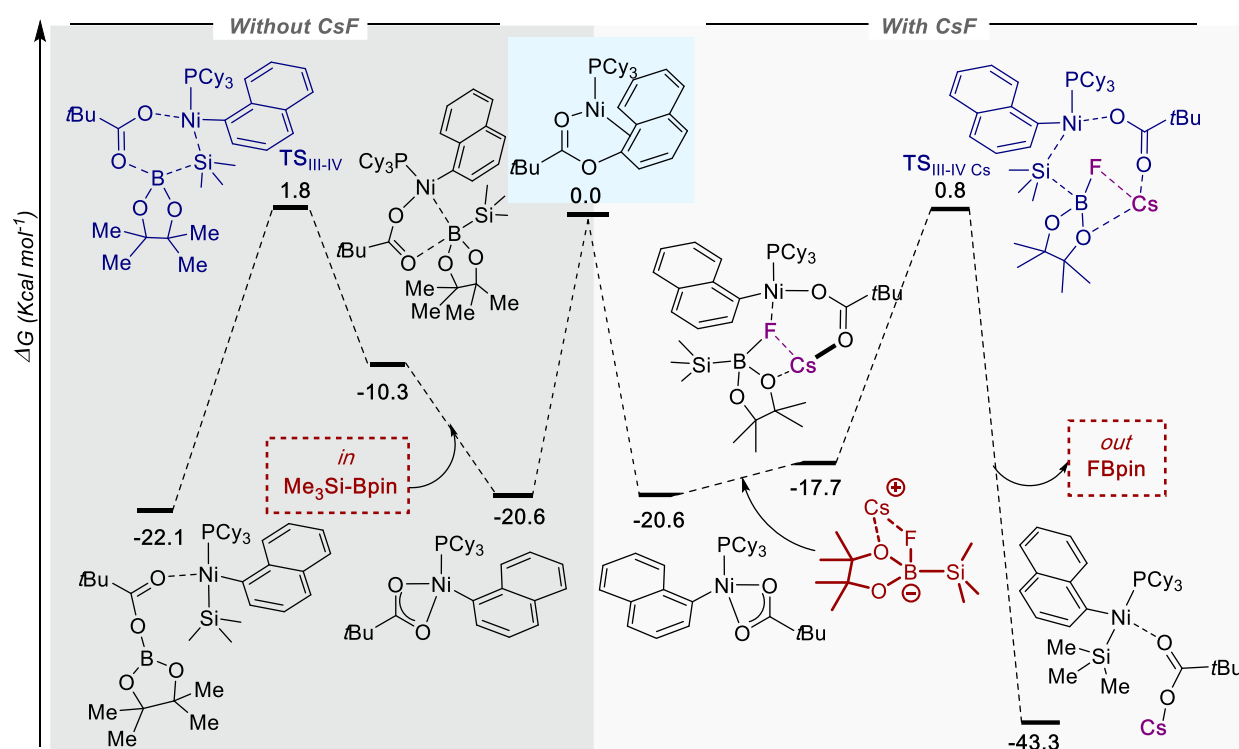
Figure 2.3.2. Free energy profile for the silylation reaction calculated in the absence and presence of fluoride sources. Energies are in kcal mol^{-1}.

Some conclusions were gathered from the DFT studies that shed some light in our borylation mechanism. First, we found a slightly lower energy pathway when CsF was involved in. Second, FBpin was released instead of PivOBpin. Third, the presence of CsF slightly lowers down the barrier of transmetalation slightly ($\Delta\Delta G^{\ddagger}$ = 1 kcal mol^{-1}). Finally, the loss of FBpin rather than PivOBpin also adds 20 kcal mol^{-1} to the barrier to the reverse reaction (figure 2.3.2, *with CsF*). Putting all these

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observations into perspective, we can speculate that our transformation might likely follow the reaction pathway of Figure 2.3.2, *right,* in which CuF_2 and CsF act as fluoride sources that help the activation of the B_2nep_2 while sequestering the Bnep byproduct. In such a way, we propose that the mechanism of our reaction operates *via* **XXVII**. Upon activation of B_2nep_2 by CsF and the nickel species (**XXVIII**), transmetalation occurs, driving the reaction forward by the formation of F–Bnep en route to intermediate **XXIX**.
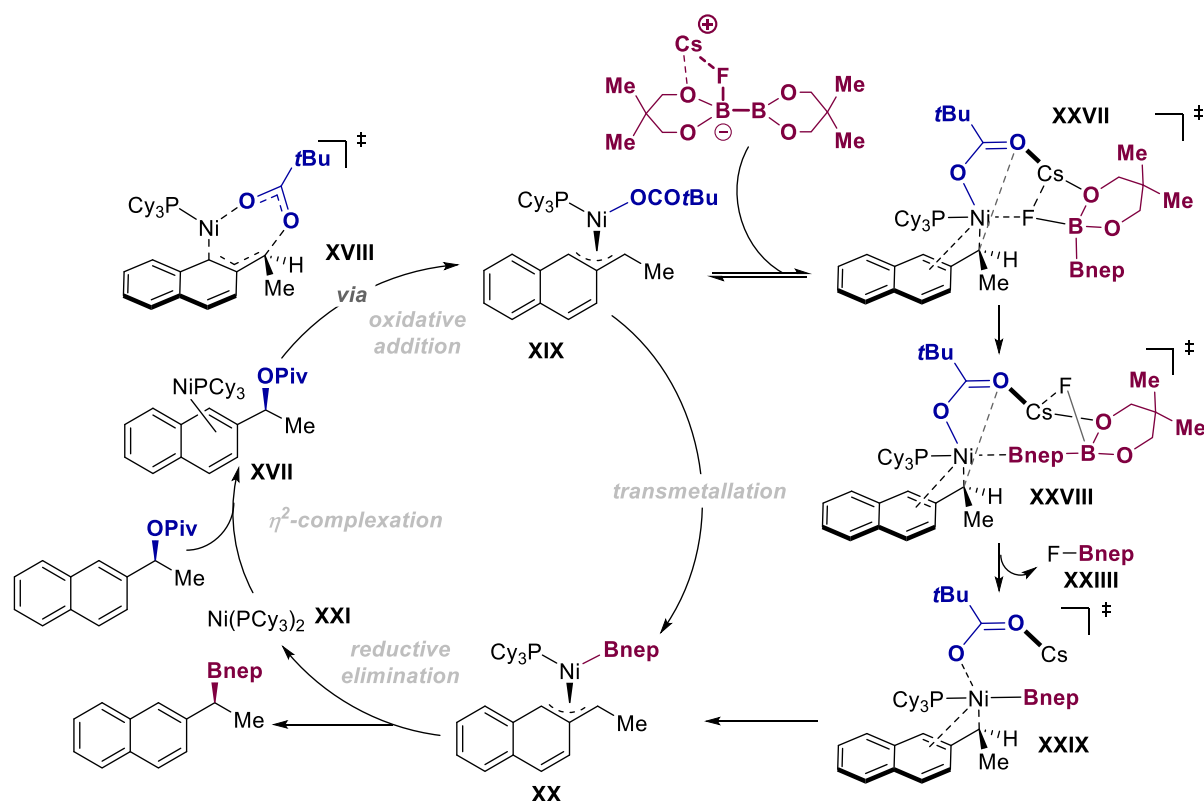
Scheme 2.3.8. Ni/F activation mechanism proposal.

2.3.7   Future outlook

Despite the results presented in this chapter, there still exist a non-negligible number of limitations that could potentially be addressed in the future. Among these are the following:

A. *Utilization of regular arenes*. As shown above, our reaction is inherently limited to π-extended systems due to the strong η^2-binding of Ni centers to these polyarenes and to the electron-poor nature of these backbones. We hypothesize that the utilization of Cr or Rh complexes might be critical for extending the scope of these reactions beyond π-extended systems.[47–49] As reported, the binding of these entities to regular arenes in a η^6-fashion makes them particularly electron-poor and, therefore susceptible to nucleophilic attack at the benzylic position. In this manner, the BDE of the C–O bond will be considerably lower, making it particularly prone to promote oxidative addition with Ni complexes.

B. *Enantioselective version*. A close look into the literature data reveals that while the development of enantioconvergent cross-coupling reactions of racemic benzyl halides or pseudohalides are known, the means to trigger a related process via C–O bond-cleavage is still not practiced as one might initially anticipate. Therefore, future efforts should be devoted to the implementation of an enantioconvergent cross-coupling of racemic benzyl pivalates with chiral ligands.

C. *Different C–O derivatives*. The ultimate goal of the C–O bond-cleavage arena is the utilization of simple C–O electrophiles. That being set, future work should be devoted to the utilization of simple benzyl alcohols via C–OH cleavage, thus obviating the need for protecting group technologies to lower down the bond-dissociation energy of the targeted C–O linkage.

2.4   Conclusions

In summary, we have reported the first stereospecific borylation of benzyl pivalates catalyzed by nickel sources. The mild conditions of this reaction allow us to trigger a borylation event of a reasonable number of substrates with an excellent stereochemical fidelity by a mechanism consisting of a stereoretentive oxidative addition that results in an overall retention of configuration. This protocol can be used as a platform to build up enantioenriched benzyl boronates, important compounds that can be used as linchpins for further derivatization.

2.5   Experimental procedures

2.5.1   General considerations

Reagents. Commercially available materials were used without further purification. Ni(COD)$_2$ (stored at low temperature in the glovebox) and PCy$_3$ were purchased from Strem Chemicals. CuF$_2$ anhydrous (98% purity), CsF anhydrous, and B$_2$nep$_2$ (96% purity) were purchased from Aldrich. Anhydrous Toluene (99.8% purity) was purchased from Alfa Aesar. All other reagents were purchased from commercial sources and used as received.

Analytical methods. ^{1}H, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker 300 MHz, 400 MHz and 500 MHz at 20 °C. All ^{1}H NMR spectra are reported in parts per million (ppm) downfield of TMS and were calibrated using the residual solvent peak of CHCl$_3$ (7.26 ppm), unless otherwise indicated. All ^{13}C NMR spectra are reported in ppm relative to TMS, were calibrated using the signal of residual CHCl$_3$ (77.0 ppm), and were obtained with ^{1}H decoupling unless otherwise indicated. Coupling constants, *J*, are reported in Hertz. Melting points were measured using open glass capillaries in a Büchi B540 apparatus. Infrared spectra were recorded on a Bruker Tensor 27. Gas chromatographic analyses were performed on Hewlett-Packard 6890 gas chromatography instrument with a FID detector. Flash chromatography was performed with EM Science silica gel 60 (230- 400 mesh). Specific Optical Rotation was obtained using a Jasco P-1030 model polarimeter

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equipped with a PMT detector using the Sodium line at 589 nm. UltraPerformance Convergence Chromatography (UPC2) analysis was performed on Acquity UPC2 Waters instrument equipped with a Chiralpack IB/Chiralpack IC/Chiralpack IG column eluting iPrOH/CO$_2$, CO$_2$/MeOH, CO$_2$/MtBE-Hex at ambient temperature and monitored by Photodiode Array Detector (PDA). High Performance Liquid Chromatography (HPLC) analyses were performed on Agilent Technologies Model 1260 Infinity HPLC chromatography instrument equipped with Daicel Chiralpack IB column eluting Hexanes/EtOH supported with UV/Visible DAD detector.

2.5.2 *Synthesis of starting material*

General procedure for the synthesis of enantiopure benzyl alcohols:
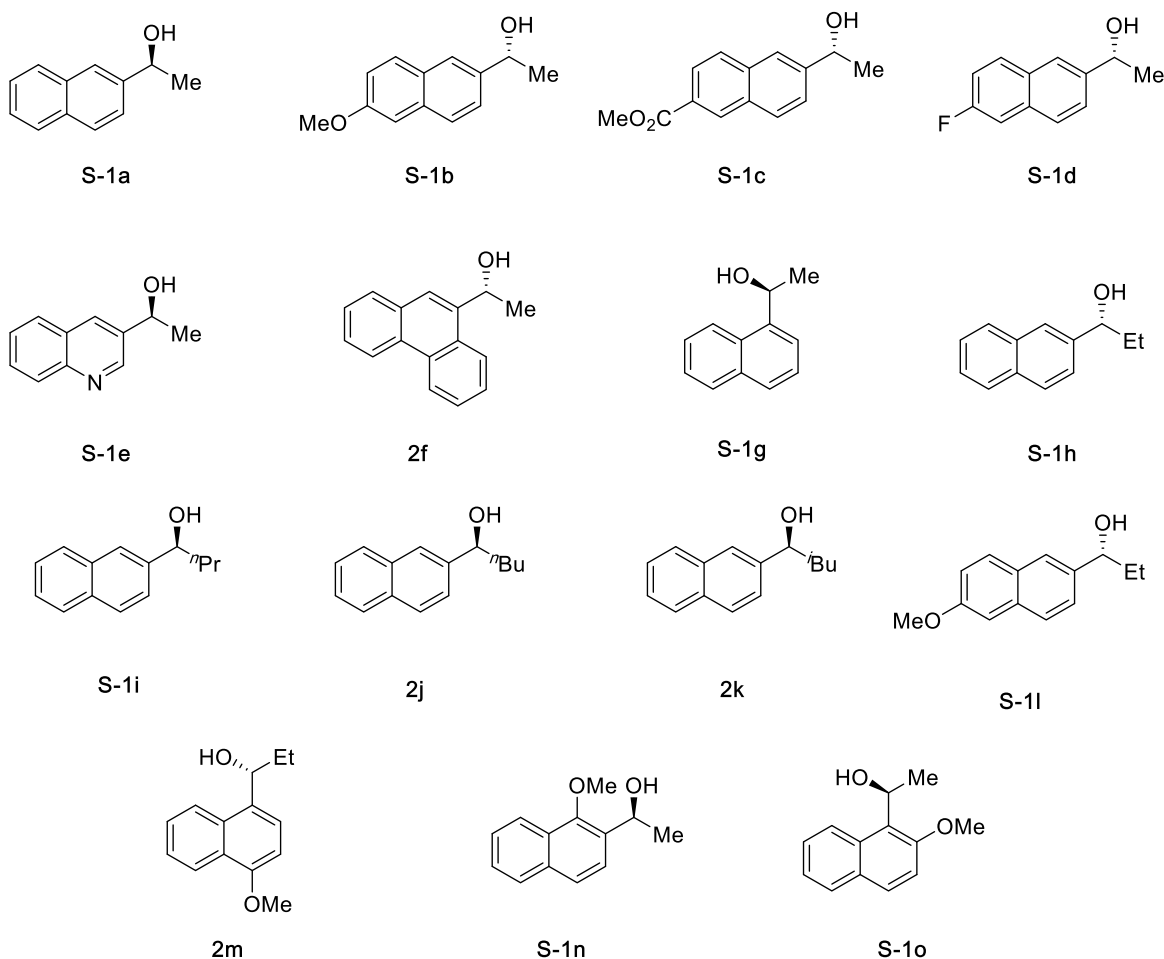
(S)-1-(Naphthalen-2-yl)ethanol (S-1a) and **(S)-(−)-1-(1-Naphthyl)ethanol** (**S-1g**) were purchased from Sigma Aldrich and Fluorochem respectively. Alcohols **S-1b**, **S-1c, S-1d**, and **S-1f**[I] were prepared according to adapted literature procedures using Corey-Bakshi-Shibata reduction of ketones. Compounds **S-1e, S-1j, S-1k, S-1l, S-1n, S-1o** were prepared by asymmetric transfer hydrogenation of ketones.[II] Alcohols **S-1h, S-1i, S-1m** were prepared according to literature procedures using asymmetric addition of diethyl zinc to the aldehydes.[III] All the enantiomeric excesses of crystalline

compounds were then increased via recrystallization from hexanes. Due to alcohols **S-1d**, **S-1f**, **S-1j**, **S-1k**, **S-1m**, **S-1n** and **S-1o** have not been prepared via these methods mentioned above, we have included the experimentals routes for the procedures below.
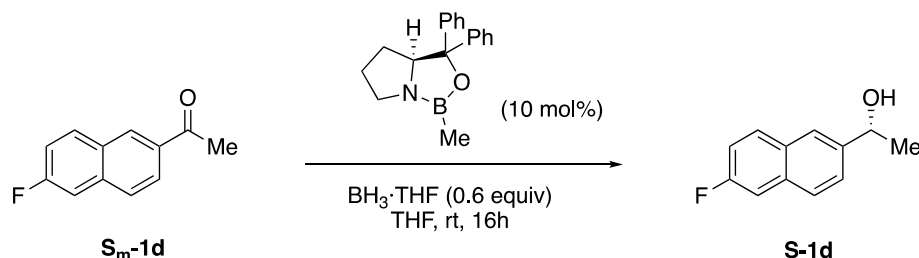
(R)-1-(6-fluoronaphthalen-2-yl)ethan-1-ol (S-1d). The following procedure is adapted from the literature.[I] A solution of CBS catalyst (1 M in THF, 0.19 mL, 0.19 mmol, 10 mol%) in THF (3 mL) was slowly added to a solution of ketone **Sm-1d** (356 mg, 1.89 mmol, 1.0 equiv), BH₃·THF (1 M, 1.1 mL, 1.1 mmol, 0.6 equiv.), and THF (35 mL). After stirring at room temperature for 16h, H₂O (25 mL) was added. The mixture was extracted with Et₂O. The combined organic layers were then dried (MgSO₄), filtered, concentrated. The resulting residue was purified by silica gel chromatography (Hexane/EtOAc 8/2) to give alcohol **S-1d** (93 mg, 26 %) as a white solid (m.p 84-86 ºC). The enantiomeric excess was determined to be 74% ee by chiral HPLC analysis (CHIRALPAK IB, 1mL/min, 0.5% EtOH/Hexane, λ=220 nm); t_R(minor)= 12.3 min, t_R(major)= 13.6 min. ^{1}H-NMR (500 MHz, CDCl₃): δ 7.83-7.76 (m, 3H), 7.53 (d, J = 8.5 Hz, 1H), 7.44 (dd, J = 9.8 2.6 Hz, 1H), 7.26 (t, J = 2.6 Hz, 1H), 5.06 (q, J = 6.4 Hz, 1H), 1.97 (s, 1H, OH), 1.58 (d, J = 6.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, CDCl₃) δ 161.8, 159.4, 142.5, 133.6, 130.3, 127.7, 124.9, 123.8, 116.6, 110.7, 70.3, 25.2 ppm. ^{19}F NMR (376 MHz, CDCl₃) δ -115.1 ppm. IR (neat, cm^{-1}): 3240, 2979, 1608, 1508, 1476, 1253, 1227, 1171, 1139, 1076, 873, 812, 479. HRMS calcd. for C₁₂H₁₀F (M-OH)$^+$: 173.0761, found 173.0758.
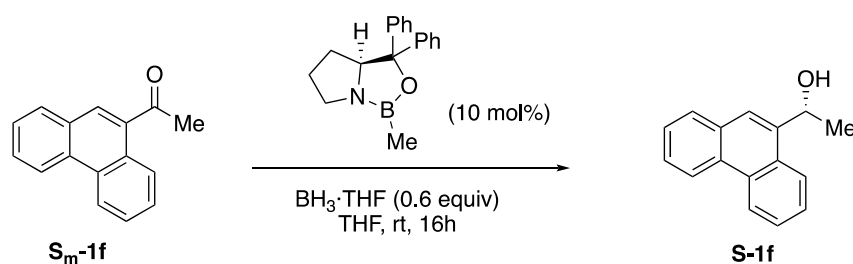
(R)-1-(phenanthren-9-yl)ethan-1-ol (S-1f). The following procedure is adapted from the literature.[I] A solution of CBS catalyst (1M in THF, 250 uL, 0.25 mmol, 0.1 equiv.) in THF (4 mL) was slowly added to a solution of ketone **Sm-1f** (541 mg, 2.46 mmol, 1.0 equiv.), BH₃·THF (1M, 1.5 mL, 1.48 mmol, 0.6 equiv.), and THF (40 mL). After stirring at room temperature for 16h, H₂O (20 mL) was added. The mixture was extracted with Et₂O. The combined organic layers were then dried (MgSO₄), filtered, concentrated. The resulting residue was purified by silica gel chromatography (hexanes/EtOAc 9/1) to give alcohol **S-1f** (330 mg, 61 %) as a white solid (m.p 102-104 ºC). The enantiomeric excess was determined to be 89% ee. ^{1}H NMR (400 MHz, CDCl₃) δ 8.84 – 8.75 (m, 1H),

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8.67 (d, *J* = 8.0 Hz, 1H), 8.18 (dd, *J* = 7.2, 2.3 Hz, 1H), 7.96 (s, 1H), 7.93 – 7.88 (m, 1H), 7.75 – 7.56 (m, 4H), 5.71 (q, *J* = 6.3 Hz, 1H), 1.94 (s, 1H), 1.75 (d, *J* = 6.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 139.5, 131.5, 130.8, 130.0, 129.6, 128.8, 126.8, 126.7, 126.6, 126.3, 123.9, 123.3, 122.7, 122.4, 67.2, 24.1 ppm. The spectral data for this compound matches that reported in literature.[IV]
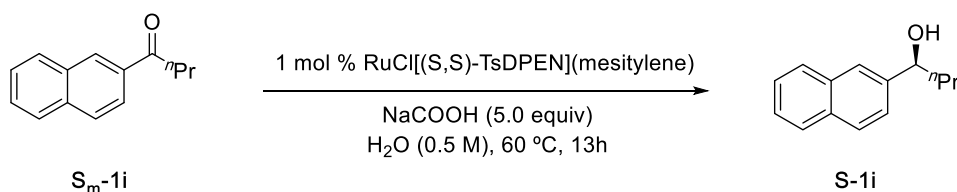
(S)-1-(naphthalen-2-yl)pentan-1-ol (S-1i). The following procedure is adapted from the literature.[II] In a N$_2$-atmosphere glovebox RuCl[(*S*,*S*)-TsDPEN](mesitylene) (13.3mg, 0.021 mmol, 1 mol%) was weighed out into a 25 mL flask. The flask was then capped and removed from glovebox. H$_2$O (degassed by sparging with N$_2$, 5mL) was added, and the resulting mixture was stirred at 40 ºC for 1h. The ketone **S$_m$-1i** (600 mg, 3.02 mmol, 1.0 equiv.) and NaCOOH (1.03 mg, 15.1 mmol, 5 equiv.) were added. The flask was evacuated and refilled with N$_2$ three times and then heated at 60 ºC for 13h. The reaction mixture was diluted with Et$_2$O (10 mL), and filtered through silica gel, which was then rinsed with additional Et$_2$O (10 ml x2). The combined organic layers were concentrated. The resulting residue was purified by silica gel chromatography (hexanes/EtOAc 9/1) and then recrystallized (hexanes) to give compound **S-1j** (480 mg, 80%, 94% ee) as a white solid (m.p 64-66 ºC).^{1}H NMR (400 MHz, CDCl$_3$) δ 7.88 – 7.70 (m, 4H), 7.57 – 7.41 (m, 3H), 4.86 (dd, *J* = 7.4, 5.9 Hz, 1H), 1.93 – 1.70 (m, 3H), 1.56 – 1.24 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 142.3, 133.3, 133.0, 128.2, 127.9, 127.7, 126.1, 125.8, 124.6, 124.1, 74.5, 41.1, 19.0, 14.0 ppm. IR (neat, cm^{-1}): 3240, 2952, 2868, 1311, 1097, 1035, 825. 746, 479. HRMS calcd. for C$_{14}$H$_{16}$O (M+Na)$^+$: 223.1093, found 223.1089
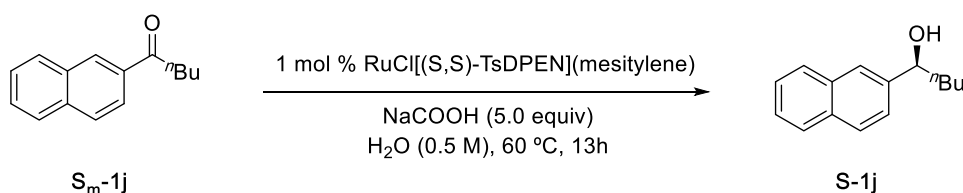

(S)-1-(naphthalen-2-yl)pentan-1-ol (**S-1j**). The following procedure is adapted from the literature.[II] In a N$_2$-atmosphere glovebox RuCl[(*S*,*S*)-TsDPEN](mesitylene) (13.3mg, 0.021 mmol, 1 mol%) was weighed out into a 25 mL flask. The flask was then capped and removed from glovebox. H$_2$O (degassed by sparging with N$_2$, 5mL) was added, and the resulting mixture was stirred at 40 ºC for 1h. The ketone **S$_m$-1j** (454 mg, 2.14 mmol, 1.0 equiv.) and NaCOOH (727 mg, 10.7 mmol, 5 equiv.) were added. The flask was evacuated and refilled with N$_2$ three times and then heated at 60 ºC for 13h. The reaction mixture was diluted with Et$_2$O (10 mL), and filtered through silica gel, which was then rinsed with additional Et$_2$O (10 ml x2). The combined organic layers were concentrated. The

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resulting residue was purified by silica gel chromatography (hexanes/EtOAc 9/1) and then recrystallized (hexanes) to give compound **S-1j** (260 mg, 57%, 99% ee) as a white solid (m.p 75-77 ºC). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.00 – 7.81 (m, 3H), 7.78 (s, 1H), 7.72 – 7.33 (m, 3H), 4.85 (dd, J = 7.3, 6.0 Hz, 1H), 2.15 – 1.68 (m, 3H), 1.62 – 1.20 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 142.4, 133.4, 133.1, 128.4, 128.1, 127.8, 126.3, 125.9, 124.8, 124.3, 75.0, 38.9, 28.1, 22.8, 14.2 ppm. The spectral data for this compound matches that reported in literature.[V]
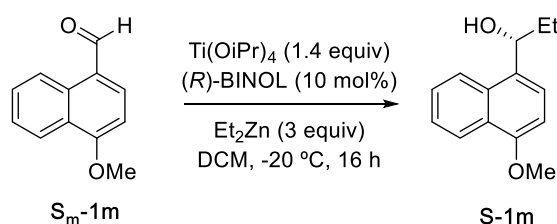
(R)-1-(4-methoxynaphthalen-1-yl)propan-1-ol (S-1m). The following procedure is adapted from the literature.[III] To a solution of (R)-binaphtol (155 mg, 0.54 mmol, 0.1 equiv.) in dichloromethane (40 mL) was added titanium tetraisopropoxide (2.2 mL, 7.46 mmol, 1.4 equiv.), and the solution was stirred 10 minutes. Diethylzinc (1 M, 16.2 mL, 16.2 mmol, 3.0 equiv.) was added and the mixture was stirred for an additional 10 minutes at room temperature. The solution was cooled to -25 ºC and a solution of 4-methoxy-1-naphthaldehyde (1 g, 5.4 mmol, 1.0 equiv.) in dichloromethane (8 mL) was added. After stirring overnight at −25 ºC, the reaction was quenched by the addition of 1 M hydrochloric acid (80 mL) and the product was extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organics were washed with brine (50 mL), dried over MgSO$_4$, and concentrated in vacuo. The product was purified by flash chromatography (hexanes/EtOAc 9/1) to afford the tittle compound as colourless oil (647 mg, 56 %). The enantiomeric excess was determined to be 87% ee by chiral HPLC analysis. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.33 (dd, J = 8.2, 1.5 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.65 – 7.39 (m, 3H), 6.81 (d, J = 8.0 Hz, 1H), 5.30 (q, J = 5.5, 1H), 4.01 (s, 3H), 2.07 – 1.91 (m, 2H), 1.89 (s, 1H, OH), 1.02 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 155.2, 132.2, 131.8, 126.7, 126.0, 125.1, 123.4, 123.3, 122.9, 103.3, 72.8, 55.7, 31.1, 10.8 ppm. IR (neat, cm^{-1}): 3379, 2961, 1585,1462, 1392, 1269, 1158, 1089, 818, 762. HRMS calcd. for C$_{14}$H$_{16}$O$_2$ (M+Na)$^+$: 239.1043, found 239.1045.
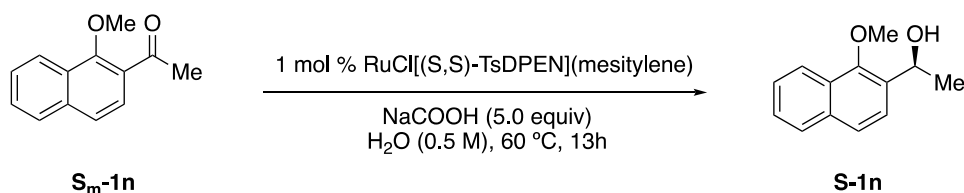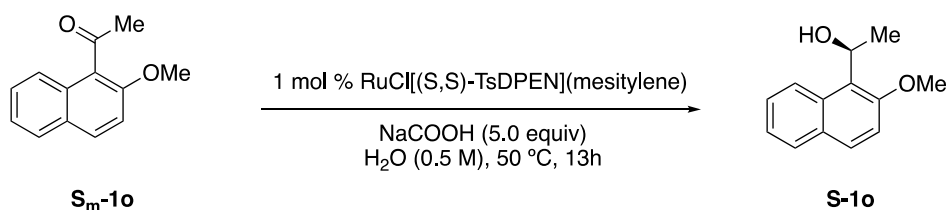

(S)-1-(1-methoxynaphthalen-2-yl)ethanol (S-1n). The following procedure is adapted from the literature.[II] In a N$_2$-atmosphere glovebox RuCl[(S,S)-TsDPEN](mesitylene) (13.3mg, 0.021 mmol, 1 mol%) was weighed out into a 25 mL flask. The flask was then capped and removed from glovebox. H$_2$O (degassed by sparging with N$_2$, 5mL) was added, and the resulting mixture was stirred at 40 ºC for 1h. The ketone **S$_m$-1n** (500 mg, 2.5 mmol) and NaCOOH (850 mg, 5 equiv.) were added. The flask

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was evacuated and refilled with N_2 three times and then heated at 60 ºC for 13h. The reaction mixture was diluted with Et_2O (10 mL), and filtered through silica gel, which was then rinsed with additional Et_2O (10 ml x2). The combined organic layers were concentrated. The resulting residue was purified by silica gel chromatography (hexanes/EtOAc 9/1) to give compound **S-1n** (390 mg, 77%, 95% ee) as colourless oil. $[\alpha]_D^{24}$ = -25.2º (c 0.12, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 7.99 (m, 1H), 7.88 – 7.78 (m, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.59 – 7.45 (m, 3H), 5.47 (d, J = 6.5 Hz, 1H), 3.98 (s, 3H), 2.25 (s, 1H, OH), 1.59 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 134.4, 133.4, 128.1, 127.7, 126.1, 126.0, 124.7, 123.8, 122.1, 64.7, 62.8, 24.2 ppm. IR (neat, cm^{-1}): 3249, 2960, 1369, 1066, 976, 747. HRMS calcd. for $C_{13}H_{14}O_2$ (M+Na)$^+$: 225.0886, found 2225.0896.

(S)-1-(2-methoxynaphthalen-1-yl)ethanol (**S-1o**). The following procedure is adapted from the literature.[II] In a N_2-atmosphere glovebox RuCl[(*S*,*S*)-TsDPEN](mesitylene) (13.3mg, 0.021 mmol, 1 mol%) was weighed out into a 25 mL flask. The flask was then capped and removed from glovebox. H_2O (degassed by sparging with N_2, 5mL) was added, and the resulting mixture was stirred at 40 ºC for 1h. The ketone **S$_m$-1o** (500 mg, 2.5 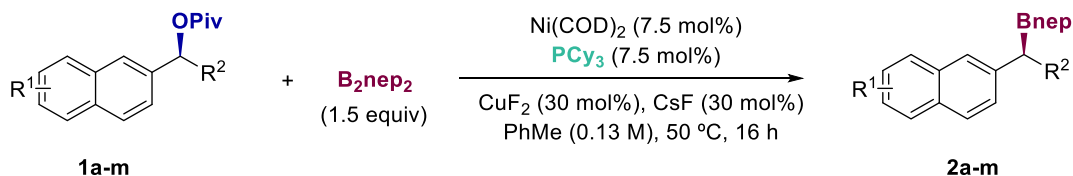mmol) and NaCOOH (850 mg, 5 equiv.) were added. The flask was evacuated and refilled with N_2 three times and then heated at 50 ºC for 13h. The reaction mixture was diluted with Et_2O (10 mL), and filtered through silica gel, which was then rinsed with additional Et_2O (10 ml x2). The combined organic layers were concentrated. The resulting residue was purified by silica gel chromatography (hexanes/EtOAc 9/1) to give compound **S-1o** (120 mg, 24%, 71% ee) as colourless oil. $[\alpha]_D^{24}$ = -19.4º (c 0.51, $CHCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dt, J = 8.4, 0.9 Hz, 1H), 7.87 – 7.68 (m, 2H), 7.49 (dd J = 8.6, 6.8 Hz, 1H), 7.36 (dd, J = 8.0, 6.7 Hz, 1H), 7.29 (d, J = 9.1 Hz, 1H), 5.75 (t, J = 7.0 Hz, 1H), 4.01 (s, 3H), 3.98 (s, 1H, OH), 1.68 (d, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 131.4, 129.5, 129.2, 128.8, 126.8, 125.8, 123.8, 122.9, 113.5, 66.2, 56.5, 23.9 ppm. The spectral data for this compound matches that reported in literature.[VI]

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2.5.3 Stereospecific borylation of benzyl pivalates.

General procedure:

An oven-dried 5 mL screw-capped test tube containing a stirring bar was charged with the benzyl pivalate (51.2 mg, 0.2 mmol). The test tube was introduced in an argon-filled glovebox where $B_2(nep)_2$ (67.8 mg, 0.3 mmol, 1.5 equiv), CuF_2 (6 mg, 30 mol%), CsF (9.1 mg, 30 mol%), Ni(COD)$_2$ (304 µL, 7.5 mol%, 0.05 M in toluene), PCy$_3$ (152 µL, 7.5 mol%, 0.1 M) and toluene (1 mL) were then added sequentially. The tube with the mixture was taken out of the glovebox and stirred at 50 ºC for 16 h. The mixture was then allowed to warm to room temperature, diluted with EtOAc (5 mL) and filtered through a Celite® plug, eluting with additional EtOAc (5mL). The filtrate was concentrated removing the volatiles. Due to the instability of these products in silica gel, the borylated product was transformed into the corresponding benzyl alcohol in order to measure the enantiomeric excess.[VII] The reaction was cooled to 0 ºC (water/ice bath) and BHT (~1mg) was added followed by anhydrous THF (1 mL). An ice-cold degassed mixture of 3 M NaOH (1.2 mL) and 30% aqueous H_2O_2 (0.75 mL) was added all at once. The reaction mixture was stirred at room temperature for 2 h. Then, the reaction mixture was diluted with water (4 mL) and extracted with Et$_2$O (3 x 10 mL). The combined organic layers were washed with brine and dried over MgSO$_4$. The filtrate was concentrated and purified by silica gel chromatography to give the corresponding benzyl alcohol.

2a
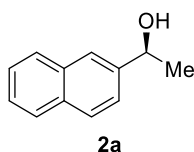
(*S*)-1-(naphthalen-2-yl)ethanol (2a). The targeted compound was prepared via the General Procedure using Pivalate **1a** (prepared in 99% ee). The crude material was purified by silica gel chromatography (hexanes/EtOAc 9/1) to give compound **2a** (30 mg, 87%) as a white solid (m.p 70-72 ºC). The enantiomeric excess was determined to be 94% ee (95% ee$_s$) by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 2% EtOH/Hexane, λ=220 nm); t_R(major)= 13.6 min, t_R(minor)= 14.8 min. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90 – 7.77 (m, 4H), 7.57 – 7.41 (m, 3H), 5.07 (q, *J* = 6.5 Hz, 1H), 1.96 (s, 1H, OH), 1.59 (d, *J* = 6.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 143.2, 133.3, 132.9, 128.3, 127.9, 127.7, 126.1, 125.8, 123.8, 123.7, 70.5, 25.1 ppm. The spectral data for this compound matches that reported in literature.[II]
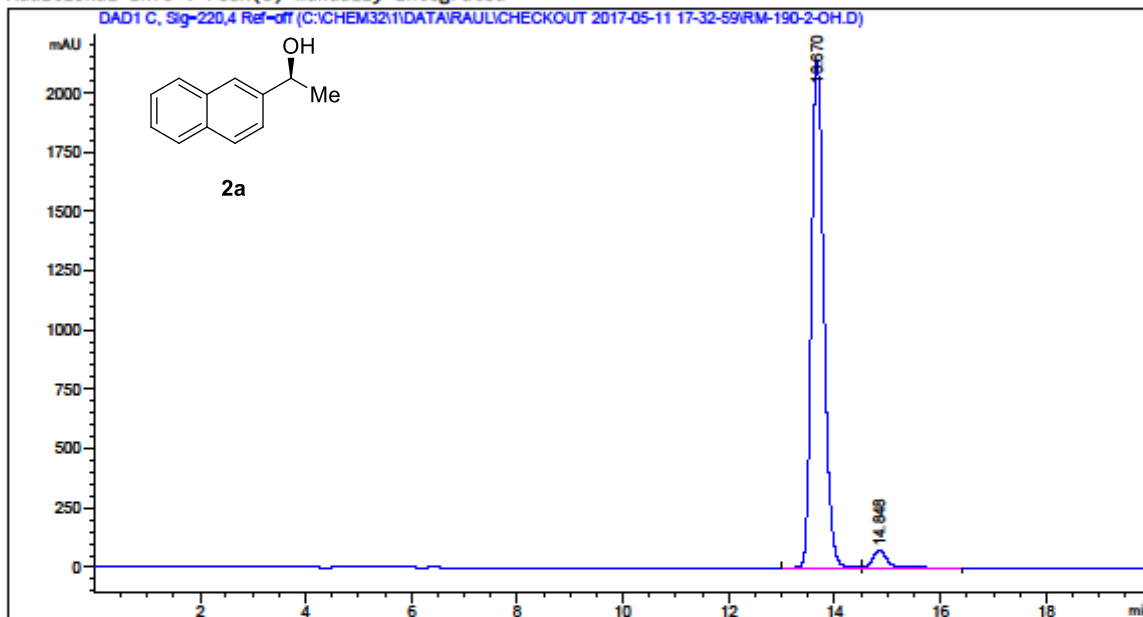
Chapter 2

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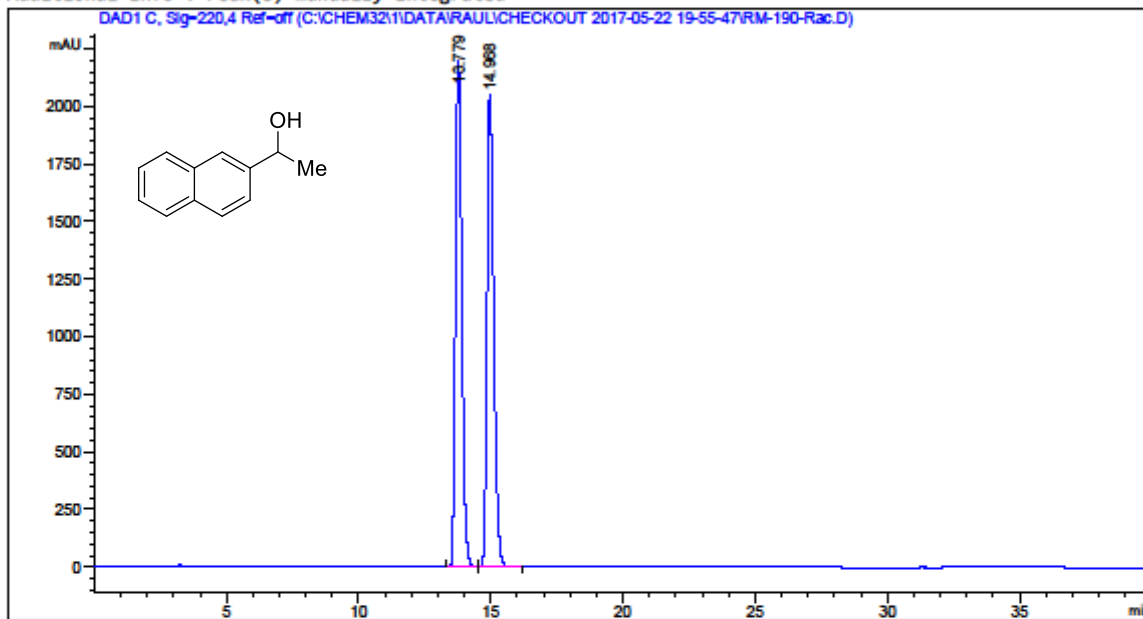
Stereospecific Borylation of Benzyl C(sp³)–O Bonds

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Use Multiplier & Dilution Factor with ISTDs


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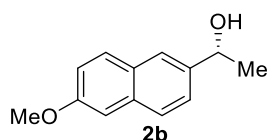
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HPLC 1260 7/17/2017 6:57:02 PM SYSTEM   Page 1 of 2

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2b

(*R*)-1-(6-methoxynaphthalen-2-yl)ethanol (2b). The targeted compound was prepared via the General Procedure using Pivalate **1b** (prepared in 87% ee). The crude material was purified by silica gel chromatography (hexanes/EtOAc 9/1) to give compound **2b** (33 mg, 80%) as a white solid (m.p 110-112 ºC). The enantiomeric excess was determined to be 85% ee (98% ee$_s$) by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 2% EtOH/Hexane, λ=220 nm); t_R(minor)= 17.3 min, t_R(major)= 23.3 min. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79 – 7.67 (m, 3H), 7.47 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.22 – 7.10 (m, 2H), 5.03 (q, *J* = 6.5 Hz, 1H), 3.92 (s, 3H), 1.95 (s, 1H, OH), 1.57 (d, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 157.6, 140.9, 134.0, 129.4, 128.7, 127.1, 124.3, 123.7, 118.9, 105.7, 70.5, 55.3, 25.0 ppm. The spectral data for this compound matches that reported in literature.[VII]
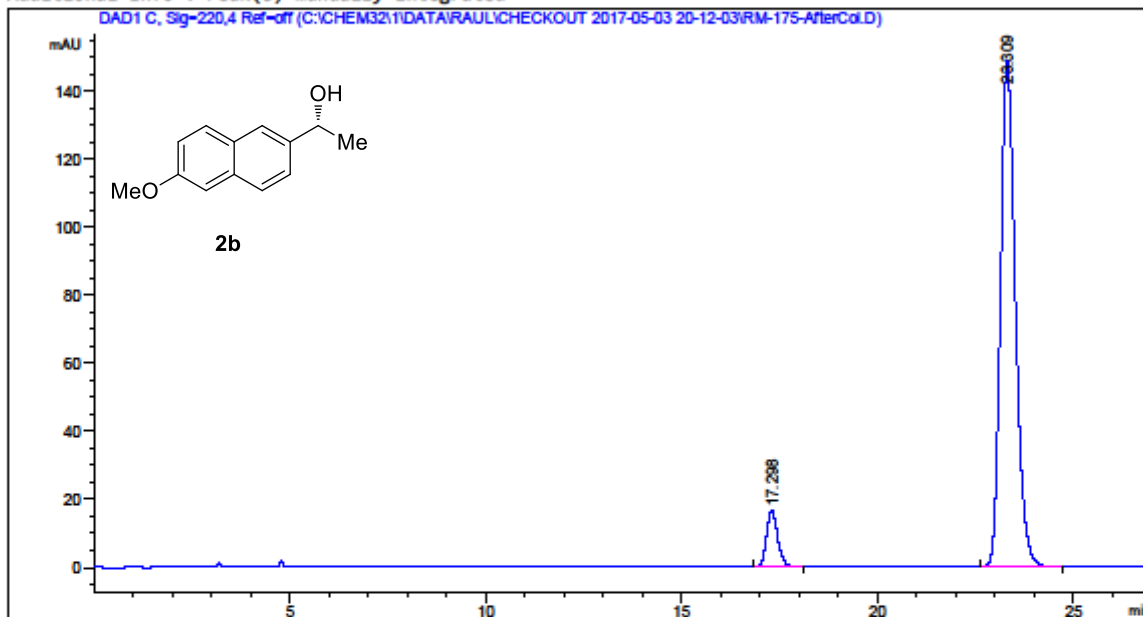
Stereospecific Borylation of Benzyl C(sp^3)–O Bonds

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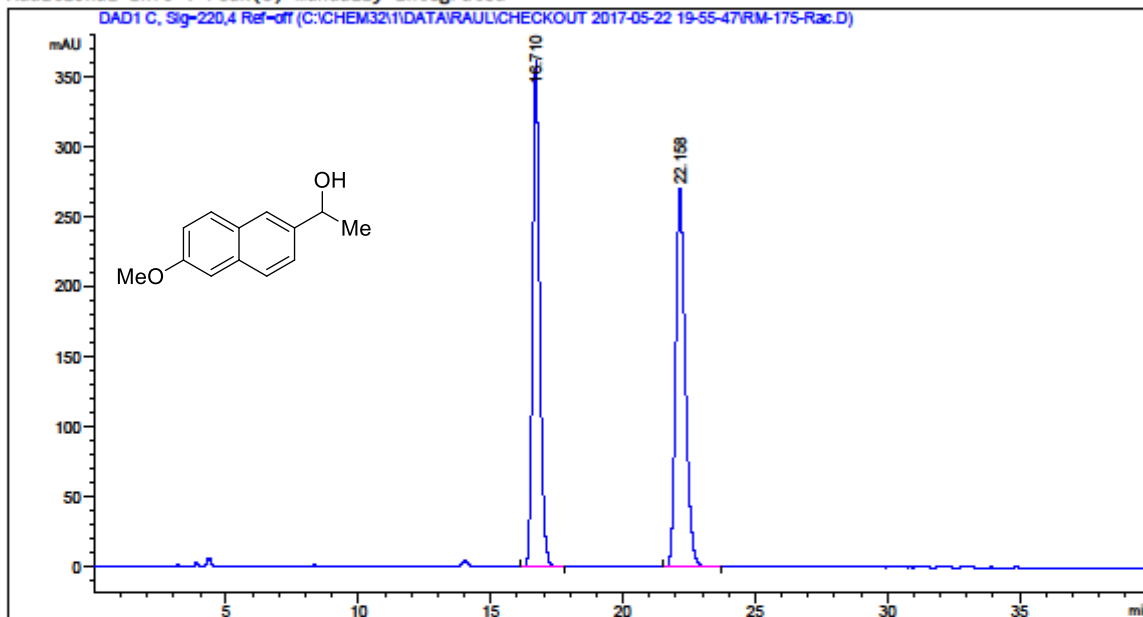
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HPLC 1260 7/17/2017 6:02:46 PM SYSTEM   Page   1 of 2

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Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-05-22 19-55-47\RM-175-Rac.D
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Additional Info : Peak(s) manually integrated
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Use Multiplier & Dilution Factor with ISTDs


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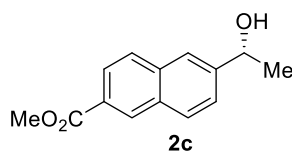
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Stereospecific Borylation of Benzyl C(sp³)–O Bonds

2c

(*R*)-methyl 6-(1-hydroxyethyl)-2-naphthoate (2c). The targeted compound was prepared via the General Procedure using Pivalate **1c** (prepared in 92% ee). The crude material was purified by silica gel chromatography (hexanes/EtOAc 9/1) to give compound **2c** (39 mg, 85%) as a white solid (m.p 74-76 ºC). The enantiomeric excess was determined to be 85% ee (92% ee$_s$) by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 2% EtOH/Hexane, λ=220 nm); t_R(minor)= 22.9 min, t_R(major)= 28.7 min. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.58 (dd, *J* = 1.8, 0.9 Hz, 1H), 8.05 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.89 – 7.83 (m, 2H), 7.57 (dd, *J* = 8.5, 1.7 Hz, 1H), 5.09 (q, *J* = 6.5 Hz, 1H), 3.98 (s, 3H), 2.01 (s, 1H, OH), 1.59 (d, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 167.2, 145.8, 135.5, 131.9, 130.8, 129.7, 128.1, 127.3, 125.5, 124.7, 123.6, 70.4, 52.2, 25.2 ppm. The spectral data for this compound matches that reported in literature.[VII]

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================================================================
                    Area Percent Report
================================================================
```
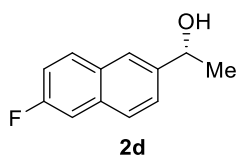
```
Sorted By           :       Signal
Multiplier          :       1.0000
Dilution            :       1.0000
Use Multiplier & Dilution Factor with ISTDs
```
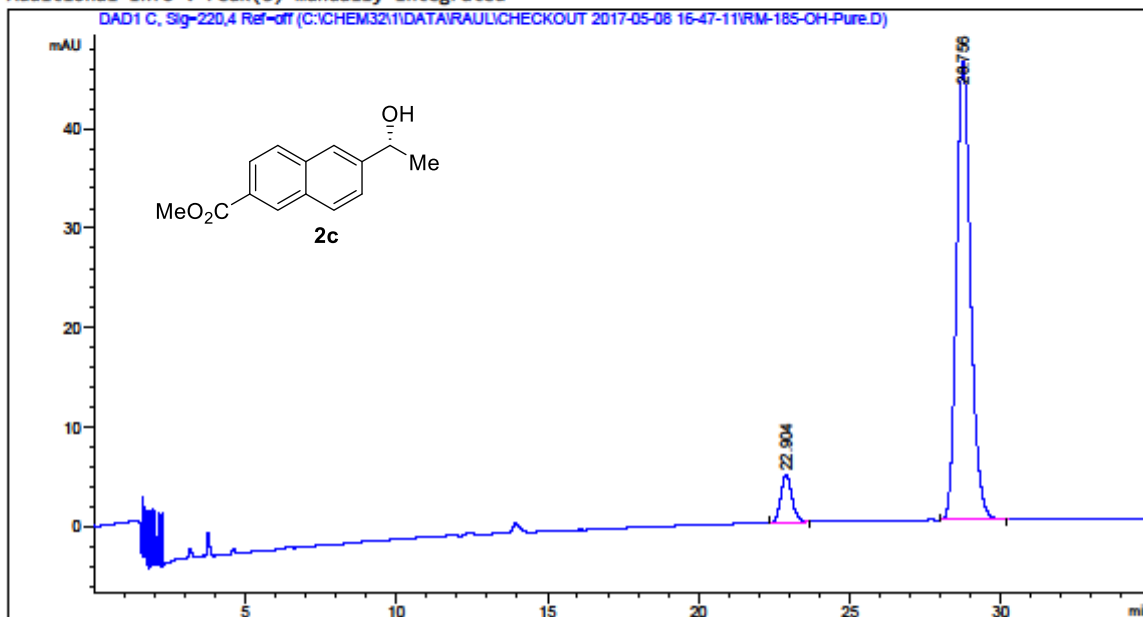
```
Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area      Height    Area
 #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1  22.904 BB   0.3908  123.06052    4.80450   7.6160
  2  28.756 BB   0.4944 1492.75366   46.02183  92.3840

Totals :                1615.81418   50.82633
```

```
================================================================
```
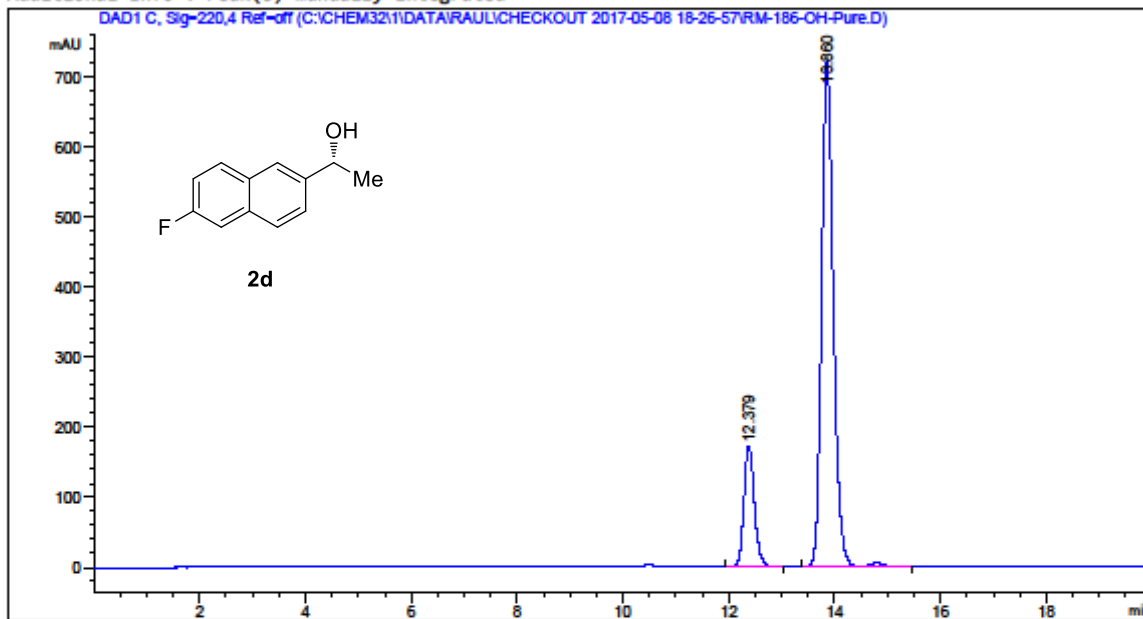
Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-01 20-26-38\013-0401.D
Sample Name: RT-3

```
=================================================================
Acq. Operator   : SYSTEM                    Seq. Line :   4
Acq. Instrument : HPLC 1260                  Location :   13
Injection Date  : 7/1/2017 10:29:31 PM           Inj :   1
                                      Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-01 20-26-38\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 7/1/2017 8:26:38 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 9:40:12 AM by SYSTEM
Additional Info : Peak(s) manually integrated
```
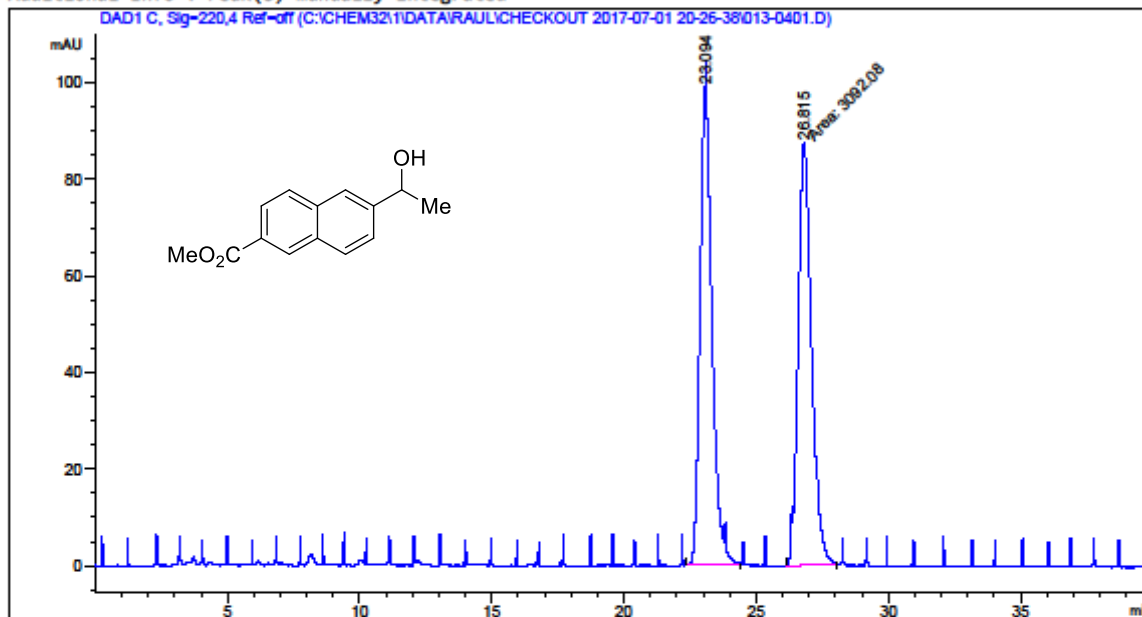


```
=================================================================
                    Area Percent Report
=================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
 #   [min]         [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1  23.094 BV R  0.3590  3116.58447  104.40434  50.1973
  2  26.815 MM    0.5895  3092.07983   87.41578  49.8027

Totals :                  6208.66431  191.82011
```

```
=================================================================
```

HPLC 1260 7/21/2017 11:56:05 AM SYSTEM   Page   1 of 2

Chapter 2

2d

(*R*)-1-(6-fluoronaphthalen-2-yl)ethanol (2d). The targeted compound was prepared via the General Procedure using Pivalate **1d** (prepared in 74% ee). The crude material was purified by silica gel chromatography (hexanes/EtOAc 9/1) to give compound **2d** (30.5 mg, 80%) as a white solid (mp 84-86 ºC). The enantiomeric excess was determined to be 65% ee (88% ee$_s$) by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 2% EtOH/Hexane, λ=220 nm); t_R(minor)= 12.4 min, t_R(major)= 13.9 min. $[\alpha]_D^{24}$ = 43.2º (c 0.06, CHCl$_3$): ^{1}H-NMR (500 MHz, CDCl$_3$): δ 7.83-7.76 (m, 3H), 7.53 (dd, *J* = 2.0 Hz, 1H), 7.44 (dd, *J* = 2.6 Hz, 1H), 7.26 (td, *J* = 2.6 Hz, 1H), 5.06 (q, *J* = 6.4 Hz, 1H), 1.97 (s, 1H, OH), 1.58 (d, *J* = 6.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 161.8, 159.4, 142.5, 133.6, 130.3, 127.7, 124.9, 123.8, 116.6, 110.7, 70.3, 25.2 ppm. ^{19}F NMR (376 MHz, CDCl$_3$) δ -115.1 ppm.

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Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-05-08 18-26-57\RM-186-OH-Pure.D
Sample Name: RM-186-OH-Pure

```
================================================================
Acq. Operator   : SYSTEM                  Seq. Line :   2
Acq. Instrument : HPLC 1260                Location :   4
Injection Date  : 5/8/2017 6:49:51 PM          Inj :   1
                                        Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-05-08 18-26-57\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 5/8/2017 6:26:58 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/17/2017 5:48:55 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```



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

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area        Height      Area
 #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1  12.379 BB   0.2094  2362.70264  172.94595   17.3299
  2  13.860 BV R 0.2380  1.12710e4   723.37933   82.6701

Totals :                 1.36337e4   896.32529
```

```
================================================================
```

Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-01 20-26-38\014-0501.D
Sample Name: RT4

```
========================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   5
Acq. Instrument : HPLC 1260                      Location :   14
Injection Date  : 7/1/2017 11:10:24 PM               Inj :   1
                                             Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-01 20-26-38\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 7/1/2017 8:26:38 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 9:40:12 AM by SYSTEM
Additional Info : Peak(s) manually integrated
```
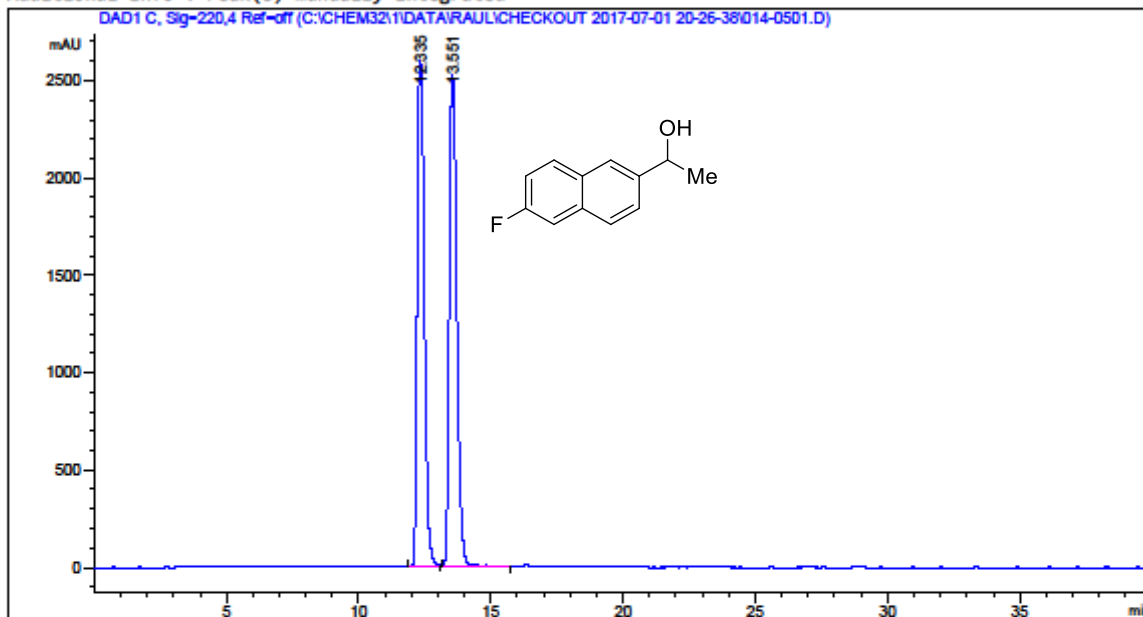


```
========================================================================
                    Area Percent Report
========================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height      Area
 #   [min]         [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
 1   12.335 BV    0.2913 4.84631e4  2602.06543  48.9588
 2   13.551 VV R  0.3125 5.05244e4  2533.07715  51.0412

Totals :                  9.89875e4  5135.14258
```
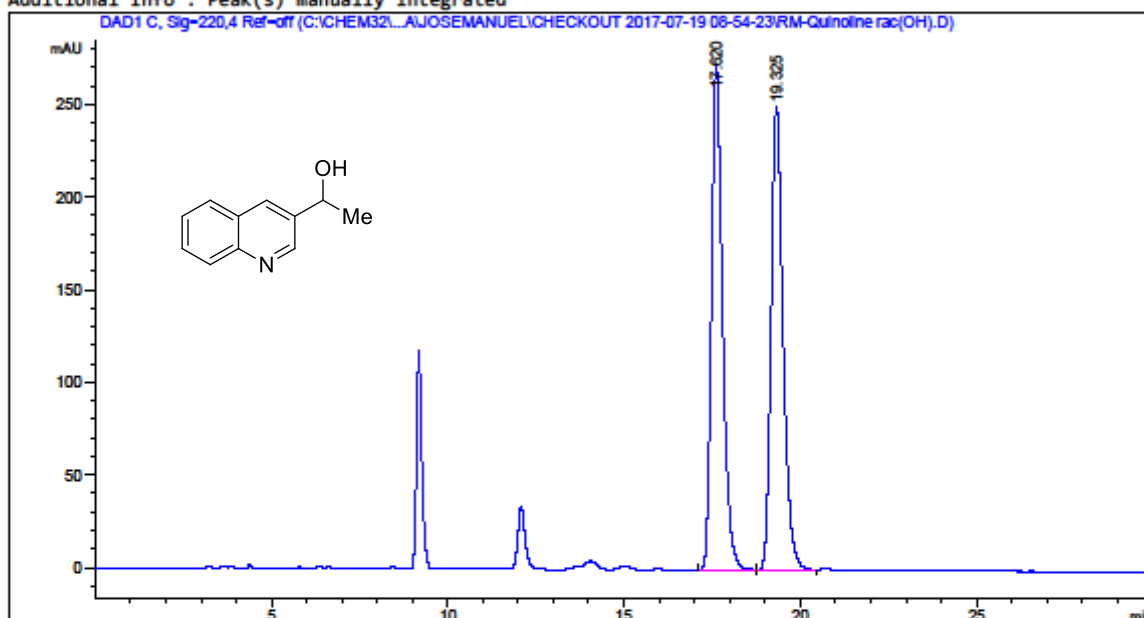
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========================================================================
```

HPLC 1260 7/21/2017 11:57:28 AM SYSTEM   Page   1 of 2

Stereospecific Borylation of Benzyl C(sp^3)–O Bonds

2e
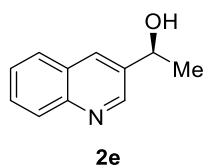
(*S*)-1-(quinolin-3-yl)ethanol (2e). The targeted compound was prepared via the General Procedure using Pivalate **1e** (prepared in 77% ee). The crude material was purified by silica gel chromatography (hexanes/EtOAc 1/1) to give compound **2e** (25 mg, 72%) as a light brown oil. The enantiomeric excess was determined to be 44% ee (57% ee$_s$) by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 4% EtOH/Hexane, λ=220 nm); t_R(major)= 17.3 min, t_R(minor)= 19.3 min. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.91 (d, *J* = 2.2 Hz, 1H), 8.19 – 8.06 (m, 2H), 7.81 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.69 (dd, *J* = 8.4, 6.9 Hz, 1H), 7.55 (dd, *J* = 8.1, 6.9 Hz, 1H), 5.14 (q, *J* = 6.3 Hz, 1H), 1.75 (s, 1H, OH), 1.62 (d, *J* = 6.5 Hz, 3H), ppm. ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.3, 147.6, 138.2, 131.9, 129.3, 129.1, 127.8, 127.8, 126.6, 68.4, 25.3 ppm. The spectral data for this compound matches that reported in literature.[VII]

Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-06-02 15-57-48\RM-236-OH(96-4).D
Sample Name: RM-236-OH(96-4)

```
====================================================================
Acq. Operator   : SYSTEM                    Seq. Line :    1
Acq. Instrument : HPLC 1260                  Location :    3
Injection Date  : 6/2/2017 3:58:38 PM            Inj :    1
                                          Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-06-02 15-57-48\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 6/2/2017 3:57:48 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/17/2017 5:48:55 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
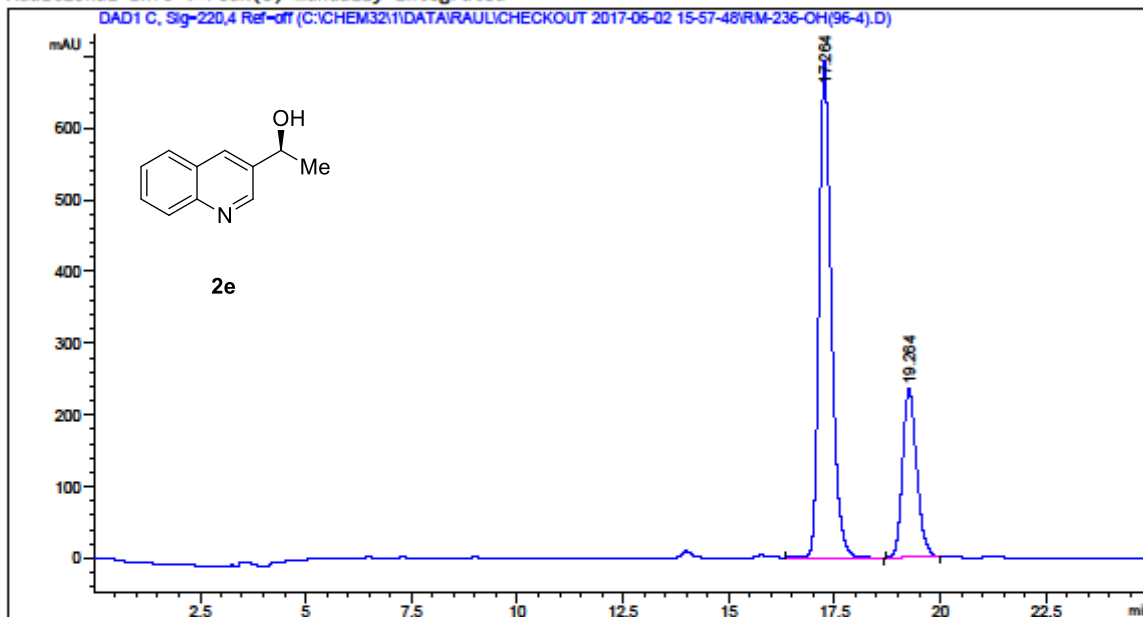


```
====================================================================
                    Area Percent Report
====================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
 #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
 1   17.264 BB   0.3048 1.39578e4   693.39600   72.0017
 2   19.264 BB   0.3515 5427.57178  236.69380   27.9983

Totals :                1.93854e4   930.08980
```

```
====================================================================
```

HPLC 1260 7/17/2017 8:13:37 PM SYSTEM   Page   1 of 2

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM32\1\DATA\JOSEMANUEL\CHECKOUT 2017-07-19 08-54-23\RM-Quinoline rac(OH).D
Sample Name: RM-Quinoline rac(OH)

```
=================================================================
Acq. Operator   : SYSTEM                    Seq. Line :   2
Acq. Instrument : HPLC 1260                  Location :   15
Injection Date  : 7/19/2017 9:26:02 AM          Inj :   1
                                         Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\JoseManuel\checkout 2017-07-19 08-54-23\Chiral coloumn IB-
                  Raul 98-2.M
Last changed    : 7/19/2017 8:54:23 AM by SYSTEM
Analysis Method : C:\Chem32\1\Data\Raul\checkout 2017-07-25 09-32-31\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M (Sequence Method)
Last changed    : 7/25/2017 9:32:40 AM by SYSTEM
Additional Info : Peak(s) manually integrated
```



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

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
 #   [min]        [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
 1   17.620 BB    0.3296  5927.14404  272.65103  50.1211
 2   19.325 BB    0.3613  5898.50293  249.97992  49.8789

Totals :                  1.18256e4   522.63095
```

Chapter 2

2f
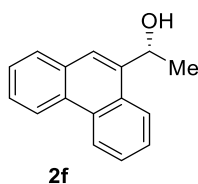
(*R*)-1-(phenanthren-9-yl)ethanol (2f). The targeted compound was prepared via the General Procedure using Pivalate **1f** (prepared in 89% ee). The crude material was purified by silica gel chromatography (hexanes/EtOAc 9/1) to give compound **2f** (33.4 mg, 75%) as a white solid (m.p 101-103 ºC). The enantiomeric excess was determined to be 68% ee (76% ee$_s$) by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 2% EtOH/Hexane, λ=220 nm); t_R(minor)= 14.4 min, t_R(major)= 19.5 min. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.80 – 8.74 (m, 1H), 8.72 – 8.63 (m, 1H), 8.17 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.98 – 7.87 (m, 2H), 7.75 – 7.55 (m, 4H), 5.69 (q, *J* = 6.5 Hz, 1H), 2.01 (s, 1H, OH), 1.74 (d, *J* = 6.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 139.5, 131.5, 130.8, 130.0, 129.6, 128.8, 126.7, 126.6, 126.5, 126.3, 123.9, 123.3, 122.7, 122.4, 67.2 24.1 ppm. The spectral data for this compound matches that reported in literature.[IV]
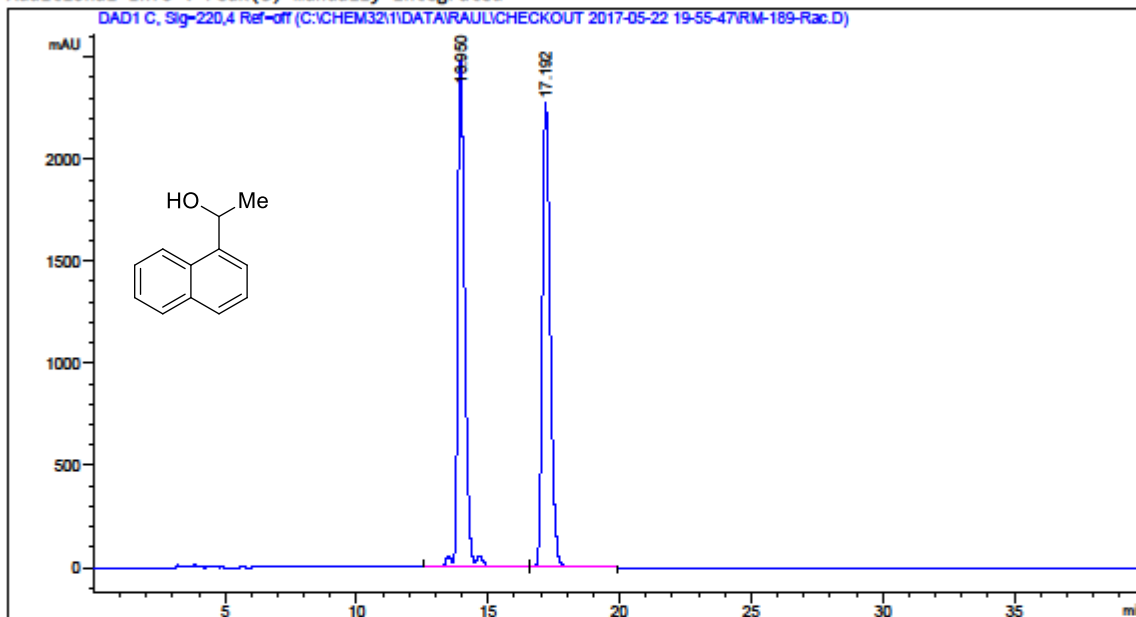
Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-05-29 17-38-16\RM-228-OH.D
Sample Name: RM-228-OH

```
=====================================================================
Acq. Operator   : SYSTEM                    Seq. Line :   3
Acq. Instrument : HPLC 1260                  Location :   38
Injection Date  : 5/29/2017 6:20:48 PM           Inj :   1
                                          Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-05-29 17-38-16\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 5/29/2017 5:38:16 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/17/2017 5:48:55 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
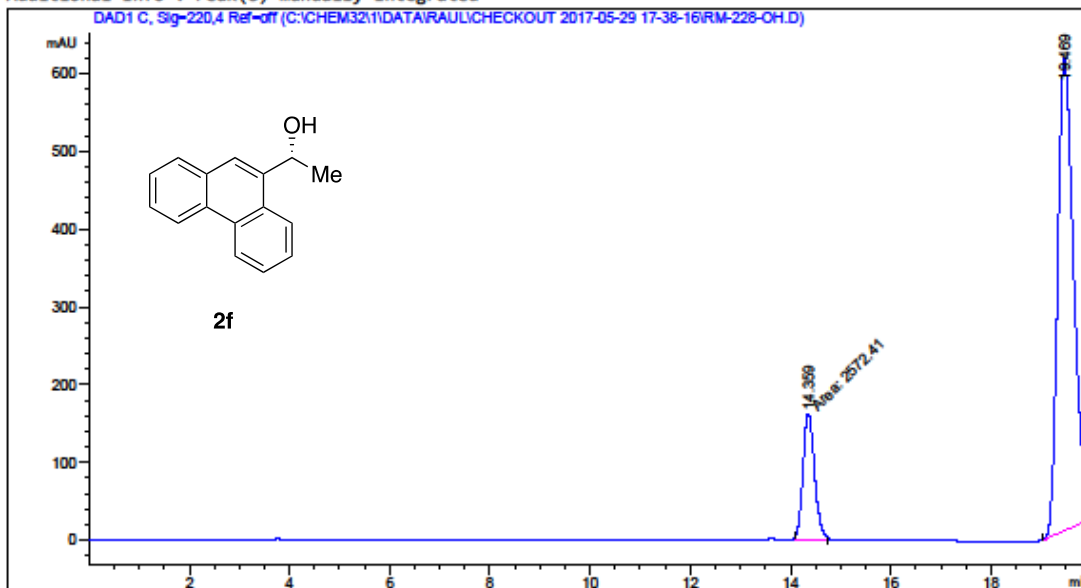


```
=====================================================================
                     Area Percent Report
=====================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
 #   [min]        [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
 1  14.359 MM    0.2659 2572.41187  161.25642  16.1864
 2  19.469 BBA   0.3376 1.33200e4   607.94171  83.8136

Totals :                 1.58924e4   769.19814


=====================================================================
```
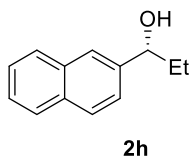
Chapter 2

Data File C:\CHEM32\1\DATA\JOSEMANUEL\CHECKOUT 2017-07-31 19-20-14\RM-228-Rac.D
Sample Name: RM-228-Rac

```
========================================================================
Acq. Operator    : SYSTEM                     Seq. Line :   2
Acq. Instrument  : HPLC 1260                   Location :   71
Injection Date   : 7/31/2017 7:46:25 PM             Inj :   1
                                           Inj Volume : 1.000 µl
Method           : C:\Chem32\1\Data\JoseManuel\checkout 2017-07-31 19-20-14\Chiral coloumn IB-
                   Raul 98-2.M (Sequence Method)
Last changed     : 7/31/2017 7:20:14 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
```
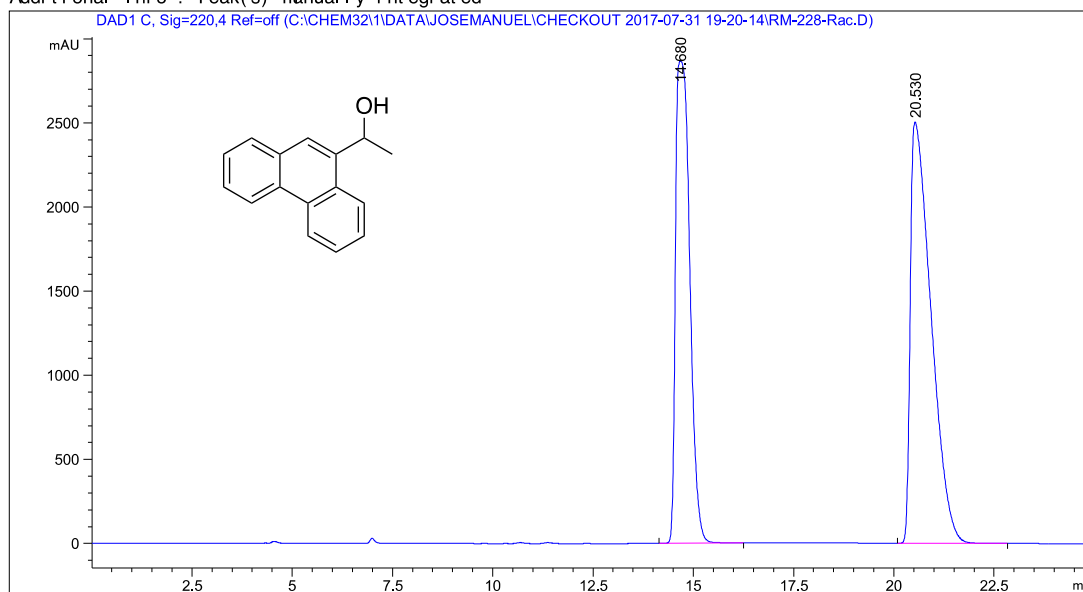

DAD1 C, Sig=220,4 Ref=off (C:\CHEM32\1\DATA\JOSEMANUEL\CHECKOUT 2017-07-31 19-20-14\RM-228-Rac.D)

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

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1  14.680 BB    0.3919 7.07513e4   2866.98315  44.0974
  2  20.530 BB    0.5518 8.96920e4   2504.26343  55.9026

Totals :                  1.60443e5   5371.24658


========================================================================
                     *** End of Report ***
```

91

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

2g
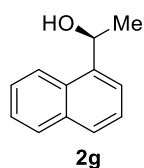
(*S*)-1-(naphthalen-1-yl)ethanol (2g). The targeted compound was prepared via the General Procedure using Pivalate **1g** (prepared in 98% ee). The crude material was purified by silica gel chromatography (hexanes/EtOAc 9/1) to give compound **2g** (25 mg, 73%) as a yellow oil. The enantiomeric excess was determined to be 87% ee (89% ee$_s$) by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 2% EtOH/Hexane, λ=220 nm); t_R(major)= 14.3 min, t_R(minor)= 18.0 min. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.13 (dq, *J* = 8.7, 1.0 Hz, 1H), 7.92 – 7.84 (m, 1H), 7.79 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.68 (dt, *J* = 7.1, 1.0 Hz, 1H), 7.58 – 7.43 (m, 3H), 5.68 (q, *J* = 6.5 Hz, 1H), 1.96 (s, 1H, OH), 1.68 (d, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.3, 133.8, 130.3, 128.9, 127.9, 126.0, 125.5, 125.5, 123.2, 122.0, 67.1, 24.3 ppm. The spectral data for this compound matches that reported in literature.[VIII]

Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-05-11 14-27-23\RM-189-2-OH.D
Sample Name: RM-189-2-OH

```
========================================================================
Acq. Operator   : SYSTEM                    Seq. Line :   2
Acq. Instrument : HPLC 1260                  Location :   71
Injection Date  : 5/11/2017 2:48:30 PM          Inj :   1
                                          Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-05-11 14-27-23\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 5/11/2017 2:27:24 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/17/2017 5:48:55 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
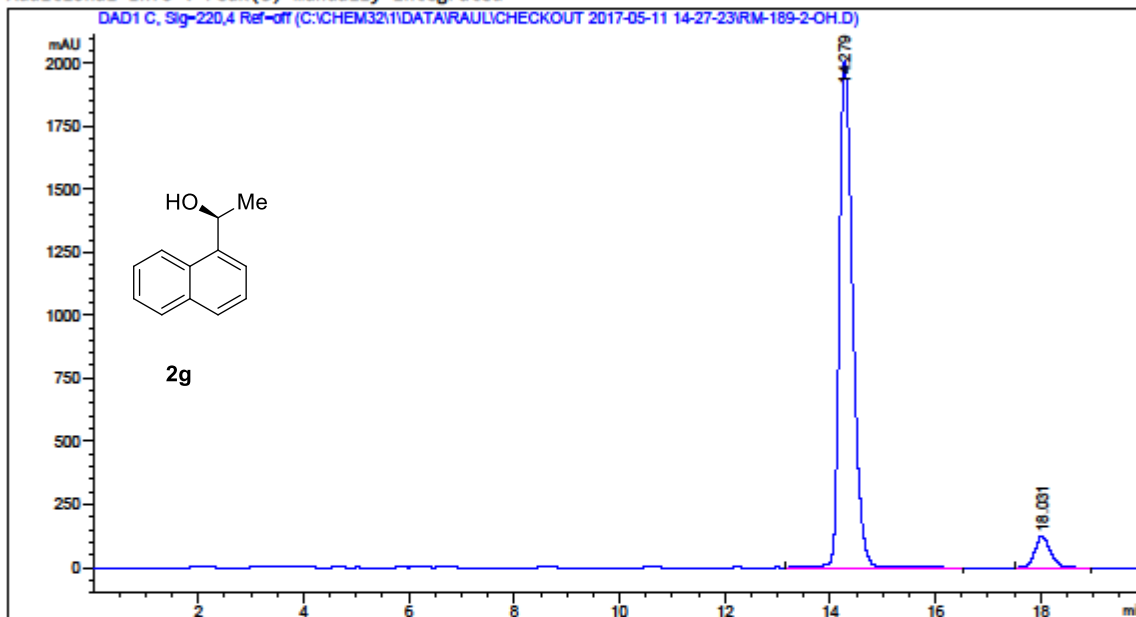


```
========================================================================
                    Area Percent Report
========================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
 #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1  14.279 VB R  0.2704 3.52513e4  2010.54358  93.4342
  2  18.031 BB    0.3042 2477.17773  124.46545   6.5658

Totals :                 3.77285e4  2135.00903
```

```
========================================================================
```
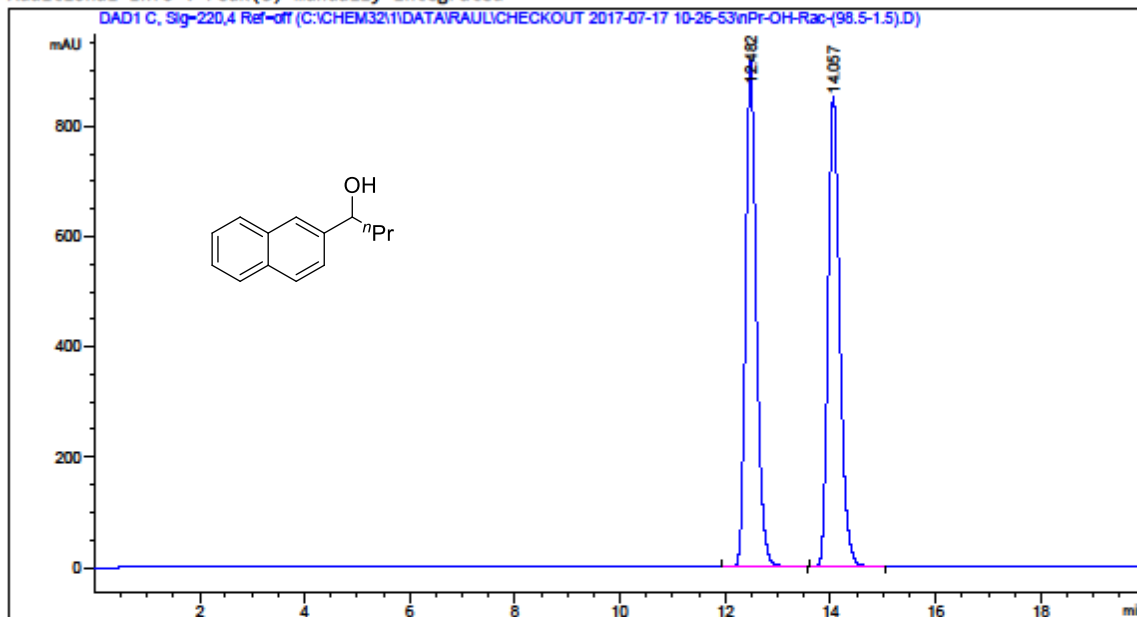
Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-05-22 19-55-47\RM-189-Rac.D
Sample Name: RM-189-Rac

```
=================================================================
Acq. Operator   : SYSTEM                    Seq. Line :  10
Acq. Instrument : HPLC 1260                  Location :  89
Injection Date  : 5/23/2017 2:05:09 AM           Inj :   1
                                          Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-05-22 19-55-47\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 5/22/2017 7:55:47 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/17/2017 5:48:55 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```



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

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
 #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  13.950 VV R  0.2865 4.73296e4  2483.45923  50.0385
   2  17.192 BB    0.3219 4.72567e4  2279.12158  49.9615

Totals :                  9.45862e4  4762.58081
```

```
=================================================================
```

HPLC 1260 7/17/2017 6:56:31 PM SYSTEM   Page   1 of 2

Chapter 2

2h

(*R*)-1-(naphthalen-2-yl)propan-1-ol (2h). The targeted compound was prepared via the General Procedure using Pivalate **1h** (prepared in 94% ee). The crude material was purified by silica gel chromatography (hexanes/EtOAc 1/1) to give compound **2h** (30 mg, 80%) as colourless oil. The enantiomeric excess was determined to be 84% ee (89% ee$_s$) by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 2% EtOH/Hexane, λ=220 nm); t_R(minor)= 11.6 min, t_R(major)= 12.9 min. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.91 – 7.76 (m, 4H), 7.48 (m, 3H), 4.78 (t, *J* = 6.6 Hz, 1H), 2.02 – 1.79 (m, 3H), 0.95 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, CDCl3) δ 141.9, 133.2, 133.0, 128.2, 127.9, 127.6, 126.1, 125.7, 124.7, 124.1, 76.1, 31.8, 10.1 ppm. The spectral data for this compound matches that reported in literature.[III]

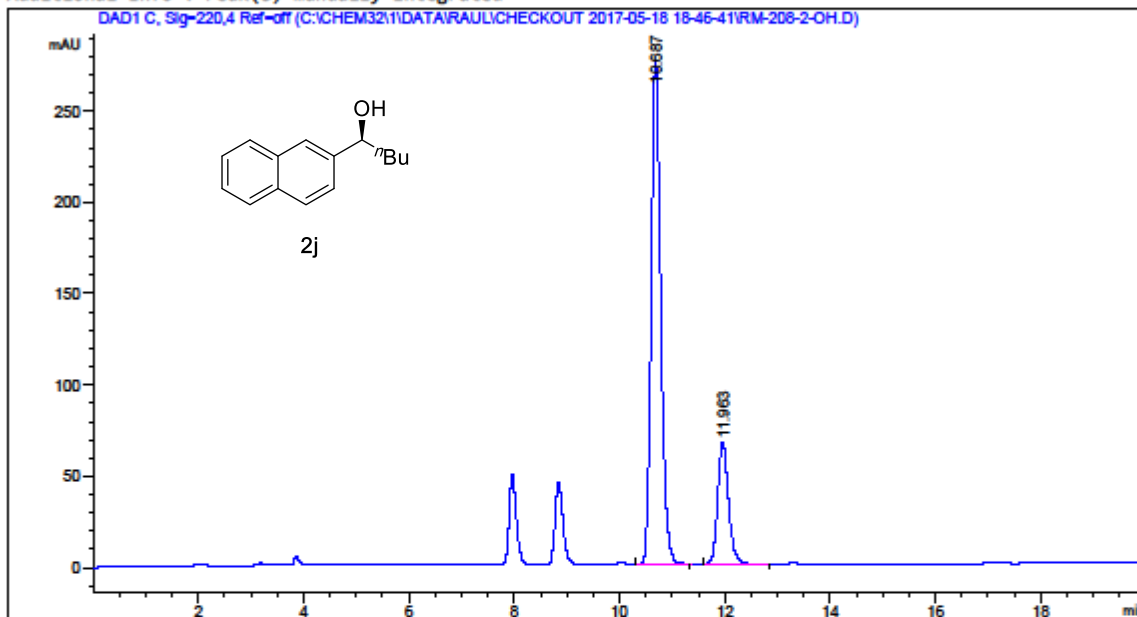Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-06-06 12-41-56\RM-241-OH-Pure.D
Sample Name: RM-241-OH-Pure

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Acq. Instrument : HPLC 1260                  Location :   7
Injection Date  : 6/6/2017 1:03:04 PM           Inj :   1
                                        Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-06-06 12-41-56\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 6/6/2017 12:41:56 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/17/2017 5:48:55 PM by SYSTEM
Additional Info : Peak(s) manually integrated
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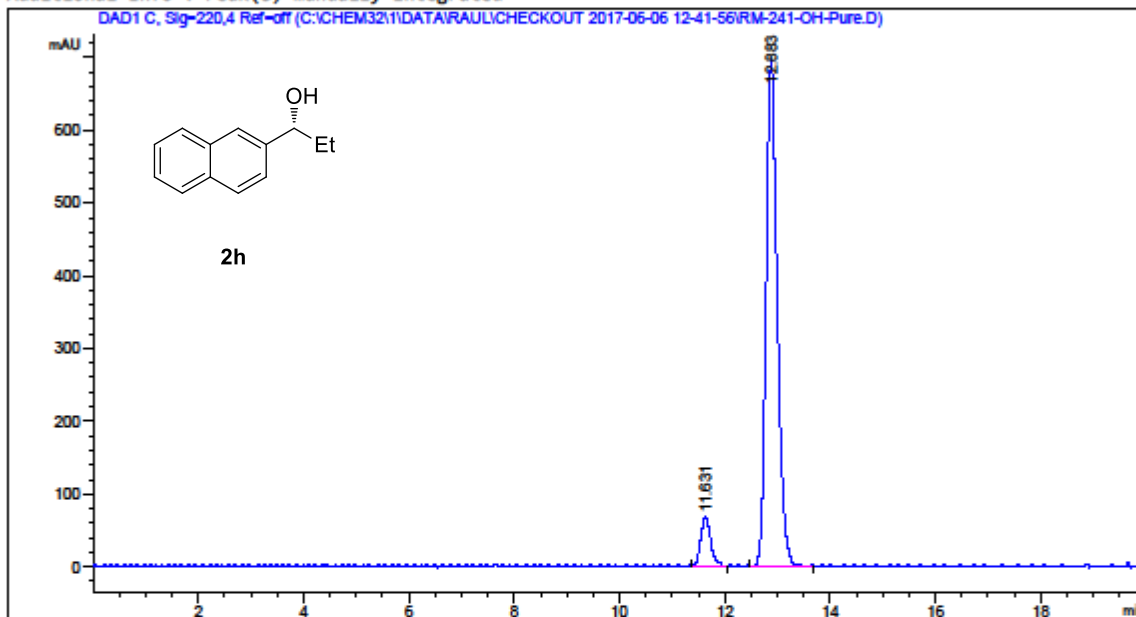


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========================================================================
                     Area Percent Report
========================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1  11.631 BV R  0.1827  916.10138   68.59631   8.1921
  2  12.883 BV R  0.2257 1.02666e4   696.09869  91.8079

Totals :                 1.11827e4   764.69500
```
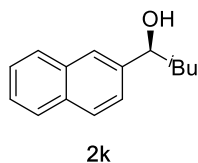
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========================================================================
```

Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-01 20-26-38\018-0901.D
Sample Name: RT-8

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Acq. Instrument : HPLC 1260                     Location :   18
Injection Date  : 7/2/2017 1:53:49 AM               Inj :   1
                                          Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-01 20-26-38\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 7/1/2017 8:26:38 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 9:40:12 AM by SYSTEM
Additional Info : Peak(s) manually integrated
```
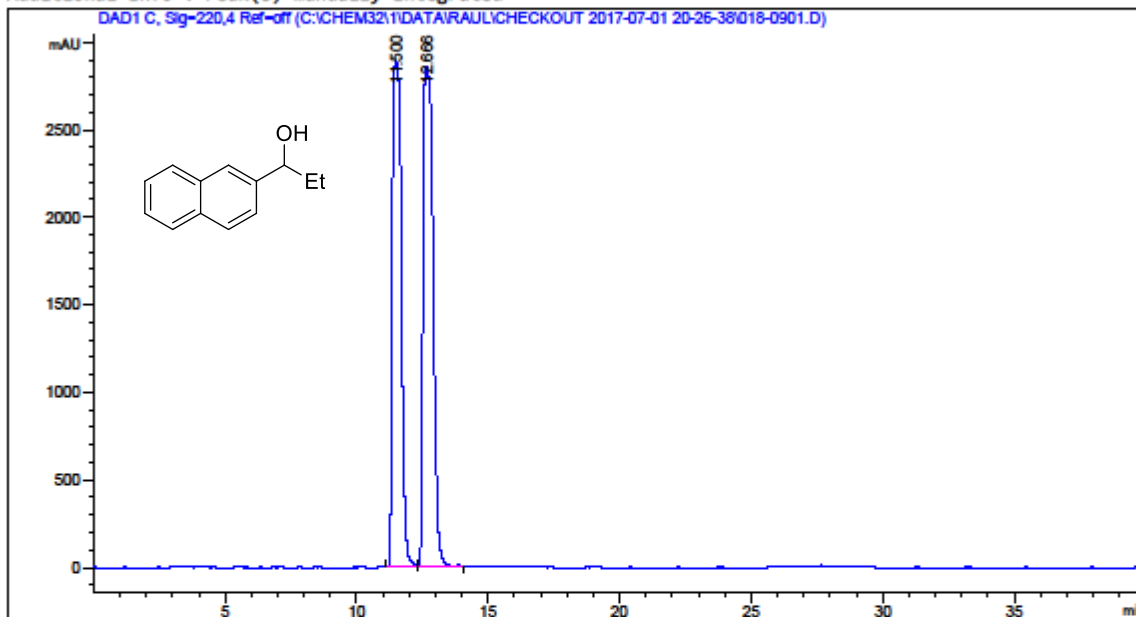


```
===================================================================
                    Area Percent Report
===================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height      Area
 #   [min]         [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
 1   11.500 BV    0.3769 6.77066e4  2894.52515   47.3185
 2   12.666 VV R  0.3613 7.53803e4  2861.42139   52.6815

Totals :                  1.43087e5  5755.94653
```

```
===================================================================
```

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

2i
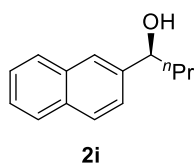
(S)-1-(naphthalen-2-yl)butan-1-ol (2i). The targeted compound was prepared via the General Procedure using Pivalate **1i** (prepared in 91% ee). The crude material was purified by silica gel chromatography (hexanes/EtOAc 9/1) to give compound **2i** (28 mg, 70%) as a white solid (85-87 ºC). The enantiomeric excess was determined to be 76% ee (83% ee$_s$) by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 1.5% EtOH/Hexane, λ=220 nm); t_R(major)= 12.4 min, t_R(minor)= 13.9 min. $[\alpha]_D^{24}$ = -32.2º (0.05, CHCl$_3$): ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90 – 7.73 (m, 4H), 7.53 – 7.42 (m, 3H), 4.92 – 4.81 (m, 1H), 1.97 – 1.74 (m, 3H), 1.51 – 1.29 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 142.3, 133.3, 133.0, 128.2, 127.9, 127.7, 126.1, 125.8, 124.6, 124.1, 74.5, 41.1, 19.1, 14.0 ppm.

Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-19 16-36-01\RM-300-1-OH(98.5-1.5).D
Sample Name: RM-300-1-OH(98.5-1.5)

```
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Acq. Operator   : SYSTEM                    Seq. Line :   2
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Injection Date  : 7/19/2017 4:58:02 PM            Inj :   1
                                          Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-19 16-36-01\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 7/19/2017 4:36:01 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
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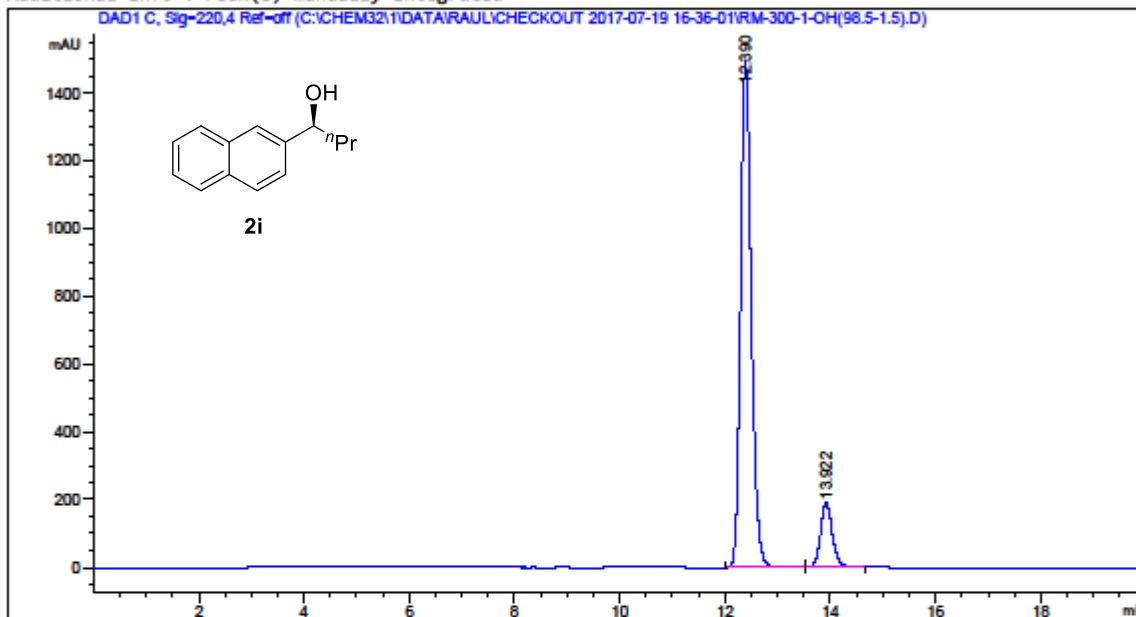


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================================================================
                     Area Percent Report
================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
 #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1  12.390 BB   0.2193 2.11825e4  1495.21533  87.7598
  2  13.922 BB   0.2407 2954.42334  188.70074  12.2402

Totals :                 2.41370e4  1683.91608
```
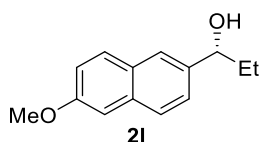
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HPLC 1260 7/27/2017 4:16:22 PM SYSTEM   Page   1 of 2

Stereospecific Borylation of Benzyl C(sp^3)–O Bonds

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-17 10-26-53\nPr-OH-Rac-(98.5-1.5).D
Sample Name: nPr-OH-Rac-(98.5-1.5)

```
==================================================================
Acq. Operator   : SYSTEM                    Seq. Line :   2
Acq. Instrument : HPLC 1260                  Location :  81
Injection Date  : 7/17/2017 10:48:27 AM         Inj :   1
                                         Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-17 10-26-53\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 7/17/2017 10:27:04 AM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 9:40:12 AM by SYSTEM
Additional Info : Peak(s) manually integrated
```



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

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area        Height     Area
  #   [min]        [min]   [mAU*s]       [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1  12.482 BB   0.2192 1.31570e4    917.97778   50.0446
  2  14.057 BB   0.2361 1.31335e4    850.56329   49.9554

Totals :                 2.62905e4  1768.54108
```
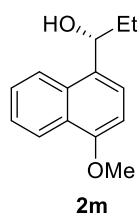
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HPLC 1260 7/21/2017 12:36:36 PM SYSTEM   Page   1 of 2

100

Chapter 2

2j
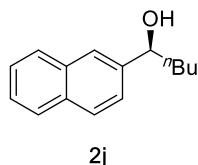
(*S*)-1-(naphthalen-2-yl)pentan-1-ol (2j). The targeted compound was prepared via the General Procedure using Pivalate **1j** (prepared in 81% ee). The crude material was purified by silica gel chromatography (hexanes/EtOAc 9/1) to give compound **2j** (26 mg, 61%) as a white solid. The enantiomeric excess was determined to be 58% ee (72% ee$_s$) by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 2% EtOH/Hexane, λ=220 nm); t_R(major)= 10.7 min, t_R(minor)= 12.0 min. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.89 – 7.74 (m, 4H), 7.54 – 7.44 (m, 3H), 4.92 – 4.77 (m, 1H), 1.98 – 1.76 (m, 3H), 1.47 – 1.23 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 142.3, 133.3, 133.0, 128.2, 127.9, 127.7, 126.0, 125.7, 124.6, 124.1, 74.8, 38.7, 28.0, 22.6, 14.0 ppm. The spectral data for this compound matches that reported in literature.[V]

Stereospecific Borylation of Benzyl C(sp³)–O Bonds
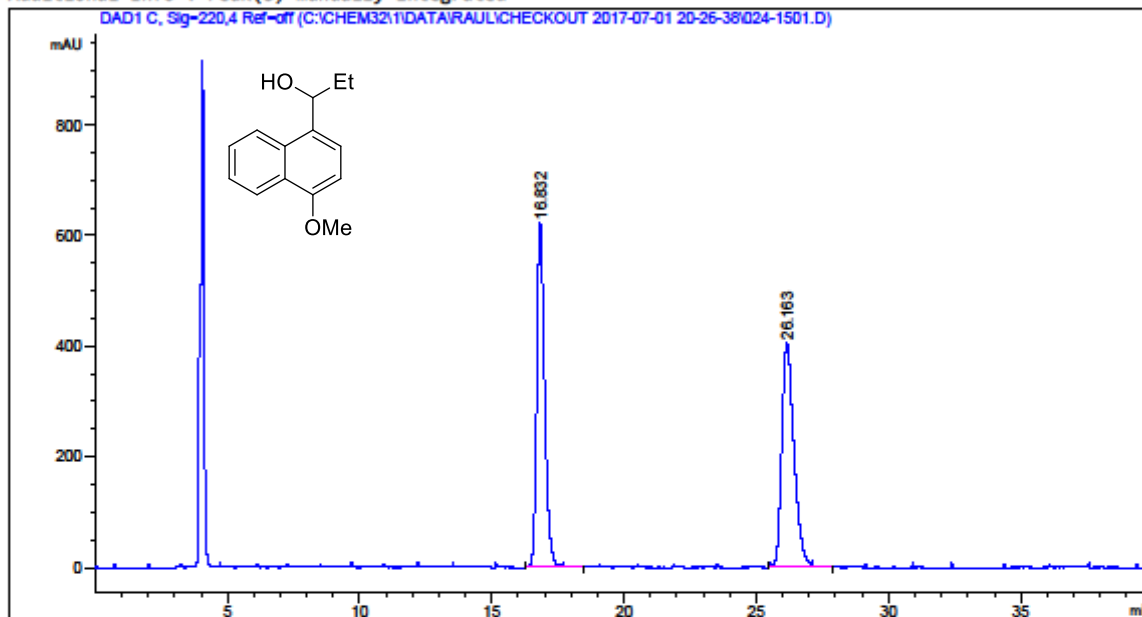
Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-05-18 18-46-41\RM-208-2-OH.D
Sample Name: RM-208-2-OH

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==================================================================
Acq. Operator   : SYSTEM                    Seq. Line :   1
Acq. Instrument : HPLC 1260                  Location :   71
Injection Date  : 5/18/2017 6:47:35 PM           Inj :   1
                                         Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-05-18 18-46-41\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 5/18/2017 6:46:41 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/17/2017 5:48:55 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```



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

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1  10.687 BB   0.1932 3481.52026   275.97122  79.0434
  2  11.963 BB   0.2148  923.04565    66.15916  20.9566

Totals :                 4404.56592  342.13038


==================================================================
```

Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-05-22 19-55-47\RM-208-Rac.D
Sample Name: RM-208-Rac

```
==================================================================
Acq. Operator   : SYSTEM                    Seq. Line :   4
Acq. Instrument : HPLC 1260                  Location :   83
Injection Date  : 5/22/2017 9:59:55 PM           Inj :   1
                                      Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-05-22 19-55-47\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 5/22/2017 7:55:47 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/17/2017 5:48:55 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
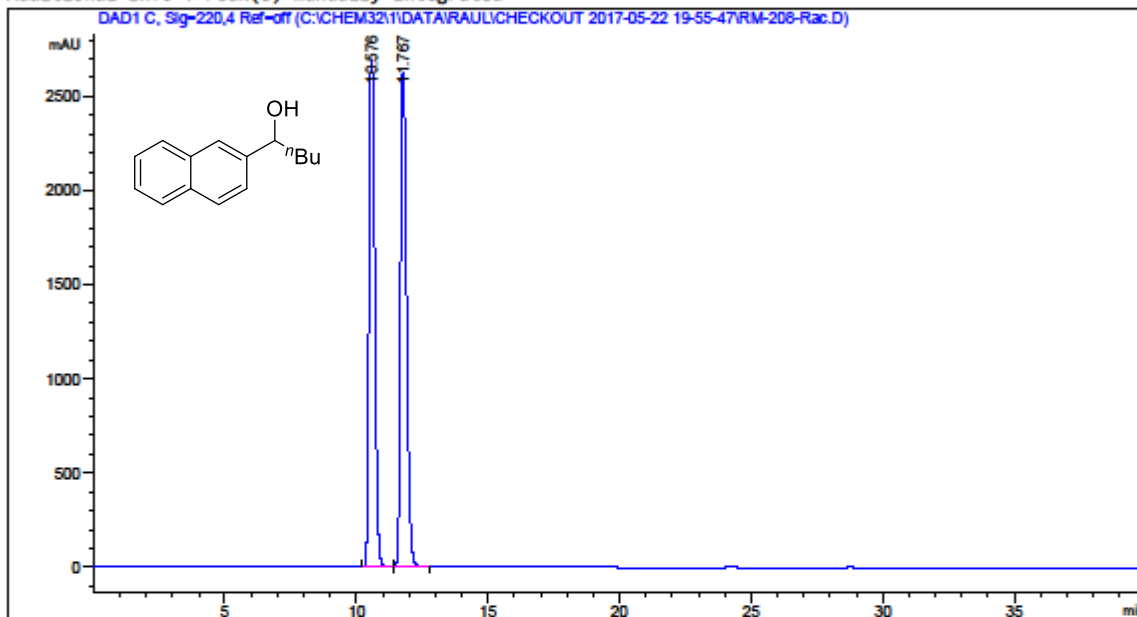


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==================================================================
                     Area Percent Report
==================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1  10.576 BB   0.2424  4.10936e4  2688.10132  48.6289
  2  11.767 BB   0.2594  4.34108e4  2618.96216  51.3711

Totals :                 8.45044e4  5307.06348
```

```
==================================================================
```

HPLC 1260 7/17/2017 6:57:37 PM SYSTEM   Page   1 of 2

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

2k

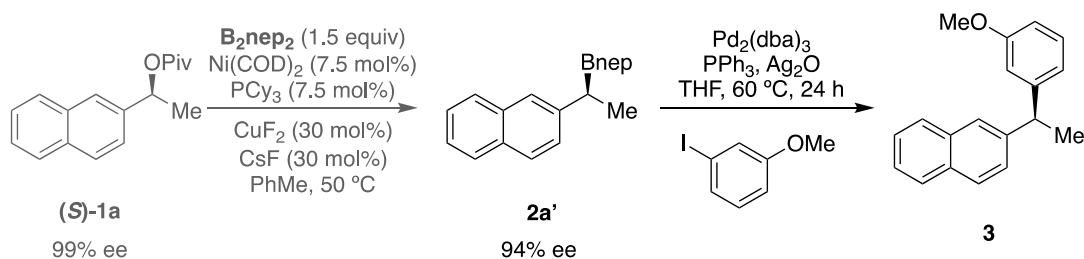**(*S*)-3-methyl-1-(naphthalen-2-yl)butan-1-ol (2k)**. The targeted compound was prepared via the General Procedure using Pivalate **1k** (prepared in 92% ee). The crude material was purified by silica gel chromatography (hexanes/EtOAc 1/1) to give compound **2k** (22 mg, 51%) as a white solid (m.p 84-86 ºC). The enantiomeric excess was determined to be 82% ee (89% ee$_s$) by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 2% EtOH/Hexane, λ=220 nm); t_R(major)= 10.1 min, t_R(minor)= 10.8 min. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90 – 7.76 (m, 4H), 7.56 – 7.42 (m, 3H), 4.93 (t, *J* = 6.4 Hz, 1H), 1.89 – 1.70 (m, 3H), 1.66 – 1.60 (m, 1H), 0.98 (dd, *J* = 6.6, 4.3 Hz, 6H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 142.6, 133.3, 133.0, 128.3, 127.9, 127.7, 126.1, 125.8, 124.5, 124.1, 73.0, 48.3, 24.9, 23.1, 22.3 ppm. The spectral data for this compound matches that reported in literature.[VII]

Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-05-18 18-46-41\RM-209-2-OH.D
Sample Name: RM-209-2-OH

```
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Acq. Operator   : SYSTEM                      Seq. Line :   2
Acq. Instrument : HPLC 1260                    Location :   72
Injection Date  : 5/18/2017 7:08:26 PM             Inj :   1
                                          Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-05-18 18-46-41\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 5/18/2017 6:46:41 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/17/2017 5:48:55 PM by SYSTEM
Additional Info : Peak(s) manually integrated
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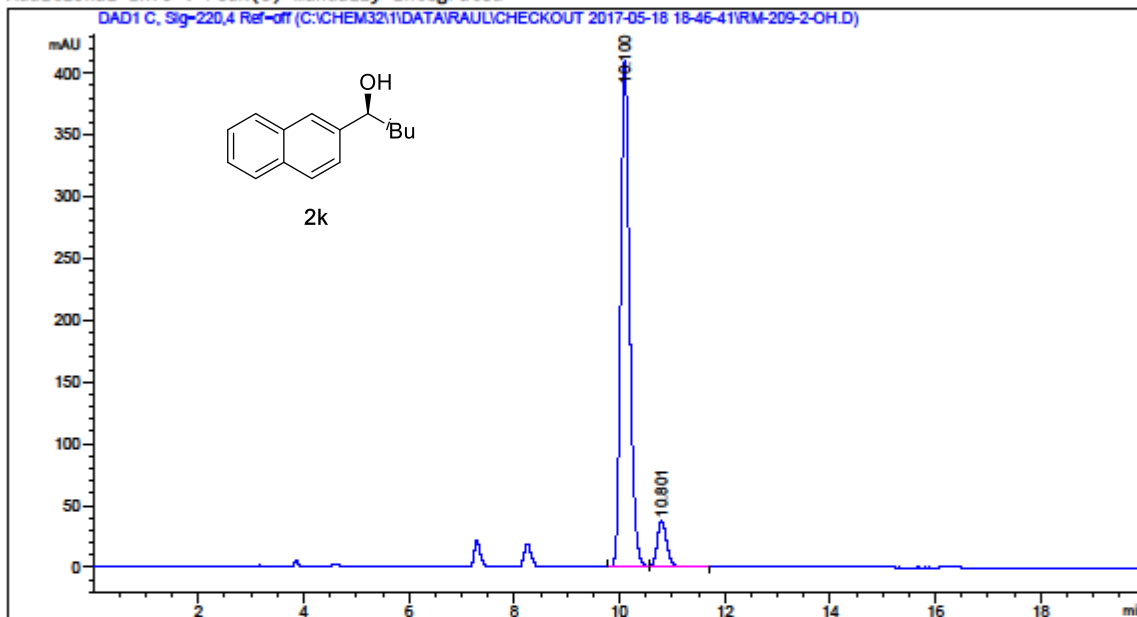


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==================================================================
                      Area Percent Report
==================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area        Height     Area
 #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
 1   10.100 BV   0.1790  4818.59717  410.39731  90.9179
 2   10.801 VB   0.1957   481.34573   37.51536   9.0821

Totals :                  5299.94290  447.91267
```

```
==================================================================
```

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-05-22 19-55-47\RM-209-Rac.D
Sample Name: RM-209-Rac

```
==================================================================
Acq. Operator   : SYSTEM                  Seq. Line :   6
Acq. Instrument : HPLC 1260                Location :   85
Injection Date  : 5/22/2017 11:21:38 PM        Inj :   1
                                     Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-05-22 19-55-47\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 5/22/2017 7:55:47 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/17/2017 5:48:55 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
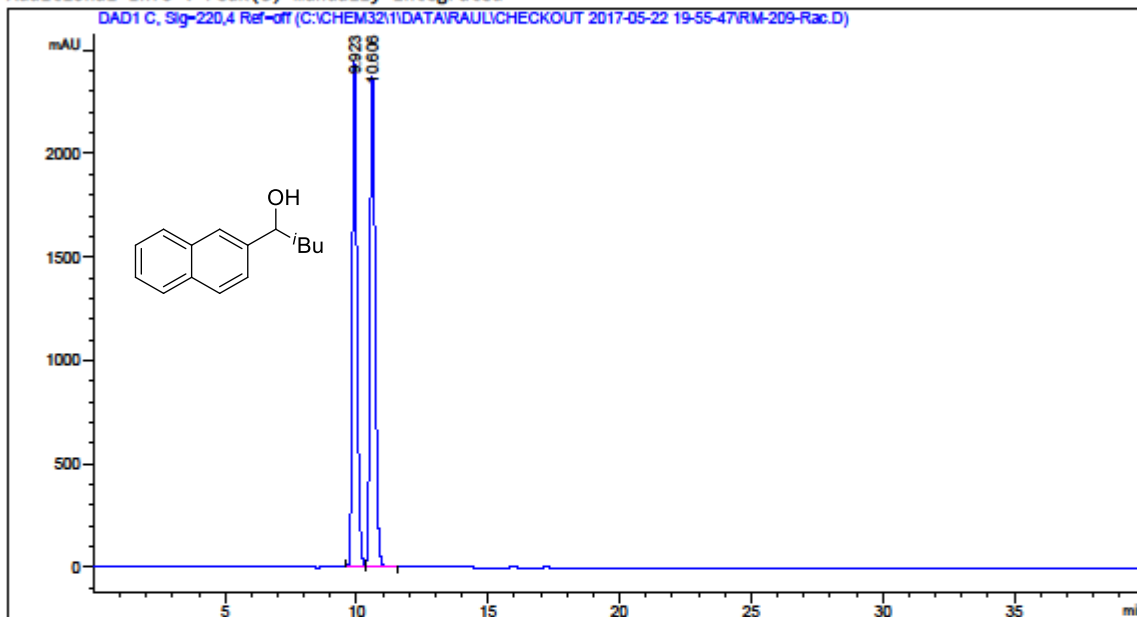
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==================================================================
                    Area Percent Report
==================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   9.923 BV    0.1993 3.13576e4   2450.07251  49.4276
  2  10.606 VB    0.2102 3.20839e4   2365.76758  50.5724

Totals :                  6.34415e4   4815.84009
```

```
==================================================================
```

HPLC 1260 7/17/2017 6:58:10 PM SYSTEM   Page   1 of 2

Chapter 2

2l

(*R*)-1-(6-methoxynaphthalen-2-yl)propan-1-ol (2l). The targeted compound was prepared via the General Procedure using Pivalate **1l** (prepared in 85% ee). The crude material was purified by silica gel chromatography (hexanes/EtOAc 1/1) to give compound **2l** (29.4 mg, 55%) as colourless oil. The enantiomeric excess was determined to be 69% ee (81% ee$_s$) by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 2% EtOH/Hexane, λ=220 nm); t_R(minor)= 14.3 min, t_R(major)= 19.4 min. ^{1}H NMR (500 MHz, CDCl3) δ 7.77 – 7.66 (m, 3H), 7.45 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.20 – 7.11 (m, 2H), 4.74 (t, *J* = 6.6 Hz, 1H), 3.92 (s, 3H), 1.96 – 1.77 (m, 3H), 0.94 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, CDCl3) δ 157.6, 139.7, 134.1, 129.4, 128.7, 127.1, 124.7, 124.6, 118.9, 105.7, 76.2, 55.6, 31.7, 10.2 ppm. The spectral data for this compound matches that reported in literature.[III]

UNIVERSITAT ROVIRA I VIRGILI
Functionalization of Strong Sigma Bonds by Nickel and Tungsten Catalysis
Raúl Martín Montero

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-05-29 18-42-53\RM-231-OH.D
Sample Name: RM-231-OH

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Acq. Operator   : SYSTEM                    Seq. Line :   1
Acq. Instrument : HPLC 1260                  Location :   38
Injection Date  : 5/29/2017 6:43:43 PM            Inj :   1
                                       Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-05-29 18-42-53\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 5/29/2017 6:42:53 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/17/2017 5:48:55 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
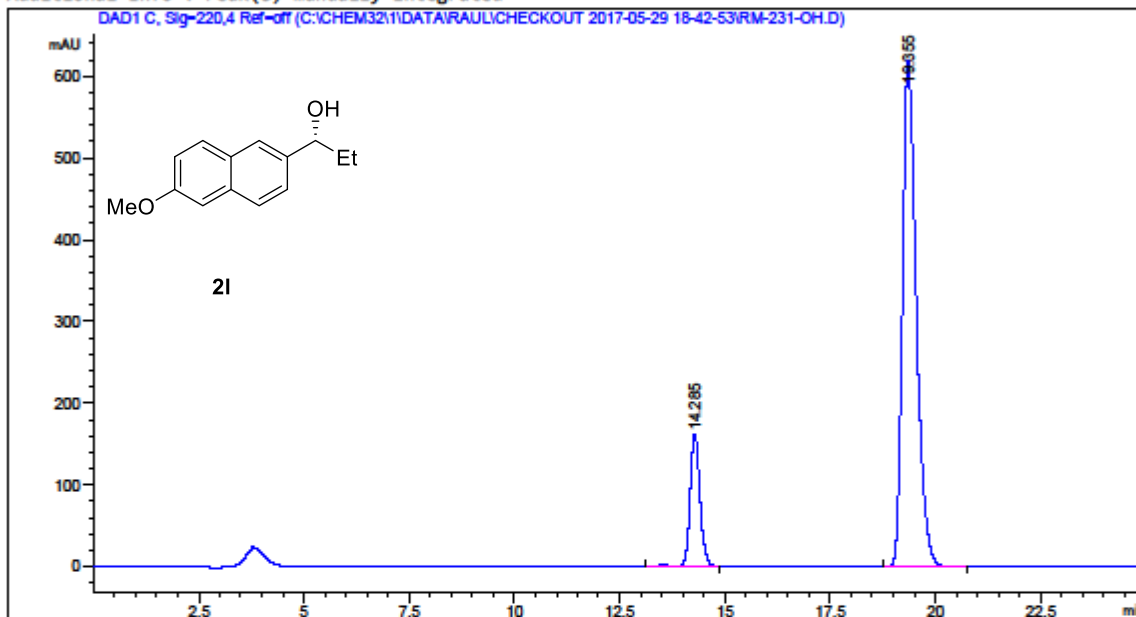


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================================================================
                    Area Percent Report
================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
 #   [min]        [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1  14.285 VB R  0.2456 2635.91138  161.51656  15.7872
  2  19.355 BB    0.3448 1.40606e4   619.52942  84.2128

Totals :                 1.66966e4   781.04597
```

==

Chapter 2

```
Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-01 20-26-38\019-1001.D
Sample Name: RT-9
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Acq. Operator   : SYSTEM                    Seq. Line :  10
Acq. Instrument : HPLC 1260                  Location :  19
Injection Date  : 7/2/2017 2:34:41 AM            Inj :   1
                                          Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-01 20-26-38\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 7/1/2017 8:26:38 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 9:40:12 AM by SYSTEM
Additional Info : Peak(s) manually integrated
```



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

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

```
Signal 1: DAD1 C, Sig=220,4 Ref=off
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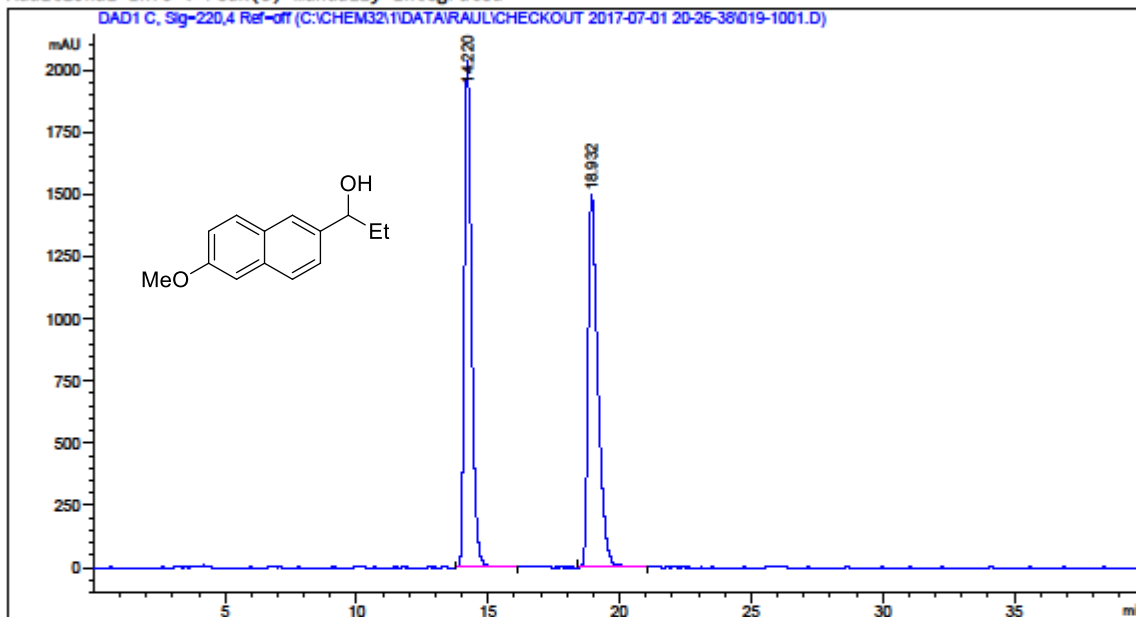
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Peak RetTime Type  Width     Area       Height     Area
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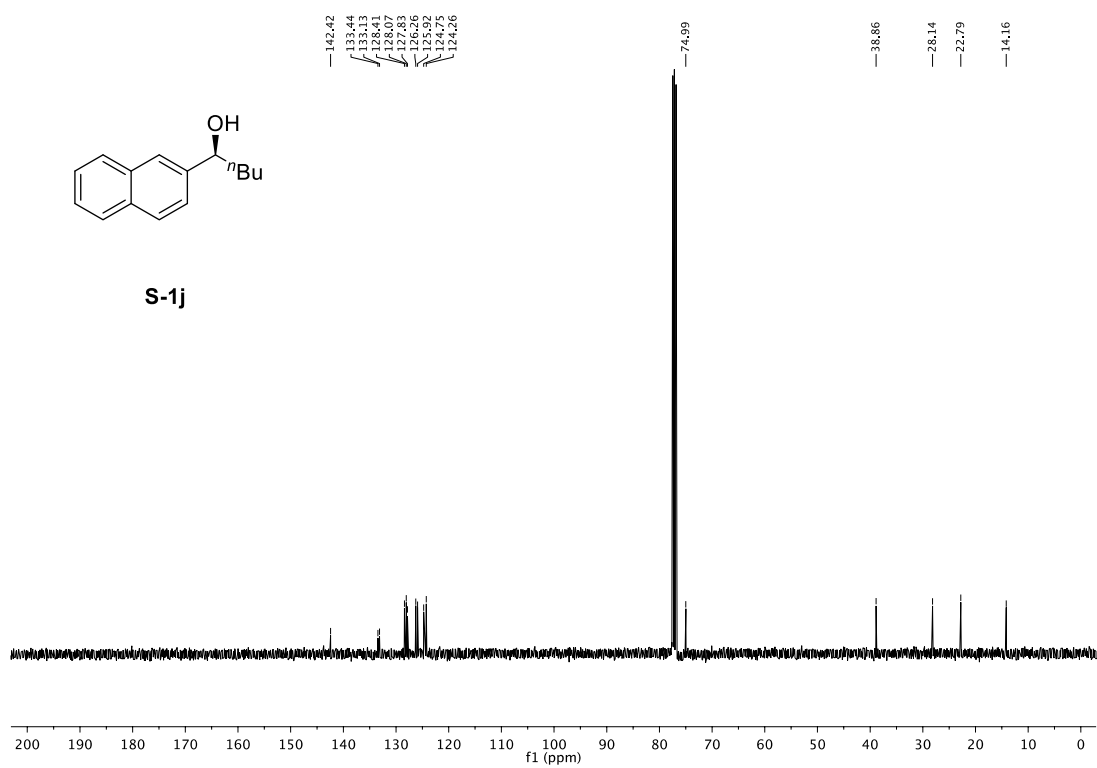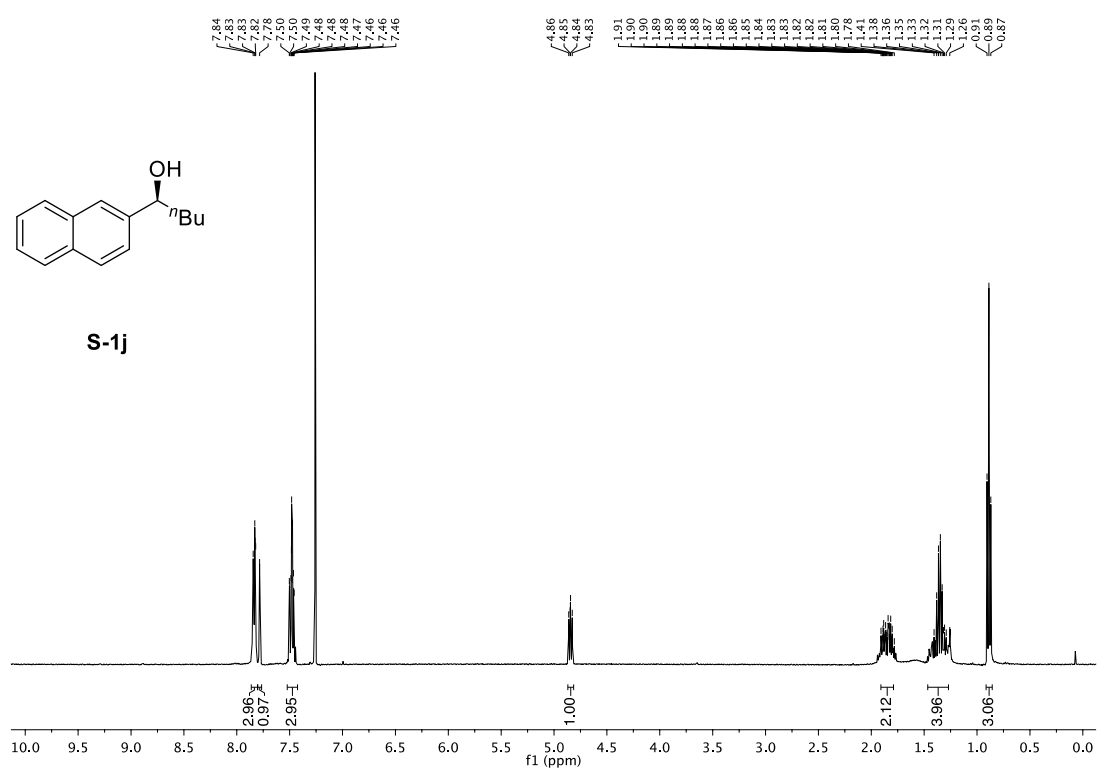
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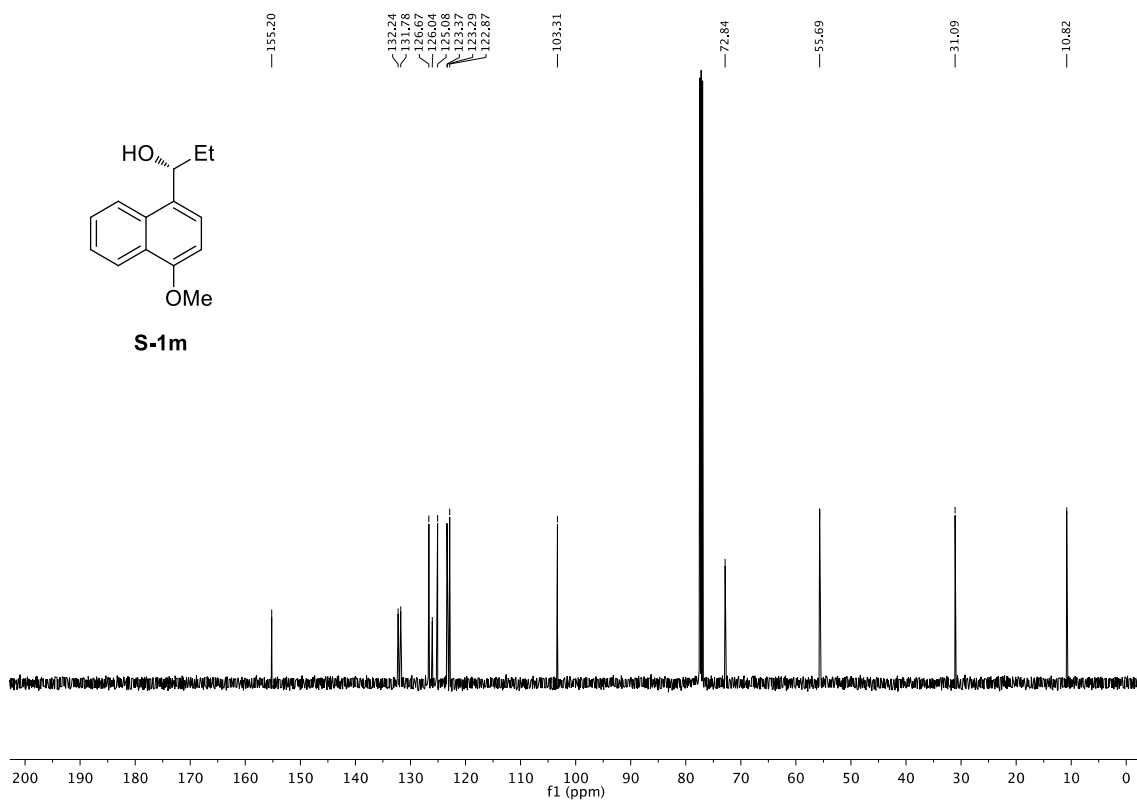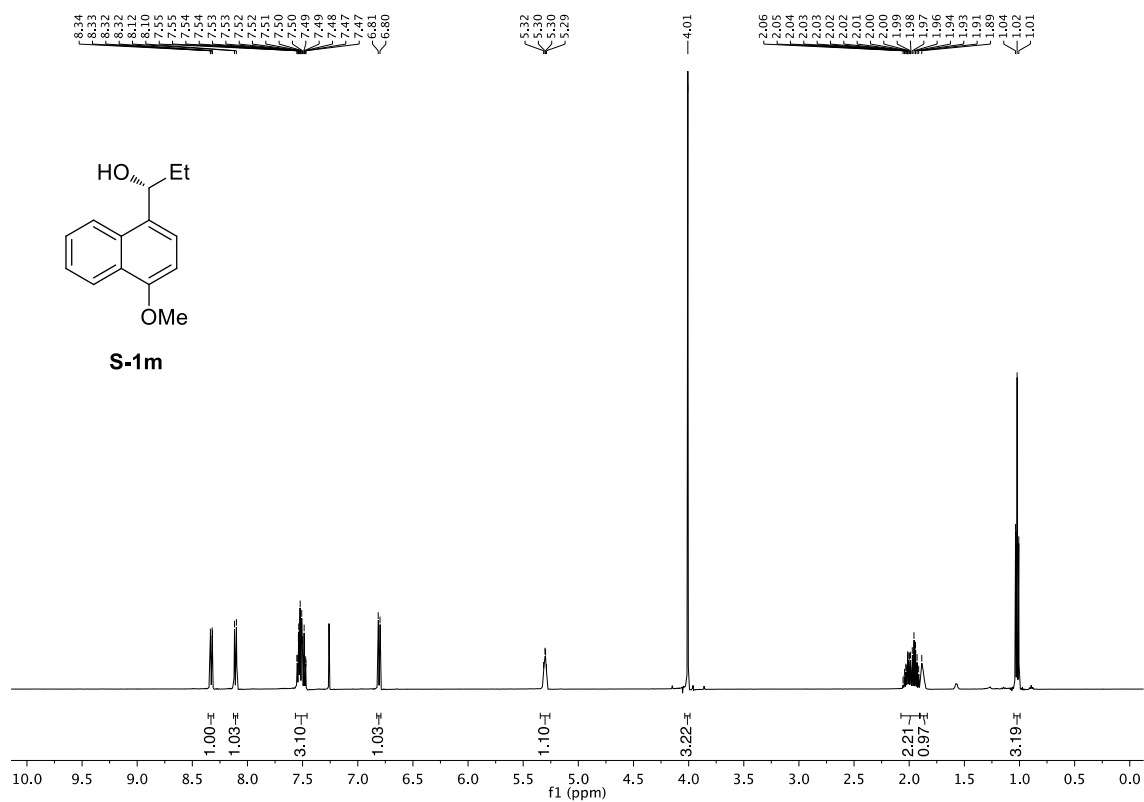*Stereospecific Borylation of Benzyl C(sp³)–O Bonds*

2m

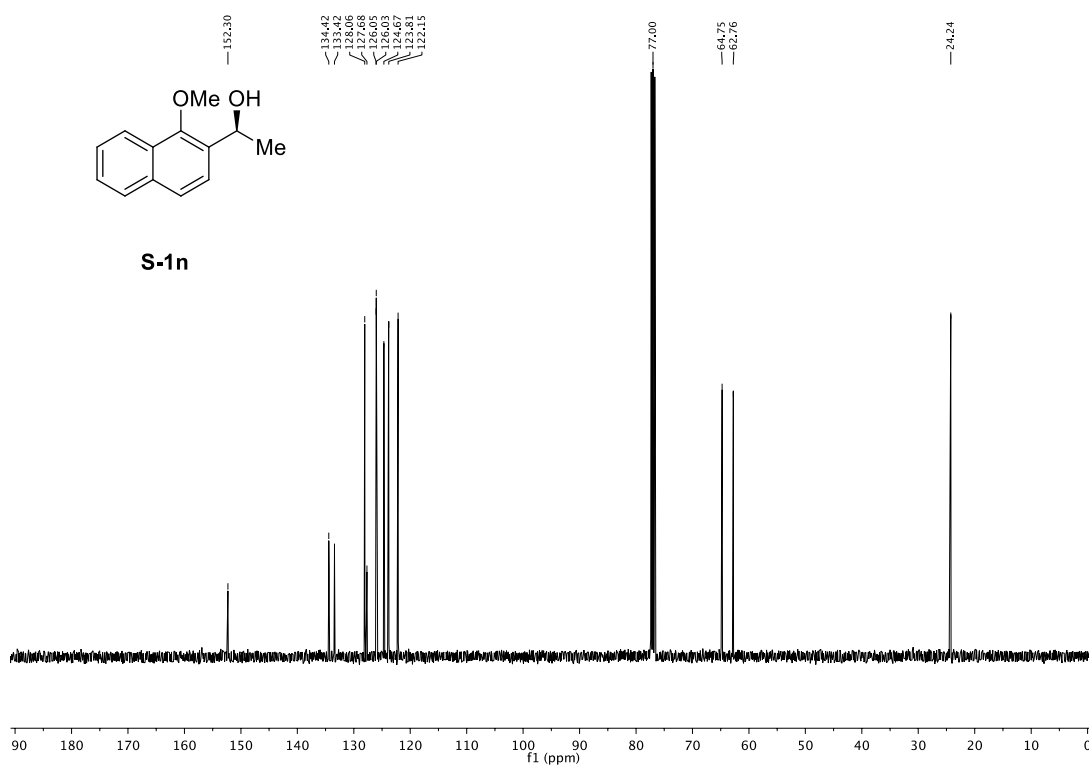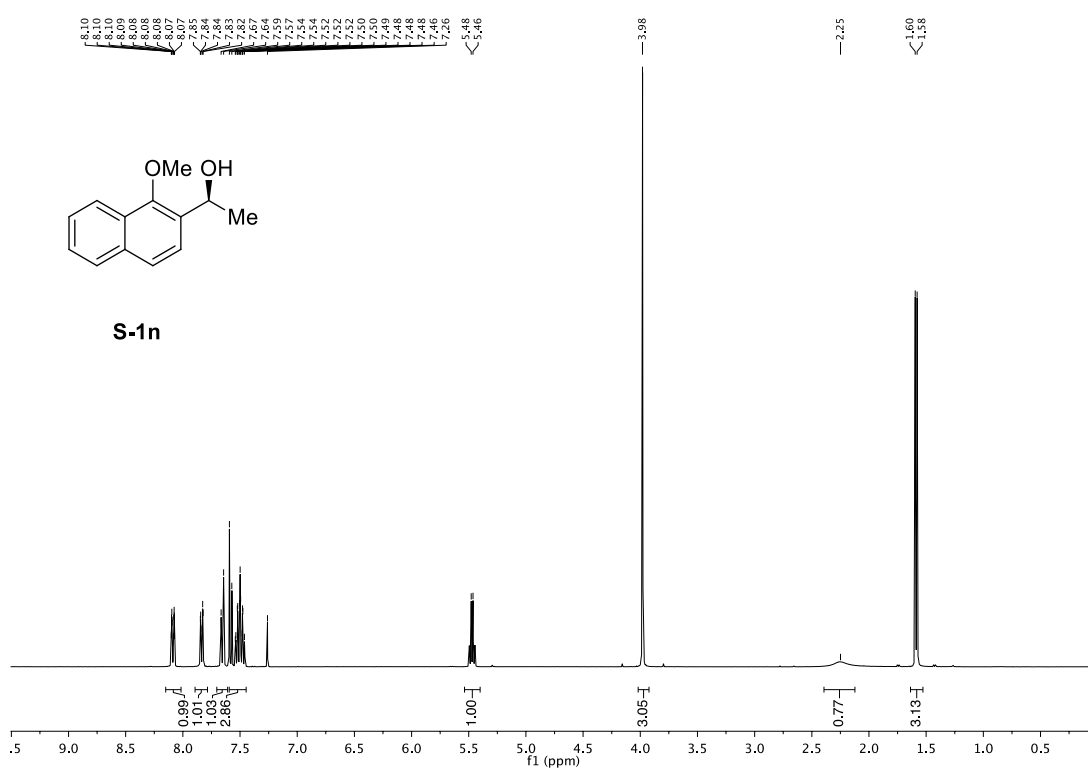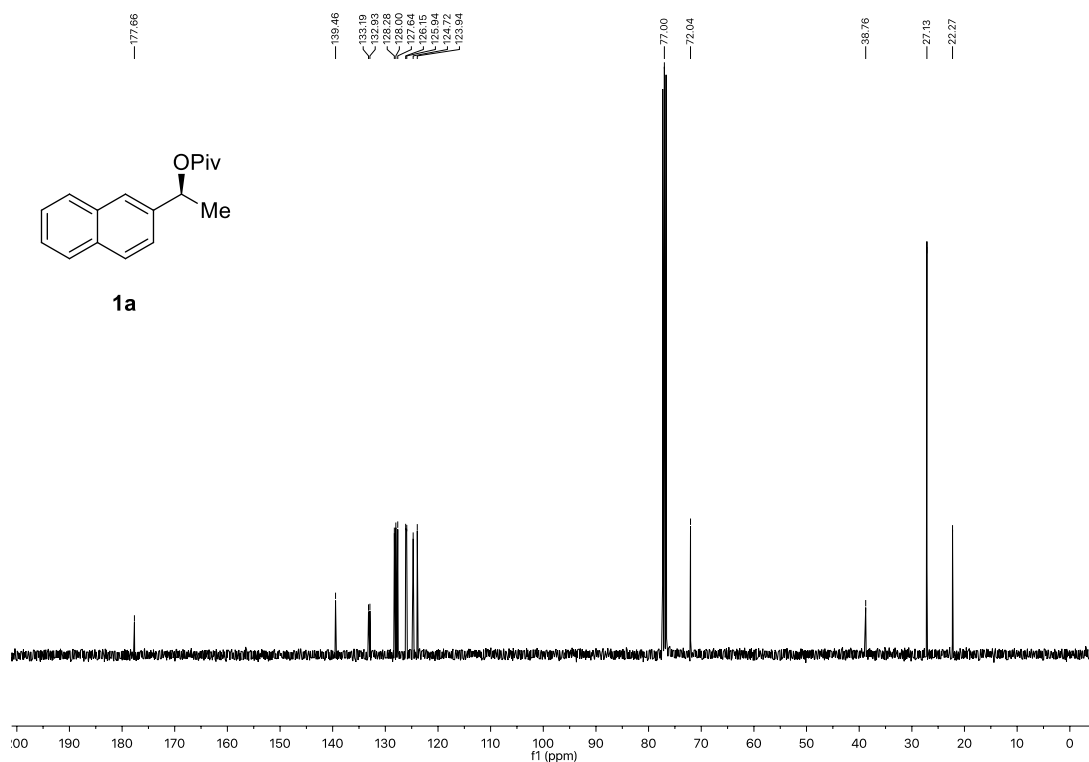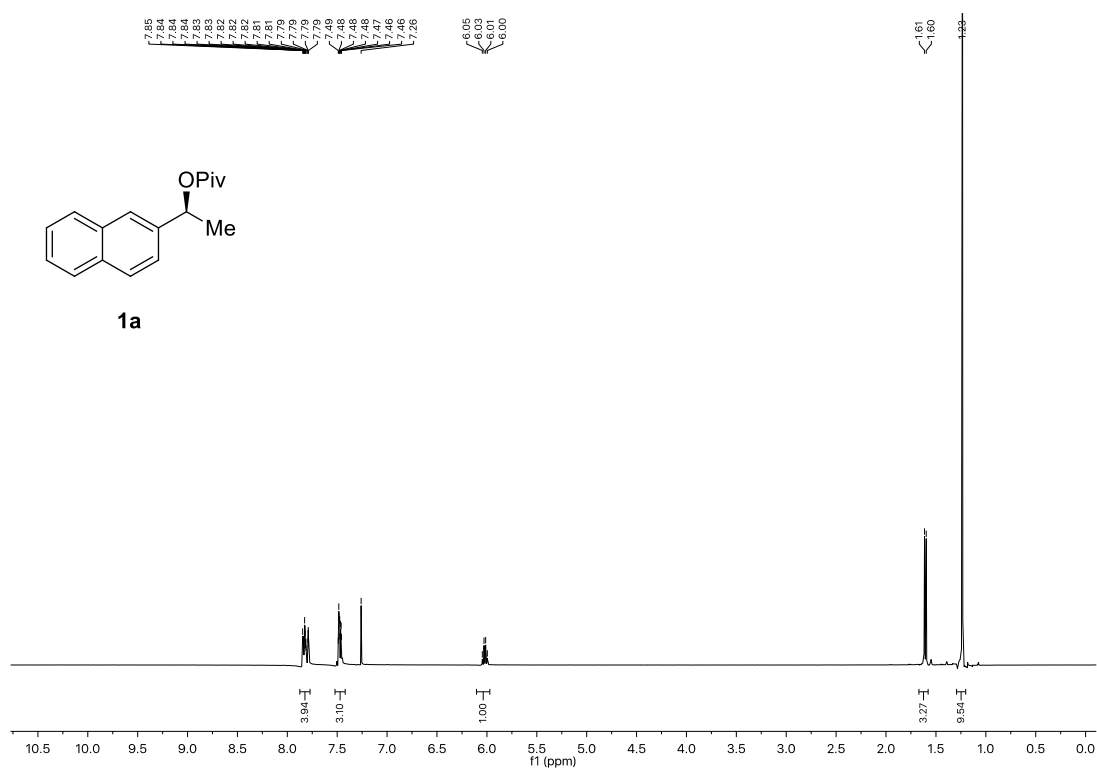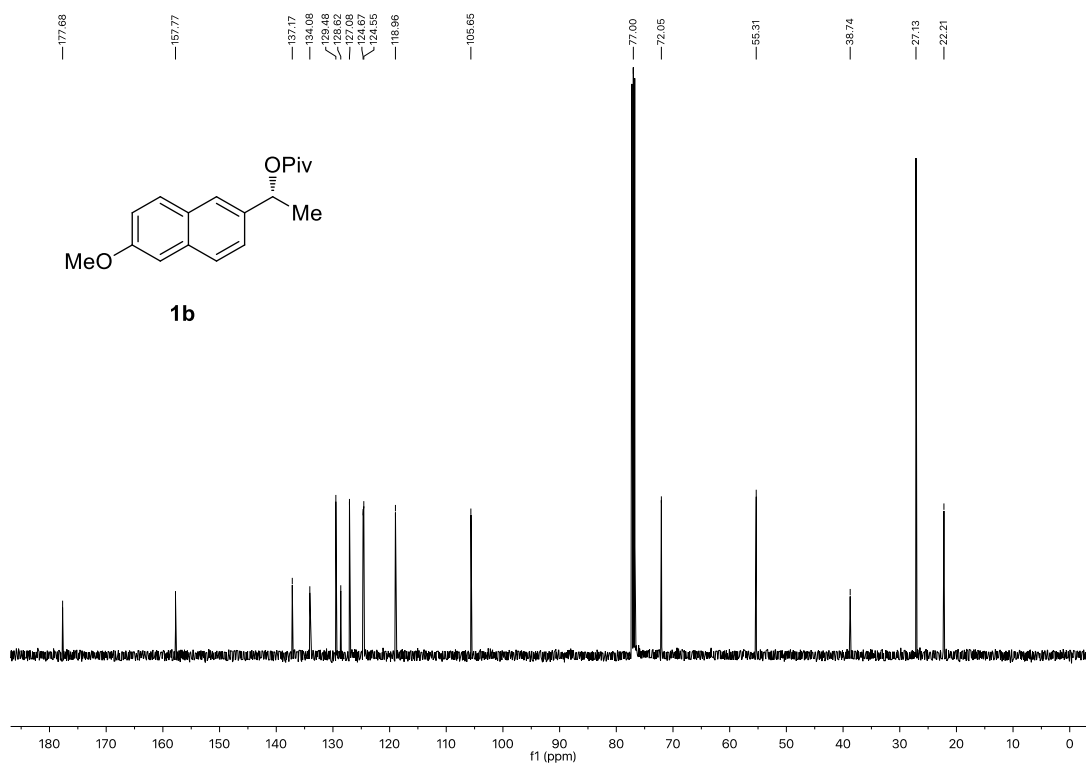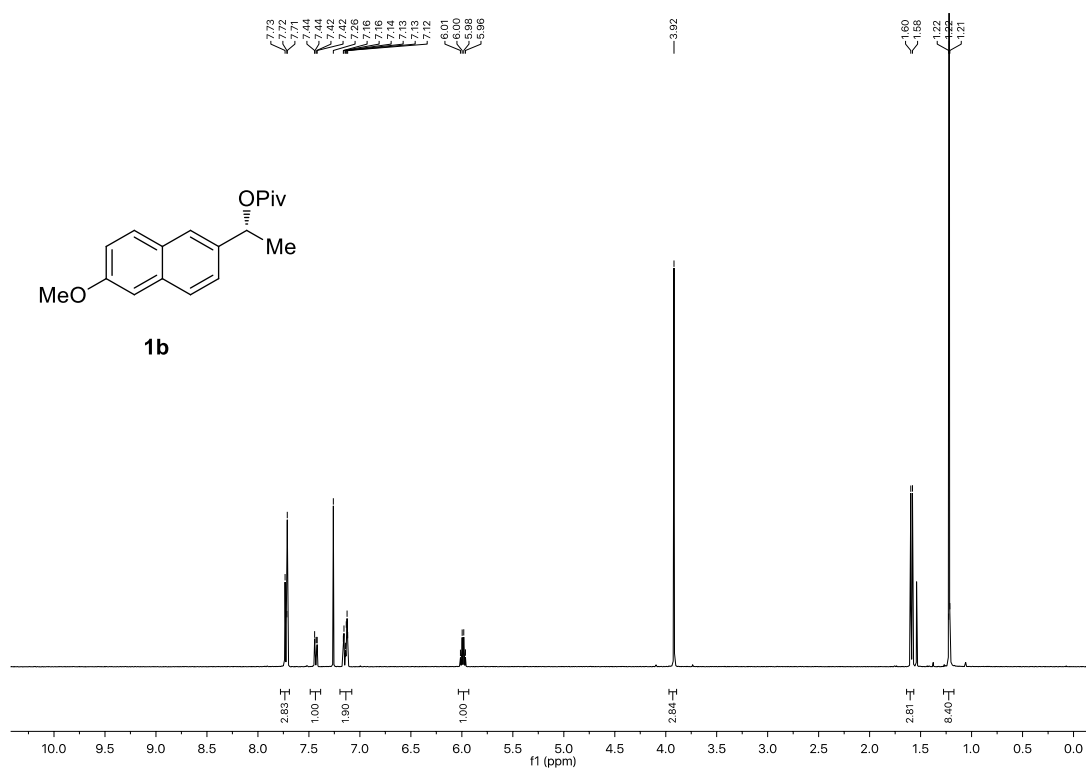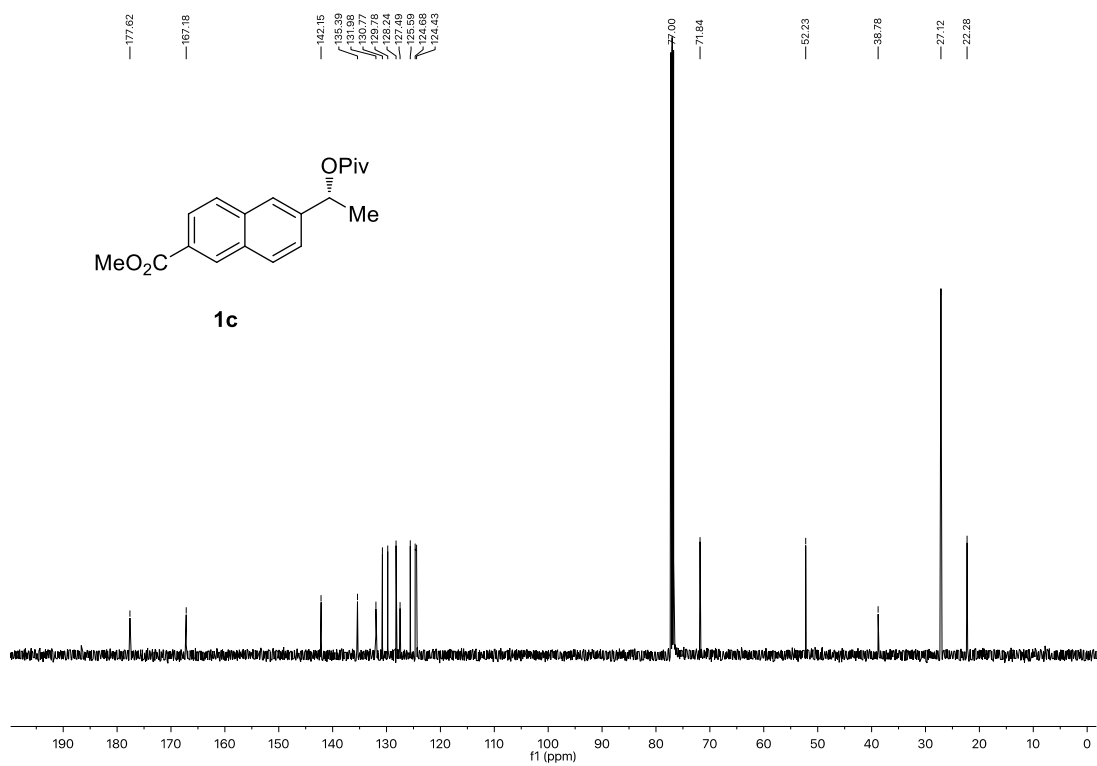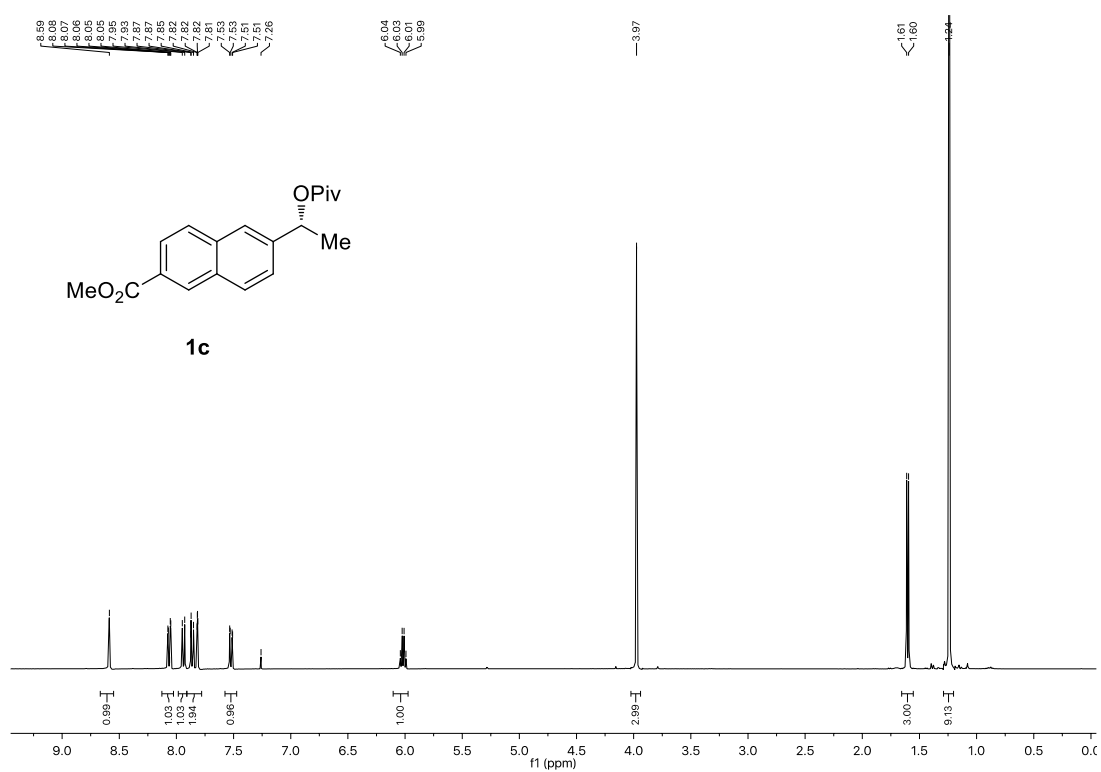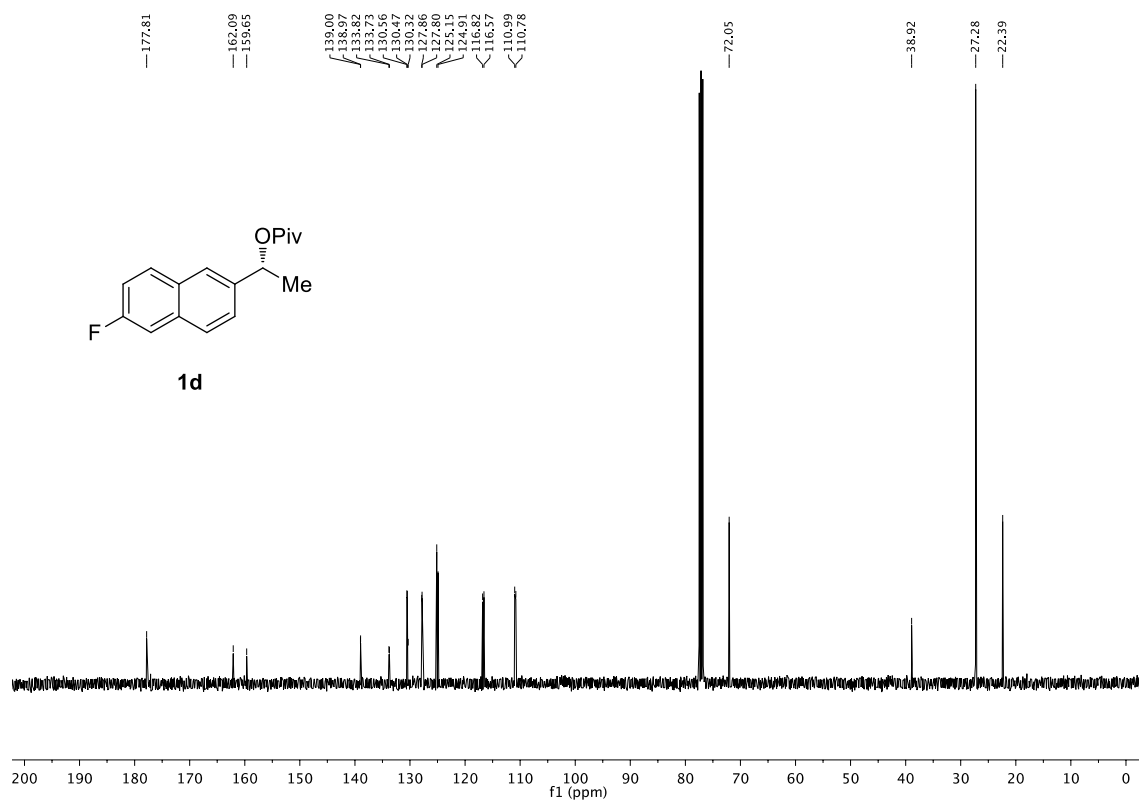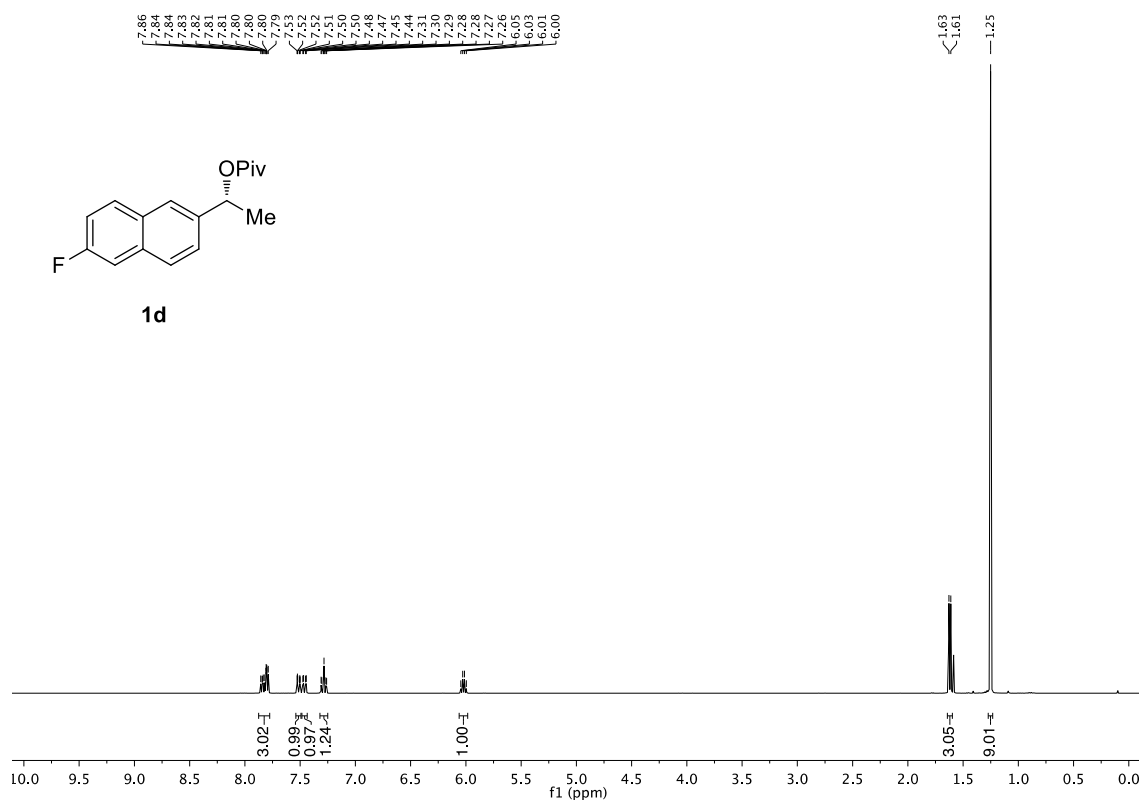**(R)-1-(4-methoxynaphthalen-1-yl)propan-1-ol (2m)**. The targeted compound was prepared via the General Procedure using Pivalate **1m** (prepared in 78% ee). The crude material was purified by silica gel chromatography (hexanes/EtOAc 9/1) to give compound **2m** (22 mg, 51%) as colourless oil. The enantiomeric excess was determined to be 68% ee (87% ee$_s$) by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 2% EtOH/Hexane, λ=220 nm); t_R(minor)= 16.4 min, t_R(major)= 25.0 min. $[\alpha]_D^{24}$ = 43.7º (0.16, CHCl$_3$): ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.34 (m, 1H), 8.13 (dd, J = 8.2, 1.3 Hz, 1H), 7.63 – 7.46 (m, 3H), 6.83 (d, J = 8.0 Hz, 1H), 5.33 (t, J = 6.5 Hz, 1H), 4.03 (s, 3H), 2.09 – 1.93 (m, 2H), 1.87 (s, 1H, OH), 1.04 (t, J = 7.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 155.0, 132.0, 131.6, 126.5, 125.8, 124.9, 123.2, 123.1, 122.7, 103.1, 72.7, 55.5, 30.1, 10.6 ppm.

Chapter 2

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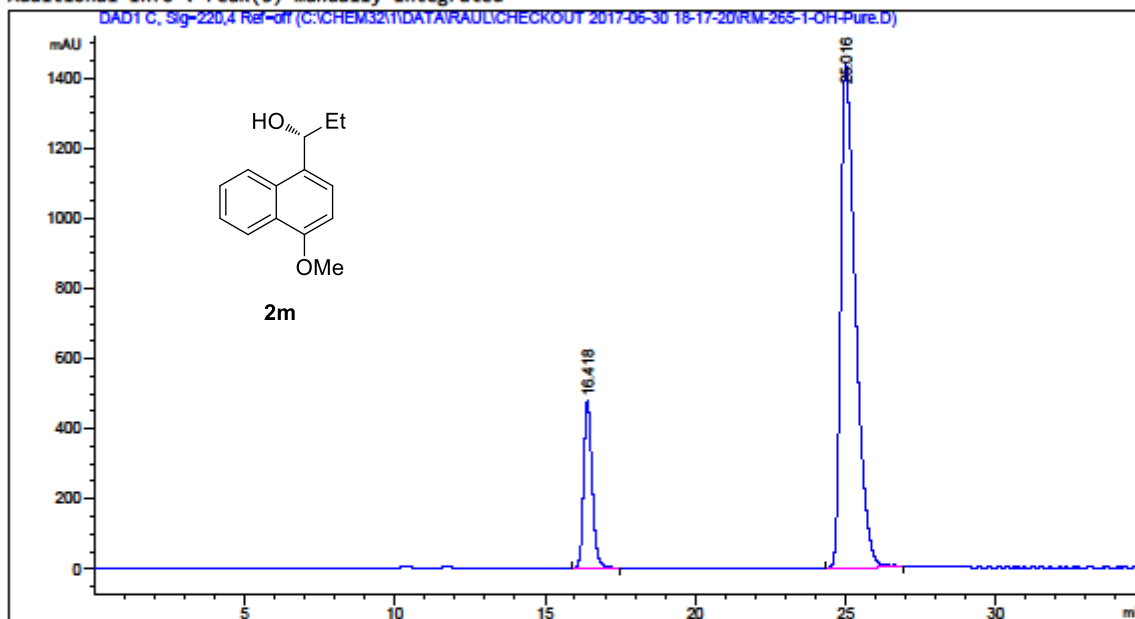


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Use Multiplier & Dilution Factor with ISTDs


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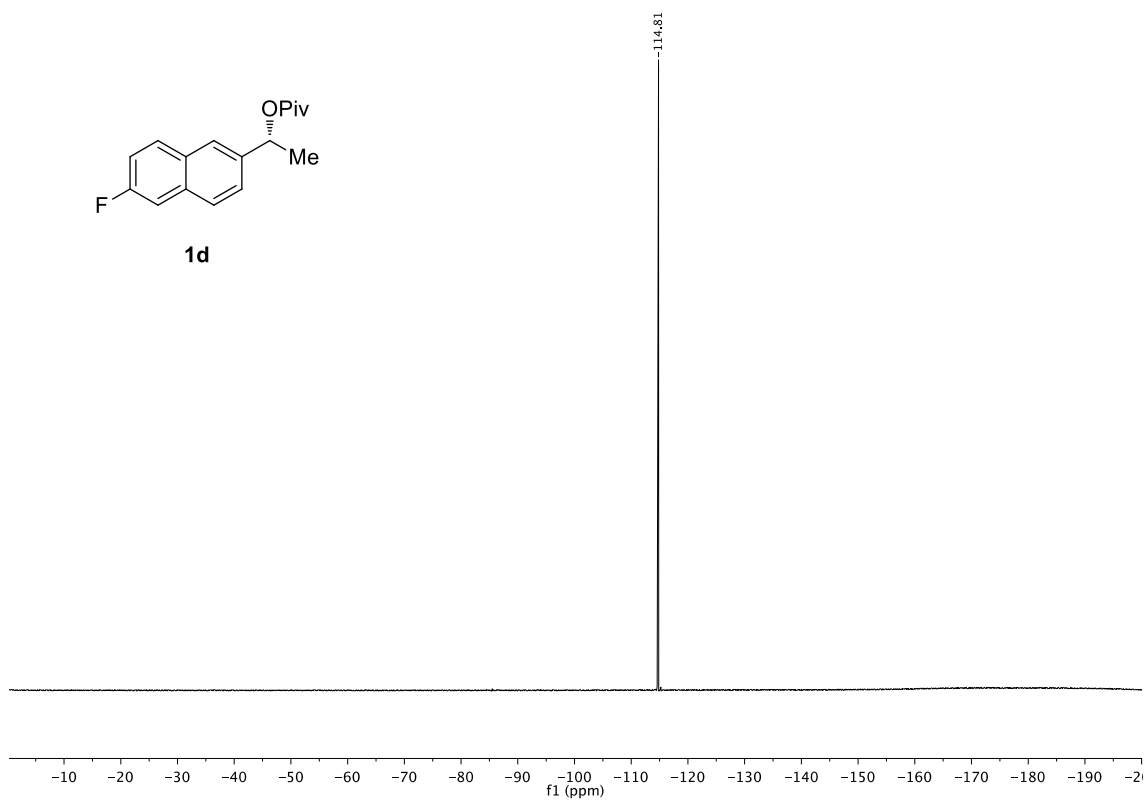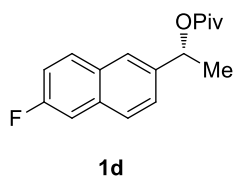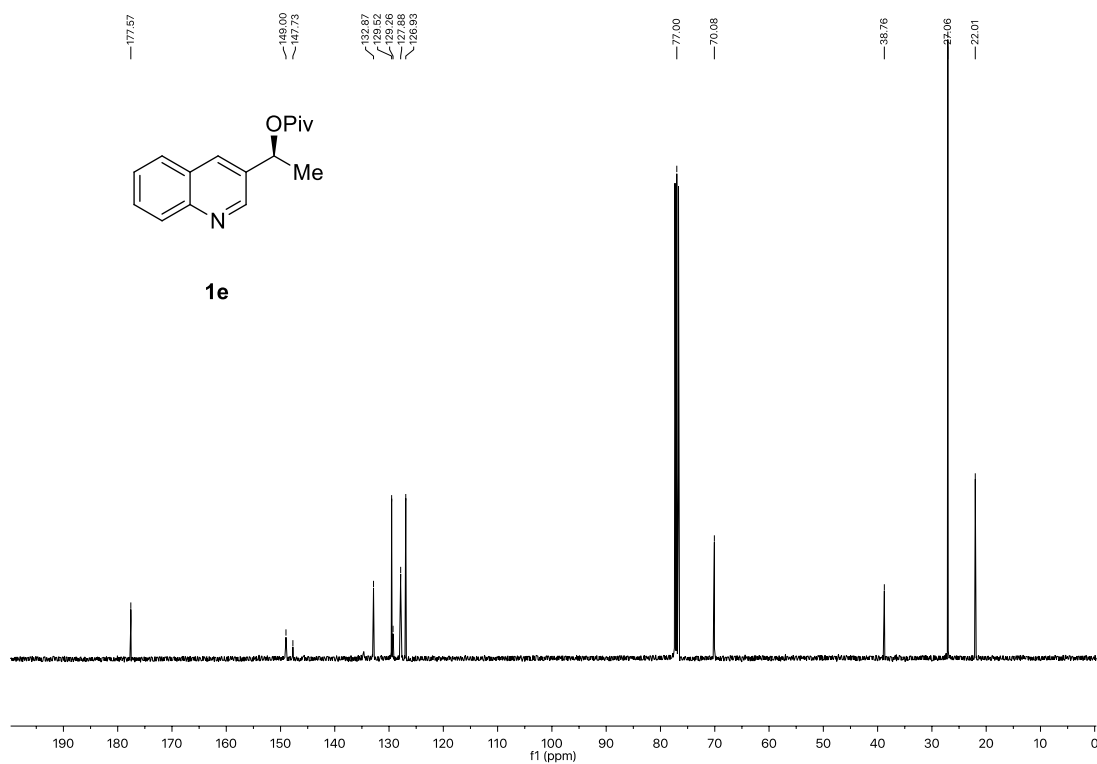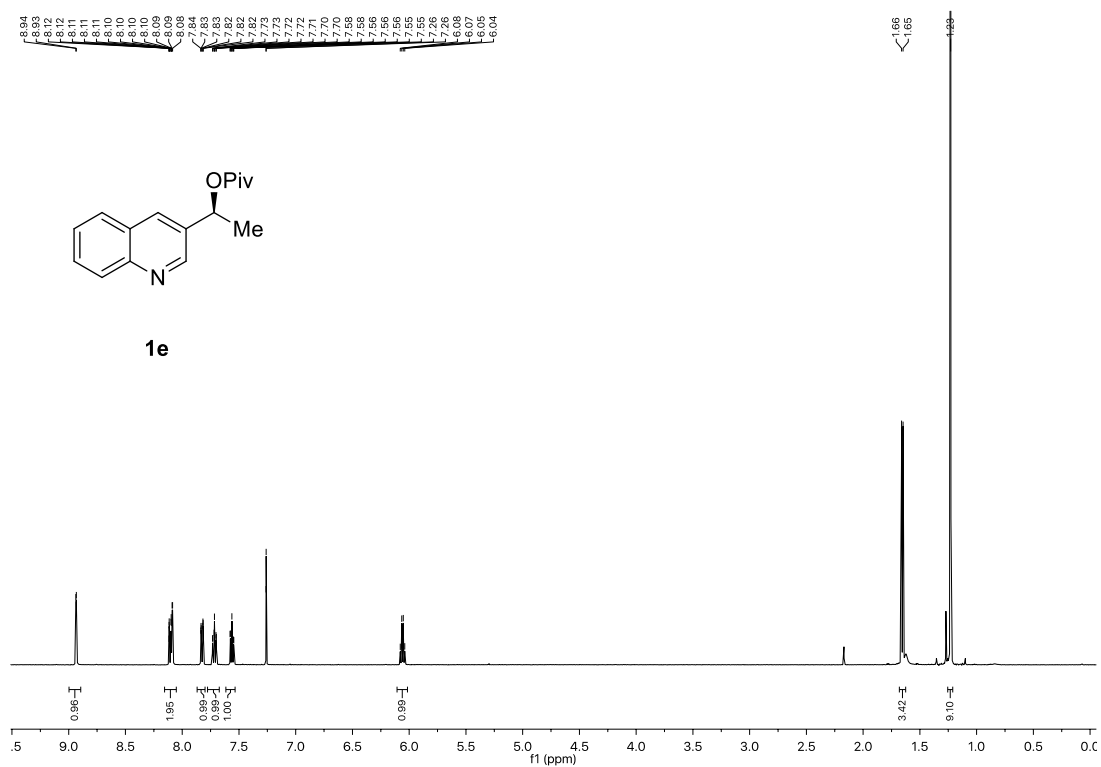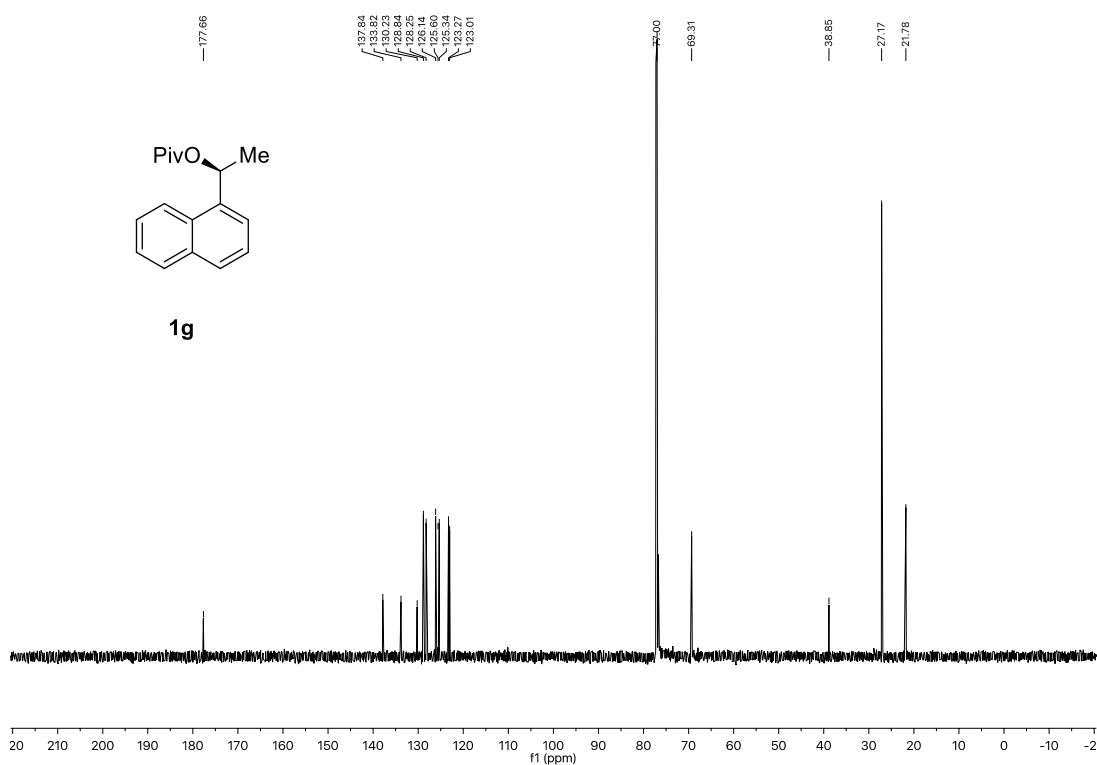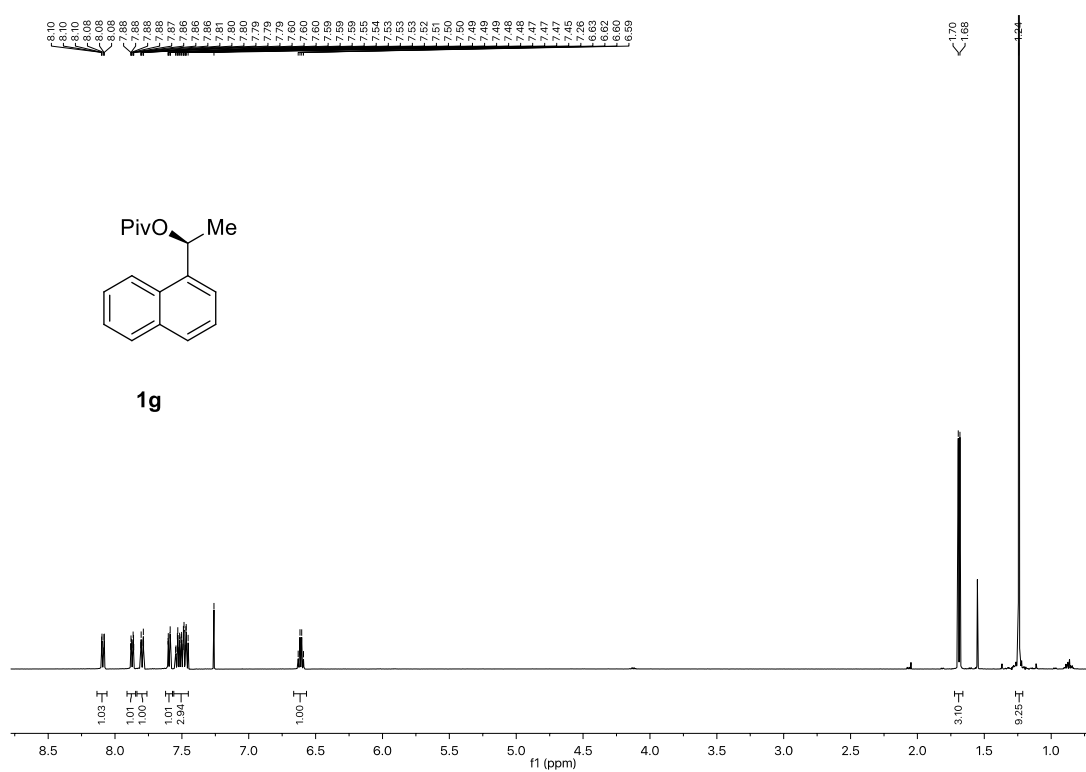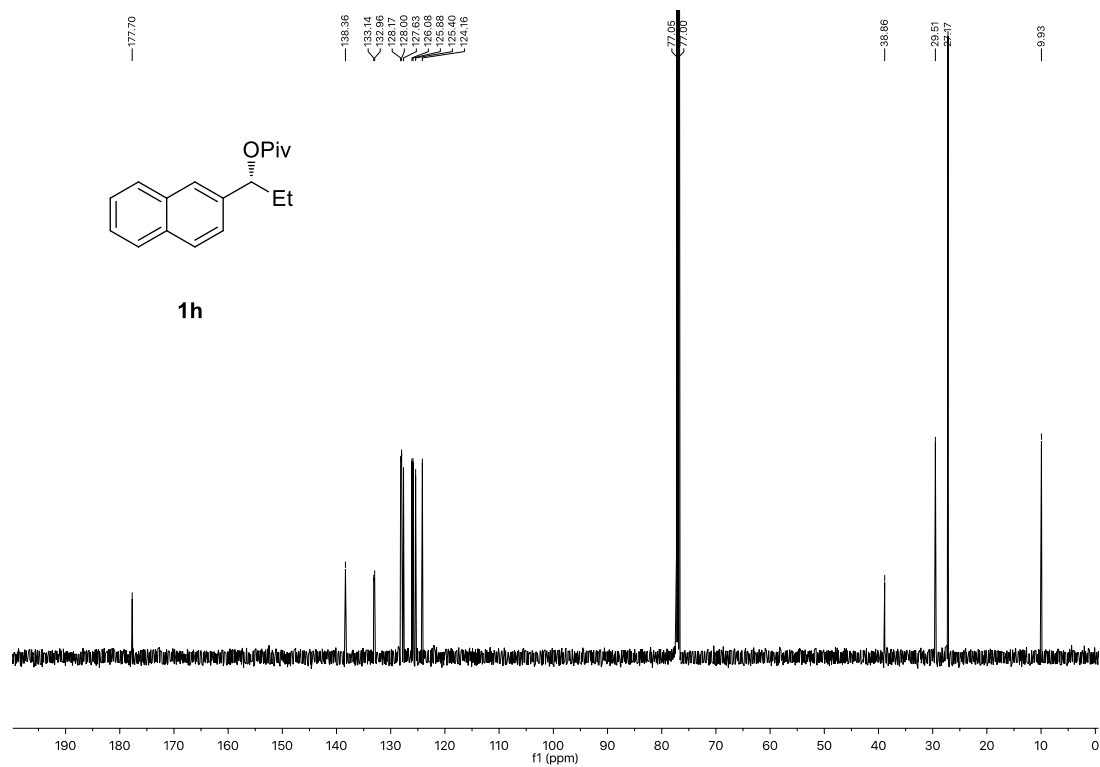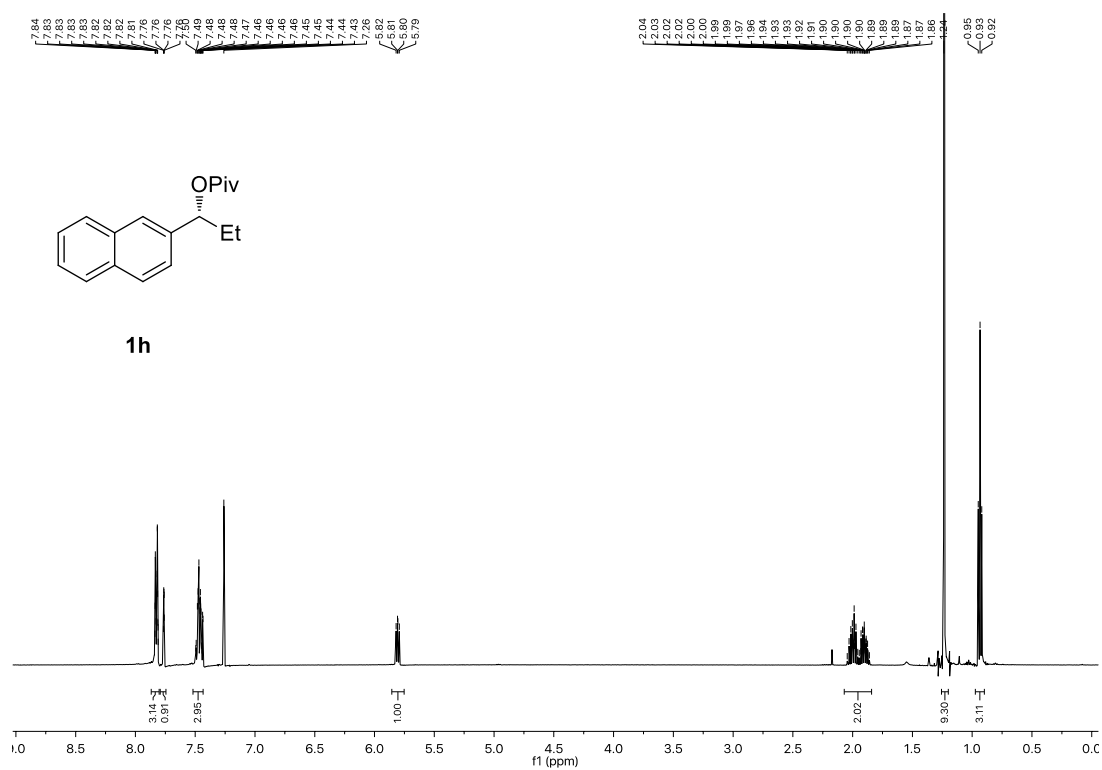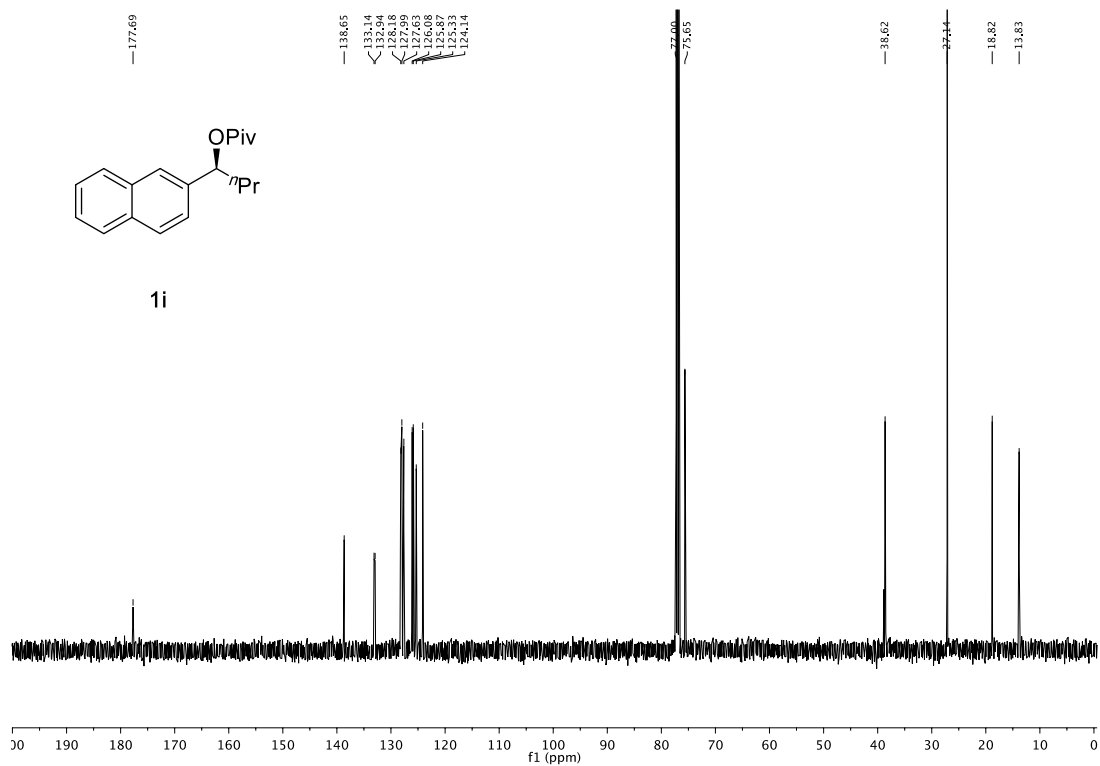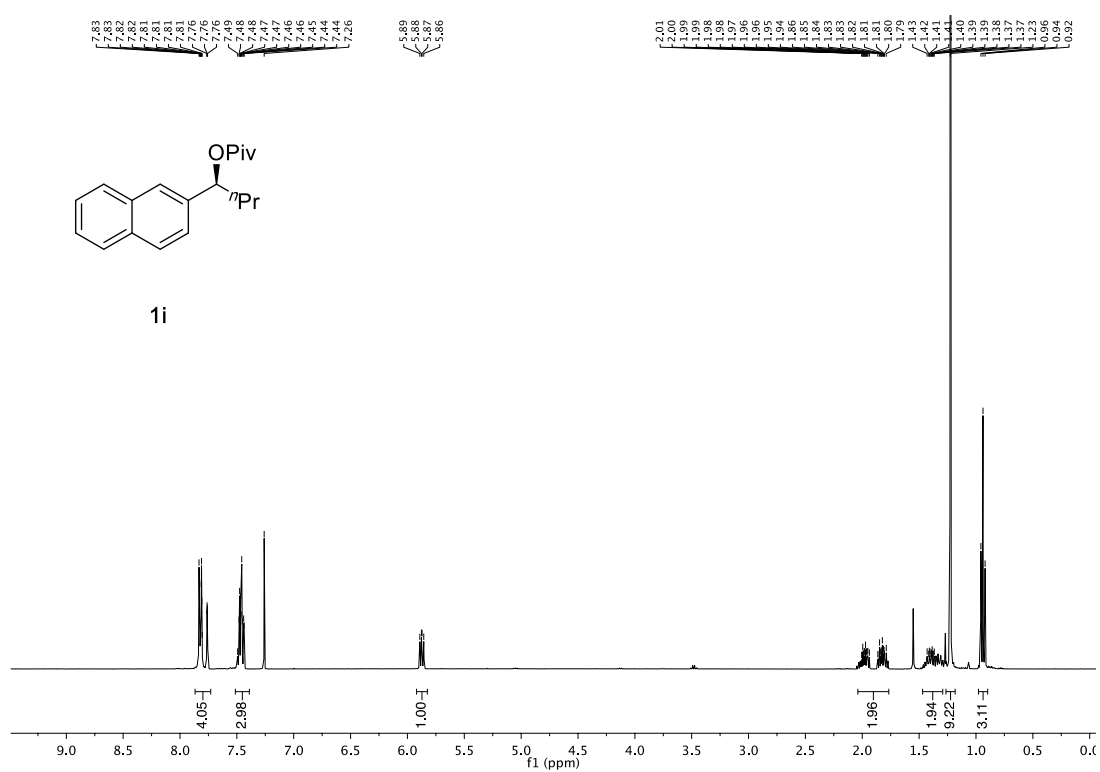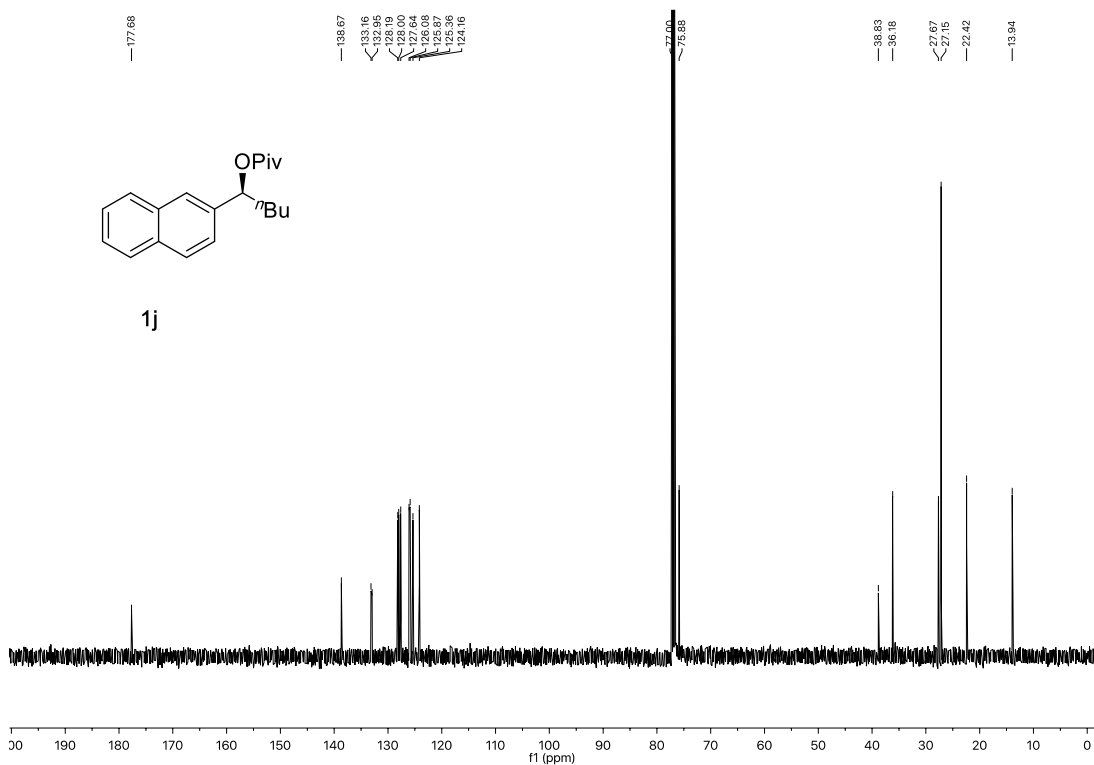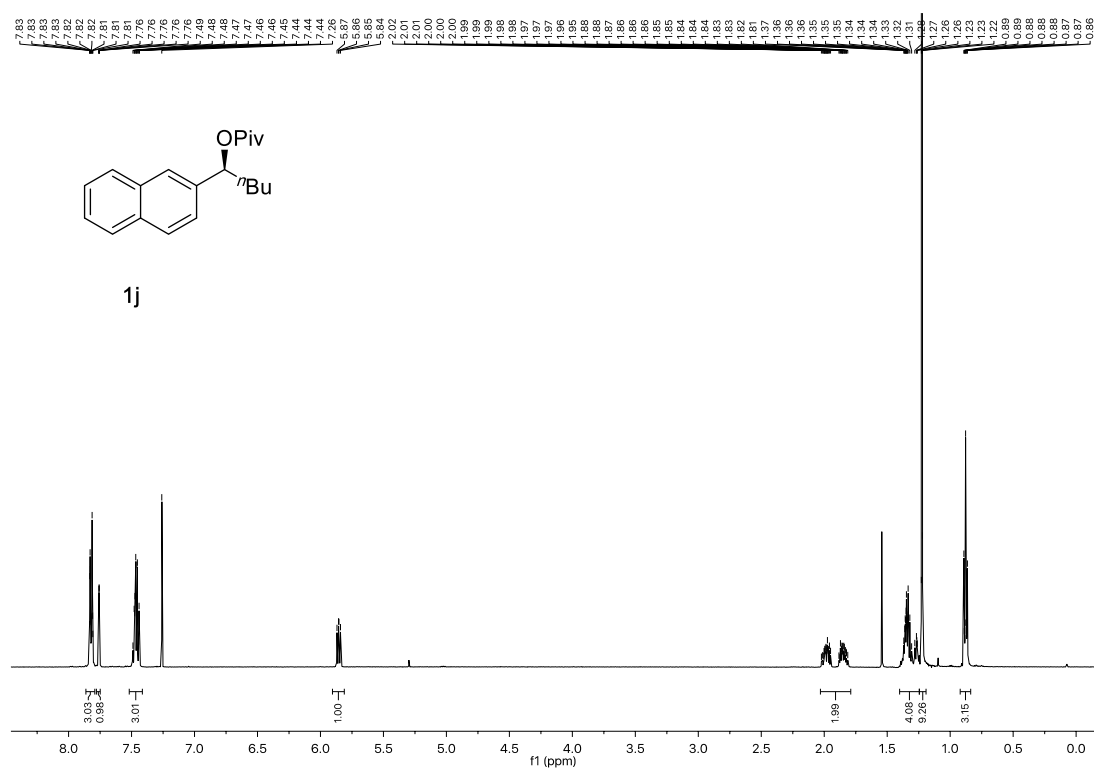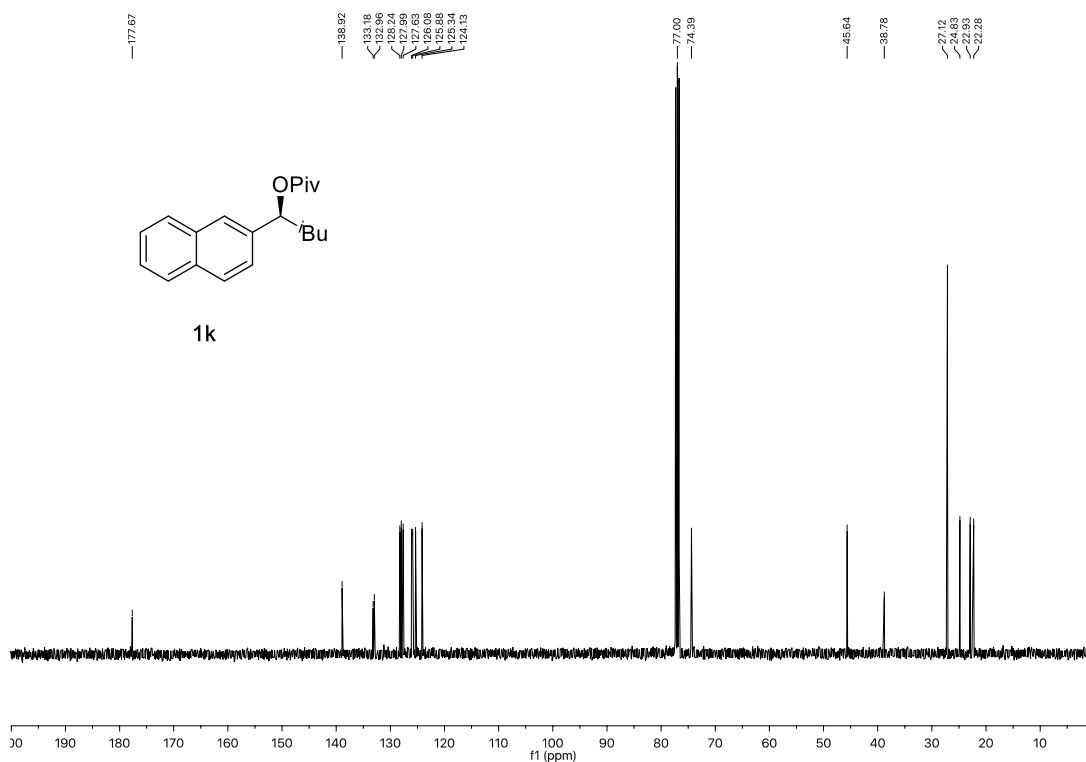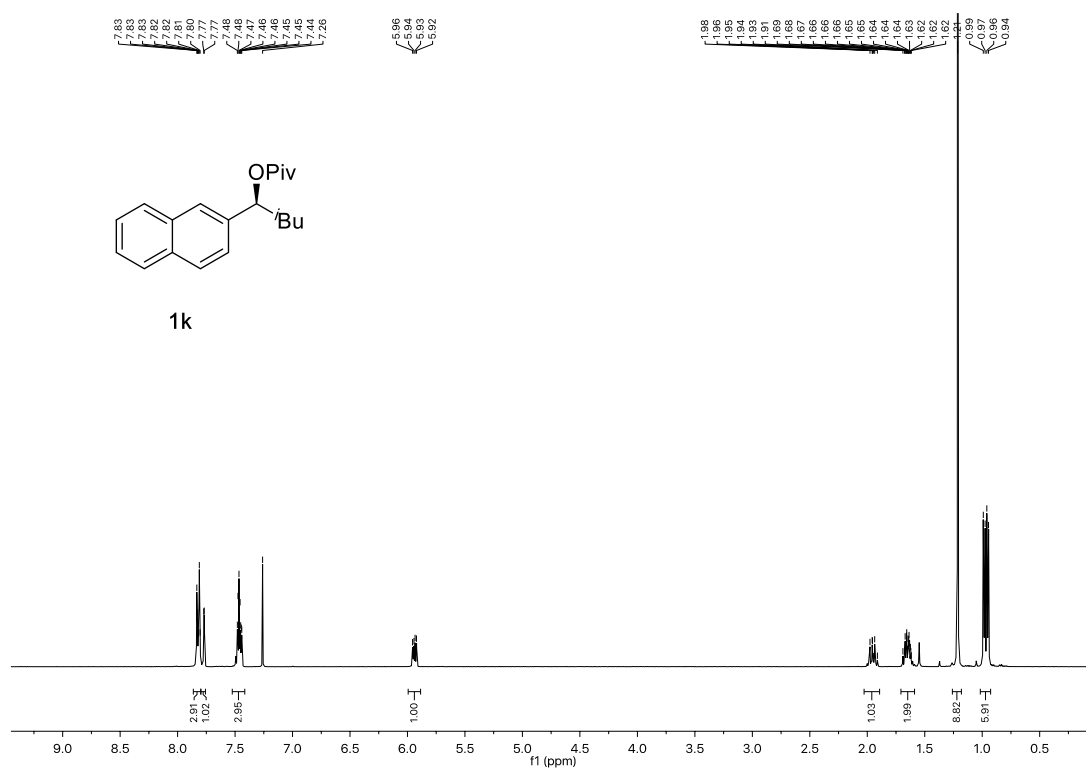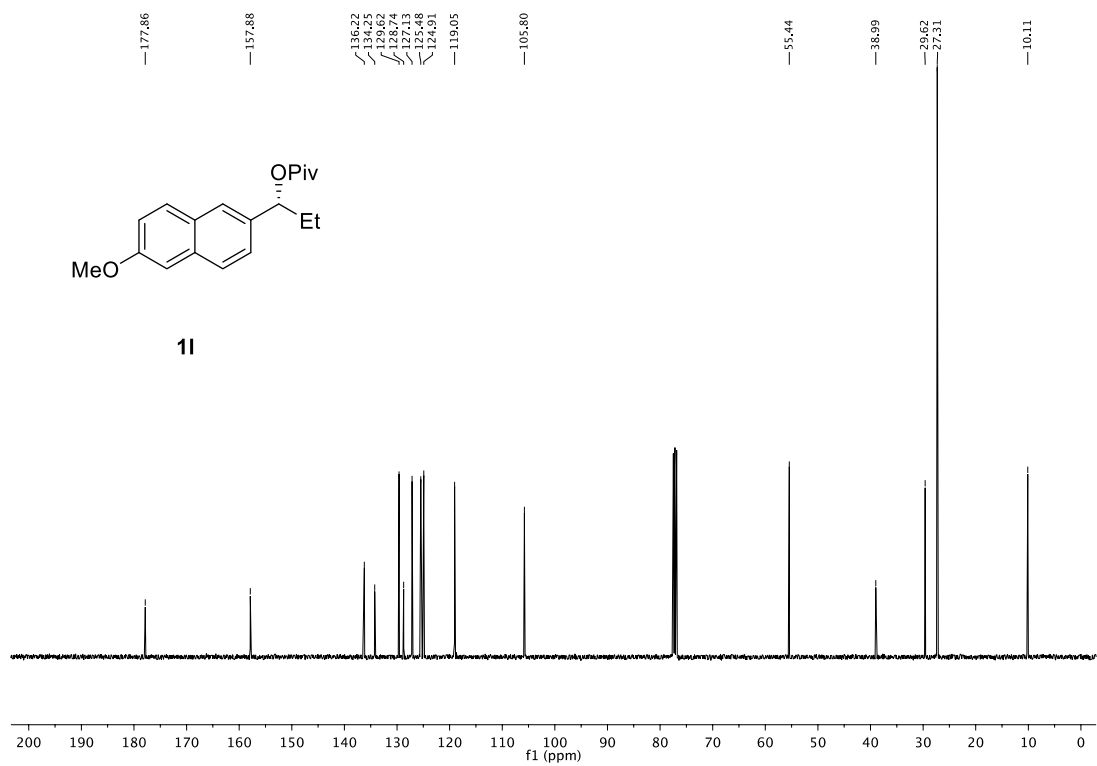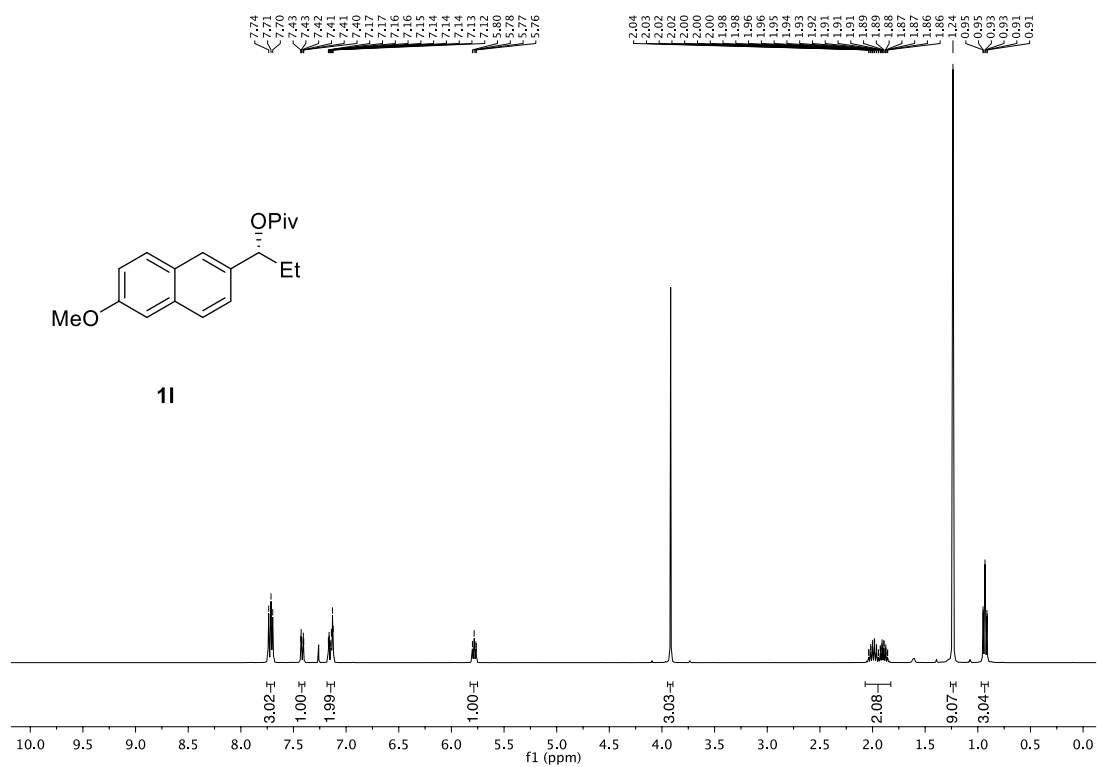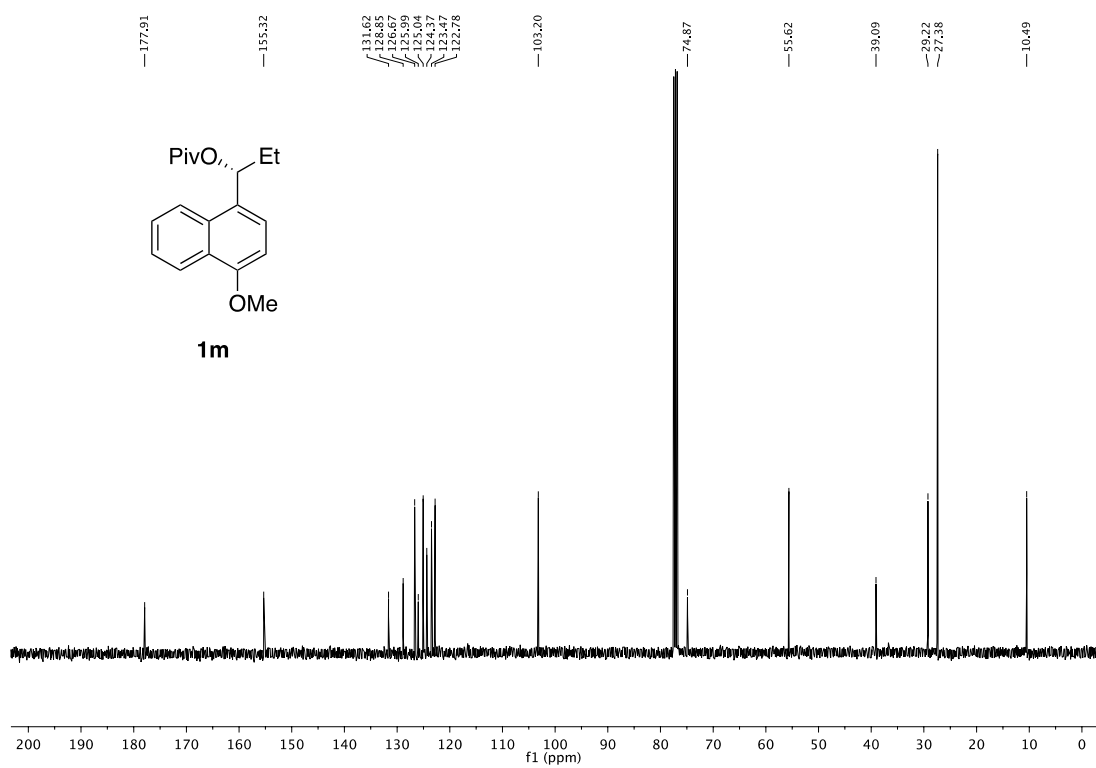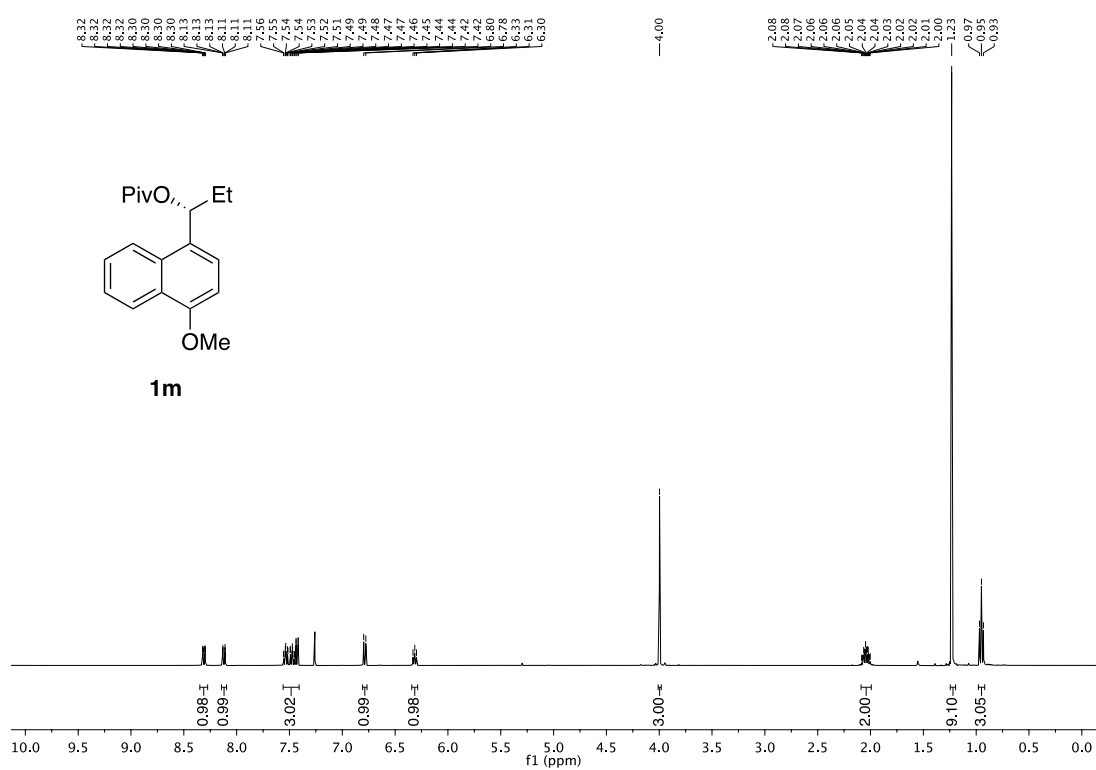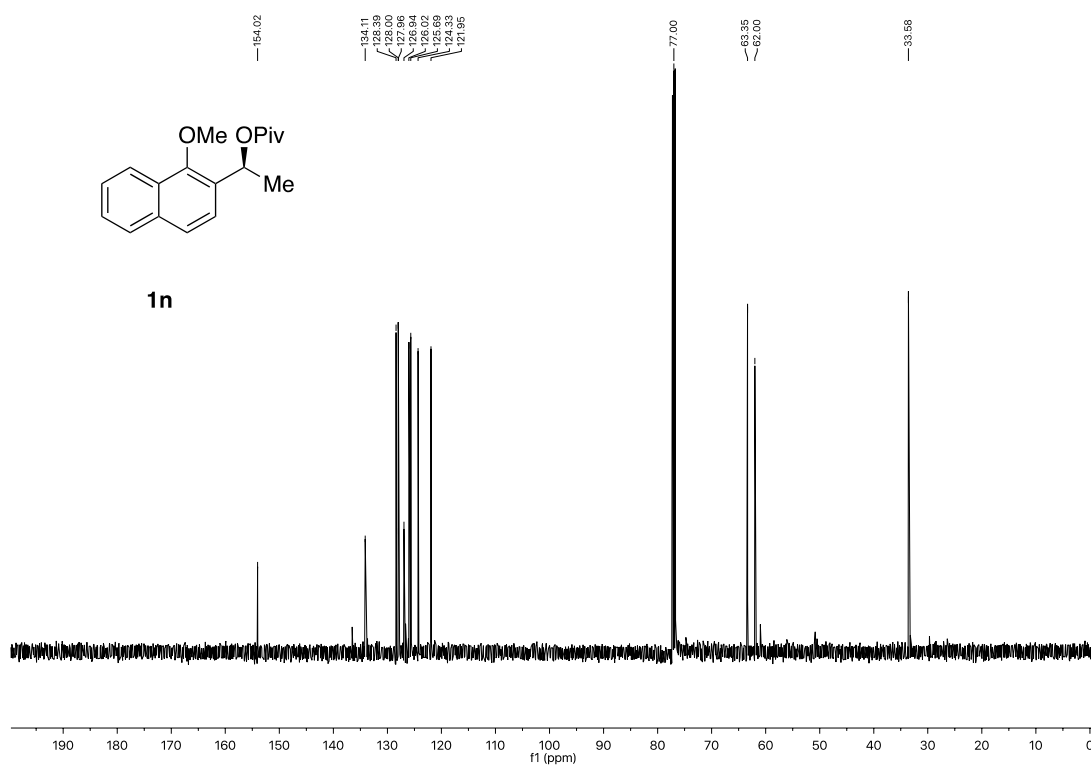
Stereospecific Borylation of Benzyl C(sp³)–O Bonds

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                  98-2.M
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Additional Info : Peak(s) manually integrated
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Dilution           :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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Chapter 2
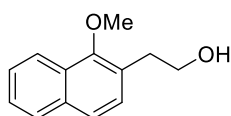
2n

2-(1-methoxynaphthalen-2-yl)ethan-1-ol (2n). The targeted compound was prepared via the General Procedure using Pivalate **1n** (prepared in 95% ee). The crude material was purified by silica gel chromatography (hexanes/EtOAc 9/1) to give compound **2n** (24 mg, 60%) as colourless oil. [1]H NMR (500 MHz, CDCl$_3$) δ 8.09 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.52 (dd, J = 8.3, 6.8 Hz, 1H), 7.46 (dd, J = 8.1, 6.8 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 3.95 (t, J = 6.5 Hz, 2H), 3.10 (t, J = 6.5 Hz, 2H), 1.87 (s, 1H, OH) ppm. [13]C NMR (126 MHz, CDCl$_3$) δ 154.0, 134.1, 128.4, 128.0, 127.9, 126.9, 126.0, 125.7, 124.3, 122.0, 63.3, 62.0, 35.6 ppm. IR (neat, cm^{-1}): 3413, 2932, 1661, 1369, 1240, 1085, 986, 814. HRMS calcd. for C$_{13}$H$_{14}$O$_2$ (M+Na)$^+$: 225.0886, found 225.0881.
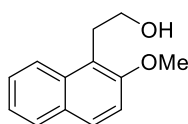
2o

2-(2-methoxynaphthalen-1-yl)ethan-1-ol (2o). The targeted compound was prepared via the General Procedure using Pivalate **1o** (prepared in 15% ee). The crude material was purified by silica gel chromatography (hexanes/EtOAc 9/1) to give compound **2o** (23 mg, 58%) as colourless oil. [1]H NMR (400 MHz, CDCl$_3$) δ 8.00 (dd, J = 8.7, 1.0 Hz, 1H), 7.85 − 7.73 (m, 2H), 7.49 (dd, J = 8.4, 6.8 Hz, 1H), 7.42 − 7.29 (m, 2H), 3.97 (s, 3H), 3.92 (t, J = 6.8 Hz, 2H), 3.42 (t, J = 6.8 Hz, 2H), 1.6 (s, 1H, OH) ppm. [13]C NMR (126 MHz, CDCl$_3$) δ 154.9, 133.3, 129.3, 128.6, 128.3,126.5, 123.4, 123.0, 119.6, 113.1, 62.9, 56.5, 28.4 ppm. IR (neat, cm^{-1}): 2929, 1624, 1594, 1513, 1464, 1249, 1095, 1026, 806. HRMS calcd. for C$_{13}$H$_{14}$O$_2$ (M+Na)$^+$: 225.0886, found 225.0887.

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UNIVERSITAT ROVIRA I VIRGILI
Functionalization of Strong Sigma Bonds by Nickel and Tungsten Catalysis
Raúl Martín Montero
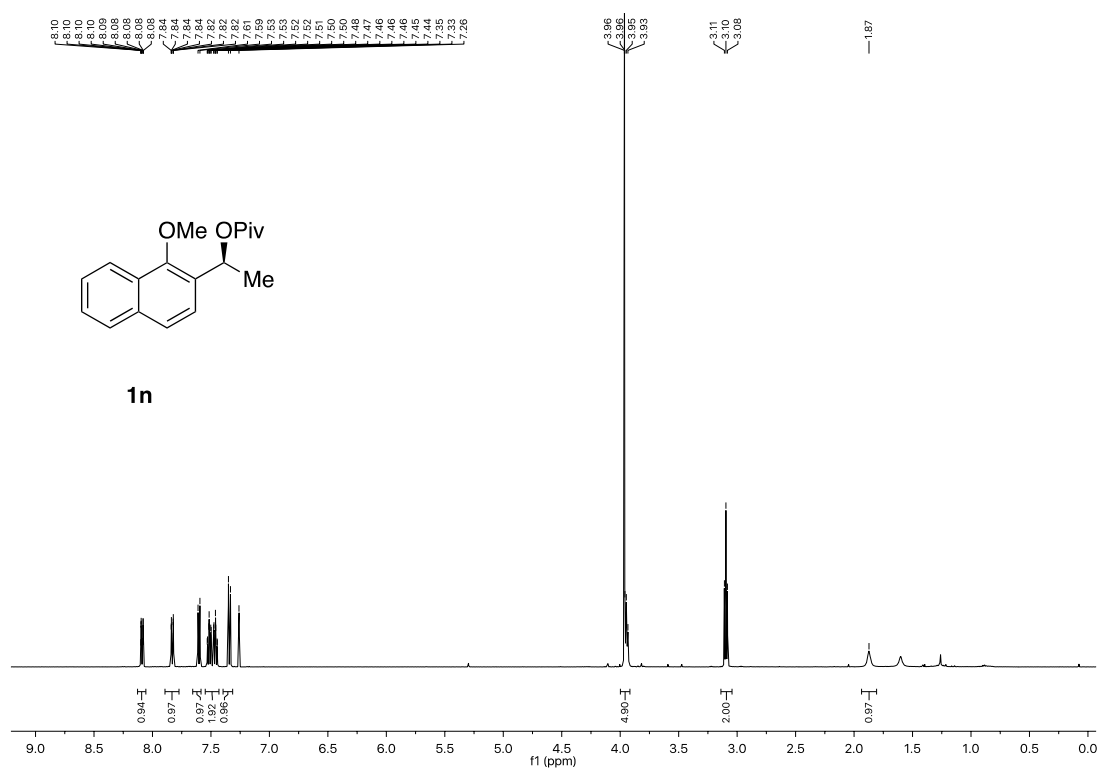
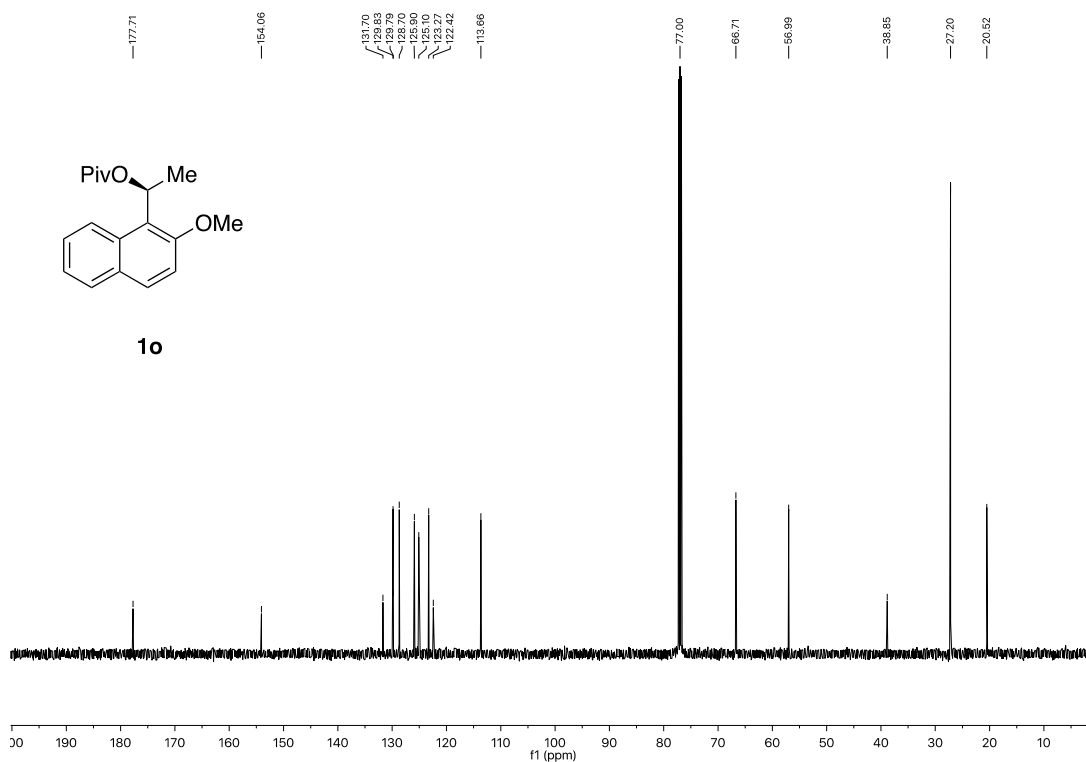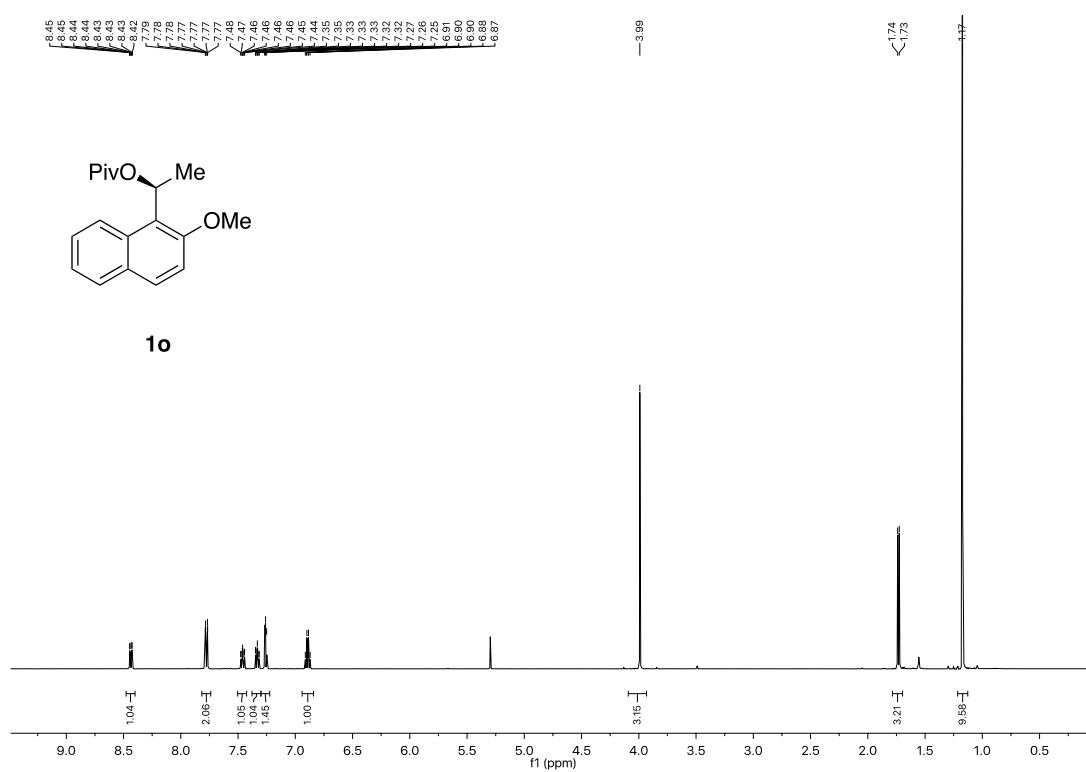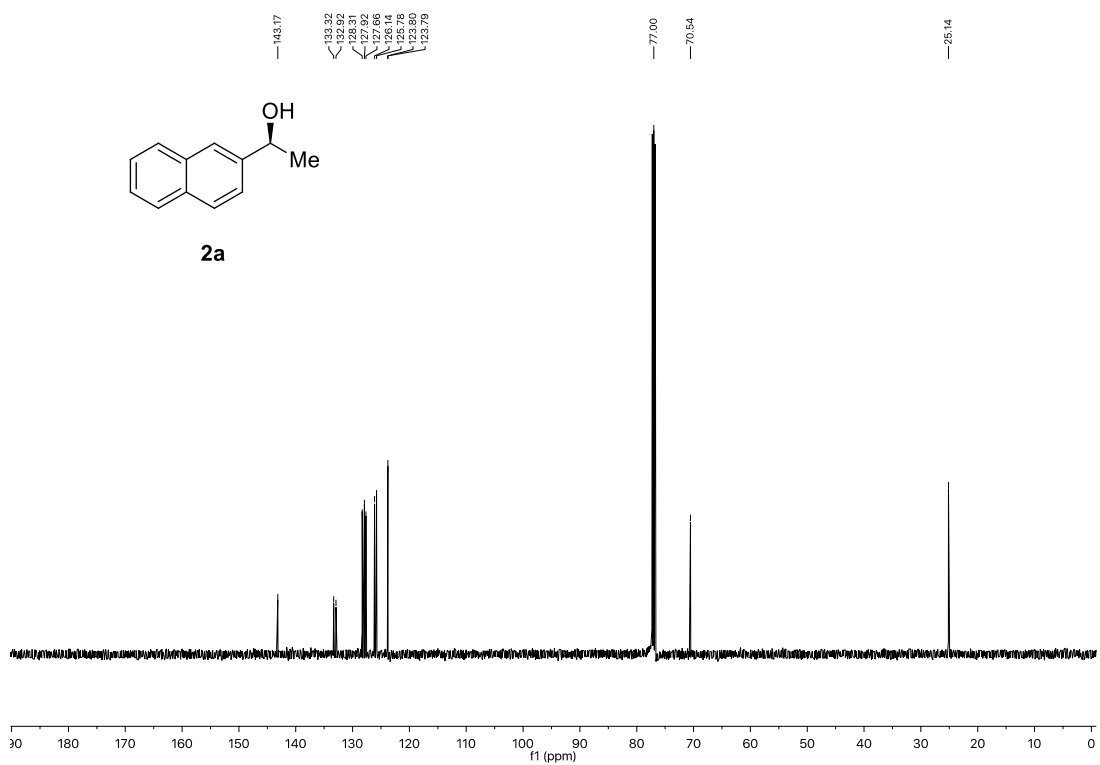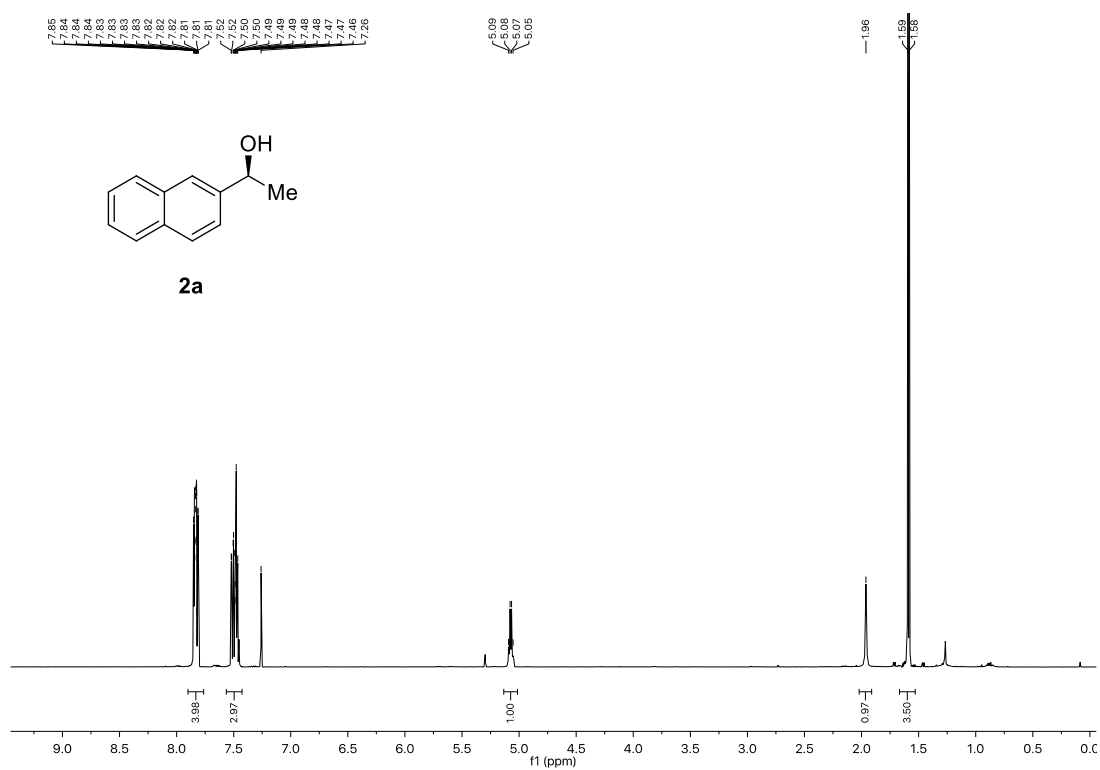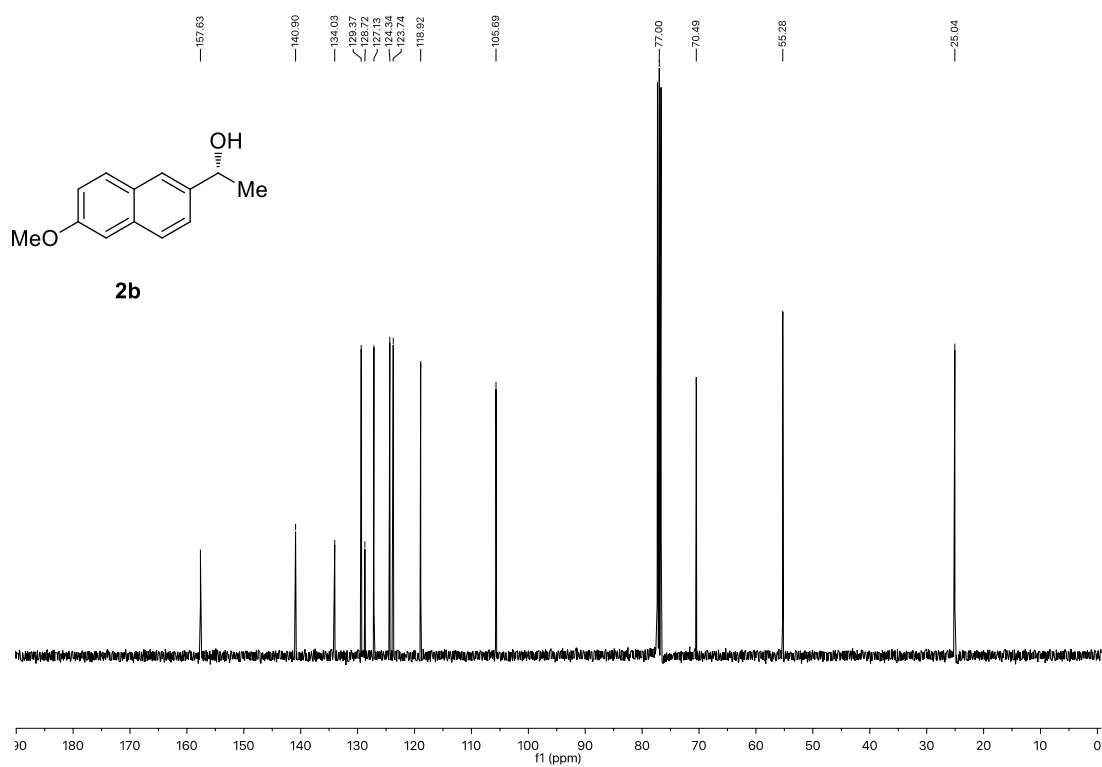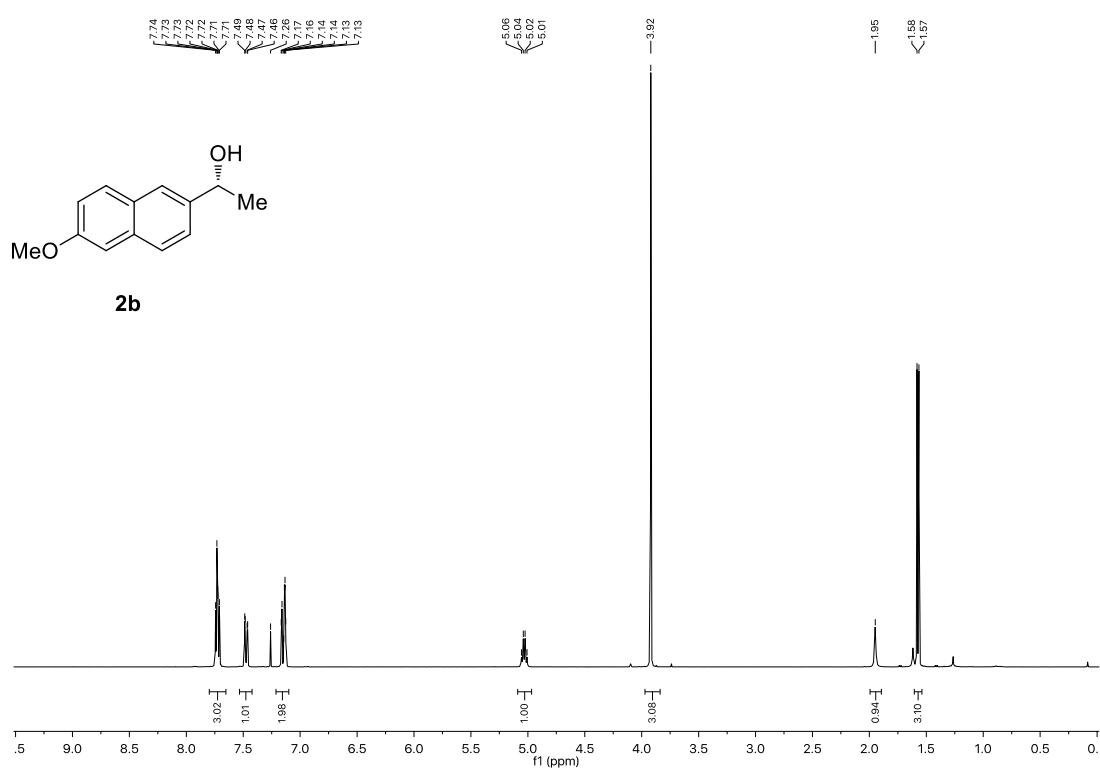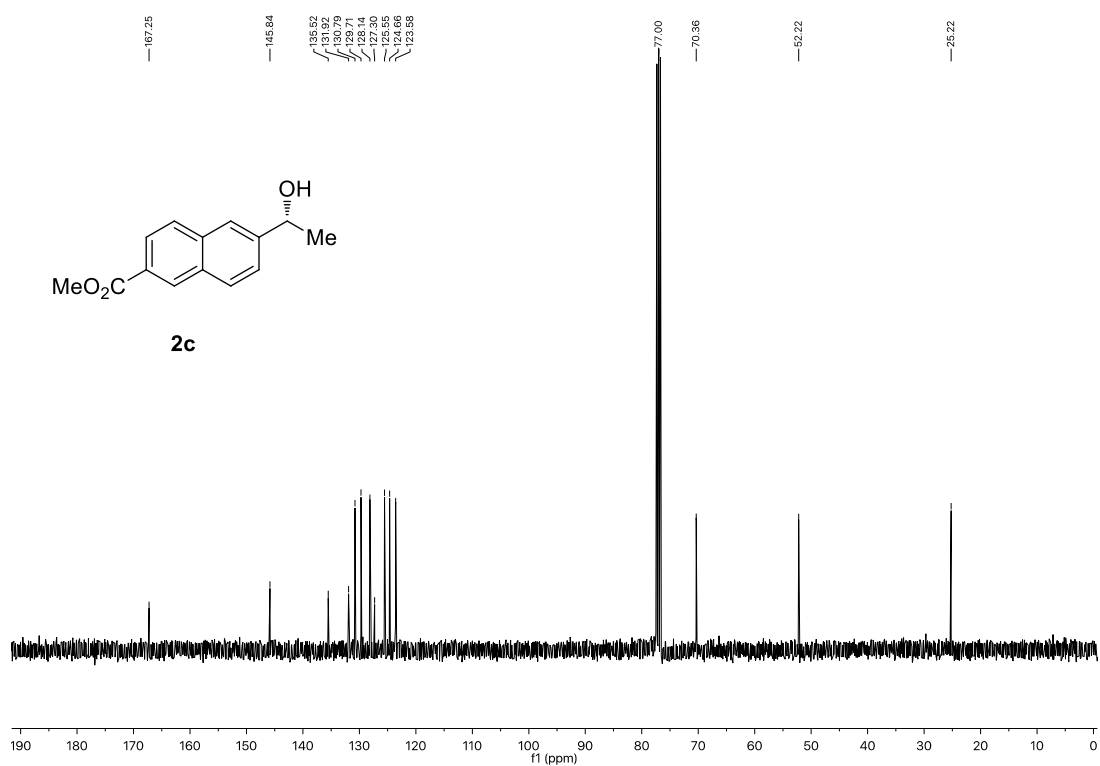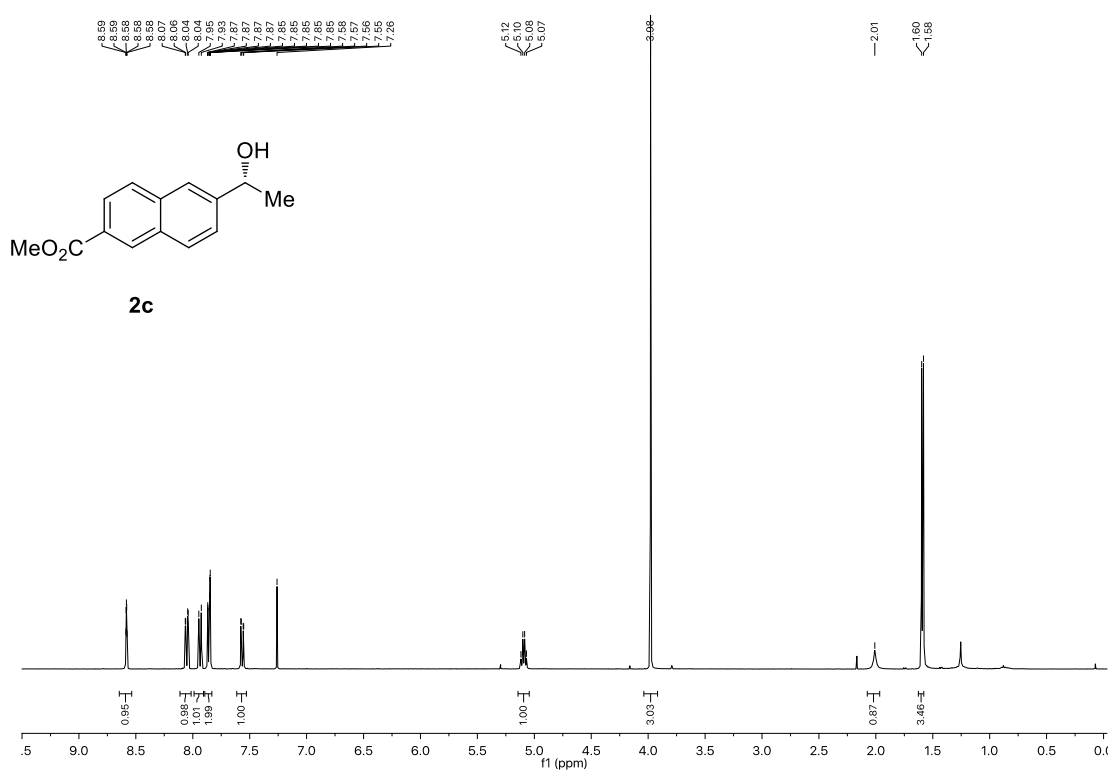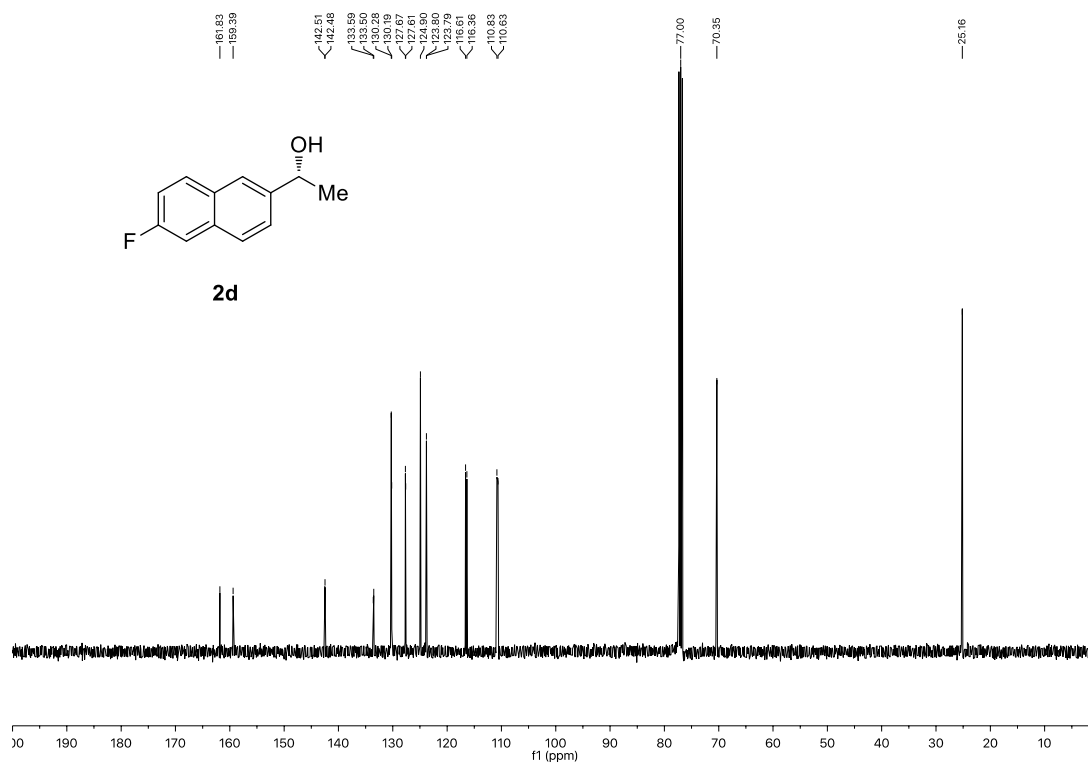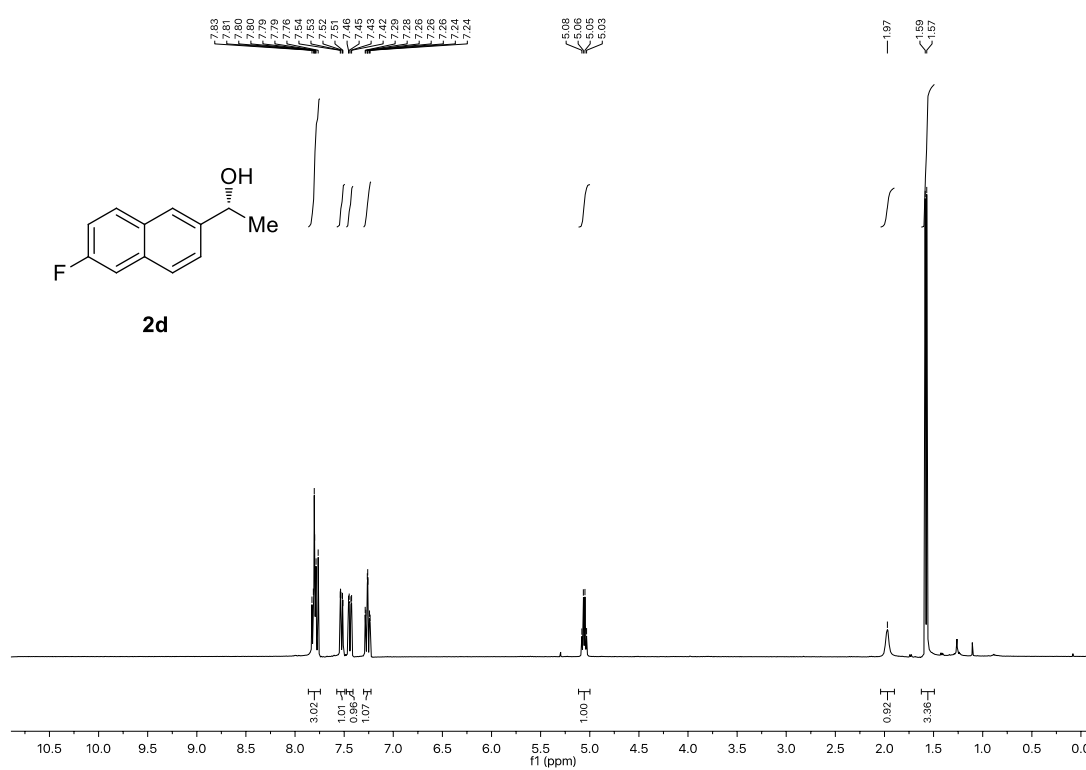*Stereospecific Borylation of Benzyl C(sp³)–O Bonds*

2.5.4   Synthetic applications.

<u>Suzuki-Miyaura Coupling reaction procedure</u>.[IX]

Prior **(S)-2a'** was prepared following the general procedure for the borylation of benzyl pivalates and was used without further purification step. Under inert atmosphere, 1-iodo-3-methoxybenzene (24 µL, 0.2 mmol), **(S)-2a'** (54 mg, 0.2 mmol), Ag_2O (48.9 mg, 0.21 mmol), $Pd_2(dba)_3$ (9.1 mg, 0.01 mmol, 10 mol% Pd), PPh_3 (70.6, 0.2 mmol) were taken up in THF (2 mL). The reaction was sealed, and stirred at 60 ºC for 24 h. The desired product was isolated by column chromatography (gradient hexanes/EtOAc 9/1) to yield the desired product **3** (29 mg, 57% yield based on **(S)-1a**) with 87% ee (93% ee_s) as a white solid (m.p 90-92 ºC). Enantiomeric ratio was determined by SFC analysis (CHIRALPAK IA, 1 mL/min, 95% CO_2/MeOH, λ=272 nm); t_R(minor)= 1.87 min, t_R(major)= 2.17 min. $[α]_D^{24}$ = -28.4º (c 0.11, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 − 7.68 (m, 4H), 7.51 − 7.40 (m, 2H), 7.33 (dd, J = 8.5, 1.8 Hz, 1H), 7.23 (dd, J = 15.6, 7.7 Hz, 1H), 6.88 − 6.80 (m, 2H), 6.75 (dd, J = 8.2, 2.6 Hz, 1H), 4.30 (q, J = 7.2 Hz, 1H), 3.77 (s, 3H), 1.74 (d, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 147.9, 143.6, 133.5, 132.1, 129.3, 127.9, 127.7, 127.5, 126.7, 125.9, 125.3, 125.2, 120.2, 113.9, 111.0, 55.1, 44.8, 21.7 ppm. The spectral data for compound **3** matches that reported in literature.[VII]
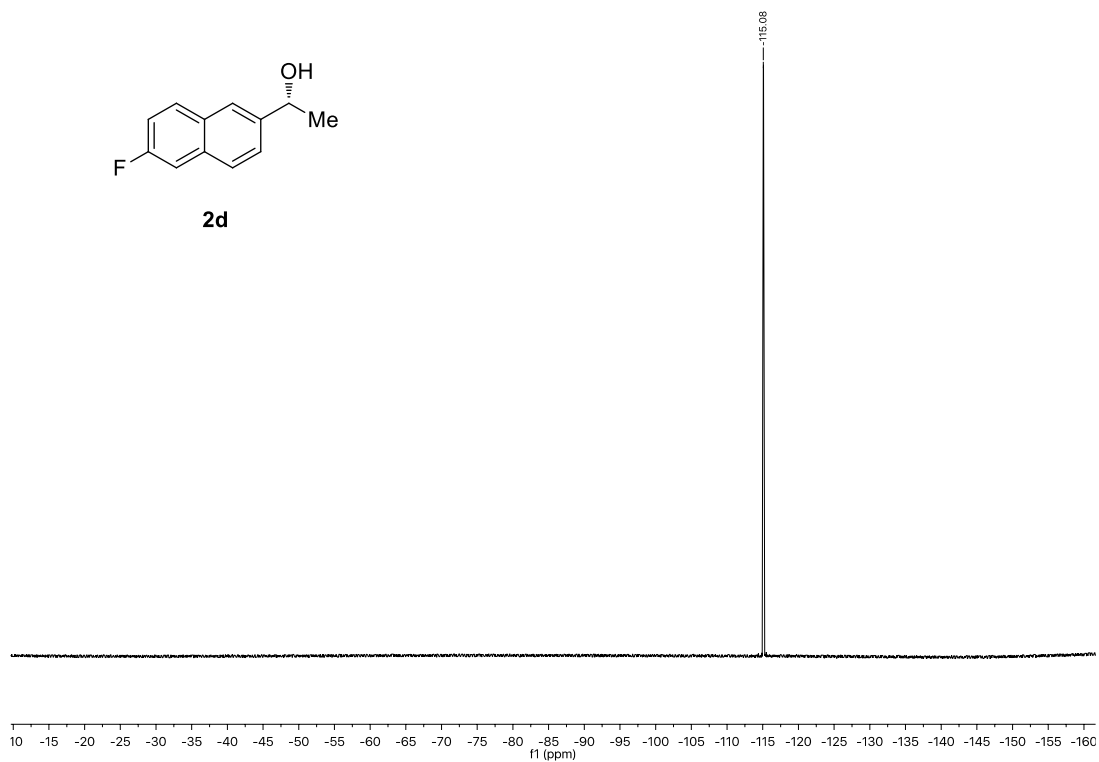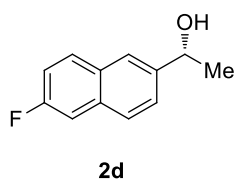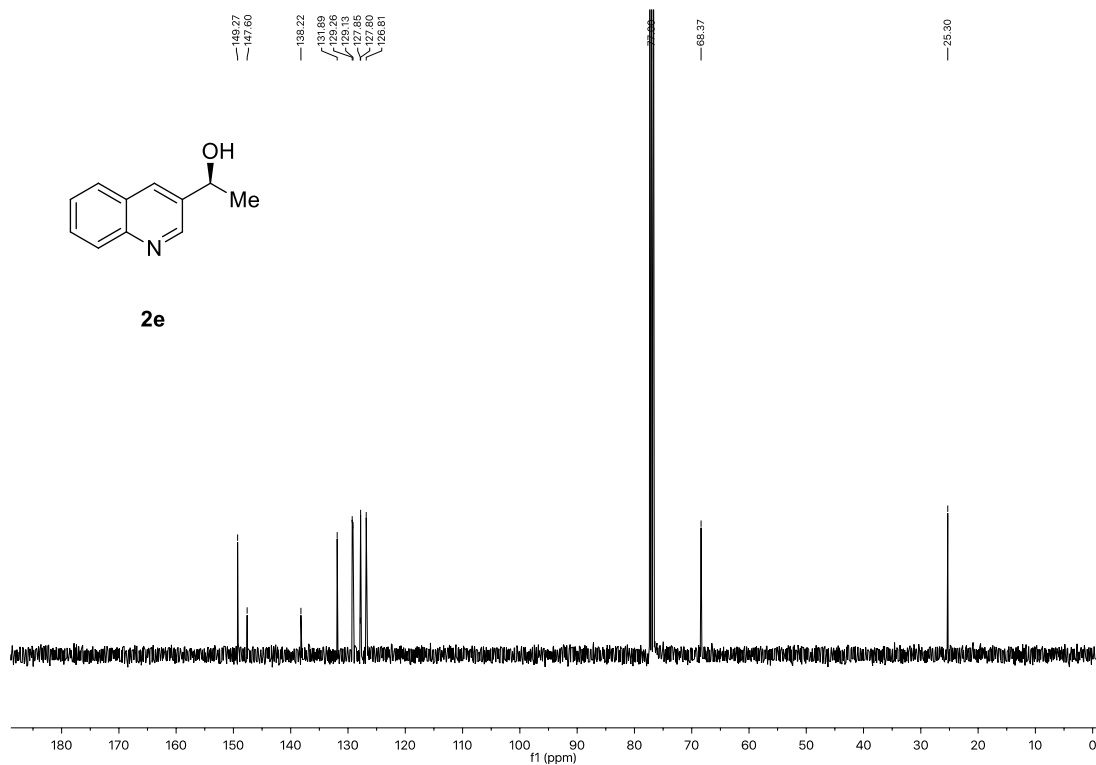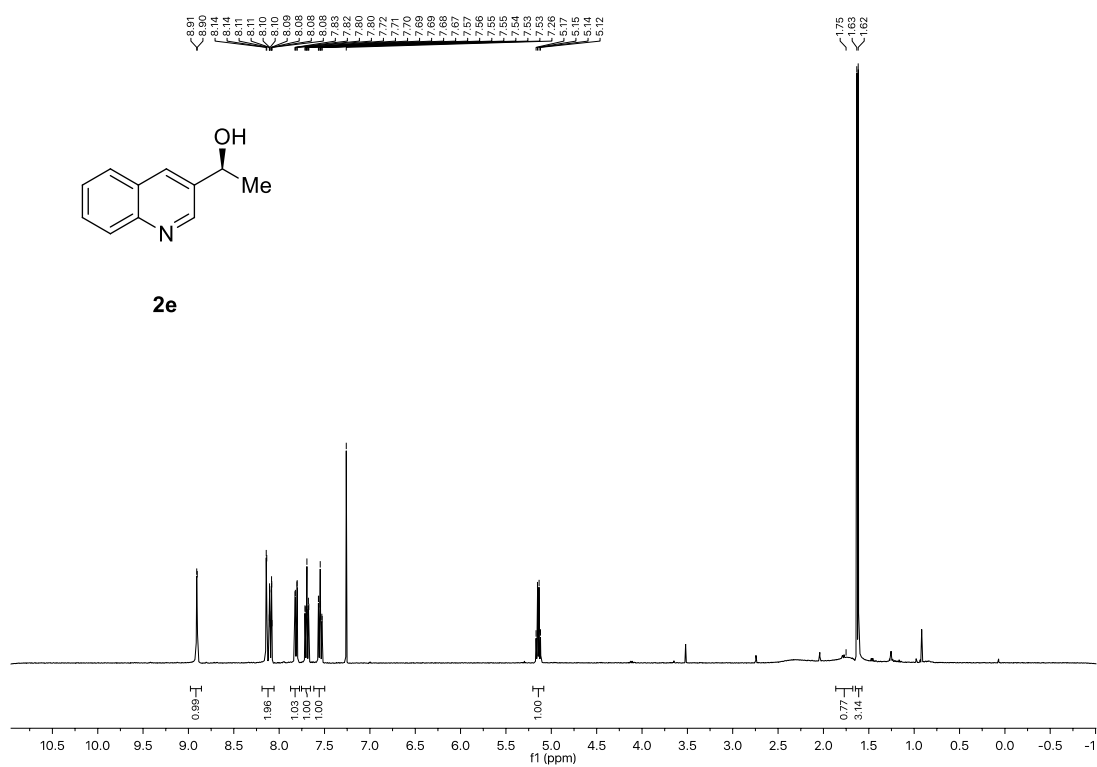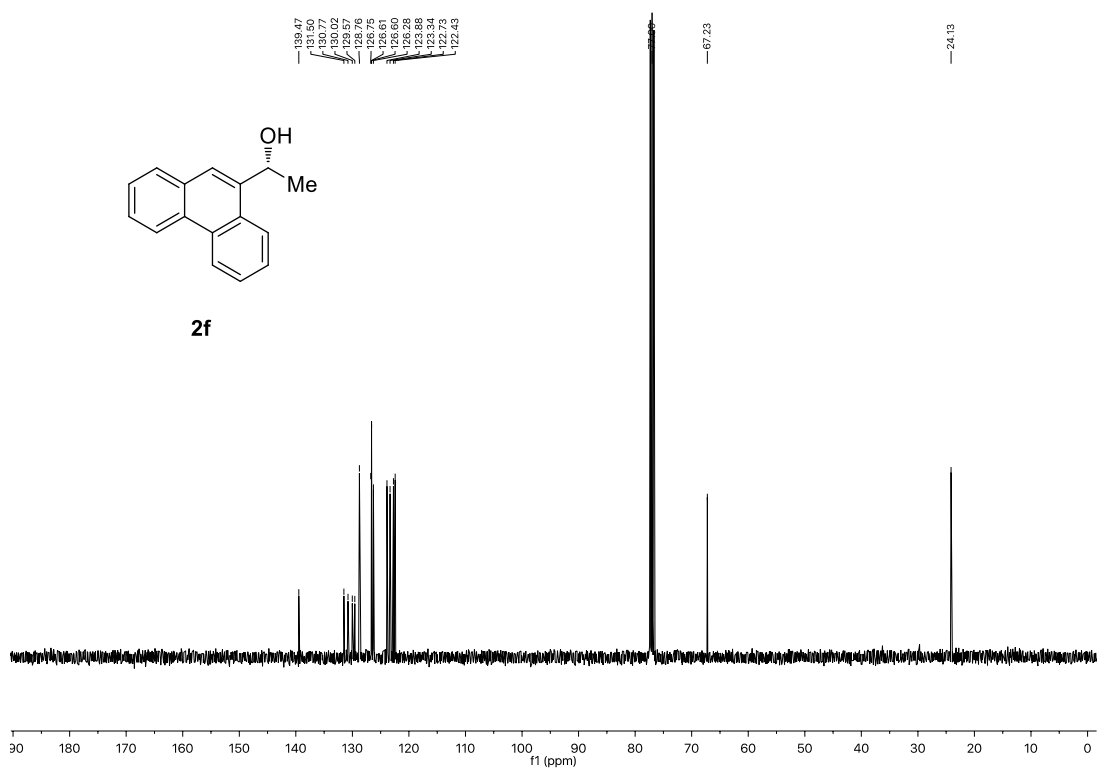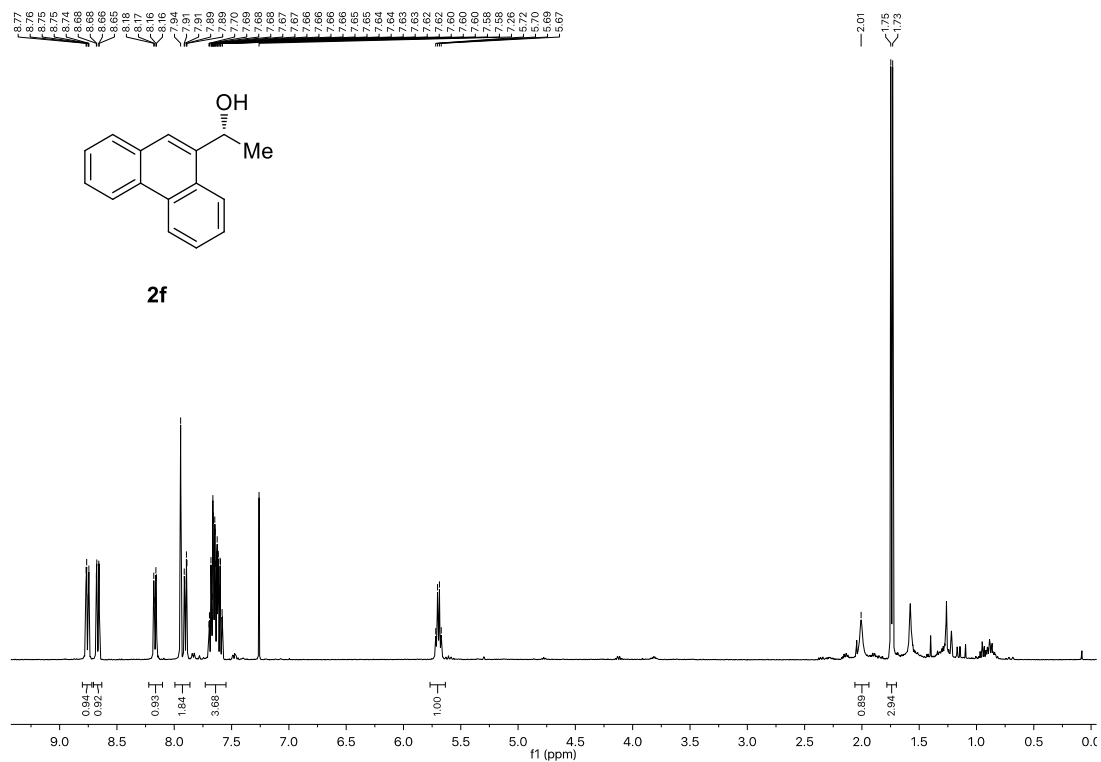
Chapter 2

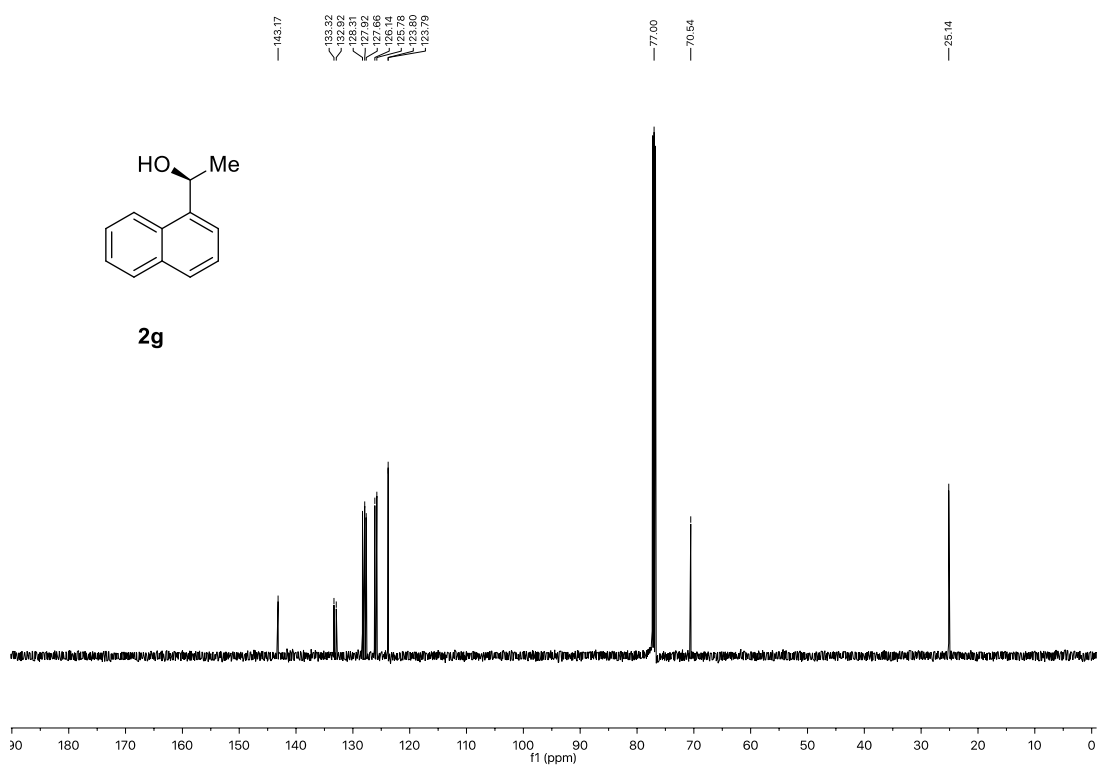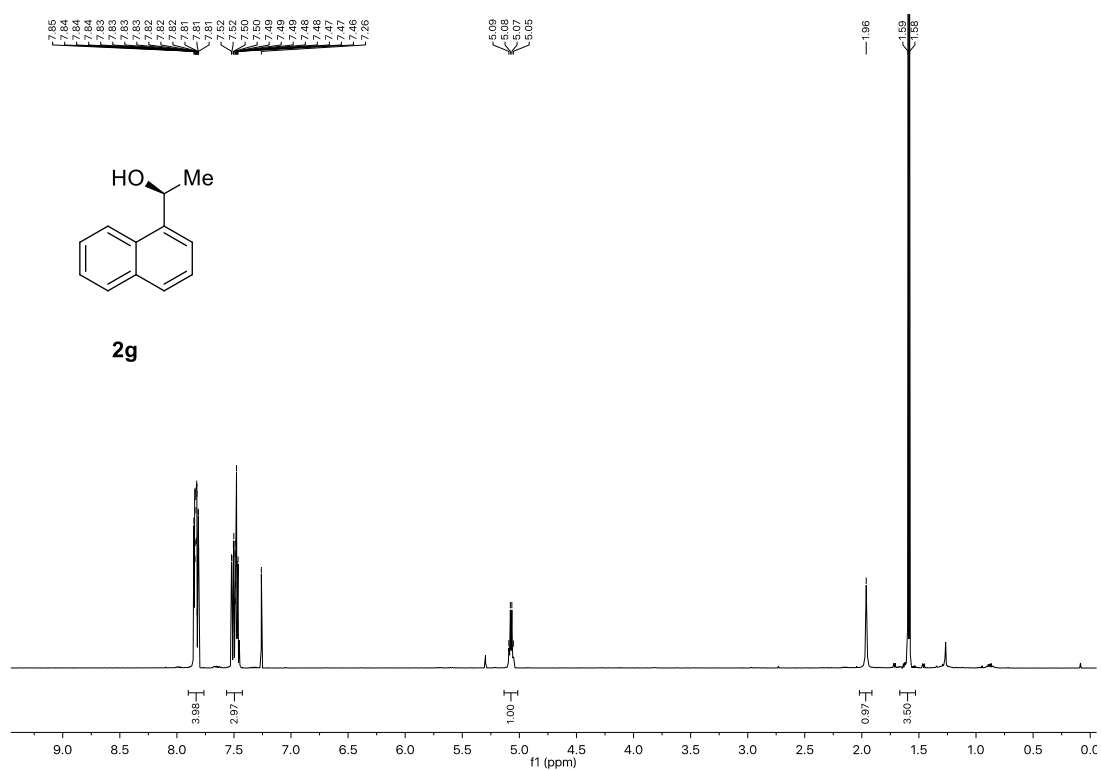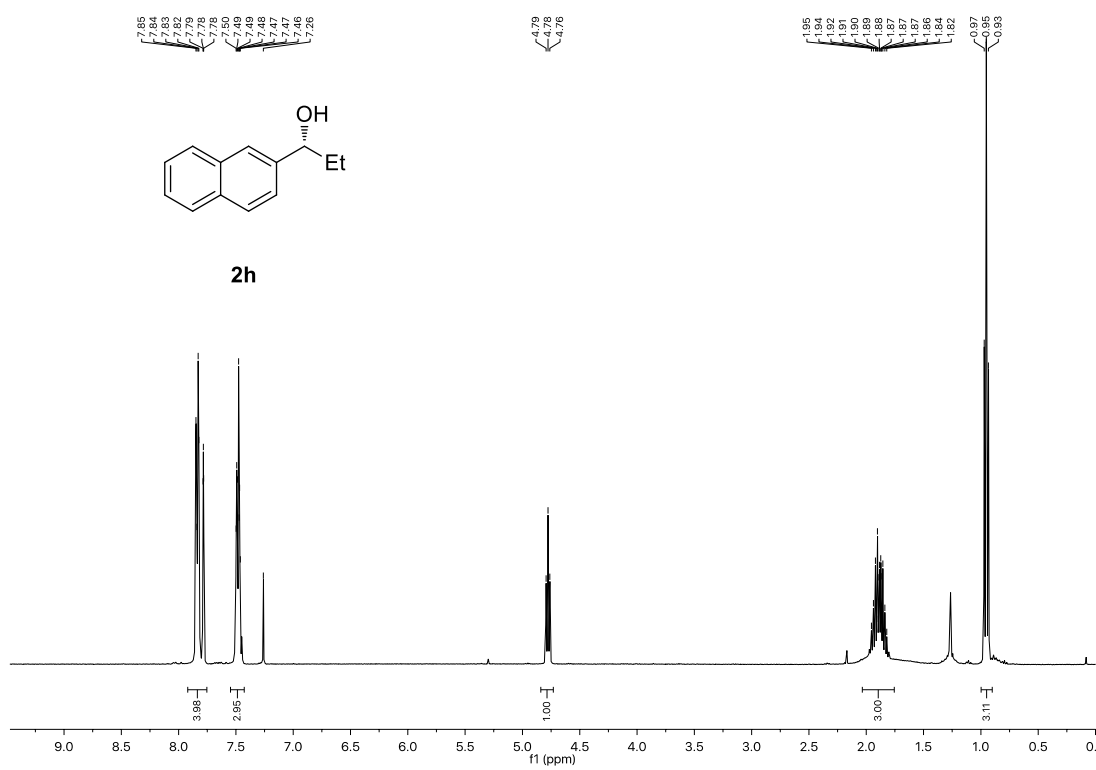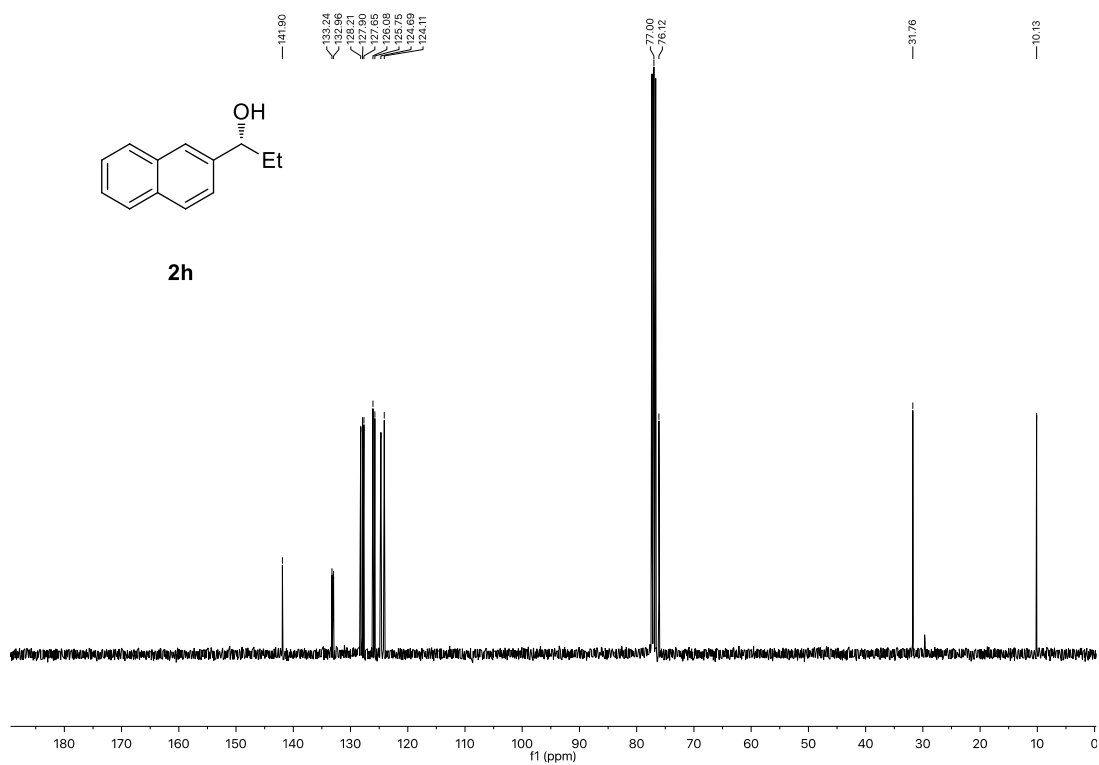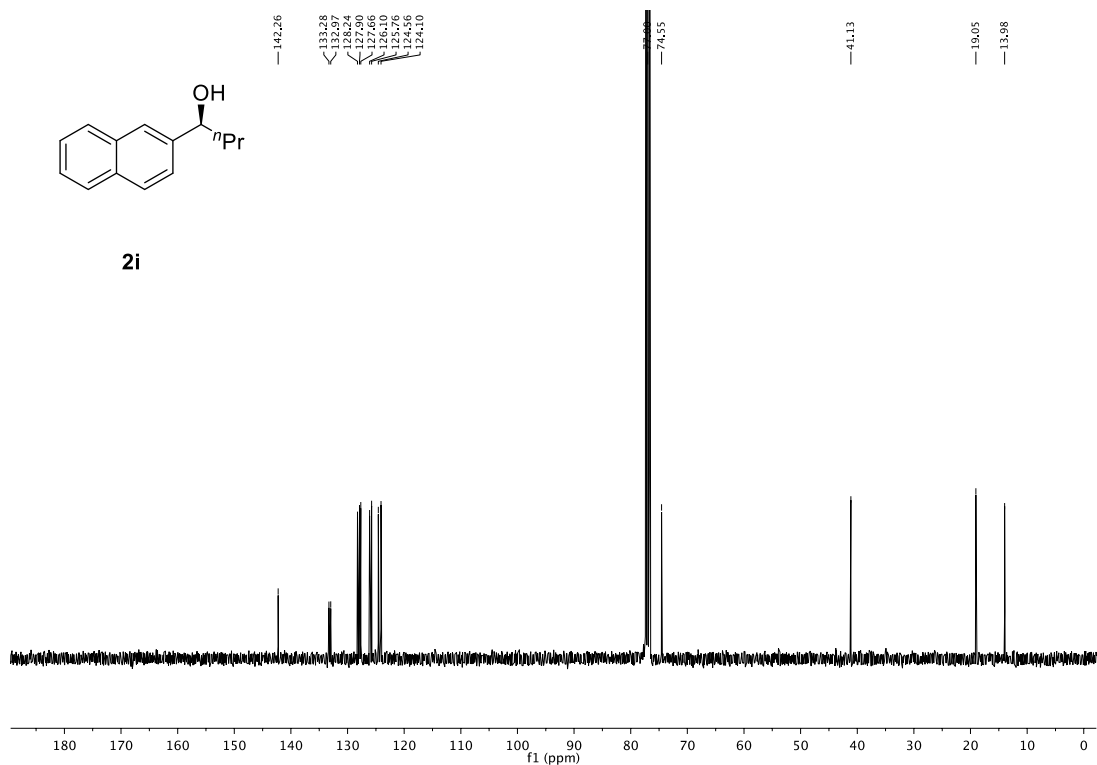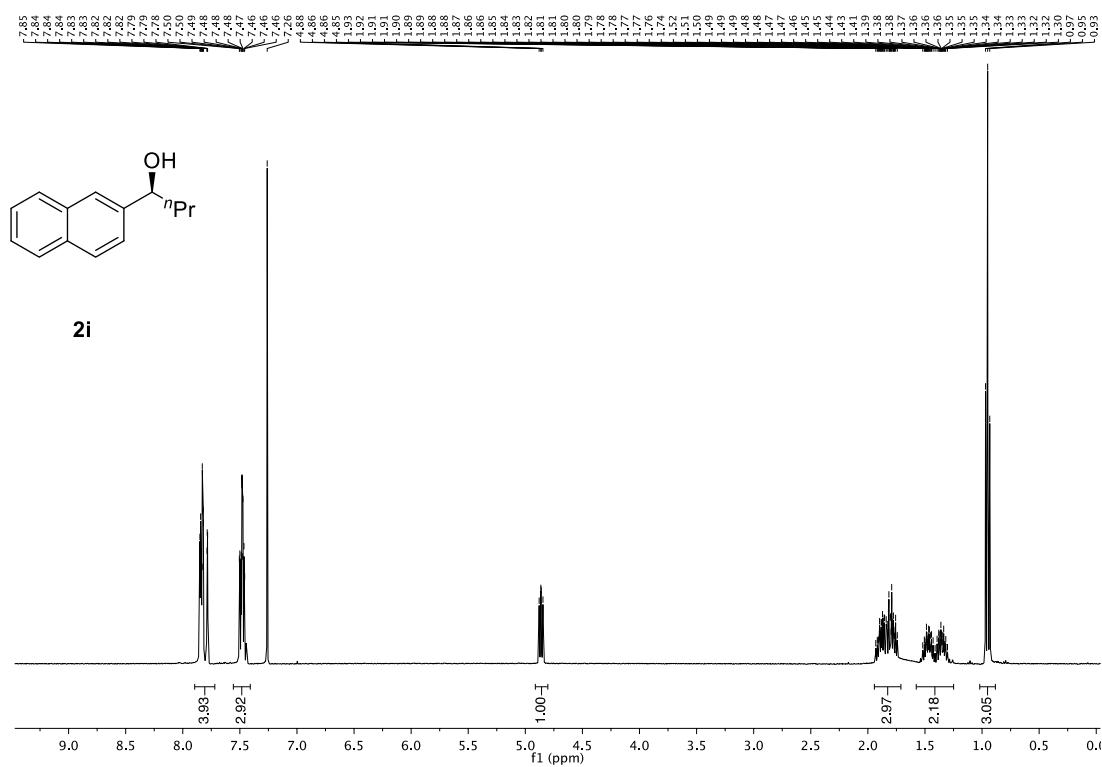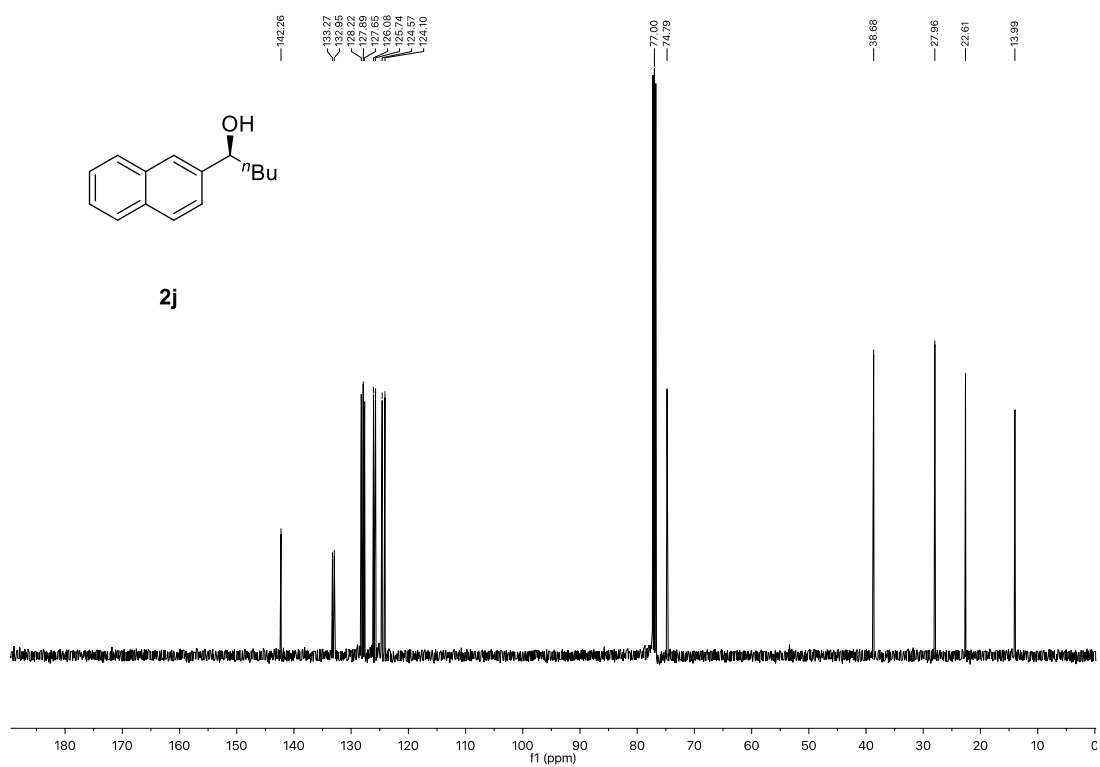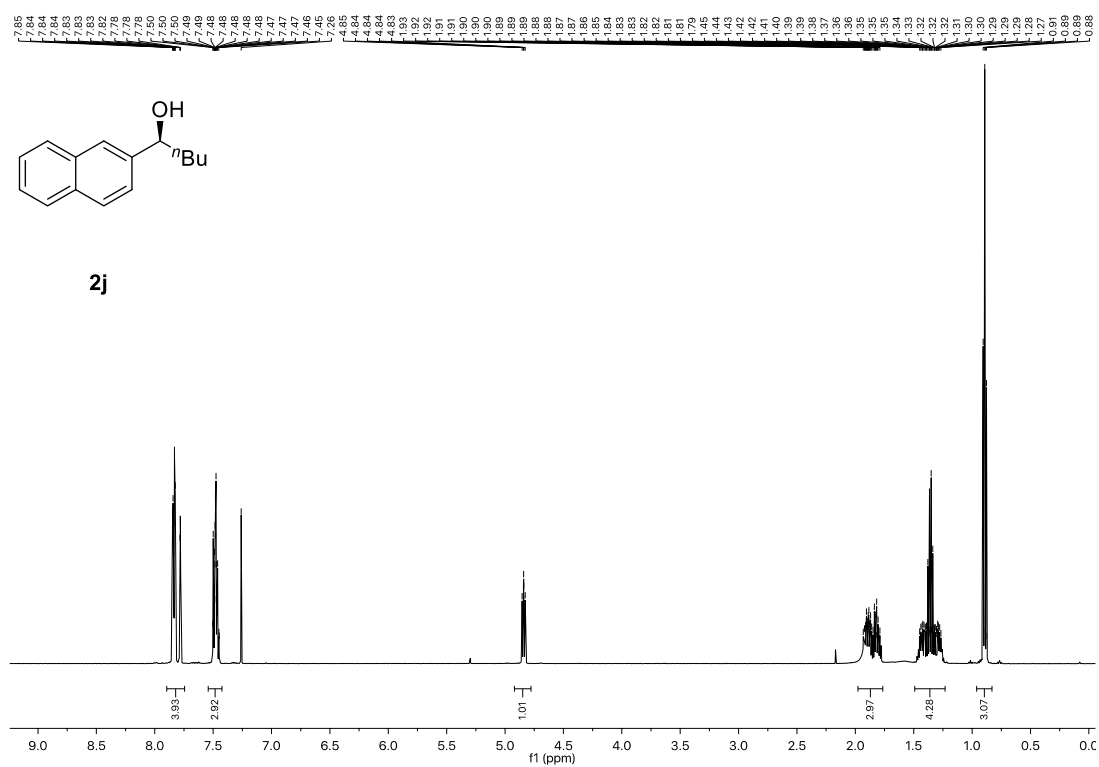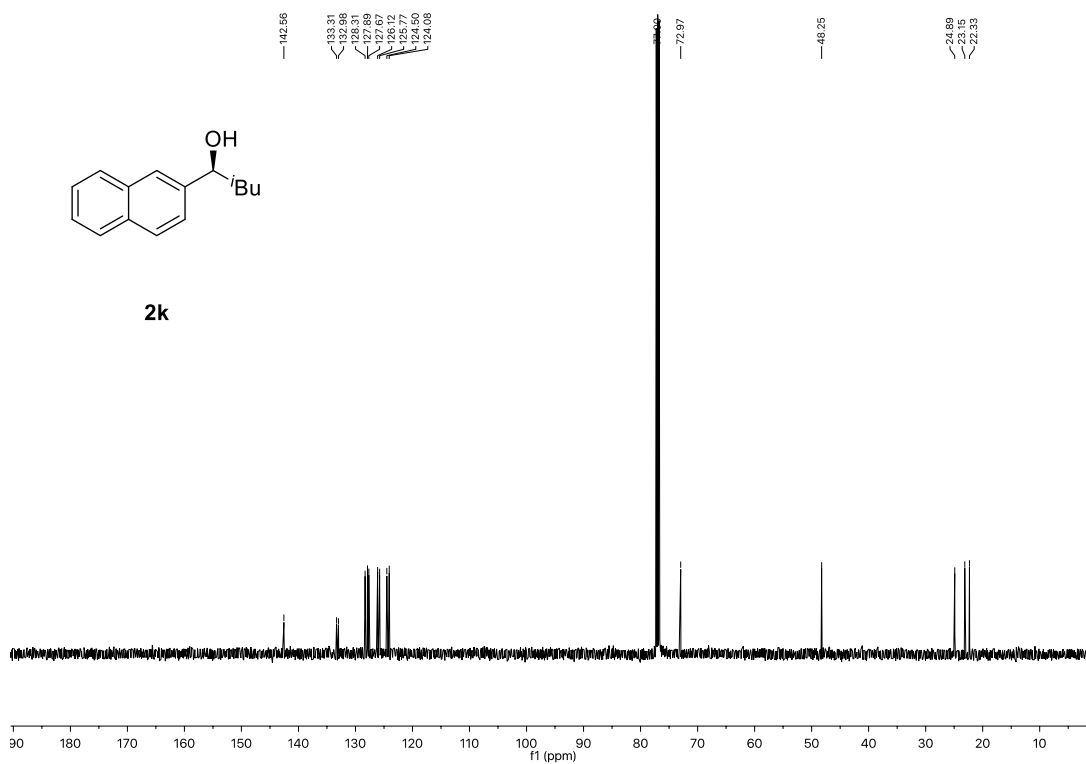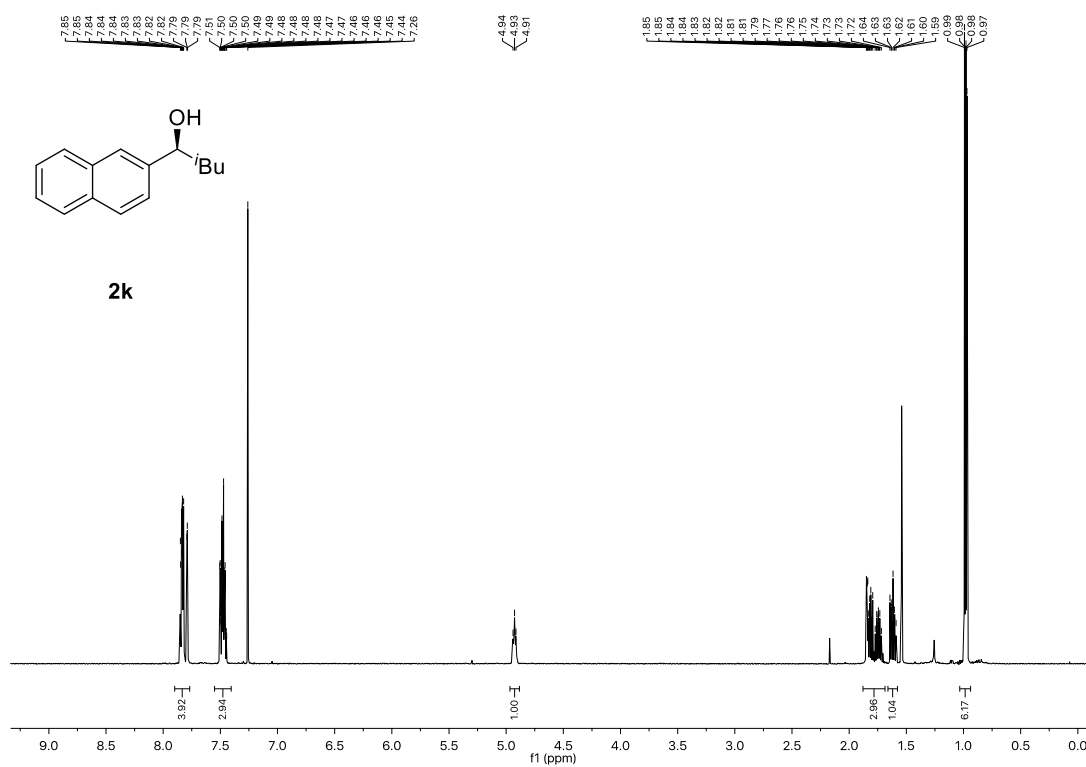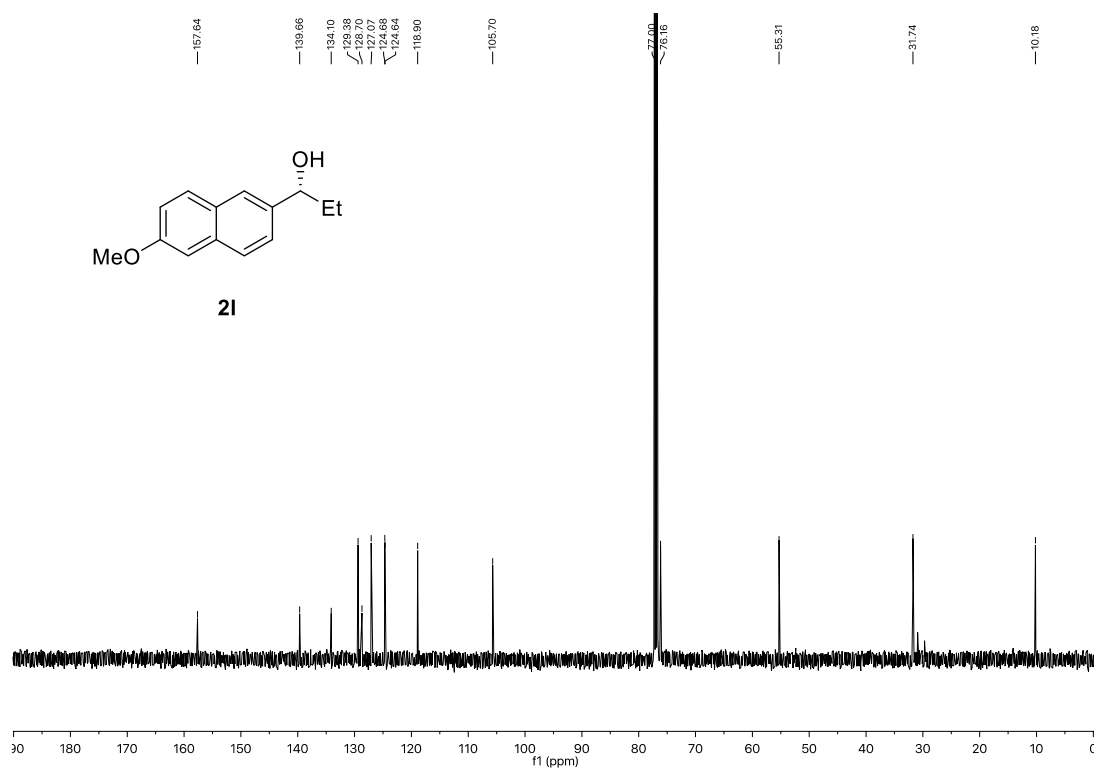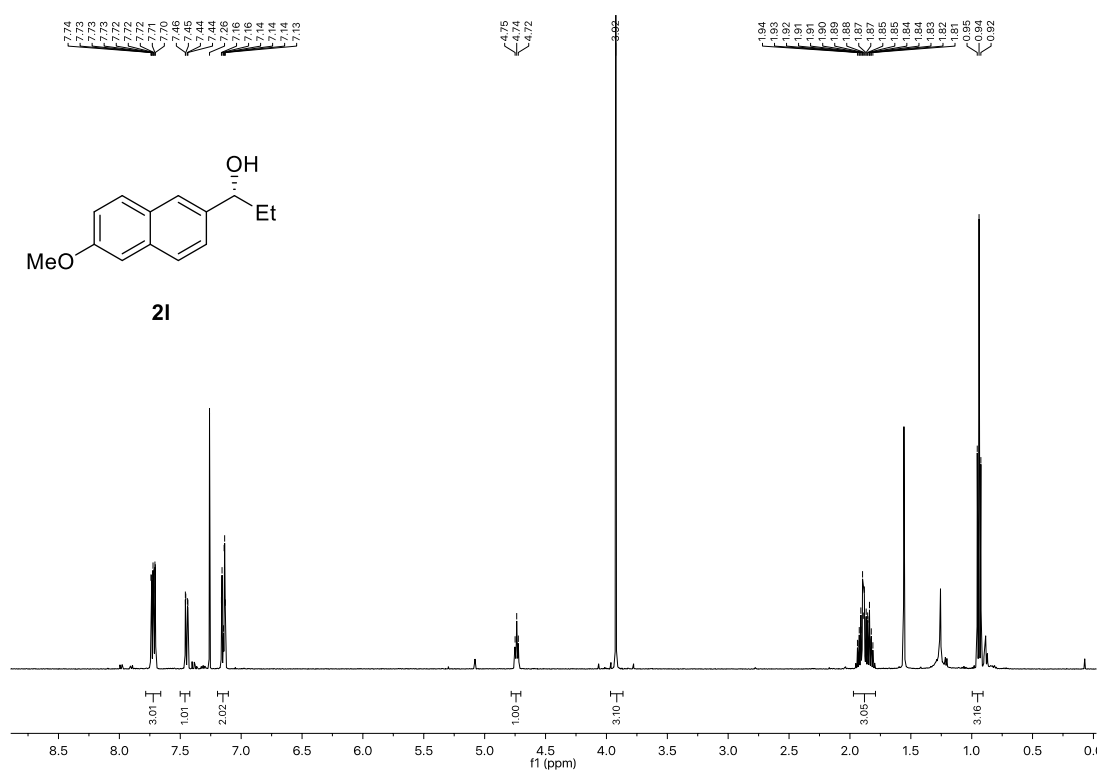*Stereospecific Borylation of Benzyl C(sp³)–O Bonds*

IA_CO2-MeOH_95:5_1500
RM-267-4_IA_MeOH-DEA_5_03 Sm (Mn, 2x3)

11-Jul-2017 10:31:55
Diode Array
272
Range: 1.267e-1

Time	Height	Area	Area%
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2.21	97096	6112.57	49.98
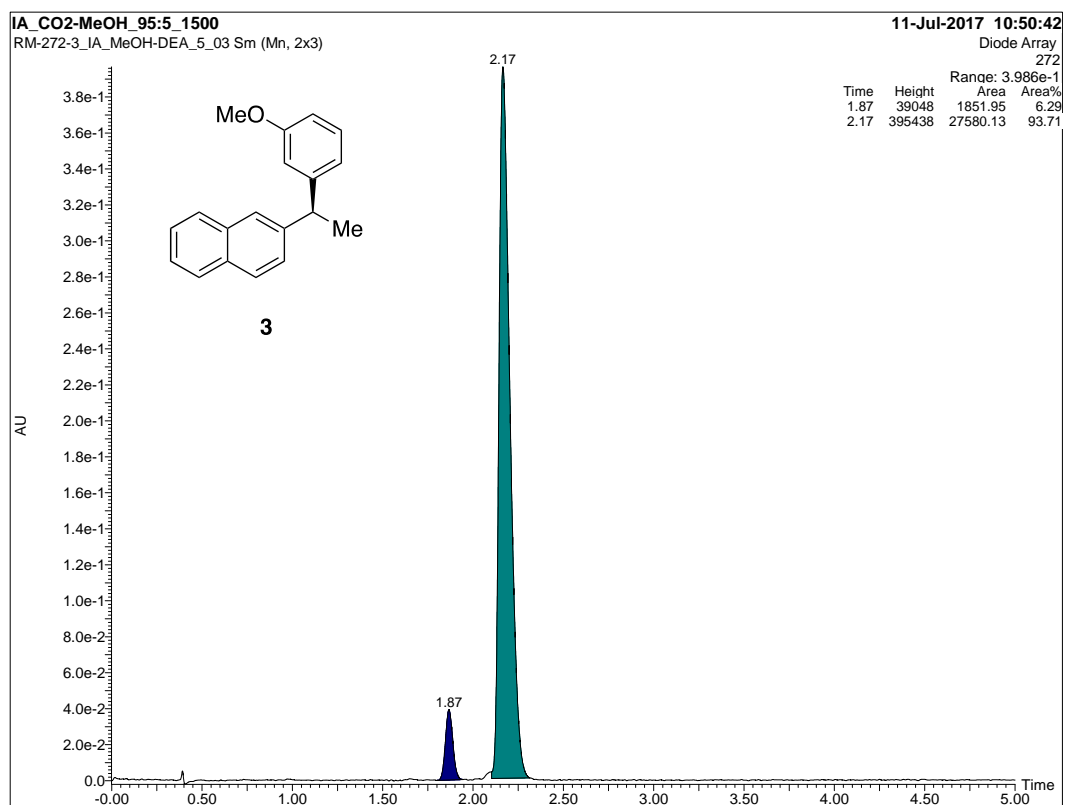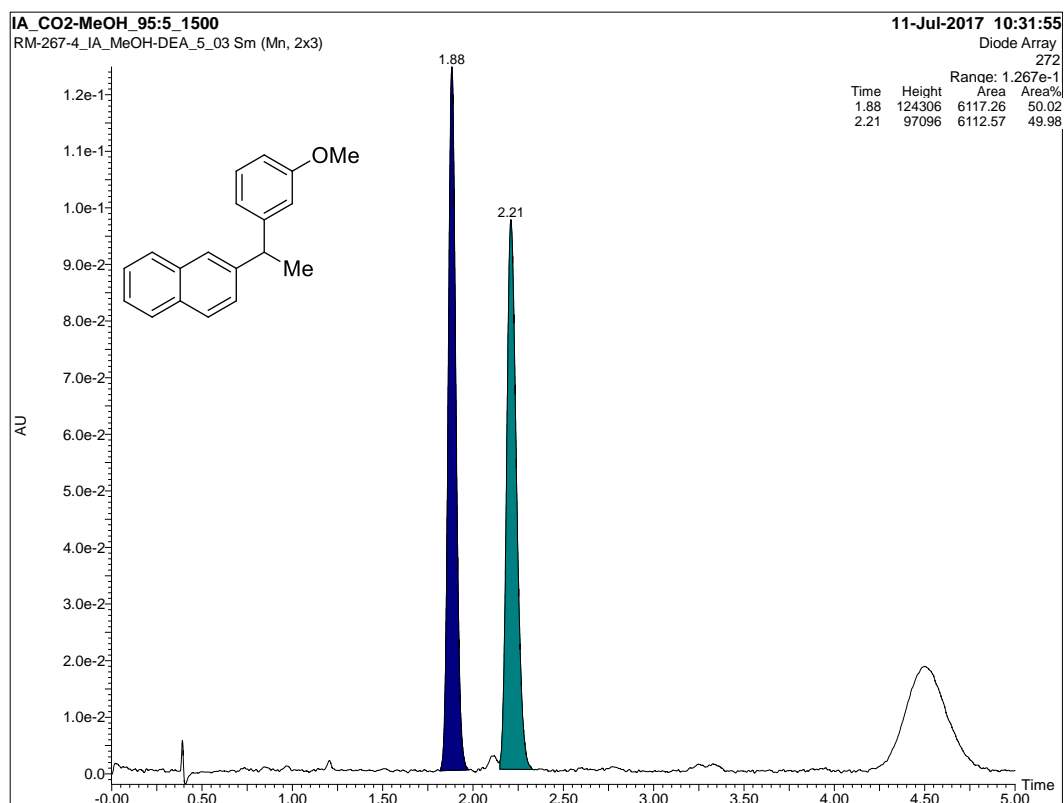
Procedure for the vinylation of benzylic boronic ester.[X]
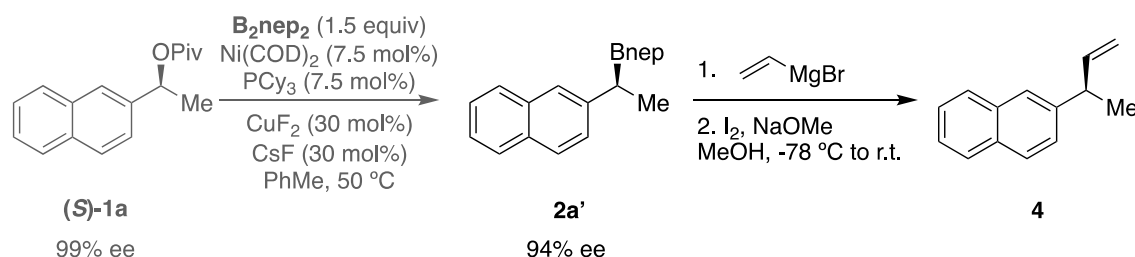
(S)-1a
99% ee

2a'
94% ee

4

Prior **(S)-2a'** was prepared following the general procedure for the borylation of benzyl pivalates and was used further without purification step. To a solution of **2a** (0.2 mmol, 1.0 equiv.) in anhydrous THF (2 mL, 0.1 M) at room temperature was added vinylmagnesium bromide (1 M in THF, 0.8 mL, 0.8 mmol, 4.0 equiv.) dropwise. The resulting mixture was stirred for 30 min and then cooled down to –78 ºC. A solution of iodine (203 mg, 0.8 mmol. 4 equiv.) in MeOH (3 mL) was added dropwise to the reaction mixture, followed 30 min later by a solution of MeONa in MeOH (25 w%, 370 mL, 1.6 mmol, 8.0 equiv.). The reaction mixture was then allowed to warm up to room temperature and stirred for an additional 1 hour, then diluted with pentane (30 mL) and washed with a 20% aq. NaS_2O_3 solution (4 mL) and water (8 mL). The phases were separated, the aqueous layer was extracted with pentane (2 x 15 mL), and the combined organic layers were washed with brine (8 mL), dried (MgSO4), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexanes 100%) to yield the desired product **4** (18.6 mg, 51 % overall yield) with 94% ee (99% ee_s) as colourless oil.

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Enantiomeric ratio was determined by SFC analysis (CHIRALPAK IG, 1 mL/min, CO_2/MtBe-Hex 50-50, gradient 0-40, λ=210 nm); t_R(minor)= 3.53 min, t_R(major)= 3.60 min. $[\alpha]_D^{24}$ = -8.4º (c 0.05, $CHCl_3$). [1]H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 8.2, 5.6 Hz, 3H), 7.65 (s, 1H), 7.44 (dd, J = 7.8, 5.7 Hz, 2H), 7.36 (dd, J = 8.5, 1.8 Hz, 1H), 6.09 (dd, J = 16.9, 10.3, 6.4 Hz, 1H), 5.15 – 5.04 (m, 2H), 3.64 (t, J = 6.9 Hz, 1H), 1.46 (d, J = 7.0 Hz, 3H) ppm. [13]C NMR (101 MHz, $CDCl_3$) δ 143.1, 143.0, 133.6, 132.2, 127.9, 127.7, 127.6, 126.2, 125.9, 125.3, 125.2, 113.4, 43.2, 20.7 ppm. The spectral data for compound **3** matches that reported in literature.[XI]

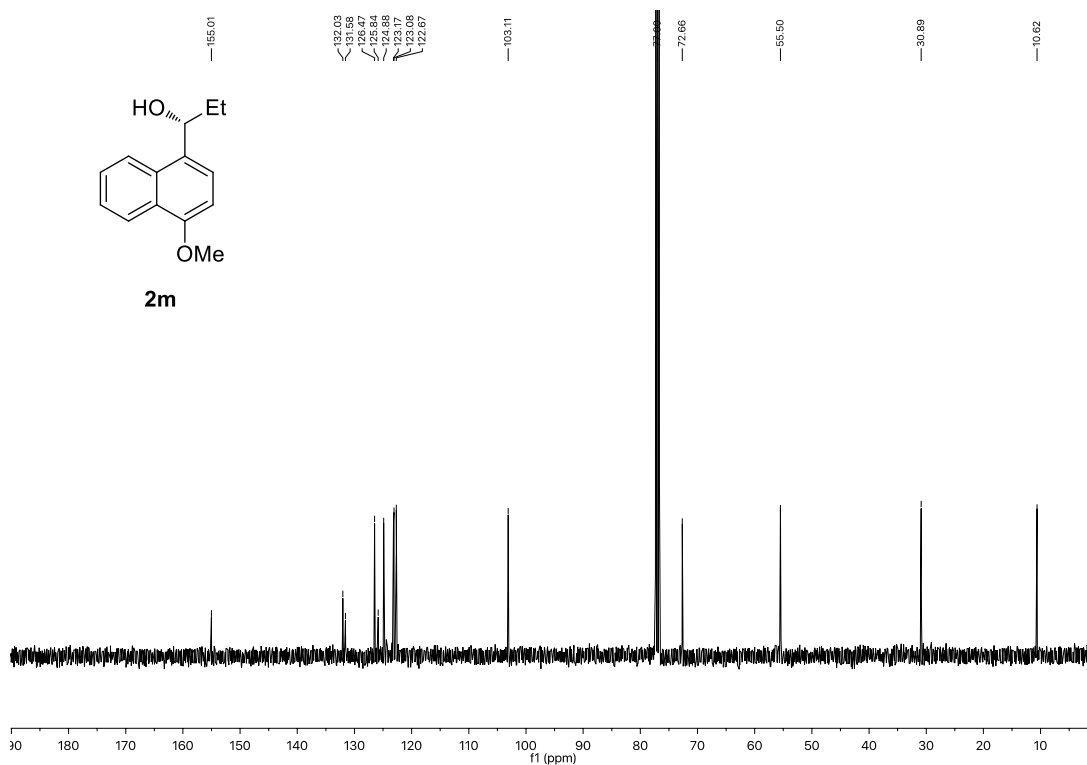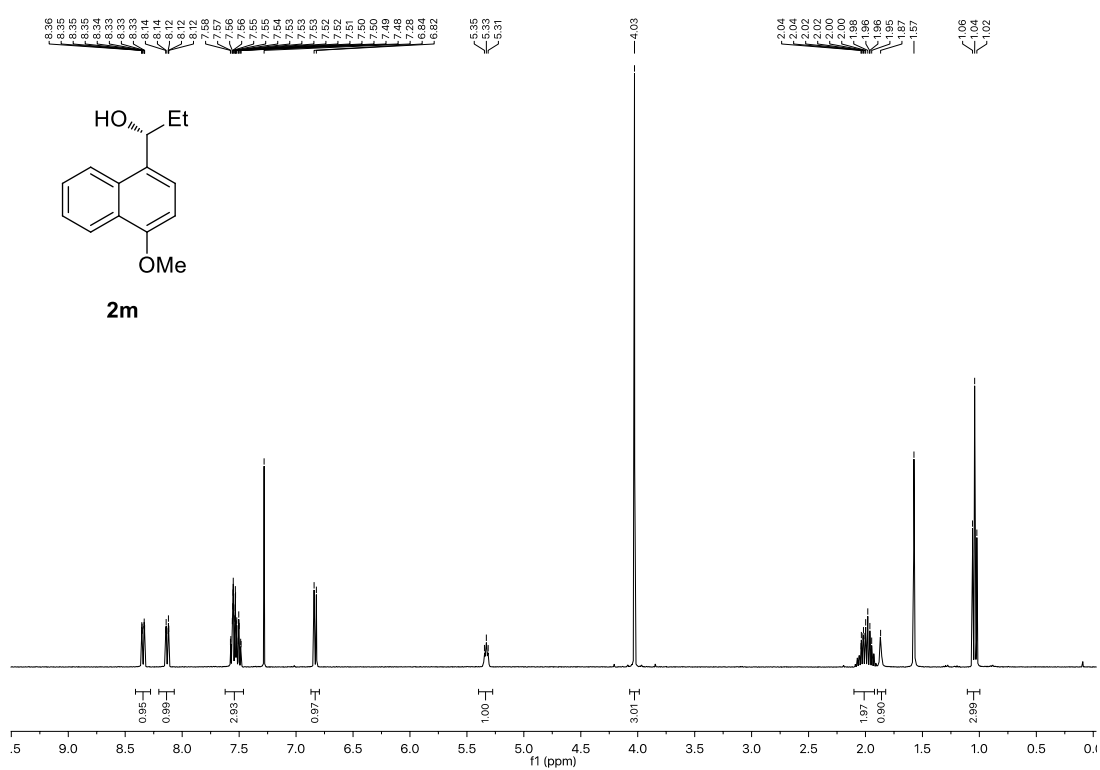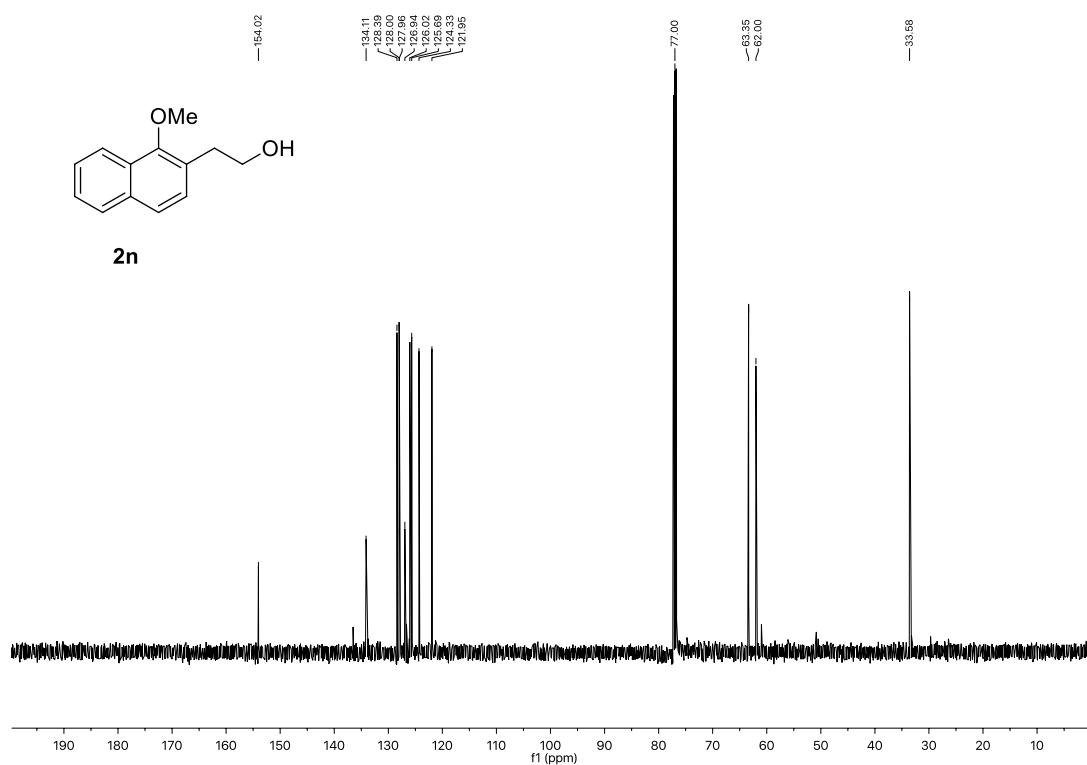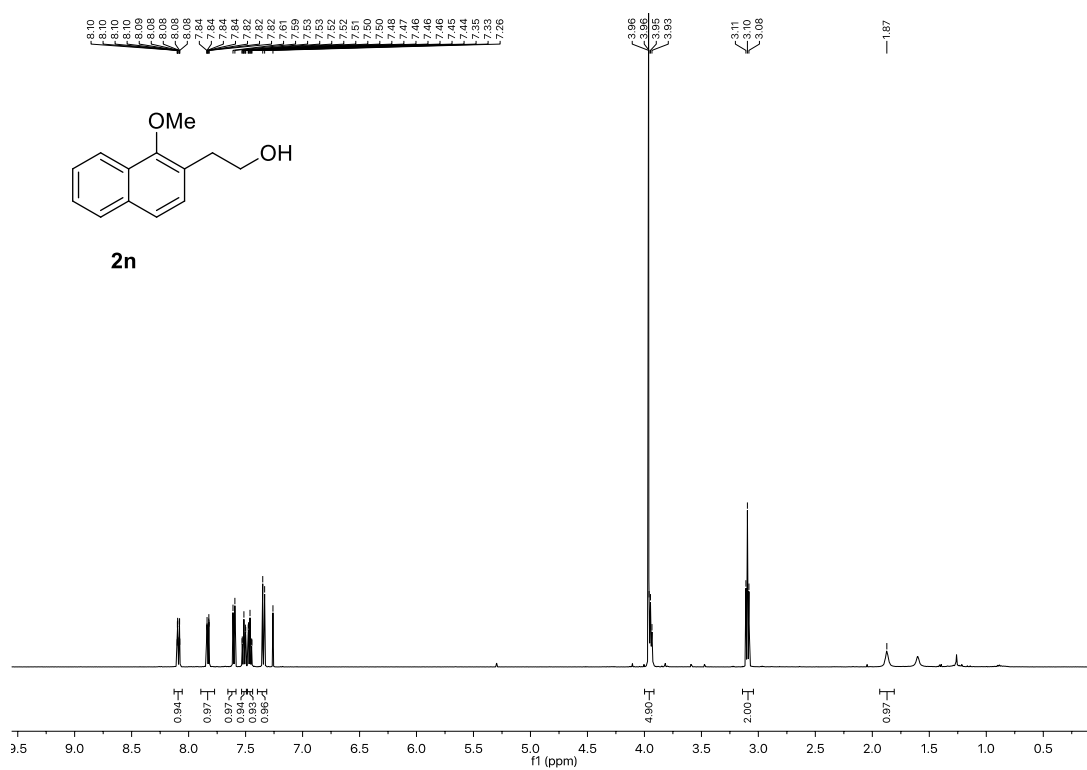*Stereospecific Borylation of Benzyl C(sp³)–O Bonds*
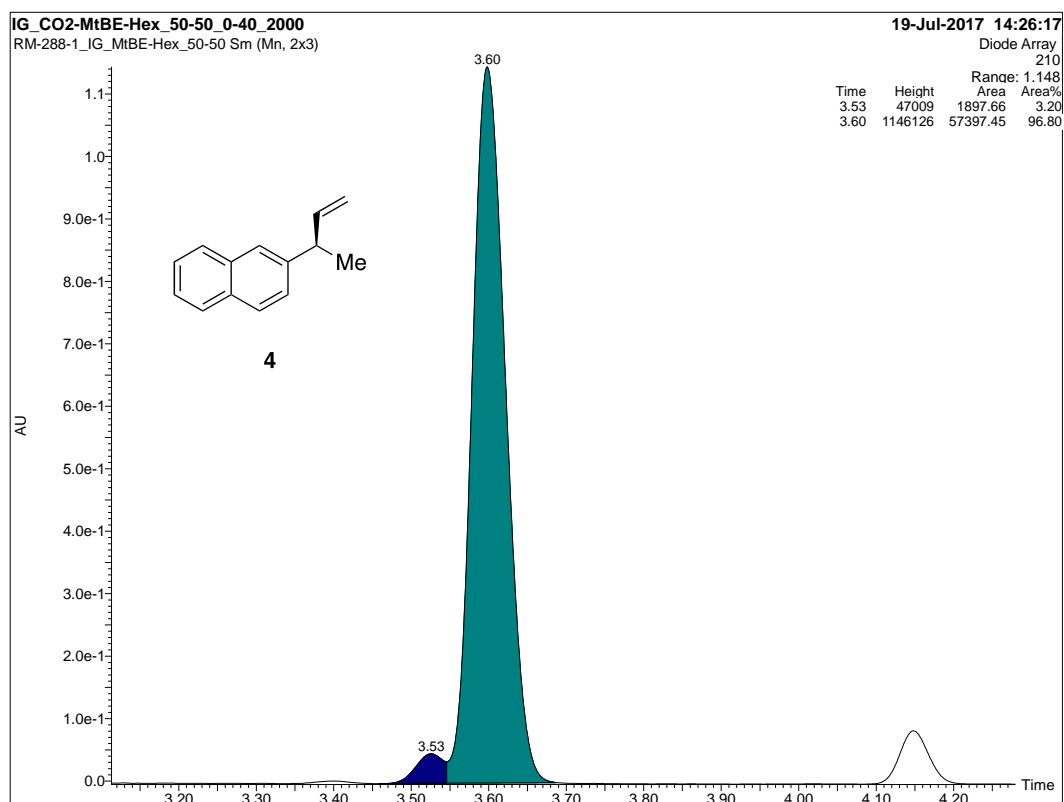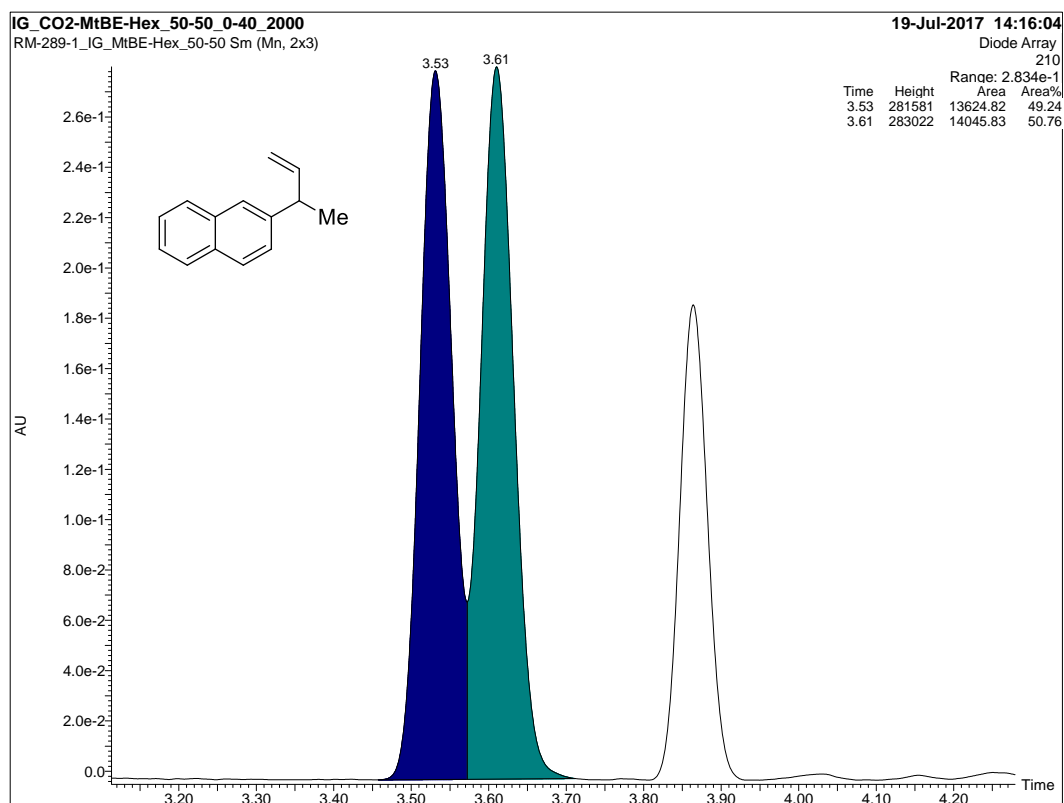
2.5.5   References of experimental procedures

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X) Sonawane. R. P.; Jheengut. V.; Rabalakos. C.; Larouche-Gauthier. R.; Scott. H. K; Aggarwal. V. K. *Angew. Chem. Int. Ed.* **2011**, *50*, 3760–3763

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Chapter 2

2.5.6 ¹H-NMR, ¹³C-NMR and ¹⁹F-NMR spectra.
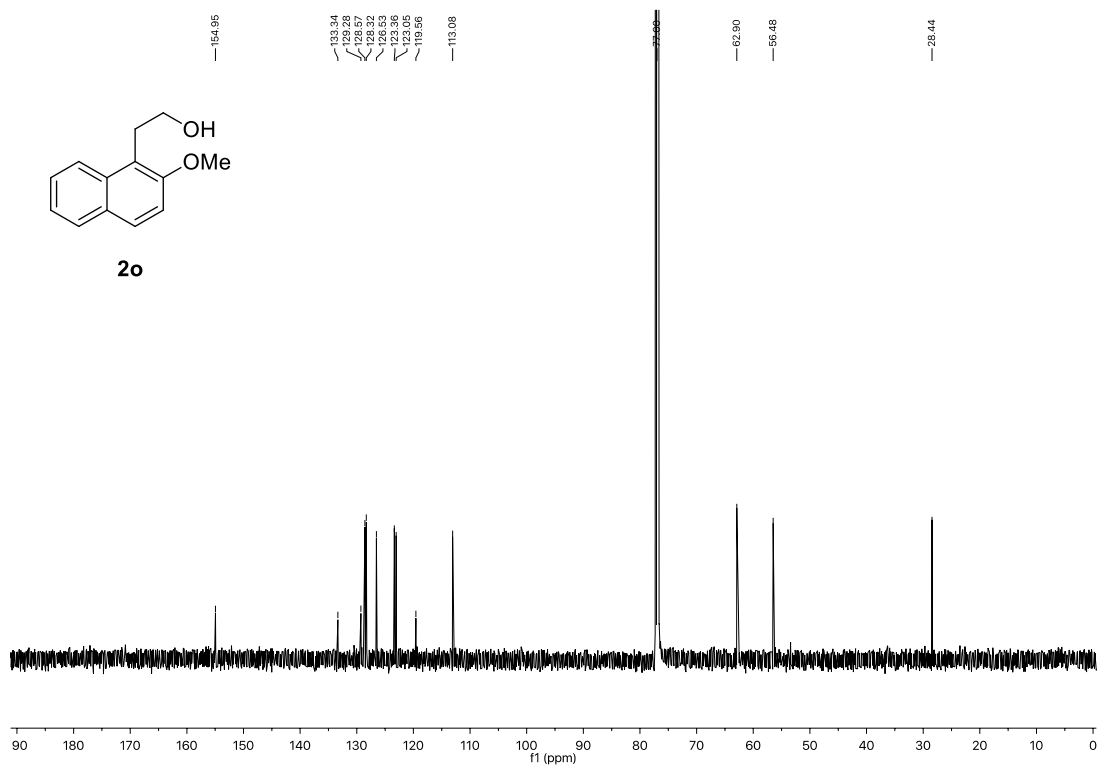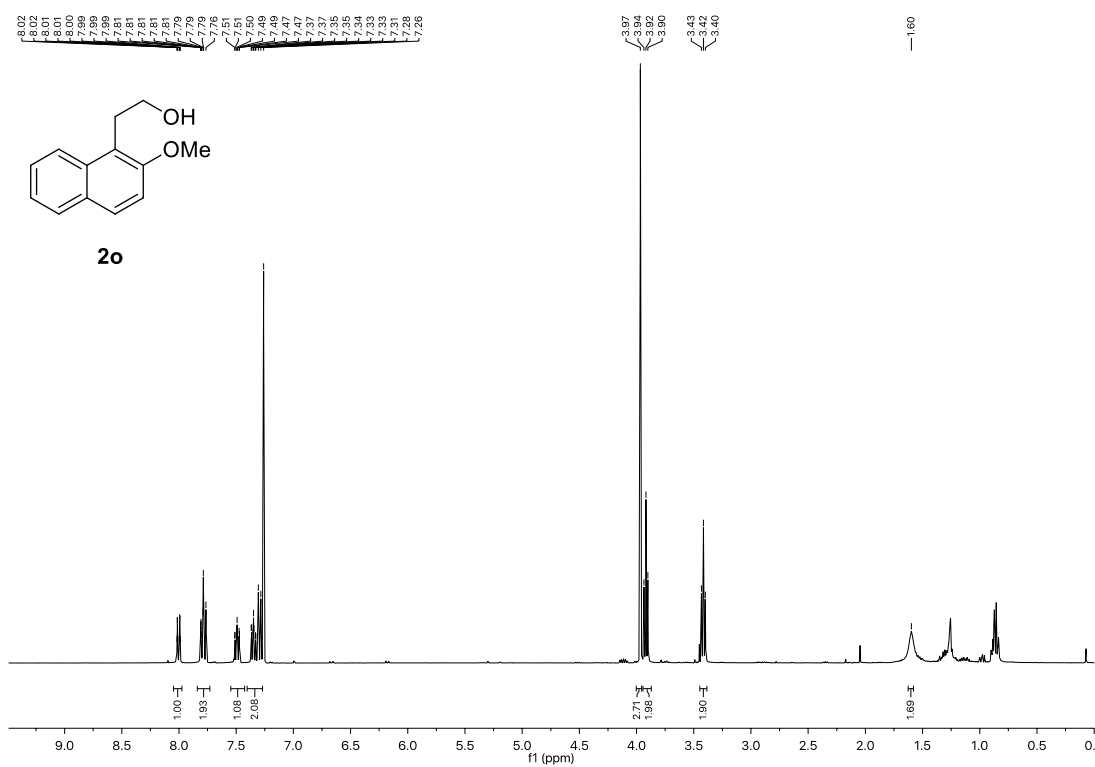
Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Chapter 2

S-1i

S-1i

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

S-1j

S-1j

Chapter 2

S-1n

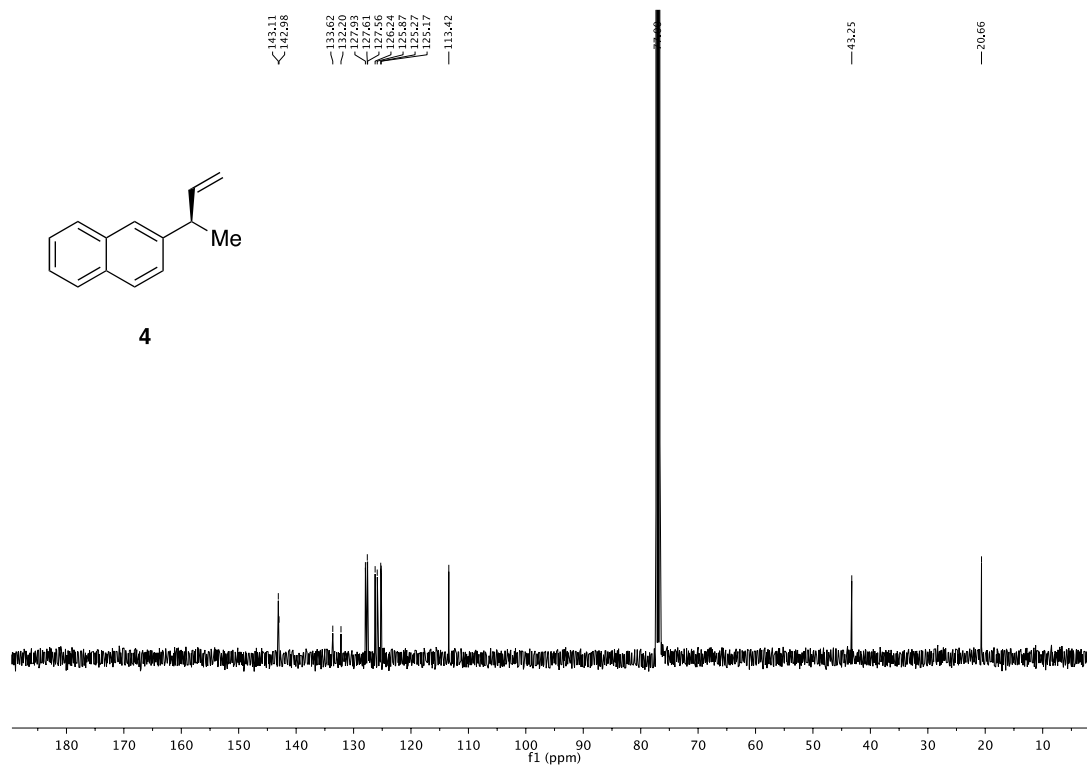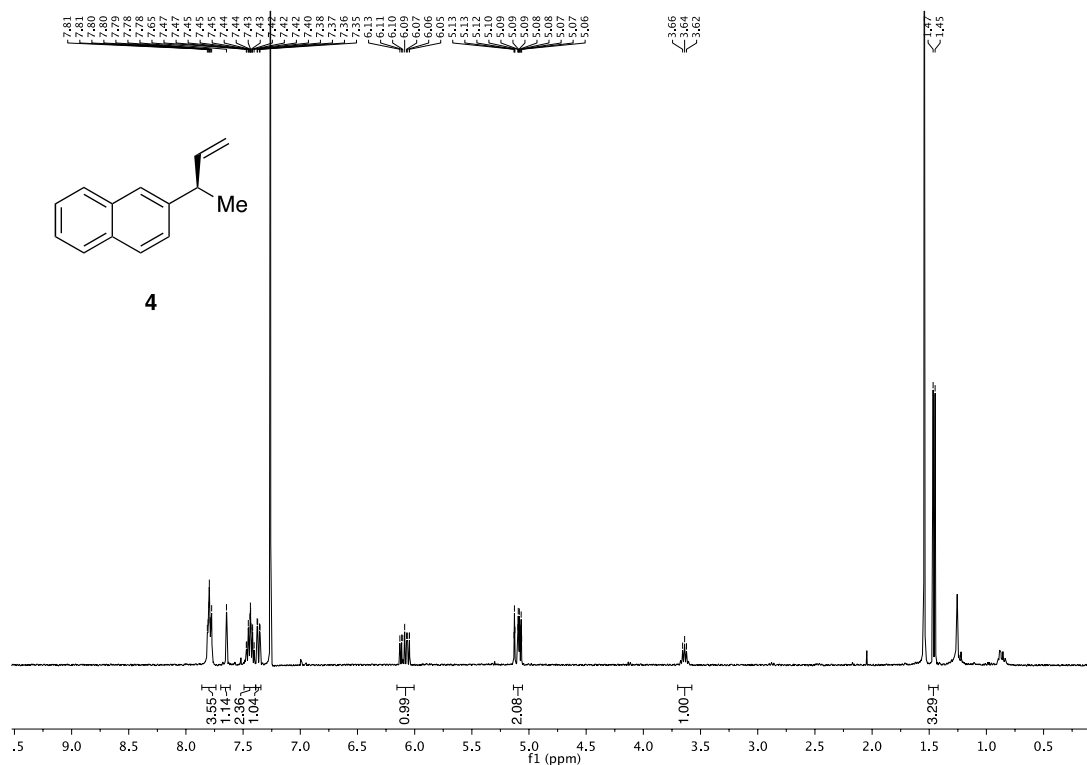**S-1n**

Chapter 2

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

1b

1b

Chapter 2

1d

1d

Chapter 2

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

1e

1e

Chapter 2

S-1f

S-1f

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

1g

1g

Chapter 2

1h

1h

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Chapter 2

1j

1j

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

1k

1k

Chapter 2

1l

1l

1m

1m

Chapter 2

1n

1n

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

PivO — Me
OMe

1o

PivO — Me
OMe

1o

Chapter 2

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

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Chapter 2

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Chapter 2

2d

2e

2e

Chapter 2

2f

2f

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Chapter 2

2h

2h

2i

2i

Chapter 2

2j

2j

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

2k

2k

Chapter 2

2l

2l

Chapter 2

2n

2n

2o

2o

Chapter 2

Chapter 2

2.5.7   HPLC

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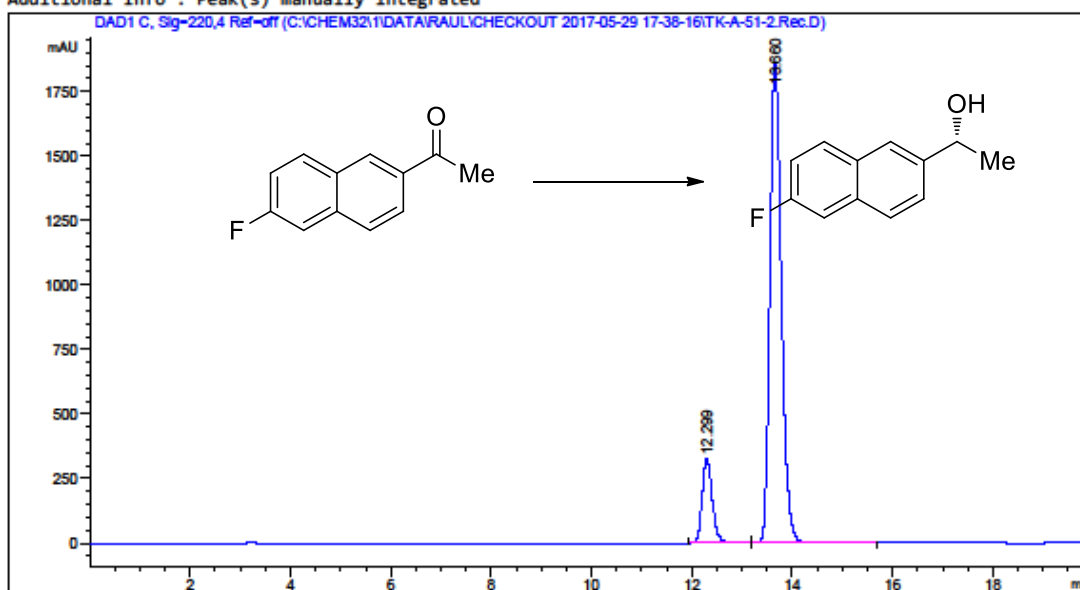


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                    Area Percent Report
================================================================

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Multiplier            :     1.0000
Dilution              :     1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
 #   [min]        [min]   [mAU*s]     [mAU]       %
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  2  13.660 BB   0.2454 2.95954e4   1862.73413  86.7211

Totals :                 3.41271e4   2192.20761


================================================================
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UNIVERSITAT ROVIRA I VIRGILI
Functionalization of Strong Sigma Bonds by Nickel and Tungsten Catalysis
Raúl Martín Montero

Stereospecific Borylation of Benzyl C(sp³)–O Bonds
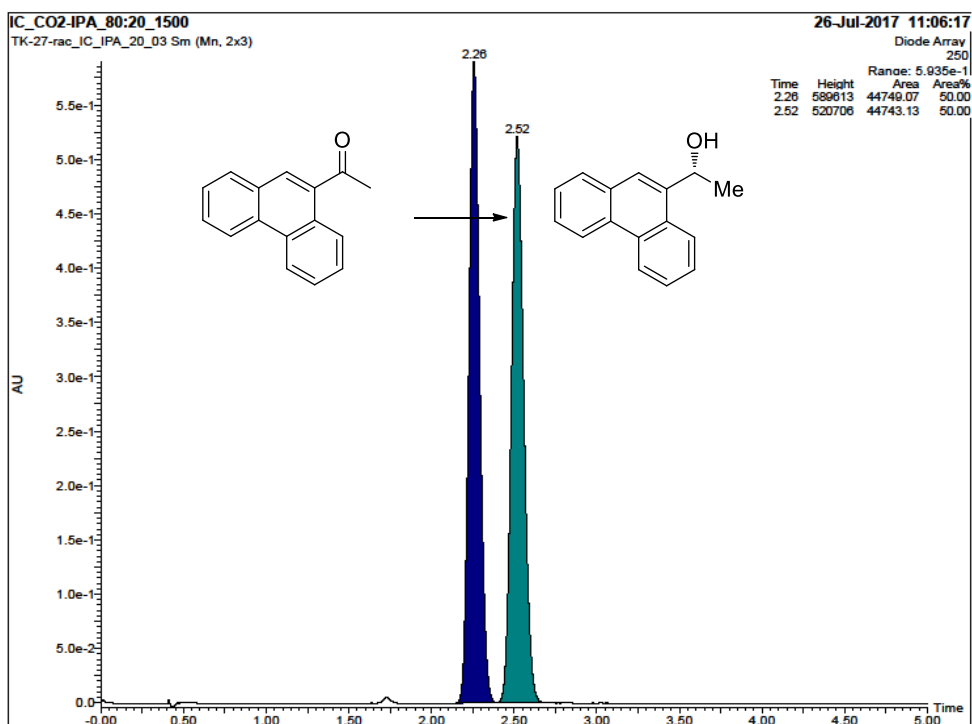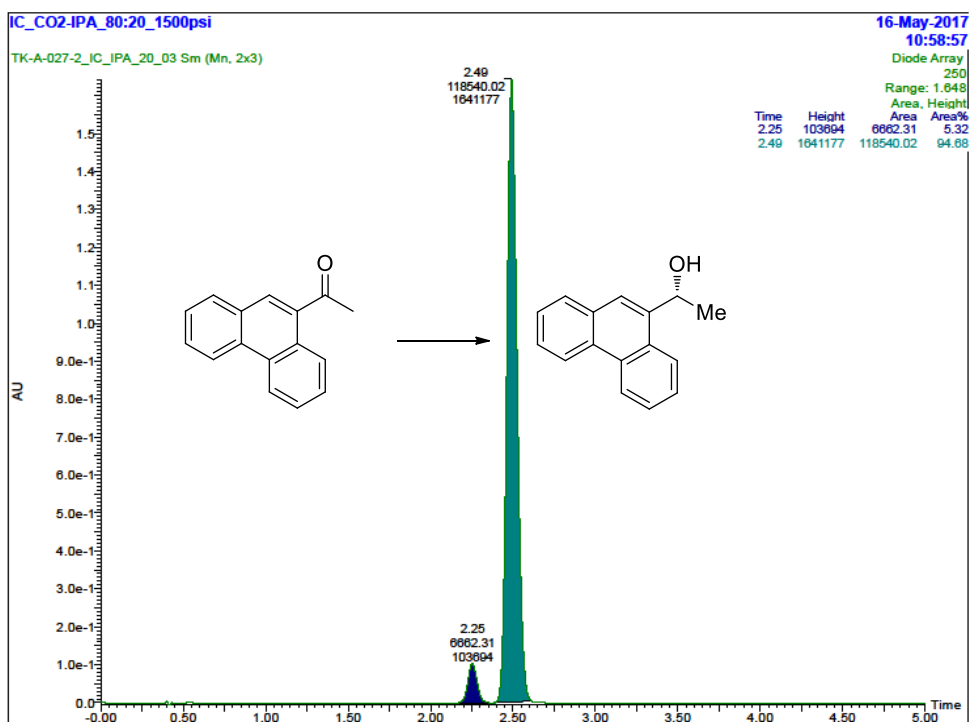
Chapter 2

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Sample Name: RMZ-81-Rec.98.5-1.5

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                   98-2.M
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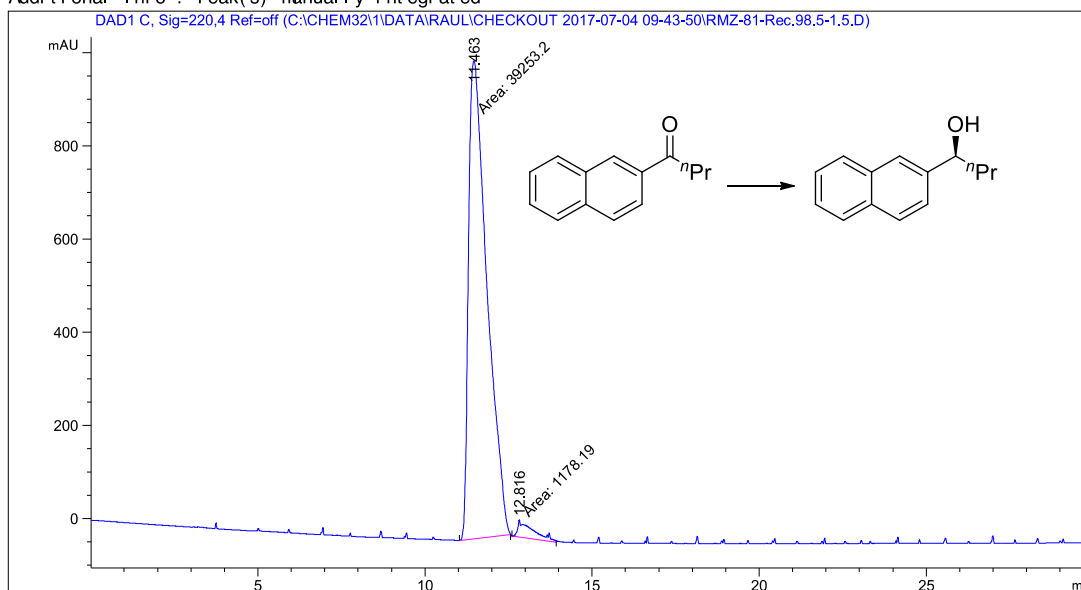


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Dilution           :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
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Totals :                 4.04314e4  1062.86647


====================================================================
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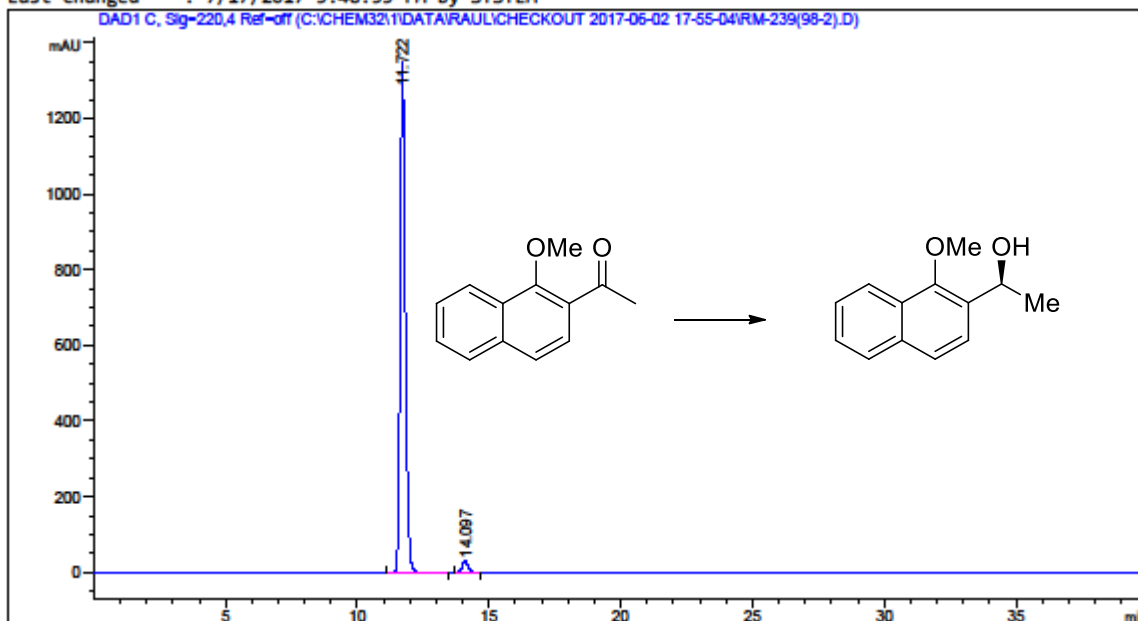
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Stereospecific Borylation of Benzyl C(sp³)–O Bonds

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Sample Name: RM-195-Aft.Rec

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                                           Inj Volume : 1.000 µl
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                  98-2.M
Last changed    : 5/16/2017 9:17:46 AM by SYSTEM
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Last changed    : 7/17/2017 5:48:55 PM by SYSTEM
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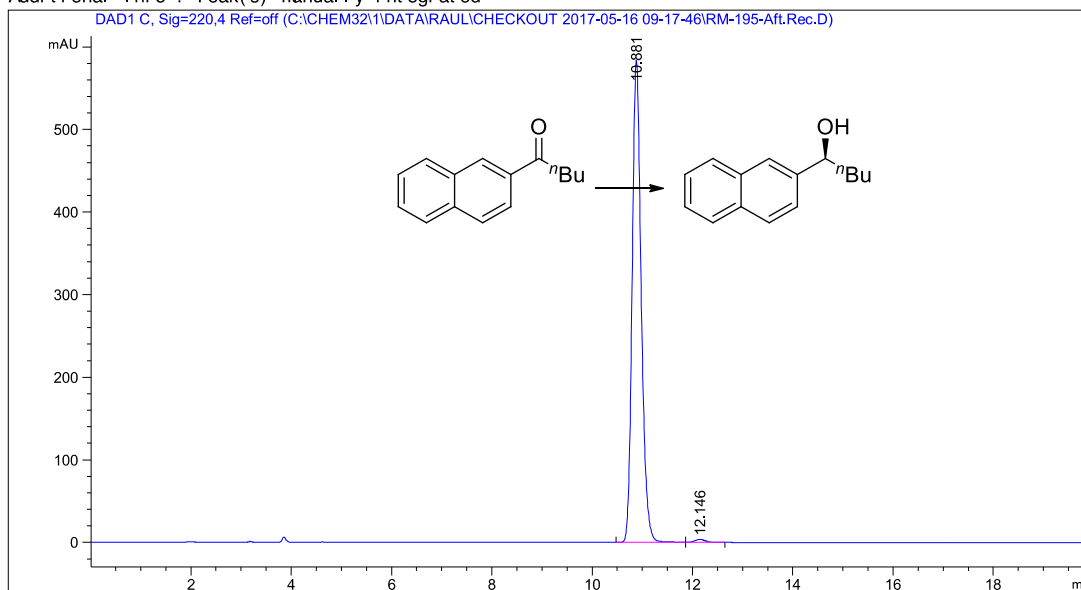


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=====================================================================
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Sorted By            :        Signal
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Dilution             :        1.0000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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
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----|-------|----|-------|----------|----------|--------|
  1  10.881  BB   0.1905  7331.90820  584.06335  99.3582
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Totals :                  7379.26843  587.54688
=====================================================================
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HPLC 1260 7/17/2017 6:30:35 PM SYSTEM   Page 1 of 2

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Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-06-29 10-58-24\TK-A-070_r995.D
Sample Name: TK-A-070_r995

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                  98-2.M
Last changed    : 6/29/2017 10:58:25 AM by SYSTEM
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Last changed    : 7/17/2017 5:48:55 PM by SYSTEM
Additional Info : Peak(s) manually integrated
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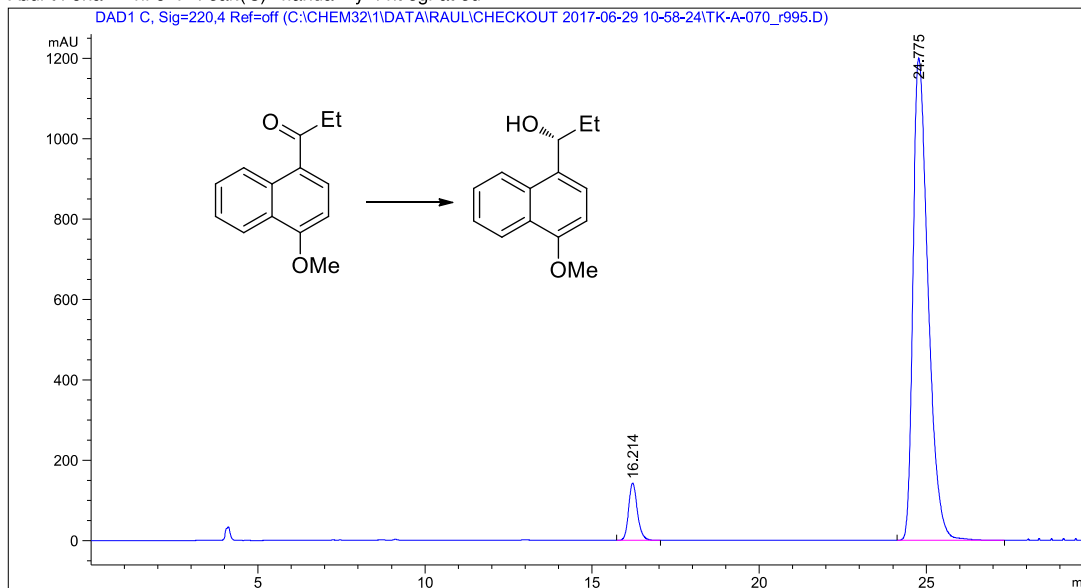


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===================================================================
                      Area Percent Report
===================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
  1  16.214 BB    0.2786 2595.00635  142.40141   6.4533
  2  24.775 BB    0.4795 3.76173e4  1200.79285  93.5467

Totals :                 4.02123e4  1343.19426


===================================================================
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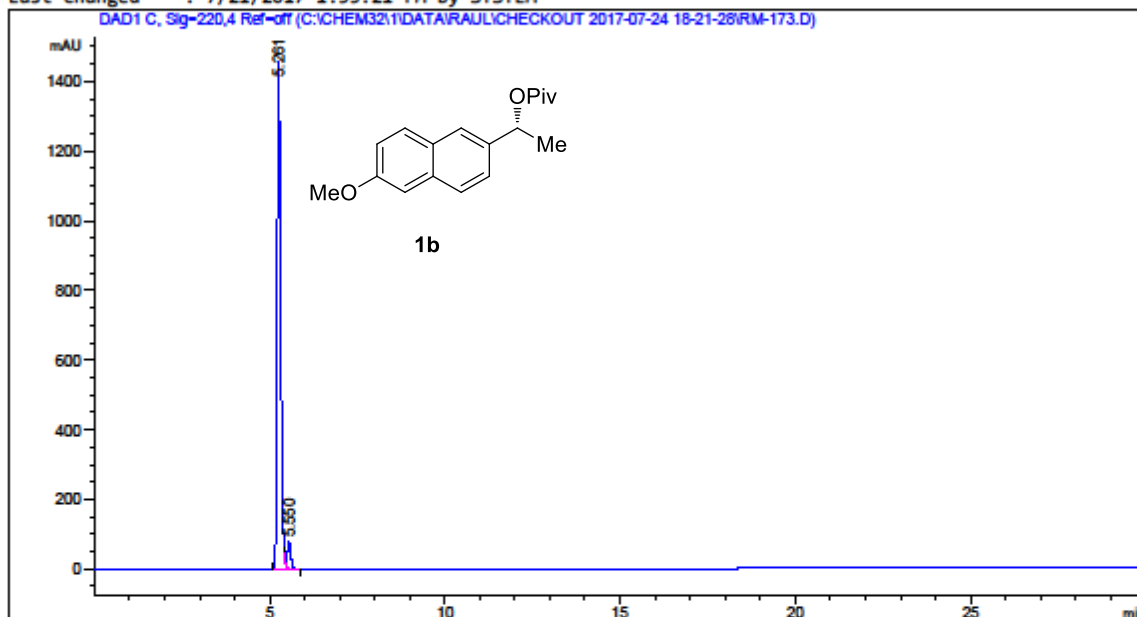
Stereospecific Borylation of Benzyl C(sp³)–O Bonds

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Sample Name: RM-239(98-2)

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                                        Inj Volume : 1.000 µl
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                  98-2.M
Last changed    : 6/2/2017 5:55:05 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/17/2017 5:48:55 PM by SYSTEM
```



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

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
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  2  14.097 BB   0.2431  473.26337   29.83288   2.5228

Totals :                 1.87592e4  1376.74927


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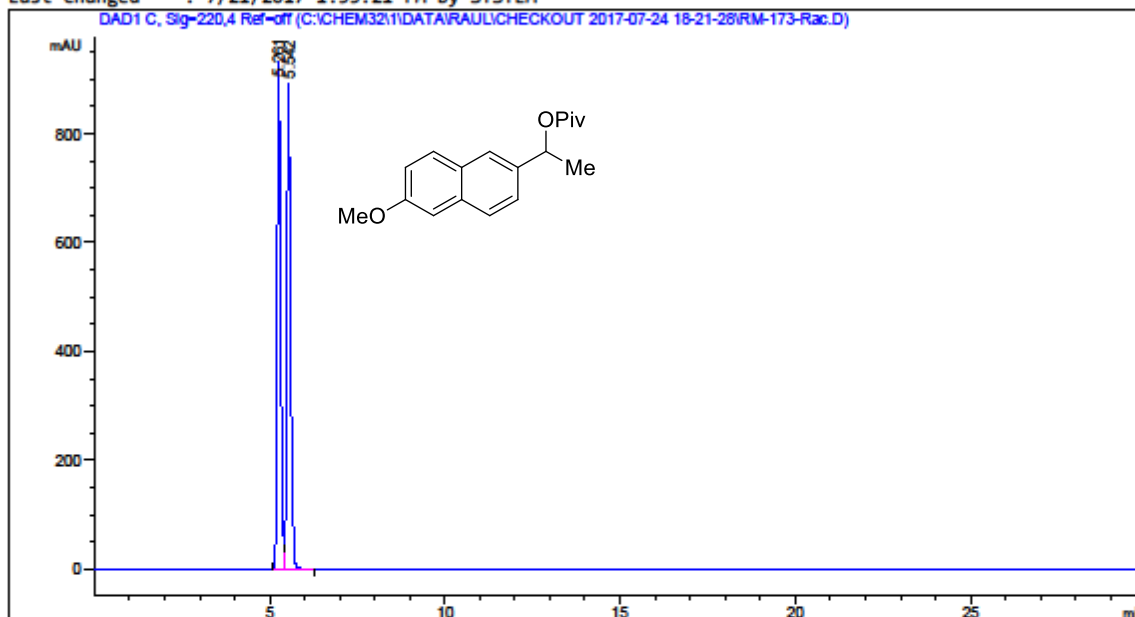
Chapter 2

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                  98-2.M
Last changed    : 6/9/2017 4:17:10 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/17/2017 5:48:55 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
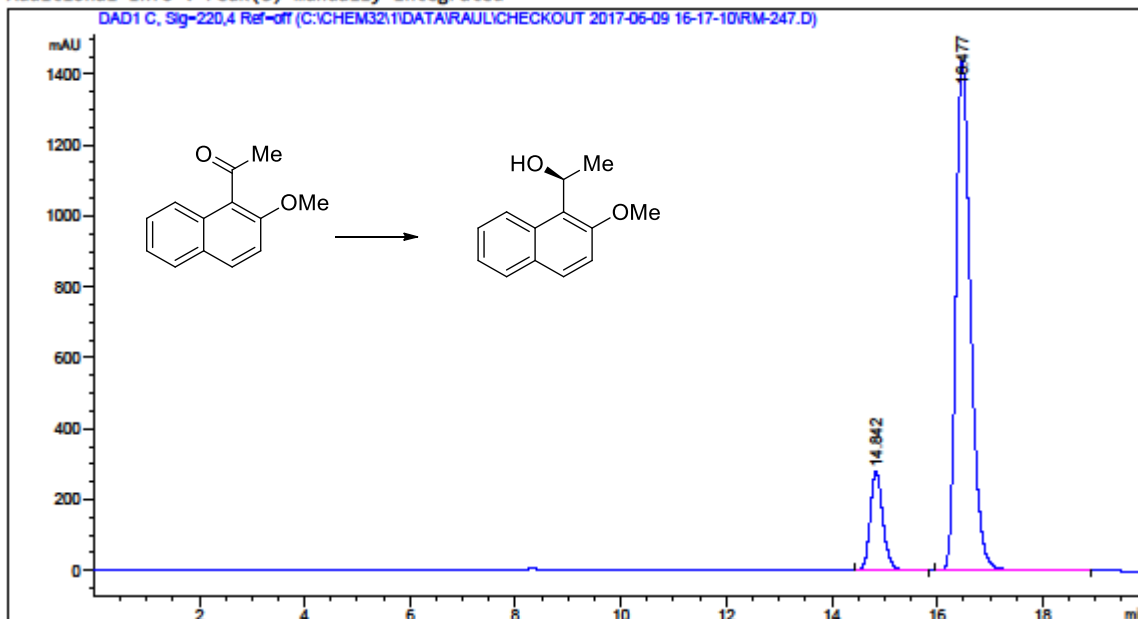


```
=================================================================
                   Area Percent Report
=================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area        Height      Area
 #   [min]        [min]   [mAU*s]       [mAU]         %
----|-------|----|-------|----------|----------|--------|
  1  14.842 BB   0.2540  4690.01709   281.98334  14.4222
  2  16.477 BB   0.2979  2.78294e4   1437.17590  85.5778

Totals :                 3.25194e4   1719.15924


=================================================================
```

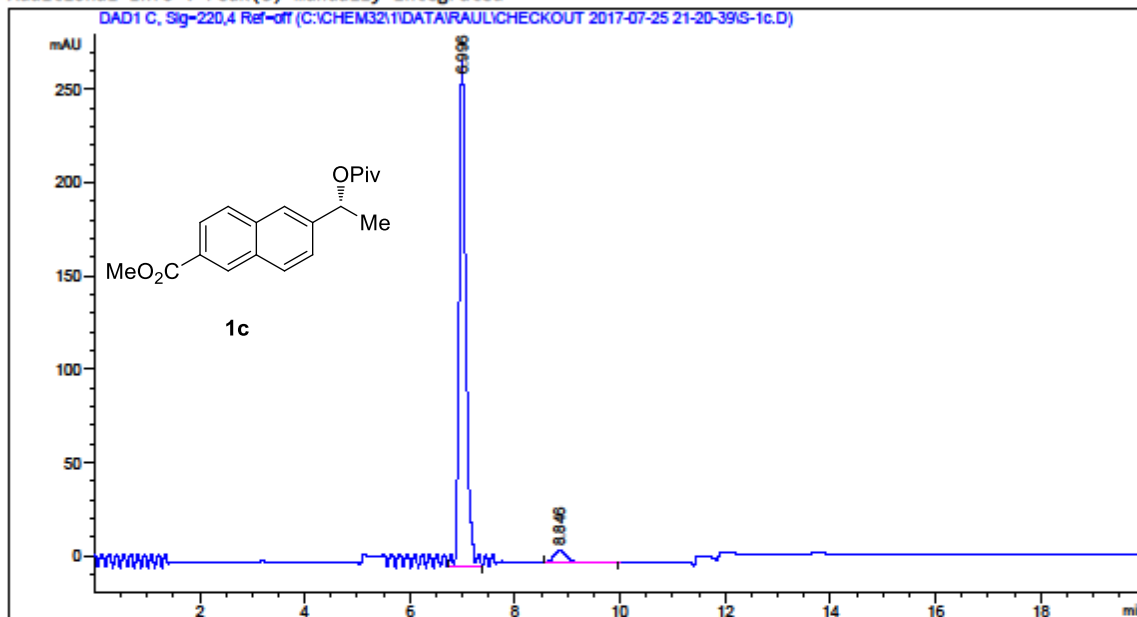HPLC 1260 7/18/2017 8:16:43 PM SYSTEM   Page   1 of 2

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-24 18-21-28\TK-81.D
Sample Name: TK-81

```
================================================================
Acq. Operator   : SYSTEM                   Seq. Line :   3
Acq. Instrument : HPLC 1260                 Location :   32
Injection Date  : 7/24/2017 7:24:03 PM          Inj :   1
                                         Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-24 18-21-28\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed    : 7/24/2017 7:28:21 PM by SYSTEM
                  (modified after loading)
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
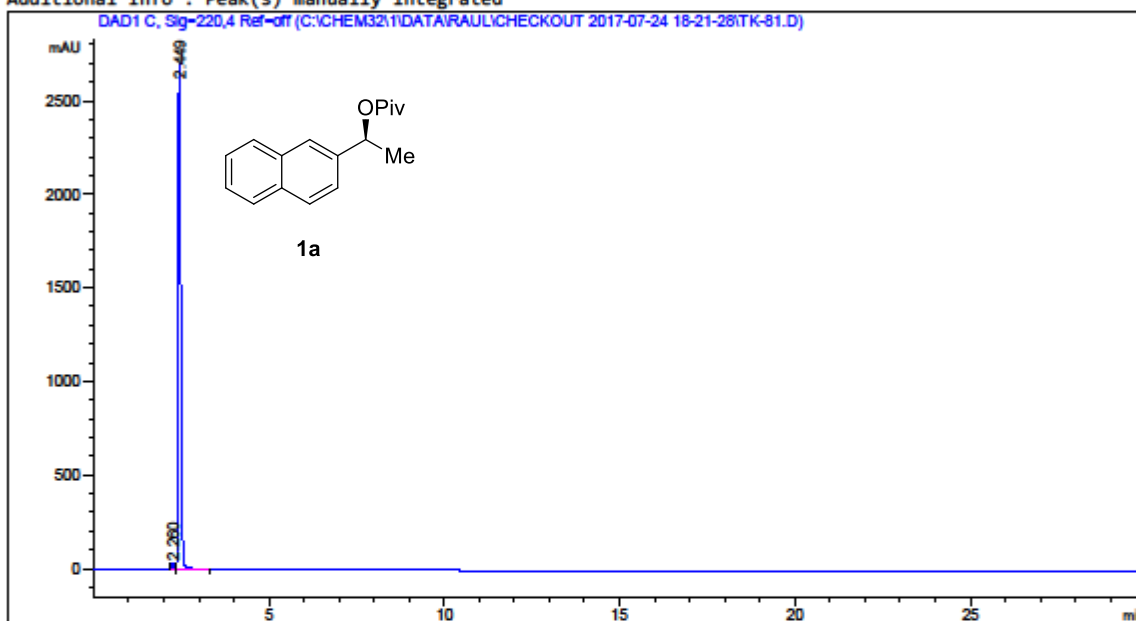


```
================================================================
                     Area Percent Report
================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
 #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
 1   2.260 BV   0.0576   86.42089   23.10045   0.6176
 2   2.449 VV R 0.0841 1.39069e4  2694.85034  99.3824

Totals :               1.39933e4  2717.95079
```

Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-24 18-21-28\RM-56.D
Sample Name: RM-56

```
==================================================================
Acq. Operator   : SYSTEM                   Seq. Line :    2
Acq. Instrument : HPLC 1260                 Location :   31
Injection Date  : 7/24/2017 6:53:12 PM           Inj :    1
                                       Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-24 18-21-28\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed    : 7/24/2017 6:21:29 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
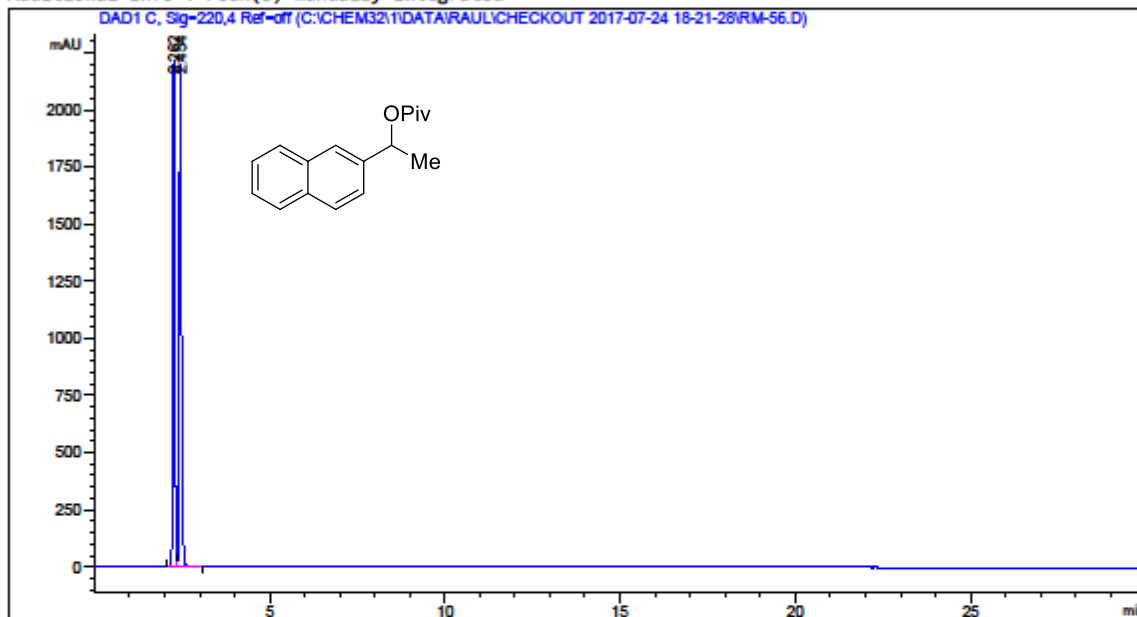


```
==================================================================
                     Area Percent Report
==================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
 #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
 1   2.262 BV    0.0624  8834.95313 2219.48340  48.9156
 2   2.454 VV R  0.0671  9226.69141 2193.05737  51.0844

Totals :                 1.80616e4  4412.54077
```

```
==================================================================
```
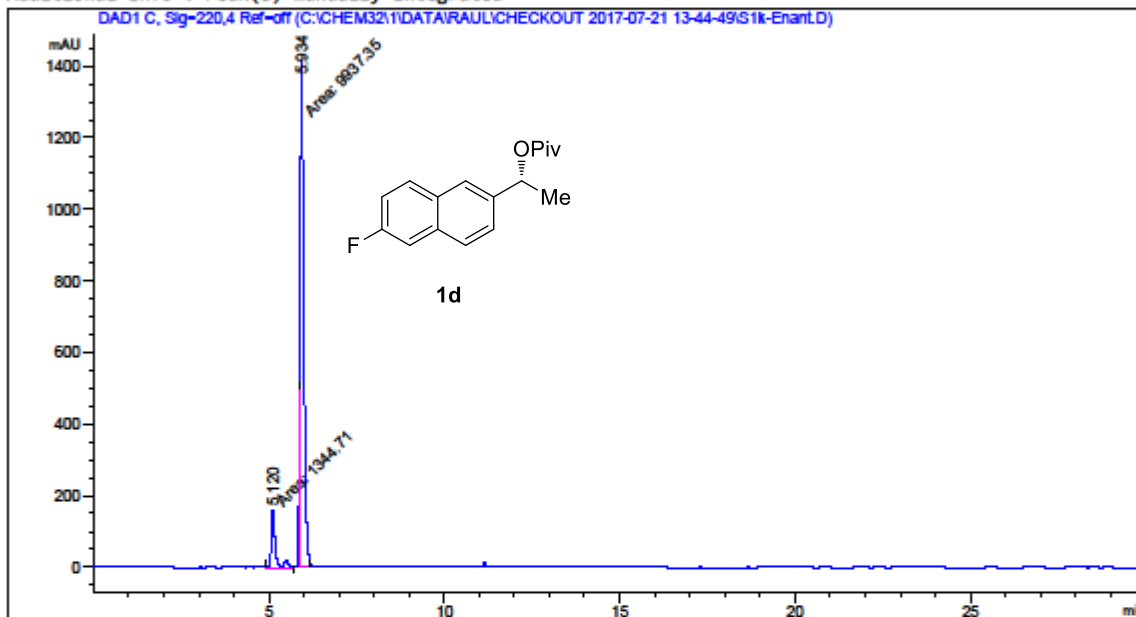
Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-24 18-21-28\RM-173.D
Sample Name: RM-173

```
==================================================================
Acq. Operator   : SYSTEM                    Seq. Line :   4
Acq. Instrument : HPLC 1260                  Location :   33
Injection Date  : 7/24/2017 7:54:55 PM           Inj :    1
                                       Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-24 18-21-28\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed    : 7/24/2017 7:28:21 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
```



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

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   5.261 BV R  0.1023 9775.69922 1457.37537  94.8688
  2   5.550 VB E  0.1022  528.74274   76.92770   5.1312

Totals :                  1.03044e4  1534.30306


==================================================================
                     *** End of Report ***

HPLC 1260 7/27/2017 9:30:41 PM SYSTEM                    Page   1 of 1
```
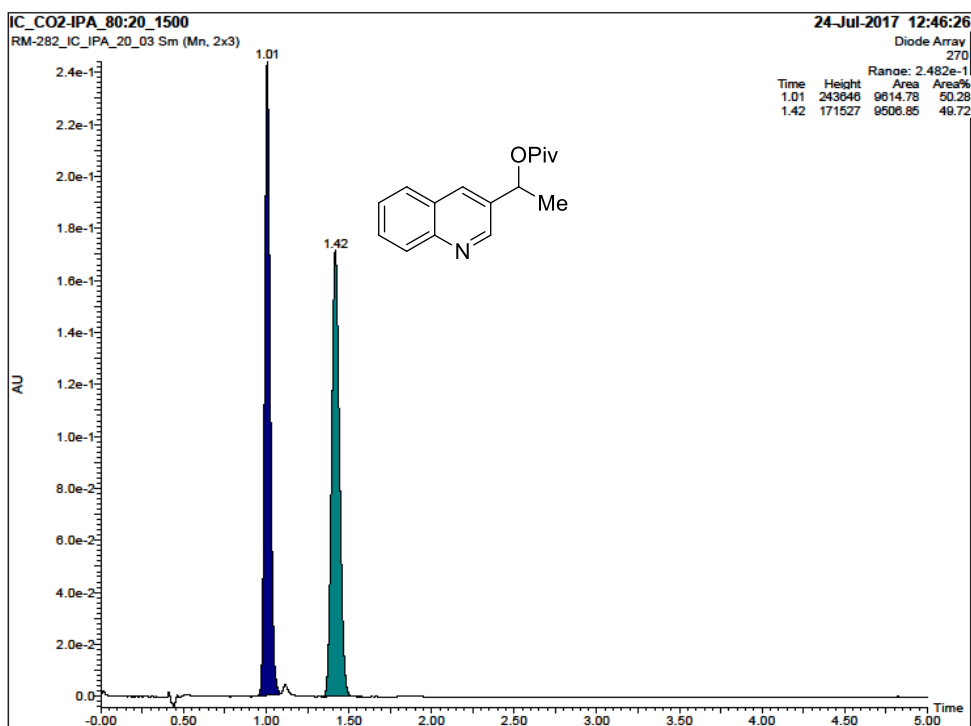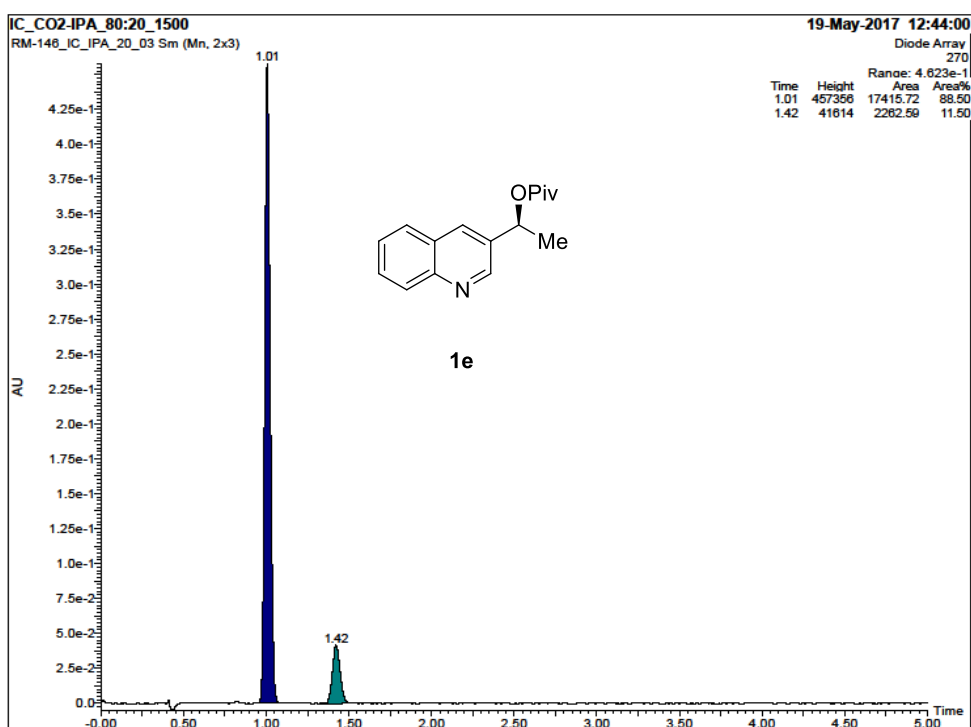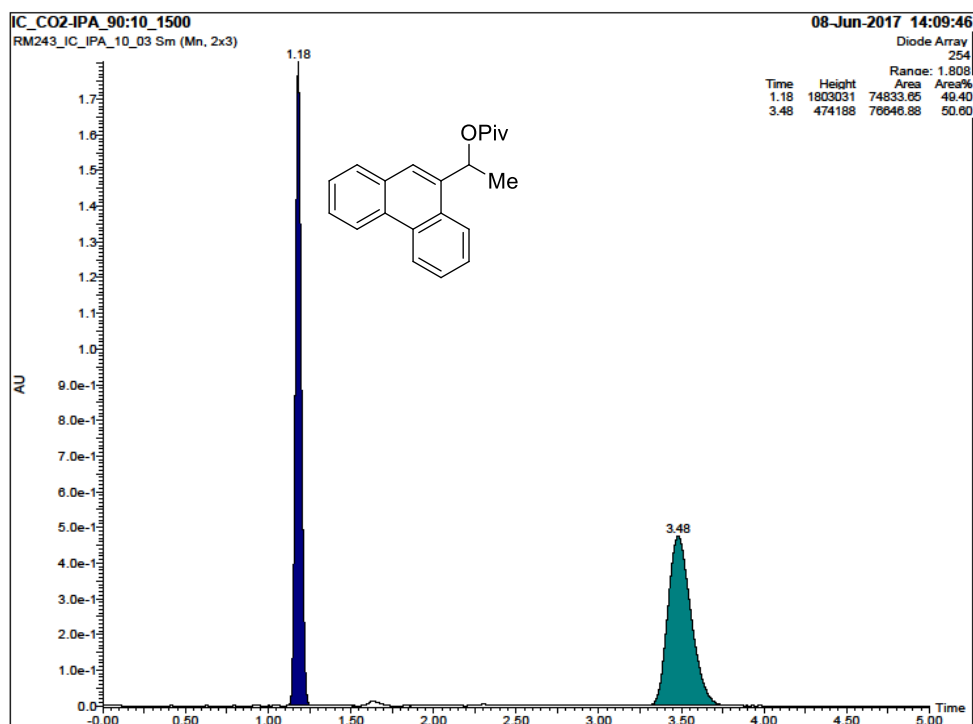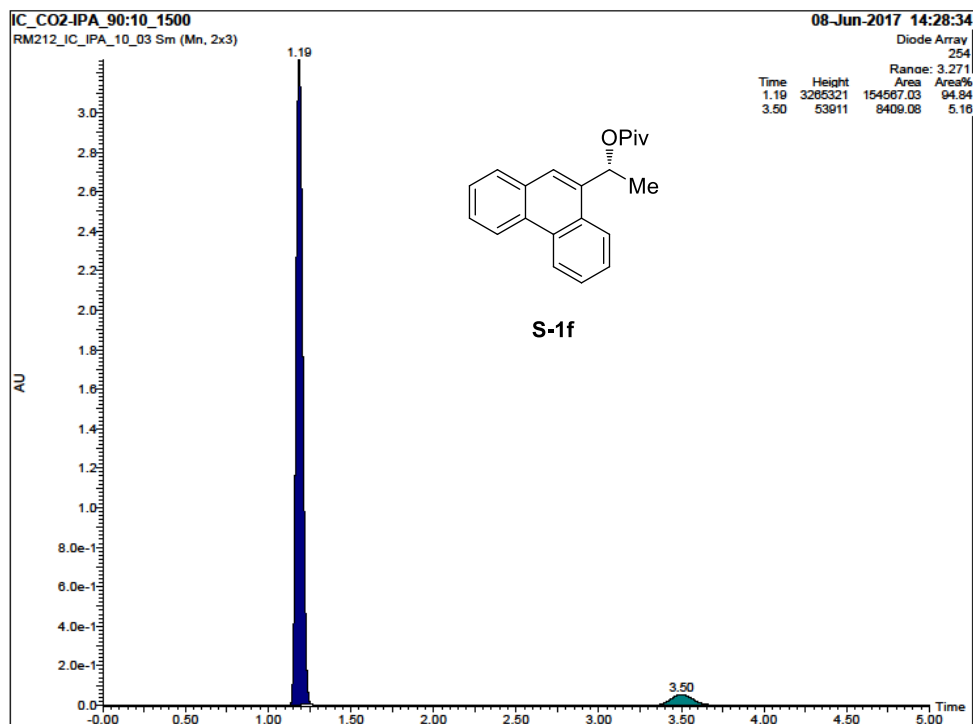
Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-24 18-21-28\RM-173-Rac.D
Sample Name: RM-173-Rac

```
==================================================================
Acq. Operator   : SYSTEM                    Seq. Line :   5
Acq. Instrument : HPLC 1260                  Location :   52
Injection Date  : 7/24/2017 8:25:46 PM          Inj :   1
                                            Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-24 18-21-28\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed    : 7/24/2017 7:28:21 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
```



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

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area        Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   5.261 BV   0.1007  6139.77197  933.83826  49.5165
  2   5.542 VB   0.1057  6259.68604  893.95709  50.4835

Totals :                 1.23995e4   1827.79535
```

```
==================================================================
                        *** End of Report ***
```

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-25 21-20-39\S-1c.D
Sample Name: S-1c

```
=================================================================
Acq. Operator   : SYSTEM                   Seq. Line :   13
Acq. Instrument : HPLC 1260                 Location :   34
Injection Date  : 7/26/2017 1:31:29 AM          Inj :    1
                                    Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-25 21-20-39\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed    : 7/25/2017 9:20:39 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
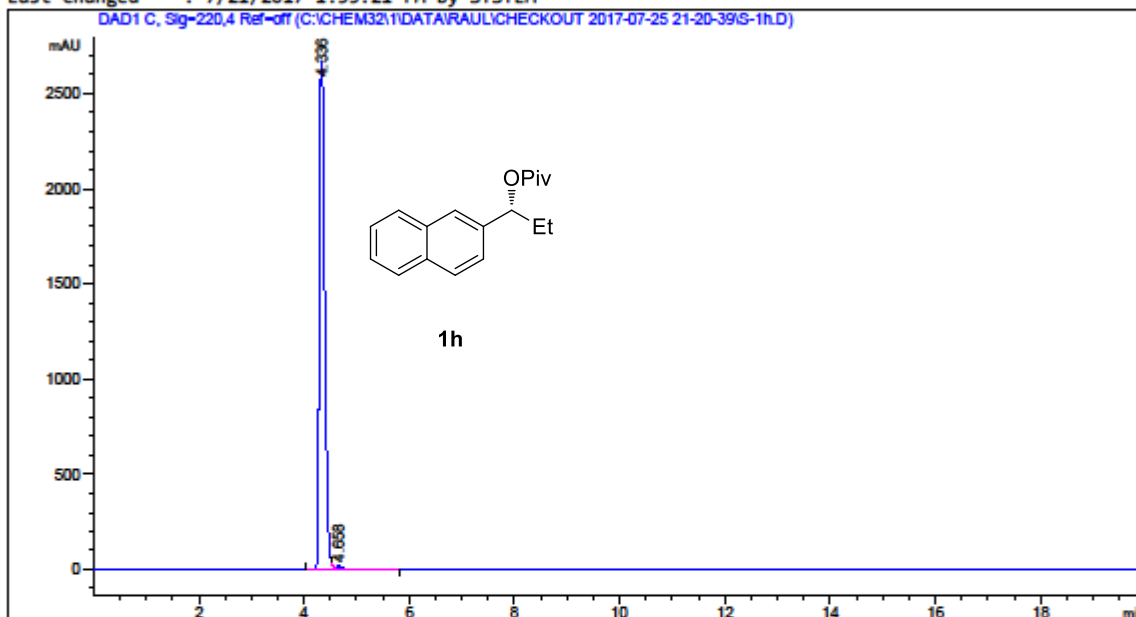


```
=================================================================
                    Area Percent Report
=================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   6.996 VV R  0.1323 2440.99951  271.42661  96.0486
  2   8.846 BB    0.2420  100.42229    6.43872   3.9514

Totals :                 2541.42180  277.86532
```

```
=================================================================
```

HPLC 1260 7/27/2017 9:31:19 PM SYSTEM   Page   1 of 2

Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-25 21-20-39\S-1cRac(all pivalates).D
Sample Name: S-1cRac(all pivalates)

```
==================================================================
Acq. Operator   : SYSTEM                      Seq. Line :   2
Acq. Instrument : HPLC 1260                    Location :  53
Injection Date  : 7/25/2017 9:41:51 PM              Inj :   1
                                         Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-25 21-20-39\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed    : 7/25/2017 9:20:39 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
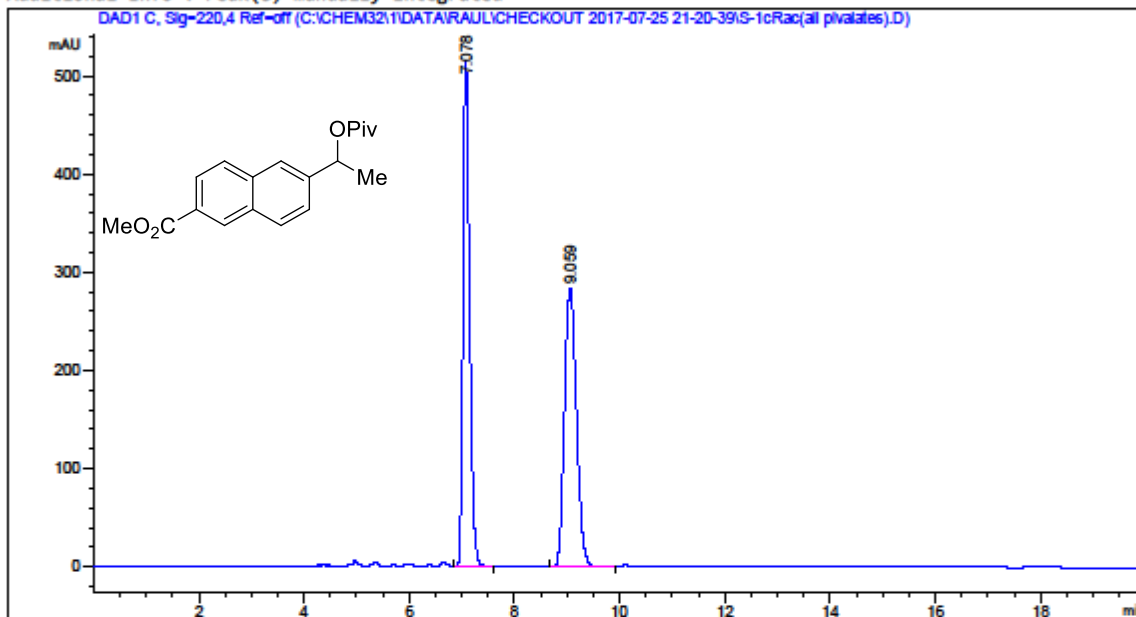


```
==================================================================
                   Area Percent Report
==================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area        Height     Area
  #   [min]        [min]   [mAU*s]       [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   7.078 BB   0.1324 4443.15039   516.21649  49.9286
  2   9.059 BB   0.2471 4455.86475   283.84906  50.0714

Totals :                8899.01514   800.06555
```

```
==================================================================
```

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-21 13-44-49\S1k-Enant.D
Sample Name: S1k-Enant

```
================================================================
Acq. Operator   : SYSTEM                    Seq. Line :  23
Acq. Instrument : HPLC 1260                  Location :   39
Injection Date  : 7/22/2017 1:04:47 AM          Inj :   1
                                         Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-21 13-44-49\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 7/21/2017 1:44:58 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```



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

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
 #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
 1   5.120 MM   0.1362 1344.71411  164.49312  11.9190
 2   5.934 MM   0.1171 9937.35254 1414.92688  88.0810

Totals :                1.12821e4   1579.42000


================================================================
```

Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-21 13-44-49\S1d.D
Sample Name: S1d

```
==================================================================
Acq. Operator   : SYSTEM                    Seq. Line :    5
Acq. Instrument : HPLC 1260                  Location :   54
Injection Date  : 7/21/2017 3:49:14 PM           Inj :    1
                                         Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-21 13-44-49\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 7/21/2017 1:44:58 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
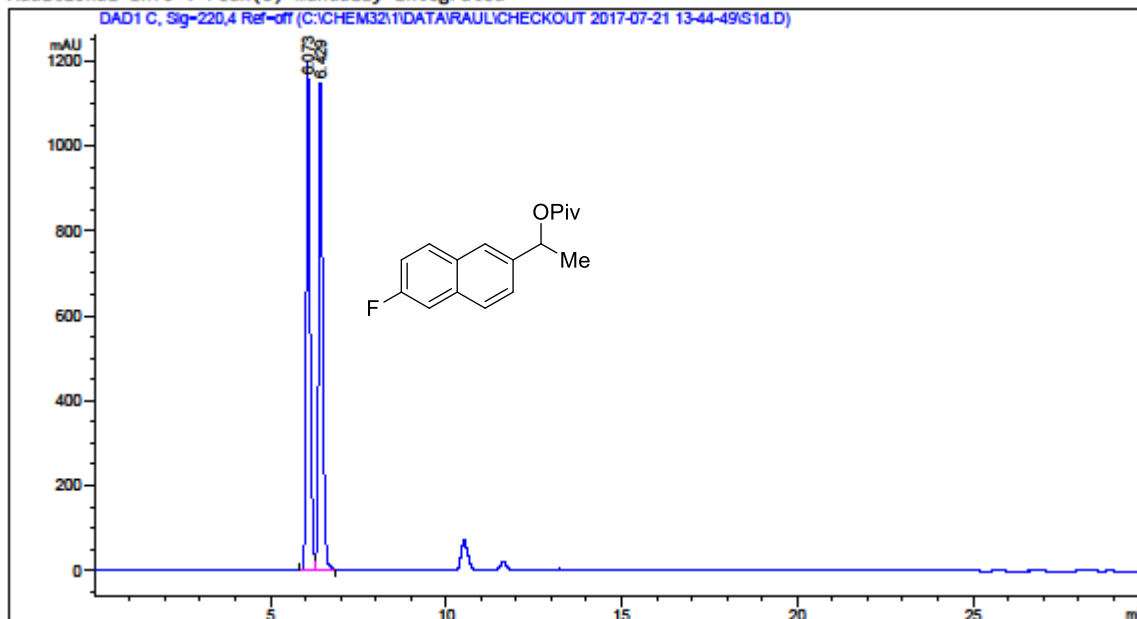


```
==================================================================
                   Area Percent Report
==================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area      Height    Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   6.073 BV    0.1143 9078.61035 1199.21814  49.6243
  2   6.429 VB    0.1217 9216.08691 1147.95068  50.3757

Totals :                  1.82947e4 2347.16882
```

```
==================================================================
```

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

IC_CO2-IPA_80:20_1500
RM-146_IC_IPA_20_03 Sm (Mn, 2x3)
19-May-2017 12:44:00
Diode Array
270
Range: 4.623e-1

Time	Height	Area	Area%
1.01	457356	17415.72	88.50
1.42	41614	2262.59	11.50

1e

IC_CO2-IPA_80:20_1500
RM-282_IC_IPA_20_03 Sm (Mn, 2x3)
24-Jul-2017 12:46:26
Diode Array
270
Range: 2.482e-1

Time	Height	Area	Area%
1.01	243646	9614.78	50.28
1.42	171527	9506.85	49.72

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Chapter 2

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-25 21-20-39\S-1g.D
Sample Name: S-1g

```
================================================================
Acq. Operator   : SYSTEM                 Seq. Line :  14
Acq. Instrument : HPLC 1260               Location :   35
Injection Date  : 7/26/2017 1:52:20 AM        Inj :   1
                                       Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-25 21-20-39\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed    : 7/25/2017 9:20:39 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
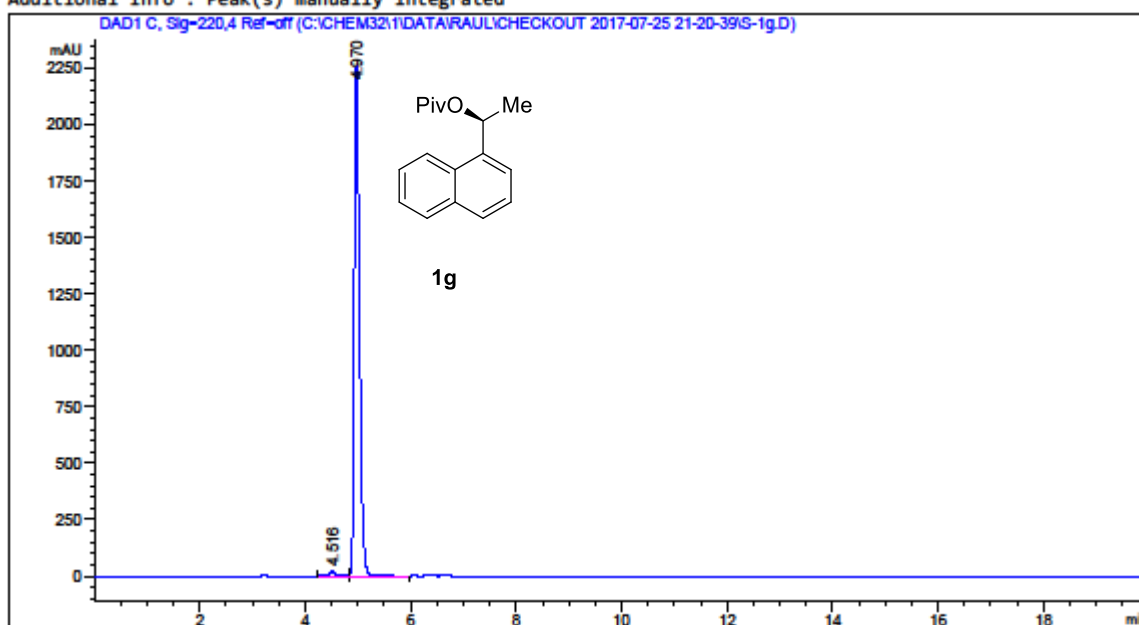


```
================================================================
                  Area Percent Report
================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   4.516 VV R  0.0894  177.19789   23.93011   1.1323
  2   4.970 VB    0.1058 1.54719e4   2262.74805  98.8677

Totals :                 1.56491e4   2286.67816
```

```
================================================================
```

HPLC 1260 7/27/2017 9:17:28 PM SYSTEM   Page   1 of 2
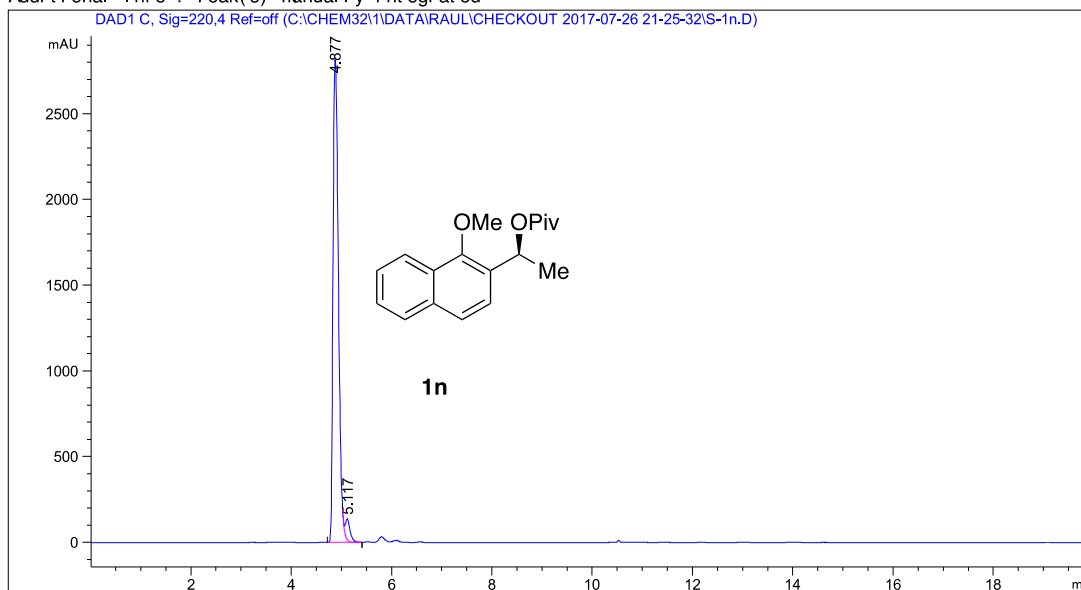
Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-25 21-20-39\S-1gRac.D
Sample Name: S-1gRac

```
=================================================================
Acq. Operator   : SYSTEM                      Seq. Line :   4
Acq. Instrument : HPLC 1260                    Location :   57
Injection Date  : 7/25/2017 10:23:37 PM             Inj :   1
                                              Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-25 21-20-39\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed    : 7/25/2017 9:20:39 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
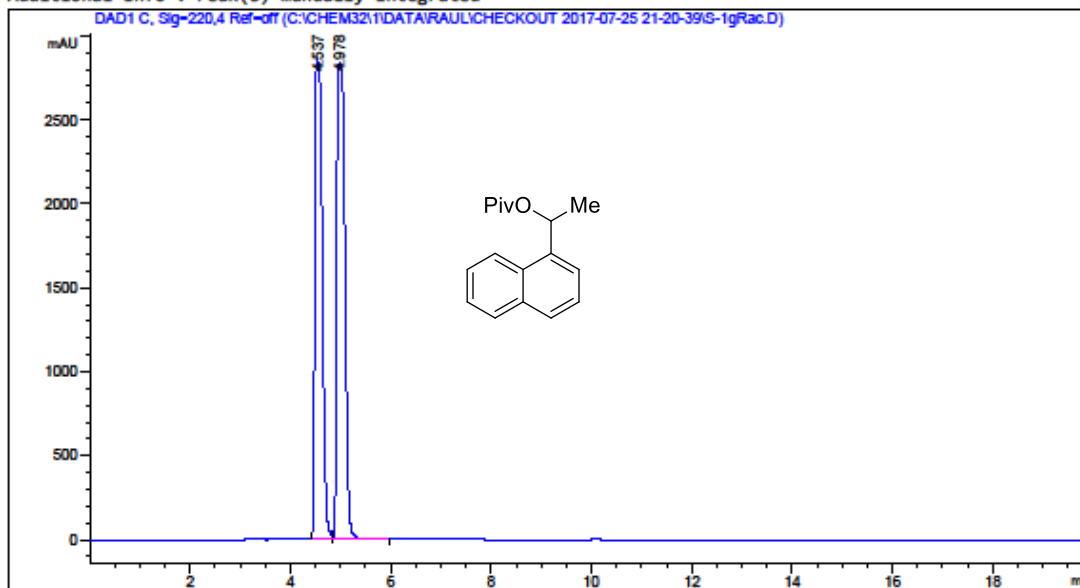


```
=================================================================
                      Area Percent Report
=================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   4.537 BV   0.1701 2.94821e4  2864.07788  48.0662
  2   4.978 VV R 0.1825 3.18543e4  2843.75659  51.9338

Totals :              6.13364e4  5707.83447


=================================================================
```

HPLC 1260 7/27/2017 9:16:54 PM SYSTEM   Page   1 of 2

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-25 21-20-39\S-1h.D
Sample Name: S-1h

```
=================================================================
Acq. Operator   : SYSTEM                    Seq. Line :  15
Acq. Instrument : HPLC 1260                  Location :   36
Injection Date  : 7/26/2017 2:13:10 AM          Inj :    1
                                         Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-25 21-20-39\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed    : 7/25/2017 9:20:39 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
```



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

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
 #   [min]         [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   4.336 BV R  0.1135 1.90674e4  2663.72827  99.3330
  2   4.658 VB E  0.1168  128.03185   15.11627   0.6670

Totals :                 1.91954e4  2678.84454


=================================================================
                  *** End of Report ***
```

HPLC 1260 7/27/2017 9:18:19 PM SYSTEM   Page   1 of 1

Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-25 21-20-39\S-1hRac.D
Sample Name: S-1hRac

```
================================================================
Acq. Operator   : SYSTEM                  Seq. Line :   5
Acq. Instrument : HPLC 1260                Location :   58
Injection Date  : 7/25/2017 10:44:28 PM        Inj :   1
                                        Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-25 21-20-39\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed    : 7/25/2017 9:20:39 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
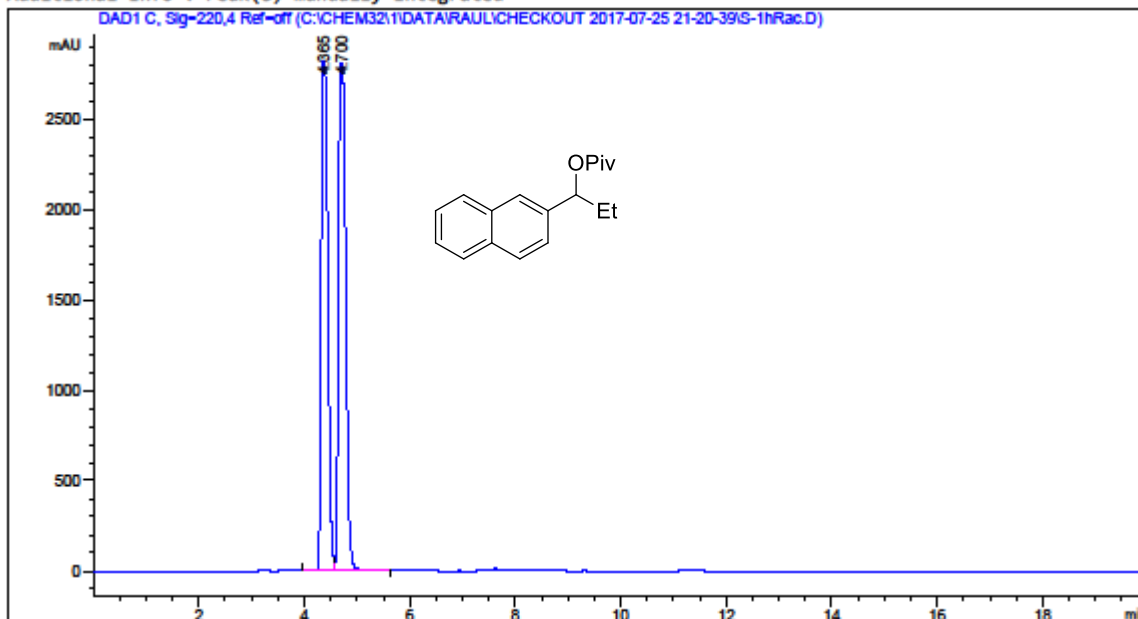


```
================================================================
                    Area Percent Report
================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   4.365 VV R  0.1428  2.48699e4  2822.26904  48.1945
  2   4.700 VV R  0.1548  2.67332e4  2812.17358  51.8055

Totals :                  5.16031e4  5634.44263


================================================================
```

HPLC 1260 7/27/2017 9:17:55 PM SYSTEM   Page   1 of 2

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM82\1\DATA\RAUL\CHECKOUT 2017-07-25 21-20-39\S-1j.D
Sample Name: S-1j

```
===================================================================
Acq. Operator    : SYSTEM                    Seq. Line :   17
Acq. Instrument  : HPLC 1260                  Location :   38
Injection Date   : 7/26/2017 2:54:52 AM           Inj :    1
                                         Inj Volume : 1.000 µl
Acq. Method      : C:\Chem82\1\Data\Raul\checkout 2017-07-25 21-20-39\Chiral coloumn IB-Raul
                   99.5(1 BOTTLE).M
Last changed     : 7/25/2017 9:20:39 PM by SYSTEM
Analysis Method  : C:\Chem82\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed     : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
```



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

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width      Area        Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   4.194  VV E  0.0838   915.73682   167.32896    4.2878
   2   4.437  VV R  0.1187  2.04411e4   2678.98560   95.7122

Totals :                     2.13569e4   2846.31456


===================================================================
```

Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-25 21-20-39\S-1jRac.D
Sample Name: S-1jRac

```
====================================================================
Acq. Operator   : SYSTEM                    Seq. Line :    7
Acq. Instrument : HPLC 1260                  Location :    60
Injection Date  : 7/25/2017 11:26:14 PM          Inj :    1
                                            Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-25 21-20-39\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed    : 7/25/2017 9:20:39 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```



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


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



Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   4.216  BV   0.1568 2.78495e4   2931.89941   47.9521
  2   4.467  VV R 0.1666 3.02283e4   2921.17505   52.0479

Totals :                 5.80778e4   5853.07446


====================================================================
```

HPLC 1260 7/27/2017 9:19:39 PM SYSTEM   Page   1 of 2

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-25 21-20-39\S-1k.D
Sample Name: S-1k

```
===================================================================
Acq. Operator   : SYSTEM                    Seq. Line :   18
Acq. Instrument : HPLC 1260                  Location :    39
Injection Date  : 7/26/2017 3:15:42 AM            Inj :    1
                                            Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-25 21-20-39\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed    : 7/25/2017 9:20:39 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```



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

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area        Height       Area
  #   [min]        [min]    [mAU*s]      [mAU]          %
----|-------|----|-------|----------|----------|--------|
  1   4.086  VV R  0.0809 1335.06897  244.57817    9.2656
  2   4.345  VV R  0.0935 1.30738e4  2131.95557   90.7344

Totals :                  1.44089e4  2376.53374


===================================================================
```

Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-25 21-20-39\S-1kRac.D
Sample Name: S-1kRac

==
Acq. Operator   : SYSTEM   Seq. Line :   8
Acq. Instrument : HPLC 1260   Location :   61
Injection Date   : 7/25/2017 11:47:08 PM   Inj :   1
                                          Inj Volume : 1.000 µl
Acq. Method   : C:\Chem32\1\Data\Raul\checkout 2017-07-25 21-20-39\Chiral coloumn IB-Raul
                   99.5(1 BOTTLE).M
Last changed   : 7/25/2017 9:20:39 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed   : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated

==
                    Area Percent Report
==
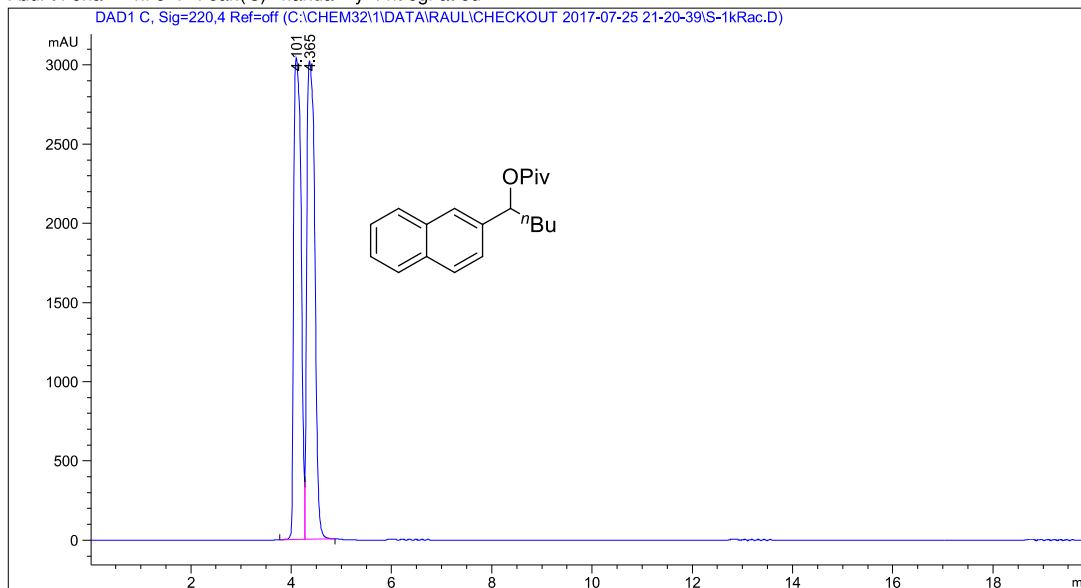
Sorted By   :   Signal
Multiplier   :   1.0000
Dilution   :   1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type Width   Area   Height   Area
 #   [min]   [min]   [mAU*s]   [mAU]   %
----|-------|----|-------|----------|----------|--------|
  1   4.101 VV R 0.1680 3.07626e4 3040.91113 47.9695
  2   4.365 VB   0.1809 3.33669e4 3020.03516 52.0305

Totals :   6.41295e4 6060.94629

==

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-26 21-25-32\S-1I.D
Sample Name: S-1I

```
==================================================================
Acq. Operator   : SYSTEM                    Seq. Line :    4
Acq. Instrument : HPLC 1260                  Location :   39
Injection Date  : 7/26/2017 10:28:40 PM          Inj :    1
                                           Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-26 21-25-32\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 7/26/2017 9:25:33 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
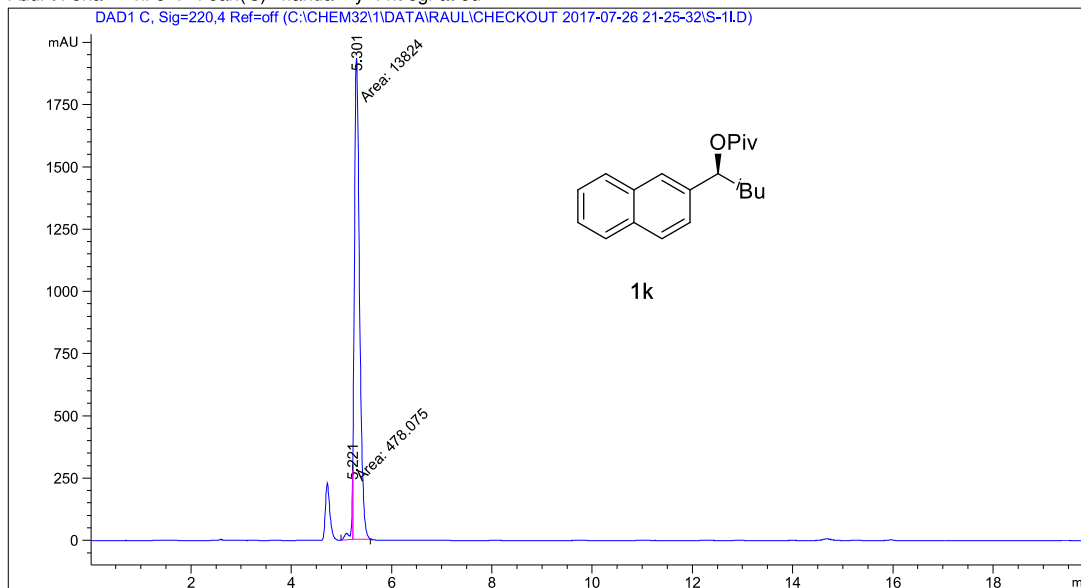


```
==================================================================
                    Area Percent Report
==================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
 #   [min]        [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
 1   5.221  MM   0.0359   478.07468  222.24596   3.3427
 2   5.301  MM   0.1191  1.38240e4  1934.95618  96.6573

Totals :                 1.43021e4  2157.20213


==================================================================
```

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Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-26 21-25-32\S-1IRac(OPiv)(99.5-0.5).D
Sample Name: S-1IRac(OPiv)(99.5-0.5)

===
Acq. Operator   : SYSTEM   Seq. Line :   2
Acq. Instrument : HPLC 1260   Location :   62
Injection Date : 7/26/2017 9:46:44 PM   Inj :   1
                                         Inj Volume : 1.000 µl
Acq. Method   : C:\Chem32\1\Data\Raul\checkout 2017-07-26 21-25-32\Chiral coloumn IB-Raul
                  98-2.M
Last changed   : 7/26/2017 9:25:33 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed   : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated

===
                     Area Percent Report
===
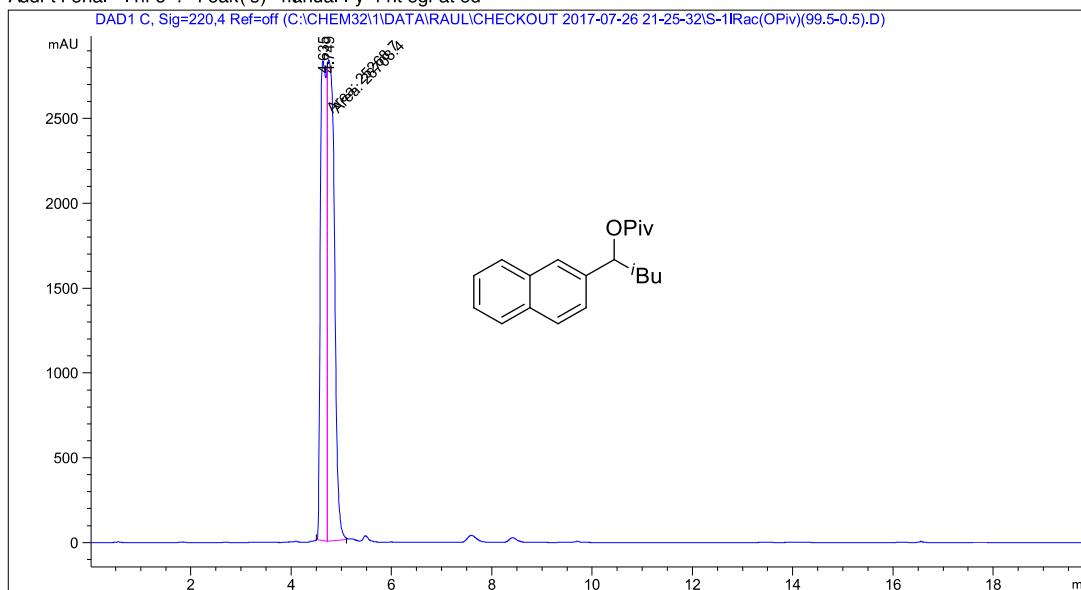
Sorted By   :   Signal
Multiplier   :   1.0000
Dilution   :   1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type Width   Area   Height   Area
  #   [min]   [min]   [mAU*s]   [mAU]   %
----|-------|----|-------|----------|----------|--------|
  1   4.635 MM   0.1490 2.52687e4 2826.07520 48.6150
  2   4.749 MM   0.1569 2.67084e4 2836.55737 51.3850

Totals :   5.19771e4 5662.63257

===

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM82\1\DATA\RAUL\CHECKOUT 2017-07-25 21-20-39\S-1i.D
Sample Name: S-1i

===
Acq. Operator   : SYSTEM   Seq. Line :   16
Acq. Instrument : HPLC 1260   Location :   37
Injection Date : 7/26/2017 2:34:01 AM   Inj :   1
                                          Inj Volume : 1.000 µl
Acq. Method   : C:\Chem82\1\Data\Raul\checkout 2017-07-25 21-20-39\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed   : 7/25/2017 9:20:39 PM by SYSTEM
Analysis Method : C:\Chem82\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed   : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated

===
                    Area Percent Report
===
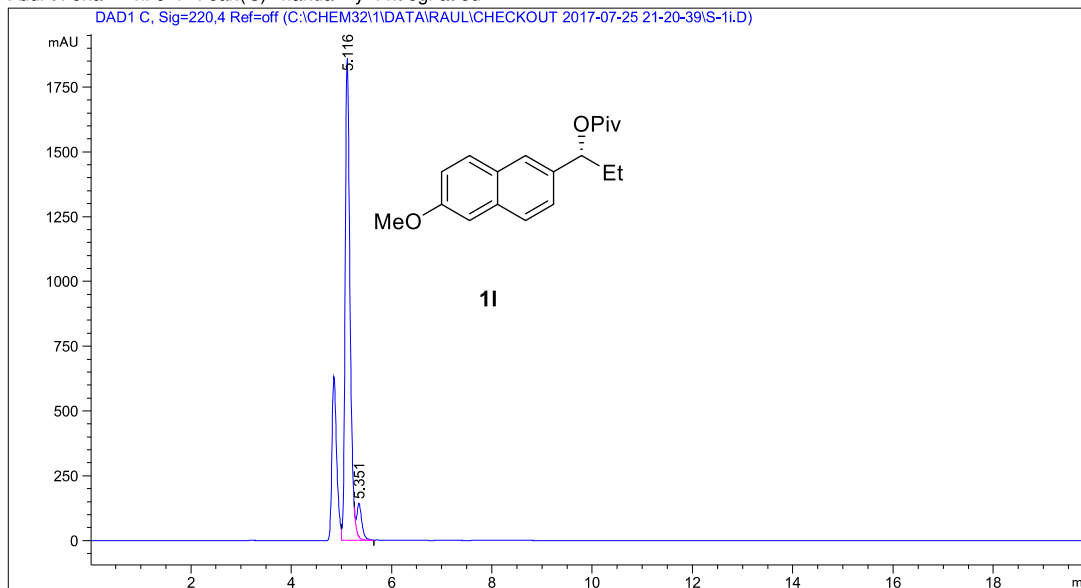
Sorted By   :   Signal
Multiplier   :   1.0000
Dilution   :   1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type Width   Area   Height   Area
  #   [min]   [min]   [mAU*s]   [mAU]   %
----|-------|----|-------|----------|----------|--------|
  1   5.116 VV R 0.1008 1.25685e4 1861.41223 93.5896
  2   5.351 VB E 0.0993 860.87994 129.90913   6.4104

Totals :   1.34294e4 1991.32137

===

Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-25 21-20-39\S-1iRac.D
Sample Name: S-1iRac

==
Acq. Operator   : SYSTEM   Seq. Line :   6
Acq. Instrument : HPLC 1260   Location :   59
Injection Date : 7/25/2017 11:05:21 PM   Inj :   1
                                           Inj Volume : 1.000 µl
Acq. Method   : C:\Chem32\1\Data\Raul\checkout 2017-07-25 21-20-39\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed   : 7/25/2017 9:20:39 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed   : 7/21/2017 1:35:21 PM by SYSTEM

==
                      Area Percent Report
==
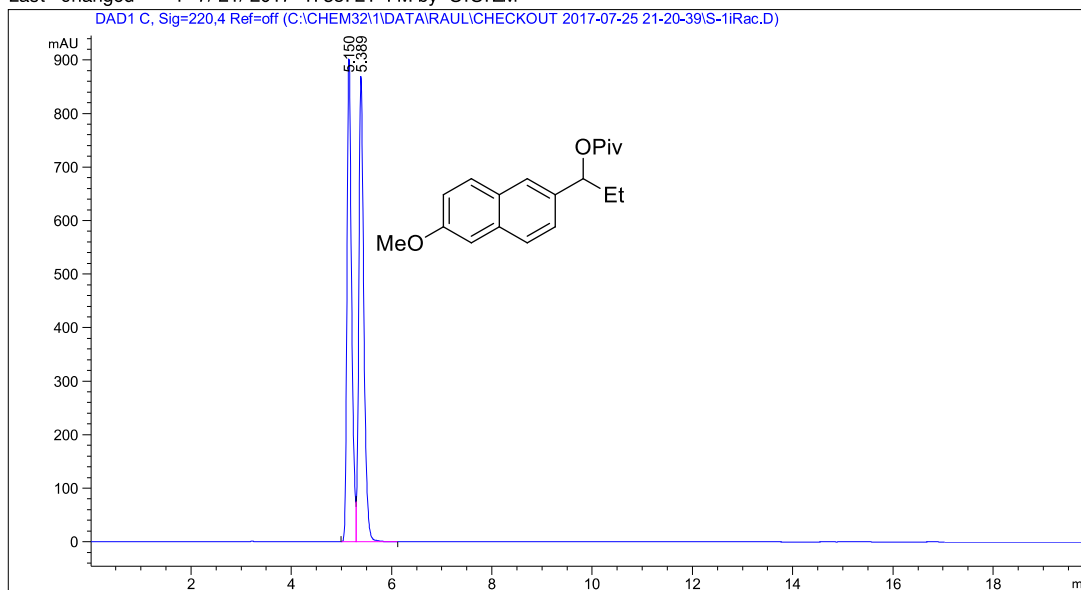
Sorted By   :   Signal
Multiplier   :   1.0000
Dilution   :   1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type Width   Area   Height   Area
  #   [min]   [min]   [mAU*s]   [mAU]   %
----|-------|----|-------|----------|----------|--------|
   1   5.150 BV   0.0969 5801.21094 903.68774   48.9639
   2   5.389 VB   0.1050 6046.73340 870.57117   51.0361

Totals :   1.18479e4   1774.25891

==
                     *** End of Report ***

HPLC 1260 7/27/2017 9:18:39 PM SYSTEM   Page   1 of 1

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM82\1\DATA\RAUL\CHECKOUT 2017-07-25 21-20-39\S-1m.D
Sample Name: S-1m

```
===================================================================
Acq. Operator   : SYSTEM                    Seq. Line :   20
Acq. Instrument : HPLC 1260                  Location  :   41
Injection Date  : 7/26/2017 3:57:28 AM            Inj :    1
                                         Inj Volume : 1.000 µl
Acq. Method     : C:\Chem82\1\Data\Raul\checkout 2017-07-25 21-20-39\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed    : 7/25/2017 9:20:39 PM by SYSTEM
Analysis Method : C:\Chem82\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```



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

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area        Height     Area
  #   [min]        [min]   [mAU*s]       [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   5.065 BV    0.0987  7806.44629 1187.15137  87.0771
  2   8.871 MM    0.2609  1158.53271   74.01201  12.9229

Totals :                  8964.97900 1261.16338


===================================================================
```

HPLC 1260 7/27/2017 9:22:54 PM SYSTEM   Page   1 of 2

Chapter 2

Data File C:\CHEM82\1\DATA\RAUL\CHECKOUT 2017-07-25 21-20-39\S-1mRac.D
Sample Name: S-1mRac

```
==================================================================
Acq. Operator   : SYSTEM                    Seq. Line :   10
Acq. Instrument : HPLC 1260                  Location :    63
Injection Date  : 7/26/2017 12:28:50 AM           Inj :    1
                                             Inj Volume : 1.000 µl
Acq. Method     : C:\Chem82\1\Data\Raul\checkout 2017-07-25 21-20-39\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed    : 7/25/2017 9:20:39 PM by SYSTEM
Analysis Method : C:\Chem82\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```



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

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
 #   [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1  5.080  VV R  0.0988  5529.80762  815.34631  50.2928
  2  8.739  BV R  0.2553  5465.41455  327.77905  49.7072

Totals :                  1.09952e4   1143.12537


==================================================================
```

HPLC 1260 7/27/2017 9:21:47 PM SYSTEM   Page   1 of 2

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Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-26 21-25-32\S-1n.D
Sample Name: S-1n

```
==================================================================
Acq. Operator   : SYSTEM                    Seq. Line :    5
Acq. Instrument : HPLC 1260                  Location :    42
Injection Date  : 7/26/2017 10:49:32 PM           Inj :    1
                                             Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-26 21-25-32\Chiral coloumn IB-Raul
                  98-2.M
Last changed    : 7/26/2017 9:25:33 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```



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

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   4.877 BV R  0.1176  2.11305e4  2813.50098  96.3800
  2   5.117 VB E  0.0993   793.65070  119.85345   3.6200

Totals :                  2.19242e4  2933.35442


==================================================================
```

Chapter 2

Data File C:\CHEM82\1\DATA\RAUL\CHECKOUT 2017-07-26 21-25-32\S-1nRac(OPiv).D
Sample Name: S-1nRac(OPiv)

==
Acq. Operator   : SYSTEM   Seq. Line :   3
Acq. Instrument : HPLC 1260   Location :   64
Injection Date   : 7/26/2017 10:07:36 PM   Inj :   1
                                            Inj Volume : 1.000 µl
Acq. Method   : C:\Chem82\1\Data\Raul\checkout 2017-07-26 21-25-32\Chiral coloumn IB-Raul
                   98-2.M
Last changed   : 7/26/2017 9:25:33 PM by SYSTEM
Analysis Method : C:\Chem82\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed   : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated

==
                     Area Percent Report
==

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

Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type Width   Area   Height   Area
  #   [min]   [min]   [mAU*s]   [mAU]   %
----|-------|----|-------|----------|----------|--------|
  1   5.046 BV   0.1006 9978.34375 1519.33752 49.0625
  2   5.302 VV R 0.1057 1.03597e4   1468.33154 50.9375

Totals :   2.03380e4   2987.66907

==

Stereospecific Borylation of Benzyl C(sp³)–O Bonds

Data File C:\CHEM82\1\DATA\RAUL\CHECKOUT 2017-07-26 21-25-32\S-1nRac(OPiv).D
Sample Name: S-1nRac(OPiv)

==
Acq. Operator   : SYSTEM   Seq. Line :   3
Acq. Instrument : HPLC 1260   Location :   64
Injection Date : 7/26/2017 10:07:36 PM   Inj :   1
                                            Inj Volume : 1.000 µl
Acq. Method   : C:\Chem82\1\Data\Raul\checkout 2017-07-26 21-25-32\Chiral coloumn IB-Raul
                  98-2.M
Last changed   : 7/26/2017 9:25:33 PM by SYSTEM
Analysis Method : C:\Chem82\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed   : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated

==
                        Area Percent Report
==

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

Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type Width   Area   Height   Area
  #   [min]   [min]   [mAU*s]   [mAU]   %
----|-------|----|-------|----------|----------|--------|
  1   5.046 BV   0.1006 9978.34375 1519.33752 49.0625
  2   5.302 VV R 0.1057 1.03597e4   1468.33154 50.9375

Totals :   2.03380e4   2987.66907

==

Chapter 2

Data File C:\CHEM32\1\DATA\RAUL\CHECKOUT 2017-07-25 21-20-39\S-1oRac.D
Sample Name: S-1oRac

```
================================================================
Acq. Operator   : SYSTEM                      Seq. Line :   12
Acq. Instrument : HPLC 1260                    Location :    65
Injection Date  : 7/26/2017 1:10:36 AM              Inj :    1
                                            Inj Volume : 1.000 µl
Acq. Method     : C:\Chem32\1\Data\Raul\checkout 2017-07-25 21-20-39\Chiral coloumn IB-Raul
                  99.5(1 BOTTLE).M
Last changed    : 7/25/2017 9:20:39 PM by SYSTEM
Analysis Method : C:\Chem32\1\Methods\Chiral coloumn IB-Raul 98-2.M
Last changed    : 7/21/2017 1:35:21 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```
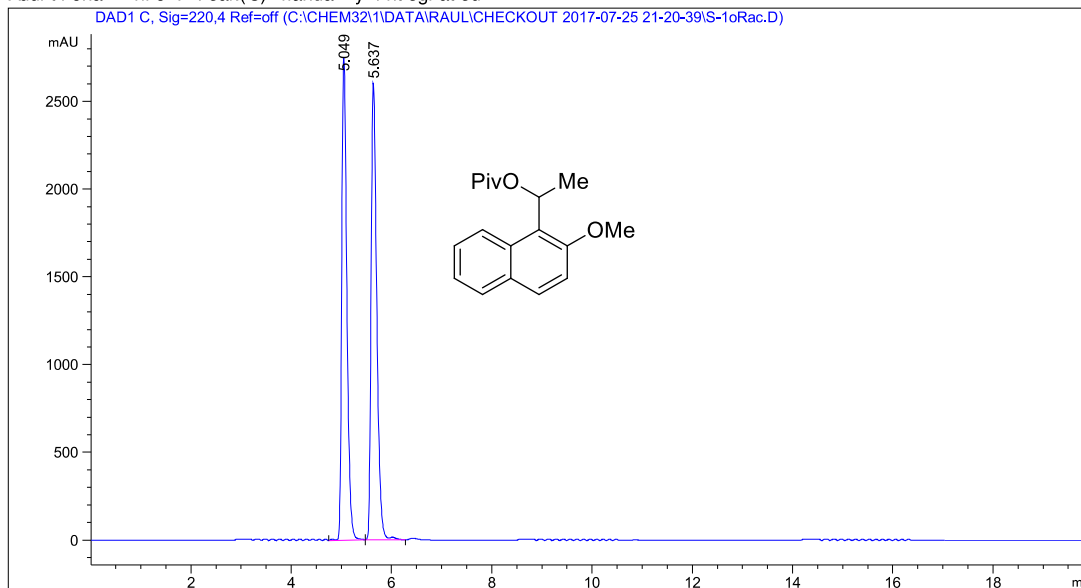


```
================================================================
                    Area Percent Report
================================================================

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


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area       Height      Area
 #   [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   5.049 VB R  0.1082 1.94062e4   2747.56250   48.7435
  2   5.637 BV R  0.1187 2.04067e4   2606.21509   51.2565

Totals :                  3.98129e4   5353.77759


================================================================
```

2.6 References

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Chapter 3.

Ni-catalyzed Reductive Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

3.1   Introduction

An increase of *sp³* character in drug candidates improves several molecular attributes that ultimately contribute to clinical success, including solubility, molecular shape (3D-structure) or substrate recognition, among others. In the last decades, transition metal-catalyzed coupling reactions of well-defined organometallic reagents (boronic acids, organozinc compounds, Grignard reagents, etc.) with electrophilic partners – typically organic (pseudo)halides – have offered new vistas for forging *sp³–sp³* linkages while providing revolutionary solutions for selectively functionalizing complex structures. These protocols operate with high regiospecificity, and have been widely utilized in both academic and industrial laboratories.[1–5] However, practicality and cost-issues associated to these processes spurred the development of new *sp³–sp³* bond-forming strategies that rely on abundant, native (or naturally-occurring) functional groups, as these entities might offer innovative solutions for bond-construction at late-stages.

Alkyl amines are chemical feedstocks with a natural abundance slightly similar to that of carboxylic acids. Indeed, primary and secondary amines are one of the most prevalent motifs across a wide range of biologically-active molecules, pharmaceuticals and natural products.[6–9] Specifically, 47000 primary alkyl amines vs about 28 000 primary and secondary alkyl halides can be found,[10] reinforcing the need for designing catalytic protocols that utilize alkyl amines as functional handles for forging C–C bonds. Such a technology will be particularly relevant in the context of late-stage functionalization of drug intermediates possessing an aliphatic amine, a feature that will certainly be of utmost relevance in the drug discovery pipeline.[11,12]

3.2   C–C and C–Heteroatom bond formation *via* C(sp³)–N bond cleavage of pyridinium salts

3.2.1   Introduction to the activation of unactivated alkyl amines by pyridinium salts

In the last decade, many efforts have been done towards the development of catalytic technologies for the cleavage of C(sp²)–N[13–16] and particularly activated C(sp³)–N bonds (Chapter 1.2.2). Unfortunately, the functionalization of unactivated alkyl amines *via* the activation of C(sp³)–N bonds remain an unexplored endeavour (Figure 3.2.1, *left*). If successful, techniques aimed at such goal will open a new gateway to build up *sp³* architectures at late stages of advanced synthetic intermediates, and a powerful alternative to the utilization of alkyl halides,[17–20] dual photoredox/nickel catalysis with oxalate counterparts,[21,22] carboxylic acids,[23,24] organoboronates[25,26] or organosilicates[27,28] among others.

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Figure 3.2.1. Activation of unactivated alkyl amines.
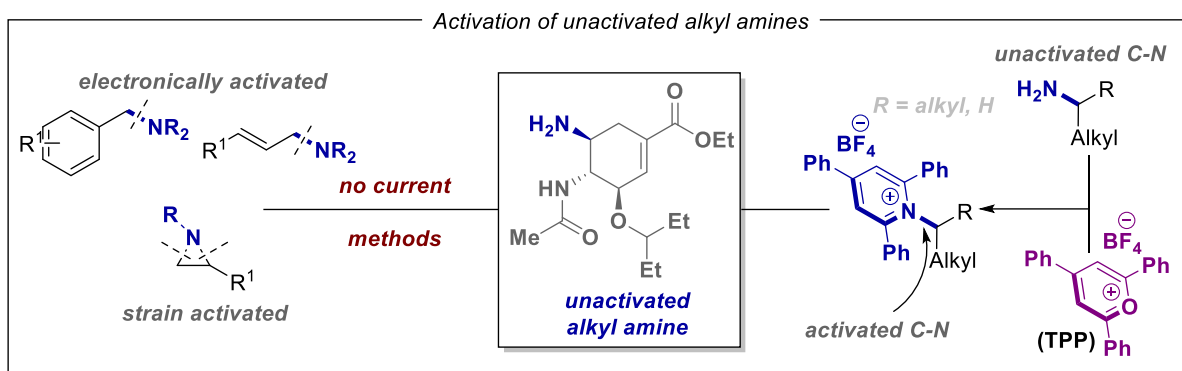
A considerable advance in the C(sp³)–N bond-cleavage arena was made by Watson and co-workers by the utilization of 2,4,6-triphenyl pyridinium salts – coined as Katritzky salts – as alkylating agents (Figure 3.2.1, *right*). These pyridinium cations have interesting features, such as being (a) air- and moisture-stable solids, crystalline and nonhygroscopic, (b) such compounds are easily prepared in one step *via* condensation of a primary or secondary alkyl amine with commercial available 2,4,6-triphenylpyrylium tetrafluoroborate (**TPP**),[29,30] and (c) they have been employed as alkyl electrophiles in S$_N$2' reactions or radical-type mechanisms.[31,32]

3.2.2   C(sp³)–C bond formation

3.2.2.1   C(sp³)–C(sp²) bond formation

Despite Watson's protocol of harnessing unactivated alkyl amines as electrophiles represented a step forward (Scheme 3.2.1),[33] the protocol was not particularly suited for the coupling of unactivated secondary alkyl amines. Nevertheless, a wide variety of boronic acids bearing different functional groups were tolerated, and late-stage functionalization could be implemented with densely functionalized alkyl amine derivatives.

Scheme 3.2.1. Cross-coupling of aryl boronic acids with alkylpyridinium salts.
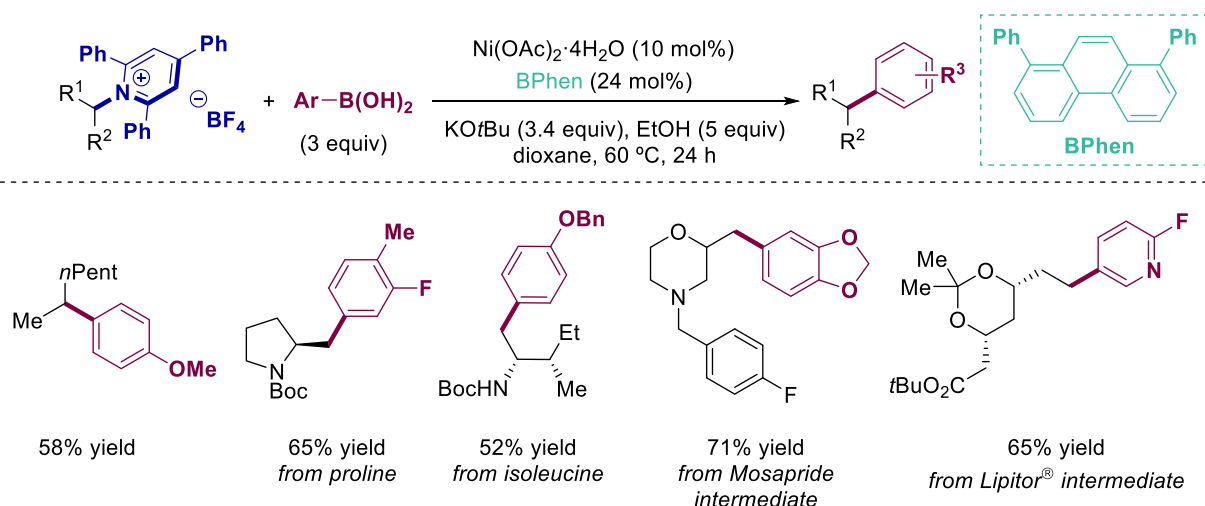
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The authors propose a catalytic manifold consisting of a Ni(I)/Ni(III) regime (Scheme 3.2.2), as racemic products were obtained by applying the methodology with enantioenriched alkyl pyridinium salts, and ring-opening products were observed with cyclopropyl-containing alkyl amines. Similarly to the utilization of redox-active esters,[34] pyridinium salts undergo single electron transfer (SET) with a Ni(I) intermediate (**I**), triggering an homolytic cleavage that recombines the resulting radical with an arylnickel(II) intermediate (**II**) to form Ni(III) species (**III**) prior to reductive elimination. However, the authors did not provide any evidence on whether a canonical transmetalation or radical chain processes come into play.
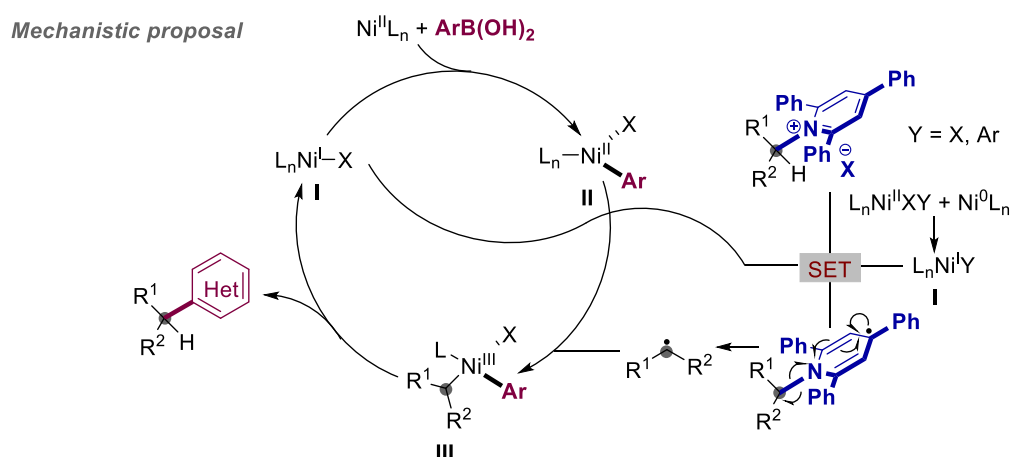
Scheme 3.2.2. Ni(I)/Ni(III) mechanistic proposal.

In 2017, Glorius and co-workers developed a photoredox process to activate pyridinium salts *via* SET en route to open-shell intermediates ($E_{1/2}$ = -0.93 V vs SCE in DMF,[35] Scheme 3.2.3).[36] Such radical intermediates react with an electron-deficient heteroarene in a Minisci-type process that occurred with a wide substrate scope and a diverse set of different heterocycles. The protocol was amenable for the coupling of amino acids and electron-rich heteroarenes.
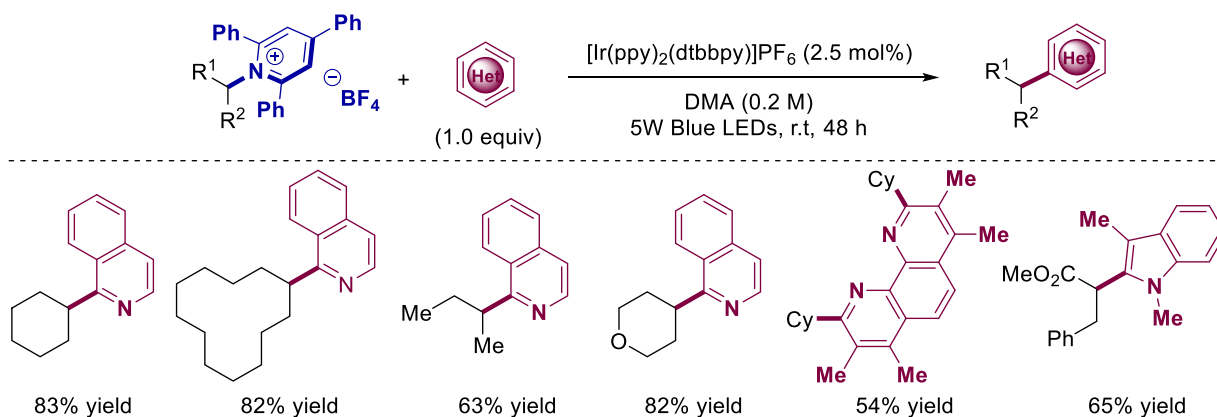
Scheme 3.2.3. Deaminative C–H alkylation of heteroarenes.

Subsequently, Lu and Xiao reported a deaminative alkyl-Heck-type reaction of alkyl amines through visible-light photoredox catalysis (Scheme 3.2.4).[37] This protocol represents a

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complementary procedure to the work of Glorius, including the coupling of a wide variety of diaryl alkenes with different electronic properties. The authors also showed a representative set of examples for a catalytic deaminative carbonylative Heck-type reactions using CO at 80 atm. Lu and Xiao suggested a mechanism *via* Ni(I)/Ni(III) regimes that is based on a SET process of the photocatalyst to the pyridinium salt, generating an alkyl radical that is intercepted with an alkene to generate a new open-shell intermediate. A final single-electron oxidation by the oxidized photocatalyst and subsequent deprotonation affords the desired alkenylation product.
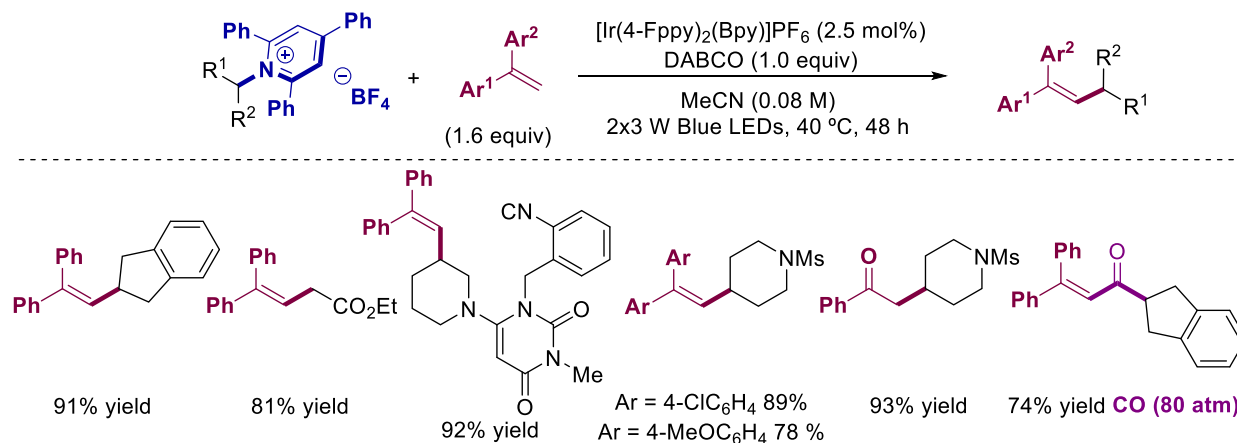
Scheme 3.2.4. Deaminative alkyl-Heck-type reaction of alkyl amines.

3.2.2.2   C(sp³)–C(sp) bond formation

In 2018, Gryko and co-workers described a deaminative alkynylation process forming C(sp³)–C(sp) and C(sp³)–C(sp²) bonds by metal free photoredox catalysis (Scheme 3.2.5).[38] In terms of scope, the methodology offered a wide tolerance to different functional groups, either for primary pyridinium salts or alkynyl precursors. However, the authors showed a limited number of examples when using secondary Katritzky salts or aromatic alkynyl substrates. It is worth noting that the technology could be applied to densely functionalized backbones. Experimental evidences collected through the work suggested the intervention of a mechanism similar to that proposed by Glorius in his photoredox scenario with pyridinium salts. In this case, single-electron transfer from the photoexcited eosin Y to the pyridinium salt released the alkyl radical, which is trapped by the alkynyl or alkenyl coupling partner, thus releasing the desired product.

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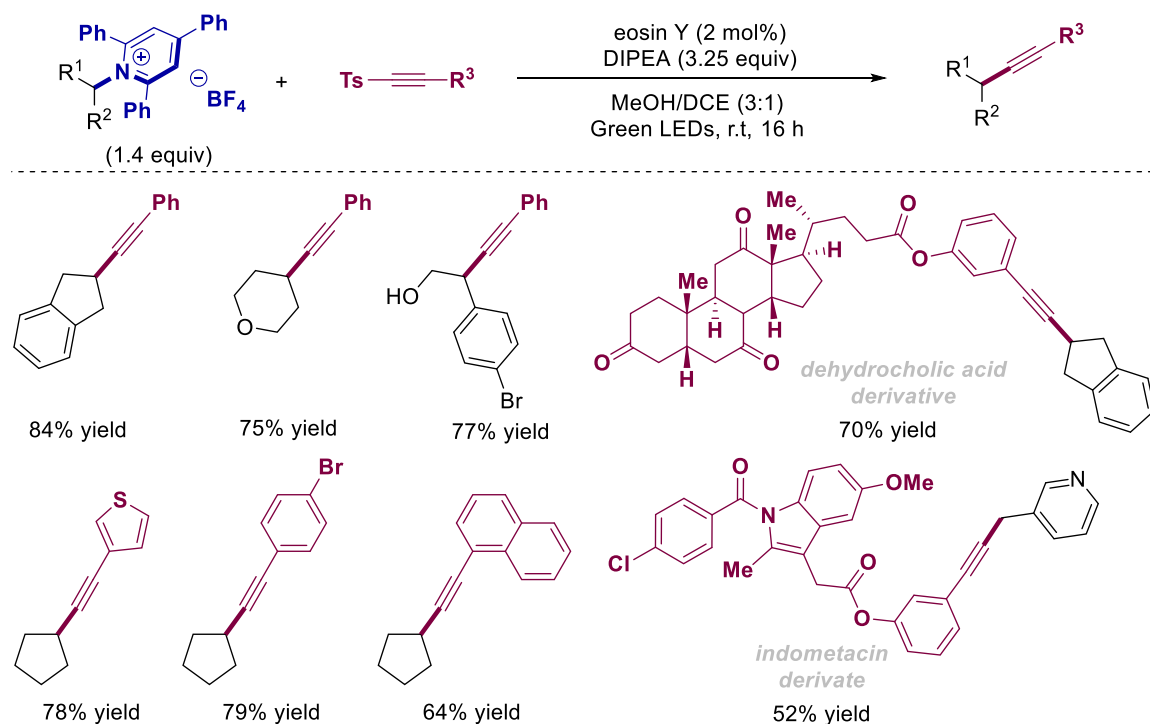
Scheme 3.2.5. Deaminative alkynylation visible-light mediated.

3.2.2.3   Three-component C–C–C bond formation

Dicarbofunctionalization processes are well-established strategies in organic synthesis that employ abundant olefins to rapidly access complex architectures in one step.[39] Glorius and Lautens envisioned that the appropriate combination of an olefin, an arene and the alkyl radical generated by C(sp^3)–N cleavage in pyridinium salts could engage an intermolecular three-component dicarbofunctionalization. With this in mind, the authors developed an intriguing dicarbofunctionalization of styrenes with *in situ* generated benzyl radicals (Scheme 3.2.6).[40] Unfortunately, the procedure was limited to benzyl amines.
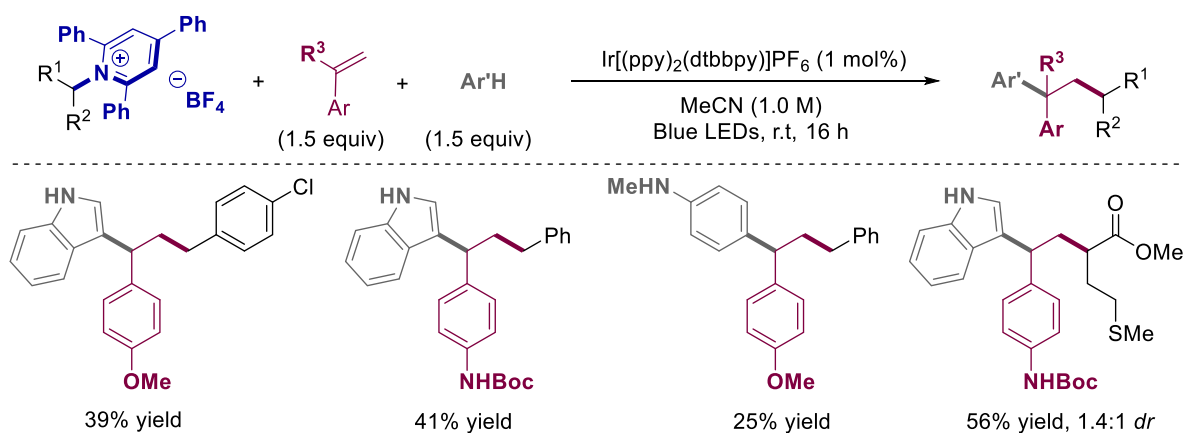
Scheme 3.2.6. Deaminative dicarbofunctionalization.

The authors proposed a mechanism based on a SET reduction of the Katritzky salt (**IV**), releasing the alkyl radical (**V**) which upon recombination with the styrene produces a new radical (**VI**) (Scheme

3.2.7). These species can reduce the oxidized photocatalyst or another molecule of pyridinium salt to maintain the chain reaction. The resulting cation (**VII**) is trapped by the nucleophilic attack of the arene to form the desired product.
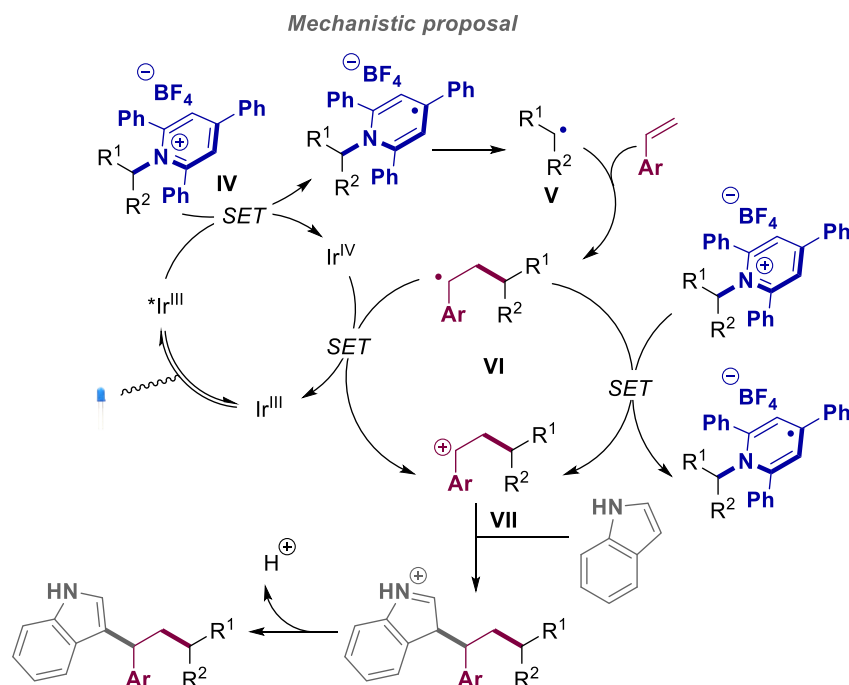
Scheme 3.2.7. Mechanistic proposal of deaminative dicarbofunctionalization.

3.2.2.4   C(sp³)–C(sp³) bond formation

Liu and co-workers reported a visible light-mediated protocol for the allylation of alkyl radicals generated by a reductive deaminative process of pyridinium salts (Scheme 3.2.8).[41] Based on Glorius' discoveries about the formation of alkyl amine radicals promoted by a light-induced process, the authors combined an iridium photocatalyst and an organic base to promote the reaction between secondary alkyl amines and allylic sulfones.
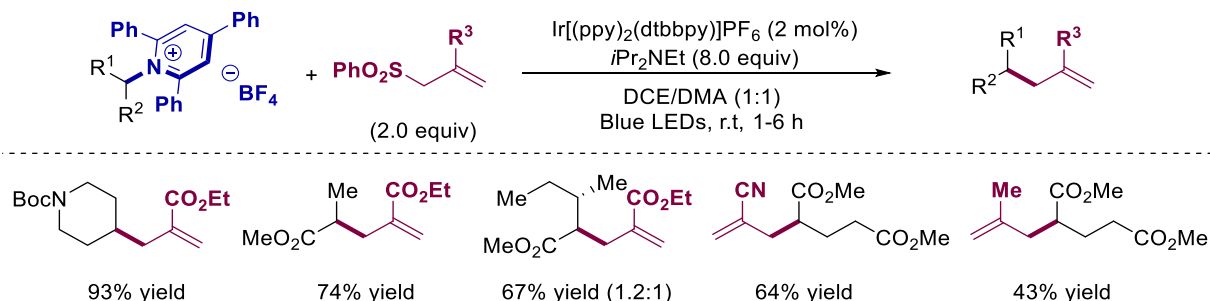
Scheme. 3.2.8. Deaminative visible-light-mediated allylation.

While the majority of the above-mentioned examples are based on the cross-coupling reaction of an *in situ* alkyl radical with an activated counterpart, Watson developed a deaminative C(sp³)–C(sp³) cross-coupling catalyzed by nickel in 2019 within the context of a Negishi-type endeavour (Scheme 3.2.9).[10] Interestingly, primary and secondary substituted alkyl amines behaved differently,

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and a different catalytic protocol had to be implemented for the successful coupling of these coupling partners. While primary alkyl amines were coupled by the utilization of tri(*tert*-butyl) terpyridine (ttbtpy) ligand, the utilization of secondary alkyl amines required 2,6-bis-(N-pyrazol)pyridine (1-bpp) ligand to deliver the targeted product in good yields. While tentative, the latter ligand is much smaller than the former, resulting in a better conformation to engage Ni(II) species with secondary alkyl radical intermediates.
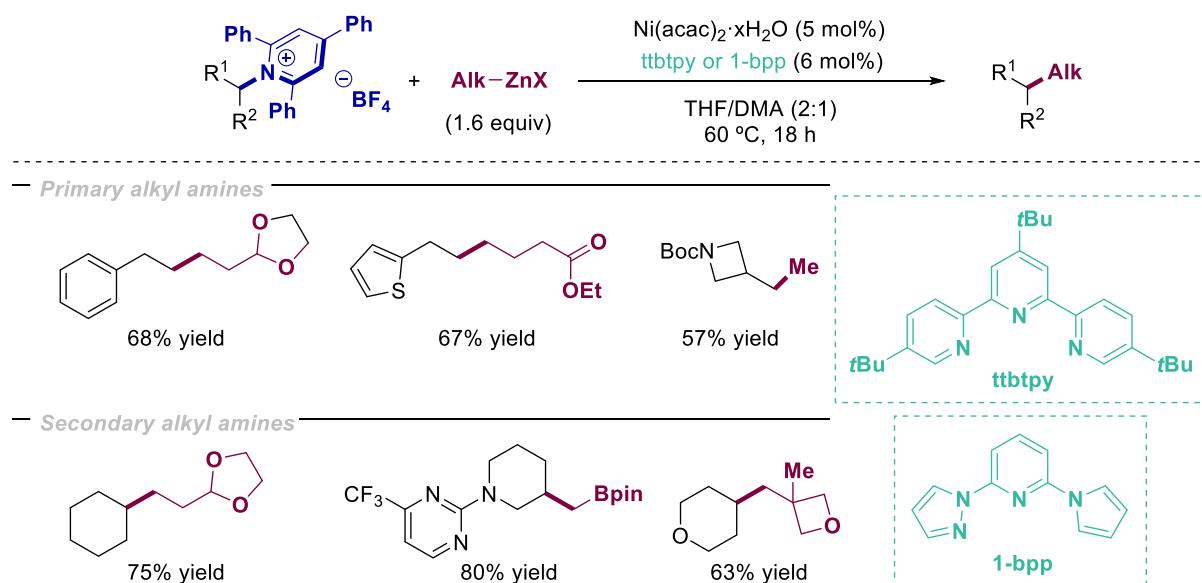
Scheme 3.2.9. Deaminative alkyl-alkyl cross-coupling reaction catalyzed by nickel.

3.2.3 *C–Heteroatom bond formation*

3.2.3.1 *C(sp²)–N, C(sp²)–O, C(sp²)–S bond formation*

In 2018, Cornella and co-workers reported a selective functionalization of aminoheterocycles bearing pyridinium salts, resulting in a *de novo* technique to forge C–Heteroatom skeletons (Scheme 3.2.10).[42] While the low nucleophilicity of the NH_2 group in aminoheterocycles made the formation of the pyridinium salt problematic, the authors solved this limitation with the design of a pyrylium reagent capable to selectively activate the amino groups in heterocyclic motifs. Once the pyridinium salt was obtained, a subsequent nucleophilic attack was carried out forming different C(sp²)–Heteroatom bonds. Remarkably, Cornella and co-workers included more than 60 examples by forging a diverse set of C–N, C–O and C–S bonds with an excellent chemoselectivity profile.
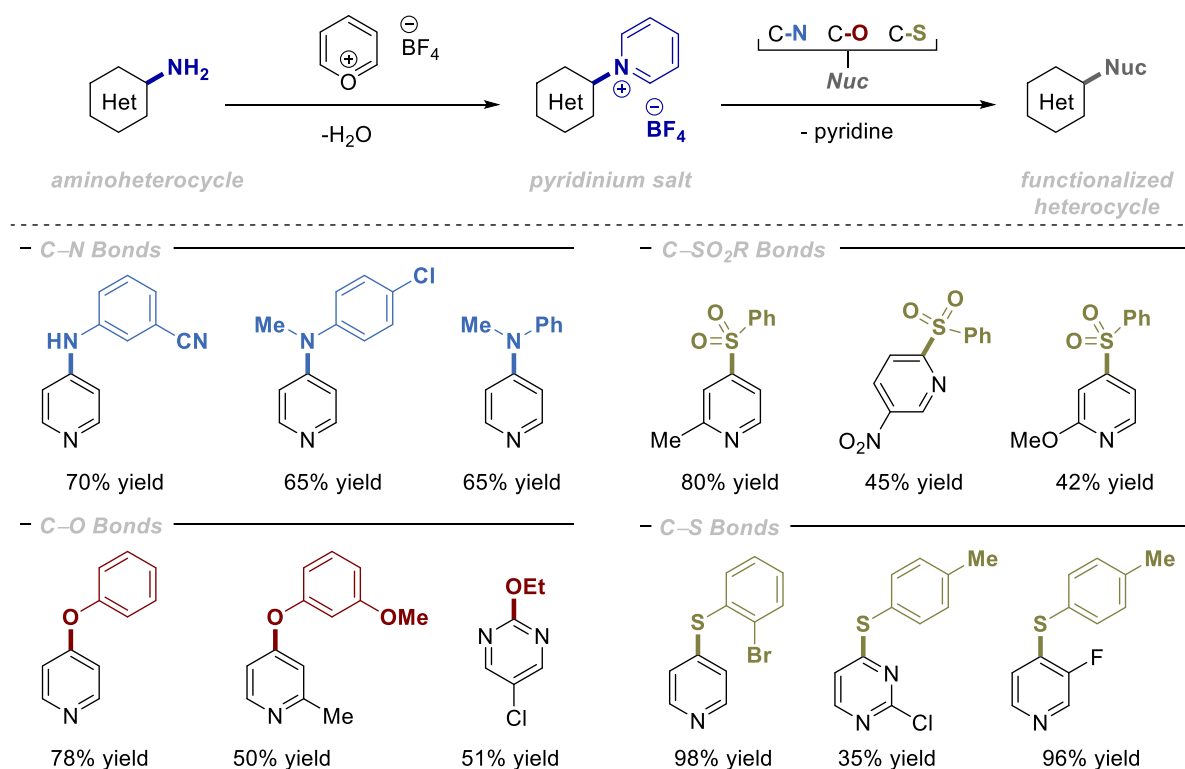
Scheme 3.2.10. Deaminative S_NAr mediated by Pyry-BF$_4$.

3.2.3.2   C(sp³)–B bond formation

Aggarwal reported an interesting catalytic deaminative borylation of pyridinium salts without the need of photocatalyst *via* the *in situ* formation of alkyl radical intermediates generated by the intermediacy of electron-donor acceptor (EDA) complexes between the pyridinium salt and B$_2$cat$_2$ (Scheme 3.2.11).[43] The authors reported that this transformation could be applied to a wide number of primary and secondary unactivated alkylamines containing esters, free alcohols, amides, acids, cyclic and non-cyclic compounds, heteroarenes and sulfones. Moreover, they were able to obtain some natural product derivatives with moderate to good yields. From a mechanistic standpoint, the alkyl radical (**X**) generated by a photoinduced SET from the EDA complex (**VIII**) is trapped by B$_2$cat$_2$, resulting in the targeted borylation product.

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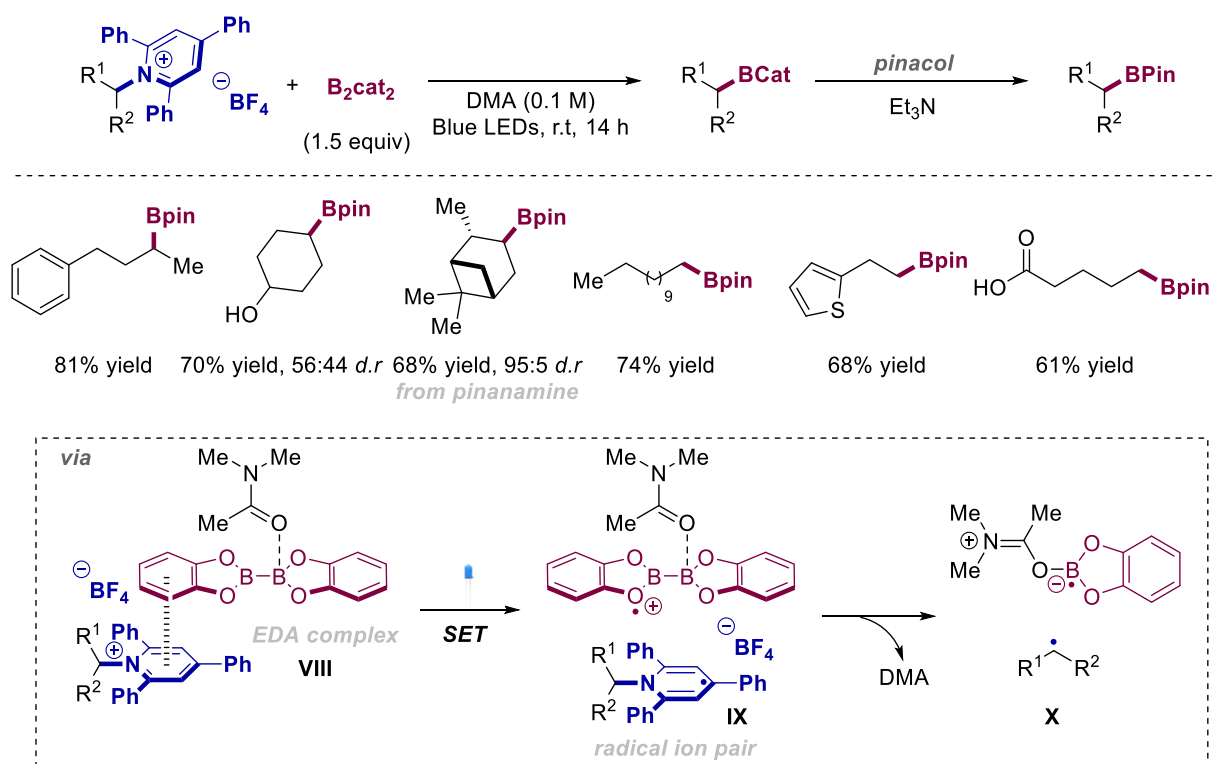
Scheme 3.2.11. Photoinduced deaminative borylation of alkyl amines.

Subsequently, Shi and Glorius reported basically an identical deaminative borylation to that shown by Aggarwal for the borylative deaminative process (Scheme 3.2.12).[44,45] Primary and secondary alkyl amines were perfectly tolerated, and the method could be applied to complex structures as well. Particularly, Shi showed that the corresponding catechol boronates can be transformed into the potassium trifluoroborate salts or to pinacol boronic esters, thus broadening the spectrum of the borylation products. While the strategy for activating B$_2$cat$_2$ in Glorius paper was the formation of an EDA complex (**VIII**), Shi proposed a Lewis acid activation pathway. The latter proposed that the dtbpy ligand facilitated the cleavage of the B$_2$cat$_2$ forming a Lewis acid adduct prior to the cleavage of the B–B bond (**XI**).

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Scheme 3.2.12. Deaminative borylation of alkyl amines.
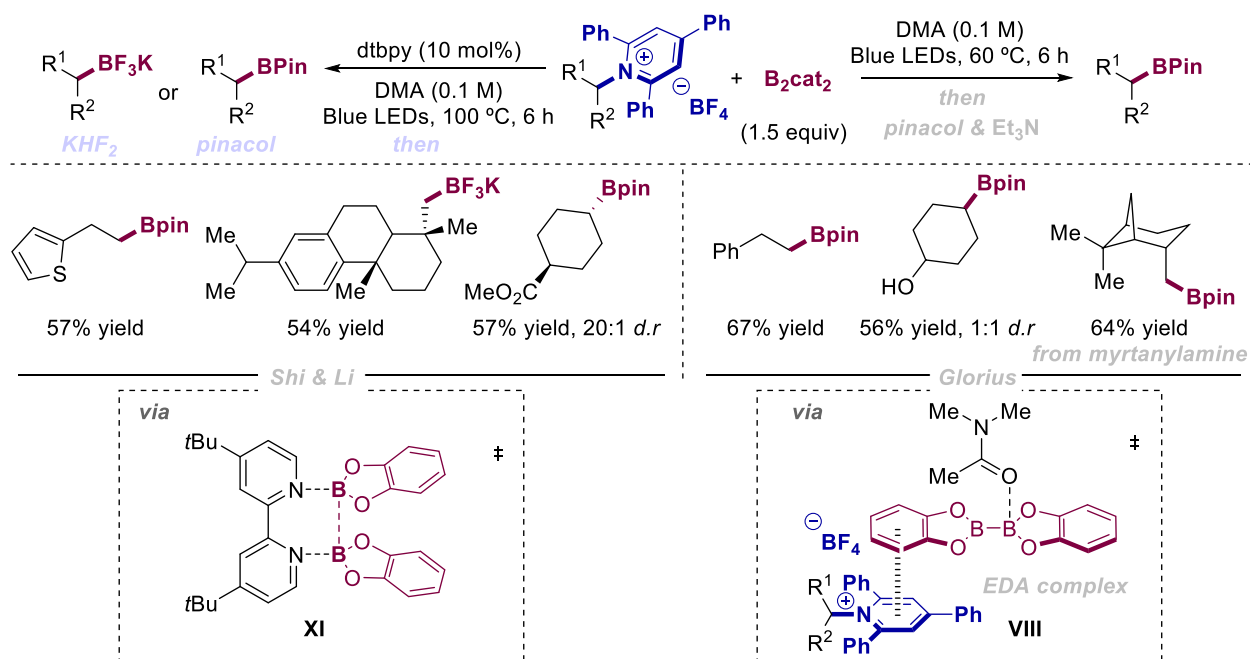
3.3 Ni-catalyzed Reductive Deaminative Arylation at sp³ Carbon Centers

3.3.1 Aim of the project

Despite the advances realized in the general area of functionalization of C(sp³) –N bonds, the formation of C(sp³)–C(sp²) bonds was accomplished *via* the utilization of organometallic species or biased heteroarenes as coupling partners (Scheme 3.2.1 & 3.2.3). Therefore, we recognized that the development of a new protocol that does not take recourse of neither organometallic reagents nor biased heteroarenes would be a worthwhile endeavour for chemical invention, particularly with easy-to-handle electrophilic counterparts, thus representing a valuable entry for enabling these methodologies within the context of late-stage functionalization of drug-type molecules (Figure 3.3.1).[46]
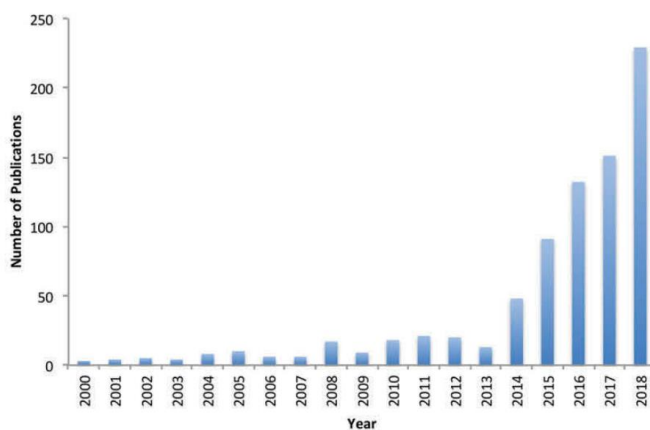
Figure 3.3.1. Publications including the concept of late-stage functionalization.

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3.3.2   *Optimization of the reaction conditions*

In view of the precedents highlighted above, we anticipated that the means to enable a catalytic deamination reaction of alkyl pyridinium salts with simple organic halides would be a particularly useful, yet practical, endeavour for building up sp^3 architectures. From a mechanistic standpoint, our strategy is based on a single electron transfer (SET) of a suitable reductant to an alkyl pyridinium salt, generating an alkyl radical that rapidly recombines with a Ni(II) oxidative addition complex generated by the reaction of an organic halide to Ni(0), allowing the formation of putative Ni(III) intermediates. The final product might be generated upon reductive elimination, and a final SET would recover back the propagating Ni(0) species within the catalytic cycle.

We began our investigations by reacting cyclohexyl pyridinium salt with *p*-methoxy iodobenzene with different Ni/ligand combinations and Zn as reducing agent in DMF (Table 3.3.1). As shown, non-negligible reactivity was observed for a different set of ligands, with better yields accomplished in the presence of electron-rich and less hindered backbones (entries **1**-**6**). In line with other catalytic reductive cross-coupling reactions,[47–49] the utilization of phosphine ligands had a deleterious effect on reactivity (entries **7**-**9**). A close inspection into the crude mixtures revealed the formation of reduced arene (**4a**) and homocoupling side-reactions (**4b**). The former can be explained by the intermediacy of either aryl radicals formed upon homolytic cleavage of the putative oxidative addition Ni(II) species or organozinc intermediates arising from either Zn insertion into the sp^2 C–I bond or transmetalation pathways.[50] The formation of homocoupling products can be attributed to an initial ligand exchange between two oxidative addition complexes followed by reductive elimination.
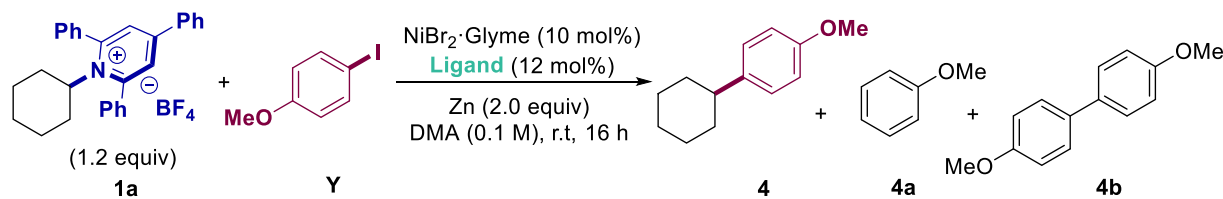
Entry	Deviation from standard conditions	Conv. (%)	4 (%)	4a (%)	4b (%)
1	L1	99	28	43	9
2	L2	100	28	47	2
3	L3	98	24	50	7
4	L4	100	0	64	9
5	L5	96	14	47	10
6	L6	98	21	72	2
7	L7	84	0	35	11
8	L8	52	0	25	2
9	L9	46	0	10	0

Reaction conditions: **1a** (0.12 mmol), **Y** (0.1 mmol), NiBr$_2$·Glyme (10 mol%), Ligand (12 mol%), Zn (2.0 equiv), DMA (1.0 mL), 25 °C, 16 h. GC conversion and yields using decane as internal standard.
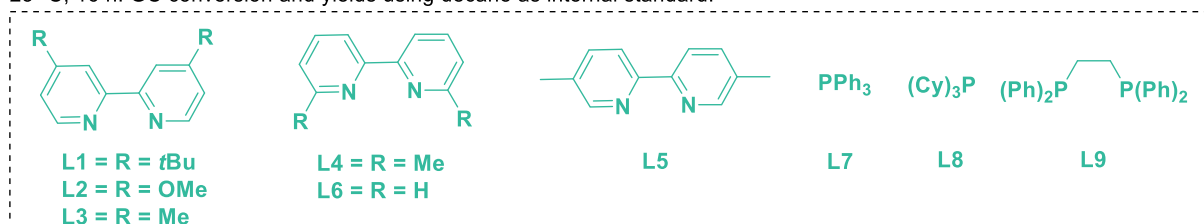
Table 3.3.1. Screening of ligands.

With these results in hand, we next focused our attention on the influence of several nickel sources and the nature of the reducing agent (Table 3.3.2). Although the yield was boosted into the 30% range when using NiCl$_2$·Glyme and NiBr$_2$·3H$_2$O (entries **2** and **3**), substantial amounts of reduced byproducts were observed in these cases (**4a**). Importantly, the utilization of Mn as reducing agent allowed to improve the yields even further without observing even traces of **4a**, but with non-negligible amounts of **4b**. While tentative, these results suggest that a higher redox potential is beneficial for the reaction to occur (E^0 [Mn^{II}/Mn^0] = -1.4 V *vs* Ag/AgCl) *vs* (E^0 [Zn^{II}/Zn^0] = -0.96 V *vs* Ag/AgCl); a conversion factor of -0.2 V was used to convert the value from that vs normal hydrogen electrode (NHE) to Ag/AgCl reference electrode.[51]

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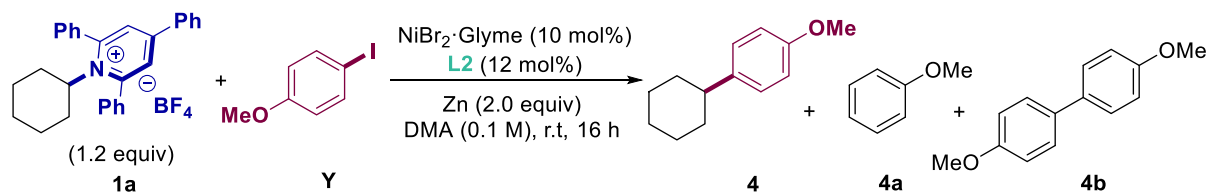
Entry	Deviation from standard conditions	Conv. (%)	4 (%)	4a (%)	4b (%)
1	Ni(COD)$_2$	100	22	74	0
2	NiCl$_2$·Glyme	100	34	60	4
3	NiBr$_2$·3H$_2$O	100	38	58	2
4	NiCl$_2$·6H$_2$O	100	24	70	4
5	NiBr$_2$	100	23	71	3
6	Ni(II)ClO$_4$·6H$_2$O	100	28	69	3
7	Ni(acac)$_2$	0	0	0	0
8	L1 and Mn (2.0 equiv)	100	47	0	16
9	L2 and Mn (2.0 equiv)	100	50	0	16

Reaction conditions: **1a** (0.12 mmol), **Y** (0.1 mmol), NiBr$_2$·Glyme (10 mol%), L2 (12 mol%), Zn (2.0 equiv), DMA (1.0 mL), 25 ºC, 16 h. GC conversion and yields using decane as internal standard.

Table 3.3.2. Screening of nickel catalysts and reducing agent.

Putting all these results into perspective, we concluded that the best results were accomplished with a regime based on NiBr$_2$·Glyme and **L2**. The next target was to explore the ratio between Ni/Ligand and the influence of different polar solvents on the reaction rate (Table 3.3.3). As shown, the utilization of NMP improved the yield (entries **6** and **8**), moreover when utilizing 6 mol% of NiBr$_2$·Glyme and 10 mol**%** of **L2** (entry **9**), the yield of **4** was increased to 76%.

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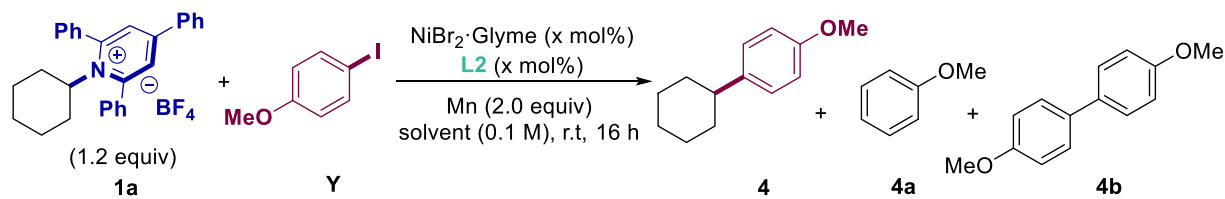
Entry	Deviation from standard conditions	Conv. (%)	4 (%)	4a (%)	4b (%)
1	Ni (5 mol%), L2 (20 mol%), DMA (0.1M)	0	0	0	0
2	Ni (5 mol%), L2 (10 mol%), DMA (0.1M)	88	43	3	13
3	Ni (5 mol%), L2 (10 mol%), DME (0.1M)	100	26	0	19
4	Ni (5 mol%), L2 (10 mol%), DMA/DME (0.1M)	100	54	0	15
5	Ni (5 mol%), L2 (10 mol%), DMF (0.1M)	38	0	0	0
6	Ni (5 mol%), L2 (10 mol%), DMA/NMP (0.1M)	100	63	0	10
7	Ni (5 mol%), L2 (10 mol%), DMA (0.06M)	100	63	0	10
8	Ni (5 mol%), L2 (10 mol%), NMP (0.1M)	100	70	0	7
9	Ni (6 mol%), L2 (10 mol%), NMP (0.1M)	100	76	0	8

Reaction conditions: **1a** (0.12 mmol), **Y** (0.1 mmol), NiBr$_2$·Glyme (x mol%), L2 (x mol%), Mn (2.0 equiv), solvent (1.0 mL), 25 ºC, 16 h. GC conversion and yields using decane as internal standard.

Table 3.3.3. Nickel/ligand ratio screening & solvent.

Despite the good results accomplished, we decided to revisit the influence of other ligands. In line with our expectations, bipyridines and phenanthrolines possessing electron-rich and non-hindered *ortho*-substituents provided the best yields (entries **2**-**13**). Unfortunately, none of the ligands analyzed afforded better yields than **L2**. Only DMA (entry **15**) was comparable to NMP, thus highlighting the critical influence of polar aprotic solvents on the reaction outcome. Notably, lower amounts of Mn gave rise to **4** in slightly better yields (entries **17** & **18**).

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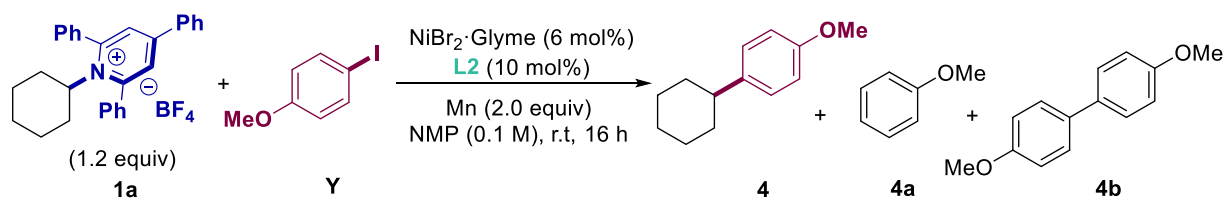
Entry	Deviation from standard conditions	Conv. (%)	4 (%)	4a (%)	4b (%)
1	None	100	75	0	8
2	L1	100	64	0	11
3	L3	35	30	0	2
4	L4	14	13	0	3
5	L5	100	14	37	15
6	L6	89	38	0	10
7	L7	100	11	13	22
8	L8	13	4	7	0
9	L9	100	20	4	20
10	L10	100	48	0	16
11	L11	100	59	0	16
12	L12	100	58	0	16
13	L13	39	18	12	3
14	DMF	13	11	3	0
15	DMA	79	67	0	6
16	DMSO	20	0	0	0
17	Mn (2.5 equiv)	100	58	0	14
18	Mn (1.5 equiv)	100	86	0	5

Reaction conditions: **1a** (0.12 mmol), **Y** (0.1 mmol), NiBr$_2$·Glyme (6 mol%), L2 (10 mol%), Mn (2.0 equiv), solvent (1.0 mL), 25 °C, 16 h. GC conversion and yields using decane as internal standard.
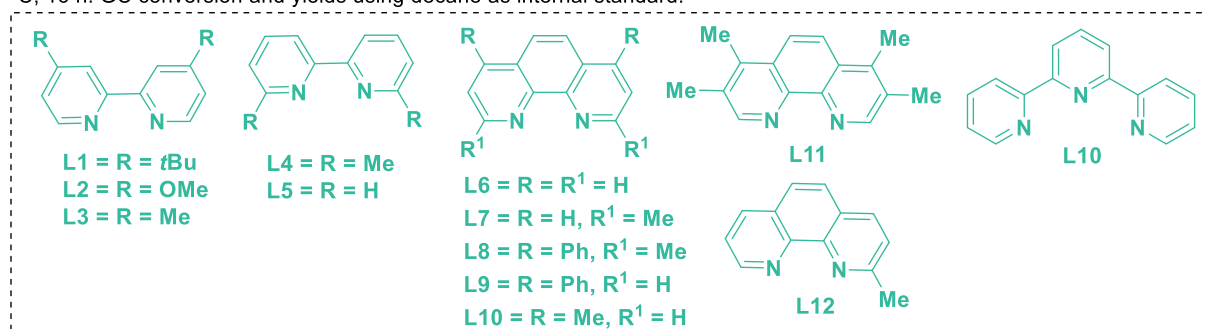
Table 3.3.4. Ligand, solvent and reducing agent screening.

Although we experienced reproducibility issues, these could be alleviated by the utilization of stock solutions of Ni/**L2** in NMP, resulting in excellent levels of reactivity while minimizing the side-reactions *en route* to both **4a** and **4b** (Table 3.3.5, entries **3** and **4**).

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Reaction conditions: **1a** (0.12 mmol), **Y** (0.1 mmol), NiBr$_2$·Glyme (6 mol%), L2 (10 mol%), Mn (1.5 equiv), NMP (1.0 mL), 25 ºC, 16 h. GC conversion and yields using decane as internal standard.
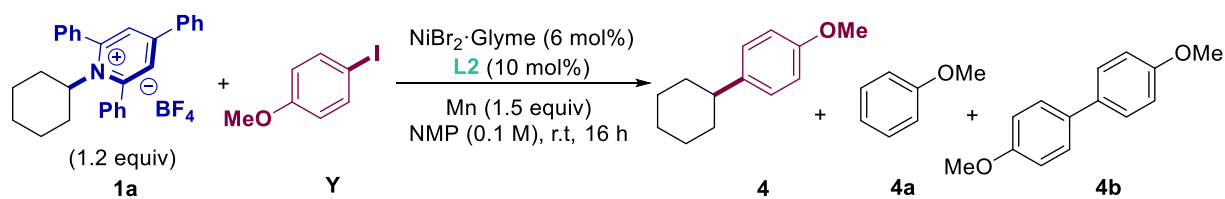
Entry	Deviation from standard conditions	Conv. (%)	4 (%)	4a (%)	4b (%)
1	no stock solution	100	61	0	12
2	no stock solution	100	72	0	8
3	stock solution	100	95	0	2
4	stock solution	100	94	0	2
5	stock solution with L1	100	89	0	2
6	stock solution with L1	100	90	0	3

Table 3.3.5. Stock solutions table.

Although we managed to optimize the targeted catalytic deaminative cross-coupling of alkyl pyridinium salts, our conditions required the utilization of rather expensive and non-particularly available aryl iodides. To this end, we wondered whether our conditions could be applied to the coupling of aryl bromides (Table 3.3.6). Unfortunately, low yields were obtained upon exposure of aryl bromide to the optimized conditions shown for aryl iodides (entry **1**). Interestingly, decent yields were obtained with 14 mol% **L2** (entry **5**), whereas lower results were obtained with lower or higher amounts of ligand (entries **4** and **6**).
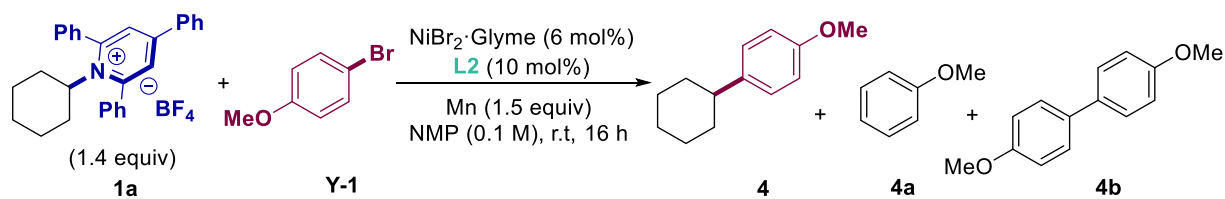
Entry	Deviation from standard conditions	Conv. (%)	4 (%)	4a (%)	4b (%)
1	**1a** (1.2 equiv)	28	6	6	6
2	none	36	12	3	5
3	Ni (8 mol%)/ L2 (12 mol%)	59	41	2	8
4	Ni (10 mol%)/ L2 (12 mol%)	79	40	4	7
5	Ni (10 mol%)/ L2 (14 mol%)	79	49	0	10
6	Ni (10 mol%)/ L2 (18 mol%)	25	17	0	1

Reaction conditions: **1a** (0.12 mmol), **Y-1** (0.1 mmol), NiBr$_2$·Glyme (6 mol%), L2 (10 mol%), Mn (1.5 equiv), NMP (1.0 mL), 25 ºC, 16 h. GC conversion and yields using decane as internal standard.

Table 3.3.6. Nickel and ligand loading amount screening with aryl bromides.

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The low yielding achieved for aryl bromides might be due to the following: (a) the significantly higher BDE required for cleaving the C_6H_5–Br bond (80 ± 2 kcal/mol) vs the C_6H_5–I linkage (65 ± 2 kcal/mol),[52] making oxidative addition particularly slow for aryl bromides, and (b) the utilization of particularly electron-rich aryl bromides possessing a *p*-methoxy unit makes oxidative addition, recombination events with electron-rich alkyl radicals and reductive elimination particularly uphill. Therefore, we decided to screen additional parameters for boosting the reactivity of aryl bromides. Unfortunately, none of the ligands analyzed afforded better yields than **L2** (Table 3.3.7).
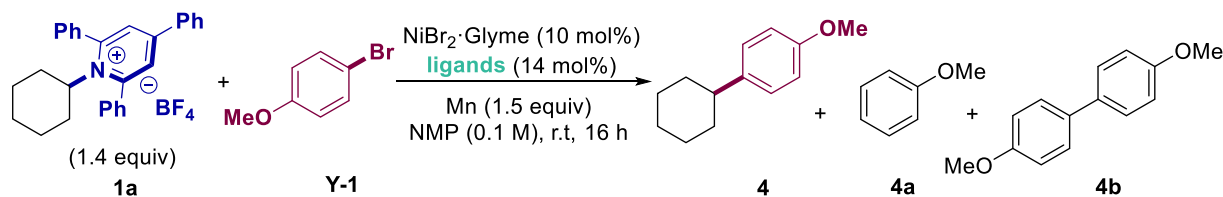
Entry	Deviation from standard conditions	Conv. (%)	4 (%)	4a (%)	4b (%)
1	L2	88	51	0	10
2	L1	100	46	12	7
3	L3	100	48	15	6
4	L4	76	6	5	5
5	L5	83	5	59	2
6	L6	16	1	14	0
7	L7	77	45	0	6
8	L8	77	2	59	2
9	L9	71	39	0	4
10	L10	81	0	56	1
11	L11	52	9	8	3
12	L12	31	14	0	0
13	PPh$_3$	23	7	9	5
14	PCy$_3$	20	13	0	0
15	dcype	13	3	0	0

Reaction conditions: **1a** (0.14 mmol), **Y-1** (0.1 mmol), NiBr$_2$·Glyme (10 mol%), ligands (14 mol%), Mn (1.5 equiv),NMP (1.0 mL), 25 ºC, 16 h. GC conversion and yields using decane as internal standard.
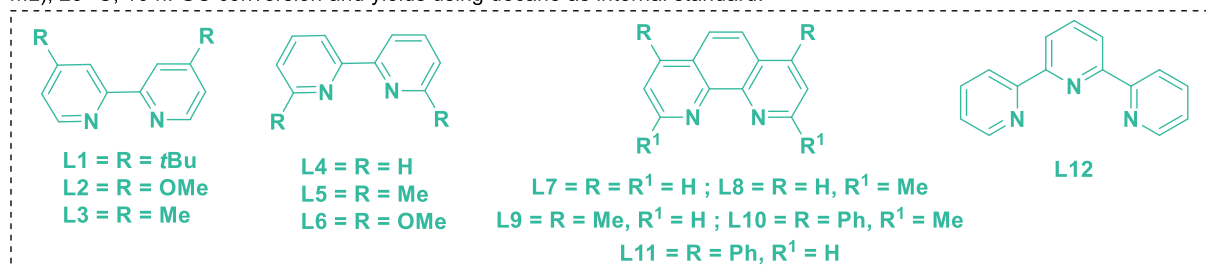
Table 3.3.7. Screening of ligands using aryl bromide.

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We further investigated he nickel source effect however, as shown in Table 3.3.8, none of the entries provided better results than NiBr₂·Glyme (entries **1**-**6**). Although replacing NMP by DMA (entry **7**) afforded similar results, it is worth noting that the amount of homocoupling increased significantly in this case. Unfortunately, the reaction did not work when utilizing DMF likely to solubility issues (entry **8**).
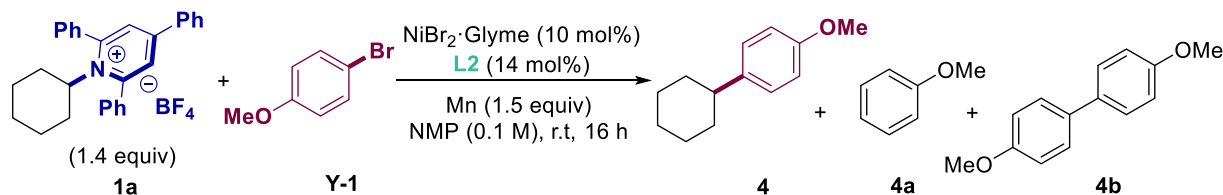
Entry	Deviation from standard conditions	Conv. (%)	4 (%)	4a (%)	4b (%)
1	NiCl₂·6H₂O	24	5	0	0
2	NiBr₂·3H₂O	99	42	0	10
3	NiI₂	57	17	0	5
4	Ni(acac)₂	0	0	0	0
5	NiCl₂·Glyme	100	25	0	17
6	Ni(COD)₂	86	10	0	18
7	DMA	80	46	0	13
8	DMF	5	0	0	0

Reaction conditions: **1a** (0.14 mmol), **Y-1** (0.1 mmol), NiBr₂·Glyme (10 mol%), L2 (14 mol%), Mn (1.5 equiv), solvent (1.0 mL), 25 ºC, 16 h. GC conversion and yields using decane as internal standard.

Table 3.3.8. Nickel sources and solvent screening.

In light of these results, we hypothesized that the inclusion of iodide additives might form *in situ* oxidative addition species bearing an iodide anion *via* halide exchange, thus boosting the yield of the targeted product. As shown in Table 3.3.9, this turned out to be the case. In addition, the escorting cation had a non-negligible influence on the reaction (entries **2**-**7**), with NaI providing the best results *en route* to **4**.

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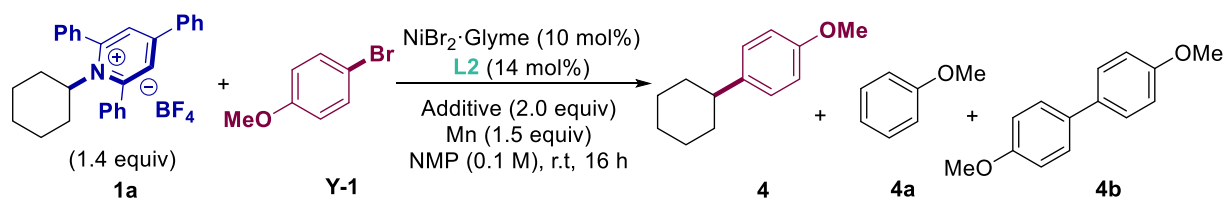
Entry	Deviation from standard conditions	Conv. (%)	4 (%)	4a (%)	4b (%)
1	none	59	41	2	8
2	KI	83	55	7	9
3	NaI	100	77	9	9
4	MgI$_2$	92	44	0	11
5	ZnI$_2$	74	41	2	0
6	CsI	75	57	7	9
7	LiI	88	61	9	10
8	(Bu)$_4$NI	90	58	8	6
9	Me$_4$NI	74	50	6	8
10	Et$_4$NI	78	55	5	8
11	EtMe$_3$NI	88	57	10	8
12	PhMe$_3$NI	92	66	7	6
13	Pr$_4$NI	67	65	8	9
14	(hep)$_4$NI	90	65	7	8
15	Ph$_4$NI	81	57	6	7

Reaction conditions: **1a** (0.14 mmol), **Y-1** (0.1 mmol), NiBr$_2$·Glyme (10 mol%), L2 (14 mol%), Additive (2.0 equiv), Mn (1.5 equiv), NMP (1.0 mL), 25 ºC, 16 h. GC conversion and yields using decane as internal standard.

Table 3.3.9. Screening of iodide salts as additives.

Notably, the application of our optimized conditions to electron-poor aryl bromides resulted in nearly quantitative yields of **3** (Table 3.3.10, entry **1**). Entry **2** shows that DMA could also be a valuable solvent for the reaction whereas the reduction of the nickel/ligand loading was detrimental for the reaction to occur (entry **3**).

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Reaction conditions: **1a** (0.14 mmol), **2a** (0.1 mmol), NiBr$_2$·Glyme (10 mol%), L2 (14 mol%), Mn (1.5 equiv), solvent (1.0 mL), 25 ºC, 16 h. GC conversion and yields using decane as internal standard.

Table 3.3.10. Substrate changing; electron-poor substrate.

Finally, we decided to look at the influence of the metal reductant (Table 3.3.11). However, significantly lower results were accomplished in this case, probably due to the lower redox potential of Zn when compared to Mn (entry **2**). As expected, the utilization of aryl iodides provided access to **3** in comparable yields whereas an aryl chloride resulted in negligible conversion to products (entries **3** and **4**). Finally, control reactions under air or in absence of either Mn or Ni/**L2** resulted in traces, if any, of the corresponding cross-coupling product (entries **5** and **6**).

Reaction conditions: **1a** (0.14 mmol), **2a** (0.1 mmol), NiBr$_2$·Glyme (10 mol%), L2 (14 mol%), Mn (1.5 equiv), NMP (1.0 mL), 25 ºC, 16 h. GC conversion and yields using decane as internal standard. [a]Isolated yield

Table 3.3.11. Aryl halides and control screening.

3.3.3 Substrate scope

Encouraged by these results, we turned our attention to explore the generality of our reductive deamination methodology. To our surprise, we had to do initial readjustments in the set of conditions when we explored less activated aryl bromides. The lack of reactivity found in these substrates was

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compensated by conducting the reaction at 60 °C and stirred for 20 h. As shown in Scheme 3.3.1, we were able to accommodate arenes bearing esters (**3** & **16**), aldehydes (**6**, **13**, **14**, **15**, **17**), ketones (**7** & **18**), free alcohols (**11**), halides (**8** & **11**) and nitrile groups (**12**). The tolerance of our protocol with aldehydic counterparts is particularly important, as related approaches aimed at the same goal make use of organometallic reagents that would undergo a nucleophilic attack into the carbonyl moiety. Due to the lower reactivity of electron-rich aryl bromides, aryl iodides were used (**4** and **5**). In addition, we could trigger the reaction of an aryl iodide possessing a pending bromide at *para* position, providing a handle for further functionalization *via* cross-coupling reactions (**8**).

Reaction conditions: **1a-h** (0.28 mmol), aryl halide (0.2 mmol), NiBr$_2$·Glyme (10 mol), L2 (14 mol%), Mn (1.5 equiv), NMP (0.1 M), 60 °C, 20 h. Isolated yields, average of two runs. [a]At r.t. [b]Using ArI. [c]DMA at 15 °C. [d]At 45 °C. [e]5.44 mmol scale. [f]NaI (2.0 equiv).
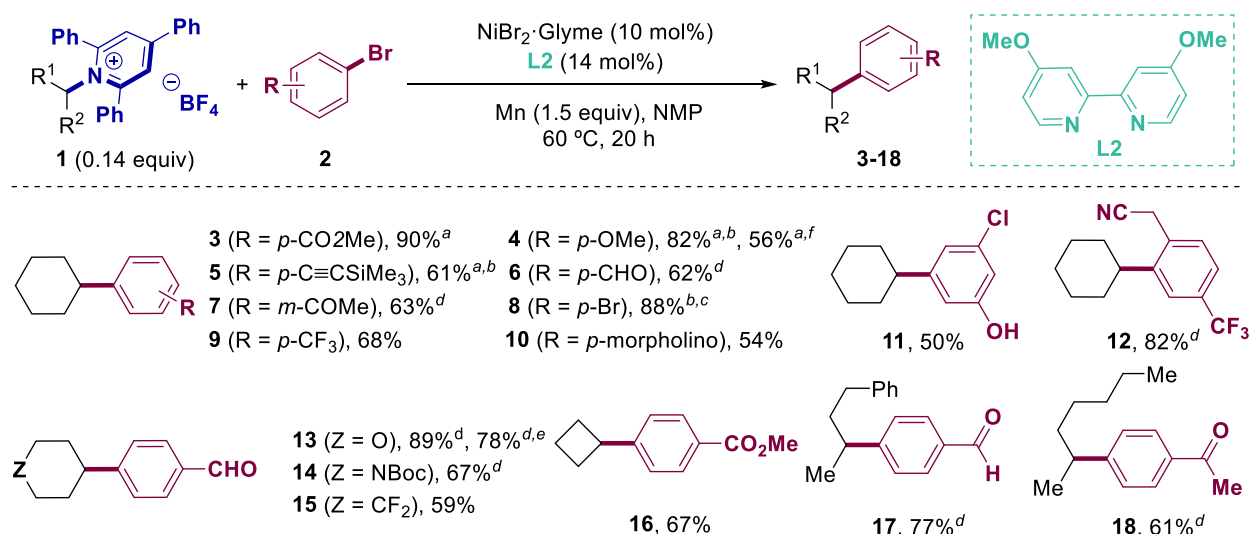
Scheme 3.3.1. Scope of unactivated secondary alkyl amines.

Next, we turned our attention to study the influence of the alkyl amine on the reaction. Cyclic substrates such as cyclobutane (**16**), cyclohexane (**3-15**) and acyclic alkyl amines (**17** & **18**) could be coupled without any problems. The ability to couple the latter is particularly important, as acyclic alkyl counterparts are commonly plagued by parasitic β-hydride elimination or homodimerization pathways. Importantly, this was not the case, and not even traces of alkene side-products were identified in the crude mixtures. Importantly for a synthetic and practical point of view, a gram scale reaction was performed giving rise to **13** in 78% isolated yield. Next, we turned our attention to study the reaction of unactivated primary amines that are particularly more difficult to employ due to their inherent reluctance to generate primary alkyl radicals *via* SET as compared to their secondary alkyl congeners. Indeed, lower yields were found for all primary alkyl pyridiniums tested (Scheme 3.3.2). To solve this problem, we hypothesized that the inclusion of electron-rich arenes at the pyridinium backbone would facilitate C–N scission albeit higher redox potentials to trigger the SET would be needed. As shown in Scheme 3.3.2, this was indeed the case. Notably, a subtle change in the reaction conditions allowed for triggering the reaction of primary alkyl pyridinium salts by adjusting the temperature of the reaction.

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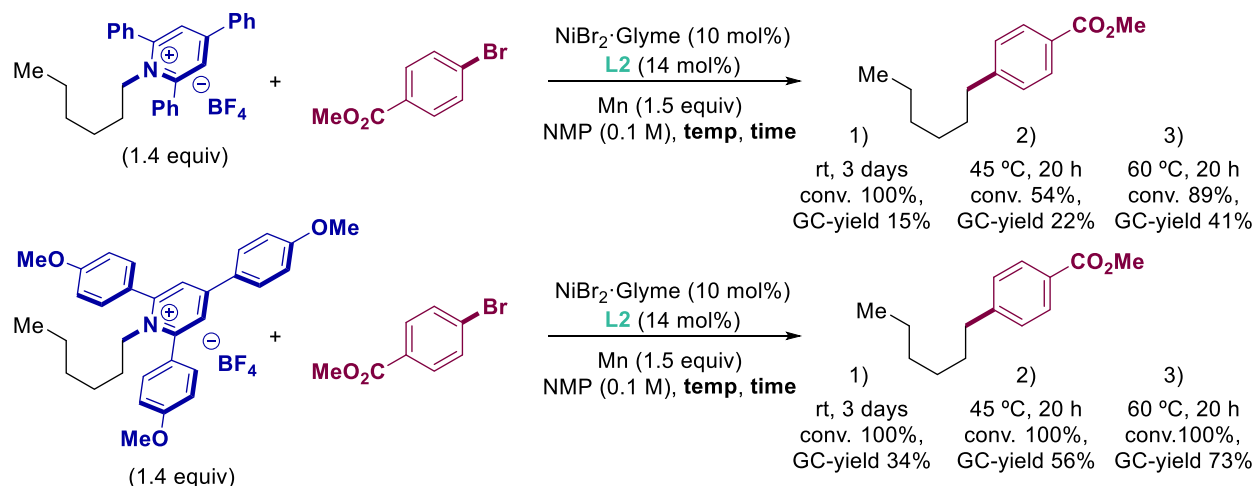
Scheme 3.3.2. Testing primary alkyl pyridinium salts.

With these results in hand, we then focused our attention to study the scope of the unactivated primary alkyl amines (Scheme 3.3.3). As shown, we were able to conduct the targeted cross-coupling reaction in the presence of esters (**26**), nitriles (**22**), alkenes (**23** & **28**), acetals (**19**-**25**, **30**), sulfonamides (**29**) and nitrogen containing heterocycles (**24**, **25**, **31**-**33**). This method could be even extended to vinyl bromides, albeit in lower yields (**30**). As for secondary alkyl pyridinium salts, the reaction could be applied to aryl bromides bearing organoboron groups (**20**, **28**, **29**) or aryl halides (**19**), thus opening a gateway to further functionalization *via* classical cross-coupling reactions.
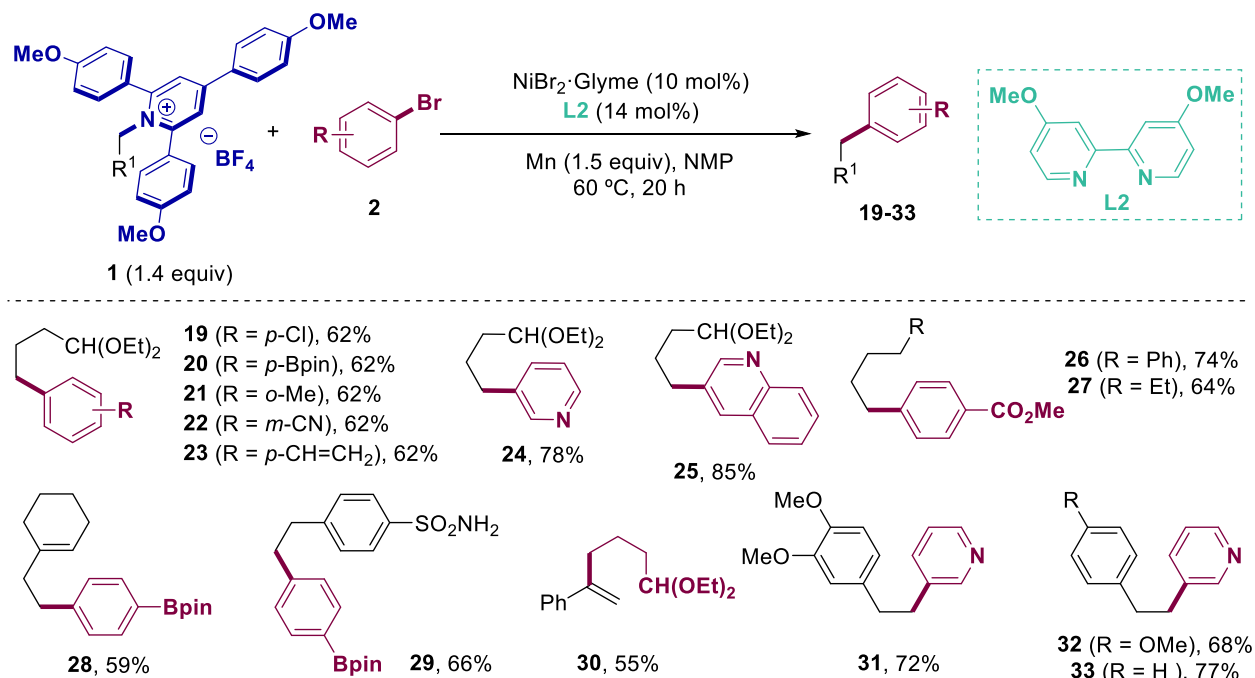
Reaction conditions: **1i-q** (0.28 mmol), aryl halide (0.2 mmol), NiBr₂·Glyme (10 mol), L2 (14 mol%), Mn (1.5 equiv), NMP (0.1 M), 60 ºC, 20 h. Isolated yields, average of two runs.

Scheme 3.3.3. Scope of unactivated primary alkyl amines.

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3.3.4   Late-Stage Functionalization

Prompted by our initial results, we then turned our attention to implement our deaminative cross-coupling protocol in advanced synthetic intermediates (Scheme 3.3.4). Indeed, a variety of biologically active compounds containing amine groups such as histamine, mexiletine, leelamine, primaquine, or mosapride could all be accommodated in our deaminative cross-electrophile coupling with aryl halides (**34**-**38**). Particularly interesting is the ability to tolerate the presence of an imidazole, ether, fused-rings, quinoline, free N–H bonds or aryl halides.

34, 65%
from histamine

35, 69%[a]
from mexiletine

36, 57%
from leelamine

37, 61%
from primaquine

38, 73%
from mosapride
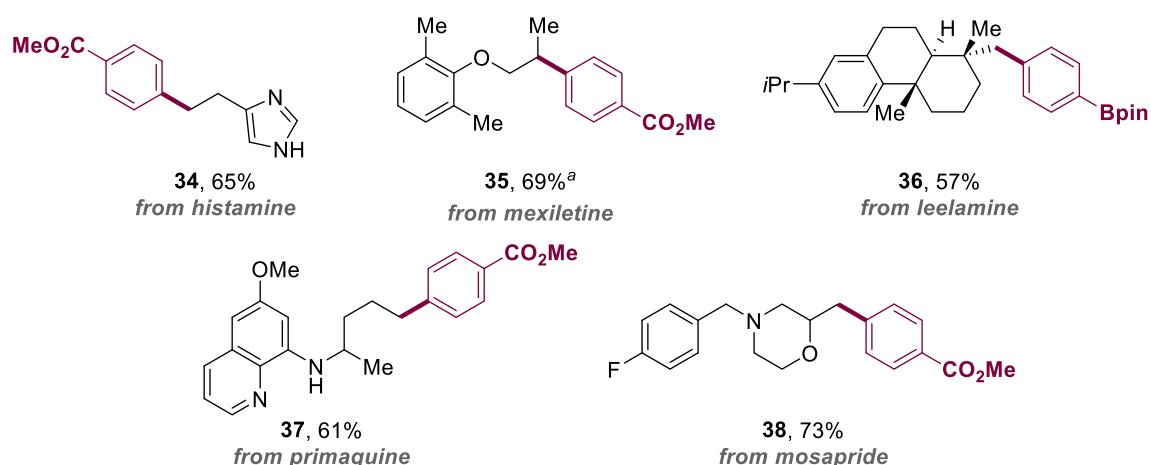
Reaction conditions: pyridinium salt (0.28 mmol), aryl halide (0.2 mmol), NiBr$_2$·Glyme (10 mol), L2 (14 mol%), Mn (1.5 equiv), NMP (0.1 M), 60 ºC, 48 h. Isolated yields, average of two runs. [a]Using ArI.

Scheme 3.3.4. Late-stage functionalization of alkyl amines.

Aimed at extending the versatility and practicality of our protocol, we hypothesized that we could trigger a non-invasive outer sphere SET mediated by a photocatalyst instead of using stoichiometric amounts of metal reductants (Table 3.3.12). Consequently, we tested a diverse set of iridium/ruthenium photocatalysts and organophotocatalysts (entries **2**-**8**), with the best results accomplished using [Ir(dF(CF$_3$)ppy)$_2$(dtbpy)]PF$_6$ and 4-CzIPN. The origin behind these results can be ascribed to the redox potential of the photocatalysts (E$_{1/2}$ [Ir^{III*}/Ir^{II}] = -1.33 V *vs* Ag/AgCl) (E$_{1/2}$ [P/P$^-$] = -1.17 V *vs* Ag/AgCl) respectively, as these are capable of reducing either primary (E$_{1/2}$ = -0.74 *vs* Ag/AgCl) or secondary alkyl pyridinium salts (E$_{1/2}$ = ≈0.90 *vs* Ag/AgCl). It was found that Hantzsch esters performed better than other organic amines as sacrificial reducing agent (entry **11**) in combination with Cs$_2$CO$_3$ (entries **9** & **10**). Surprisingly, moderate yield was observed when performing the reaction without base, indicating that the pyridine generated might act as a base (entry **12**). As expected, no product was observed in the absence of light (entries **12**-**13**).

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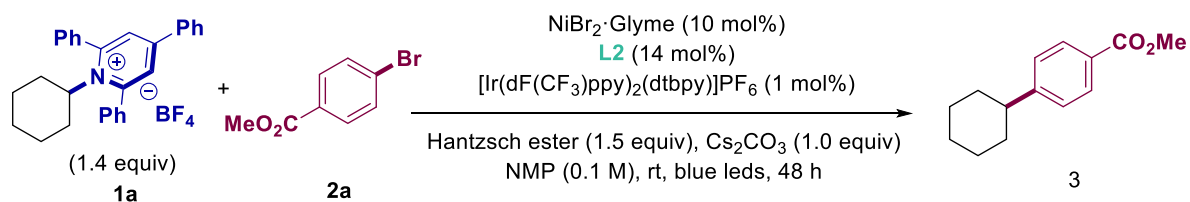
Entry	Deviation from standard conditions	Conversion of 1a (%)	3 (%)
1	None	100	95 (88)[a]
2	2 equivalents of Hantzsch ester	85	70
3	[Ru(bpy)$_3$]Cl$_2$ and 2 equiv. of Hantzsch ester	11	3
4	4-CzIPN and 2 equiv. of Hantzsch ester	100	75
5	MesAcrClO$_4$ and 2 equiv. of Hantzsch ester	20	4
6	[Ir(ppy)$_2$(dtbpy)]PF$_6$ and 2 equiv. of Hantzsch ester	100	74
7	[Ir(dF(CF$_3$)ppy)$_2$(ppy)]PF$_6$ and 2 equiv. of Hantzsch ester	100	69
8	[Ir(ppy)$_3$] and 2 equiv. of Hantzsch ester	51	32
9	K$_2$CO$_3$ instead of Cs$_2$CO$_3$	83	17
10	Rb$_2$CO$_3$ instead of Cs$_2$CO$_3$	4	0
11	DIPEA instead of Hantzsch ester	44	19
12	No base	100	39
13	No light	3	0

Reaction conditions: **1a** (0.14 mmol), **2a** (0.1 mmol), NiBr$_2$·Glyme (10 mol%), L2 (14 mol%), [Ir(dF(CF$_3$)ppy)$_2$(dtbpy)]PF$_6$ (1 mol%), Hantzsch ester (1.5 equiv), NMP (1.0 mL), 25 ºC, 48 h, blue LEDs. GC conversion and yields using decane as internal standard. [a]Isolated yield.

Table 3.3.12. Optimization of the photocatalytic conditions.

With these conditions in hand, we tested our hypothesis with a pinanamine derivative, as this compound could not be employed under Mn-mediated protocol (Scheme 3.3.5, *left*). Fortunately, a dual photoredox/Ni catalytic regime with Hantzsch ester as reductant cleanly furnished the desired product (**39**) in good yield. At present, we do not have any rationale behind these results.

Scheme 3.3.5. Dual photoredox/Ni catalyst regime for late-stage functionalization.

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3.3.5   *Unsuccessful substrates*

Unfortunately, a variety of different coupling partners cannot be employed as substrates (Figure 3.3.1). As shown, a variety of heteroaryl bromides were not suitable for the reaction possibly due to the competitive binding of the nitrogen atom to the Ni catalyst. Substrates possessing sterically congested backbones or the inclusion of free alcohols or amines were not suited for the reaction. Unfortunately, no reaction was found by using alkyl or alkynyl bromides (*conditions A* and *B*). Although we managed to synthesize pyridinium salts for all of the alkyl amines listed in Figure 3.3.1, the coupling event was found to be particularly problematic. *A priori*, one could expect that secondary alkyl amines would work better than their primary congeners, but we observed an opposite behaviour, likely explained by the strong activation of primary alkyl amines with the electron-rich pyridiniums. In addition, the utilization of pyridinium salts derived from α, β, γ-aminoacids or ester derivatives did not result in the targeted products due to the presence of free acids or coordination to the catalyst. A similar lack of reactivity was found for aromatic and tertiary alkyl amines. The lack of activation might be the cause for the former while the stereoelectronic effects in the radical formation can be accused in the latter. Unfortunately, the application of our technology in more functionalized backbones resulted in negligible yields of the targeted coupling products, probably due to the presence of multiple functional groups that might interfere with the Ni catalyst.

Figure 3.3.1. Unsuccessful deaminative arylation.

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3.3.6   *Mechanistic proposal*

A priori, the reaction might be explained by either (a) the activation of the alkyl amine derivative *via* oxidative addition to Ni(0)L$_n$ or (b) the formation of alkyl radicals by SET from either Ni(0)L$_n$ or Ni(I)L$_n$. To this end, we turned our attention to conduct stoichiometric studies of **1** with Ni(COD)$_2$/**L2** and **Ni-1**, hoping that it will reveal the mode of action by which this reaction operates at the molecular level (Scheme 3.3.6). In both cases, negligible conversion to product were observed, obtaining instead traces of homodimerization and absence of alkene formation, suggesting that the reaction might occur *via* other mechanistic manifolds.
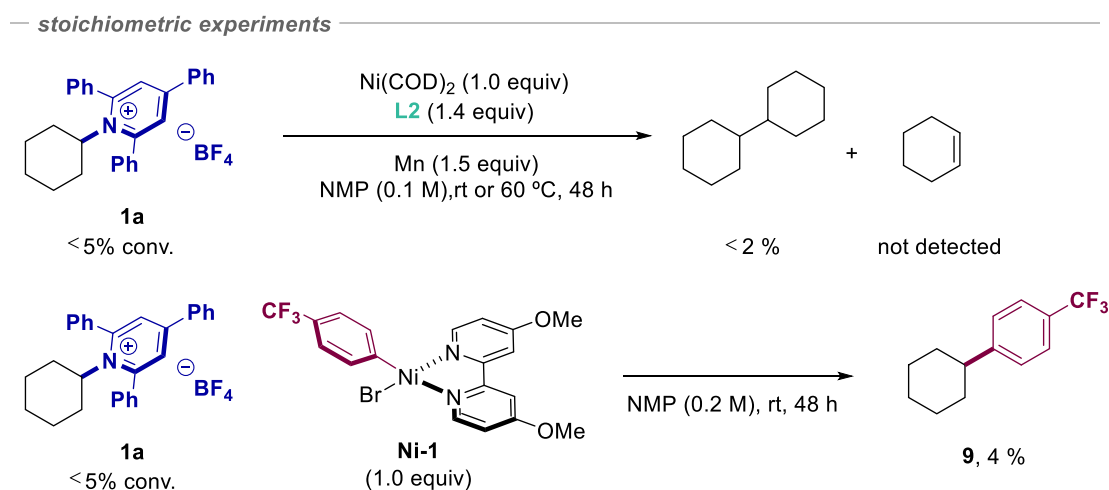
Scheme 3.3.6. Stoichiometric mechanistic experiments.

Prompted by these results, we decided to check the redox potential of all reaction components. After some experimentation, we managed to do so and obtained the following data: **Ni-1** (E$_{1/2}$ [Ni^{II}/Ni^{I}] = -1.37 V *vs* Ag/AgCl), **1a** (E$_{1/2}$ = -0.74 *vs* Ag/AgCl), **1m** (E$_{1/2}$ = -0.90 *vs* Ag/AgCl) and Mn (E^0 [Mn^{II}/Mn^0] = -1.39 V *vs* Ag/AgCl). A close look at this information indicates that both **Ni-1** and Mn might *a priori* be able to reduce either primary or secondary alkyl pyridinium salts (Scheme 3.3.7, *top*). Therefore, the lack of reactivity found in Scheme 3.3.6 might be explained by the inability of Ni(II) species or Ni(0) to promote C–N scission. Such uncertainty prompted us to study the reaction of Mn with **1a** in the presence of TEMPO, as Mn might be suited for triggering a SET to the alkyl pyridinium salt. Importantly, 80% yield of **40** was obtained, strongly advocating the notion that a SET process into **1a** takes place, generating an alkyl radical that is trapped in the presence of TEMPO. To gather evidences about the radical formation and to determine whether or not an oxidative addition pathway takes place, we performed three control reactions (Scheme 3.3.7, *bottom*). Interestingly, (1) the addition of TEMPO resulted in a significant inhibition, (2) racemic product was observed (**41**) upon subjecting our optimized conditions to enantiopure alkyl pyridinium salts and (3) ring-opening was observed with alkylpyridinium salts containing adjacent cyclopropyl rings (**42**).

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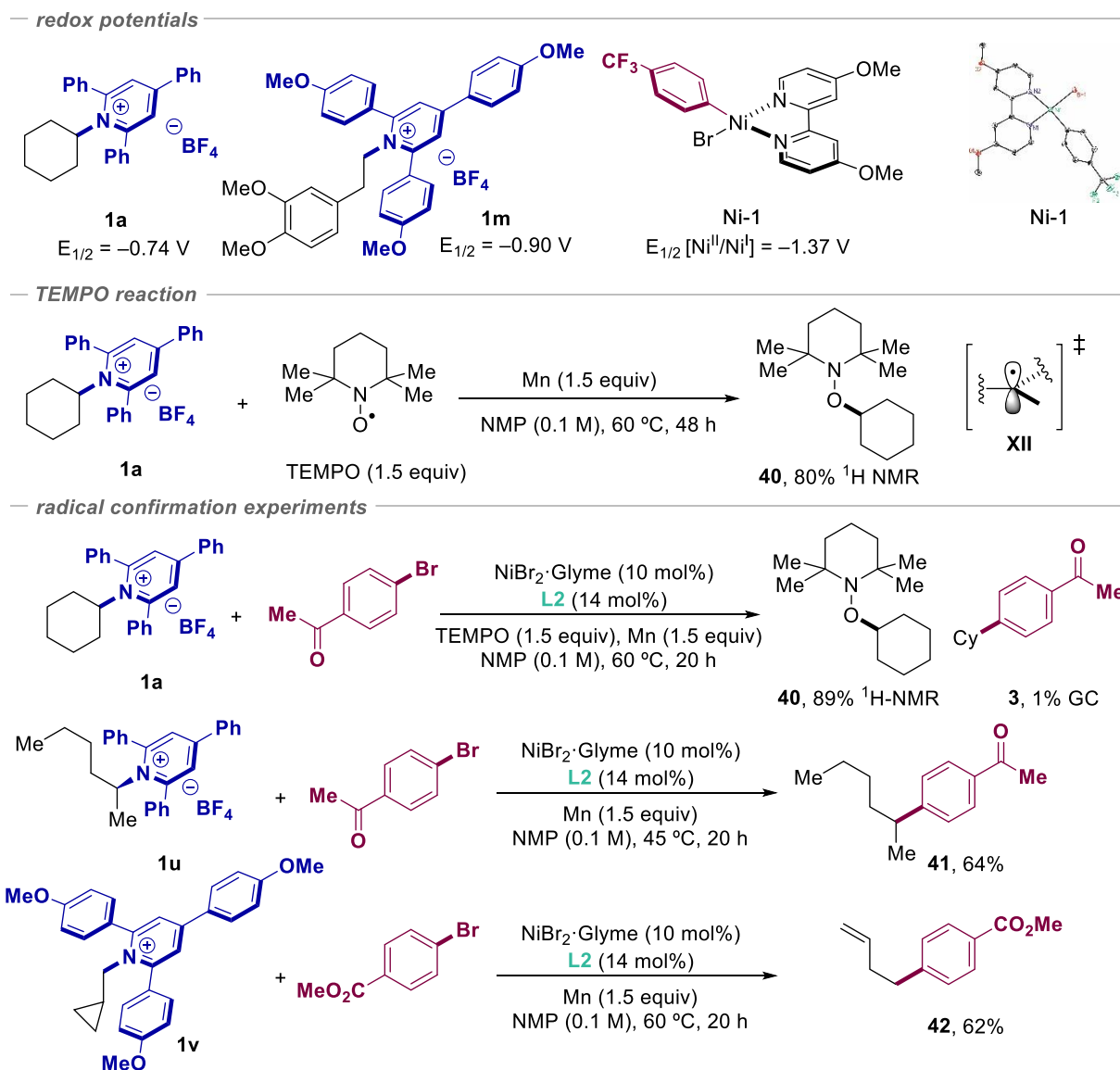
Scheme 3.3.7. Redox potentials, TEMPO and radical experiments.

These results argued against Ni being involved in C(sp^3)–N scission but rather revealing that Mn might be triggering a downhill SET to **1a** or **1m**. This hypothesis was confirmed by a bulk electrolysis experiment (Figure 3.3.2, *top*), as **9** was obtained in 18% at r.t and 48% at 60 °C from **1a** and **Ni-1** at −0.8 V of constant potential (SI for more information). These results strongly suggest a catalytic regime in which C(sp^3)–C(sp^2) bond formation occurred by intercepting alkyl radicals of type **II** with **Ni-1** followed by reductive elimination (Figure 3.3.2, *bottom*).

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Figure 3.3.2. Proposed mechanism.

3.3.7 *Future outlook*

Despite the potential application profile of the work described above, there are several aspects that deserve further consideration for the future:

A. *Atom economy*. Unfortunately, our deaminative arylation technique is inherently limited to the utilization of pyridinium salts, thus lowering down the potential usefulness of this technology from an atom-economical standpoint. That being set, efforts should be devoted to finding new C–N electrophiles with improved practicality.

B. *Site-selective sp³–sp³ C–C bond formation.* While we developed a Deaminative arylation, future efforts should be directed towards the development of an otherwise related *sp³-sp³* cross-coupling reaction with unactivated alkyl halides instead. The latter offers new possibility for bond-formation, either at the initial C–Halide site or at a remote position via chain-walking reactions.[53]

C. *Chiral deaminative version*. Particularly attractive will be the development of a stereoselective deaminative cross-coupling reaction, either via using enantioenriched

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pyridinium salts, quaternary ammonium salts[54,55] or via enantioconvergent scenarios with racemic pyridinium salts and chiral ligands.

3.4 *Conclusions*

In summary, we have developed a mild, robust and tolerant nickel-catalyzed deaminative arylation strategy with aryl halide counterparts. The potential of the methodology is illustrated by the wide functional group compatibility and by the possibility of applying this technology within the context of late-stage functionalization of advanced synthetic intermediates, thus opening a gateway to structural diversity in lead generation approaches. Although our procedure required the utilization of Mn, the stoichiometric metal reductant can be replaced by Hantzsch esters in combination with a photocatalyst under light irradiation, allowing to extend the scope of substrates that were difficult to couple otherwise. It is worth noting that while our paper was being revised, two publications from Han group[56] and Rueping group[57] reported similar transformations. In addition, the groups of Watson[58] and Molander[59] described an otherwise identical manifold, ending up in back-to-back-to-back publications in the same journal.

3.5 *Experimental procedures*

3.5.1 *General considerations*

Reagents. Commercially available materials were used as received without further purification. NiBr$_2$·glyme (97% purity) were purchased from Aldrich. 4-4'-Dimethoxy-2-2'-bipyridine (97% purity) was purchased from Aldrich. Manganese powder (≥ 99.9 trace metal base) was purchased from Aldrich. Anhydrous 1-methyl-2-pyrrolidinone (NMP, 99.5% purity) and *N,N*-Dimethylacetamide (DMA, 99.5% purity) were purchased from Across.

Analytical methods. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 MHz, Bruker 400 MHz and Bruker 500 MHz at 20 °C. All ^{1}H NMR spectra are reported in parts per million (ppm) downfield of TMS and were calibrated using the residual solvent peak of CHCl$_3$ (7.26 ppm), unless otherwise indicated. All ^{13}C NMR spectra are reported in ppm relative to TMS, were calibrated using the signal of residual CHCl$_3$ (77.16 ppm), ^{11}B NMR and ^{19}F NMR were obtained with ^{1}H decoupling unless otherwise indicated. Coupling constants, *J*, are reported in Hertz. Melting points were measured using open glass capillaries in a Büchi B540 apparatus. Gas chromatographic analyses were performed on Hewlett-Packard 6890 gas chromatography instrument with a FID detector. Flash chromatography was performed with EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was used to monitor reaction progress and analysed fractions from column chromatography. To this purpose TLC Silica gel 60 F$_{254}$ aluminium sheets from Merck were used and visualization was achieved using UV irradiation and/or staining with Potassium Permanganate or Cerium Molybdate solution. The yields reported in Scheme 3.3.3, 4 and 5 refer to isolated yields and represent an average of at least two independent runs. The procedures described in this section are

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representative. Thus, the yields may differ slightly from those given in the Schemes of the manuscript. In the cases the High-Resolution Mass Spectra of the molecular ion could not be obtained using ESI and APCI ionization modes the GC-MS of the compound was given. UltraPerformance Convergence Chromatography (UPC2) analysis was performed on Acquity UPC2 Waters instrument equipped with a Chiralpack IG column eluting ACN/CO_2 at ambient temperature and monitored by Photodiode Array Detector (PDA).

3.5.2 Reaction conditions

General procedure: An oven-dried 8 mL screw-cap test tube containing a stirring bar was charged with methyl 4-bromobenzoate (**2a**, 21.5 mg, 0.10 mmol) and 1-cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1a**, 66.9 mg, 0.14 mmol). The test tube was introduced in an argon-filled glovebox where manganese (8.2 mg, 0.15 mmol), NiBr$_2$·glyme (3.05 mg, 10 % mol) and 4,4'-dimethoxy-2,2'-bipyridine (**L2**, 3.0 mg, 14 mol %) in NMP were subsequently added followed by addition of NMP (0.8 mL, 0.1 M). The tube was taken out of the glovebox and stirred at r.t for 20 h. After diluting with EtOAc (10 mL) the yields were determined by GC FID analysis using 1-decane as internal standard. The sample was then extracted with water (10 mL) and brine (10 mL) and the organic layers were collected, dried with MgSO$_4$, concentrated under vacuum and the product was purified by column chromatography on silica gel (Hexane/ EtOAc 9.5/0.5).

3.5.3 Synthesis of Pyridinium salts
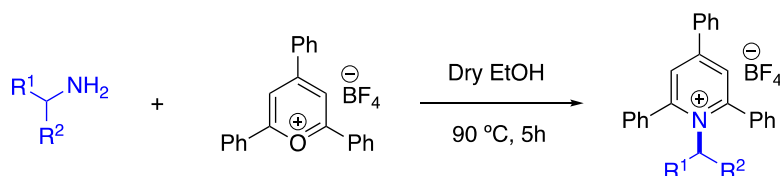
General Procedure A (secondary alkyl pyridinium salts): 2,4,6-triphenylpyrylium tetrafluoroborate (1.0 equiv) and a secondary amine (1.2 equiv) were added to a Schlenk containing a stirring bar. This was followed by addition of dry EtOH (1.0 M), resulting in a colour change from yellow to black orange. The mixture was then stirred and heated at reflux in an oil bath at 90 ºC for 5h. At that time, the mixture was allowed to cool to room temperature. Et$_2$O was then added (15 mL) and shaken vigorously, forming a solid precipitate. The solid thus obtained was filtered, washed with Et$_2$O (2x15 mL) and dried under high vacuum. If the pyridinium salt failed to precipitate, it was subjected to flash column chromatography, eluting with DCM/Acetone mixtures.

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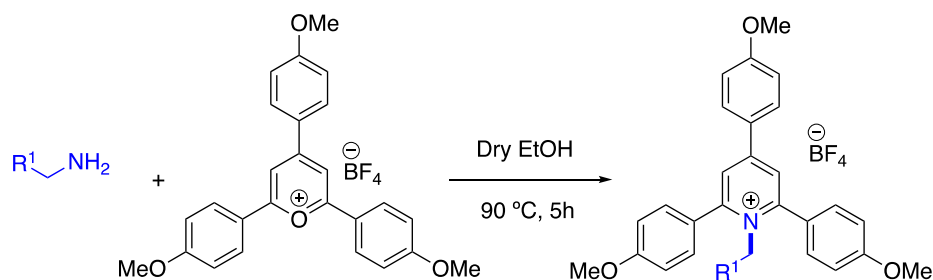
General Procedure B (primary alkyl pyridinium salts): 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate[I] (1.0 equiv) and the corresponding primary amine (1.2 equiv) were added to a Schlenk containing a stirring bar. This was followed by addition of dry EtOH (0.5-1.0 M), resulting in a colour change from yellow to black orange. The mixture was then stirred and heated at reflux in an oil bath at 90 ºC for 5h. At that time, the mixture was allowed to cool to room temperature. Et_2O was then added (15 mL) and shaken vigorously, forming a solid precipitate. The solid thus obtained was filtered, washed with Et_2O (2x15 mL) and dried under high vacuum. The crude was purified by flash column chromatography, eluting with DCM/Acetone mixtures.

If the pyridinium salt failed to precipitate with the addition of Et_2O, the mixture was subjected to flash column chromatography.

The corresponding amine hydrochloride salts or phosphoric salts can also be used by adding Et_3N (1.2 eq.) to the initial mixture. Flash column chromatography must be done in DCM/Acetone.

1a
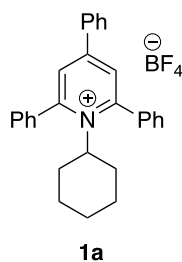
1-cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1a). Following the General Procedure A, cyclohexylamine (275.5 mg, 2.78 mmol) and 2,4,6-triphenylpyrylium tetrafluoroborate (922.3 mg, 2.32 mmol) in 2.5 mL of EtOH were used, affording the product as a pale yellow powder (1.0 g, 90% yield). **Mp**: 183 − 182 ºC. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.95 − 7.40 (m, 17H), 4.67 − 4.55 (m, 1H), 2.13 (d, *J* = 12.0 Hz, 2H), 1.65 − 1.14 (m, 5H), 0.75 (q, *J* = 13.0 Hz, 2H), 0.62 (t, *J* = 13.0 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 157.1, 155.0, 134.2, 134.1, 131.9, 130.9, 129.6, 129.4, 128.9, 128.3, 128.2, 72.0, 33.6, 26.6, 24.7 ppm. **^{19}F NMR** (376 MHz, CDCl$_3$) δ = -153.0 (minor, ^{10}BF$_4$), -153.1 (major, ^{11}BF$_4$) ppm. Spectroscopic data for **1a** match those previously reported in the literature.[II]

1b
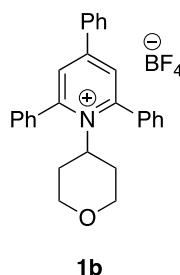
2,4,6-triphenyl-1-(tetrahydro-2*H*-pyran-4-yl)pyridin-1-ium tetrafluoroborate (1b). Following the General Procedure A, 4-aminotetrahydropyran (302.8 mg, 2.8 mmol) and 2,4,6-triphenylpyrylium tetrafluoroborate (1.0 g, 2.5 mmol) in 2.5 mL of EtOH were used, affording the product as a pale yellow powder (970 mg, 80% yield). **Mp:** 195 - 197 ºC. **¹H NMR** (400 MHz, CDCl₃) δ = 7.79 – 7.68 (m, 6H), 7.68 – 7.61 (m, 2H), 7.57 – 7.48 (m, 6H), 7.48 – 7.46 (m, 1H), 7.40 – 7.35 (m, 2H), 4.85 (tt, J = 12.3, 3.2 Hz, 1H), 3.69 (dd, J = 11.7, 4.0 Hz, 2H), 2.78 (td, J = 11.7, 1.8 Hz, 2H), 2.05 (dt, J = 12.6, 2.4 Hz, 2H), 1.86 (tt, J = 12.2, 4.4 Hz, 2H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 157.1, 155.2, 133.9, 133.7, 131.9, 131.0, 129.5, 129.3, 128.9, 128.2, 128.1, 69.0, 67.7, 33.7 ppm. **¹⁹F NMR** (376 MHz, CDCl₃) δ = -152.7 (s), -152.8 (d, J = 2.3 Hz). Spectroscopic data for **1b** match those previously reported in the literature.[III]

1c
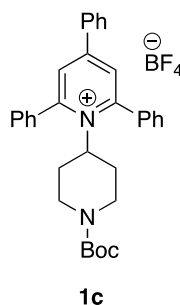
1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1c). Following the General Procedure A, *tert*-butyl 4-aminopiperidine-1-carboxylate (630 mg, 3 mmol) and 2,4,6-triphenylpyrylium tetrafluoroborate (1.0 g, 2.5 mmol) in 2.5 mL of EtOH were used, affording the product as a white powder (1.1 g, 76% yield). **Mp:** 175 - 177 ºC. **¹H NMR** (400 MHz, CDCl₃) δ = 7.75 – 7.71 (m, 5H), 7.70 – 7.64 (m, 2H), 7.62 – 7.52 (m, 6H), 7.49 (d, J = 7.4 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 4.75 (t, J = 12.6 Hz, 1H), 3.90 (brs, 2H), 2.11 (brs, 4H), 1.68 (brs, 2H), 1.30 (s, 9H) ppm. **¹³C NMR** (101 MHz, CDCl₃). δ = 157.1, 155.3, 154.1, 133.9, 133.7, 131.9, 131.0, 129.5, 129.3, 128.9, 128.2, 128.2, 80.0, 69.9, 44.7, 32.6, 28.2 ppm. **¹⁹F NMR** (376 MHz, CDCl₃) δ = -152.9 (s), -153.0 (d, J = 2.9 Hz). Spectroscopic data for **1c** match those previously reported in the literature.[II]

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1d
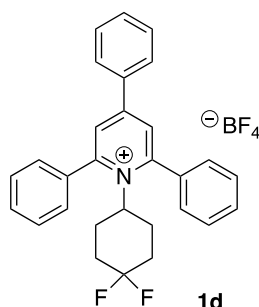
1-(4,4-difluorocyclohexyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1d). Following the General Procedure A, 4,4-difluorocyclohexan-1-amine HCl salt (308.9 mg, 1.80 mmol), triethylamine (251 μL, 1.80 mmol) and 2,4,6-triphenylpyrylium tetrafluoroborate (594.3 mg, 1.50 mmol) in 1.5 mL of EtOH were used. The title compound was obtained as a white powder (497 mg, 65% yield). **Mp**: 207 – 206 ºC. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.84 (s, 2H), 7.75 (t, J = 7.2 Hz, 6H), 7.66 – 7.38 (m, 9H), 4.72 (t, J = 12.2 Hz, 1H), 2.22 (d, J = 12.4 Hz, 2H), 2.05 – 1.74 (m, 4H), 1.32 – 1.07 (m, 2H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 157.3, 155.8, 134.0, 133.8, 132.3, 131.4, 129.8, 129.3, 129.2, 128.5, 128.4, 120.7 (dd, J = 328.1, 318.8 Hz), 68.7, 33.7 (t, J = 25.4 Hz), 28.7 (d, J = 10.2 Hz) ppm. **^{19}F NMR** (376 MHz, CDCl$_3$) δ = -94.3 (d, J = 241.6 Hz), -102.9 (d, J = 241.3 Hz), 152.7 (s), -152.8 (d, J = 2.2 Hz) ppm. Spectroscopic data for **1d** match those previously reported in the literature.[III]

1e
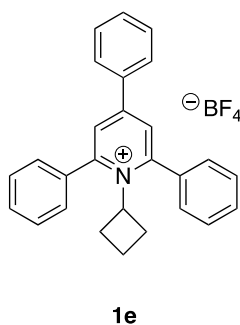
1-cyclobutyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1e). Following the General Procedure A, cyclobutanamine (154.7 μL, 1.80 mmol) and 2,4,6-triphenylpyrylium tetrafluoroborate (594.3 mg, 1.50 mmol) in 1.5 mL of EtOH were used. The title compound was obtained as a pale yellow powder (577 mg, 86% yield). **Mp**: 191 – 192 ºC. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 8.01 – 7.73 (m, 8H), 7.60 – 7.57 (m, 9H), 5.74 – 5.31 (m, 1H), 1.83 (s, 2H), 1.30 – 1.19 (m, 4H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 157.5, 155.6, 134.2, 134.1, 132.2, 131.6, 129.9, 129.7, 129.5, 128.2, 126.2, 64.4, 33.2, 14.3 ppm. **^{19}F NMR** (376 MHz, CDCl$_3$) δ = -152.7 (s), -152.9 (d, J = 2.4 Hz) ppm. IR (neat, cm^{-1}): 3005, 1615, 1551, 1456, 1404, 1324, 1150, 1044, 880, 826. **HRMS** calcd. for (C$_{27}$H$_{24}$N) [M-BF$_4$]$^+$: 362.1903, found 362.1906.

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1f
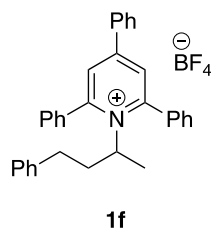
2,4,6-triphenyl-1-(4-phenylbutan-2-yl)pyridin-1-ium tetrafluoroborate (1f). Following the General Procedure A, 4-phenylbutan-2-amine (223.2 mg, 1.5 mmol) and 2,4,6-triphenylpyrylium tetrafluoroborate (500 mg, 1.3 mmol) in 1.5 mL of EtOH were used, affording the product as a pale yellow solid (507 mg, 76% yield). **Mp**: 87 – 86 ºC. **¹H NMR** (400 MHz, CDCl₃) δ = 7.78 (s, 2H), 7.72 – 7.63 (m, 4H), 7.61 – 7.31 (m, 10H), 7.16 – 7.05 (m, 4H), 6.92 – 6.81 (m, 2H), 4.95 – 4.87 (m, 1H), 2.44 – 2.32 (m, 1H), 2.23 – 2.10 (m, 2H), 1.86 – 1.70 (m, 1H), 1.45 (d, J = 7.0 Hz, 3H) ppm. **¹³C NMR** (101 MHz, CDCl₃). δ = 155.3, 138.9, 133.9, 133.7, 132.0, 130.8, 129.6, 128.7, 128.5, 128.4, 128.3, 128.0, 126.5, 66.0, 37.9, 32.5, 21.6 ppm. (*1 aromatic carbon signal is not observed due to signal broadening*) **¹⁹F NMR** (376 MHz, CDCl₃) δ = -152.4 (s), -152.4 (s). Spectroscopic data for **1f** match those previously reported in the literature.[IV]

1g
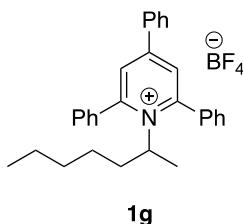
1-(heptan-2-yl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1g). Following the General Procedure A, heptan-2-amine (214 mg, 1.5 mmol) and 2,4,6-triphenylpyrylium tetrafluoroborate (500 mg, 1.3 mmol) in 1.5 mL of EtOH were used, affording the product as a white solid (320 mg, 51% yield). **Mp:** 162 - 164 ºC. **¹H NMR** (400 MHz, CDCl₃) δ = 7.99 – 7.65 (m, 7H), 7.64 – 7.53 (m, 6H), 7.53-7.42 (m, 3H), 4.90 (dq, J = 13.4, 7.0 Hz, 1H), 1.86 – 1.70 (m, 1H), 1.47 – 1.34 (m, 4H), 1.19 – 1.08 (m, 2H), 1.05 – 0.92 (m, 3H), 0.87 – 0.80 (m, 1H), 0.78 (t, J = 7.3 Hz, 3H) ppm (*1 aromatic proton signal is not observed due to signal broadening*). **¹³C NMR** (101 MHz, CDCl₃). δ = 155.2, 134.0, 133.9, 131.9, 130.8, 129.6, 129.3, 128.8, 128.3, 67.0, 36.8, 30.8, 26.3, 22.2, 21.6, 13.8. ppm (*5 aromatic carbon signals are not observed due to signal broadening*). **¹⁹F NMR** (376 MHz, CDCl₃) δ = -153.4 (s), -153.5 (d, J = 2.2 Hz). Spectroscopic data for **1g** match those previously reported in the literature.[IV]

1h
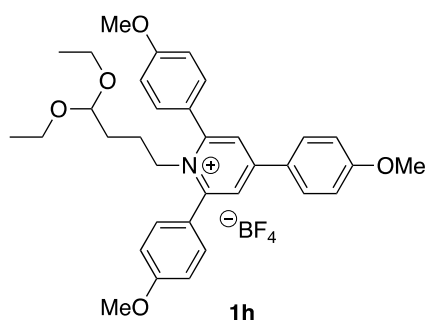
Chapter 3

1-(4,4-diethoxybutyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate (1h). Following the General Procedure B, 4,4-diethoxybutan-1-amine (401.2 mg, 2.5 mmol) and 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate (1.0 g, 2.05 mmol) in 2.5 mL of EtOH were used. Purification by flash column chromatography (DCM/Acetone 8/2) gave the desired product as a sticky yellow solid (1.1 g, 85% yield). **Mp:** 54 - 56 ºC. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.74 – 7.70 (m, 4H), 7.69 – 7.65 (m, 4H), 7.10 – 7.04 (m, 4H), 6.99 (d, J = 8.9 Hz, 2H), 4.48 (t, J = 8 Hz, 2H), 4.02 (t, J = 5.2 Hz, 1H), 3.85 (s, 6H), 3.84 (s, 3H), 3.36 (dq, J = 9.3, 7.0 Hz, 2H), 3.18 (dq, J = 9.3, 7.0 Hz, 2H), 1.41 (dq, J = 6.9, 3.9, 2.7 Hz, 2H), 1.09 – 1.05 (m, 2H), 1.03 (t, J = 7.0 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$). δ = 163.2, 161.4, 156.4, 154.3, 130.6, 129.7, 125.5, 125.0, 115.2, 114.7, 101.5, 61.5, 55.6, 55.4, 54.4, 30.4, 24.8, 15.1 ppm. **^{19}F NMR** (376 MHz, CDCl$_3$) δ = -153.2 (s), -153.2 (d, J = 2.6 Hz). **IR** (neat, cm-1): 2970, 2932, 1593. 1508. 1439, 1294, 1178, 1015, 820. **HRMS** calcd. for (C$_{34}$H$_{40}$NO$_5$) [M-BF$_4$]$^+$: 542.2901, found 542.2891.
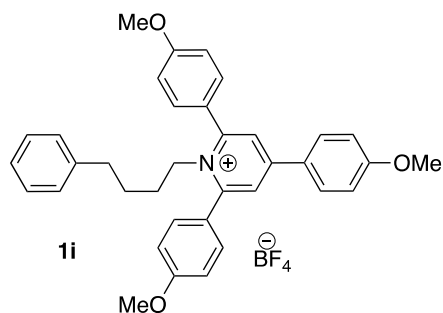
2,4,6-tris(4-methoxyphenyl)-1-(4-phenylbutyl)pyridin-1-ium tetrafluoroborate (1i). Following the General Procedure B, 4-phenylbutan-1-amine (178.9 mg, 1.20 mmol) and 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate (486.2 mg, 1.0 mmol) in 1.5 mL of EtOH were used, affording the title compound as a yellow powder (524 mg, 85% yield) by using (DCM/Acetone 5/1) as eluent. **Mp**: 82 – 83 ºC. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.71 (d, J = 9.2 Hz, 4H), 7.61 (d, J = 8.4 Hz, 4H), 7.17 (dd, J = 10.7, 8.7 Hz, 3H), 7.03 (d, J = 8.7 Hz, 4H), 7.00 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 6.8 Hz, 2H), 4.47 (t, J = 8.0 Hz, 2H), 3.86 (s, 6H), 3.85 (s, 3H), 2.20 (t, J = 7.2 Hz, 2H), 1.33 (quint, J = 7.8 Hz, 2H), 1.08 (quint, J = 7.1 Hz, 2H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 163.3, 161.5, 156.6, 154.4, 140.9, 130.8, 129.9, 128.4, 128.3, 126.0, 125.7, 125.2, 115.4, 114.9, 55.8, 55.6, 54.6, 34.3, 29.0, 27.6 ppm *(1 aromatic carbon signal is not observed due to signal broadening).* **^{19}F NMR** (376 MHz, CDCl$_3$) δ = -153.1 (s), -153.2 (d, J = 2.4 Hz) ppm. IR (neat, cm^{-1}): 3062, 2934, 2835, 1593, 1507, 1447, 1440, 1294, 1249, 1177, 1049, 1016, 889, 831. **HRMS** calcd. for (C$_{36}$H$_{36}$NO$_3$) [M-BF$_4$]$^+$: 530.2690, found 530.2683.
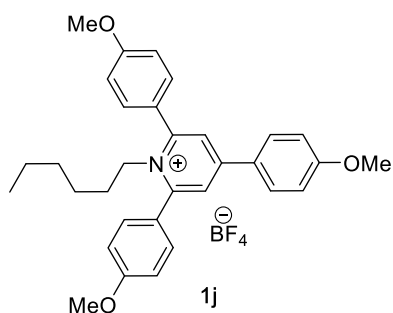
1-hexyl-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate (1j). Following the General Procedure B, 1-hexylamine (121.2 mg, 1.20 mmol) and 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate (486.2 mg, 1.0 mmol) in 1.5 mL of EtOH were used, affording the title compound as a yellow powder (500 mg, 88% yield) by using (DCM/acetone 10/1) as eluent **Mp**: 70 – 71 ºC. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 8.02 – 7.58 (m, 8H), 7.07 (d, J = 8.8 Hz, 4H), 6.99 (d, J = 8.9 Hz, 2H), 4.58 – 4.37 (m, 2H), 3.85 (s, 6H), 3.83 (s, 3H), 1.29 (quint, J = 8.9 Hz, 2H), 0.93 (q, J = 7.0 Hz, 2H), 0.75 (quint, J = 3.6 Hz, 4H), 0.65 (t, J = 7.3 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 163.3, 161.6, 156.5, 154.4, 130.8, 129.9, 125.8, 125.3, 125.2, 115.4, 114.8, 55.7, 55.6, 54.6, 30.3, 29.5, 25.7, 21.9, 13.8 ppm. **^{19}F NMR** (376 MHz, CDCl$_3$) δ = -153.2 (s), -153.3 (d, J = 2.3 Hz) ppm. IR (neat, cm^{-1}): 2931, 2840, 1594, 1508, 1455, 1294, 1241, 1179, 1049, 1019, 889, 832. **HRMS** calcd. for (C$_{32}$H$_{36}$NO$_3$) [M-BF$_4$]$^+$: 482.2690, found 482.2672.
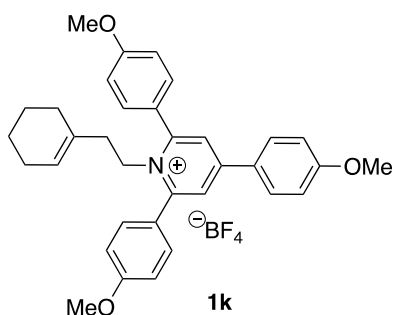
1-(2-(cyclohex-1-en-1-yl)ethyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate (1k). Following the General Procedure B, 2-(cyclohex-1-en-1-yl)ethan-1-amine (233.4 mg, 1.85 mmol) and 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate (750.0 mg, 1.54 mmol) in 2.0 mL of EtOH were used. Purification by flash column chromatography (DCM/Acetone 9/1) gave the desired product as a brown solid (800 mg, 87% yield). **Mp:** 103 - 105 ºC. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.88 – 7.61 (m, 8H), 7.17 – 7.07 (m, 4H), 7.03 (d, J = 8.9 Hz, 2H), 4.88 (s, 1H), 4.54 (m, J = 8 Hz, 2H), 3.89 (s, 6H), 3.87 (s, 3H), 1.93 (t, J = 8.1 Hz, 2H), 1.74 (s, 2H), 1.35 (dq, J = 6.3, 3.0 Hz, 4H), 1.20 (s, 2H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$). δ = 163.2, 161.6, 156.6, 154.3, 131.8, 130.8, 129.7, 125.8, 125.3, 125.2, 125.1, 115.3, 114.8, 55.6, 55.6, 53.8, 38.0, 27.3, 25.0, 22.4, 21.6 ppm. **^{19}F NMR** (376 MHz, CDCl$_3$) δ = -153.0 (s), -153.0 (d, J = 2.2 Hz). **IR** (neat, cm-1): 2930, 2835, 1593, 1506, 1456, 1436, 1240, 1177, 1017, 832. **HRMS** calcd. for (C$_{34}$H$_{36}$NO$_3$) [M-BF$_4$]$^+$: 506.2690, found 506.2675.

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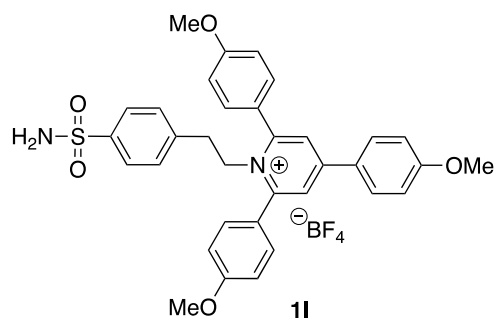
2,4,6-tris(4-methoxyphenyl)-1-(4-sulfamoylphenethyl)pyridin-1-ium   tetrafluoroborate   (1l).
Following the General Procedure B, 4-(2-aminoethyl)benzenesulfonamide (146.2 mg, 0.73 mmol) and
2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate (300 mg, 0.61 mmol) in 1.0 mL of EtOH were
used. Purification by flash column chromatography (DCM/Acetone 8/2) gave the desired product as
a brown solid (340 mg, 83% yield). **Mp:** 144 - 146 ºC. **^{1}H NMR** (400 MHz, (CD$_3$)$_2$CO) δ = 8.28 (s, 2H),
8.24-8.22 (m, 2H), 7.79 – 7.69 (m, 4H), 7.65 – 7.63 (m, 2H), 7.28 – 7.21 (m, 4H), 7.20 – 7.17 (m, 2H),
6.80 – 6.78 (m, 2H), 6.55 (brs, 2H, NH$_2$), 4.97 (t, J = 7.3 Hz, 2H), 3.96 (s, 6H), 3.94 (s, 3H), 2.88 (t, J =
7.3 Hz, 2H), 2.09 (s, 2H) ppm. **^{13}C NMR** (101 MHz, CD$_3$)$_2$CO). δ = 164.5, 162.7, 157.7, 155.5, 144.1,
141.2, 131.9, 131.3, 129.9, 127.4, 126.5, 126.4, 125.9, 116.1, 115.6, 56.5, 56.2, 56.1, 35.8 ppm. **^{19}F
NMR** (376 MHz, CD$_3$)$_2$CO) δ = 151.8 (s), -151.9 (s). **IR** (neat, cm-1): 2929, 2836, 1593, 1507, 1456,
1436, 1241, 1178, 1017, 832. **HRMS** calcd. for (C$_{34}$H$_{33}$N$_2$O$_5$S) [M-BF$_4$]$^+$: 581.2105, found 581.2102.
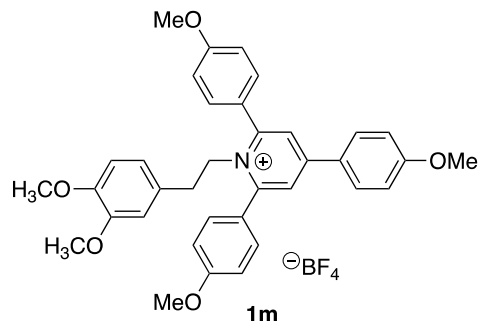
**1-(3,4-dimethoxyphenethyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium   tetrafluoroborate
(1m).** Following the General Procedure B, 2-(3,4-dimethoxyphenyl)ethan-1-amine (217.3 mg, 1.20
mmol) and 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate (486.2 mg, 1.0 mmol) in 1.5 mL of
EtOH were used, affording the title compound as a yellow powder (730 mg, 91% yield) by using
(DCM/Acetone 5/1) as eluent. **Mp**: 96 – 97 ºC. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.75 (d, J = 8.8 Hz, 2H),
7.73 (s, 2H), 7.63 (d, J = 8.5 Hz, 4H), 7.09 (d, J = 8.5 Hz, 4H), 7.03 (d, J = 8.8 Hz, 2H), 6.55 (d, J = 8.1 Hz,
1H), 6.00 (dd, J = 8.1, 1.7 Hz, 1H), 5.80 (d, J = 1.7 Hz, 1H), 4.76 (t, J = 7.3 Hz, 2H), 3.88 (s, 9H), 3.78 (s,
3H), 3.56 (s, 3H), 2.52 (t, J = 7.3 Hz, 2H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 163.4, 161.7, 156.8, 154.6,
149.3, 148.4, 131.1, 130.0, 127.9, 125.8, 125.3, 125.1, 120.5, 115.5, 114.9, 111.3, 56.1, 56.1, 55.8,
55.7, 55.7, 35.3 ppm *(1 aromatic carbon signal is not observed due to signal broadening)*. **^{19}F NMR**
(376 MHz, CDCl$_3$) δ = -152.6 (s), -152.7 (d, J = 2.2 Hz) ppm. IR (neat, cm^{-1}): 3067, 2935, 2837, 1592,
1507, 1439, 1240, 1177, 1049, 1015, 852, 760. **HRMS** calcd. for (C$_{36}$H$_{36}$NO$_5$) [M-BF$_4$]$^+$: 562.2588, found

562.2587.

1m'
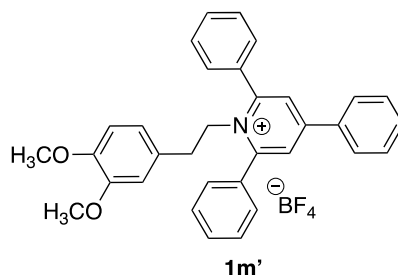
1-(3,4-dimethoxyphenethyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1m'). Following the General Procedure A, 2-(3,4-dimethoxyphenyl)ethan-1-amine (217.3 mg, 1.20 mmol) and 2,4,6-triphenylpyrylium tetrafluoroborate (396.1 mg, 1.0 mmol) in 1.5 mL of EtOH were used, affording the product as a pale yellow solid (458.6 mg, 82% yield). **Mp:** 174 - 176 ºC. **¹H NMR** (400 MHz, CDCl₃) δ = 7.77 – 7.74 (m, 6H), 7.72 – 7.63 (m, 2H), 7.62 – 7.52 (m, 6H), 7.52 – 7.34 (m, 3H), 6.51 (d, J = 8.1 Hz, 1H), 5.87 (dd, J = 8.2, 2.0 Hz, 1H), 5.68 (d, J = 2.0 Hz, 1H), 4.66 – 4.46 (m, 2H), 3.72 (s, 3H), 3.52 (s, 3H), 2.69 – 2.45 (m, 2H) ppm. **¹³C NMR** (101 MHz, CDCl₃). δ = 156.3, 155.7, 148.9, 148.0, 133.9, 132.7, 131.9, 130.8, 129.5, 129.1, 129.1, 128.0, 127.6, 126.5, 120.2, 111.2, 111.0, 55.9, 55.8, 55.6, 35.1 ppm **¹⁹F NMR** (376 MHz, CDCl₃) δ = -152.90, -152.96 (d, J = 2.3 Hz) ppm. Spectroscopic data for **1m'** match those previously reported in the literature.[XXIII]

1n
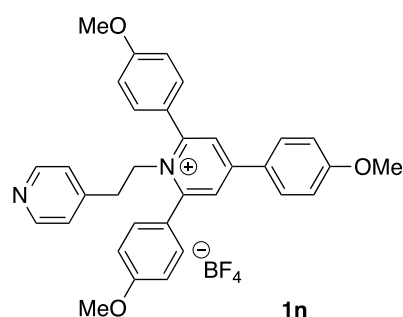
2,4,6-tris(4-methoxyphenyl)-1-(2-(pyridin-4-yl)ethyl)pyridin-1-ium tetrafluoroborate (1n). Following the General Procedure B, 2-(pyridin-4-yl)ethan-1-amine (73.2 mg, 0.60 mmol) and 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate (243.1 mg, 0.50 mmol) in 0.5 mL of EtOH were used, affording the title compound as a yellow powder (250 mg, 85% yield) by using (DCM/Acetone 1/1) as eluent. **Mp**: 94 – 95 ºC. **¹H NMR** (300 MHz, CDCl₃) δ = 8.40 – 8.17 (m, 2H), 7.83 – 7.72 (m, 4H), 7.66 (d, J = 8.8 Hz, 4H), 7.10 (d, J = 8.9 Hz, 4H), 7.02 (d, J = 8.9 Hz, 2H), 6.37 (d, J = 6.0 Hz, 2H), 4.78 (t, J = 7.7 Hz, 2H), 3.89 (s, 6H), 3.87 (s, 3H), 2.63 (t, J = 7.7 Hz, 2H) ppm. **¹³C NMR** (75 MHz, CDCl₃) δ = 163.5, 161.8, 156.7, 155.0, 150.2, 144.6, 130.9, 130.0, 125.7, 125.3, 125.0, 123.7, 115.4, 115.0, 55.8, 55.7, 54.6, 34.6 ppm. **¹⁹F NMR** (376 MHz, CDCl₃) δ = -152.9 (s), -153.0 (d, J = 2.2 Hz) ppm. IR (neat, cm⁻¹): 2838, 1593, 1506, 1456, 1417, 1295, 1242, 1178, 1051, 1018, 833. **HRMS** calcd. for (C₃₃H₃₁N₂O₃) [M-BF₄]⁺: 503.2329, found 503.2326.

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1o
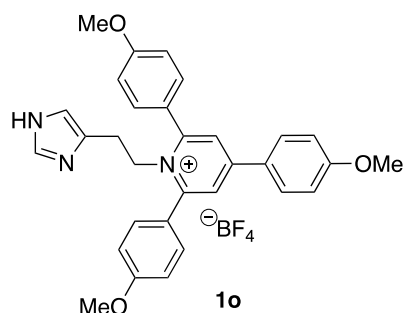
1-(2-(1H-imidazol-4-yl)ethyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate (1o). Following the General Procedure B, 2-(2-Methyl-1H-imidazol-4-yl)ethanamine dihydrochloride (300 mg, 1.63 mmol) and 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate (665 mg, 1.36 mmol), triethylamine (0.54 mL, 3.9 mmol) in 2.0 mL of EtOH were used. Extraction was done using H_2O (2 x 15) and brine (2 x 15) and the purification by flash column chromatography (DCM/Acetone 6/4) gave the desired product as a yellow solid (330 mg, 42% yield) without the anion BF_4^-. **Mp:** 100 - 102 ºC. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.84 − 7.75 (m, 2H), 7.71 (s, 2H), 7.59 − 7.47 (m, 4H), 7.39 (s, 1H), 7.07 − 7.02 (m, 6H), 6.33 (s, 1H), 4.89 (t, J = 6.2 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 6H), 2.60 (t, J = 6.2 Hz, 2H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$). δ = 163.5, 161.8, 157.1, 154.4, 135.3, 130.6, 129.9, 125.4, 125.1, 124.9, 115.4, 115.0, 55.9, 55.7, 55.6, 26.7 ppm. **IR** (neat, cm-1): 2928, 2838, 1592, 1507, 1456, 1240, 1177, 1017, 832. **HRMS** calcd. for ($C_{31}H_{30}N_3O_3$) [M]$^+$: 492.2282, found 492.2291.
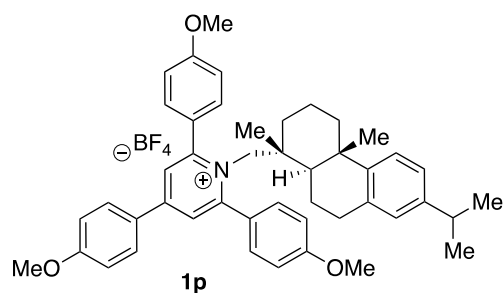
1p

1-(((1R,4aS,10aR)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate (1p). Following the General Procedure B, *Leelamine* (500 mg, 1.75 mmol) and 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate (714.5 mg, 1.46 mmol) in 2.0 mL of EtOH were used. Purification by flash column chromatography (DCM/Acetone 9/1) gave the desired product as a red solid (310 mg, 28% yield). **Mp:** 175 - 177 ºC. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 8.05 − 7.86 (m, 2H), 7.86 − 7.81 (m, 2H), 7.76 − 7.71 (m, 2H), 7.68 − 7.31 (m, 2H), 7.18 − 7.10 (m, 2H), 7.09 − 7.02 (m, 3H), 6.97 − 6.86 (m, 3H), 6.77 (d, J = 1.9 Hz, 1H), 5.19 (d, J = 14.7 Hz, 1H), 4.87 (d, J = 14.7 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.71 (s, 3H), 2.77 (quint, J = 6.9 Hz, 1H), 2.66 (dd, J = 17.6, 6.8 Hz, 1H), 2.49 (ddd, J = 17.9, 11.0, 7.8 Hz, 1H), 2.10 − 2.00 (m, 1H), 1.65 (brs, 1H), 1.38 − 1.34 (m, 2H), 1.25 (s, 1H), 1.19 (d, J = 6.9 Hz, 6H), 1.10 − 0.96 (m, 2H), 0.94 (s, 3H), 0.75 (dd, J = 12.4, 2.0 Hz, 1H), 0.59 − 0.48 (m, 1H), 0.41 (s, 3H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$). δ = 163.5, 161.7, 161.7, 159.0, 153.9, 146.4, 145.7, 134.2, 132.0, 129.9, 127.0, 126.9, 126.7, 125.1, 124.0, 124.0, 123.6, 123.4, 115.4, 114.9, 65.4, 55.7, 55.6, 55.4, 47.6, 41.7, 37.6, 37.5, 37.1,

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Functionalization of Strong Sigma Bonds by Nickel and Tungsten Catalysis
Raúl Martín Montero

Deaminative Arylation at sp³ Carbon Centers

33.4, 29.3, 25.2, 23.9, 19.5, 19.0, 18.0 ppm. (*3 aromatic carbon signals are not observed due to signal broadening*) **¹⁹F NMR** (376 MHz, CDCl₃) δ = -152.7, -152.7 (d, J = 2.8 Hz). **IR** (neat, cm-1): 2930, 1592, 1507, 1456, 1240, 1177, 832, 785. **HRMS** calcd. for (C₄₆H₅₂NO₃) [M-BF₄]⁺: 666.3942, found 666.3935.
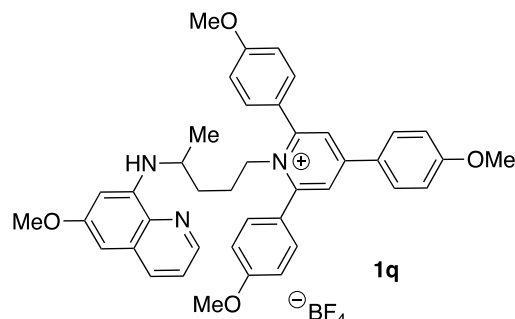
2,4,6-tris(4-methoxyphenyl)-1-(4-((6-methoxyquinolin-8-yl)amino)pentyl)pyridin-1-ium tetrafluoroborate (1q). Following the General Procedure B, 2-(pyridin-4-yl)ethan-1-amine (455.3 mg, 1.10 mmol), triethylamine (307 μL, 2.20 mmol) and 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate (486.2 mg, 1.0 mmol) in 1.0 mL of EtOH were used, affording the title compound as a yellow powder (330 mg, 45% yield) by using (DCM/Acetone 5/1) as eluent. **Mp**: 109 – 110 ºC. **¹H NMR** (400 MHz, CDCl₃) δ = 8.54 (dd, J = 4.2, 1.6 Hz, 1H), 7.93 (dd, J = 8.3, 1.7 Hz, 1H), 7.76 – 7.61 (m, 7H), 7.33 (dd, J = 8.2, 4.3 Hz, 1H), 7.15 – 6.97 (m, 6H), 6.31 (d, J = 2.5 Hz, 1H), 6.02 (d, J = 2.5 Hz, 1H), 5.70 (d, J = 8.4 Hz, 1H), 4.54 (t, J = 7.8 Hz, 2H), 3.85 (s, 6H), 3.84 (s, 3H), 1.23 – 1.14 (m, 4H), 1.05 (d, J = 6.4 Hz, 3H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 163.3, 161.6, 159.4, 156.7, 154.4, 144.6, 144.4, 135.3, 135.0, 130.8, 129.9, 125.8, 125.1, 125.0, 122.1, 115.4, 114.9, 97.0, 92.1, 55.8, 55.6, 55.3, 54.7, 47.0, 32.5, 26.2, 20.4 ppm (*1 aromatic carbon signal is not observed due to signal broadening*). **¹⁹F NMR** (376 MHz, CDCl₃) δ = -153.4 (s), -153.4 (d, J = 2.2 Hz) ppm. IR (neat, cm⁻¹): 2934, 2837, 1594, 1506, 1456, 1440, 1386, 1294, 1241, 1178, 1049, 1020, 892, 831, 791. **HRMS** calcd. for (C₄₁H₄₂N₃O₄) [M-BF₄]⁺: 640.3170, found 640.3186.
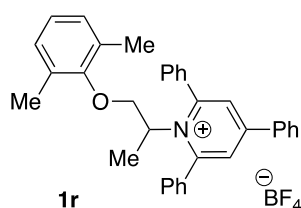
1-(1-(2,6-dimethylphenoxy)propan-2-yl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1r). Following the General Procedure A, Mexiletine·HCl (215.7 mg, 1.65 mmol), triethylamine (230 μL, 1.65 mmol) and 2,4,6-triphenylpyrylium tetrafluoroborate (594.3 mg, 1.50 mmol) in 1.5 mL of EtOH were used. The title compound was obtained as yellow powder (340 mg, 42% yield) by extraction with dichloromethane and water. **Mp**: 122 – 123 ºC. **¹H NMR** (400 MHz, CDCl₃) δ = 8.02 – 7.72 (m, 7H), 7.62 – 7.47 (m, 10H), 7.02 – 6.72 (m, 3H), 5.49 (sext, J = 7.0 Hz, 1H), 4.12 (dd, J = 9.9, 6.7 Hz, 1H), 3.53 (dd, J = 9.9, 6.9 Hz, 1H), 1.92 (s, 6H), 1.54 (d, J = 7.2 Hz, 3H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ =

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155.9, 154.4, 134.1, 133.7, 132.2, 131.2, 130.1, 129.8, 129.4, 129.3, 129.0, 128.5, 124.6, 73.6, 65.4, 19.4, 16.4 ppm (*2 aromatic carbon signals are not observed due to signal broadening*). **¹⁹F NMR** (376 MHz, CDCl₃) δ = -153.1 (s), -153.2 (d, *J* = 2.2 Hz) ppm. IR (neat, cm⁻¹): 2309, 1616, 1558, 1196, 1047, 1020, 888. **HRMS** calcd. for (C₃₄H₃₂NO) [M-BF₄]⁺: 470.2478, found 470.2469.
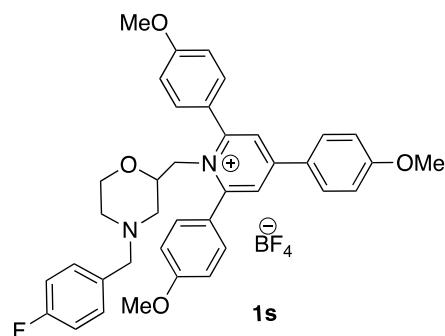
1-((4-(4-fluorobenzyl)morpholin-2-yl)methyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate (1s). Following the General Procedure B, (4-(4-fluorobenzyl)morpholin-2-yl)methanamine (268.9 mg, 1.20 mmol) and 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate (486.2 mg, 1.0 mmol) in 1.5 mL of EtOH were used, affording the title compound as a yellow powder (484 mg, 70% yield) by using (DCM/Acetone 10/1) as eluent. **Mp**: 120 – 121 ºC. **¹H NMR** (400 MHz, CDCl₃) δ = 7.89 – 7.53 (m, 8H), 7.05 (dd, *J* = 16.5, 7.1 Hz, 8H), 6.93 (t, *J* = 7.4 Hz, 2H), 4.72 (d, *J* = 14.9 Hz, 1H), 4.59 (dt, *J* = 14.6, 7.0 Hz, 1H), 3.87 (s, 6H), 3.85 (s, 3H), 3.56 (brs, 1H), 3.24 (brs, 4H), 2.40 (d, *J* = 9.0 Hz, 1H), 2.09 (t, *J* = 7.9 Hz, 1H), 1.91 (d, *J* = 7.2 Hz, 1H), 1.37 (d, *J* = 5.6 Hz, 1H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 163.5, 161.6, 157.6 (d, *J* = 7.2 Hz), 131.2, 130.6 (d, *J* = 6.6 Hz), 130.6, 129.9, 125.6 (br), 124.6 (br), 115.4, 115.2 (d, *J* = 21.2 Hz), 114.8, 72.7, 66.4, 61.8, 56.3, 55.8, 55.6, 55.4, 52.2 ppm (*2 aromatic carbon signals are not observed due to signal broadening*). **¹⁹F NMR** (376 MHz, CDCl₃) δ = -115.5 (s), -152.9 (s), -152.9 (d, *J* = 2.4 Hz) ppm. IR (neat, cm⁻¹): 1593, 1506, 1455, 1294, 1241, 1178, 1016, 892, 831. **HRMS** calcd. for (C₃₈H₃₈FN₂O₄) [M-BF₄]⁺: 605.2810, found 605.2808.
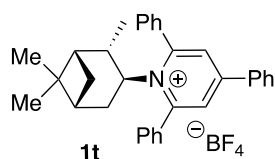
2,4,6-triphenyl-1-((1S,2S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)pyridin-1-ium tetrafluoroborate (1t). To a solution of triphenylpyrylium tetrafluoroborate (978 mg g, 2.47 mmol) and commercially available Pinanamine (454.5 mg, 2.96 mmol) in anhydrous DCM (10 mL), it was added acetic acid (3 drops). The solution was stirred at room temperature for 3 h, then concentrated in vacuo and purified by flash column chromatography (DCM/acetone = 99:1 to 88:12) to give the desired product **1t** (570 mg, 43% yield) as a pink solid. **Mp**: 132 - 134 ºC. **¹H NMR** (400 MHz, CDCl₃) δ = 8.03 – 7.83 (m, 3H), 7.78 – 7.68 (m, 3H), 7.67 – 7.48 (m, 9H), 7.47 – 7.37 (m, 2H), 5.32 (q, *J* = 9.7 Hz, 1H), 2.94 – 2.65 (m, 2H), 2.41 (dddd, *J* = 14.1, 10.2, 4.0, 1.8 Hz, 1H), 1.88 – 1.64 (m, 2H), 1.51 (td, *J* =

5.9, 1.6 Hz, 1H), 0.99 (s, 3H), 0.79 (d, *J* = 6.9 Hz, 3H), 0.22 (s, 3H), -0.80 (d, *J* = 10.1 Hz, 1H) ppm. **¹³C NMR** (101 MHz, CDCl₃) *δ* = 159.1, 157.6, 155.1, 134.3, 133.7, 133.4, 131.9, 131.5, 130.8, 130.3, 130.2, 129.5, 129.3, 128.6, 128.4, 128.3, 128.3, 126.4, 70.1, 48.0, 42.0, 41.7, 40.1, 35.2, 30.9, 28.3, 21.8, 19.2 ppm. **₁₉F NMR** (376 MHz, CDCl₃) *δ* = -153.3, -153.3 (d, *J* = 2.2 Hz). Spectroscopic data for **1t** match those previously reported in the literature.[IV]

1u
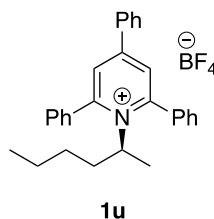
1-(hexan-2-yl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1u). Following the General Procedure A, hexan-2-amine (200 mg, 1.5 mmol) and 2,4,6-triphenylpyrylium tetrafluoroborate (500 mg, 1.3 mmol) in 1.5 mL of EtOH were used, affording the product as a white solid (358 mg, 59% yield). **Mp:** 153 - 155 ºC. **¹H NMR** (400 MHz, CDCl₃) δ = 7.95 – 7.64 (m, 7H), 7.65 – 7.53 (m, 6H), 7.53 – 7.42 (m, 3H), 4.89 (dq, *J* = 13.6, 7.0 Hz, 1H), 1.78 (ddt, *J* = 13.8, 11.3, 5.9 Hz, 1H), 1.49 – 1.33 (m, 4H), 1.15 – 1.01 (m, 2H), 1.01 – 0.88 (m, 1H), 0.87 – 0.78 (m, 1H), 0.75 (t, *J* = 7.3 Hz, 3H) ppm (*1 aromatic proton signal is not observed due to signal broadening*). **¹³C NMR** (101 MHz, CDCl₃). *δ* = 155.2, 134.0, 133.9, 131.9, 130.8, 129.6, 129.3, 128.8, 128.3, 67.1, 36.4, 28.7, 21.8, 21.7, 13.7. ppm. (*5 aromatic carbon signals are not observed due to signal broadening*) **¹⁹F NMR** (376 MHz, CDCl₃) *δ* = -153.4 (s), -153.5 (d, *J* = 2.1 Hz). **IR** (neat, cm⁻¹): 2928, 1595, 1507, 1456, 1241, 1178, 1024, 865. **HRMS** calcd. for (C₂₉H₃₀N) [M-BF₄]⁺: 392.2373, found 392.2382.

1v
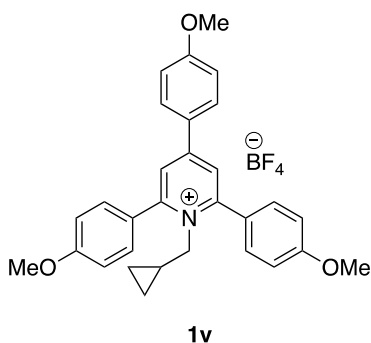
1-(cyclopropylmethyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate (1v). Following the General Procedure B, cyclopropylmethanamine (85.3 mg, 1.20 mmol) and 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate (486.2 mg, 1.0 mmol) in 1.5 mL of EtOH were used, affording the title compound as a yellow powder (420.6 mg, 78% yield) by using (DCM/Acetone 10/1) as eluent. **Mp**: 96 – 98 ºC. **¹H NMR** (400 MHz, CDCl₃) *δ* = δ 7.85 – 7.68 (m, 8H), 7.17 – 7.07 (m, 4H), 7.06 – 6.94 (m, 2H), 4.56 (d, *J* = 7.1 Hz, 2H), 3.89 (s, 9H), 0.67 – 0.52 (m, 1H), 0.31 – 0.21 (m, 2H), -0.29 – -0 .31(m, 2H) ppm. **¹³C NMR** (101 MHz, CDCl₃) *δ* = 163.2, 161.6, 156.8, 154.3, 131.1, 129.8, 125.6, 124.9, 115.3, 114.8, 59.4, 55.6, 55.5, 10.8, 4.8 ppm (*1 aromatic carbon signals is not observed*

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due to signal broadening). **¹⁹F NMR** (376 MHz, CDCl₃) δ = -153.2 (d, J = 6.5 Hz), -153.3 (d, J = 5.7 Hz) ppm. IR (neat, cm⁻¹): 2931, 1601, 1507, 1454, 1242, 1177, 1024, 832. HRMS calcd. for ($C_{30}H_{30}NO_3$) [M-BF₄]⁺: 452.2220, found 452.2215.

Deaminative Arylation at sp³ Carbon Centers

3.5.4   *Ni-catalyzed reductive deaminative arylation with aryl halides*
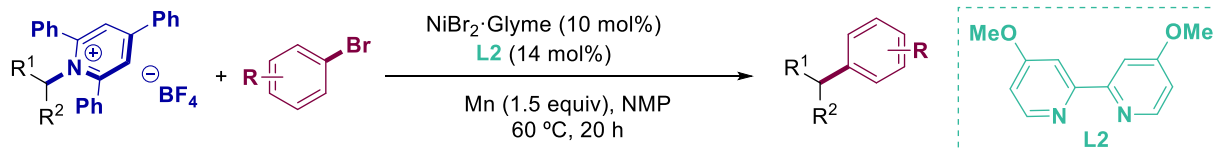
General procedure C: An oven-dried 8 mL screw-cap test tube containing a stirring bar was charged with the aryl bromide (0.20 mmol) and the corresponding pyridinium tetrafluoroborate salt (0.28 mmol, 1.40 equiv). The test tube was introduced in an argon-filled glovebox where manganese (16.5 mg, 0.30 mmol), and a mixture of $NiBr_2$·glyme (6.2 mg, 10 mol%) and 4,4'-dimethoxy-2,2'-bipyridine (**L2**, 6.0 mg, 14 mol%) in NMP (2 mL) was subsequently added by syringe from a stock solution. The tube was taken out of the glovebox and stirred at 60 °C for 20 h. After the reaction was finished, the reaction mixture was extracted with ethyl acetate and water/brine (3 times). Then, the organic layers were combined, dried over $MgSO_4$ and concentrated under vacuum. The product was purified by flash chromatography column on silica gel.
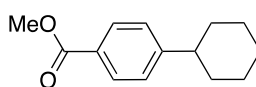
3

methyl 4-cyclohexylbenzoate (3). Following **General Procedure C** at r.t, methyl 4-bromobenzoate (43.0 mg, 0.20 mmol) and 1-cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1a**) (133.6 mg, 0.28 mmol) were used, affording the title compound as a colourless liquid (40.1 mg, 92% yield) by using toluene as eluent. In an independent experiment, 38.0 mg (87% yield) were obtained, giving an average of 90% yield. In an independent experiment, a one pot experiment was performed, starting from the amine by precipitation of the pyridinium salt (**1a**) and removing the solvent by filtration: methyl 4-bromobenzoate (137.6 mg, 0.64 mmol) and 1-cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1a**) (427.5 mg, 0.90 mmol) were used at r.t, affording the title compound in 125.6 mg (90%). **¹H NMR** (400 MHz, CDCl₃) δ = 7.96 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 3.90 (s, 3H), 2.56 (tt, J = 11.5, 3.6 Hz, 1H), 1.92 – 1.82 (m, 4H), 1.76 (ddd, J = 12.5, 3.1, 1.6 Hz, 1H), 1.50 – 1.18 (m, 5H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 167.3, 153.6, 129.8, 127.9, 127.0, 52.1, 44.8, 34.3, 26.9, 26.2 ppm. Spectroscopic data for **3** match those previously reported in the literature.[V]
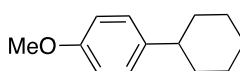
4

1-cyclohexyl-4-methoxybenzene (4). Following the **General Procedure C** at r.t, methyl 4-iodoanisole (37.4 mg, 0.20 mmol) and 1-cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate

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(**1a**) (133.6 mg, 0.28 mmol) were used at room temperature, affording the title compound as a white solid (31.2 mg, 82% yield) by using Hexane/EtOAc (95/5) as eluent. In an independent experiment, 31.0 mg (81%) were obtained, giving an average of 82% yield. **Mp:** 81 - 83 ºC. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.20 – 7.07 (m, 2H), 6.91 – 6.79 (m, 2H), 3.79 (s, 3H), 2.45 (td, J = 8.0, 4.0 Hz, 1H), 1.93 – 1.79 (m, 4H), 1.75 (dtt, J = 12.8, 3.1, 1.5 Hz, 1H), 1.39 (ddt, J = 11.1, 9.6, 1.7 Hz, 4H), 1.31 – 1.18 (m, 1H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 157.6, 140.4, 127.6, 113.6, 55.2, 43.7, 34.7, 26.9, 26.2 ppm. Spectroscopic data for **4** match those previously reported in the literature.[VI]

5
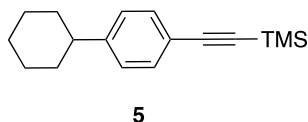
((4-cyclohexylphenyl)ethynyl)trimethylsilane (5). Following **General Procedure C** at r.t, ((4-iodophenyl)ethynyl)trimethylsilane (60 mg, 0.20 mmol) and 1-cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1a**) (133.6 mg, 0.28 mmol) were used, affording the title compound at room temperature as a colourless liquid (32.0 mg, 62% yield) by using pentane as eluent. In an independent experiment, 30.0 mg (59% yield) were obtained, giving an average of 61% yield. **^{1}H NMR** (300 MHz, CDCl$_3$) δ = 7.38 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 2.64 – 2.28 (m, 1H), 1.85 – 1.73 (m, 5H), 1.46 – 1.00 (m, 5H), 0.24 (s, 9H) ppm. **^{13}C NMR** (75 MHz, CDCl$_3$) δ = 148.9, 132.1, 126.9, 120.5, 105.6, 93.3, 44.7, 34.4, 26.9, 26.2, 0.2 ppm. Spectroscopic data for **5** match those previously reported in the literature.[VII]

6
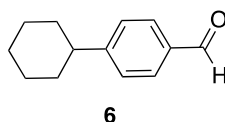
4-cyclohexylbenzaldehyde (6). Following **General Procedure C** at 45 ºC, 4-bromobenzaldehyde (39.8 mg, 0.20 mmol) and 1-cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1a**) (133.6 mg, 0.28 mmol) were used at 45 ºC, affording the title compound as a white solid (23.7 mg, 63% yield) by using Hexane/*tert*-butyl-methyl ether (98/2) as eluent. In an independent experiment, 23.0 mg (61%) were obtained, giving an average of 62% yield. **Mp:** 116 - 118 ºC. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 9.97 (s, 1H), 7.81 – 7.80 (m, 2H), 7.38 – 7.36 (m, 2H), 2.63 – 2.54 (m, 1H), 1.92 – 1.85 (m, 4H), 1.80 – 1.75 (m, 1H), 1.48 – 1.37 (m, 4H), 1.19 (s, 1H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 192.0, 155.4, 134.5, 130.0, 127.5, 44.9, 34.1, 26.7, 26.0 ppm. Spectroscopic data for **6** match those previously reported in the literature.[VIII]

7
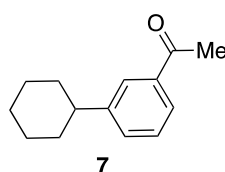
1-(3-cyclohexylphenyl)ethan-1-one (7). Following **General Procedure C** at 45 ºC, 1-(3-bromophenyl)ethan-1-one (39.8 mg, 0.20 mmol) and 1-cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1a**) (133.6 mg, 0.28 mmol) were used, affording the title compound as a white solid (26 mg, 64% yield) by using Hexane/ *tert*-butyl-methyl ether (95/5) as eluent. In an independent experiment, 24.6 mg (61%) were obtained, giving an average of 63% yield. **Mp:** 110 - 112 ºC. **¹H NMR** (400 MHz, CDCl₃) δ = 7.85 – 7.80 (m, 2H), 7.77 (dt, *J* = 7.3, 1.7 Hz, 2H), 7.43 (dt, *J* = 7.3, 1.7 Hz, 2H), 7.40 – 7.36 (m, 1H), 2.60 (s, 3H), 2.59 – 2.50 (m, 1H), 1.96 – 1.81 (m, 4H), 1.81 – 1.73 (m, 1H), 1.50 – 1.34 (m, 4H), 1.31 – 1.26 (m, 1H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 198.5, 148.6, 137.2, 131.8, 128.5, 126.6, 126.1, 44.5, 34.3, 26.8, 26.7, 26.0 ppm. **IR** (neat, cm⁻¹): 3029, 2921, 2848, 1682, 1591, 1544, 1490, 1394, 1260, 1072. **HRMS** calcd. for (C₁₄H₁₉O) [M+H]⁺: 203.1430, found 203.1422.

8
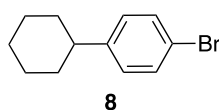
1-bromo-4-cyclohexylbenzene (8). Following **General Procedure C** in DMA at 15 ºC, 1-bromo-4-iodobenzene (56.6 mg, 0.20 mmol) and 1-cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1a**) (133.6 mg, 0.28 mmol) were used in DMA at 15 ºC, affording the title compound as a colourless oil (42.3 mg, 89% yield) by using Hexane (100) as eluent. In an independent experiment, 41.4 mg (87%) were obtained, giving an average of 88% yield. **¹H NMR** (400 MHz, CDCl₃) δ = 7.44 – 7.29 (m, 2H), 7.16 – 7.02 (m, 2H), 2.46 (td, *J* = 8.7, 4.2 Hz, 1H), 1.91 – 1.79 (m, 4H), 1.79 – 1.69 (m, 1H), 1.38 (td, *J* = 9.0, 3.0 Hz, 4H), 1.29 – 1.21 (m, 1H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 147.0, 131.3, 128.6, 119.3, 44.0, 34.3, 26.8, 26.0 ppm. Spectroscopic data for **8** match those previously reported in the literature.[IX]

9
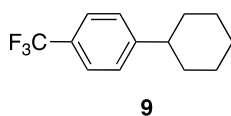
1-cyclohexyl-4-(trifluoromethyl)benzene (9). Following **General Procedure C**, 1-bromo-4-(trifluoromethyl)benzene (45.0 mg, 0.20 mmol) and 1-cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1a**) (133.6 mg, 0.28 mmol) were used, affording the title compound as a colourless oil (30.6 mg, 67% yield) by using Hexane (100) as eluent. In an independent experiment, 30.4 mg (67%) were obtained, giving an average of 67% yield. *Compound volatile under high vacuum*. **¹H NMR** (400 MHz, CDCl₃) δ = 7.55 – 7.53 (m, 2H), 7.32 – 7.30 (m, 2H), 2.60 – 2.53 (m, 1H), 1.91 – 1.83 (m, 4H), 1.80 – 1.73 (m, 1H), 1.49 – 1.35 (m, 4H), 1.32 – 1.24 (m, 1H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 152.4, 128.6, 127.5, 125.6, 125.6, 125.6, 125.5, 44.9, 34.6, 27.1, 26.4 ppm. **¹⁹F NMR** (376 MHz, CDCl₃) δ = -62.3 ppm. Spectroscopic data for **9** match those previously reported in the literature.[X]

10
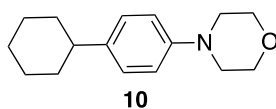
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4-(4-cyclohexylphenyl)morpholine (10). Following **General Procedure C**, 4-(4-bromophenyl)morpholine (48.2 mg, 0.20 mmol) and 1-cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1a**) (105 mg, 0.20 mmol) were used, affording the title compound as a white solid (27.0 mg, 55% yield) by using Hexane/EtOAc (90/10) as eluent. In an independent experiment, 26.0 mg (53%) were obtained, giving an average of 54% yield. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.14 – 7.12 (m, 2H), 6.87 – 6.85 (m, 2H), 3.94 – 3.80 (m, 4H), 3.20 – 3.07 (m, 4H), 2.50 – 2.37 (m, 1H), 1.92 – 1.78 (m, 4H), 1.73 (ddd, J = 13.9, 3.0, 1.5 Hz, 1H), 1.47 – 1.32 (m, 4H), 1.31 – 1.18 (m, 1H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 149.3, 139.9, 127.4, 115.8, 67.0, 49.7, 43.6, 34.6, 26.9, 26.2 ppm. Spectroscopic data for **10** match those previously reported in the literature.[X]
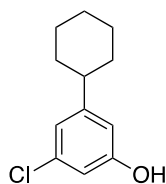
11

3-chloro-5-cyclohexylphenol (11). Following **General Procedure C**, 3-bromo-5-chlorophenol (36.8 mg, 0.20 mmol) and 1-cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1a**) (133.6 mg, 0.28 mmol) were used, affording the title compound as a colourless oil (21.4 mg, 51% yield) by using Hexane/Et$_2$O (90/10) as eluent. In an independent experiment, 20.7 mg (49%) were obtained, giving an average of 50% yield. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 6.82 – 6.74 (m, 1H), 6.71 – 6.59 (m, 1H), 6.57 –6.56 (m, 1H), 4.75 (s, 1H), 2.48 – 2.36 (m, 1H), 1.85 – 1.82 (m, 4H), 1.74 (dd, J = 12.5, 1.8 Hz, 1H), 1.40 – 1.31 (m, 4H), 1.28 – 1.18 (m, 1H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 156.1, 151.4, 134.5, 119.7, 113.2, 112.3, 44.4, 34.1, 26.7, 26.0 ppm **HRMS** calcd. for (C$_{12}$H$_{14}$ClO) [M-H]$^-$: 209.0739, found 209.0749
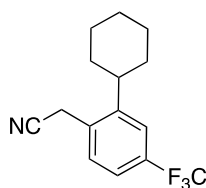
12

2-(2-cyclohexyl-4-(trifluoromethyl)phenyl)acetonitrile (12). Following **General Procedure C** at 45 ºC, 2-(2-bromo-4-(trifluoromethyl)phenyl)acetonitrile (52.6 mg, 0.20 mmol) was used and 1-cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1a**) (133.6 mg, 0.28 mmol) were used, affording the title compound as a colourless liquid (45.4 mg, 85% yield) by using Pentane/EtOAc (30/1) as eluent. In an independent experiment, 41.6 mg (78% yield) were obtained (average of 82% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.55 (s, 1H), 7.52 – 7.40 (m, 2H), 3.80 (s, 2H), 2.65 (ddd, J = 11.5, 8.3, 3.1 Hz, 1H), 1.95 – 1.79 (m, 5H), 1.60 – 1.25 (m, 5H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 146.7, 131.4 – 130.9 (m), 129.7, 124.0 (q, J = 272.3 Hz), 123.7 (q, J = 3.7 Hz), 123.4 (q, J = 3.7 Hz), 117.4, 40.4, 33.9, 26.9, 26.0, 21.6 ppm. **^{19}F NMR** (376 MHz, CDCl$_3$) δ = -62.8 ppm. **IR** (neat, cm^{-1}): 2926, 2854, 2247,

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Functionalization of Strong Sigma Bonds by Nickel and Tungsten Catalysis
Raúl Martín Montero

Deaminative Arylation at sp³ Carbon Centers

1617, 1419, 1328, 1276, 1097, 1004, 910, 817. **HRMS** calcd. for ($C_{15}H_{16}F_3N$) [M+H]⁺: 268.1308, found 268.1310.
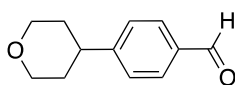
13

4-(tetrahydro-2*H*-pyran-4-yl)benzaldehyde (13). Following **General Procedure C** at 45 ºC, 4-bromobenzaldehyde (36.8 mg, 0.20 mmol) and 2,4,6-triphenyl-1-(tetrahydro-2*H*-pyran-4-yl)pyridin-1-ium tetrafluoroborate (**1b**) (134 mg, 0.28 mmol) were used at 45 ºC, affording the title compound as a pale yellow solid (34 mg, 89% yield) by using Hexane/EtOAc (90/10) as eluent. In an independent experiment, a gram scale was performed: 4-bromobenzaldehyde (1.0 g, 5.44 mmol) and 2,4,6-triphenyl-1-(tetrahydro-2*H*-pyran-4-yl)pyridin-1-ium tetrafluoroborate (**1b**) (3.6 g, 7.6 mmol) were used at 45 ºC during 48h, affording the title compound in 807 mg (78%). **Mp:** 54 - 55 ºC. **¹H NMR** (400 MHz, CDCl₃) *δ* = 9.99 (s, 1H), 7.89 – 7.80 (m, 2H), 7.40 – 7.38 (m, 2H), 4.18 – 4.03 (m, 2H), 3.55 (td, *J* = 11.5, 2.5 Hz, 2H), 2.86 (tt, *J* = 11.6, 4.4 Hz, 1H), 1.93 – 1.74 (m, 4H) ppm. **¹³C NMR** (101 MHz, CDCl₃) *δ* = 191.9, 152.9, 134.9, 130.1, 127.5, 68.1, 41.9, 33.5 ppm. **IR** (neat, cm⁻¹): 3044, 2947, 2839, 2752, 1690, 1602, 1572, 1312, 1166, 1120. **HRMS** calcd. for ($C_{12}H_{15}O_2$) [M+H]⁺: 191.1067, found 191.1072.
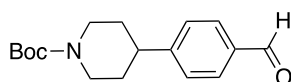
14

***tert*-butyl 4-(4-formylphenyl)piperidine-1-carboxylate (14)**. Following **General Procedure C** at 45 ºC, 4-bromobenzaldehyde (36.8 mg, 0.20 mmol) and 1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1c**) (168 mg, 0.28 mmol) were used at 45 ºC, affording the title compound as a white solid (40.0 mg, 69% yield) by using Hexane/EtOAc (90/10) as eluent. In an independent experiment, 38 mg (65%) were obtained, giving an average of 67% yield. **Mp:** 120 - 122 ºC. **¹H NMR** (400 MHz, CDCl₃) *δ* = 9.98 (s, 1H), 7.89 – 7.77 (m, 2H), 7.43 – 7.31 (m, 2H), 4.27 (d, *J* = 13.4 Hz, 1H), 2.82 (t, *J* = 12.8 Hz,2H), 2.72 (dt, *J* = 12.2, 3.6 Hz, 1H), 1.84 (d, *J* = 13.4 Hz, 2H), 1.65 (dq, *J* = 12.6, 4.4 Hz, 2H), 1.49 (s, 9H) ppm. **¹³C NMR** (101 MHz, CDCl₃) *δ* = 191.9, 154.8, 152.9, 134.9, 130.1, 127.5, 79.6, 43.0, 32.8, 28.5 ppm. Spectroscopic data for **14** match those previously reported in the literature.[XI]
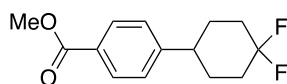
15

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methyl 4-(4,4-difluorocyclohexyl)benzoate (15). Following **General Procedure C**, methyl 4-bromobenzoate (43 mg, 0.20 mmol) and 1-(4,4-difluorocyclohexyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1d**) (143.6 mg, 0.28 mmol) were used, affording the title compound (30.0 mg, 59% yield) as a colourless oil by using toluene as eluent. In an independent experiment, 29.6 mg (58% yield) were obtained, giving an average of 59% yield. **¹H NMR** (400 MHz, CDCl₃) δ = 7.98 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 3.91 (s, 3H), 2.67 (t, J = 11.4 Hz, 1H), 2.30 – 2.16 (m, 2H), 2.00 – 1.75 (m, 6H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 167.1, 150.6 (d, J = 2.4 Hz), 130.1, 128.7, 127.0, 121.9 (dd, J = 242.9, 238.1 Hz), 52.2, 42.8 (d, J = 1.8 Hz), 34.1 (dd, J = 25.7, 22.8 Hz), 30.2 (d, J = 10.0 Hz) ppm. **¹⁹F NMR** (376 MHz, CDCl₃) δ = -91.9 (d, J = 236.4 Hz), -102.5 (dt, J = 235.9, 34.6 Hz) ppm. IR (neat, cm⁻¹): 2940, 1717, 1608, 1434, 1275, 1096, 957, 761. **HRMS** calcd. for ($C_{14}H_{17}F_2O_2$) [M+H]⁺: 255.1191, found 255.1181
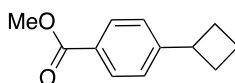
16

methyl 4-cyclobutylbenzoate (16). Following **General Procedure C**, methyl 4-bromobenzoate (43 mg, 0.20 mmol) and 1-cyclobutyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1e**) (125.7 mg, 0.28 mmol) were used, affording the title compound (25.0 mg, 65% yield) as a colourless oil by using Pentane/EtOAc (50/50) as eluent. In an independent experiment, 26.2 mg (69% yield) were obtained, giving an average of 67% yield. **¹H NMR** (400 MHz, CDCl₃) δ = 7.96 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 3.90 (s, 3H), 3.60 (quint, J = 8.6 Hz, 1H), 2.38 (dt, J = 10.4, 8.0 Hz, 2H), 2.23 – 2.10 (m, 2H), 2.09 – 1.97 (m, 1H), 1.93 – 1.82 (m, 1H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 167.3, 151.8, 129.7, 127.7, 126.4, 52.1, 40.4, 29.7, 18.4 ppm. Spectroscopic data for **16** match those previously reported in the literature.[XII]
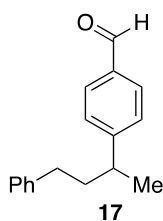
17

4-(4-phenylbutan-2-yl)benzaldehyde (17). Following **General Procedure C** at 45 ºC, 4-bromobenzaldehyde (37.0 mg, 0.20 mmol) and 1-(4-phenylbutan-2-yl) triphenylpyridin-1-ium tetrafluoroborate (**1f**) (147.6 mg, 0.28 mmol) were used, affording the title compound as a colourless liquid (36.7 mg, 77% yield) at 45 ºC by using toluene as eluent. In an independent experiment, 36.0 mg (76% yield) were obtained, giving an average of 77% yield. **¹H NMR** (400 MHz, CDCl₃) δ = 9.99 (s, 1H), 7.84 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.30 – 6.93 (m, 5H), 2.82 (h, J = 7.0 Hz, 1H), 2.59 – 2.42 (m, 2H), 2.01 – 1.86 (m, 2H), 1.31 (d, J = 7.0 Hz, 3H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 192.2, 154.9, 142.1, 134.9, 130.2, 128.5, 128.5, 127.9, 126.0, 39.9, 39.8, 33.9, 22.3 ppm. IR (neat, cm⁻¹): 3024, 2958, 2924, 2854, 1684, 1603, 1574, 1454, 1418, 1210, 1167, 828, 720. **HRMS** calcd. for

(C$_{17}$H$_{18}$O) [M+H]$^+$: 239.1430, found 239.1431.

18
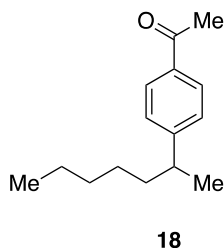
1-(4-(heptan-2-yl)phenyl)ethan-1-one (18). Following **General Procedure C** at 45 ºC, 1-(4-bromophenyl)ethan-1-one (39.8 mg, 0.20 mmol) and 1-(heptan-2-yl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1g**) (147.6 mg, 0.28 mmol) were used at 45 ºC, affording the title compound as a colourless oil (28.3 mg, 65% yield) by using Hexane/ *tert*-butyl-methyl ether (95/5) as eluent. In an independent experiment, 26.6 mg (61%) were obtained, giving an average of 63% yield. ^{1}**H NMR** (400 MHz, CDCl$_3$) δ = 7.90 – 7.88 (m, 2H), 7.31 – 7.25 (m, 2H), 2.75 (sext, J = 7.0 Hz, 1H), 2.58 (s, 3H), 1.60 – 1.54 (m, 3H), 1.27 – 1.22 (m, 7H), 1.15 – 1.13 (m, 1H), 0.8 (t, J = 7.0 Hz, 3H) ppm. ^{13}**C NMR** (101 MHz, CDCl$_3$) δ = 197.9, 153.8, 135.1, 128.5, 127.2, 40.1, 38.1, 31.8, 27.3, 26.5, 22.5, 22.0, 14.0 ppm. **IR** (neat, cm^{-1}): 2955, 2924, 2853, 1682, 1604, 1507, 1456, 4263, 1180. **HRMS** calcd. for (C$_{15}$H$_{23}$O) [M+H]$^+$: 219.1743, found 219.1749.

19
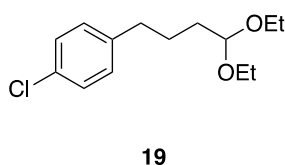
1-chloro-4-(4,4-diethoxybutyl)benzene (19). Following **General Procedure C**, 1-bromo-4-chlorobenzene (39.1 mg, 0.20 mmol) and 1-(4,4-diethoxybutyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate (**1h**) (176 mg, 0.28 mmol) were used, affording the title compound as a white solid (31.7 mg, 62% yield) by using Hexane/EtOAc (95/5) as eluent. In an independent experiment, 31.2 mg (61%) were obtained, giving an average of 62% yield. **Mp:** 117 - 119 ºC. ^{1}**H NMR** (400 MHz, CDCl$_3$) δ = 7.50 – 7.48 (m, 2H), 7.29 – 7.17 (m, 2H), 4.51 (t, J = 5.4 Hz, 1H), 3.63 (dq, J = 9.4, 7.0 Hz, 2H), 3.48 (dq, J = 9.4, 7.1 Hz, 2H), 2.67 (t, J = 7.3 Hz, 2H), 1.80 – 1.63 (m, 4H), 1.20 (t, J = 7.0 Hz, 6H) ppm. ^{13}**C NMR** (101 MHz, CDCl$_3$) δ = 141.2, 138.6, 128.8, 126.9, 102.8, 2·61.0, 35.3, 33.3, 26.6, 2·15.3 ppm. **IR** (neat, cm^{-1}): 3029, 1685, 1490, 109, 1310, 1200, 1014, 802. **GC-MS** calcd. for (C$_{14}$H$_{21}$ClO$_2$) [M]$^+$: 256.1, found m/z 256.1.

20
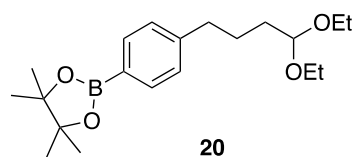
2-(4-(4,4-diethoxybutyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (20). Following **General Procedure C**, 2-(4-bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (56.4 mg, 0.20

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mmol) and 1-(4,4-diethoxybutyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate (**1h**) (176 mg, 0.28 mmol) were used, affording the title compound as a yellow oil (52.2 mg, 75% yield) by using Hexane/EtOAc (90/10) as eluent. In an independent experiment, 45.4 mg (71%) were obtained, giving an average of 73% yield. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.73 – 7.73 (m, 2H), 7.23 – 7.14 (m, 2H), 4.48 (t, J = 5.4 Hz, 1H), 3.61 (dq, J = 9.4, 7.0 Hz, 2H), 3.46 (dq, J = 9.4, 7.1 Hz, 2H), 2.64 (t, J = 7.3 Hz, 2H), 1.73 – 1.61 (m, 4H), 1.34 (s, 12H), 1.19 (t, J = 7.1 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 145.8, 134.9, 127.9, 102.8, 83.6, 60.9, 35.9, 33.2, 26.4, 24.8, 15.3 ppm. *(the signal for the aromatic carbon attached to boron is not observed due to quadrupolar relaxation).* **^{11}B NMR** (128 MHz, CDCl$_3$) δ = 32.1 ppm. **IR** (neat, cm^{-1}): 2974, 2928,1724, 1610, 1356, 1318, 1141, 1087, 858. **HRMS** calcd. for (C$_{22}$H$_{32}$O$_4$^{10}B) [M+Na]$^+$: 370.2424, found 370.2413.
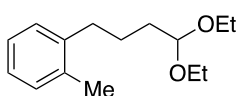
21

1-(4,4-diethoxybutyl)-2-methylbenzene (21). Following **General Procedure C**, 1-bromo-2-methylbenzene (56.4 mg, 0.20 mmol) and 1-(4,4-diethoxybutyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate (**1h**) (176 mg, 0.28 mmol) were used, affording the title compound as a yellow oil (36.4 mg, 77% yield) by using Hexane/EtOAc (95/5) as eluent. In an independent experiment, 36.3 mg (77%) were obtained, giving an average of 77% yield. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.18 – 7.02 (m, 4H), 4.51 (t, J = 5.5 Hz, 1H), 3.64 (dq, J = 9.4, 7.0 Hz, 2H), 3.49 (dq, J = 9.4, 7.1 Hz, 2H), 2.62 (t, J = 7.1 Hz, 2H), 2.31 (s, 3H), 1.76 – 1.62 (m, 4H), 1.20 (t, J = 7.1 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 140.5, 135.8, 130.1, 128.8, 125.9, 102.8, 77.0, 60.9, 33.5, 33.0, 25.4, 19.3, 15.3 ppm. **IR** (neat, cm^{-1}): 2971, 2927, 1570, 1456, 1122, 1058, 976. **HRMS** calcd. for (C$_{11}$H$_{13}$) [M-(CH$_2$)$_3$(OEt)$_2$]$^+$: 145.1012, found 145.1013.
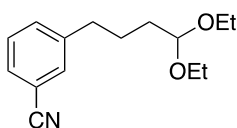
22

3-(4,4-diethoxybutyl)benzonitrile (22). Following **General Procedure C**, 3-bromobenzonitrile (36.4 mg, 0.20 mmol) and 1-(4,4-diethoxybutyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate (**1h**) (176 mg, 0.28 mmol) were used, affording the title compound as a yellow oil (42.0 mg, 85% yield) by using Hexane/EtOAc (95/5) as eluent. In an independent experiment, 40.0 mg (81%) were obtained, giving an average of 83% yield. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.52 – 7.46 (m, 2H), 7.45 – 7.32 (m, 2H), 4.49 (t, J = 5.3 Hz, 1H), 3.63 (dq, J = 9.4, 7.0 Hz, 2H), 3.48 (dq, J = 9.4, 7.0 Hz, 2H), 2.67 (t, J = 7.4 Hz, 2H), 1.77 – 1.57 (m, 4H), 1.20 (t, J = 7.0, Hz, 6H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 143.7, 133.0, 132.0, 129.6, 129.1, 119.0, 112.3, 102.6, 61.2, 35.2, 33.0, 26.1, 15.3 ppm. **IR** (neat, cm^{-1}): 2956, 2925, 2855, 1720, 1604, 1508, 1387, 1269, 1144, 1112, 1089, 966, 853, 767. **HRMS** calcd. for (C$_{15}$H$_{21}$NNaO$_2$) [M+Na]$^+$: 270.1464, found 270.1470.

23
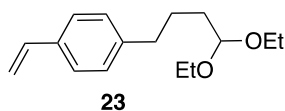
1-(4,4-diethoxybutyl)-4-vinylbenzene (23). Following **General Procedure C**, 1-bromo-4-vinylbenzene (36.6 mg, 0.20 mmol) and 1-(4,4-diethoxybutyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate **(1h)** (151.8 mg, 0.28 mmol) were used, affording the title compound (30.0 mg, 60% yield) as a colorless oil by using Pentane/EtOAc (30/1) as eluent. In an independent experiment, 28.0 mg (56% yield) were obtained, giving an average of 58% yield. **¹H NMR** (400 MHz, CDCl₃) δ = 7.32 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 6.69 (dd, J = 17.6, 10.9 Hz, 1H), 5.70 (dd, J = 17.6, 1.1 Hz, 1H), 5.19 (dd, J = 10.9, 1.0 Hz, 1H), 4.49 (t, J = 5.3 Hz, 1H), 3.62 (dq, J = 9.4, 7.1 Hz, 2H), 3.47 (dq, J = 9.4, 7.1 Hz, 2H), 2.62 (t, J = 7.0 Hz, 2H), 1.72 – 1.60 (m, 4H), 1.19 (t, J = 7.1 Hz, 6H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 142.2, 136.8, 135.4, 128.7, 126.3, 113.1, 102.9, 61.1, 35.6, 33.3, 26.7, 15.5 ppm. **¹⁹F NMR** (376 MHz, CDCl₃) δ = -115.68 ppm. IR (neat, cm⁻¹): 2972, 2925, 2870, 1867, 1646, 1557, 1517, 1456, 1127, 1063, 988. HRMS calcd. for (C₁₆H₂₄O₂) [M+H]⁺: 249.1849, found 249.1852.

24
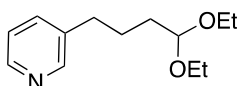
3-(4,4-diethoxybutyl)pyridine (24). Following **General Procedure C**, 3-pyridine (31.6 mg, 0.20 mmol) and 1-(4,4-diethoxybutyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate **(1h)** (151.8 mg, 0.28 mmol) were used, affording the title compound (34.9 mg, 78% yield) as a colourless oil by using Pentane/EtOAc (60/30) as eluent. In an independent experiment, 35.0 mg (78% yield) were obtained, giving an average of 78% yield. **¹H NMR** (400 MHz, CDCl₃) δ = 8.44 (brs, 2H), 7.49 (d, J = 7.8 Hz, 1H), 7.20 (dd, J = 7.6, 4.8 Hz, 1H), 4.49 (t, J = 5.3 Hz, 1H), 3.62 (dq, J = 9.4, 7.1 Hz, 2H), 3.47 (dq, J = 9.4, 7.1 Hz, 2H), 2.63 (t, J = 7.2 Hz, 2H), 1.81 – 1.53 (m, 4H), 1.19 (t, J = 7.1 Hz, 6H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 150.1, 147.5, 137.6, 136.0, 123.4, 102.8, 61.3, 33.2, 32.9, 26.4, 15.5 ppm. IR (neat, cm⁻¹): 2971, 2920, 2869, 1420, 1373, 1124, 1057, 978, 720. **HRMS** calcd. for (C₁₃H₂₂NO₂) [M+H]⁺: 224.1645, found 224.1645.

25
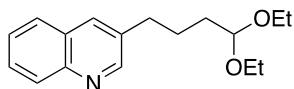
3-(4,4-diethoxybutyl)quinolone (25). Following **General Procedure C**, 3-bromoquinoline (41.6 mg, 0.20 mmol) and 1-(4,4-diethoxybutyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate **(1h)** (176 mg, 0.28 mmol) were used, affording the title compound as a yellow oil (47.0 mg, 86% yield) by using Hexane/EtOAc (85/15) as eluent. In an independent experiment, 45.9 mg (84%) were obtained, giving an average of 85% yield. **¹H NMR** (400 MHz, CDCl₃) δ = 8.79 (d, J =

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2.2 Hz, 1H), 8.17 – 8.02 (m, 1H), 7.93 (dd, *J* = 2.2, 1.0 Hz, 1H), 7.77 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.66 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 4.52 (t, *J* = 5.5 Hz, 1H), 3.63 (dq, *J* = 9.4, 7.1 Hz, 2H), 3.48 (dq, *J* = 9.4, 7.1 Hz, 2H), 2.83 (t, *J* = 7.5 Hz, 2H), 1.87 – 1.75 (m, 2H), 1.74 – 1.67 (m, 2H), 1.20 (t, *J* = 7.0 Hz, 6H) ppm. **13C NMR** (101 MHz, CDCl$_3$) *δ* = 151.8, 146.6, 134.8, 134.4, 129.0, 128.7, 128.1, 127.3, 126.6, 102.7, 61.1, 33.1, 32.9, 26.2, 15.3 ppm. **IR** (neat, cm-1): 2971, 2925, 2862, 1716, 1512, 1495, 1373, 1329, 1122, 1058, 958. **HRMS** calcd. for (C$_{17}$H$_{24}$NO$_2$) [M+H]$^+$: 274.1802, found 274.1811.

26
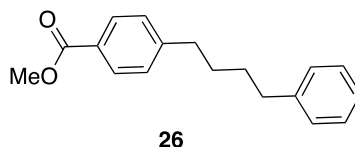
methyl 4-(4-phenylbutyl)benzoate (26). Following **General Procedure C**, methyl 4-bromobenzoate (43 mg, 0.20 mmol) and 2,4,6-tris(4-methoxyphenyl)-1-(4-phenylbutyl)pyridin-1-ium tetrafluoroborate **(1i)** (172.0 mg, 0.28 mmol) were used, affording the title compound (40.2 mg, 75% yield) as a colorless oil by using Pentane/EtOAc (30/1) as eluent. In an independent experiment, 39.0 mg (72% yield) were obtained, giving an average of 74% yield. **1H NMR** (400 MHz, CDCl$_3$) *δ* = 7.94 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.19 – 7.14 (m, 3H), 3.90 (s, 3H), 2.69 (t, *J* = 7.1 Hz, 2H), 2.64 (t, *J* = 7.1 Hz, 2H), 1.67 (dt, *J* = 6.8, 2.6 Hz, 4H) ppm. **13C NMR** (101 MHz, CDCl$_3$) *δ* = 167.3, 148.2, 142.5, 129.8, 128.6, 128.5, 128.4, 125.9, 52.1, 36.0, 35.9, 31.1, 30.8 ppm. IR (neat, cm^{-1}): 2926, 2853, 1717, 1607, 1433, 1272, 1176, 1106, 1019, 760, 719. **HRMS** calcd. for (C$_{18}$H$_{21}$O$_2$) [M+H]$^+$: 269.1536, found 269.1547.

27
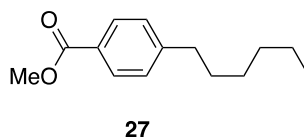
methyl 4-hexylbenzoate (27). Following **General Procedure C**, methyl 4-bromobenzoate (43 mg, 0.20 mmol) and 2,4,6-tris(4-methoxyphenyl)-1-hexylpyridin-1-ium tetrafluoroborate **(1j)** (160.0 mg, 0.28 mmol) were used, affording the title compound (28.6 mg, 65% yield) as a colorless oil by using Pentane/EtOAc (30/1) as eluent. In an independent experiment, 27.8 mg (63% yield) were obtained, giving an average of 64% yield. **1H NMR** (400 MHz, CDCl$_3$) *δ* = 7.95 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 3.90 (s, 3H), 3.04 – 2.27 (m, 2H), 1.62 (p, *J* = 7.7 Hz, 2H), 1.41 – 1.17 (m, 6H), 1.02 – 0.74 (m, 3H) ppm. **13C NMR** (101 MHz, CDCl$_3$) *δ* = 167.3, 148.6, 129.7, 128.5, 127.8, 52.0, 36.1, 31. 8, 31.2, 29.0, 22.7, 14.2 ppm. Spectroscopic data for **16** match those previously reported in the literature.[XIII]

Deaminative Arylation at sp³ Carbon Centers
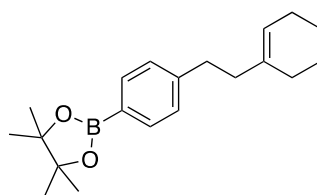
28

2-(4-(2-(cyclohex-1-en-1-yl)ethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane   **(28).**
Following **General Procedure C**, 2-(4-bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (56.4 mg, 0.20 mmol) and 1-(2-(cyclohex-1-en-1-yl)ethyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate (**1k**) (167 mg, 0.28 mmol) were used, affording the title compound as a white solid (37.4 mg, 60% yield) by using Hexane/EtOAc (95/5) as eluent. In an independent experiment, 36 mg (58%) were obtained, giving an average of 59% yield. **Mp:** 66 - 68 ºC. **¹H NMR** (400 MHz, CDCl₃) δ = 7.80 – 7.67 (m, 2H), 7.22 – 7.15 (m, 2H), 5.41 (dq, *J* = 3.8, 1.7 Hz, 1H), 2.79 – 2.65 (m, 2H), 2.22 (t, *J* = 7.9 Hz, 2H), 1.99 – 1.95 (m, 4H), 1.69 – 1.48 (m, 4H), 1.34 (s, 12H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 146.1, 137.2, 134.8, 127.9, 121.4, 83.6, 39.8, 34.7, 28.5, 25.2, 24.8, 23.0, 22.5 ppm. *(the signal for the aromatic carbon attached to boron is not observed due to quadrupolar relaxation).* **¹¹B NMR** (128 MHz, CDCl₃) δ = 30.2 ppm. **IR** (neat, cm⁻¹): 2977, 2922, 1610, 1396, 1357, 1319, 1261, 1087, 1140. **HRMS** calcd. for (C₂₀H₂₉NaO₂¹⁰B) [M+Na]⁺: 334.2189, found 334.2175.
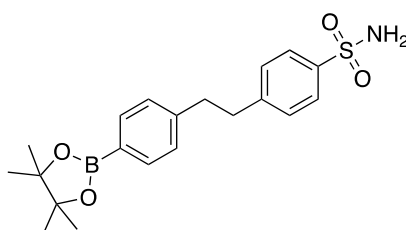
29

4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)benzenesulfonamide   **(29).**
Following **General Procedure C**, 2-(4-bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (56.4 mg, 0.20 mmol) and 2,4,6-tris(4-methoxyphenyl)-1-(4-sulfamoylphenethyl)pyridin-1-ium tetrafluoroborate (**1l**) (188 mg, 0.28 mmol) were used, affording the title compound as a white solid (51.1 mg, 66% yield) by using Hexane/EtOAc (70/30) as eluent. In an independent experiment, 50 mg (65%) were obtained, giving an average of 66% yield. **Mp:** 138 - 140 ºC. **¹H NMR** (400 MHz, CDCl₃) δ = 7.87 – 7.79 (m, 2H), 7.75 – 7.68 (m, 2H), 7.29 – 7.26 (m, 2H), 7.22 – 7.11 (m, 2H), 4.91 (brs, 2H, NH₂), 3.0 – 2.94 (m, 4H), 1.34 (s, 12H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 147.0, 144.0, 139.6, 135.0, 129.2, 127.9, 126.5, 83.7, 37.5, 37.4, 24.8 ppm. *(the signal for the aromatic carbon attached to boron is not observed due to quadrupolar relaxation).* **¹¹B NMR** (128 MHz, CDCl₃) δ = 30.8 ppm. **IR** (neat, cm⁻¹): 3307, 3243, 2943, 2922, 2856, 1605, 1396, 1361, 1313, 1141, 1087. **HRMS** calcd. for (C₂₀H₂₆NaNO₄S¹⁰B) [M+Na]⁺: 410.1568, found 410.1578.

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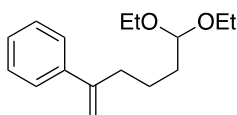
30

(6,6-diethoxyhex-1-en-2-yl)benzene (30). Following **General Conditions C**, (1-bromovinyl)benzene (36.7 mg, 0.20 mmol) and 1-(4,4-diethoxybutyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate (**1h**) (176 mg, 0.28 mmol) were used, affording the title compound as a colourless oil (27.3 mg, 55% yield) by using Hexane/EtOAc (90/10) as eluent. In an independent experiment, 26.8 mg (54%) were obtained, giving an average of 55% yield. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.44 – 7.35 (m, 2H), 7.34 – 7.30 (m, 2H), 7.28 – 7.15 (m, 1H), 5.27 (d, J = 1.5 Hz, 1H), 5.06 (d, J = 1.4 Hz, 1H), 4.47 (t, J = 5.7 Hz, 1H), 3.60 (dq, J = 9.4, 7.0 Hz, 2H), 3.45 (dq, J = 9.4, 7.1 Hz, 2H), 2.53 (td, J = 7.5, 1.3 Hz, 2H), 1.70 – 1.59 (m, 2H), 1.58 – 1.47 (m, 2H), 1.17 (t, J = 7.1 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 148.2, 141.2, 128.2, 127.3, 126.1, 112.5, 102.7, 60.8, 35.0, 33.1, 23.3, 15.3 ppm. **IR** (neat, cm^{-1}): 2971, 2927, 2869, 1652, 1373, 1122, 1058. **HRMS** calcd. for (C$_{20}$H$_{29}$NaO$_2$^{10}B) [M]$^+$: 248.1771, found 248.1775.
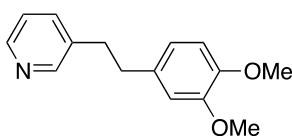
31

3-(3,4-dimethoxyphenethyl)pyridine (31). Following **General Procedure C**, 3-bromopyridine (31.6 mg, 0.20 mmol) and 1-(3,4-dimethoxyphenethyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium (**1m**) (181.7 mg, 0.28 mmol) were used, affording the title compound as a colourless liquid (34.0 mg, 70% yield) by using Pentane/EtOAc (60/30) as eluent. In an independent experiment, 35.6 mg (73% yield) were obtained, giving an average of 72% yield. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 8.45 – 8.42 (m, 2H), 7.41 (d, J = 7.8 Hz, 1H), 7.18 (dd, J = 7.7, 4.8 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 6.67 (dd, J = 8.1, 2.0 Hz, 1H), 6.61 (d, J = 1.9 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.96 – 2.80 (m, 4H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 150.1, 148.9, 147.5, 137.0, 136.2, 133.5, 123.3, 120.5, 112.0, 111.4, 56.0, 55.9, 37.2, 35.3 ppm. IR (neat, cm^{-1}): 2931, 2831, 1589, 1512, 1456, 1418, 1257, 1233, 1145, 1025, 933, 853, 803, 720. **HRMS** calcd. for (C$_{15}$H$_{18}$NO$_2$) [M+H]$^+$: 244.1338, found 244.1341.
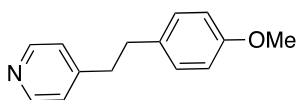
32

4-(4-methoxyphenethyl)pyridine (32). Following **General Procedure C**, 4-bromoanisole (37.2 mg, 0.20 mmol) and 2,4,6-tris(4-methoxyphenyl)-1-(2-(pyridin-4-yl)ethyl)pyridin-1-ium (**1n**) (165.2 mg, 0.28 mmol) were used, affording the title compound as a colourless liquid (28.0 mg, 66% yield) by

using Pentane/EtOAc (50/10) as eluent. In an independent experiment, 30.0 mg (70% yield) were obtained, giving an average of 68% yield. **¹H NMR** (400 MHz, CDCl₃) δ = 8.47 (d, J = 5.4 Hz, 2H), 7.11 − 7.01 (m, 4H), 6.85 − 6.78 (m, 2H), 3.78 (s, 3H), 2.88 (s, 4H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 158.2, 150.7, 149.8, 132.8, 129.5, 124.1, 114.0, 55.4, 37.4, 35.8 ppm. **HRMS** calcd. for (C₁₄H₁₆NO) [M+H]⁺: 214.1232, found 214.1229. Spectroscopic data for **16** match those previously reported in the literature.[XIV]

33
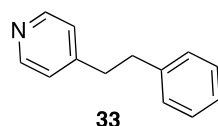
4-phenethylpyridine (33). Following **General Conditions C**, bromobenzene (31.4 mg, 0.20 mmol) and 2,4,6-tris(4-methoxyphenyl)-1-(2-(pyridin-4-yl)ethyl)pyridin-1-ium (**1n**) (165.2 mg, 0.28 mmol) were used, affording the title compound as a colourless liquid (28.2 mg, 77% yield) by using Petane/EtOAc (50/10) as eluent. In an independent experiment, 27.6 mg (75% yield) were obtained, giving an average of 76% yield. **¹H NMR** (400 MHz, CDCl₃) δ = 8.49 (d, J = 5.0 Hz, 2H), 7.31 − 7.25 (m, 2H), 7.22 (d, J = 7.3 Hz, 1H), 7.17 − 7.12 (m, 2H), 7.08 (d, J = 6.0 Hz, 2H), 2.93 (s, 4H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 150.6, 149.8, 140.8, 128.6, 128.5, 126.4, 124.1, 37.2, 36.7 ppm. **HRMS** calcd. for (C₁₃H₁₄N) [M+H]⁺: 184.1126, found 184.1126. Spectroscopic data for **16** match those previously reported in the literature.[XV]

34
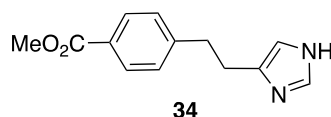
methyl 4-(2-(1H-imidazol-4-yl)ethyl)benzoate (34). Following **General Condition C** for 48 h, methyl 4-bromobenzoate (43 mg, 0.20 mmol) and 1-(2-(1H-imidazol-4-yl)ethyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate (**1o**) (163 mg, 0.28 mmol) were used, affording the title compound as a yellow oil (29.9 mg, 65% yield) by using DCM/MeOH (95/5) as eluent. **¹H NMR** (400 MHz, CDCl₃) δ = 7.96 − 7.86 (m, 2H), 7.70 (s, 1H), 7.56 (s, 1H), 7.24 − 7.17 (m, 2H), 6.72 (s, 1H), 3.89 (s, 3H), 3.03 (t, J = 7.4 Hz, 2H), 2.96 (t, J = 7.4 Hz, 2H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 167.1, 146.7, 136.3, 134.0, 129.7, 128.5, 128.1, 116.1 52.0, 35.5, 28.1 ppm. **IR** (neat, cm⁻¹): 3125, 3074, 2845, 2614, 1708, 1607, 1507, 1434, 1276, 1178, 1018. **HRMS** calcd. for (C₁₃H₁₃N₂O₂) [M]⁻: 229.0983, found 229.0979.

35
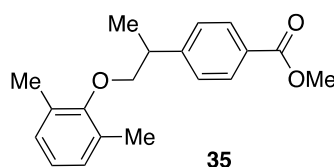
methyl-4-(1-(2,6-dimethylphenoxy)propan-2-yl)benzoate (35). Following **General Procedure C** for 48 h, methyl 4-iodobenzoate (52.2 mg, 0.20 mmol) and 1-(1-(2,6-dimethylphenoxy)propan-2-yl)-

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2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1r**) (156.0 mg, 0.28 mmol) were used, affording the title compound (40.0 mg, 67% yield) at room temperature as a colourless oil by using Pentane/EtOAc (100/2) as eluent. In an independent experiment, 41.5 mg (70% yield) were obtained, giving an average of 69% yield. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 8.53 (dd, J = 4.2, 1.6 Hz, 1H), 7.92 (d, J = 8.3 Hz, 3H), 7.23 (d, J = 8.4 Hz, 2H), 6.34 (s, 1H), 6.26 (s, 1H), 6.01 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.62 (dt, J = 13.1, 6.9 Hz, 1H), 2.70 (t, J = 6.4 Hz, 2H), 1.90 – 1.61 (m, 4H), 1.29 (d, J = 6.3 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 167.3, 159.6, 148.0, 145.1, 144.4, 134.9, 130.0, 129.8, 128.6, 127.9, 122.0, 96.8, 91.7, 55.3, 52.1, 48.1, 36.4, 36. 0, 27.7, 20.6 ppm. IR (neat, cm^{-1}): 2950, 2917, 1717, 1609, 1472, 1434, 1274, 1193, 1108, 1006, 971, 854, 760. **HRMS** calcd. for (C$_{19}$H$_{22}$NaO$_3$) [M+Na]$^+$: 321.1461, found 321.1454.

36
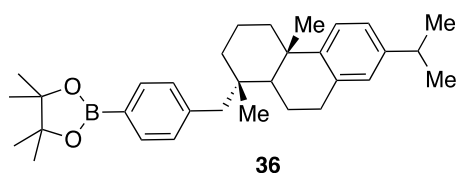
2-(4-(((1S,4aS)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (36). Following **General Procedure C** for 48 h, 2-(4-bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (56.4 mg, 0.20 mmol) and 1-(((1R,4aS,10aR)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate (**1p**) (212 mg, 0.28 mmol) were used, affording the title compound as a yellow solid (55.7 mg, 59% yield) by using Hexane/EtOAc (95/5) as eluent. In an independent experiment, 51.9 mg (55%) were obtained, giving an average of 57% yield. **Mp:** 133 - 135 ºC. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.74 – 7.62 (m, 2H), 7.15 – 7.10 (m, 3H), 6.95 (dd, J = 8.2, 2.1 Hz, 1H), 6.88 (d, J = 2.0 Hz, 1H), 2.97 – 2.88 (m, 1H), 2.81 (quint, J = 6.9 Hz, 1H), 2.69 (d, J = 13.0 Hz, 1H), 2.57 (d, J = 13.0 Hz, 1H), 2.19 (d, J = 12.9 Hz, 1H), 2.15 – 2.05 (m, 1H), 1.89 – 1.73 (m, 1H), 1.72 – 1.60 (m, 1H), 1.61 – 1.52 (m, 2H), 1.43 – 1.37 (m, 1H), 1.33 (s, 12H), 1.29 – 1.25 (m, 2H), 1.25 – 1.19 (m, 9H), 1.00 (s, 3H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 147.6, 145.4, 142.2, 134.7, 134.1, 130.5, 126.8, 124.1, 123.7, 83.6, 50.0, 46.8, 38.3, 37.8, 37.7, 37.3, 33.4, 30.1, 25.7, 24.9, 24.8, 24.0, 23.9, 20.8, 19.4, 18.8 ppm. *(the signal for the aromatic carbon attached to boron is not observed due to quadrupolar relaxation).* **^{11}B NMR** (128 MHz, CDCl$_3$) δ = 30.8 ppm. **IR** (neat, cm^{-1}): 2926, 2156, 1770, 1739, 1652, 1517, 1395, 1267. **HRMS** calcd. for (C$_{32}$H$_{45}$NaNO$_2$^{10}B) [M+Na]$^+$: 494.3441, found 494.3440.

37
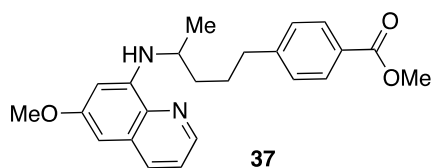
methyl-4-(4-(((6-methoxyquinolin-8-yl)amino)pentyl)benzoate (37). Following **General Procedure C** for 48 h, methyl 4-bromobenzoate (43.0 mg, 0.20 mmol) and 2,4,6-tris(4-

methoxyphenyl)-1-(4-((6-methoxyquinolin-8-yl)amino)pentyl)pyridin-1-ium tetrafluoroborate (**1q**) (203.6 mg, 0.28 mmol)were used, affording the title compound (45.0 mg, 60% yield) as a colourless oil by using Pentane/EtOAc (100/5) as eluent. In an independent experiment, 47.0 mg (62% yield) were obtained, giving an average of 61% yield. **¹H NMR** (400 MHz, CDCl₃) δ = 8.03 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 6.98 (d, J = 7.3 Hz, 2H), 6.94 – 6.88 (m, 1H), 3.94 (s, 3H), 3.90 – 3.82 (m, 2H), 3.34 (h, J = 7.0 Hz, 1H), 2.16 (s, 6H), 1.50 (d, J = 7.0 Hz, 3H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 167.3, 155.6, 149.7, 131.0, 129.9, 129.0, 128.6, 127.7, 124.0, 52.2, 41.0, 18.1, 16.3 ppm. IR (neat, cm⁻¹): 3377, 2932, 2854, 1715, 1609, 1574, 1515, 1384, 1273, 1158, 1105, 1049, 966, 818, 760. **HRMS** calcd. for ($C_{23}H_{27}NO_3$) [M+H]⁺: 379.2016, found 379.2025.

38
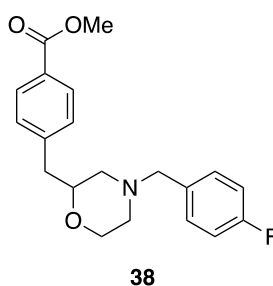
methyl 4-((4-(4-fluorobenzyl)morpholin-2-yl)methyl)benzoate (38). Following **General Procedure C** for 48 h, methyl 4-bromobenzoate (43 mg, 0.20 mmol) and 1-((4-(4-fluorobenzyl)morpholin-2-yl)methyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate (**1s**) (194.0 mg, 0.28 mmol) were used, affording the title compound (50.2 mg, 73% yield) as a colorless oil by using Pentane/EtOAc (50/50) as eluent. In an independent experiment, 49.8 mg (72% yield) were obtained, giving an average of 73% yield. **¹H NMR** (400 MHz, CDCl₃) δ = 7.97 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 7.7 Hz, 4H), 7.01 (t, J = 8.7 Hz, 2H), 3.92 (s, 3H), 3.88 – 3.82 (m, 2H), 3.68 – 3.59 (m, 1H), 3.46 (q, J = 19.5 Hz, 2H), 2.88 (dd, J = 14.0, 7.6 Hz, 1H), 2.79 – 2.70 (m, 2H), 2.63 (d, J = 11.3 Hz, 1H), 2.16 (td, J = 11.3, 3.1 Hz, 1H), 1.97 (t, J = 10.5 Hz, 1H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 167.2, 163.5, 161.0, 143.8, 130.8 (d, J = 7.9 Hz), 129.8, 129.4, 128.5, 115.3 (d, J = 21.2 Hz), 76.2, 66.9, 62.5, 58.4, 52.8, 52.1, 40.3 ppm. **¹⁹F NMR** (376 MHz, CDCl₃) δ = -115.7 ppm. IR (neat, cm⁻¹): 2946, 2857, 2802, 1716, 1601, 1506, 1273, 1217, 1104, 1019, 834, 760. **HRMS** calcd. for ($C_{20}H_{23}FNO_2$) [M+H]⁺: 344.1656, found 344.1663.

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3.5.5   Photochemical conditions

NiBr$_2$·Glyme (10 mol%)
L2 (14 mol%)
[Ir(dF(CF$_3$)ppy)$_2$(dtbpy)]PF$_6$ (1 mol%)

Hantzsch ester (1.5 eq) Cs$_2$CO$_3$ (1 eq)
NMP (0.1 M), r.t, blue LEDs, 48 h
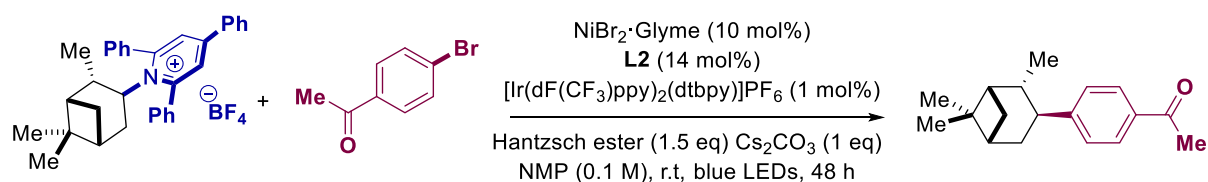
NOTE: No product was detected upon exposure of the starting precursors to our optimized conditions based on Mn. No products were detected by GC-MS and starting precursor was recovered.

40
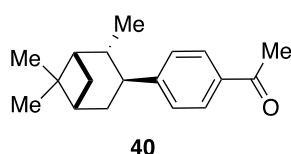
1-(4-((1*S*,2*S*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)phenyl)ethan-1-one (40). An oven-dried 8 mL screw-cap test tube containing a stirring bar was charged with 1-(4-bromophenyl)ethan-1-one (39.8 mg, 0.20 mmol), 2,4,6-triphenyl-1-((1*S*,2*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)pyridin-1-ium tetrafluoroborate (**2t**) (148.8 mg, 0.28 mmol, 1.4 equiv.), **[Ir{dF(CF$_3$)ppy}$_2$(dtbpy)]PF$_6$** (1.1 mg, 1 mol%) and Hantzsch ester (diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate). The test tube was introduced in an argon-filled glovebox where Cs$_2$CO$_3$ (32.5 mg, 0.2 mmol, 1 eq.), and 0.4 mL precatalyst mixture of NiBr$_2$·glyme (6.2 mg, 10 mol%) with 4,4'-dimethoxy-2,2'-bipyridine (**L2**, 6.0 mg, 14 mol%) in NMP (1.60 mL). The tube with the mixture was taken out of the glovebox and stirred at room temperature for 48 h under blue leds irradiation. After the reaction was finished, the reaction mixture was extracted with ethyl acetate and water/brine (3 times). Then the organic layers were combined, dried over MgSO$_4$, concentrated under vacuum and the product was purified by flash chromatography column on silica gel Hexane/*tert*-buthyl-methyl ether (95/5), affording the title compound as a colourless oil (30 mg, 58% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.92 – 7.90 (m, 2H), 7.40 – 7.38 (m, 2H), 3.07 (dt, J = 10.3, 7.8 Hz, 1H), 2.59 (s, 3H), 2.52 (dtd, J = 9.7, 6.2, 2.2 Hz, 1H), 2.42 (tdd, J = 10.3, 3.7, 1.9 Hz, 1H), 2.14 – 1.99 (m, 2H), 1.96 – 1.82 (m, 2H), 1.28 (s, 3H), 1.17 (s, 3H), 0.99 (d, J = 7.1 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 197.8, 155.2, 134.9, 128.6, 128.6, 47.9, 45.7, 45.0, 41.8, 39.2, 37.2, 34.9, 28.5, 26.6, 23.0, 20.9 ppm. **IR** (neat, cm^{-1}): 2900, 1680, 1603, 1356, 1263, 954. **HRMS** calcd. for (C$_{13}$H$_{13}$N$_2$O$_2$) [M+H]$^+$: 257.1900, found 257.1898.

3.5.6   Oxidative addition complex, Ni-1

Ni-1
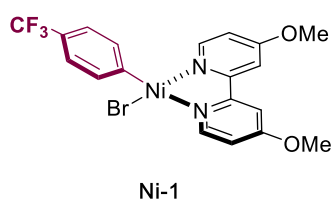
Following procedure described by our group,[XVI] in a nitrogen-filled glove box, a 50 mL round bottom flask containing a stirring bar was charged with Ni(COD)$_2$ (138 mg, 0.5 mmol, 1.0 equiv), 4,4'-di-methoxy-2,2'-pyridine **L2**(118 mg, 0.5 mmol, 1.0 equiv) and dry THF (5 mL) giving a dark purple mixture which was stirred for 20 h hours at 25 °C. 1-bromo-4-(trifluoromethyl)benzene (0.7 mL, 5 mmol, 10.0 equiv) was added and stirred for additional 45 min. Dry pentane (30 mL) was added to the deep red coloured mixture and filtered. The resulting precipitate was washed with pentane (3 x 10 mL) and dried under vacumm to afford Ni-1 as a yellow solid (185 mg, 74% yield). The product was used without further purification. The complex was stored in a nitrogen filled glove box at -35 ºC and showed to be stable in solid form. The product turned out to be highly insoluble in the vast majority of solvents used for NMR spectroscopy, obtaining in all cases broad signals. **¹H NMR**(300 MHz, CD$_2$Cl$_2$) δ = 9.14 (s, 1H), 7.79 (d, *J* = 7.6 Hz, 2H), 7.35 (s, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 6.99 (s, 2H), 6.69 (s, 1H), 4.00 (s, 3H), 3.94 (s, 3H) ppm. **¹⁹F NMR**(376 MHz, CD$_2$Cl$_2$) δ = -62.0 ppm. Spectroscopic data for **Ni-1** match those previously reported in the literature.[XVI]

3.5.7 *Attempted reactions with sp³ and sp-hybridized organic halides*
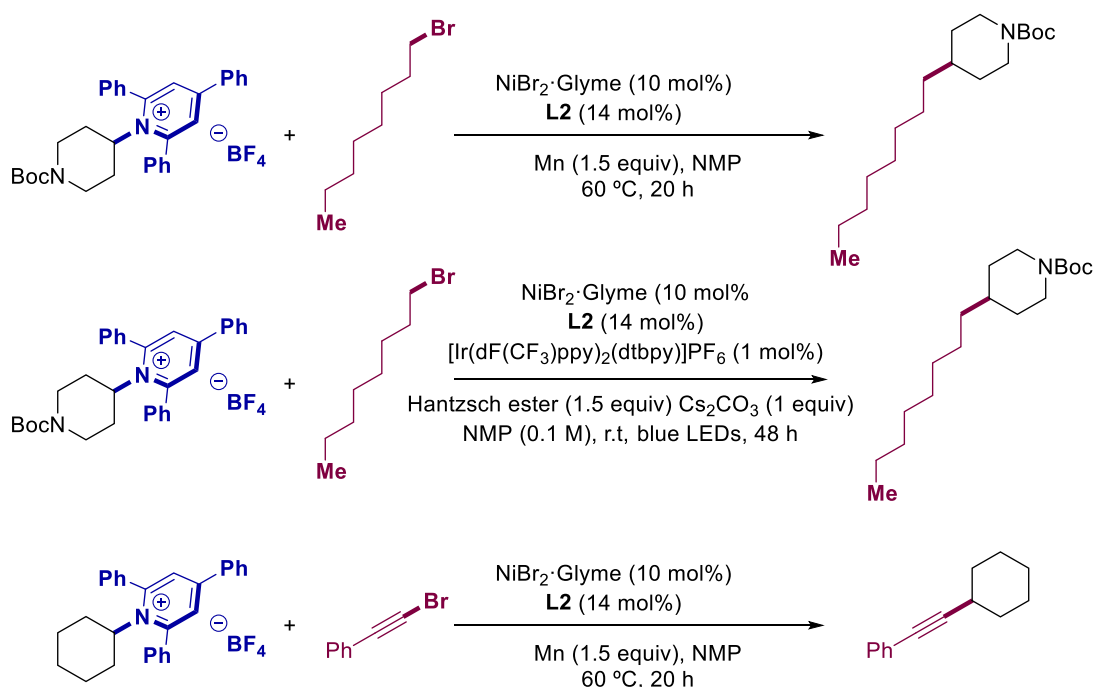
sp³ hybridized organic halides: In all cases (both using Mn or Ir photoredox catalysts), no conversion to product was observed for a protocol based on Ni/**L2**, recovering substantial amounts of the starting alkyl halide and with non-negligible amounts of homodimerization being observed in the crude mixtures.

sp hybridized organic halides: Traces of the targeted alkynylation product were observed in the crude mixtures, recovering the majority of the starting alkynyl bromide.

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3.5.8   Mechanistic studies

3.5.8.1.   Electrochemical studies

A) Experimental details

A.1 Cyclic Voltammetry

Cyclic voltammetry was conducted on a PARSTAT 2273 potentiometer (Princeton Applied Research) using a 3-electrode cell configuration. A glassy carbon working electrode was employed alongside a platinum flag counter electrode and a Ag/AgCl (KCl sat.) reference electrode. The distance between the working and reference electrode was 1cm. A ferrocene solution was used as an internal standard to determine the precise potential scale.[xx] The pyridiniums (**1a, 1m and 1m'**) were made up as 5 mM solutions in NMP (dry) along with 0.1 M supporting electrolyte (tetrabutylammonium hexafluorophosphate). The solution of Ni-complex (**Ni-1**) (10 mM) in NMP along with 0.1 M supporting electrolyte (tetrabutylammonium hexafluorophosphate) was made up in the glovebox to avoid exposure to air or moisture. Argon was passed through the samples for 10 minutes before taking any measurements and an Ar atmosphere was maintained for the duration to avoid the deleterious influence of oxygen reduction. Samples were examined at scan rates from 10 to 1000 mV s^{-1} depending on the substrate. For quasi-reversible species, a wide range of scan rates were tested to investigate the proposed fragmentation in more detail. In the situations where there is no apparent return oxidation (or reduction) peak, we have stated the E_p (the potential corresponding to the maximum reductive or oxidative current). For reversible or quasi-reversible cyclic voltammograms, we have determined the ratio between the (baseline corrected) peak currents (i_p) to provide a quantitative measure of the degree of reversibility.

A.2 Bulk electrolysis

Bulk electrolysis was conducted on a PARSTAT 2273 potentiometer using a 3-electrode cell configuration at room temperature and at 60 ºC (see scheme 1). The same electrodes were used as for CV experiments, namely a glassy carbon working electrode, platinum flag counter electrode and Ag/AgCl (KCl sat.) reference electrode. The solution of Ni-complex (**Ni-1**) (15 mg, 1.0 eq.) in NMP (10 mM) along with 0.1 M supporting electrolyte (tetrabutylammonium hexafluorophosphate) was made up in the glovebox to avoid exposure to air or moisture. After recording a CV of Ni-complex (**Ni-1**), cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1a**) (14 mg, 1.0 eq.) was added and stirred for 5 minutes. Decane was also added as an internal standard to allow quantification of the product. Another CV was taken of the **Ni-1/1a** mixture before starting the bulk electrolysis. A potential of -0.8 V vs Ag/AgCl was then applied for 22 h. Aliquots were analyzed by GC to determine the yield of **9**.

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Deaminative Arylation at sp^3 Carbon Centers
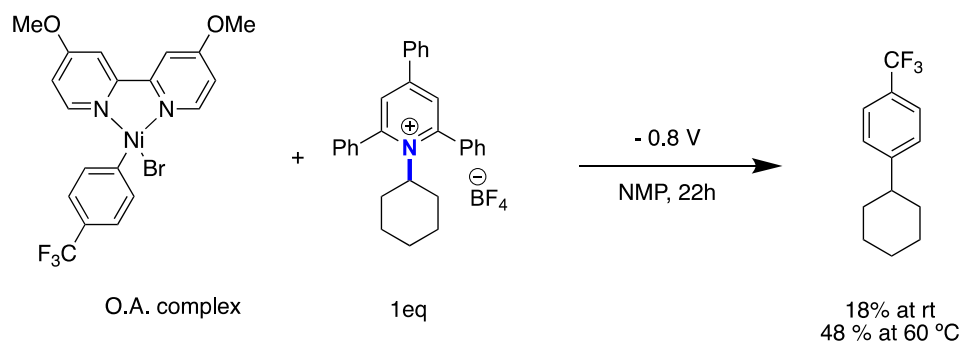
Scheme A.1.

B) Discussion

B.1 Cyclic Voltammetry of Pyridinium Precursors

The reduction profile of the pyridinium precursors investigated were reversible or quasi-reversible on the time scale of the CV experiments (Schemes 2-10). The secondary alkyl pyridinium precursor **1a** was the least reversible (illustrated by the ratio of the peak heights, $i_{pc}/i_{pa} \gg 1$) which was expected from the generation of a more stable secondary carbon-radical upon fragmentation. We expected to observe a difference in the reversibility of primary alkyl pyridiniums (**1m** and **1m'**[23]) considering that **1m** performs significantly better than **1m'** in the deaminative arylation reaction. Both, however, showed highly reversible CVs ($i_{pc}/i_{pa} \approx 1$) over all scan rates tested. The reduction potential of **1m** is higher than unsubstituted **1m'** ($E_{1/2}$ = -0.90 V and -0.77 V respectively) as expected from the electron donating substituents increasing the level of the LUMO. Interestingly, if the CVs are pushed to higher potentials, a second reduction profile is observed suggesting the formation of a radical dianion (Schemes 3, 6 and 9). Considering the extended aromatic moiety over which the charge can delocalize, such a scenario is feasible. Moreover, the stability of the pyridinium to fragmentation seems to decrease upon this second reduction in a more pronounced way for **1m** than unsubstituted **1m'** (i_{pc}/i_{pa} = 7 and 2 at 50 mVs^{-1} respectively). However, the second reduction potential of **1m** is -1.5 V which would be an uphill electron transfer from manganese (Mn/ Mn^{2+} = -1.4 V vs. Ag/ AgCl).[XXI] The deaminative arylation reactions with primary pyridiniums give significantly higher yields

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at 60°C than at rt and therefore cyclic voltammetry was also carried out at this elevated temperature (Schemes 4, 7 and 10). Even at 60ºC, however, primary pyridiniums still exhibited highly reversible CVs (Table 3) with **1m** being slightly less reversible than **1m´** (i_{pc}/i_{pa} = 1.5 and 1.2 at 50 mVs^{-1} respectively). In contrast, secondary pyridinium **1a** proved significantly less reversible at 60ºC with completely irreversible CVs observed until 200 mVs^{-1} (Scheme 10). These results indicate that the higher temperature aids the reaction by promoting fragmentation of reduced pyridiniums but this is still thought to be thermodynamically challenging in the case of primary pyridiniums **1m** and **1m´**.

B.2 Cyclic Voltammetry of Ni-complex **Ni-1**

The Ni(II)-complex (**Ni-1)** exhibited rather complex electrochemical behavior, but comparable to that displayed by related Ni-complexes[XVII]. A first partially reversible reduction (E_{R1}) is observed at -1.0 V (vs. Ag/AgCl) which is followed by 2 more significant reductions (E_{R1} and E_{R2}) at -1.4 V and -1.5 V respectively (Scheme 11). Further peaks are observed if the CV is pushed to higher potentials, but the origin of these reductions can only be speculated and they are far out the range of reduction by manganese (Mn/ Mn^{2+} = -1.4 V vs. Ag/AgCl). By using a ferrocene solution as an internal standard, these values have been standardized to permit direct comparison with the work of Klein *et. al.[XVII]*. It has been shown by spectroscopic methods and quantum chemical calculations that the LUMO of Ni-complexes (such as **Ni-1**) baring α-diimine ligands is localized in the α-diimine π* levels[XVIII]. This indicates that the reduction of these complexes is largely ligand centered and will be highly dependent on the type and substitution of the α-diimine bound. Klein observed an irreversible reduction of [(4,4´-Mebpy)Ni(Mes)Br] at -1.85 V (vs. Fc/Fc$^+$ at 100 mVs^{-1}) which was followed by 2 more reductions at -2.00 V (reversible) and -2.61 V (irreversible). These latter peaks were proposed to be a result of *in situ* generated Ni-species (solvated and Ni-Ni dimers) following the initial reduction and subsequent loss of bromide. In our case, the more basic 4,4´-MeObpy should result in a higher potential, which is in better agreement with the second reduction, E_{R2} at -2.00 V (vs. Fc/Fc$^+$) than the initial shoulder, E_{R1} at -1.62 V (vs. Fc/Fc$^+$). Moreover, on the back scan, oxidation peaks (E_{O1} and E_{O2}) are observed only when E_{R2} has been reached but not E_{R1}. Klein observed similar peaks for [(4,4´-Mebpy)Ni(Mes)Br] and speculated that E_{O1} (-1.42 V Fc/Fc$^+$) resulted from oxidation of the solvated Ni(I) species formed *in situ* after reduction and bromide loss. Notably, this suggests that [(N^N)Ni(Ar)solv] complexes are relatively weak reductants. In our case, E_{O1} = -1.35 V vs. Fc/Fc$^+$ or -0.73 V vs. Ag/AgCl which is essentially the same as secondary pyridinium **1a** and out the range of primary pyridinium **1m**. In contrast, the reduction of pyridinium precursors by manganese (Mn/ Mn^{2+} = -1.4 V vs. Ag/AgCl) would have a gain of 0.4-0.7 V and thus seems the more likely scenario. The origin of E_{R1} is still uncertain but may result from the reduction of the electron-poor *p*-CF$_3$ substituted phenyl. Further irreversible oxidations (E_{O3} and E_{O4}) are observed at more positive potentials which are independent of any previous reduction and can be assigned to Ni(II)/Ni(III) couples.

B.3 Bulk electrolysis

To investigate whether the arylated product is formed by alkyl radical addition to Ni(II)-complex **Ni-1** followed by reductive elimination, a bulk electrolysis was first performed on **Ni-1** and pyridinium **1a** (1:1) at room temperature. Before starting the electrolysis, a CV was taken of Ni-complex **Ni-1** before and after addition of **1a** (Scheme 12) but no noticeable change except the expected combination of the two reduction profiles was observed. A constant potential of -0.8 V was then applied to reduce **1a** and generate the cyclohexyl radical whilst avoiding reduction of **Ni-1** and the formation of any Ni(I)-species. Aliquots were taken at 2 and 6 h internals did not show any coupled product but after 22 h 18% of **9** was detected by GC analysis. Although the ability to form **9** was exciting from a mechanistic standpoint, we were disappointed at the very sluggish reaction. As elevated temperature is required to make the deaminative arylation go to completion in 24 h, a repeat electrolysis experiment at 60 °C was performed. Again CVs taken before starting showed no noticeable change except the expected combination of the **Ni-1** and pyridinium **1a** reduction profiles, neither at rt nor 60 °C (Scheme 13). Pleasingly, after applying a constant potential of -0.8 V for 22 h, 48% of **9** was observed by GC analysis. CVs taken after the experiment showed no sign of **1a** or seemingly **Ni-1** with new reduction peaks observed that presumably correspond to (unidentified) Ni-species.

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3.5.8.2. Electrochemical potentials

Table 1: First reduction of Pyridinium precursors at r.t.
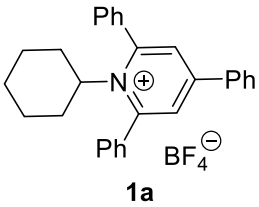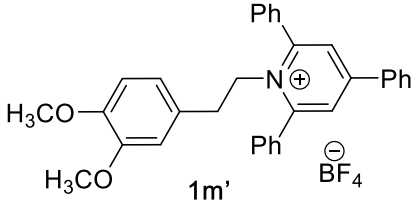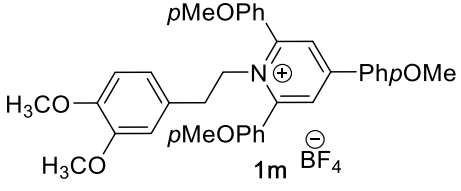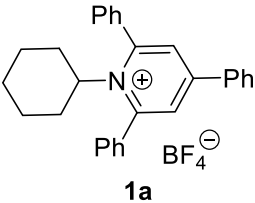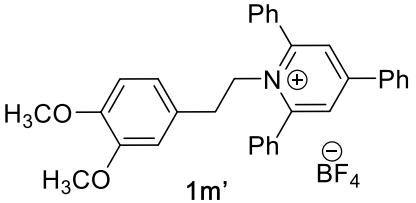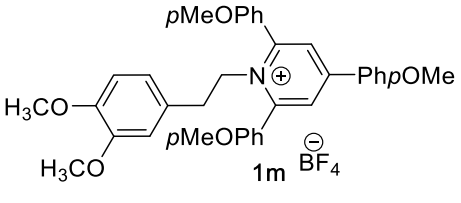
Substrate	Scan rate (mV s^{-1})	E$_{1/2}$ (V) vs. Ag/ AgCl	E$_{1/2}$ (V) vs. Fc/ Fc$^+$	Profile	i$_{pc}$/i$_{pa}$
	10	-0.72	-1.34	Quasi-reversible	3.69
	20	-0.73	-1.35	Quasi-reversible	3.09
	50	-0.74	-1.35	Quasi-reversible	2.00
1a	100	-0.74	-1.35	Quasi-reversible	1.54
	500	-0.74	-1.36	Reversible	1.22
	1000	-0.74	-1.36	Reversible	1.09
	50	-0.77	-1.39	Reversible	1.01
	100	-0.77	-1.39	Reversible	1.02
	500	-0.77	-1.39	Reversible	1.06
1m'	1000	-0.78	-1.40	Reversible	1.26
	10	-0.89	-1.51	Reversible	1.24
	50	-0.89	-1.51	Reversible	1.14
	100	-0.90	-1.52	Reversible	1.07
	500	-0.91	-1.53	Reversible	1.06
1m	1000	-0.91	-1.52	Reversible	1.25

Table 2: First and second reductions of Pyridinium precursors at r.t.

Substrate	Scan rate (mV s⁻¹)	First $E_{1/2}$ (V) vs. Ag/ AgCl	Profile	i_{pc}/i_{pa}	Second $E_{1/2}$ (V) vs. Ag/ AgCl	Profile
1a	20	-0.72	Quasi-reversible	4.2	-1.21	Quasi-reversible
	50	-0.73	Quasi-reversible	3.7	-1.22	Quasi-reversible
	100	-0.75	Quasi-reversible	2.7	-1.24	Quasi-reversible
	500	-0.74	Quasi-reversible	1.5	-1.25	Quasi-reversible
1m'	50	-0.77	Quasi-reversible	2.0	-1.39	Quasi-reversible
	100	-0.77	Quasi-reversible	1.8	-1.39	Quasi-reversible
	500	-0.77	Quasi-reversible	1.5	-1.39	Quasi-reversible
1m	10	-0.89	Quasi-reversible	7.0	-1.51	Quasi-reversible
	50	-0.89	Quasi-reversible	6.3	-1.51	Quasi-reversible
	100	-0.90	Quasi-reversible	5.2	-1.52	Quasi-reversible

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Table 3: First reduction of Pyridinium precursors at 60 °C.
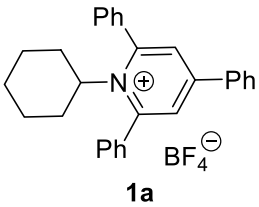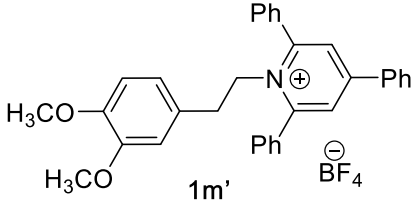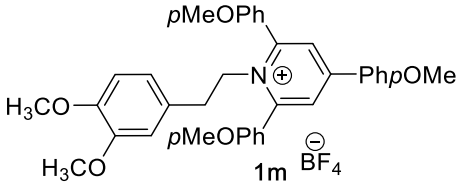
Substrate	Scan rate (mV s^{-1})	E$_{1/2}$ (V) vs. Fc/ Fc$^+$	Profile	i$_{pc}$/i$_{pa}$
	100	-1.31	Irreversible	-
	200	-1.25	Quasi-reversible	4.52
1a	500	-1.28	Quasi-reversible	3.81
	1000	-1.29	Quasi-reversible	2.67
	2000	-1.29	Quasi-reversible	1.85
	50	-1.34	Reversible	1.21
	100	-1.34	Reversible	1.19
1m'	500	-1.34	Reversible	1.15
	1000	-1.34	Reversible	1.15
	50	-1.44	Reversible	1.48
	100	-1.45	Reversible	1.40
1m	500	-1.45	Reversible	1.20
	1000	-1.45	Reversible	1.16

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Table 4: Reduction and oxidation potentials of **Ni-1**

Peak	$E_{1/2}$ or E_p (V) vs. Ag/AgCl	$E_{1/2}$ or E_p (V) vs. Fc/Fc⁺	Profile
E_{R1}	-1.0	-1.62	Quasi-reversible
E_{R2}	-1.37	-2.00	Irreversible
E_{R3}	-1.49	-2.11	Quasi-reversible
E_{R4}	-1.78	-2.40	Quasi-reversible
E_{R5}	-2.22	-2.84	Irreversible
E_{O1}	-0.73	-1.35	Irreversible
E_{O2}	-0.01	-0.63	Irreversible
E_{O3}	0.48	-0.14	Irreversible
E_{O4}	0.91	0.30	Irreversible

3.5.8.3. *Cyclic voltammograms*
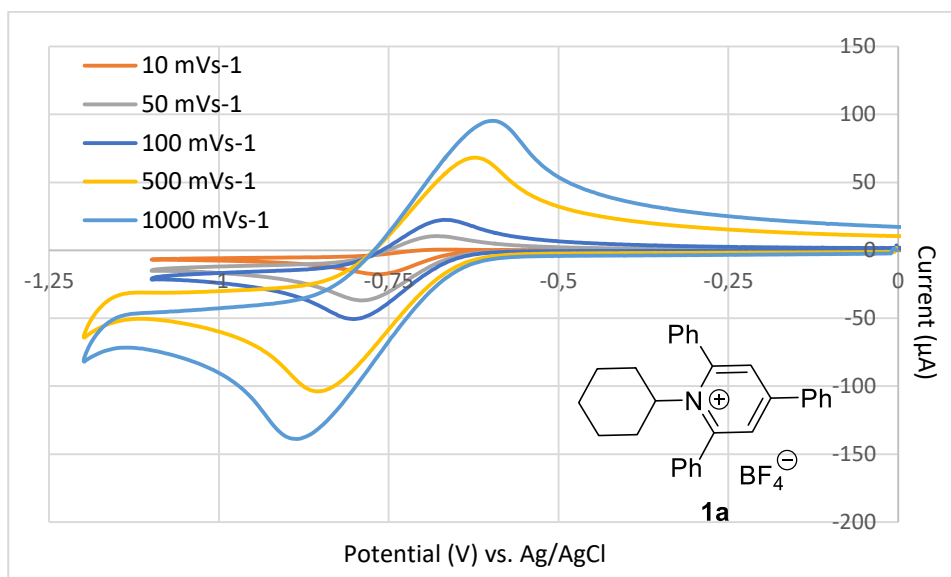
Scheme 2: Pyridinium **1a** short scan range at r.t
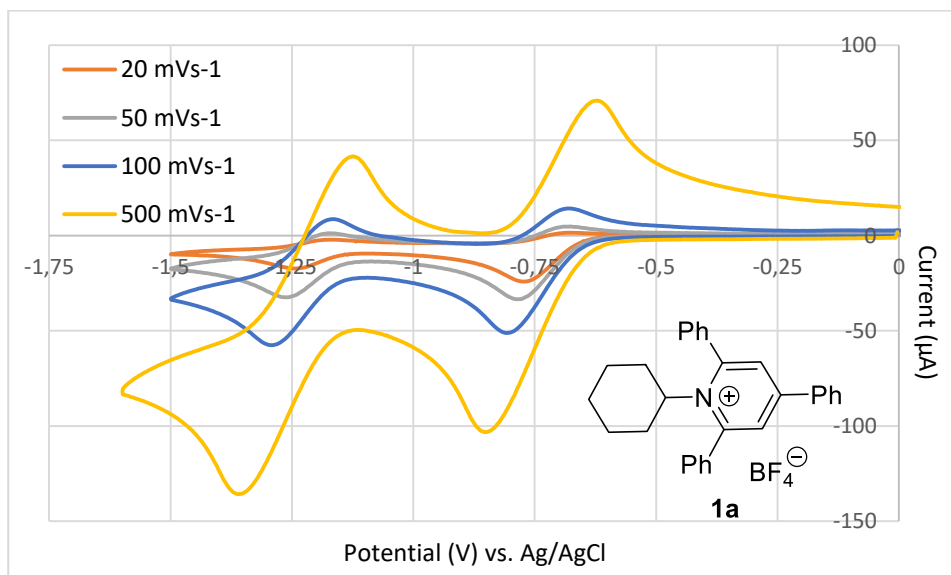
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Scheme 3: Pyridinium **1a** long scan range at r.t
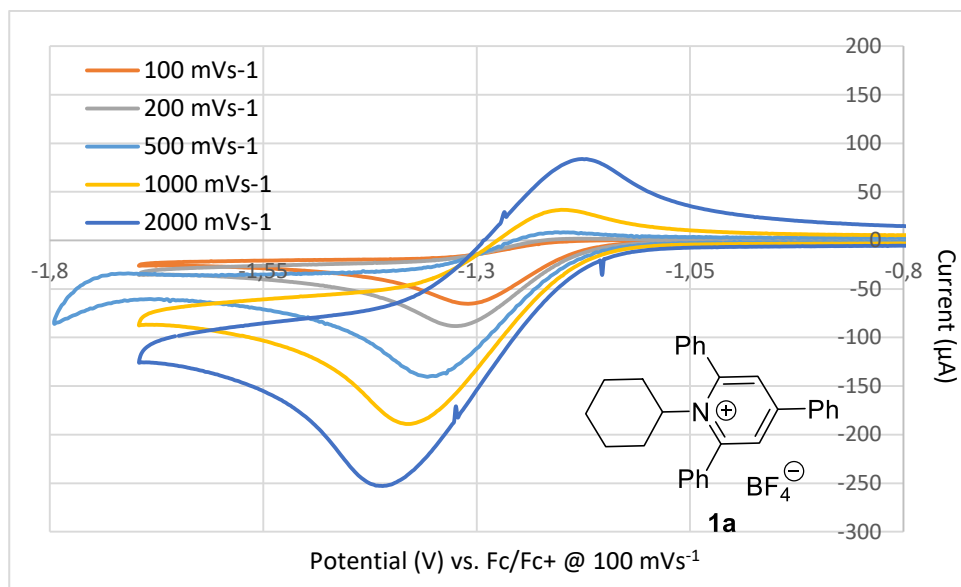
Scheme 4: Pyridinium **1a** short scan range at 60 ºC
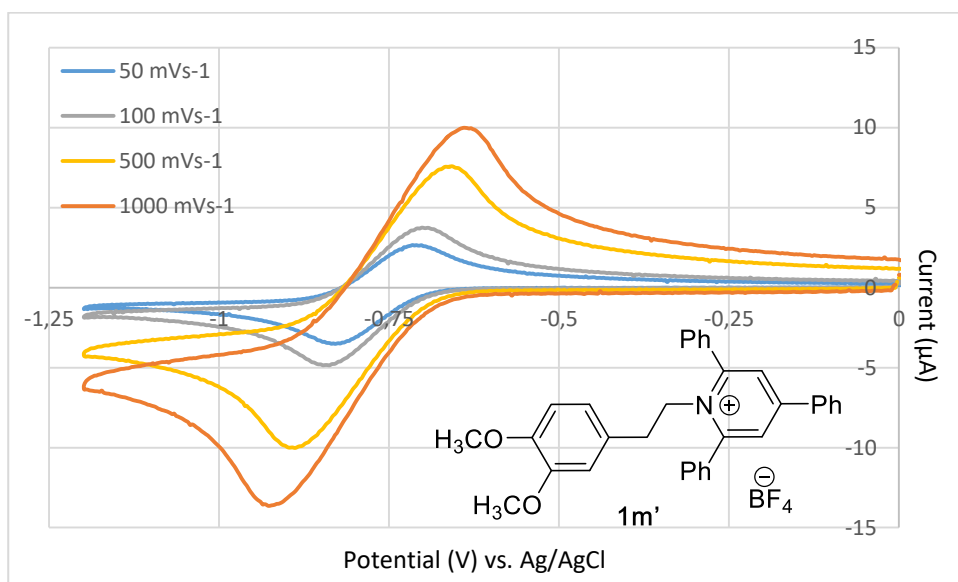
Scheme 5: Pyridinium **1m´** short scan range at r.t

Deaminative Arylation at sp³ Carbon Centers
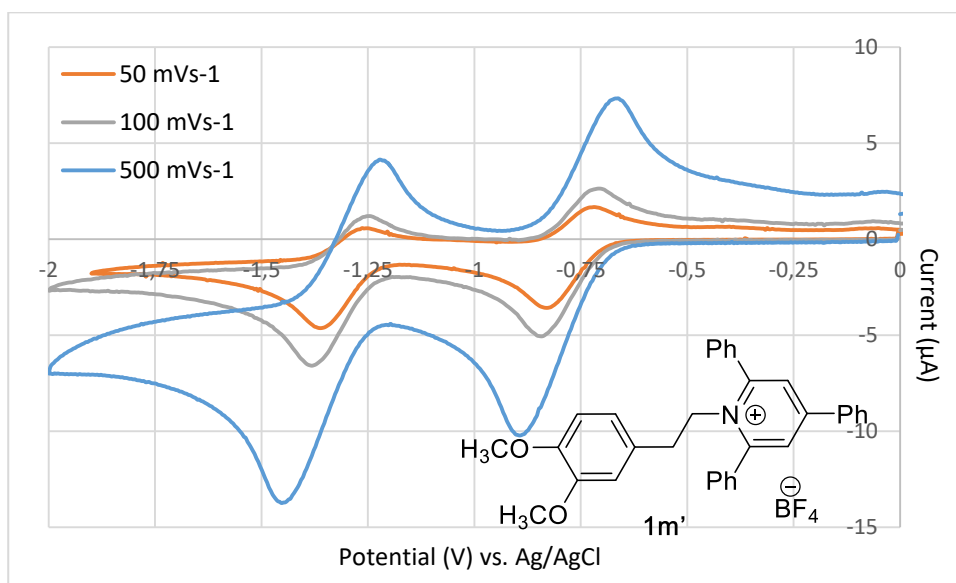
Scheme 6: Pyridinium **1m´** long scan range at r.t
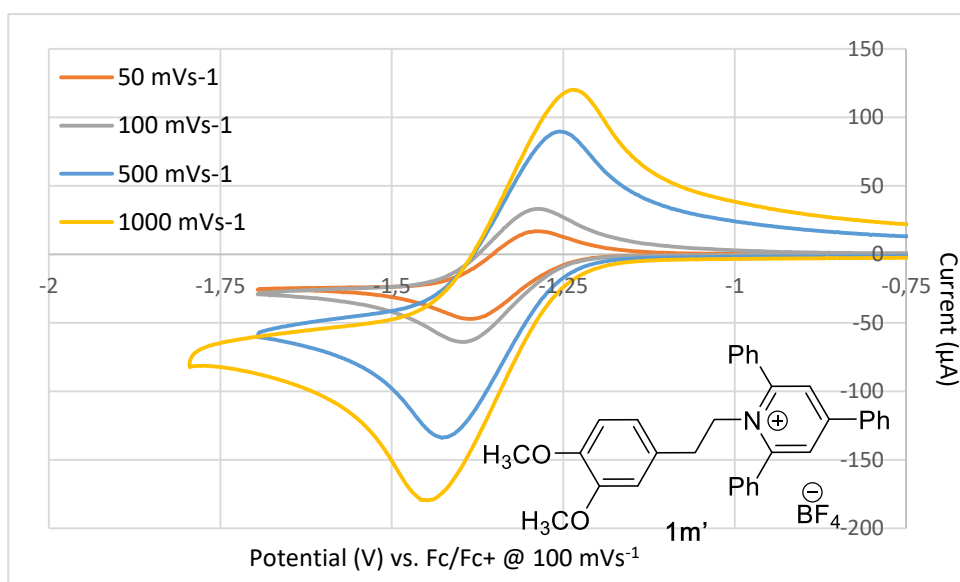
Scheme 7: Pyridinium **1m´** short scan range at 60 ºC
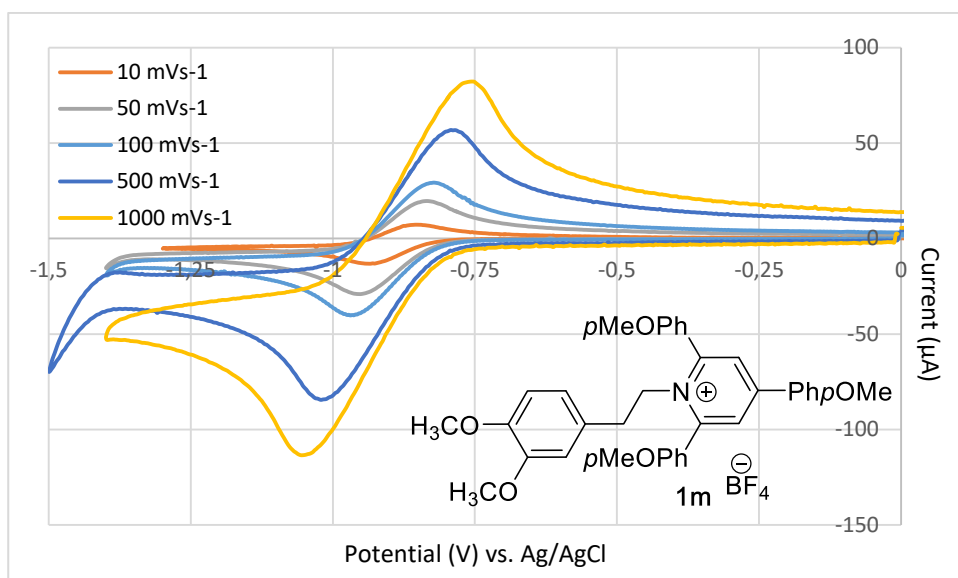
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Scheme 8: Pyridinium **1m** short scan range at r.t
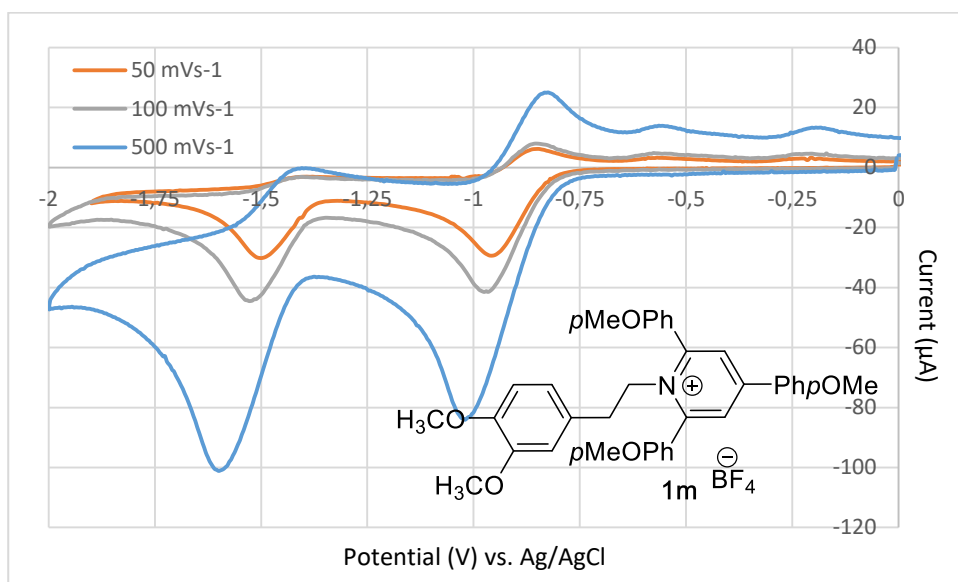
Scheme 9: Pyridinium **1m** long scan range at r.t

Deaminative Arylation at sp³ Carbon Centers
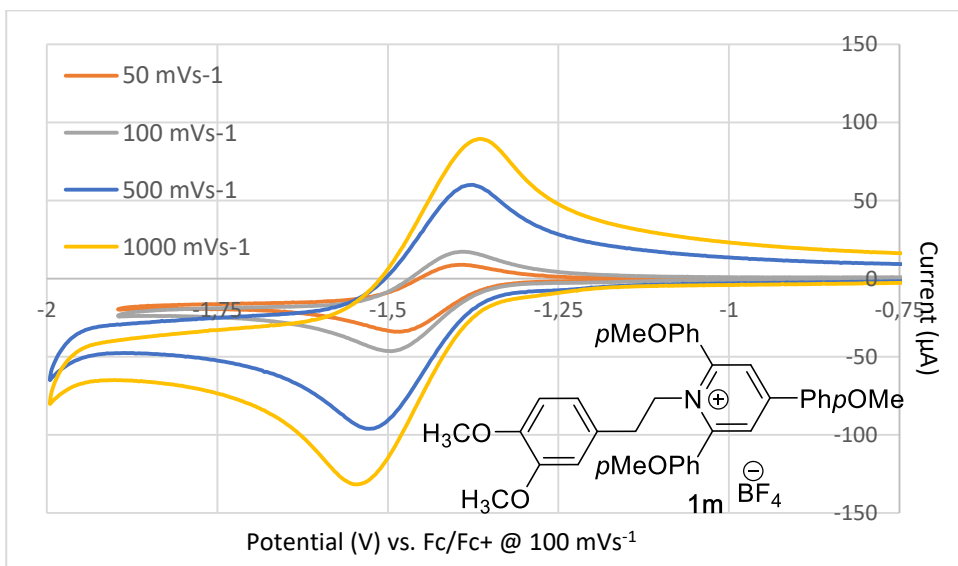
Scheme 10: Pyridinium **1m** short scan range at 60 ºC
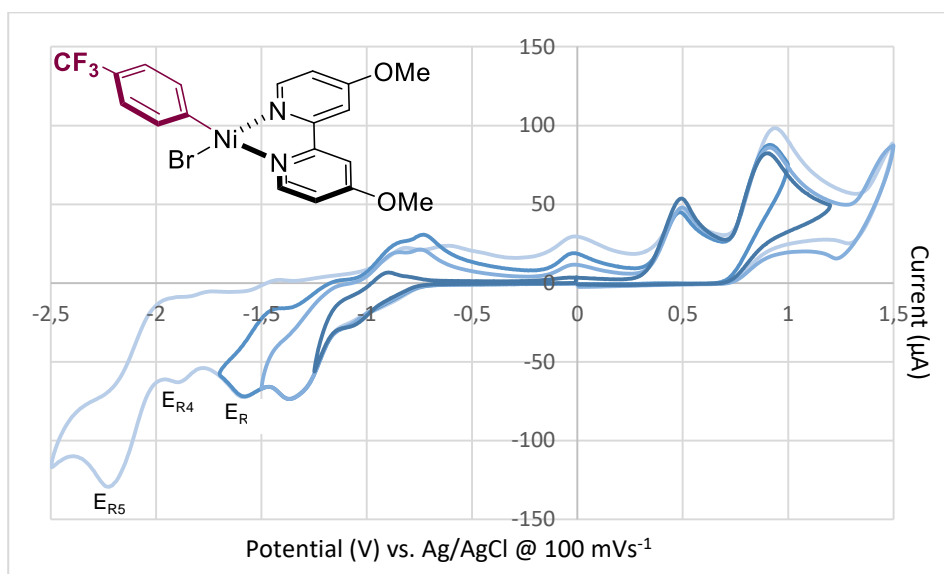
Scheme 11: Ni-complex **Ni-1**
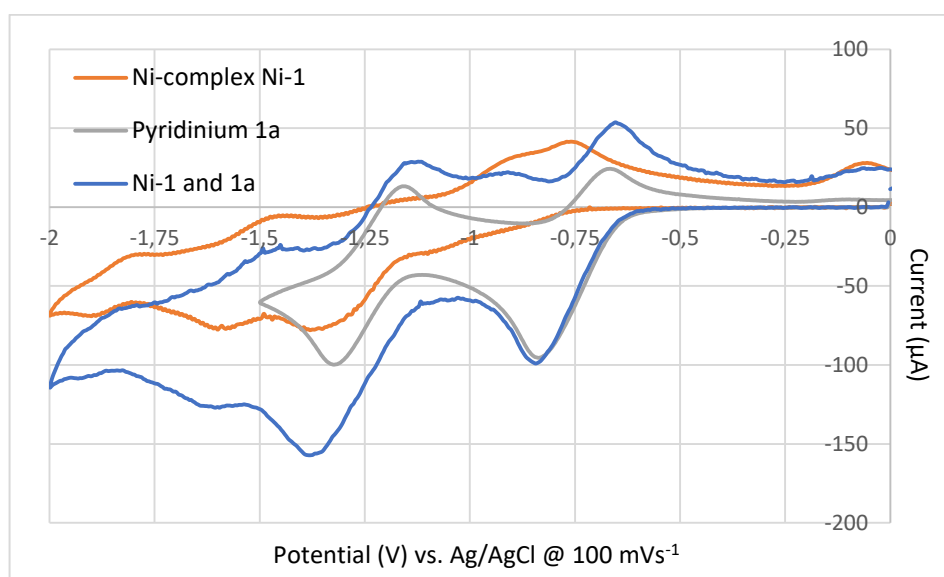
Scheme 12: CVs recorded before room temperature bulk electrolysis
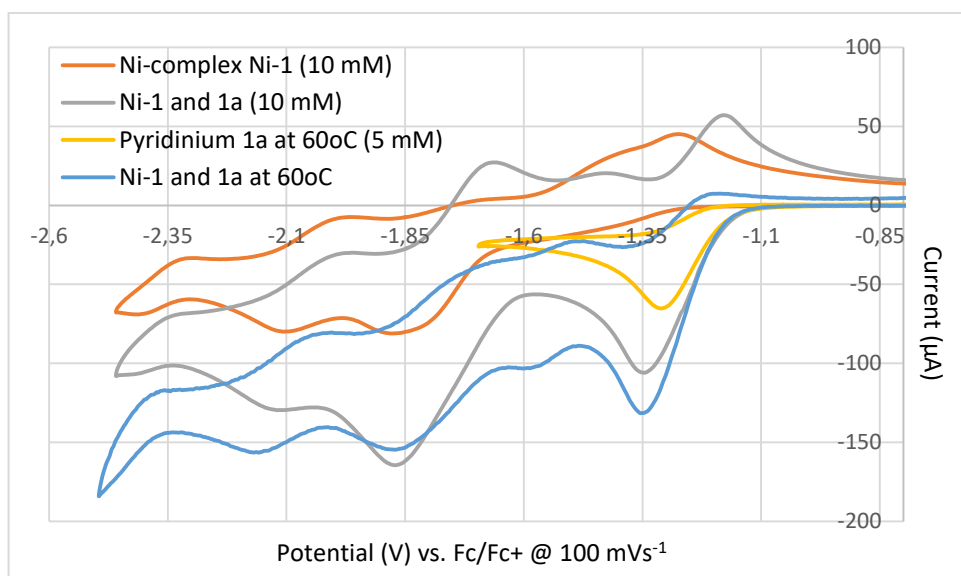
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Scheme 13: CVs recorded before 60 ºC bulk electrolysis
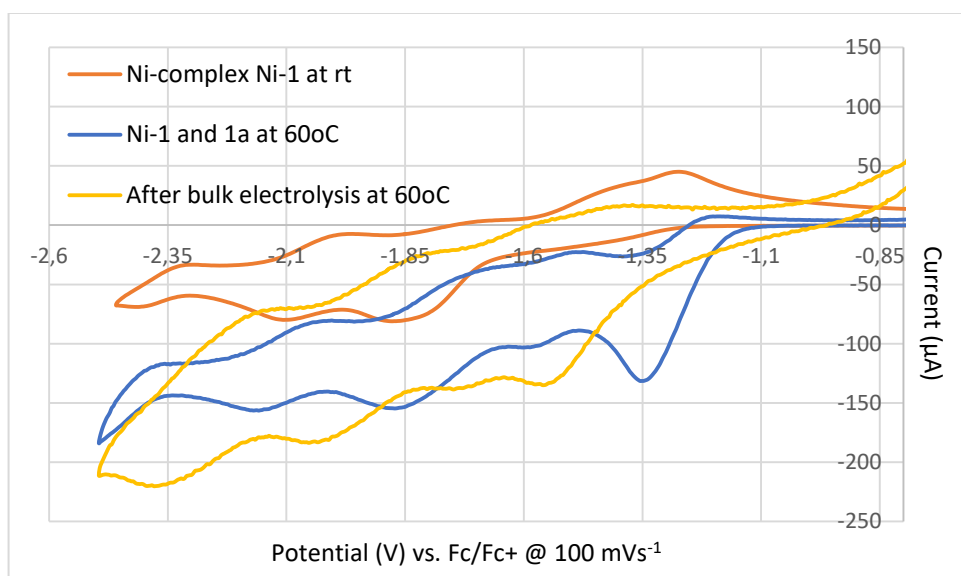
Scheme 14: Comparison of CVs before and after 60 ºC bulk electrolysis

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3.5.8.4. *Radical trap experiments with TEMPO*

40
80% ¹H-NMR yield
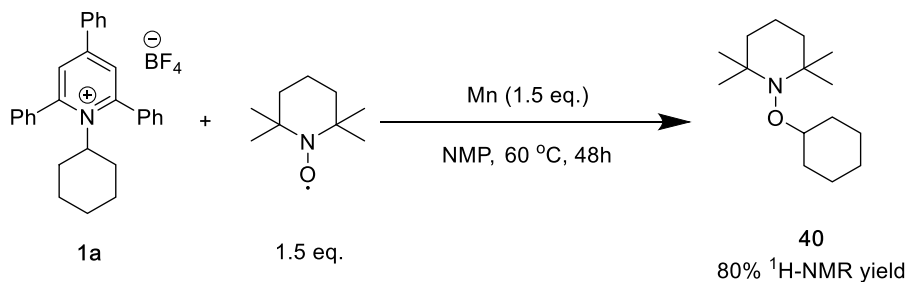
Entry	Mn (equiv)	Yield (%)
1	1.5	80
2	0	0

Procedure for the radical trap experiment with TEMPO: To an oven-dried 8 mL screw-cap test tube containing a stirring bar was charged with 1-cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1a**) (23.8 mg, 0.05 mmol). The test tube was introduced in an argon-filled glovebox where Mn (4.2 mg, 0.075 mmol) and TEMPO (11.7 mg, 0.075 mmol) was added, followed by the addition of NMP (0.5 mL, 0.1 M). The tube was then sealed firmly and taken out of the glovebox. The resulting reaction mixture was heated to 60 °C and stirred vigorously for 48 h. After the reaction was finished, the reaction mixture was extracted with ethyl acetate and water (3 times). Then the organic layers were combined and washed with water and brine, dried over MgSO₄, concentrated under vacuum. Mesitylene (7 μL, 0.05 mmol) was added as an internal standard and the yield of known TEMPO adduct (**40**) was determined to be 80% by analysis of the ¹H NMR spectrum of the crude reaction mixture.

3
1 % yield by GC-FID

40
89% ¹H-NMR yield
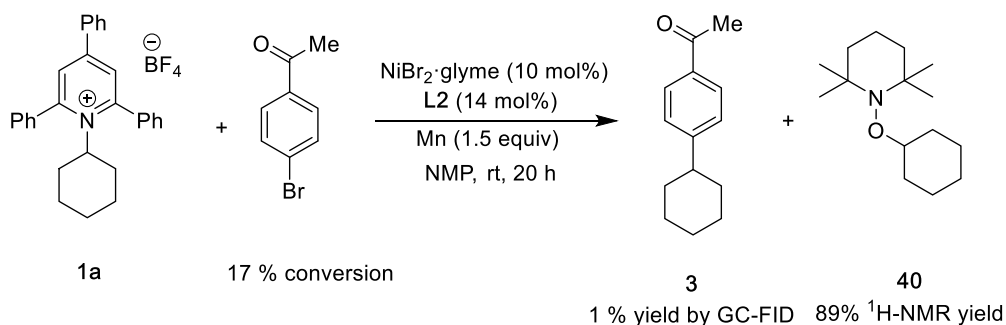
Inhibition of Ni-catalyze deaminative arylation in the presence of TEMPO: To an oven-dried 8 mL screw-cap test tube containing a stirring bar was charged with methyl 4-bromobenzoate (21.5 mg, 0.10 mmol), 1-cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1a**) (66.9 mg, 0.14 mmol). The test tube was introduced in an argon-filled glovebox where Mn (8.4 mg, 1.5 eq.), TEMPO (15.6 mg, 0.10 mmol, 1eq.), 0.2 mL precatalyst mixture of NiBr₂·glyme (3.0 mg, 10 mol%) with 4,4'-

dimethoxy-2,2'-bipyridine (**L2**, 3.0 mg, 14 mol%) in NMP were added, followed by the addition of NMP (0.8 mL, 0.1 M). The tube was then sealed firmly and taken out of the glovebox. The resulting reaction mixture was stirred vigorously for 20 h. After the reaction was finished, the reaction mixture was extracted with ethyl acetate and water (3 times). Then the organic layers were combined and washed with water and brine, dried over MgSO₄, concentrated under vacuum. Mesitylene (14 μL, 0.1 mmol) was added as an internal standard and the yield of known TEMPO adduct (**40**)[XIX] was determined to be 89% by analysis of the ¹H NMR spectrum of the crude reaction mixture and 1 % yield formation of **3** by GC-FID.

3.5.8.5.   *Stoichiometric experiment with Ni(COD)₂*

1a
< 5% conversion

< 2 %   not detected
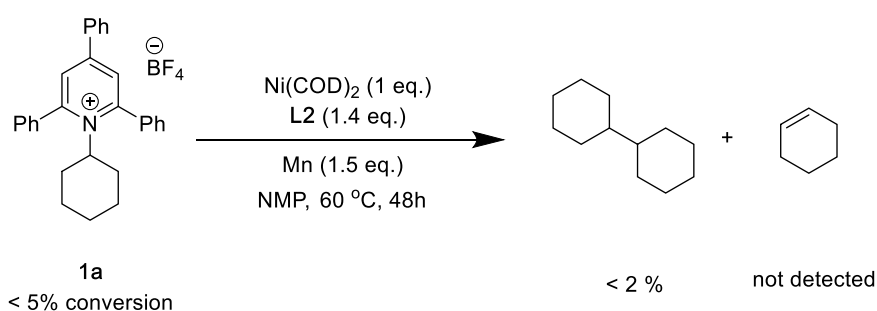
To an oven-dried 8 mL screw-cap test tube containing a stirring bar was charged with cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**1a**) (23.8 mg, 0.05 mmol), 4,4'-dimethoxy-2,2'-bipyridine (**L2**, 15.1 mg, 0.07 mmol, 1.4 equiv). The test tube was introduced in an argon-filled glovebox where Mn (4.2 mg, 1.5 equiv) and Ni(COD)₂ (13.8 mg, 0.05 mmol, 1 equiv) were added, followed by the addition of NMP (0.5 mL, 0.1 M). The tube was then sealed firmly and taken out of the glovebox. The resulting reaction mixture was stirred vigorously for 48 h. After that the reaction was stopped, ethyl acetate was added and measured by GC-FID obtaining less than 2% homodimerization product and not even traces of alkene.

3.5.8.6.   *Deaminative arylation of enantiopure secondary alkyl pyridinium salts*

1u   **41**
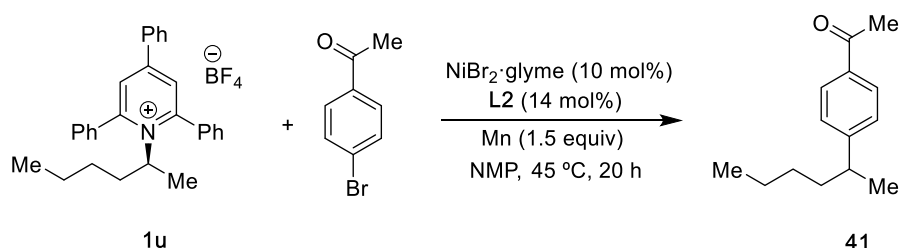
1-(4-(hexan-2-yl)phenyl)ethan-1-one   (41). Following **General conditions C**, 1-(4-bromophenyl)ethan-1-one (19.9 mg, 0.10 mmol) and 1-(hexan-2-yl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate **(1u)** (73.8 mg, 0.14 mmol) were used at 45 ºC, affording the title compound as a yellow oil (13 mg, 64% yield) by using Hexane/ *tert*-butyl-methyl ether (95/5) as eluent. The

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enantiomeric excess was determined to be racemic by chiral UPC2 analysis (CHIRALPAK IG, 2 mL/min, Isocratic CO_2/ACN 90:10, 2000 psi, λ=248 nm); t_{R1} = 2.27 min, t_{R2} = 2.66 min. **¹H NMR** (400 MHz, CDCl₃) δ = 7.90 – 7.88 (m, 2H), 7.28 – 7.26 (m, 2H), 2.74 (q, *J* = 7.1 Hz, 1H), 2.58 (s, 3H), 1.61 – 1.52 (m, 2H), 1.34 – 1.16 (m, 6H), 1.15 – 1.06 (m, 1H), 0.85 (t, *J* = 7.2 Hz, 3H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 197.9, 153.8, 135.1, 128.5, 127.2, 40.1, 37.8, 29.8, 26.5, 22.7, 22.0, 14.0 ppm. **IR** (neat, cm⁻¹): 2956, 2924, 2856, 1680, 1605, 1356, 1264, 954. **HRMS** calcd. for ($C_{14}H_{21}O$) [M+H]⁺: 205.1587, found 205.1579.
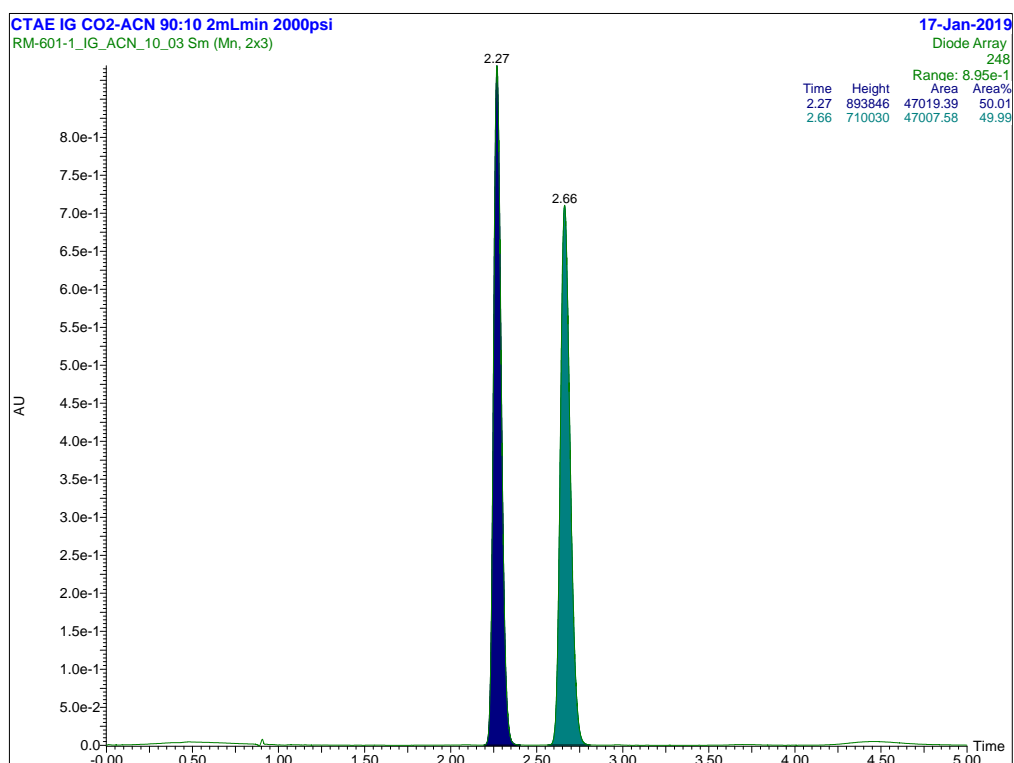
3.5.8.7.   *Radical clock experiment*
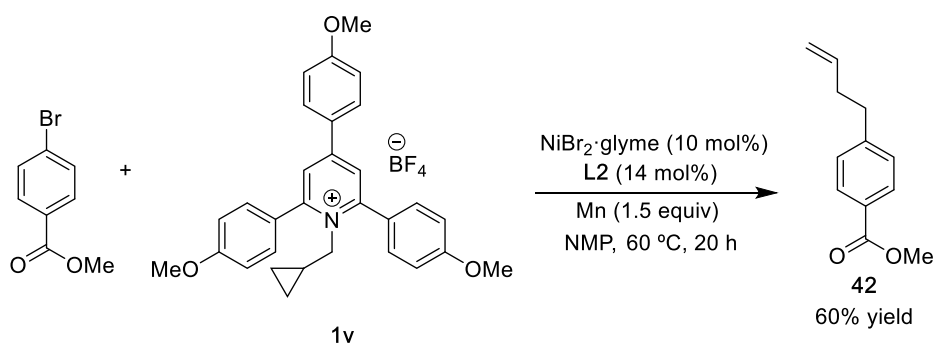
1-(4-(hexan-2-yl)phenyl)ethan-1-one (41). Following **General conditions C**, methyl 4-bromobenzoate (21.5 mg, 0.10 mmol) and 1-(cyclopropylmethyl)-2,4,6-tris(4-methoxyphenyl)pyridin-1-ium tetrafluoroborate **(1v)** (75.5 mg, 0.14 mmol) were used at 60 ºC,

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Functionalization of Strong Sigma Bonds by Nickel and Tungsten Catalysis
Raúl Martín Montero

Deaminative Arylation at *sp³* Carbon Centers

affording the title compound as a yellow oil (11.4 mg, 60% yield) by using Hexane/ *tert*-butyl-methyl ether (95/5) as eluent. **¹H NMR** (400 MHz, CDCl₃) δ = 8.07 − 7.85 (m, 2H), 7.35 − 7.17 (m, 3H), 5.83 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.11 − 4.87 (m, 2H), 3.90 (s, 3H), 2.76 (dd, J = 8.8, 6.7 Hz, 2H), 2.45 − 2.29 (m, 2H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 167.1, 147.3, 137.5, 129.6, 128.5, 127.8, 115.3, 77.0, 52.0, 35.3, 35.0 ppm. Spectroscopic data for **42** match those previously reported in the literature.[XXII]

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3.5.9   References of experimental procedures.

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XX) An oxidation potential of 0.62 V was measured for ferrocene solution in NMP (2mM). This provided a conversion factor of -0.62 V to convert between Ag/AgCl and Fc/Fc$^+$ reference electrodes.

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3.5.10 X-Ray Crystallography data for Ni(II) Complex Ni-1
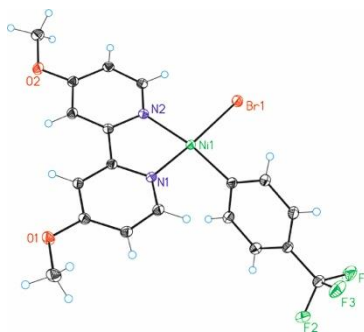
X-ray quality crystals were obtained from a saturated solution of **Ni-1** in toluene and drops of pentane were slowly added, and left it in glove box few days. A CIF file is available as a separate Supporting Information file.

Table 1. Crystal data and structure refinement for **Ni-1**.

_____

Identification code	**Ni-1**
Empirical formula	C19 H16 Br F3 N2 Ni O2
Formula weight	499.96
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 10.4282(2)Å a= 90°.
	b = 11.9745(2)Å b = 96.161(2)°.
	c = 14.7268(3)Å g = 90°.
Volume	1828.35(6) Å³
Z	4
Density (calculated)	1.816 Mg/m³
Absorption coefficient	3.294 mm⁻¹
F(000)	1000
Crystal size	? x ? x ? mm³

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Theta range for data collection	2.197 to 37.420°.
Index ranges	-16<=h<=17,-20<=k<=19,-25<=l<=19
Reflections collected	26930
Independent reflections	9139[R(int) = 0.0241]
Completeness to theta =37.420°	95.4%
Absorption correction	Multi-scan
Max. and min. transmission	0.880 and 0.677
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9139/ 0/ 317
Goodness-of-fit on F^2	1.008
Final R indices [I>2sigma(I)]	R1 = 0.0291, wR2 = 0.0639
R indices (all data)	R1 = 0.0474, wR2 = 0.0688
Largest diff. peak and hole	0.777 and -0.503 e.$Å^{-3}$

Table 2. Bond lengths [Å] and angles [°] for **Ni-1**.

_____

Bond lengths----

Br1-Ni1	2.30613(19)
N1-C1	1.3437(15)
N1-C5	1.3614(15)
N1-Ni1	1.9142(10)
Ni1-C13	1.8808(12)
Ni1-N2	1.9805(10)
O1-C3	1.3450(14)
O1-C11	1.4430(15)
C1-C2	1.3834(16)
C1-H1	0.945(15)
F1-C19	1.3517(16)

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O2-C8	1.3407(14)
O2-C12	1.4384(15)
N2-C10	1.3414(14)
N2-C6	1.3563(15)
C2-C3	1.3918(17)
C2-H2	0.898(18)
F2-C19	1.3408(15)
F3-C19	1.3413(17)
C3-C4	1.4001(16)
C6-C7	1.3806(16)
C6-C5	1.4767(15)
C5-C4	1.3795(16)
C4-H4	0.901(18)
C7-C8	1.3962(16)
C7-H7	0.920(19)
C8-C9	1.3942(17)
C9-C10	1.3901(17)
C9-H9	0.902(17)
C10-H10	0.888(18)
C11-H111	0.950(16)
C11-H112	0.973(17)
C11-H113	0.91(2)
C12-H121	0.99(2)
C12-H122	1.026(19)
C12-H123	0.972(18)
C13-C18	1.3984(17)
C13-C14	1.4025(17)

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C14-C15	1.3896(17)
C14-H14	0.942(18)
C15-C16	1.3865(18)
C15-H15	0.956(16)
C16-C17	1.3915(17)
C16-C19	1.4904(17)
C17-C18	1.3926(17)
C17-H17	0.957(18)
C18-H18	0.928(18)

Angles----------

C1-N1-C5	117.02(10)
C1-N1-Ni1	126.86(8)
C5-N1-Ni1	115.75(7)
C13-Ni1-N1	92.67(5)
C13-Ni1-N2	168.48(5)
N1-Ni1-N2	82.74(4)
C13-Ni1-Br1	88.93(4)
N1-Ni1-Br1	169.12(3)
N2-Ni1-Br1	97.57(3)
C3-O1-C11	117.16(10)
N1-C1-C2	124.00(11)
N1-C1-H1	117.6(11)
C2-C1-H1	118.4(11)
C8-O2-C12	117.78(10)
C10-N2-C6	117.37(10)
C10-N2-Ni1	128.69(8)
C6-N2-Ni1	113.76(7)

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C1-C2-C3	118.42(11)
C1-C2-H2	121.4(11)
C3-C2-H2	120.2(11)
O1-C3-C2	125.05(10)
O1-C3-C4	116.41(10)
C2-C3-C4	118.54(10)
N2-C6-C7	122.85(10)
N2-C6-C5	113.71(10)
C7-C6-C5	123.43(10)
N1-C5-C4	122.79(10)
N1-C5-C6	113.82(10)
C4-C5-C6	123.38(10)
C5-C4-C3	119.13(11)
C5-C4-H4	120.9(11)
C3-C4-H4	120.0(11)
C6-C7-C8	119.02(11)
C6-C7-H7	119.8(12)
C8-C7-H7	121.1(12)
O2-C8-C9	125.57(11)
O2-C8-C7	115.53(10)
C9-C8-C7	118.90(11)
C10-C9-C8	118.02(10)
C10-C9-H9	118.6(11)
C8-C9-H9	123.3(11)
N2-C10-C9	123.85(11)
N2-C10-H10	115.3(12)
C9-C10-H10	120.8(12)

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O1-C11-H111	110.8(10)
O1-C11-H112	111.5(10)
H111-C11-H112	111.2(14)
O1-C11-H113	107.1(12)
H111-C11-H113	109.2(16)
H112-C11-H113	106.8(16)
O2-C12-H121	108.8(12)
O2-C12-H122	112.2(10)
H121-C12-H122	109.8(15)
O2-C12-H123	110.6(11)
H121-C12-H123	106.9(15)
H122-C12-H123	108.4(15)
C18-C13-C14	117.96(11)
C18-C13-Ni1	125.00(9)
C14-C13-Ni1	116.93(9)
C15-C14-C13	121.26(12)
C15-C14-H14	118.5(11)
C13-C14-H14	120.2(11)
C16-C15-C14	119.59(11)
C16-C15-H15	121.1(10)
C14-C15-H15	119.3(10)
C15-C16-C17	120.47(11)
C15-C16-C19	119.97(11)
C17-C16-C19	119.51(11)
C16-C17-C18	119.46(11)
C16-C17-H17	120.7(11)
C18-C17-H17	119.7(11)

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C17-C18-C13	121.21(11)
C17-C18-H18	117.1(11)
C13-C18-H18	121.7(11)
F2-C19-F3	106.60(11)
F2-C19-F1	105.77(11)
F3-C19-F1	105.21(11)
F2-C19-C16	113.21(11)
F3-C19-C16	113.09(11)
F1-C19-C16	112.32(10)

Table 3. Torsion angles [°] for **Ni-1**.

_____

C5-N1-C1-C2	0.74(17)
Ni1-N1-C1-C2	173.44(9)
N1-C1-C2-C3	1.93(19)
C11-O1-C3-C2	5.24(17)
C11-O1-C3-C4	-174.58(10)
C1-C2-C3-O1	177.31(11)
C1-C2-C3-C4	-2.88(17)
C10-N2-C6-C7	-0.37(17)
Ni1-N2-C6-C7	-175.94(9)
C10-N2-C6-C5	-179.61(10)
Ni1-N2-C6-C5	4.81(12)
C1-N1-C5-C4	-2.47(16)
Ni1-N1-C5-C4	-175.99(9)
C1-N1-C5-C6	176.63(10)
Ni1-N1-C5-C6	3.12(12)

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N2-C6-C5-N1	-5.21(14)
C7-C6-C5-N1	175.55(11)
N2-C6-C5-C4	173.89(11)
C7-C6-C5-C4	-5.35(18)
N1-C5-C4-C3	1.47(17)
C6-C5-C4-C3	-177.55(11)
O1-C3-C4-C5	-178.88(11)
C2-C3-C4-C5	1.29(17)
N2-C6-C7-C8	0.20(18)
C5-C6-C7-C8	179.37(11)
C12-O2-C8-C9	-7.09(18)
C12-O2-C8-C7	172.63(11)
C6-C7-C8-O2	-179.53(11)
C6-C7-C8-C9	0.21(17)
O2-C8-C9-C10	179.28(11)
C7-C8-C9-C10	-0.43(17)
C6-N2-C10-C9	0.13(17)
Ni1-N2-C10-C9	174.94(9)
C8-C9-C10-N2	0.27(18)
N1-Ni1-C13-C18	-103.44(11)
N2-Ni1-C13-C18	-169.57(19)
Br1-Ni1-C13-C18	65.79(10)
N1-Ni1-C13-C14	72.69(10)
N2-Ni1-C13-C14	6.6(3)
Br1-Ni1-C13-C14	-118.08(9)
C18-C13-C14-C15	1.27(18)
Ni1-C13-C14-C15	-175.15(10)

C13-C14-C15-C16	0.53(19)
C14-C15-C16-C17	-1.25(19)
C14-C15-C16-C19	-178.60(12)
C15-C16-C17-C18	0.14(18)
C19-C16-C17-C18	177.50(11)
C16-C17-C18-C13	1.73(18)
C14-C13-C18-C17	-2.40(18)
Ni1-C13-C18-C17	173.69(9)
C15-C16-C19-F2	-27.72(17)
C17-C16-C19-F2	154.90(12)
C15-C16-C19-F3	-149.10(12)
C17-C16-C19-F3	33.52(16)
C15-C16-C19-F1	91.99(15)
C17-C16-C19-F1	-85.38(15)

Chapter 3

3.5.11 ^{1}H NMR, ^{13}C NMR & ^{19}F NMR spectra

Deaminative Arylation at sp^3 Carbon Centers

Chapter 3

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

Deaminative Arylation at sp^3 Carbon Centers

Chapter 3

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

Deaminative Arylation at sp^3 Carbon Centers

Chapter 3

Deaminative Arylation at sp^3 Carbon Centers

Chapter 3

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

Deaminative Arylation at sp^3 Carbon Centers

1h

Chapter 3

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

Deminative Arylation at sp^3 Carbon Centers

Chapter 3

1k

1k

Deaminative Arylation at sp^3 Carbon Centers

1k

Chapter 3

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

Deaminative Arylation at *sp³* Carbon Centers

1m'

Chapter 3

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

1o

1o

Deaminative Arylation at sp^3 Carbon Centers

1p

1p

Chapter 3

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

Deaminative Arylation at sp³ Carbon Centers

Chapter 3

1r

153.13
153.18

-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

1t

Deaminative Arylation at sp³ Carbon Centers

Chapter 3

1u

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

Deaminative Arylation at sp^3 Carbon Centers

Chapter 3

Deaminative Arylation at sp^3 Carbon Centers

TMS

5

TMS

5

Chapter 3

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

8

8

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

62.35

CF$_3$

9

−10 −20 −30 −40 −50 −60 −70 −80 −90 −100 −110 −120 −130 −140 −150 −160 −170 −180 −190
f1 (ppm)

Deaminative Arylation at sp^3 Carbon Centers

10

10

Chapter 3

11

11

Deaminative Arylation at sp³ Carbon Centers

Chapter 3

-62.79

CF₃

CN

12

-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

Deaminative Arylation at sp^3 Carbon Centers

Chapter 3

Deaminative Arylation at sp^3 Carbon Centers

Chapter 3

Deaminative Arylation at *sp*³ Carbon Centers

Chapter 3

Deaminative Arylation at sp^3 Carbon Centers

Chapter 3

19

19

Deaminative Arylation at *sp*³ Carbon Centers

20

20

Chapter 3

20

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

Deminative Arylation at *sp*^{3} Carbon Centers

Chapter 3

8.44

7.50
7.48
7.21
7.20
7.19
7.18

4.50
4.49
4.47
3.66
3.64
3.63
3.62
3.60
3.58
3.51
3.49
3.48
3.47
3.45
3.43
2.65
2.63
2.61

1.72
1.72
1.71
1.71
1.70
1.70
1.69
1.68
1.68
1.67
1.67
1.66
1.66
1.65
1.64
1.64
1.63
1.62
1.62
1.21
1.19
1.17

24

1.91
1.00
0.93
0.98
2.02
2.02
1.98
4.05
6.03

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
f1 (ppm)

150.07
147.45
137.61
135.98
123.43
102.78
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
61.25
33.24
32.91
26.37
15.47

24

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Deaminative Arylation at *sp³* Carbon Centers

25

25

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26

26

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

28

28

Deaminative Arylation at sp^3 Carbon Centers

28

Chapter 3

29

29

Deaminative Arylation at *sp³* Carbon Centers

29

Chapter 3

30

30

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

Deaminative Arylation at sp³ Carbon Centers

Chapter 3

Deaminative Arylation at sp^3 Carbon Centers

34

Chapter 3

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

38

38

Deaminative Arylation at *sp³* Carbon Centers

Chapter 3

Deaminative Arylation at sp³ Carbon Centers

Chapter 3

Deaminative Arylation at sp³ Carbon Centers

40 crude with mesitlyene

40 crude with mesitlyene

Chapter 3

Deaminative Arylation at sp^3 Carbon Centers

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Chapter 4.

Remote Hydroboration of Alkenes Catalyzed by Tungsten Complexes

Research carried out in collaboration with

Tanner Jankins, Phillippa Cooper, Prof. Keary Engle*

In Preparation

Chapter 4

4.1   Introduction

Boron-containing molecules rank amongst the most versatile synthons in organic synthesis,[1] finding immediate application in small-molecule synthesis, pharmaceuticals[2,3] and polymer synthesis.[4] Such versatility and applicability prompted chemists to develop new catalytic reactions to forge sp^2 and sp^3 C–B bonds.[5–7] Beyond any reasonable doubt, one of the most attractive and atom-economical protocols to incorporate the boron atom into organic scaffolds is the catalytic hydroboration[8,9] of olefins. Recently, we have witnessed the development of remote functionalization strategies (Chapter 1.2.3),[10] allowing C–B bond-forming reactions at distal positions within an alkyl side chain. Of particular relevance is the observation that this strategy allows mixtures of olefins to be converted into a single regioisomer by means of a chain-walking processes. Despite the advances realized in these endeavours, the C–B bond-forming reaction can be enabled at (a) an electronically activated position adjacent to a directing group or at (b) a sterically less-congested position within the alkyl side-chain. However, the ability to incorporate the C–B bond at different positions still remains largely problematic, thus representing a worthwhile challenge for chemical invention.

4.2   Hydroboration of alkenes

4.2.1   Uncatalyzed and catalyzed hydroboration of alkenes

The hydroboration reaction is undoubtedly one of the most powerful methods for synthesizing organoboron compounds.[11,12] This reaction was originally reported in 1956 by H. C. Brown,[13] establishing new opportunities in organic synthesis for the regioselective hydrofunctionalization of alkenes and alkynes. The utilization of diborane (B_2H_6), borane-tetrahydrofuran complex ($BH_3 \cdot THF$) and commonly used 9-borabicyclo[3.3.1]nonane (9-BBN) resulted in exergonic C–B bond forming reactions without the need for a catalyst (Figure 4.2.1, *top*).[14] Introduction of HBpin or HBcat as boranes offered improved stability and handling; however, these compounds resulted in a lower reactivity profile with alkenes or alkynes unless transition metals were employed (Figure 4.2.1, *bottom*).[11,12,15,16] Indeed, the utilization of transition metals opened a gateway to impart chemoselectivity, regioselectivity and enantioselectivity, enabling a powerful tool for the synthesis of advanced organoboron intermediates, thus holding promise for the implementation of these techniques in synthetic applications.

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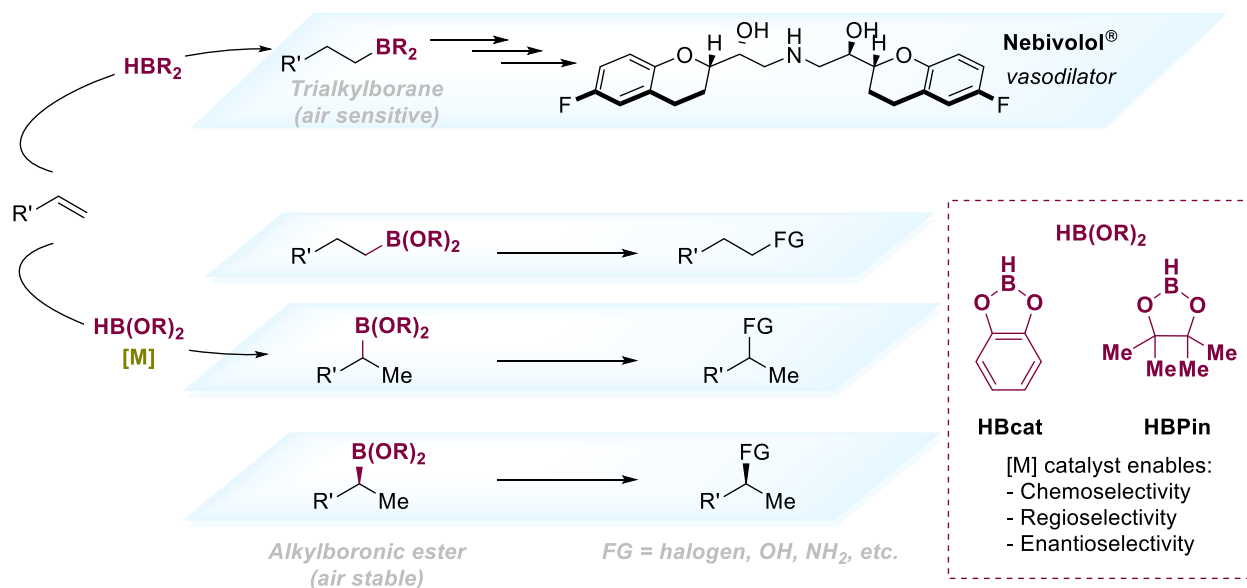
Figure 4.2.1 Uncatalyzed and catalyzed hydroboration of alkenes.

4.2.2   Overview of metal-catalyzed hydroboration of alkenes

In 1985, Nöth and co-workers described the utilization of Wilkinson's catalyst [(Ph₃P)₃RhCl] for enabling the addition of HBPin to alkenes.[17] Generally, hydroboration reactions occur with terminal selectivity following an anti-Markovnikov pathway (Figure 4.2.2, **I**). Indeed, branched-selective hydroboration *via* Markovnikov selectivity is not particularly common, although achievable in the presence of control elements within the alkyl side-chain or by using different catalysts (Figure 4.2.2).[18]
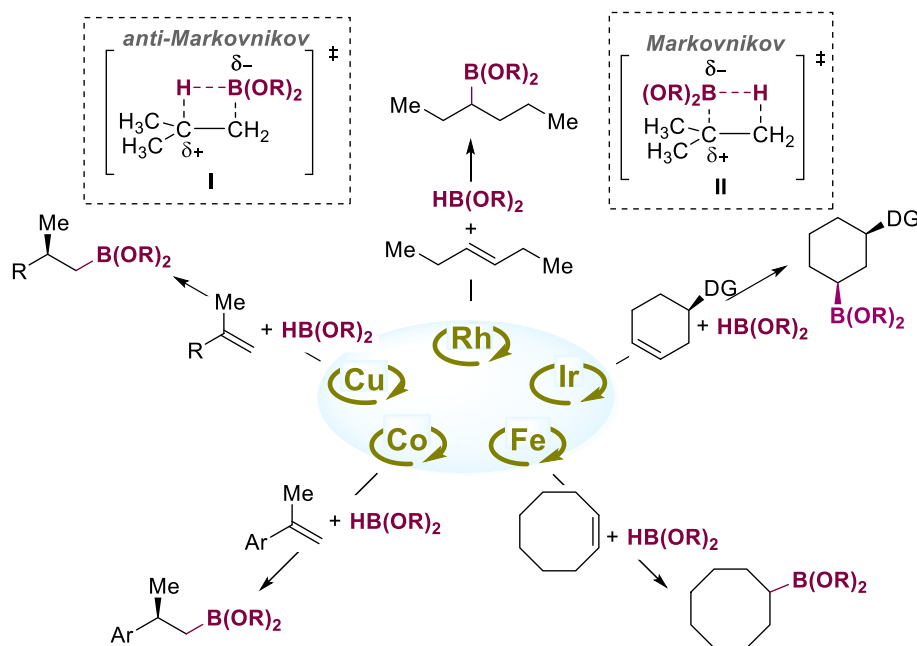
Figure 4.2.2. Metal-catalyzed hydroboration of alkenes.

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Raúl Martín Montero

W-catalyzed remote β-hydroboration of alkenes

4.2.3   Metal-catalyzed remote hydroboration of alkenes

In recent years, metal-catalyzed chain-walking reactions of olefins have offered a new manifold for enabling bond-formation at remote, yet previously unfunctionalized, sp^3 C–H bonds with an exquisite control of the regioselectivity profile (Chapter 1.2.3).[19] In the absence of a functional group or directing group proximal to the alkene, an iterative series of β-hydride elimination/migratory insertion occurs, causing a dynamic displacement over the alkyl side-chain that locates the metal center at the terminal, primary sp^3 C–H site due to steric effects. This concept has been applied by Chirik, Stradiotto and Turculet, among others, allowing the establishment of a new rationale for triggering a remote borylation at distal sp^3 C–H bonds of an unsaturated hydrocarbon chain.[20–23] Importantly, these authors showed that the interception of the metal secondary alkyl intermediate with HBpin, either by σ-bond metathesis or oxidative addition, is kinetically less favourable than the primary terminal metal-alkyl intermediate (Figure 4.2.3, *B*).
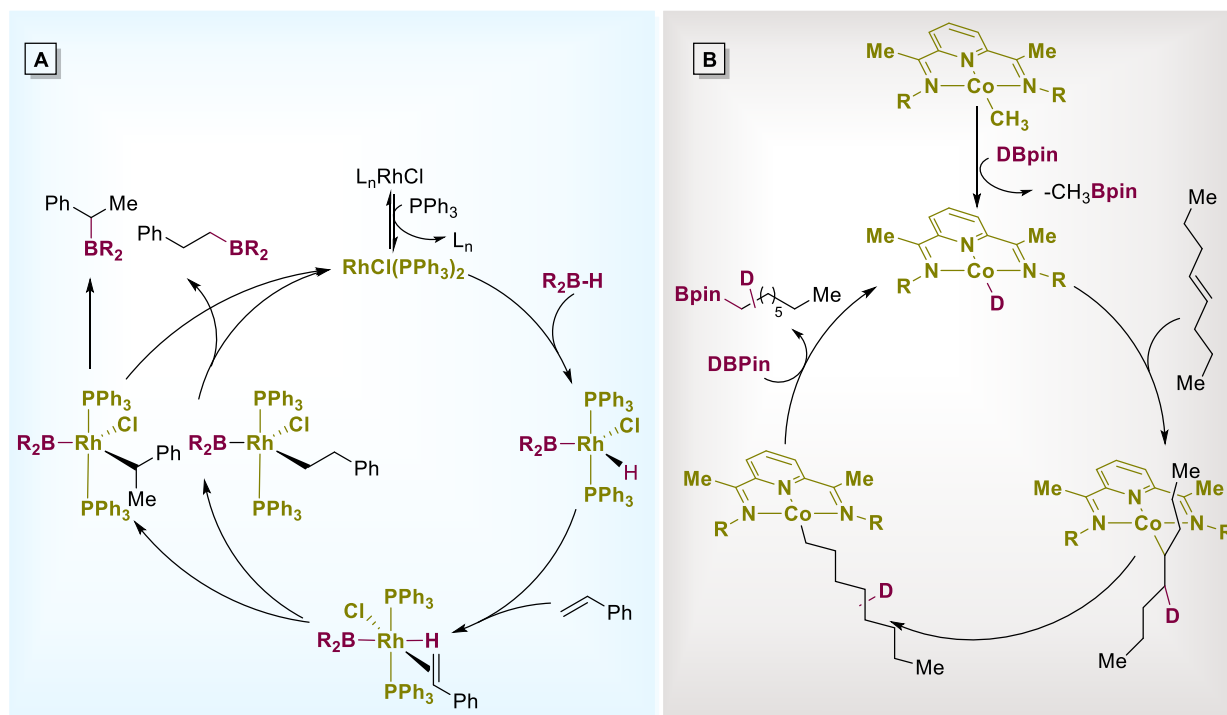
Figure 4.2.3. Formal hydroboration mechanism *vs* remote hydroboration mechanism.

4.2.3.1   Co-catalyzed site-selective hydroboration of alkenes

Given the intermediacy of discrete alkyl metal species in chain-walking reactions, one might argue whether these reactions could be directed in the presence of a suitable functional group within the alkyl side-chain. In line with this notion, Chirik's group described an interesting alkene isomerization-hydroboration promoted by cobalt catalysts supported by phosphine ligands (Scheme 4.2.1, *A*).[24] The authors found that the utilization of (PPh₃)₃CoH(N₂) catalyst (**Co-1**) resulted in an excellent selectivity at the remote benzyl sp^3 C–H site. The selectivity of the reaction was attributed to electronic rather

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than steric effects, an observation that is correlated with the ability of sterically demanding redox-active α-diimine and bis(imino)pyridines to yield the borylation event at the terminal, primary sp^3 C–H bond. Notably, the methodology allowed for preparing 1,1-diboron compounds from readily available α,ω-dienes.[25]
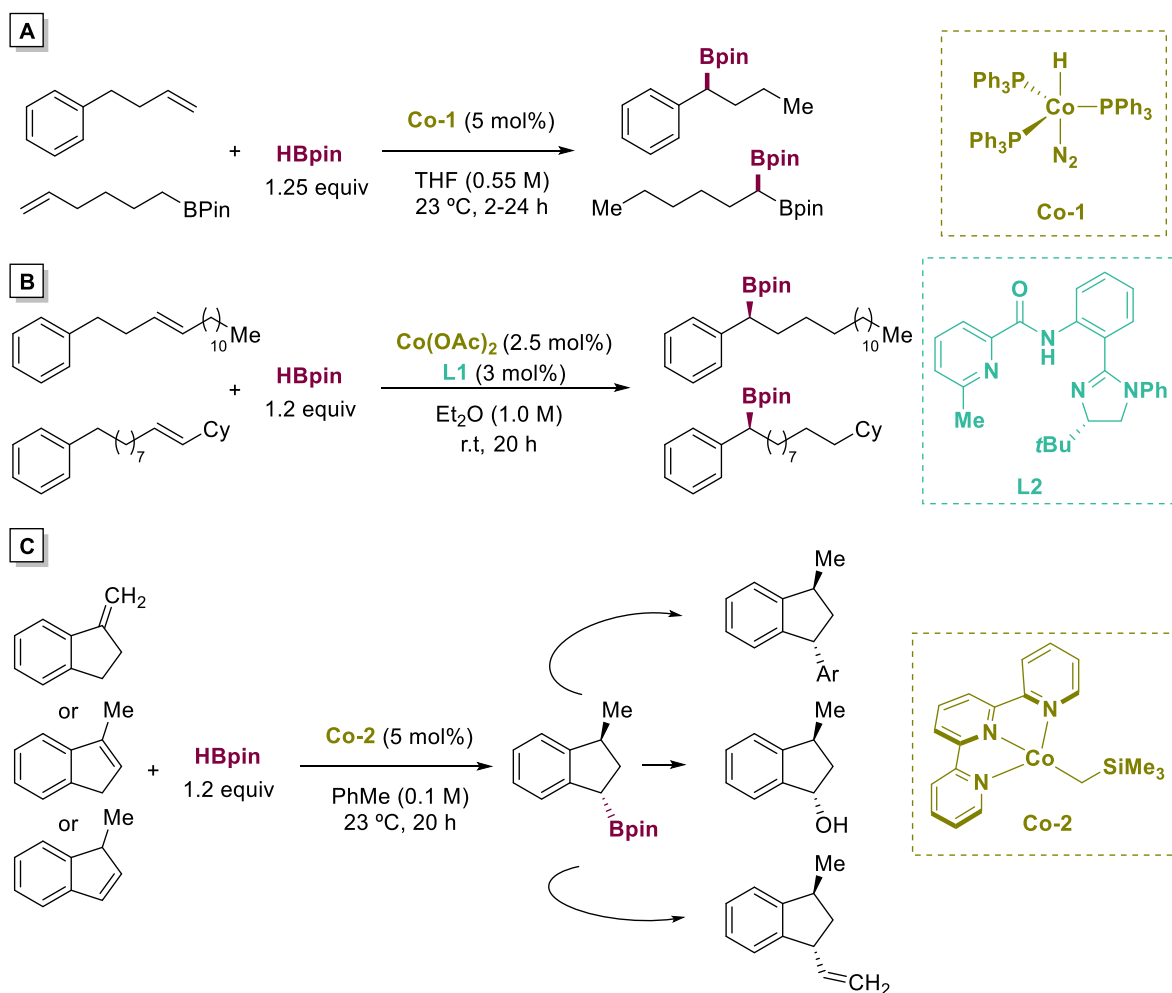
Scheme 4.2.1. Remote non-terminal hydroboration of internal & terminal alkenes.

In 2018, Zhan Lu and co-workers reported an asymmetric remote C–H borylation of internal olefins *via* alkene isomerization by using simple Co(OAc)$_2$ as catalyst (Scheme 4.2.1, *B*).[26] The transformation tolerated the presence of a great number of functional groups both on the phenyl ring and on the side chain, allowing isomerization of up to 8 positions along the hydrocarbon. In 2019, Chirik and co-workers reported a remote diastereoselective cobalt-catalyzed alkene isomerization-hydroboration of 2- and 3-substituted indenes (Scheme 4.2.1, *C*).[27] In this protocol, selective 1,3-*trans*-disubstituted indanyl boronic esters were obtained independently from the initial position of the alkene. The authors claimed that the regioselectivity followed a different mechanism than a classical anti-Markovnikov hydroboration due to the open coordination environment imparted to the cobalt center by the terpyridine ligand, thus lowering down the barrier for secondary C–B bond formation (Figure 4.2.3, *B*). While these contributions represented an interesting platform for

incorporating C–B atoms into side-chains, the means to incorporate these fragments at other unactivated positions still remains an elusive endeavour.

4.2.3.2   Fe-catalyzed site-selective hydroboration of alkenes

Similar to cobalt, other metals have been employed as catalysts for hydrofunctionalization reactions of alkenes, even at remote reaction sites. Among them, iron has attracted much attention for hydroborations of alkenes due to its low cost and abundance.[10] Particularly illustrative are the contributions by Stradiotto, Sydora and Turculet on the utilization of cobalt- and iron-catalysts for the isomerization-hydroboration of branched alkenes at terminal sp^3 reaction sites.[21,23] In 2020, Koh and co-workers developed the first catalytic regime that incorporated boryl groups at unactivated sites in olefins in the absence of strongly coordinating auxiliaries, triggering the borylation at the β-position[28,29] (Scheme 4.2.2, *top*).[30] Similar to the work shown in Scheme 4.2.1, this reaction is enabled by the formation of a η^3-benzyl intermediate. Notably, not only alkenes possessing arenes, but also silicon- and boron-containing motifs worked with similar ease. Later on, Koh's group was able to perform the reaction with olefins placed at distal positions within the side chain, achieving good yields and regioselectivities of the targeted boron compounds. Based on these empirical observations, the authors proposed a mechanism with an initiation step followed by two intertwined catalytic cycles (Scheme 4.2.2, *bottom*). The reaction begins with the addition of *in situ* generated iron-boryl species (**I**) across the alkene (**III**) followed by β-hydride elimination, furnishing iron-hydride intermediates (**IV**). This complex insers into the olefin and, upon isomerization *via* chain-walking, the most stable olefin is released (**V**). This alkene is subsequently trapped by iron-boryl species en route to **VI**. Site-selectivity might arise from the stabilization of iron by the electron density at the α-position of the functional group (FG) and/or by steric repulsion between the Bpin and FG. Subsequently, protonolysis from the *tert*-butanol generated by the solvent leads to the final β-borylated product (**VII**), with turnover accomplished by reaction of the iron-boryl species (**I**) with the iron-*tert*-butoxide intermediate. Taking all these results into consideration, new strategies should be implemented for broadening even further the scope of the reaction, improving the functional group compatibility and to functionalize sites other than terminal positions or adjacent to functional groups.

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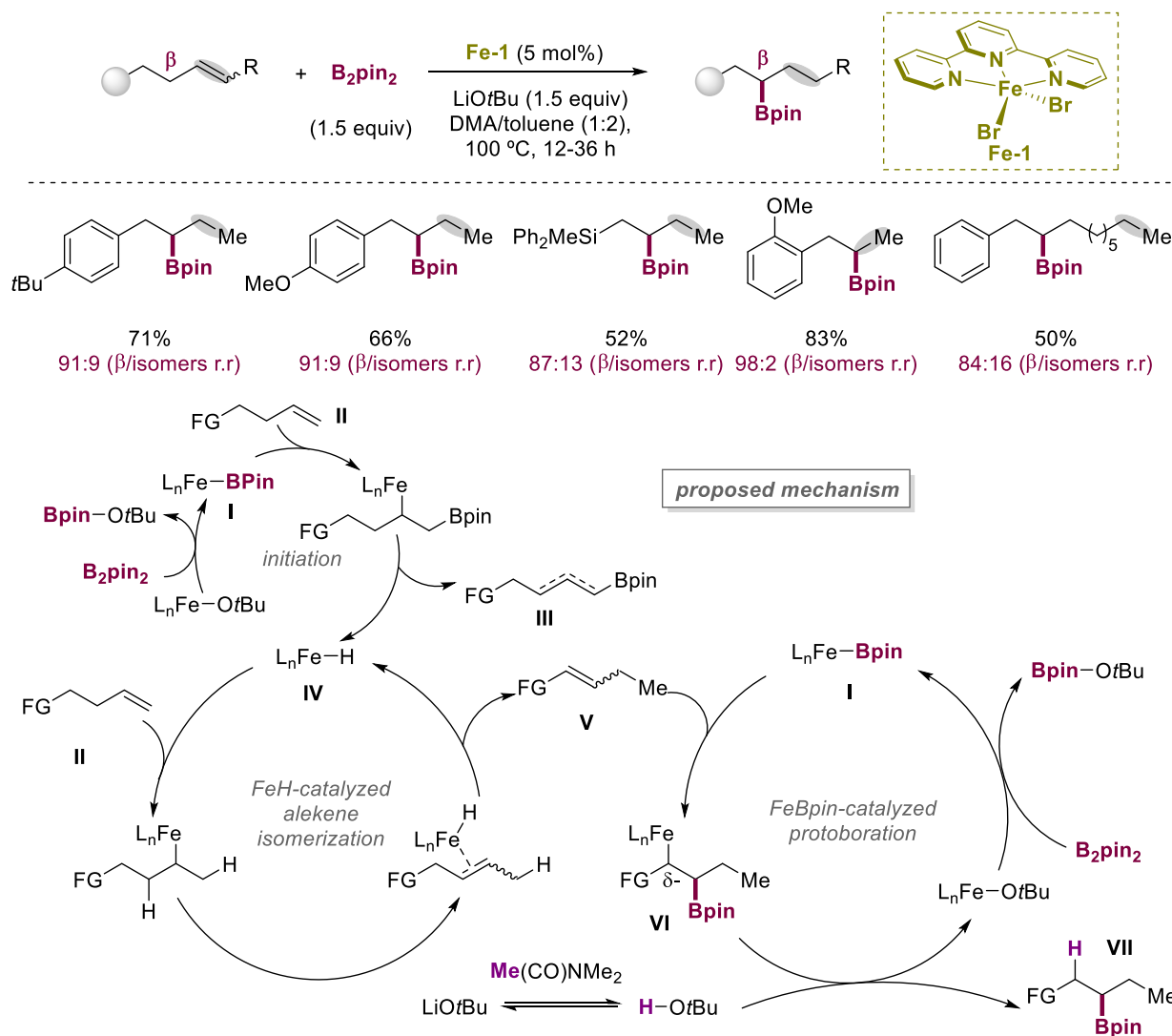
Scheme 4.2.2. Site-selective alkene borylation & proposed mechanism.

4.2.4   Tungsten as catalysts

Historically, tungsten has played an important role in the field of homogenous catalysis, though its use has been limited to a few specific reaction types, including alkene/alkyne metathesis[31] and polymerization of alkenes/alkynes,[32] among others. These applications employ tungsten in high oxidation states (e.g., +6), where the overall reaction is redox-neutral. In these reactions, the metal center is generally Lewis acidic and oxophilic, features that make these reactions particularly sensitive to air, moisture and other Lewis basic functional groups. These limitations notwithstanding, the low cost (~10^3 cheaper than Rh, Ir, or Pd), low toxicity, and ease of preparation of many tungsten catalysts make them particularly attractive as catalysts for industrial applications.

4.2.4.1   Hydrofunctionalization reactions using tungsten catalysis

Pioneering reports by Szymanska-Buzar demonstrated the ability of tungsten catalysts to trigger hydrofunctionalization of alkenes and alkynes. The authors reported an intriguing reactivity profile

of norbornene carbonyl complexes, obtaining different products depending on the reaction conditions and the reagents employed (Scheme 4.2.4, *1*).[33] Ring Opening Metathesis Polymerization (ROMP) and selective addition of $CHCl_3$, $CDCl_3$ or, CCl_4 to norbornene were found depending on the solvent and reaction conditions used in the presence of **W-1**. Interestingly, the Lewis acidic complex **W-2** catalyzed the C–H arylation of norbornene at room temperature using simple arenes such as benzene in solvent quantities, paving the way for triggering new reactivity principles within the general area of tungsten catalysis (*4*).
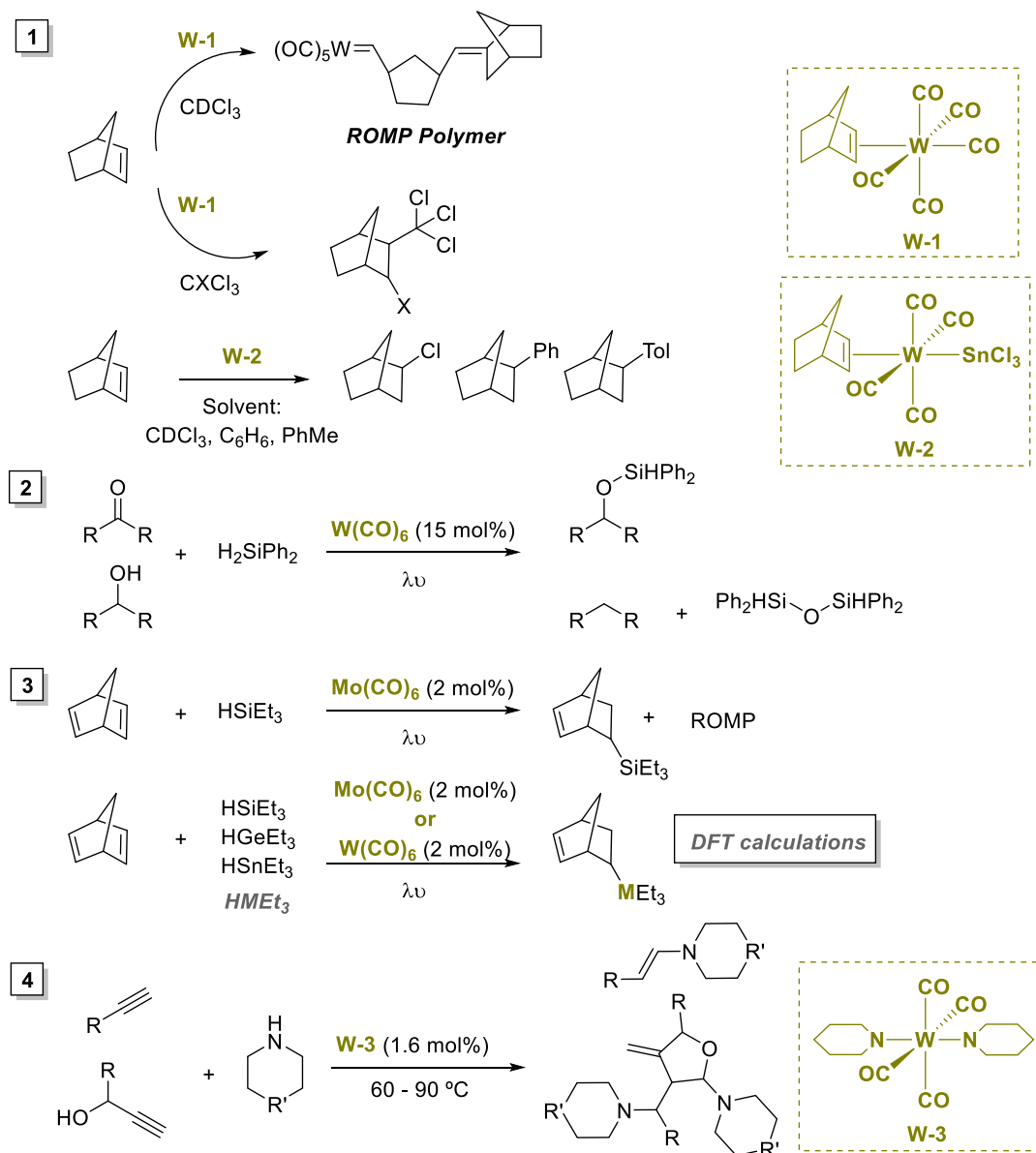
Scheme 4.2.4. Tungsten catalyzed hydrofunctionalization of alkenes & alkynes.

Tungsten has been shown to be particularly suited for triggering hydrosilylation of ketones and dehydrosilylation of alcohols with simple $W(CO)_6$ catalysts (Scheme 4.2.4, *2*).[34] This proof of concept established applications for the activation of the Si–H bond by the catalyst under photochemical conditions. Prompted by the ability of molybdenum catalysts to trigger hydrofunctionalization

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reactions,[35,36] DFT studies were performed to understand the behaviour of Mo and related W in these processes (Scheme 4.2.4, *3*).[37] These studies showed an endergonic oxidative addition to X–H bonds (X = Sn, Ge, Si) (11-13 kcal/mol), thus preventing the reaction of the resulting complexes with alkenes abandoning further investigations. Tungsten catalysts have also been employed in hydroamination of alkynes (Scheme 4.2.4, *4*).[38,39] The authors obtained an *anti*-Markovnikov selectivity, resulting in *E*-isomers for terminal alkynes using W(0) catalysts (**W-3**). However, tetrahydrofurans were obtained when using propargylic alcohols after a double rearrangement with the cyclic amine. The observed reactivity is likely attributed to the propensity of W(0) to form alkylidenes with terminal alkynes. However, the hydrofunctionalization of alkenes remained unknown with W(0) and carbene intermediates.

4.2.4.2   Tungsten possibilities

Despite the advances in low valent tungsten catalysis, its application in catalytic endeavors is still in its infancy. It is worth noting, however, that the potential to enable olefin isomerization is known since the mid 70's.[40] The attenuated reactivity of W towards the activation of X–H bonds may prove to be beneficial for allowing complementary regioselectivity profile to that shown by other transition metals in chain-walking reactions.

4.3   Remote Hydroboration of Alkenes Catalyzed by Tungsten Complexes

4.3.1   Aim of the project

While significant progress has been made in remote functionalization of sp^3 C–H bonds by means of chain-walking reactions, the vast majority of these processes rely on C–C bond-forming reactions at a specific location within the alkyl side-chain. Driven by the unique reactivity of tungsten and its abundance compared to other transition metals, we wondered whether we could employ simple tungsten catalysts within the context of remote functionalization of olefins, allowing us to forge C–B bonds at unconventional sp^3 C–H sites.

4.3.2   Optimization of the reaction conditions

This work was initiated during my predoctoral stage at Scripps, San Diego, under the supervision of Prof. Keary Engle in 2019. Specifically, the project was aimed at triggering a remote W-catalyzed hydroboration of terminal alkenes at the β-position of a weakly coordinating directing group, thus representing the first example of a remote functionalization of unconventional unactivated sp^3 C–H reaction sites by tungsten catalysis. We began our investigations by using **1a** as substrate and the influence of the alkene, boron source and catalyst was explored (Table 4.3.1). Based on Engle's group experience, the presence of an amide could serve as a directing group by coordination to the catalyst. Interestingly, we obtained preliminary encouraging results by using commercially available W(CO)$_3$(MeCN)$_3$ as catalyst (entry **1**). In order to confirm the structure of the final product, the

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organoboron compound was transformed into the corresponding alcohol by conventional oxidation techniques. The formation of the reduced compound (**2a**) and the isomerization of the alkene along the side chain (**2b**) accounted for the mass balance of the reaction. Importantly, many of these results gave >50:1 regioselectivity. Interestingly, we observed a similar reactivity profile when using Mo(CO)$_3$(MeCN)$_3$ as catalyst (entry **2**), whereas the use of light irradiation had a deleterious effect on the reaction outcome, thus likely coming from decomposition of the catalyst (entries **3-6**).
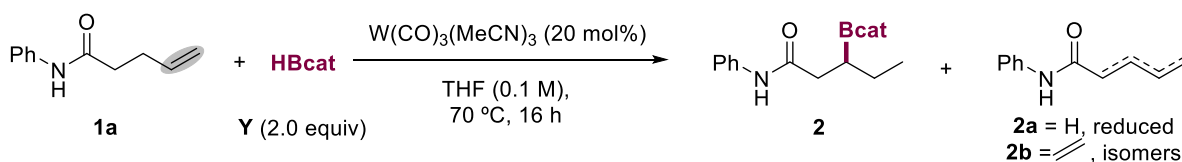
Entry	Deviation from standard conditions	Conv. (%)	2 (%)	2a (%)	2b (%)
1	None	86	42	26	14
2	Mo(CO)$_3$(MeCN)$_3$	80	38	24	16
3	λυ at rt	75	12	22	19
4	λυ at rt, MeCN (0.1 M)	41	6	10	10
5	Mo(CO)$_3$(MeCN)$_3$ λυ at rt	52	4	13	8
6	Mo(CO)$_3$(MeCN)$_3$ λυ at rt, MeCN (0.1 M)	21	3	9	6

Reaction conditions: **1a** (0.1 mmol), **Y** (2.0 equiv), W(CO)$_3$(MeCN)$_3$ (20 mol%), solvent (1.0 mL), 70 ºC, 16 h. GC conversion and yields using decane as internal standard.

Table 4.3.1. First screening of a remote hydroboration reaction of alkenes.

With these conditions in hand, we next turned our attention to studying the effect of the boron source (Table 4.3.2). As shown, both HBcat and HBpin showed a similar trend (entries **1-9**). Although poor yields were obtained at room temperature, these conditions led to low amounts of isomeric products (**2b**) (entries **4** and **9**). The utilization of aminoborane reagent HBdan did not afford any traces of desired product, likely due to steric and/or electronic effects (entry **10**). Quite illustrative, a control reaction was performed in the absence of the tungsten catalyst that delivered mixtures of both **2a** and **2b** sideproducts, and *anti*-Markovnikov product with no traces of β-hydroboration (entry **11**).

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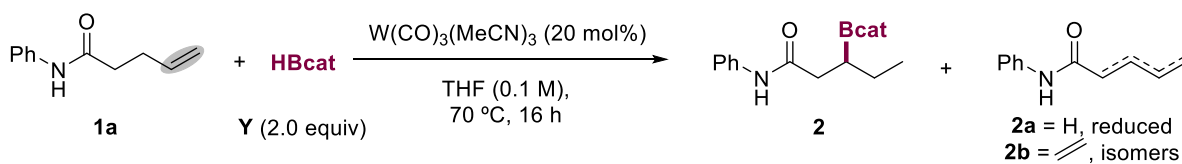
Entry	Deviation from standard conditions	Conv. (%)	2 (%)	2a (%)	2b (%)
1	HBcat (3.0 equiv)	100	65	16	16
2	HBcat (4.0 equiv)	100	74	13	13
3	HBcat (5.0 equiv)	100	75	13	12
4	HBcat (3.0 equiv), rt	52	32	16	2
5	HBpin (2.0 equiv)	40	18	22	0
6	HBpin (3.0 equiv)	49	28	21	0
7	HBpin (4.0 equiv)	82	42	40	0
8	HBpin (5.0 equiv)	100	43	46	0
9	HBpin (3.0 equiv), rt	25	10	16	0
10	HBdan (3.0 equiv)	21	0	15	5
11	No W(CO)$_3$(MeCN)$_3$	53	0	16	8

Reaction conditions: **1a** (0.1 mmol), **Y** (2.0 equiv), W(CO)$_3$(MeCN)$_3$ (20 mol%), THF (1.0 mL), 70 ºC, 16 h. GC conversion and yields using decane as internal standard.

Table 4.3.2. Boron source and equivalents screening.

Next, we examined the influence of different tungsten and molybdenum catalysts at different concentrations (Table 4.3.3). However, none of the catalysts analyzed improved the reactivity of the borylation event when compared with previous conditions (entries **1**-**8** and **10-11**). While slightly better results were found at higher concentrations (entries **1**-**8**), higher yields were found by lowering the catalyst loading to 5 mol% (entry **9**).
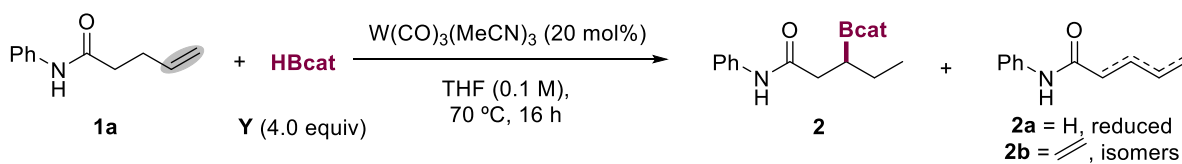
Entry	Deviation from standard conditions	Conv. (%)	2 (%)	2a (%)	2b (%)
1	W(CO)$_4$(MeCN)$_2$ (0.5 mL)	72	48	12	11
2	W(CO)$_4$(MeCN)$_2$ (1.0 mL)	100	56	13	13
3	W(CO)$_4$(MeCN)$_2$ (1.5 mL)	100	56	14	13
4	W(CO)$_3$(MeCN)$_3$ (0.5 mL)	100	76	10	10
5	W(CO)$_3$(MeCN)$_3$ (1.5 mL)	100	61	22	13
6	Mo(CO)$_3$(MeCN)$_3$ (0.5 mL)	100	65	21	11
7	Mo(CO)$_3$(MeCN)$_3$ (1.0 mL)	100	72	16	10
8	Mo(CO)$_3$(MeCN)$_3$ (1.5 mL)	100	71	16	10
9	W(CO)$_3$(MeCN)$_3$ (5 mol%)	100	76	10	11
10	Mo(CO)$_3$(PrCN)$_3$	100	46	18	9
11	W(CO)$_3$(PrCN)$_3$	100	51	17	11

Reaction conditions: **1a** (0.1 mmol), **Y** (4.0 equiv), W(CO)$_3$(MeCN)$_3$ (20 mol%), THF (1.0 mL), 70 ºC, 16 h. GC conversion and yields using decane as internal standard.

Table 4.3.3. Screening of W and Mo catalysts.

Our attempts to isolate the final product revealed an inherent instability of the borylated product, a result of competing decomposition pathways during column chromatography and the need for converting the catechol borane into the more robust Bpin derivative. Therefore, we anticipated that the best-case scenario would be the employment of HBpin as the boron reagent. In this manner, we will make use of the inherent potential of the resulting alkylBPin reagents that can be further functionalized. Interestingly, we found that 5% of catalyst performed equally well (Table 4.3.4, entry **1**). After testing different solvents, equivalents of HBpin and different temperatures (entry **2**-**6**), we found that the concentration of the reaction was critical for success, delivering the targeted borylation in good yields (entry **3**).

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Reaction conditions: **1a** (0.1 mmol), **Y** (4.0 equiv), $W(CO)_3(MeCN)_3$ (5 mol%), THF (1.0 mL), 70 ºC, 16 h. GC conversion and yields using decane as internal standard.
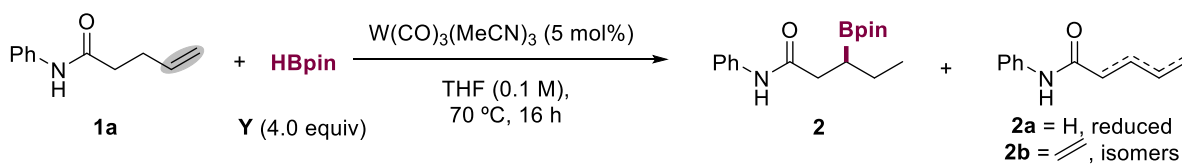
Entry	Deviation from standard conditions	Conv. (%)	2 (%)	2a (%)	2b (%)
1	None	95	41	42	3
2	THF (2.0 mL)	94	25	68	3
3	THF (0.5 mL)	100	65	32	1
4	HBpin (2 equiv) and 100 ºC	50	12	30	6
5	Dioxane (1.0 ml)	30	3	25	3
6	Me-THF (1.0 ml)	20	1	0	11

Table 4.3.4. Screening with HBpin.

An improved **2:2a** ratio was found by conducting the reaction with just 0.20 mL of solvent (entry **1**). Remarkably, the reaction performed similarly well at 2 mol% catalyst loading (entries **2** & **3**). Gathering all the data, one might argue that the observed reactivity might be attributed to the intermediacy of an α,β-unsaturated compound prior to the C–B bond-formation step. To this end, we conducted the reaction in the absence of tungsten catalyst but using the hypothetical acrylamide intermediate. As shown in entries **4** and **5**, the reaction did not deliver the product, although trace amounts of **2a** were obtained at 40 °C whereas quantitative formation of the latter was found at 70 °C. These two entries indicate that the catalyst is needed to promote the β-hydroboration and it does not serve as a mere isomerization source for the alkene.

W-catalyzed remote β-hydroboration of alkenes
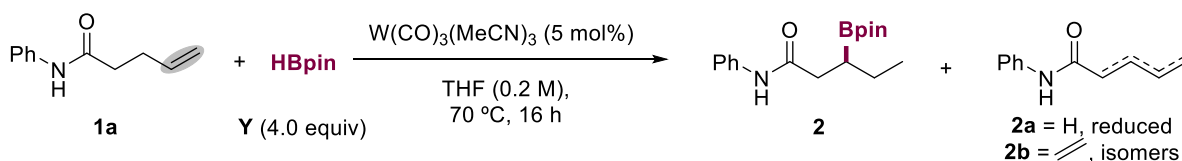
Entry	Deviation from standard conditions	Conv. (%)	2 (%)	2a (%)	2b (%)
1	THF (0.2 mL)	100	78	20	0
2	W(CO)₃(MeCN)₃ (2 mol%) and THF (0.2 mL)	96	66	30	1
3	W(CO)₃(MeCN)₃ (2 mol%)	100	52	38	2
4	No W, 40 ºC	0	0	5	0
5	No W, 70 ºC	100	0	96	2

Reaction conditions: **1a** (0.1 mmol), **Y** (4.0 equiv), W(CO)$_3$(MeCN)$_3$ (5 mol%), THF (0.5 mL), 70 ºC, 16 h. GC conversion and yields using decane as internal standard.

Table 4.3.5. Screening of concentrations & control reactions.

In light of these results, we wondered if subtle modification of the reaction conditions would allow us to improve the selectivity while minimizing the formation of side-reactions (Table 4.3.6). Unfortunately, no improvement was found by the addition of the boron source in multiple batches or by its slow addition with a syringe pump. Notably, the reaction behaved equally well at low concentrations (entry **3**), whereas excellent yields were accomplished at 40 °C (entries **4-8**).
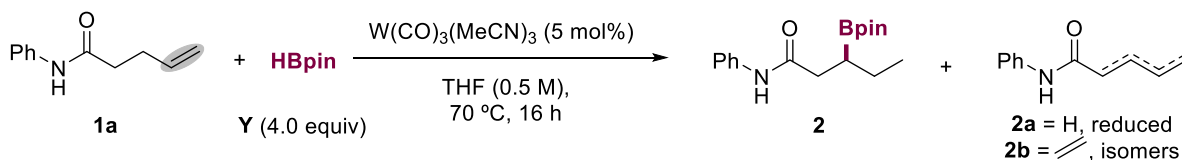
Entry	Deviation from standard conditions	Conv. (%)	2 (%)	2a (%)	2b (%)
1	HBpin (2 equiv + 2 equiv 2 h later)	71	31	20	25
2	HBpin (Syringe pump addition)	89	46	23	14
3	THF (0.1 mL)	100	79	20	0
4	50 ºC	50	12	30	6
5	40 ºC	94	90	4	0
6	30 ºC	68	42	2	20
7	30 ºC using 10% [W]	76	58	2	15
8	50 ºC and 3 equiv of HBpin	98	72	9	9

Reaction conditions: **1a** (0.1 mmol), **Y** (4.0 equiv), W(CO)$_3$(MeCN)$_3$ (5 mol%), THF (0.2 mL), 70 ºC, 16 h. GC conversion and yields using decane as internal standard.

Table 4.3.6. Further reaction optimization.

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Subsequently, we studied at the influence of other reaction parameters (Table 4.3.7). As shown, similar results were found by conducting the reaction for different durations (entries **1** & **2**). The reaction could not be improved at high catalyst loadings or at higher temperatures (entries **3** and **4**). However, quantitative yields were found by adjusting the concentration of the reaction (entry **5**). Importantly, no β-hydroboration was found by performing the reaction in the absence of the W catalyst, with the mass balance accounted for by the formation of small amounts of *anti*-Markovnikov and Markovnikov products (entry **6**). Although we tested the inclusion of a variety of ligands, none of these proved to be beneficial for the reaction outcome (entries **7**-**9**).
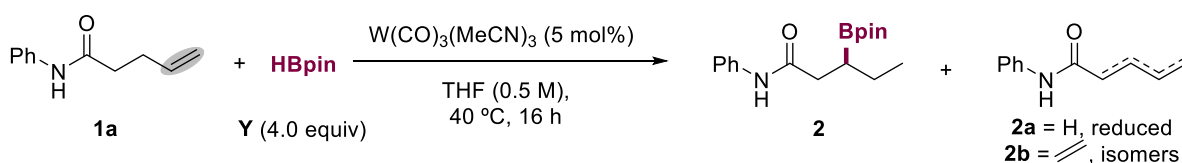
Entry	Deviation from standard conditions	Conv. (%)	2 (%)	2a (%)	2b (%)
1	20 h	95	90	4	0
2	24 h	95	90	4	0
3	$W(CO)_3(MeCN)_3$ (7.5 mol%)	100	79	20	0
4	45 ºC	96	76	16	0
5	**1a** (0.2 mmol) in THF (0.3 mL)	100	98	0	0
6	No W catalyst	20	0	5	0
7	PCy_3 (10 mol%)	18	10	8	0
8	*i*Pr-NHC (10 mol%)	6	0	4	2
9	4,4-dtbpy (10 mol%)	13	0	7	3

Reaction conditions: **1a** (0.1 mmol), **Y** (4.0 equiv), $W(CO)_3(MeCN)_3$ (5 mol%), THF (0.2 mL), 40 ºC, 16 h. GC conversion and yields using decane as internal standard.

Table 4.3.7. Further optimization to achieve full conversion of the starting material.

4.3.3 Substrate scope

Encouraged by these results, we next turned our attention to studying the preparative scope of this reaction with a wide number of different alkenes (Scheme 4.3.1). As shown, electron-donor (**7**), electron-withdrawing (**8**) and organoboron functional groups (**9**) were found to be accommodated in this transformation. In addition, the presence of halogen atoms (**3**-**6**) did not interfere with productive C–B bond-formation. This finding is particularly important, offering not only the possibility of triggering orthogonal cross-coupling reactions in the presence of halide congeners, but also a complementary reactivity mode with Ni or Pd catalysis, as these metal species would likely enable the cleavage of the corresponding sp^3 C–halide bond.

W-catalyzed remote β-hydroboration of alkenes

Next, we investigated the influence of the substitution pattern adjacent to the carbonyl group. As shown in Scheme 4.3.1, α-substituted derivatives **10** and **11** could be obtained in good to excellent yields. The inclusion of a benzyl group (**12**) was perfectly tolerated, obtaining a good diastereoselectivity of the targeted product (>20:1). In this case, X-ray crystallography unequivocally identified an anti-stereochemistry pattern of the final product. Our available literature data revealed that the borylation could effectively be promoted with free N–H groups, but it left a reasonable doubt on whether this motif was critical for success. As shown by the successful preparation of **13** and **14**, this was not the case and tertiary amides could equally be employed as substrates.[41] The identity of **14** was confirmed by X-ray crystallography. Moreover, a gram scale reaction was carried out to test the viability of the methodology as well as the robustness in higher catalyst and substrate amounts affording an even greater yield of **14** (85% yield).

Reaction conditions: 1 (0.2 mmol), HBpin (4 equiv), W(MeCN)$_3$(CO)$_3$ (5 mol%), THF (0.67 M), 40 °C, 20 h. Isolated yields. [a]Bpin converted to the alcohol. [b]HBpin 5 equiv. [c]Reaction at 5.0 mmol.
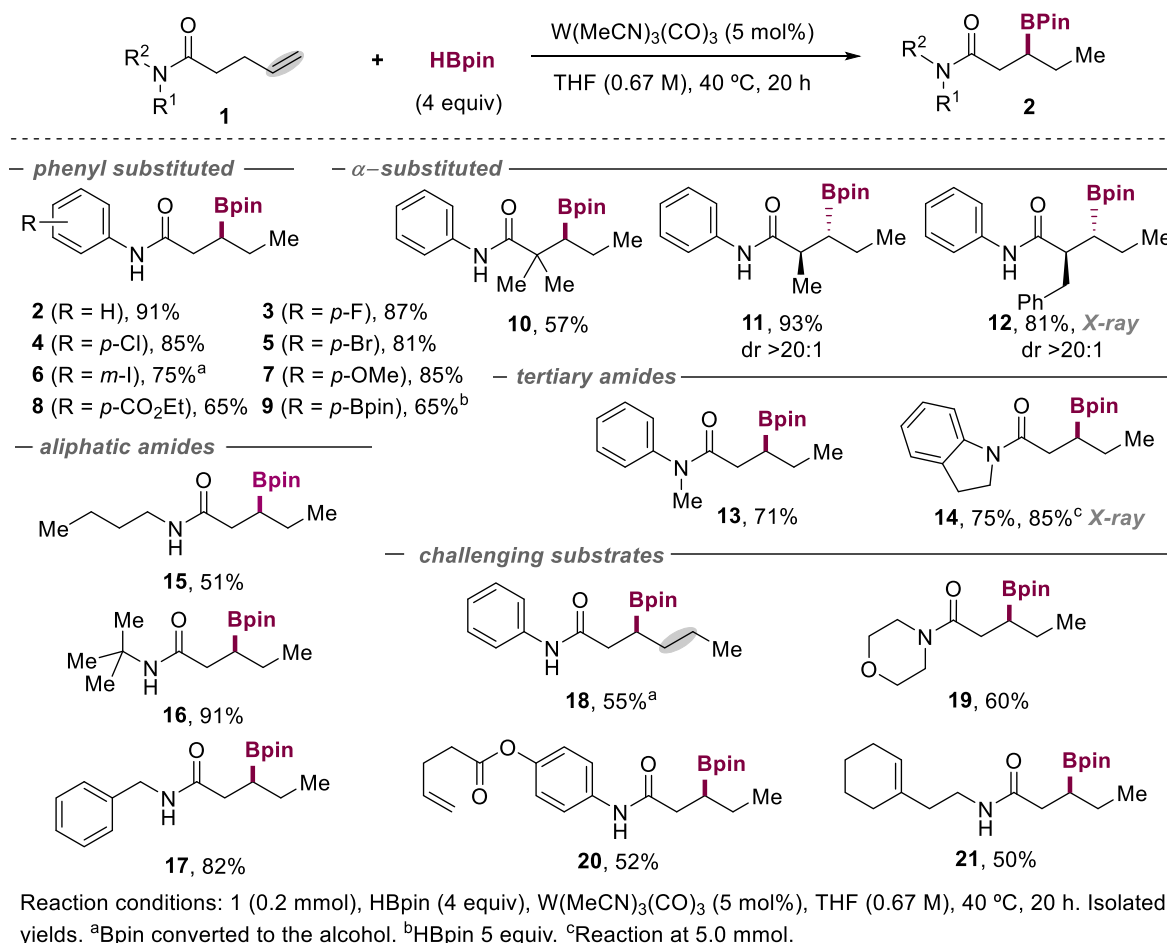
Scheme 4.3.1. W-catalyzed remote C(sp^3)–H hydroboration of alkenes.

Gratifyingly, we found that the remote hydroboration is not limited to aromatic amides but it could be applied to aliphatic amides (**15-17**). Finally, we decided to test the suitability of our reaction with a series of challenging substrates to assess the selectivity, robustness and simplicity of the current protocol. Importantly, the utilization of internal alkenes afforded exclusively the corresponding β–hydroboration in moderate yields (**18**). In other hand, the utilization of bioactive

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morpholine derivatives allowed the formation of the borylated product in good yield (**19**). Amides possessing a pendent alkene exclusively resulted in β–hydroboration with respect to the amide group, while leaving the other alkene completely untouched (**20**, **21**). This result is particularly important, offering an opportunity that is beyond reach with other transition metals that otherwise would have resulted in competitive hydrofunctionalization of the other alkene moiety.

4.3.4   *Applicability of W-catalysis*

Next, we turned our attention to study the applicability of our W-catalyzed transformation. Based on our experience in catalytic silylation reactions,[42,43] we wondered whether utilization of silylating reagent Et$_3$SiBpin might trigger an otherwise related silylation event at the β-position (Scheme 4.3.2, *A, 22*). As shown, the reaction could be conducted with similar ease in the presence of fluoride sources, obtaining the targeted product with an exquisite regioselectivity profile. Moreover, we decided to tackle the challenge of promoting the β-borylation event with longer alkene side-chains (Scheme 4.3.2, *B*). Unfortunately, the reaction was not observed under the standard conditions with **1u**. After some experimentation, a cocktail similar to *A* was applied, finding out that the targeted borylation could be within reach (**23**), but in moderate yields, suggesting that the coordination of the catalyst to the amide backbone might be an important factor for success in the targeted borylation. In this case, an α,β-unsaturated carbonyl compound is likely formed followed by a 1,4-borylation in the presence of copper species (See SI for more information).
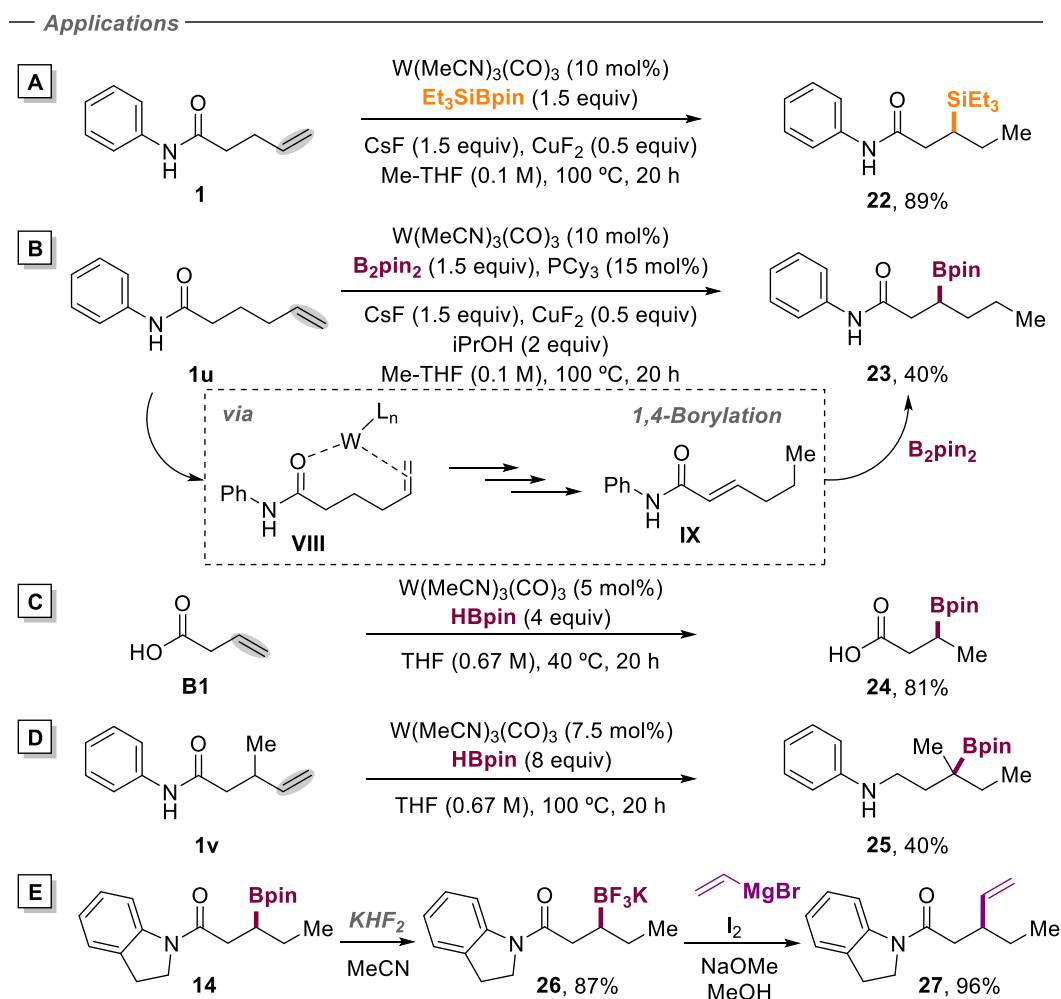
Scheme 4.3.2. Applications of tungsten catalysis.

At first sight, one might argue that our reaction could be limited to alkenes containing amide-side chains. However, we found that carboxylic acids (**B1**) could be used for similar purposes, resulting in **24** in good yields (Scheme 4.3.2, *C*), thus suggesting that the carboxylic acid might serve as a directing group for triggering a borylation event. In addition, quaternary borylated centers could be within reach (**25**); in this case, after the borylation takes place, the high temperature and equivalents of HBpin triggered a reduction of the carbonyl group delivering the final amine bearing a fully substituted borylated center.[44,45] Finally, we decided to test the applicability of the reaction to a downstream manipulation by synthesizing trifluoroborate salts (**26**) and reacting it with vinyl magnesium bromide in the presence of iodine and NaOMe. This sequence delivered product **27** in 96% yield.

4.3.5   Mechanistic proposal

A priori, we conceived two conceivable mechanistic pathways which account for the observed reactivity: A) coordination of the alkene (**X**) to the catalyst followed by an oxidative addition into the HBpin, thus generating tungsten-hydride species (**XI**). Upon olefin insertion/β-hydride elimination

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sequence (**XII**), and reductive elimination (**XIII**) delivers the desired product **2** (Scheme 4.3.3, *A*). B) a 1,3-hydride shift mechanism might occur with the catalyst coordinating the alkene (**X**) and subsequently abstracting and hydride from the allylic position. The newly formed allyl-tungsten hydride species (**XIV**) undergoes hydride insertion at the other terminus of the allyl species, thus forming the β/γ alkene intermediate (**XV**). Next, oxidative addition into the HBpin, olefin insertion into the W–H bond (**XVI**) and reductive elimination releases the borylated product (Scheme 4.3.3, *B*).
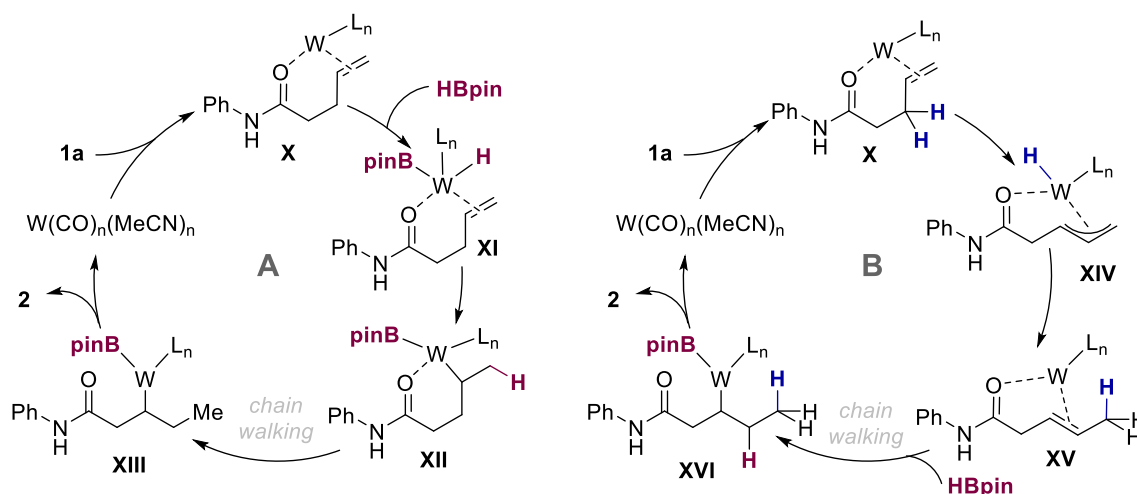
Scheme 4.3.3. Possible mechanisms for the tungsten catalyzed remote hydroboration.

Although more experimental and computational studies are needed to establish the mechanism profile of this transformation, preliminary deuterium-labelling experiments have been carried out. Specifically, DBpin was synthesized and reacted with **1a** and **1m** (Scheme 4.3.4), resulting in 53% and 48% deuteration at γ position, respectively, indicating that the mechanism might follow the path **B** shown in scheme 4.3.3. This proposal is in line with the slow oxidative addition reported for W(0) species.[37,46] However, further kinetic isotope studies still need to be conducted to provide a stronger evidence for pathway **B**.
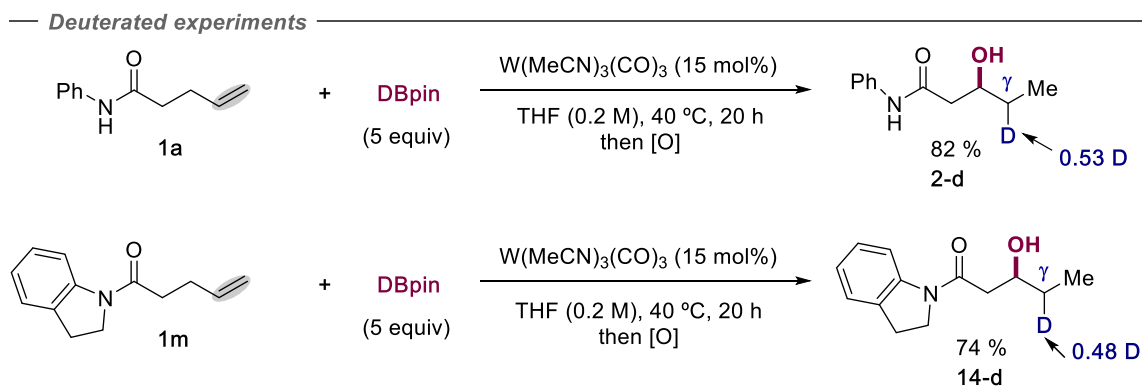
Scheme 4.3.4. Deuterium-labelling.

4.3.6   Future outlook

Although this chapter is not yet finished and subject of ongoing investigations, it is worth mentioning future objectives and scenarios that could be envisioned in this arena:

A. *Site-selectivity at unactivated sp³ positions.* In view of our results, one might perfectly wonder whether we could extend our β-hydroboration catalyzed by tungsten catalysts to other positions within the alkyl side-chain. This could *a priori* be executed in the presence of other directing groups and modular ligands that might prevent the reaction from occurring at the β-position.

B. *Extension to longer alkyl chain lengths and to other substrates.* A close look at our technology reveals that the protocol is somewhat limited to amides or carboxylic acids with specific hydrocarbon alkyl side-chains. That being set, a particularly attractive endeavour would be the extension of this methodology beyond the utilization of these carbonyl groups and also the ability to trigger chain-walking scenarios with longer alkyl side-chains without a significant erosion in yield and site-selectivity.

C. *C–C bond formation.* While we have shown the ability of tungsten catalysts to trigger a borylation at the β-position, this technology should by no means be limited to C-B bond-formation. Therefore, future efforts will be directed to the development of C-C bond-forming reactions aided by the ability of tungsten catalysts to trigger chain-walking events.

4.4   Conclusions

Overall, we have documented a catalytic strategy that enables a remote directed β-hydroboration of unactivated C–H bonds by means of tungsten catalysis. Such protocol offers a complementary reactivity mode for promoting the functionalization at unactivated *sp³* C–H sites of alkyl side-chains, thus leading to a different strategy mode than those proposed for related Pd-, Ni- or Co-catalyzed chain-walking reactions. Interestingly, this protocol can be applied across a wide range of alkenes possessing different carbonyl-type compounds, including highly substituted amide backbones. The ability to enable a β-borylation of simple carbonyl compounds possessing alkene side-chains with an exquisite site-selectivity pattern is particularly attractive, opening a new gateway for future applications of this technology. Although preliminary studies have been performed, more experiments are still required to unravel the intricacies of these processes.

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4.5   Experimental procedures

4.5.1   General considerations

Reagents. Commercially available materials were used as received without further purification: W(CO)$_3$(MeCN)$_3$ (99% purity) was purchased from Aldrich. 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (97% purity) was purchased from Aldrich. Anhydrous tetrahydrofuran (THF, 99.5% purity) and anhydrous 2-methyltetrahydrofuran (2-MeTHF, 99.5% purity) were purchased from Across.

Analytical methods. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 MHz, Bruker 400 MHz and Bruker 500 MHz at 20 °C. All ^{1}H NMR spectra are reported in parts per million (ppm) downfield of TMS and were calibrated using the residual solvent peak of CHCl$_3$ (7.26 ppm), unless otherwise indicated. All ^{13}C NMR spectra are reported in ppm relative to TMS, were calibrated using the signal of residual CHCl$_3$ (77.16 ppm), ^{11}B NMR and ^{19}F NMR were obtained with ^{1}H decoupling unless otherwise indicated. Coupling constants, *J*, are reported in Hertz. Melting points were measured using open glass capillaries in a Büchi B540 apparatus. Gas chromatographic analyses were performed on Hewlett-Packard 6890 gas chromatography instrument with an FID detector. Flash chromatography was performed with EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was used to monitor reaction progress and analysed fractions from column chromatography. To this purpose TLC Silica gel 60 F$_{254}$ aluminium sheets from Merck were used and visualization was achieved using UV irradiation and/or staining with Potassium Permanganate or Cerium Molybdate solution. The yields reported in Scheme 4.3.2.1 and 2 refer to isolated yields. The procedures described in this section are representative. In the cases the High-Resolution Mass Spectra of the molecular ion could not be obtained using ESI and APCI ionization modes the GC-MS of the compound was given.

4.5.2   Optimization of the reaction conditions

General procedure: An oven-dried 8 mL screw-cap test tube containing a stirring bar was charged with the alkene (**1a**, 35 mg, 0.20 mmol). The test tube was introduced in an argon-filled glovebox where W(CO)$_3$(MeCN)$_3$ (3.8 mg, 5 mol%) was subsequently added followed by addition of THF (0.3 mL, 0.67 M). Then HBpin was introduced (118 µl, 4 equiv) and the tube was taken out of the glovebox and stirred at 40 °C for 20 h. After diluting with EtOAc (10 mL) the yields were determined by GC FID analysis using decane as internal standard. The sample was purified by column chromatography on silica gel (Hexane/ EtOAc 8/2).

W-catalyzed remote β-hydroboration of alkenes

4.5.3   Synthesis of alkene amides
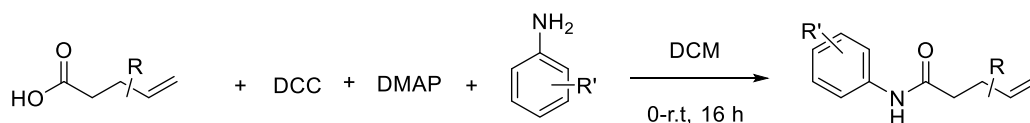
General Procedure A: a solution of the corresponding acid (1.0 equiv), primary amine (1.1 equiv) and DMAP (10 mol%) in DCM (0.33 M) was cooled to 0 °C. Subsequently, DCC (1.5 equiv) was added to the reaction and the bath was removed leaving the reaction stirring overnight. Aqueous HCl (1 M) was then added (2 times) and stirred vigorously. The organic layer was separated and then washed with sat. aq. NaHCO$_3$ and brine (3 times). Finally, the organic phase was dried with MgSO4 and the solvent was evaporated with the rotavapor. Flash column chromatography, was performed eluting with Hexane/EtOAc mixtures.
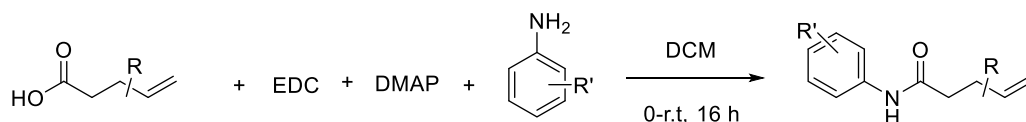
General Procedure B: A round-bottomed flask was charged with DCM (25 mL, 0.4 M), EDC-HCl (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 13 mmol, 1.3 equiv), and DMAP (14 mmol, 1.4 equiv). The reaction flask was cooled to 0 °C in an ice-bath and the carboxylic acid (10 mmol, 1.0 equiv) was added. After five minutes of stirring, the substituted aniline (12 mmol, 1.2 equiv) was added. The ice-bath was then removed and the reaction allowed to stir for 16 hours at r.t. Then, the reaction was quenched with 1M aq. HCl (25 mL) and the organics separated. The aqueous layer was then extracted with DCM (2 x 25 mL). The organic layers were combined and dried over MgSO$_4$ and concentrated. The crude product was purified by silica gel column chromatography.
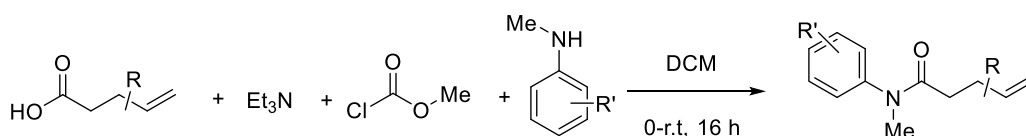
General Procedure C: a solution of the corresponding acid (1.0 equiv) and Et$_3$N (4.2 equiv) in THF (0.4 M) was cooled to 0 °C. Then methyl chloroformate (1 equiv) was added dropwise and stirred during 10 minutes at 0 °C. Subsequently, a solution of the secondary amine in THF (3 M) was added to the reaction mixture. The ince-bath cooled solution was stirred for 60 minutes then the precipate formed was filtered off and the solution concentrated under vacuum. The crude was purified by flash column chromatography using Hexane/EtOAc mixtures.

405
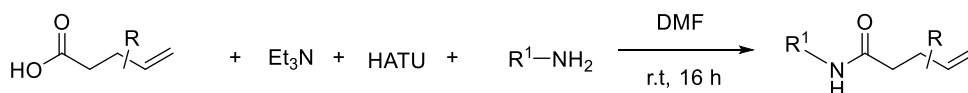
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General Procedure D: HATU (1.2 equiv) was added to a solution of the appropriate carboxilic acid (1.0 equiv), primary amine (1.2 equiv) and Et₃N (2.4 equiv) in DMF (0.2 M). The reaction was left stirring overnight at r.t. Then, quenched with aq. NaOH 1M and extracted with DCM. Finally, the organic phase was dried with MgSO₄ and the solvent was evaporated with the rotavapor. Flash column chromatography, was performed eluting with Hexane/EtOAc mixtures.

1a
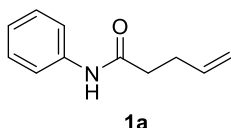
N-(4-methoxyphenyl)pent-4-enamide (1a). Following the General Procedure A, 4-pentenoic acid (0.5 mL, 4.89 mmol), aniline (0.39 mL, 5.38 mmol), DMAP (61 mg, 0.48 mmol) and DCC (1.03 g, 7.34 mmol) in 15 mL of DCM were used, affording the product as a white solid (658 mg, 77% yield). **¹H NMR** (500 MHz, CDCl₃) δ = 7.53 – 7.44 (m, 2H), 7.38 – 7.27 (m, 2H), 7.21 (s, 1H), 7.14 – 7.08 (m, 1H), 5.89 (ddt, J = 16.8, 10.9, 6.0 Hz, 1H), 5.27 – 4.96 (m, 2H), 2.54 – 2.40 (m, 4H) ppm. **¹³C NMR** (126 MHz, CDCl₃) δ = 170.4, 137.8, 136.9, 129.0, 124.3, 119.8, 116.0, 36.9, 29.4 ppm. Spectroscopic data for **1a** match those previously reported in the literature.[I]


1b
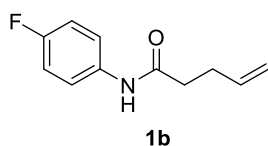
N-(4-fluorophenyl)pent-4-enamide (1b). Following the General Procedure B, 4-pentenoic acid (1.22 mL, 12.0 mmol), 4-fluoroaniline (1.33 g, 12.0 mmol), DMAP (146 mg, 1.22 mmol) and EDC (2.53 g, 13.2 mmol) in 20 mL of DCM were used, affording the product as a white solid (1.83 g, 79% yield). **¹H NMR** (600 MHz, CDCl₃) δ = 7.45 (dd, J = 8.8, 4.8 Hz, 2H), 7.19 (s, 1H), 7.00 (t, J = 8.5 Hz, 2H), 5.88 (td, J = 10.5, 5.1 Hz, 1H), 5.13 (d, J = 17.1 Hz, 1H), 5.06 (d, J = 10.2 Hz, 1H), 2.46 (dq, J = 12.3, 6.7 Hz, 4H) ppm. **¹³C NMR** (151 MHz, CDCl₃) δ = 170.0, 158.9 (d, J = 243.6 Hz), 136.3, 133.3, 121.2 (dd, J = 7.8, 3.5 Hz), 115.6, 115.1 (d, J = 22.6 Hz), 36.2, 28.9 ppm. **¹⁹F NMR** (376 MHz, CDCl₃) δ = -118.2 ppm. Spectroscopic data for **1b** match those previously reported in the literature.[II]

1c
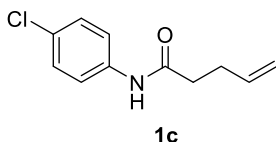
N-(4-chlorophenyl)pent-4-enamide (1c). Following the General Procedure B, 4-pentenoic acid (1.22 mL, 12.0 mmol), 4-chloroaniline (1.53 g, 12.0 mmol), DMAP (146 mg, 1.22 mmol) and EDC (2.53 g, 13.2 mmol) in 20 mL of DCM were used, affording the product as a white solid (2.21 g, 88% yield). **¹H NMR** (600 MHz, CDCl₃) δ = 7.46 (d, J = 8.3 Hz, 2H), 7.30 – 7.22 (m, 2H), 7.20 (s, 1H), 5.95 – 5.76 (m, 1H), 5.18 – 4.98 (m, 2H), 2.53 – 2.43 (m, 4H) ppm. **¹³C NMR** (151 MHz, CDCl₃) δ = 170.6, 136.8, 136.5,

129.3, 129.1, 121.1, 116.2, 36.9, 29.4 ppm. Spectroscopic data for **1c** match those previously reported in the literature.[II]

1d
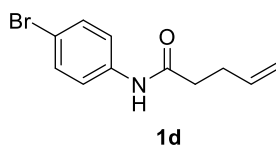
N-(4-bromophenyl)pent-4-enamide (1d). Following the General Procedure B, 4-pentenoic acid (1.22 mL, 12.0 mmol), 4-bromoaniline (2.064 g, 12.0 mmol), DMAP (146 mg, 1.22 mmol) and EDC (2.53 g, 13.2 mmol) in 20 mL of DCM were used, affording the product as a white solid (1.93 g, 62% yield). **¹H NMR** (600 MHz, CDCl₃) δ = 7.58 – 7.31 (m, 4H), 6.05 – 5.74 (m, 1H), 5.13 (d, *J* = 17.2 Hz, 1H), 5.08 (d, *J* = 10.3 Hz, 1H), 2.48 (tt, *J* = 14.6, 10.5, 8.4 Hz, 4H) ppm. **¹³C NMR** (151 MHz, CDCl₃) δ = 170.8, 137.0, 136.8, 132.0, 121.5, 116.9, 116.1, 36.8, 29.4 ppm. Spectroscopic data for **1d** match those previously reported in the literature.[III]

1e
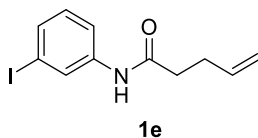
N-(3-iodophenyl)pent-4-enamide (1e) Following the General Procedure B, 4-pentenoic acid (1.22 mL, 12.0 mmol), 3-iodoaniline (2.62 g, 12.0 mmol), DMAP (146 mg, 1.22 mmol) and EDC (2.53 g, 13.2 mmol) in 20 mL of DCM were used, affording the product as a white solid (2.11 g, 58% yield). **¹H NMR** (400 MHz, CDCl₃) δ = 7.92 (s, 1H), 7.45 (dd, *J* = 14.8, 8.0 Hz, 2H), 7.02 (dd, *J* = 8.9, 7.2 Hz, 1H), 5.87 (ddt, *J* = 16.9, 10.6, 5.9 Hz, 1H), 5.09 (dd, *J* = 24.1, 13.6 Hz, 2H), 2.47 (d, *J* = 8.8 Hz, 4H) ppm **¹³C NMR** (151 MHz, CDCl3) δ = 170.6, 139.0, 136.8, 133.4, 130.6, 128.6, 119.0, 116.2, 94.2, 36.8, 29.4 ppm. Spectroscopic data for **1e** match those previously reported in the literature.[IV]

1f
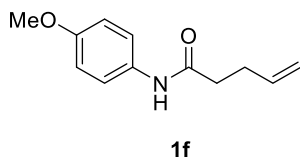
N-(4-methoxyphenyl)pent-4-enamide (1f). Following the General Procedure A, 4-pentenoic acid (0.5 mL, 4.89 mmol), p-anisidine (615 mg, 5.38 mmol), DMAP (61 mg, 0.48 mmol) and DCC (1.03 g, 7.34 mmol) in 15 mL of DCM were used, affording the product as a brown solid powder (832 mg, 83% yield). **¹H NMR** (500 MHz, CDCl₃) δ = 7.50 – 7.31 (m, 2H), 7.24 (bs, 1H), 6.90 – 6.77 (m, 2H), 5.88 (ddt, *J* = 16.8, 10.2, 6.3 Hz, 1H), 5.09 (dd, *J* = 17.1, 10.2 Hz, 2H), 3.75 (s, 3H), 2.54 – 2.38 (m, 4H) ppm. **¹³C NMR** (126 MHz, CDCl₃) δ = 170.4, 156.4, 136.9, 130.9, 121.8, 115.8, 114.1, 55.5, 36.6, 29.5 ppm. Spectroscopic data for **1f** match those previously reported in the literature.[II]

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1g
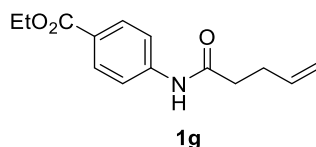
Ethyl 4-(pent-4-enamido)benzoate (1g). Following the General Procedure A, 4-pentenoic acid (0.5 mL, 4.89 mmol), p-anisidine (826 mg, 5.38 mmol), DMAP (61 mg, 0.48 mmol) and DCC (1.03 g, 7.34 mmol) in 15 mL of DCM were used, affording the product as a white solid (966 mg, 80% yield). **^{1}H NMR** (500 MHz, CDCl3) δ = 8.08 – 7.90 (m, 2H), 7.59 (d, J = 8.7 Hz, 2H), 7.53 (s, 1H), 5.96 – 5.77 (m, 1H), 5.22 – 4.97 (m, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.49 (dt, *J* = 3.5, 0.9 Hz, 4H), 1.38 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, CDCl$_3$) δ = 170.7, 166.1, 141.9, 136.6, 130.8, 125.9, 118.7, 116.1, 60.8, 36.9, 29.2, 14.3 ppm. Spectroscopic data for **1g** match those previously reported in the literature.[V]

1h
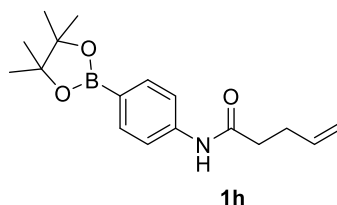
N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pent-4-enamide (1h). Following the General Procedure B, 4-pentenoic acid (2.00 mL, 20.0 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (4.38 g, 20.0 mmol), DMAP (244 mg, 2.00 mmol) and EDC (4.17 g, 22.0 mmol) in 40 mL of DCM were used, affording the product as a white solid (4.49 g, 75% yield). **^{1}H NMR** (600 MHz, CDCl$_3$) δ = 7.76 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.23 (s, 1H), 5.88 (ddt, *J* = 16.8, 10.6, 6.0 Hz, 1H), 5.12 (d, *J* = 17.1 Hz, 1H), 5.06 (d, *J* = 10.3 Hz, 1H), 2.47 (p, *J* = 6.6 Hz, 4H), 1.33 (s, 12H) ppm. **^{13}C NMR** (151 MHz, CDCl$_3$) δ = 170.5, 140.6, 136.9, 135.9, 118.6, 116.1, 83.8, 37.1, 29.4, 25.0 ppm. *(The carbon attached to boron was not observed due to quadrupolar relaxation).* HRMS calcd. for (C$_{17}$H$_{25}$NO$_3$B) [M+H]$^+$: 302.1922, found 302.1920.

1i
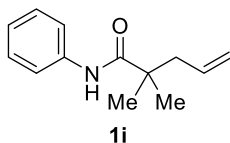
2,2-Dimethyl-N-phenylpent-4-enamide (1i). Following the General Procedure D, 2,2-dimethylpent-4-enoic acid (0.5 g, 3.9 mmol), aniline (0.42 mL, 4.68 mmol), Et$_3$N (1.36 mL, 9.4 mmol) and HATU (1.76 g, 4.68 mmol) in 20 mL of DMF were used, affording the product as a white solid (657 mg, 82% yield). **^{1}H NMR** (500 MHz, CDCl$_3$) δ = 7.53 – 7.48 (m, 2H), 7.36 – 7.29 (m, 3H), 7.13 – 7.07 (m, 1H), 5.93 – 5.76 (m, 1H), 5.21 – 5.09 (m, 2H), 2.38 (d, *J* = 7.4 Hz, 2H), 1.30 (s, 6H) ppm. **^{13}C NMR** (126 MHz, CDCl$_3$) δ = 175.6, 138.0, 134.4, 129.1, 124.4, 120.2, 118.6, 45.4, 43.0, 25.4 ppm. HRMS calcd. for (C$_{13}$H$_{17}$NO) [M+H]$^+$: 204.1388, found 204.1390.

1j
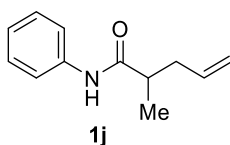
2-Methyl-*N*-phenylpent-4-enamide (1j). Following the General Procedure D, 2-methylpent-4-enoic acid (0.80 mL, 6.86 mmol), aniline (0.57 mL, 6.24 mmol), HATU (2.61 g, 6.86 mmol) and pyridine (0.50 mL, 6.24 mmol) in 12 mL of DCM were used, affording the product as a beige solid (980 mg, 83% yield). **^{1}H NMR** (600 MHz, CDCl$_3$) δ = 7.56 − 7.46 (m, 2H), 7.38 (br. s, 1H), 7.36 − 7.27 (m, 2H), 7.14 − 7.00 (m, 1H), 5.89 − 5.74 (m, 1H), 5.11 (d, *J* = 17.1 Hz, 1H), 5.06 (d, *J* = 8.4 Hz, 1H), 2.55 − 2.36 (m, 2H), 2.28 − 2.16 (m, 1H), 1.24 (d, *J* = 6.8 Hz, 3H) ppm. **^{13}C NMR** (151 MHz, CDCl$_3$) δ = 174.3, 138.0, 135.8, 129.1, 124.4, 120.1, 117.4, 42.3, 38.5, 17.6 ppm. Spectroscopic data for **1j** match those previously reported in the literature.[VI]

1k Ph
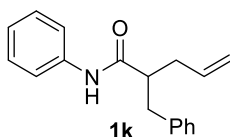
2-benzyl-N-phenylpent-4-enamide (1k). Following the General Procedure B, 2-benzylpent-4-enoic acid (500 mg, 2.63 mmol), aniline (240 µL, 2.63 mmol), DMAP (32 mg, 0.26 mmol) and EDC (554 mg, 2.63 mmol) in 20 mL of DCM were used, affording the product as a white solid (390 mg, 56% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.37 − 7.18 (m, 10H), 7.15 − 7.05 (m, 1H), 6.85 (s, 1H), 5.87 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H), 5.17 (dq, J = 17.1, 1.5 Hz, 1H), 5.11 (ddt, J = 10.1, 1.9, 1.0 Hz, 1H), 3.03 (dd, J = 13.5, 9.0 Hz, 1H), 2.88 (dd, J = 13.5, 5.1 Hz, 1H), 2.56 (ddtd, J = 22.7, 10.1, 8.5, 6.1 Hz, 2H), 2.45 − 2.28 (m, 1H) ppm. **^{13}C NMR** (151 MHz, CDCl$_3$) δ 172.6, 139.7, 137.5, 135.5, 129.0, 128.7, 126.6, 124.4, 120.3, 117.6, 51.1, 38.9, 36.9 ppm. HRMS calcd. for (C$_{20}$H$_{16}$NO) [M+H]$^+$: 266.1539, found 266.1538.

Me
1l
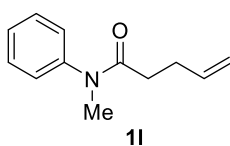
***N*-methyl-N-phenylpent-4-enamide (1l).** Following the General Procedure C, 4-pentenoic acid (1.0 mL, 9.78 mmol), N-methylaniline (1.62 mL, 15.11 mmol), Et$_3$N (5.71 mL, 40.9 mmol) and methyl carbonochloridate (0.87 mL, 9.78 mmol) in 30 mL of THF were used, affording the product as yellow oil (1.40 g, 74% yield). **^{1}H NMR** (500 MHz, CDCl$_3$) δ = 7.43-7.38 (m, 2H), 7.36-7.30 (m, 1H), 7.22 − 7.10 (m, 2H), 5.76-5.68 (m, 1H), 4.99 − 4.82 (m, 2H), 3.26 (s, 3H), 2.32 (q, *J* = 7.2 Hz, 2H), 2.15 (t, *J* = 7.6 Hz, 2H) ppm. **^{13}C NMR** (126 MHz, CDCl$_3$) δ = 172.3, 144.1, 137.5, 129.7, 127.7, 127.3, 114.9, 37.3, 33.4, 29.4 ppm. Spectroscopic data for **1l** match those previously reported in the literature.[VII]

1m
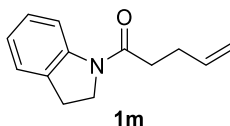
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1-(indolin-1-yl)pent-4-en-1-one (1m). Following the General Procedure B, 4-pentenoic acid (2.00 mL, 20.0 mmol), indoline (2.25 mL, 20.0 mmol), DMAP (244 mg, 2.0 mmol) and EDC (4.17 g, 22.0 mmol) in 40 mL of DCM were used, affording the product as a white solid (2.04 g, 51% yield). **^{1}H NMR** (600 MHz, CDCl$_3$) δ = 8.24 (d, *J* = 8.1 Hz, 1H), 7.19 (q, *J* = 7.0, 6.2 Hz, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 5.93 (ddt, *J* = 16.1, 11.0, 5.7 Hz, 1H), 5.15 − 5.07 (m, 1H), 5.03 (d, *J* = 10.1 Hz, 1H), 4.06 (t, *J* = 8.5 Hz, 2H), 3.20 (t, *J* = 8.5 Hz, 2H), 2.51 (q, *J* = 5.9, 5.1 Hz, 4H) ppm. **^{13}C NMR** (151 MHz, CDCl$_3$) δ = 170.6, 143.1, 137.5, 131.1, 127.7, 124.6, 123.6, 117.1, 115.4, 48.0, 35.3, 28.7, 28.1 ppm. HRMS calcd. for (C$_{13}$H$_{16}$NO) [M+H]$^+$: 202.1226, found 202.1224.

1n
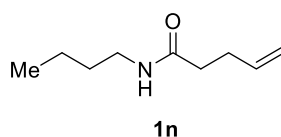
_N_-butylpent-4-enamide (1n). Following the General Procedure D, 4-pentenoic acid (0.5 mL, 4.89 mmol), n-butylamine (0.58 mL, 5.85 mmol), Et$_3$N (1.7 mL, 11.75 mmol) and HATU (2.2 g, 5.85 mmol) in 25 mL of DMF were used, affording the product as pale yellow oil (623 mg, 82% yield). **^{1}H NMR** (500 MHz, CDCl$_3$) δ = 5.81 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.57 (bs, 1H), 5.19 − 4.89 (m, 2H), 3.24 (td, *J* = 7.2, 5.6 Hz, 2H), 2.43 − 2.35 (m, 2H), 2.29 − 2.12 (m, 2H), 1.46 (p, *J* = 7.4 Hz, 2H), 1.33 (dq, *J* = 14.3, 7.3 Hz, 2H), 0.91 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, CDCl$_3$) δ = 172.2, 137.1, 115.5, 39.2, 35.9, 31.7, 29.7, 20.0, 13.7 ppm. Spectroscopic data for **1n** match those previously reported in the literature.[VIII]

1o
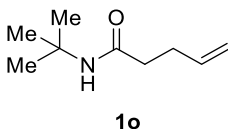
_N_-(tert-butyl)pent-4-enamide (1o). Following the General Procedure D, 4-pentenoic acid (0.5 mL, 4.89 mmol), t-butylamine (0.61 mL, 5.85 mmol), Et$_3$N (1.7 mL, 11.75 mmol) and HATU (2.2 g, 5.85 mmol) in 25 mL of DMF were used, affording the product as pale yellow oil (521 mg, 68% yield). **^{1}H NMR** (500 MHz, CDCl3) δ = 5.81 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.10 − 4.83 (m, 2H), 2.35 (q, *J* = 7.4 Hz, 2H), 2.17 (t, *J* = 7.5 Hz, 2H), 1.33 (s, 9H) ppm. **^{13}C NMR** (126 MHz, CDCl$_3$) δ = 171.6, 137.2, 115.4, 51.2, 36.7, 29.7, 28.8 ppm. **IR** (neat, cm-1): 3364, 3081, 2979, 1736, 1681, 1535, 1508, 1406, 1151. HRMS calcd. for (C$_9$H$_{17}$NNaO) [M+Na]$^+$: 178.1202, found 178.1195.

1p
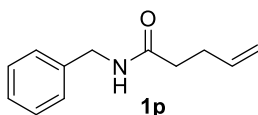
_N_-benzylpent-4-enamide (1p). Following the General Procedure B, 4-pentenoic acid (2.00 mL, 20.0 mmol), benzylamine (2.14 g, 20.0 mmol), DMAP (244 mg, 2.0 mmol) and EDC (4.17 g, 22.0 mmol) in 40 mL of DCM were used, affording the product as a white solid (3.36 g, 89% yield). **^{1}H NMR** (600

MHz, CDCl$_3$) δ = 7.38 – 7.31 (m, 2H), 7.31 – 7.26 (m, 3H), 5.83 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.74 (s, 1H), 5.07 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.01 (dq, *J* = 10.3, 1.4 Hz, 1H), 4.44 (d, *J* = 5.6 Hz, 2H), 2.43 (dd, *J* = 6.0, 1.1 Hz, 2H), 2.37 – 2.23 (m, 2H) ppm. **^{13}C NMR** (151 MHz, CDCl$_3$) δ = 172.1, 138.4, 137.1, 128.8, 127.9, 127.6, 115.8, 43.7, 36.0, 29.7 ppm. HRMS calcd. for (C$_{12}$H$_{16}$NO) [M+H]$^+$: 190.1226, found 190.1226.

1q
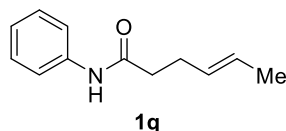
(E)-*N*-phenylhex-4-enamide (1q). Following the General Procedure A, (E)-hex-4-enoic acid (1.14 g, 10.0 mmol), aniline (0.91 mL, 11.1 mmol), DMAP (120 mg, 1.0 mmol) and DCC (2.05 g, 13.35 mmol) in 30 mL of DCM were used, affording the product as a white solid (1.2 g, 63% yield). **^{1}H NMR** (500 MHz, CDCl3) δ = 7.56 – 7.46 (m, 2H), 7.38 – 7.25 (m, 2H), 7.21 (bs, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 5.89 (ddt, *J* = 16.8, 10.9, 6.0 Hz, 1H), 5.35 – 4.94 (m, 2H), 2.63 – 2.37 (m, 4H), 1.66 (d, *J* = 6.0 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 170.4, 137.8, 136.9, 129. 0, 124.3, 119.8, 116.0, 36.9, 29.4, 17.8 ppm. Spectroscopic data for **1q** match those previously reported in the literature.[I]

1r
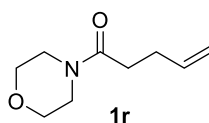
1-Morpholinopent-4-en-1-one (1r). Following the General Procedure D, pent-4-enoic acid (0.70 mL, 6.86 mmol), morpholine (0.54 mL, 6.24 mmol), HATU (2.61 g, 6.86 mmol) and pyridine (0.50 mL, 6.24 mmol) in 12 mL of DCM were used, affording the product as a colorless oil (550 mg, 52% yield). **^{1}H NMR** (600 MHz, CDCl$_3$) δ = 5.91 – 5.77 (m, 1H), 5.05 (dd, *J* = 17.0, 1.7 Hz, 1H), 4.99 (dd, *J* = 10.0, 1.7 Hz, 1H), 3.70 – 3.56 (m, 6H), 3.48 – 3.42 (m, 2H), 2.42 – 2.36 (m, 4H) ppm. **^{13}C NMR** (151 MHz, CDCl$_3$) δ = 171.1, 137.4, 115.5, 67.1, 66.8, 46.1, 42.0, 32.4, 29.3 ppm. Spectroscopic data for **1r** match those previously reported in the literature.[IX]

1s
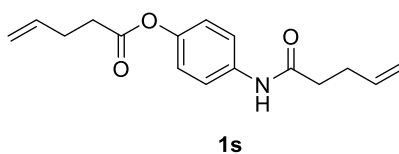
4-(pent-4-enamido)phenyl pent-4-enoate (1s). Following the General Procedure A, 4-pentenoic acid (0.5 mL, 4.89 mmol), 4-aminophenol (545 mg, 5.38 mmol), DMAP (61 mg, 0.48 mmol) and DCC (1.03 g, 7.34 mmol) in 15 mL of DCM were used, affording the product as a pale brown solid (400 mg, 59% yield). **Mp**: 111 – 109 ºC. **^{1}H NMR** (500 MHz, CDCl$_3$) δ = 7.55 – 7.36 (m, 2H), 7.23 (bs, 1H), 7.10 – 6.96 (m, 2H), 5.89 (m, 2H), 5.20 – 4.95 (m, 4H), 2.65 (t, *J* = 7.4 Hz, 2H), 2.55 – 2.39 (m, 6H) ppm. **^{13}C NMR** (126 MHz, CDCl$_3$) δ = 171.7, 170.4, 146.8, 136.8, 136.2, 135.5, 121.9, 120.8, 115.9, 36.7, 33.6,

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29.4, 28.8 ppm. **IR** (neat, cm^{-1}): 3364, 1736, 1681, 1535, 1508, 1151, 913. HRMS calcd. for (C$_{16}$H$_{17}$NO$_3$) [M+H]$^+$: 272.1292, found 272.1284.

1t
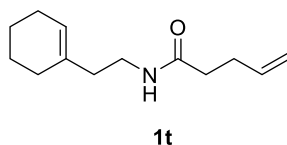
N-(2-(cyclohex-1-en-1-yl)ethyl)pent-4-enamide (1t). Following the General Procedure D, 4-pentenoic acid (0.5 mL, 4.89 mmol), 2-(cyclohex-1-en-1-yl)ethan-1-amine (0.82 mL, 5.85 mmol), Et$_3$N (1.7 mL, 11.75 mmol) and HATU (2.2 g, 5.85 mmol) in 25 mL of DMF were used, affording the product as pale yellow semisolid-oil (670 mg, 66% yield). **Mp**: 30 – 32 °C. **^{1}H NMR** (500 MHz, CDCl$_3$) δ = 5.95 – 5.68 (m, 1H), 5.45 (s, 2H), 5.10 – 4.96 (m, 2H), 3.32 (q, J = 6.2 Hz, 2H), 2.37 (q, J = 7.2 Hz, 2H), 2.25 (t, J = 7.4 Hz, 2H), 2.11 (t, J = 6.7 Hz, 2H), 1.99 (s, 2H), 1.91 (s, 2H), 1.62 (p, J = 5.8 Hz, 2H), 1.55 (p, J = 6.1 Hz, 2H) ppm. **^{13}C NMR** (126 MHz, CDCl$_3$) δ = 172.1, 137.1, 134.6, 123.5, 115.5, 37.6, 37.0, 35.9, 29.6, 27.8, 25.2, 22.8, 22.3 ppm. **IR** (neat, cm^{-1}): 3235, 3127, 2954, 2908, 2875, 1648, 1595, 1546, 1443, 710. HRMS calcd. for (C$_{13}$H$_{21}$NO) [M+H]$^+$: 208.1696, found 208.1692.

1u
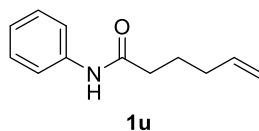
N-phenylhex-5-enamide (1u). Following the General Procedure A, 5-pentenoic acid (1.0 g, 8.76 mmol), aniline (0.8 mL, 9.63 mmol), DMAP (106 mg, 0.88 mmol) and DCC (1.80 g, 13.14 mmol) in 30 mL of DCM were used, affording the product as a white solid (1.28 g, 77% yield). **^{1}H NMR** (300 MHz, CDCl$_3$) δ = 7.55 – 7.50 (m, 2H), 7.36 – 7.28 (m, 2H), 7.16 – 7.13 (bs, 1H), 7.14 – 7.08 (m, 1H), 5.91 – 5.69 (m, 1H), 5.18 – 4.87 (m, 2H), 2.36 (t, J = 7.5 Hz, 2H), 2.16 (q, J = 7.1 Hz, 2H), 1.84 (p, J = 7.4 Hz, 2H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 171.0, 137.8, 129.0, 124.2, 119.7, 115.5, 36.9, 33.0, 24.5 ppm. Spectroscopic data for **1u** match those previously reported in the literature.[X]

1v
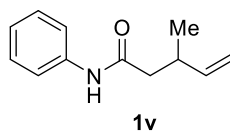
3-methyl-N-phenylpent-4-enamide (1v). Following the General Procedure A, 3-methylpent-4-enoic acid (1.0 mL, 8.76 mmol), aniline (0.8 mL, 9.6 mmol), DMAP (106 mg, 0.88 mmol) and DCC (1.80 g, 13.14 mmol) in 30 mL of DCM were used, affording the product as a white solid (1.16 g, 70% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.57 – 7.44 (m, 2H), 7.31 (m, 2H), 7.10 (t, J = 7.4 Hz, 1H), 5.84 (ddd, J = 17.3, 10.3, 7.0 Hz, 1H), 5.08 (dd, J = 7.0, 10.0 Hz, 2H), 2.80 (qddd, J = 17.2, 10.2, 7.0, 2.1 Hz, 1H), 2.49 – 2.24 (m, 2H), 1.12 (d, J = 6.8 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 167.0, 142.6, 137.8, 129.0, 124.3, 119.9, 113.9, 44.8, 34.8, 19.7 ppm. Spectroscopic data for **1v** match those previously reported in the literature.[VI]

4.5.4   Remote alkene hydroboration of amides catalyzed by tungsten
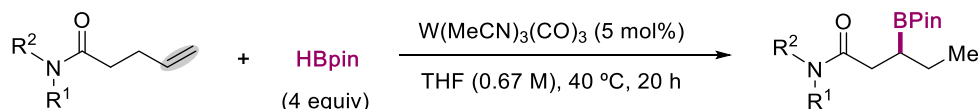
General procedure E: An oven-dried 8 mL screw-cap test tube containing a stirring bar was charged with the alkene-amide (0.20 mmol). The test tube was introduced in an argon-filled glovebox where W(MeCN)$_3$(CO)$_3$ (3.8 mg, 5 mol%) was charged in THF (0.3 mL). Subsequently, HBpin (116 µL, 4 equiv) was added and the tube was taken out of the glovebox and stirred at 40 °C for 20 h at 800 rpm approximately. After the reaction was finished, the reaction mixture was diluted with EtOAc and transferred to a round bottom flask. After evaporation, the crude mixture was purified by flash chromatography column on silica gel eluting with Hexane/EtOAc.

2
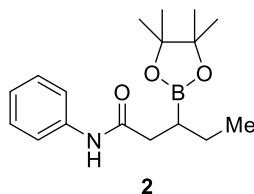
***N*-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanamide (2)** Following General Procedure E, *N*-(phenyl)pent-4-enamide (**1a**) (35.0 mg, 0.20 mmol), W(CO)$_3$(MeCN)$_3$ (4 mg, 5 mol %) and HBpin (116 µL, 4 equiv) were used at 40 °C affording the title compound as a white solid (62 mg, 91% yield) by using DCM/MeCN (95/5) as eluent. **^{1}H NMR** (600 MHz, CDCl$_3$) δ = 7.61 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 7.7 Hz, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 2.51 (dd, *J* = 14.7, 9.4 Hz, 1H), 2.42 (dd, *J* = 14.7, 5.3 Hz, 1H), 1.52 (ddq, *J* = 39.5, 13.7, 7.0 Hz, 2H), 1.38 (dq, *J* = 9.9, 5.5, 3.9 Hz, 1H), 1.26 (d, *J* = 4.2 Hz, 1H), 0.96 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (151 MHz, CDCl$_3$) δ = 171.7, 138.4, 129.0, 123.9, 119.6, 83.5, 39.1, 24.9, 24.9, 24.8, 23.9, 13.4 ppm. HRMS calcd. for (C$_{18}$H$_{28}$BClNO$_3$) [M+H]$^+$: 304.2079, found 304.2078.

3
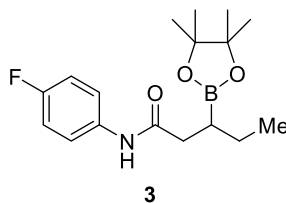
***N*-(4-fluorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanamide (3)**. Following General Procedure E, *N*-(4-fluorophenyl)pent-4-enamide (**1b**) (38.6 mg, 0.20 mmol), W(CO)$_3$(MeCN)$_3$ (4 mg, 5 mol %) and HBpin (116 µL, 4 equiv) were used at 40 °C affording the title compound as a white solid (56 mg, 87% yield) by using DCM/MeCN (95/5) as eluent. Single crystals suitable for X-ray diffraction were grown by slow evaporation from a concentrated EtOAc solution (CCDC 2012996). **^{1}H NMR** (600 MHz, CDCl$_3$) δ = 7.61 (s, 1H), 7.45 (dd, *J* = 8.7, 4.8 Hz, 2H), 6.98 (t, *J* = 8.5 Hz, 2H), 2.49 (dd,

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J = 14.7, 9.5 Hz, 1H), 2.41 (dd, J = 14.7, 5.3 Hz, 1H), 1.54 (dq, J = 14.7, 7.3 Hz, 1H), 1.46 (dq, J = 14.2, 7.2 Hz, 1H), 1.37 (p, J = 6.4, 6.0 Hz, 1H), 1.25 (d, J = 4.8 Hz, 12H) 0.96 (t, J = 7.4 Hz, 3H) ppm. **^{13}C NMR** (151 MHz, CDCl$_3$) δ = 171.1, 158.6 (d, J = 242.7 Hz), 133.8 (d, J = 2.8 Hz), 120.7 (d, J = 7.7 Hz), 115.0 (d, J = 22.5 Hz), 83.0, 38.4, 24.4, 24.3, 23.4, 21.8, 12.8 ppm. **^{19}F NMR** (376 MHz, CDCl$_3$) δ = -118.9 ppm. **HRMS** calcd. for (C$_{18}$H$_{28}$BFNO$_3$) [M+H]$^+$: 322.1984, found 322.1984.

4
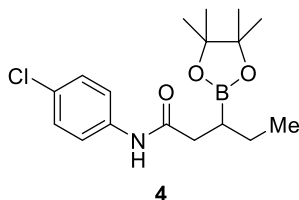
N-(4-chlorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanamide (4). Following General Procedure E, N-(4-chlorophenyl)pent-4-enamide (**1c**) (42.0 mg, 0.20 mmol), W(CO)$_3$(MeCN)$_3$ (4 mg, 5 mol %) and HBpin (116 μL, 4 equiv) were used at 40 °C affording the title compound as a white solid (60 mg, 85% yield) by using DCM/MeCN (95/5) as eluent. **^{1}H NMR** (600 MHz, CDCl$_3$) δ = 7.62 (s, 1H), 7.46 (d, J = 8.5 Hz, 2H), 7.25 (s, 1H), 2.52 – 2.36 (m, 2H), 1.62 – 1.42 (m, 2H), 1.41 – 1.33 (m, 1H), 1.25 (d, J = 5.3 Hz, 12H), 0.96 (t, J = 7.4 Hz, 3H) ppm. **^{13}C NMR** (151 MHz, CDCl$_3$) δ = 171.8, 136.9, 129.0, 128.8, 120.8, 83.6, 39.1, 25.0, 24.9, 24.0, 13.3 ppm (*The carbon attached to boron was not observed due to quadrupolar relaxation*). **HRMS** calcd. for (C$_{18}$H$_{28}$BClNO$_3$) [M+H]$^+$: 338.1689, found 338.1689.

5
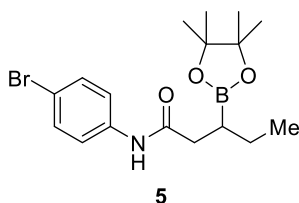
N-(4-bromophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanamide (5). Following General Procedure E, N-(4-bromophenyl)pent-4-enamide (**1d**) (50.8 mg, 0.20 mmol), W(CO)$_3$(MeCN)$_3$ (4 mg, 5 mol %) and HBpin (116 μL, 4 equiv) were used at 40 °C affording the title compound as a white solid (62 mg, 81% yield) by using DCM/MeCN (95/5) as eluent. **^{1}H NMR** (600 MHz, CDCl$_3$) δ = 7.67 (s, 1H), 7.45 – 7.34 (m, 4H), 2.49 (dd, J = 14.8, 9.5 Hz, 1H), 2.41 (dd, J = 14.8, 5.2 Hz, 1H), 1.60 – 1.50 (m, 1H), 1.46 (dp, J = 14.2, 7.2 Hz, 1H), 1.40 – 1.33 (m, 1H), 1.25 (d, J = 5.2 Hz, 12H), 0.95 (t, J = 7.4 Hz, 3H) ppm. **^{13}C NMR** (151 MHz, CDCl$_3$) δ = 171.8, 137.4, 132.0, 121.1, 116.3, 83.6, 39.1, 24.9, 24.9, 23.9, 22.3, 13.3 ppm. **HRMS** calcd. for (C$_{18}$H$_{28}$BBrNO$_3$) [M+H]$^+$: 382.1184, found 382.1183.

6
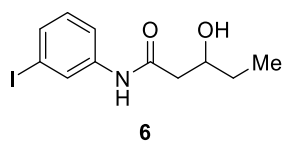
3-hydroxy-N-(3-iodophenyl)pentanamide (6) Following General Procedure E, (**1e**) (60.2 mg, 0.20 mmol) and HBpin (116 µL, 4 equiv) were used at 40 °C. The oxidation to the alcohol was promoted by using H_2O_2 (30 % v/v) (41 uL, 0.400 mmol) with 1 mL aq. NaOH (3 M) and 1 mL THF affording the title compound as a white powder (48 mg, 75% yield) by using Hexane/EtOAc (70/30) as eluent. **¹H NMR** (600 MHz, CDCl₃) δ = 8.00 (s, 1H), 7.94 (t, *J* = 2.0 Hz, 1H), 7.51 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 4.05 (qd, *J* = 7.2, 5.9, 2.5 Hz, 1H), 2.58 (dd, *J* = 15.5, 2.6 Hz, 1H), 2.49 (dd, *J* = 15.5, 8.9 Hz, 1H), 1.69 − 1.50 (m, *J* = 6.8 Hz, 2H), 1.02 (t, *J* = 7.5 Hz, 3H) ppm. **¹³C NMR** (151 MHz, CDCl₃) δ = 170.5, 138.9, 133.4, 130.6, 128.7, 119.2, 94.2, 70.3, 43.6, 30.1, 9.9 ppm. **HRMS** calcd. for ($C_{11}H_{15}INO_2$) [M+H]⁺: 320.0142 , found 320.0141.

7
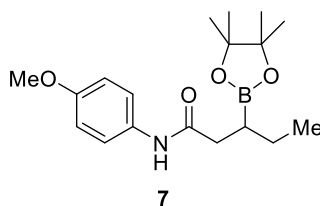
**_N_-(4-methoxyphenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanamide** **(7).** Following General Procedure E, *N*-(4-methoxyphenyl)pent-4-enamide (**1f**) (41.0 mg, 0.20 mmol) and HBpin (116 µL, 4 equiv) were used at 40 °C, affording the title compound as a brownish solid (55 mg, 85% yield) by using Hexane/EtOAc (70/30) as eluent. **Mp:** 107 - 105 °C. **¹H NMR** (500 MHz, CDCl₃) δ = 7.51 (bs, 1H), 7.43 − 7.36 (m, 2H), 6.89 − 6.77 (m, 2H), 3.77 (s, 3H), 2.53 − 2.35 (m, 2H), 1.60 − 1.42 (m, 2H), 1.42 − 1.35 (m, 1H), 1.25 (s, 12H), 0.95 (t, *J* = 7.4 Hz, 3H) ppm. **¹³C NMR** (126 MHz, CDCl₃) δ = 171.4, 156.0, 131.4, 121.3, 114.0, 83.3, 55.4, 38.8, 24.8, 24.7, 23.9, 13.2 ppm. (*The carbon attached to boron was not observed due to quadrupolar relaxation*). **IR** (neat, cm⁻¹): 3365, 2961, 1677, 1508, 1408, 1299, 1218, 1142, 828. **HRMS** calcd. for ($C_{18}H_{29}BNO_4$) [M+H]⁺: 333.2220, found 333.2224.

8
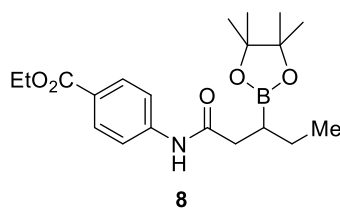
Ethyl 4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanamido)benzoate (8). Following General Procedure E, Ethyl 4-(pent-4-enamido)benzoate (**1g**) (50 mg, 0.20 mmol) and HBpin (116 µL, 4 equiv) were used at 40 °C, affording the title compound as a white solid (51 mg, 65% yield) by using Hexane/EtOAc (75/25) as eluent. **Mp:** 119 - 117 °C. **¹H NMR** (400 MHz, CDCl₃) δ = 8.08 − 7.94 (m, 2H), 7.83 (bs, 1H), 7.66 − 7.52 (m, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.58 − 2.41 (m, 2H), 1.62 − 1.43 (m, 2H), 1.42-1.34 (m, 4H), 1.25 (d, *J* = 3.3 Hz, 12H), 0.96 (t, *J* = 7.3 Hz, 3H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 171.9, 166.2, 142.4, 130.7, 125.5, 118.4, 83.5, 60.8, 39.1, 24.8, 24.7, 23.8, 14.3, 13.2 ppm. (*The carbon attached to boron was not observed due to quadrupolar relaxation*). **IR** (neat, cm⁻¹): 3286,

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2961, 1690, 1595, 1527, 1370, 1255, 1143, 1096. **HRMS** calcd. for ($C_{20}H_{31}BNO_5$) [M+H]$^+$: 375.2326, found 375.2324.

9
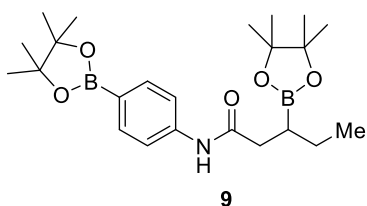
3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)hexanamide (9) Following a modified General Procedure E, *N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pent-4-enamide (**1h**) (60.2 mg, 0.20 mmol), W(CO)$_3$(MeCN)$_3$ (4 mg, 5 mol %) and HBpin (145 µL, 5 equiv) were used at 40 °C for 48 hr affording the title compound as a white solid (58 mg, 65% yield) by using Acetone/Hexanes (10/90) as eluent. **^{1}H NMR** (600 MHz, CDCl$_3$) δ = 7.74 (d, *J* = 8.2 Hz, 2H), 7.63 (s, 1H), 7.51 (d, *J* = 7.9 Hz, 2H), 2.50 (dd, *J* = 14.7, 9.5 Hz, 1H), 2.43 (dd, *J* = 14.7, 5.3 Hz, 1H), 1.55 (dq, *J* = 14.8, 7.3 Hz, 1H), 1.47 (dp, *J* = 14.1, 7.2 Hz, 1H), 1.43 – 1.36 (m, 1H), 1.33 (s, 12H), 1.24 (d, *J* = 4.9 Hz, 12H), 0.96 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (151 MHz, CDCl$_3$) δ = 171.8, 141.0, 135.9, 118.3, 83.8, 83.6, 39.3, 25.0, 24.8, 24.7, 24.0, 13.3 ppm. (*The carbons attached to boron was not observed due to quadrupolar relaxation*). **HRMS** calcd. for ($C_{24}H_{40}B_2NO_5$) [M+H]$^+$: 430.2931, found 430.2939.

10
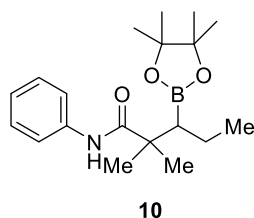
2,2-dimethyl-*N*-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanamide (10). Following General Procedure E, 2,2-dimethyl-*N*-phenylpent-4-enamide (**1i**) (40.6 mg, 0.20 mmol) and HBpin (116 µL, 4 equiv) were used at 40 °C, affording the title compound as a white solid (38 mg, 57% yield) by using Hexane/EtOAc (80/20) as eluent. **Mp:** 162 - 164 °C. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 8.37 (bs, 1H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 1.53 – 1.41 (m, 2H), 1.32 (d, *J* = 1.9 Hz, 12H), 1.29 (bs, 3H), 1.30 – 1.17 (m, 3H), 0.91 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 176.2, 138.8, 128.8, 123.6, 119.5, 83.8, 44.9, 26.5, 25.7, 25.0, 24.9, 20.5, 14.5 ppm. (*The carbon attached to boron was not observed due to quadrupolar relaxation*). **IR** (neat, cm^{-1}): 3284, 2981, 2962, 2871, 1656, 1596, 1532, 1258, 1132, 754. **HRMS** calcd. for ($C_{19}H_{30}BNO_3$) [M+Na]$^+$: 353.2247, found 353.2248.

W-catalyzed remote β-hydroboration of alkenes

11
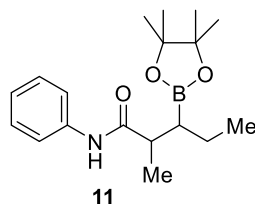
2-Methyl-*N*-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanamide **(11).**
Following General Procedure E, 2-methyl-*N*-phenylpent-4-enamide (**1j**) (37.8 mg, 0.20 mmol) and HBpin (116 μL, 4 equiv) were used at 40 °C, affording the title compound as a colourless solid (58.8 mg, 93% yield) by using CH_2Cl_2/MeCN (97.5/2.5) as eluent. **¹H NMR** (400 MHz, CDCl₃) δ = 7.88 (bs, 1H), 7.57 − 7.50 (m, 2H), 7.33 − 7.27 (m, 2H), 7.18 − 7.00 (m, 1H), 2.58 (m, 1H), 1.59 − 1.48 (m, 2H), 1.32 − 1.18 (m, 16H), 0.95 (t, *J* = 7.5 Hz, 3H) ppm. **¹³C NMR** (151 MHz, CDCl₃) δ = 175.2, 138.7, 129.1, 123.8, 119.5, 83.7, 44.1, 25.1, 25.0, 21.9, 17.5, 13.6 ppm (*The carbon attached to boron was not observed due to quadrupolar relaxation*). **HRMS** calcd. for ($C_{18}H_{28}BNO_3$) [M+H]⁺: 317.2277, found 317.2272.

11a
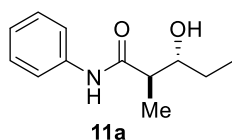
(+/-)-3-Hydroxy-2-methyl-*N*-phenylpentanamide (11a). To a rapidly stirred solution of **11** (22.0 mg, 0.069 mmol) in THF/Et2O (1:1, 0.6 mL) at 0 °C, was added a solution of aq. NaOH (2M)/H_2O_2 (30%) (2:1, 0.7 mL) dropwise. The resulting solution was then warmed to ambient temperature and stirred for 2 h. Et₂O and water were added, and the organic phase was separated, washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification of the residue by FCC hexane/EtOAc (30/70) afforded the title compound as a colourless solid (13.4 mg, 93% yield, >20:1 d.r.). **¹H NMR** (600 MHz, CDCl₃) δ = 7.84 (br. s, 1H), 7.57 − 7.44 (m, 2H), 7.34 − 7.30 (m, 2H), 7.18 − 7.03 (m, 1H), 3.66 (br. s, 1H), 2.81 (br. s, 1H), 2.56 − 2.37 (m, 1H), 1.69 − 1.49 (m, 2H), 1.34 (d, *J* = 7.0 Hz, 3H), 1.01 (t, *J* = 7.0 Hz, 3H) ppm. **¹³C NMR** (151 MHz, CDCl₃) = δ 174.2, 137.9, 129.1, 124.5, 120.1, 75.4, 47.2, 28.4, 15.8, 10.2 ppm. Spectroscopic data for **11a** match those previously reported in the literature.[XI]

12
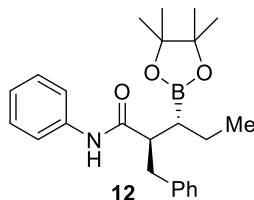
2-benzyl-*N*-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanamide (12). Following General Procedure E, 2-benzyl-*N*-phenylpent-4-enamide (**1k**) (53.1 mg, 0.20 mmol), W(CO)₃(MeCN)₃ (4 mg, 5 mol %) and HBpin (116 μL, 4 equiv) were used at 40 °C affording the title compound as a white solid (66 mg, 81% yield) by using DCM/MeCN (95/5) as eluent. **¹H NMR** (500 MHz, CDCl₃) δ =

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7.38 – 7.18 (m, 10H), 7.06 (t, *J* = 7.3 Hz, 1H), 3.01 (d, *J* = 7.5 Hz, 2H), 2.67 (q, *J* = 7.4 Hz, 1H), 1.65 (p, *J* = 7.3 Hz, 2H), 1.31 (s, 6H), 1,31 (m, 1H), 1.30 (s, 6H), 1.02 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}**C NMR** (126 MHz, CDCl$_3$) δ = 173.6, 140.3, 138.1, 129.1, 128.8, 128.6, 126.4, 123.8, 119.7, 83.5, 52.8, 38.4, 25.0, 25.0, 22.2, 13.5 ppm (*The carbon attached to boron was not observed due to quadrupolar relaxation*). **HRMS** calcd. for (C$_{25}$H$_{35}$BNO$_3$) [M+H]$^+$: 394.2548, found 394.2550.

13
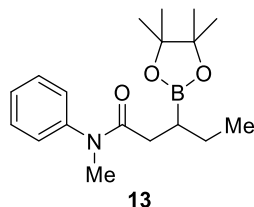
N-methyl-N-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanamide **(13).** Following General Procedure E, *N*-methyl-*N*-phenylpent-4-enamide (**1l**) (37.9 mg, 0.20 mmol) and HBpin (116 µL, 4 equiv) were used at 40 °C, affording the title compound as a yellow oil (45.1 mg, 71% yield) by using Hexane/EtOAc (90/10) as eluent. ^{1}**H NMR** (500 MHz, CDCl$_3$) δ = 7.38 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.3 Hz, 2H), 3.23 (s, 3H), 2.20 – 2.13 (m, 2H), 1.43 – 1.32 (m, 1H), 1.25 (d, *J* = 5.5 Hz, 12H), 1.23 – 1.09 (m, 2H), 0.80 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}**C NMR** (126 MHz, CDCl$_3$) δ = 173.6, 144.2, 129.5, 127.5, 127.2, 82.6, 37.3, 36.1, 24.8, 24.8, 23.5, 13.4 ppm. (*The carbon attached to boron was not observed due to quadrupolar relaxation*). **IR** (neat, cm^{-1}): 3286, 2976, 2930, 1748, 1686, 1655, 1596, 1372, 1134. **HRMS** calcd. for (C$_{18}$H$_{28}$NO$_3$B) [M+H]$^+$: 317.2271, found 317.2266.

14
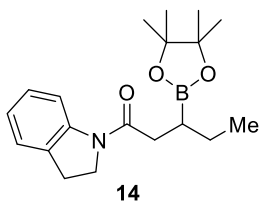
1-(indolin-1-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-1-one **(14)** Following General Procedure E, 1-(indolin-1-yl)pent-4-en-1-one (**1m**) (40.2 mg, 0.20 mmol), W(CO)$_3$(MeCN)$_3$ (4 mg, 5 mol %) and HBpin (116 µL, 4 equiv) were used at 40 °C affording the title compound as a white solid (51 mg, 75% yield) by using DCM/MeCN (95/5) as eluent. Same reaction was performed at gram scale (**1m**, 5 mmol) affording the product in 1.4 g, 85% yield. Single crystals suitable for x-ray diffraction were grown by slow evaporation from acetone (CCDC 2033217). ^{1}**H NMR** (600 MHz, CDCl$_3$) δ = 8.22 (d, *J* = 8.6 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 2H), 7.02 – 6.93 (m, 1H), 4.04 (dtd, *J* = 18.4, 10.1, 8.3 Hz, 2H), 3.17 (t, *J* = 8.5 Hz, 2H), 2.52 (h, *J* = 9.7, 8.9 Hz, 2H), 1.60 – 1.50 (m, 1H), 1.44 (dp, *J* = 14.4, 7.3 Hz, 1H), 1.37 – 1.29 (m, 1H), 1.25 (d, *J* = 15.7 Hz, 12H), 0.97 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}**C NMR** (151 MHz, CDCl$_3$) δ = 171.7, 143.3, 131.0, 127.5, 124.5, 123.3, 117.0, 82.9, 47.8, 38.0, 28.1, 24.9, 24.8, 23.7, 13.7 ppm (*The carbon attached to boron was not observed due to quadrupolar relaxation*). **HRMS** calcd. for (C$_{19}$H$_{29}$NBO$_3$) [M+H]$^+$: 330.2235, found 330.2235.

15
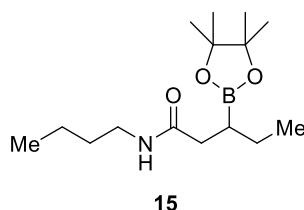
N-butyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanamide (15). Following General Procedure E, *N*-butylpent-4-enamide (**1n**) (31.0 mg, 0.20 mmol) and HBpin (116 μL, 4 equiv) were used at 40 °C, affording the title compound as a white solid (29 mg, 51% yield) by using Hexane/EtOAc (90/10) as eluent. **Mp:** 56 - 58 °C. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 5.59 (s, 1H), 3.31 – 3.18 (m, 2H), 2.40 – 2.17 (m, 2H), 1.54 – 1.39 (m, 4H), 1.39 – 1.30 (m, 2H), 1.30 – 1.28 (m, 1H), 1.25 (d, *J* = 2.4 Hz, 12H), 0.97 – 0.89 (m, 6H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 173.1, 83.1, 39.2, 38.0, 31.8, 24.8, 24.8, 23.8, 20.1, 13.7, 13.3 ppm. (*The carbon attached to boron was not observed due to quadrupolar relaxation*). **IR** (neat, cm^{-1}): 3285, 2974, 2928, 1655, 1597, 1541, 1368, 1145, 725. **HRMS** calcd. for (C$_{15}$H$_{31}$BNO$_3$) [M+H]$^+$: 283.2428, found 283.2434.

16
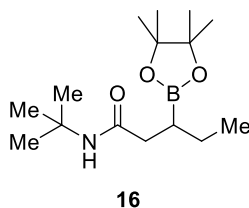
N-(tert-butyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanamide (16). Following General Procedure E, *N*-(tert-butyl)pent-4-enamide (**1o**) (31.0 mg, 0.20 mmol) and HBpin (116 μL, 4 equiv) were used at 40 °C, affording the title compound as a white powder (51 mg, 91% yield) by using Hexane/EtOAc (90/10) as eluent. **Mp:** 41 - 43 °C. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 5.47 (s, 1H), 1.50 – 1.37 (m, 2H), 1.36 – 1.32 (m, 1H), 1.30 (s, 9H), 1.23 (d, *J* = 2.7 Hz, 12H), 0.90 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 172.6, 83.0, 50.9, 38.7, 28.8, 24.8, 24.7, 23.7, 13.3 ppm. (*The carbon attached to boron was not observed due to quadrupolar relaxation*). **IR** (neat, cm^{-1}): 3280, 2971, 2921, 2873, 1650, 1598, 1543, 1368, 1145, 726. **HRMS** calcd. for (C$_{15}$H$_{30}$NO$_3$B) [M+H]$^+$: 283.2428, found 283.2427.

17
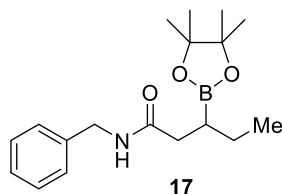
N-benzyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanamide (17): Following General Procedure E, *N*-benzylbut-3-enamide (**1p**) (35 mg, 0.20 mmol), W(CO)$_3$(MeCN)$_3$ (4 mg, 5 mol %) and HBpin (116 μL, 4 equiv) were used at 40 °C affording the title compound as a white solid (52 mg, 82% yield) by using EtOAc/Hexanes (85/15) as eluent. **^{1}H NMR** (600 MHz, CDCl$_3$) δ = 7.49 – 7.22 (m, 5H),

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6.01 (s, 1H), 4.51 – 4.37 (m, 2H), 2.47 – 2.25 (m, 2H), 1.50 (ddq, J = 41.4, 13.7, 7.1 Hz, 2H), 1.38 – 1.32 (m, 1H), 1.31 – 1.15 (m, 12H), 0.96 (t, J = 7.4 Hz, 3H) ppm. ^{13}**C NMR** (151 MHz, CDCl$_3$) δ = 173.2, 138.64, 128.7, 128.0, 127.5, 83.3, 43.7, 37.9, 24.8, 24.8, 24.0, 13.4 ppm (*The carbon attached to boron was not observed due to quadrupolar relaxation*). **HRMS** calcd. for (C$_{18}$H$_{29}$NBO$_3$) [M+H]$^+$: 318.2235, found 318.2234.

18
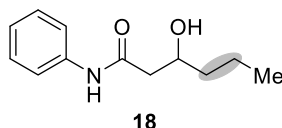
3-hydroxy-N-phenylhexanamide (18). Following General Procedure E, (E)-N-phenylhex-4-enamide (**1q**) (39.0 mg, 0.20 mmol) and HBpin (116 µL, 4 equiv) were used at 40 °C. The oxidation to the alcohol was promoted by using H$_2$O$_2$ (30 % v/v)/aq. NaOH (3 M) in THF/H$_2$O and BHT affording the title compound as a white powder (21 mg, 50% yield) by using Hexane/EtOAc (70/30) as eluent. **Mp:** 82 - 84 °C. ^{1}**H NMR** (400 MHz, CDCl$_3$) δ = 7.77 (s, 1H), 7.51 (d, J = 8.6 Hz, 2H), 7.33 (t, J = 7.9 Hz, 2H), 7.11 (t, J = 7.4 Hz, 1H), 4.12 (td, J = 7.7, 3.2 Hz, 1H), 2.62 – 2.37 (m, 2H), 2.03 (s, 1H), 1.63 – 1.41 (m, 4H), 0.96 (t, J = 7.1 Hz, 3H) ppm. ^{13}**C NMR** (101 MHz, CDCl$_3$) δ = 170.4, 137.6, 129.0, 124.4, 120.0, 68.5, 43.9, 39.1, 18.7, 13.9 ppm. **IR** (neat, cm^{-1}): 3285, 2930, 1748, 1656, 1538, 1505, 1372, 1298, 1133. Spectroscopic data for **18** match those previously reported in the literature.[XII]

19
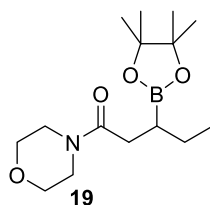
1-Morpholino-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-1-one (19). Following General Procedure E, 1-morpholinopent-4-en-1-one (**1r**) (33.8 mg, 0.20 mmol) and HBpin (116 µL, 4 equiv) were used at 40 °C, affording the title compound as a colourless oil (35.6 mg, 60% yield) by using Hexane/EtOAc (10/90) as eluent. ^{1}**H NMR** (500 MHz, CDCl$_3$) δ = 3.69 – 3.61 (m, 4H), 3.61 – 3.35 (m, 4H), 2.58 – 2.30 (m, 2H), 1.57 – 1.45 (m, 1H), 1.42 – 1.30 (m, 1H), 1.29 – 1.17 (m, 13H), 0.93 (t, J = 7.4 Hz, 3H) ppm. ^{13}**C NMR** (126 MHz, CDCl$_3$) δ = 172.5, 82.7, 67.1, 66.7, 45.9, 42.3, 35.0, 25.0, 24.9, 23.8, 13.7 ppm (*The carbon attached to boron was not observed due to quadrupolar relaxation*). **HRMS** calcd. for (C$_{15}$H$_{28}$BNO$_4$) [M+OH]$^-$: 313.2175, found 313.2177.

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Functionalization of Strong Sigma Bonds by Nickel and Tungsten Catalysis
Raúl Martín Montero

W-catalyzed remote β-hydroboration of alkenes
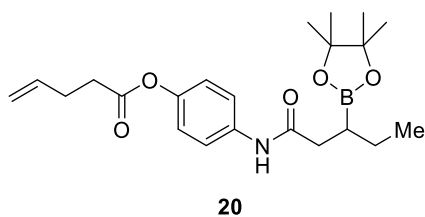
4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanamido)phenyl pent-4-enoate (20). Following General Procedure E, 4-(pent-4-enamido)phenyl pent-4-enoate (**1s**) (54.6 mg, 0.20 mmol) and HBpin (116 μL, 4 equiv) were used at 40 °C, affording the title compound as a white solid (42 mg, 52% yield) by using Hexane/EtOAc (75/25) as eluent. **Mp:** 79 - 81 °C. **¹H NMR** (400 MHz, CDCl₃) δ = 7.64 (bs, 1H), 7.57 – 7.39 (m, 2H), 7.08 – 6.85 (m, 2H), 5.98 – 5.81 (m, 1H), 5.21 – 5.01 (m, 2H), 2.64 (td, *J* = 7.3, 0.9 Hz, 2H), 2.55 – 2.41 (m, 4H), 1.68-1.35 (m, 2H), 1.41 – 1.31 (m, 1H), 1.25 (d, *J* = 3.1 Hz, 12H), 0.96 (t, *J* = 7.3 Hz, 3H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 171.7, 171.5, 146.5, 136.3, 135.9, 121.8, 120.3, 115.9, 83.4, 38.9, 33.6, 28.8, 24.8, 24.7, 23.8, 13.2 ppm (*The carbon attached to boron was not observed due to quadrupolar relaxation*). **IR** (neat, cm⁻¹): 3368, 1686, 1545, 1510, 1251, 913. **HRMS** calcd. for (C₂₂H₃₃BNO₅) [M+H]⁺: 401.2483, found 401.2483.

21
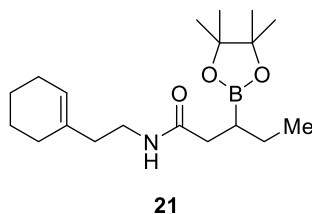
N-(2-(cyclohex-1-en-1-yl)ethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanamide (21). Following General Procedure E, *N*-(2-(cyclohex-1-en-1-yl)ethyl)pent-4-enamide (**1t**) (41.4 mg, 0.20 mmol) and HBpin (116 μL, 4 equiv) were used at 40 °C, affording the title compound as a colorless oil (34 mg, 50% yield) by using Hexane/EtOAc (90/10) as eluent. **¹H NMR** (400 MHz, CDCl₃) δ = 5.51 (bs, 1H), 5.45 (bs, 1H), 3.30 (p, *J* = 6.5 Hz, 2H), 2.35 – 2.16 (m, 2H), 2.10 (t, *J* = 6.8 Hz, 2H), 2.02 – 1.95 (m, 2H), 1.93 – 1.88 (m, *J* = 5.7 Hz, 2H), 1.65 – 1.59 (m, 2H), 1.58 – 1.50 (m, 2H), 1.50 – 1.35 (m, 2H), 1.24 (s, 6H), 1.23 (m, 1H), 1.22 (s, 6H), 0.91 (t, *J* = 7.4 Hz, 3H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 173.0, 134.7, 123.3, 83.1, 37.9, 37.7, 37.1, 27.9, 25.2, 24.8, 24.8, 23.7, 22.8, 22.3, 13.3 ppm. (*The carbon attached to boron was not observed due to quadrupolar relaxation*). **IR** (neat, cm⁻¹): 3226, 2950, 2901, 2875, 1756, 1649, 1595, 1545, 1448, 1263. **HRMS** calcd. for (C₁₉H₃₃BNO₃) [M+H]⁺: 333.2595, found 333.2604.

22
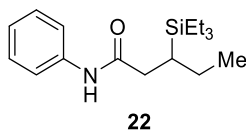
N-phenyl-3-(triethylsilyl)pentanamide (22). Following a modified General Procedure E, N-phenylpent-4-enamide (**1a**) (35.0 mg, 0.20 mmol), B₂Pin₂ (76 mg, 1.5 equiv), CsF (30.4 mg, 1 equiv) and CuF₂ (11.2 mg, 0.5 equiv) were used at 100 °C in Me-THF (1.0 mL) affording the title compound as a white powder (52 mg, 89% yield) by using Hexane/EtOAc (80/20) as eluent. **Mp:** 86 - 84 ºC. **¹H NMR** (400 MHz, CDCl₃) δ = 7.52 (d, *J* = 7.8 Hz, 2H), 7.34 – 7.24 (m, 3H), 7.09 (t, *J* = 7.4 Hz, 1H), 2.44 (dd, *J* = 15.0, 3.8 Hz, 1H), 2.28 – 2.14 (m, 1H), 1.64 – 1.54 (m, 1H), 1.47 – 1.37 (m, 2H), 0.97 (t, *J* = 7.9 Hz, 12H), 0.59 (q, *J* = 7.9 Hz, 6H) ppm. **¹³C NMR** (101 MHz, CDCl₃) δ = 172.0, 138.1, 128.9, 124.1, 119.7,

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38.4, 23.5, 21.6, 14.0, 7.7, 2.7 ppm. **IR** (neat, cm⁻¹): 3234, 2954, 2908, 2874, 1649, 1595, 1545, 1443, 1261, 709. **HRMS** calcd. for ($C_{17}H_{29}NO_2Si$) [M-H]⁻: 290.1946, found 290.1942.

23
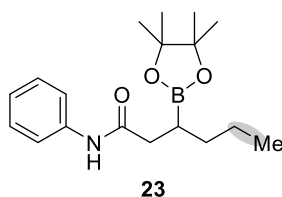
N-(4-bromophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanamide (23). Following a modified General Procedure E, N-(phenyl)hex-5-enamide (**1u**) (37.8 mg, 0.20 mmol), W(CO)₃(MeCN)₃ (7.8 mg, 10 mol %), CuF₂ (15 mg, 50 mol%), cesium fluoride (30,4mg, 0.15 mmol), PCy₃ (8.4 mg, 15 mol%), B₂Bpin₂ (76 mg, 3.0 mmol) were added followed by 2-methyl tetrahydrofuran (1 mL) and isopropyl alcohol (30 µL, 0.40 mmol) and heated to 100 °C affording the title compound as a white solid (25.5 mg, 40% yield) by using acetone/hex (15/85) as eluent. **¹H NMR** (600 MHz, CDCl₃) δ = 7.52 (bs, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.30 (t, J = 7.7 Hz, 2H), 7.07 (t, J = 7.5 Hz, 1H), 2.53 – 2.39 (m, 2H), 1.52 – 1.43 (m, 2H), 1.42 – 1.34 (m, 3H), 1.26 (d, J = 4.4 Hz, 12H), 0.91 (t, J = 7.0 Hz, 3H) ppm. **¹³C NMR** (151 MHz, CDCl₃) δ = 171.65, 138.48, 129.09, 123.95, 119.59, 83.56, 39.44, 33.17, 25.01, 24.92, 22.06, 14.42 ppm. (*The carbon attached to boron was not observed due to quadrupolar relaxation*). HRMS calcd. for ($C_{18}H_{29}BNO_3$) [M+H]⁺: 318.2235, found 318.2235.

24
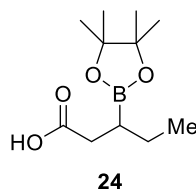
3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoic acid (24) Following General Procedure E, vinyl acetic acid (**B1**) (17 uL, 0.20 mmol), W(CO)₃(MeCN)₃ (4 mg, 5 mol %) and HBpin (116 µL, 4 equiv) were used at 40 °C affording the title compound as a white solid (52 mg, 82% yield) by using EtOAc/Hexanes (65/35) with 1% acetic acid as eluent. The reduced starting material could not be separated from the product. Both the desired product and butanoic acid are known compounds which have previously been characterized. **¹H NMR** (600 MHz, CDCl₃) δ = 2.43 (qd, *J* = 16.8, 7.1 Hz, 2H), 1.40 – 1.31 (m, 1H), 1.25 – 1.18 (m, 12H), 1.00 (d, *J* = 7.5 Hz, 3H) ppm. **¹³C NMR** (151 MHz, CDCl₃) δ = 178.4, 83.4, 37.3, 34.3, 24.8, 15.8, 15.1 ppm.

25

W-catalyzed remote β-hydroboration of alkenes
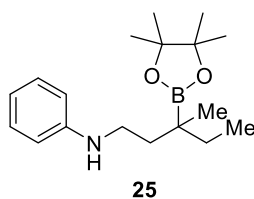
N-(3-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)aniline (25). Following General Procedure E, 3-methyl-N-phenylpent-4-enamide (**1v**) (39.0 mg, 0.20 mmol), W(CO)$_3$(MeCN)$_3$ (6 mg, 7.5 mol %) and HBpin (230 μL, 8 equiv) were used at 100 °C affording the title compound as a brown oil (24 mg, 40% yield) by using Hexane/EtOAc (80/20) as eluent. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.22 − 7.12 (m, 2H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 7.6 Hz, 2H), 3.10 (ddd, *J* = 8.7, 6.4, 2.1 Hz, 2H), 1.77 (ddd, *J* = 13.2, 8.9, 6.9 Hz, 1H), 1.54 − 1.41 (m, 2H), 1.31 (dd, *J* = 13.6, 7.5 Hz, 1H), 1.24 (d, *J* = 3.4 Hz, 12H), 0.96 (s, 3H), 0.87 (t, *J* = 7.5 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 129.2, 117.3, 113.1, 41.5, 38.1, 31.8, 24.9, 24.8, 24.6, 21.0, 9.8 ppm (*The carbon attached to boron was not observed due to quadrupolar relaxation*). **IR** (neat, cm^{-1}): 3364, 2970, 2927, 1602, 1453, 1326, 1143. **HRMS** calcd. for (C$_{18}$H$_{30}$NBO$_2$) [M+H]$^+$: 303.2479, found 303.2474.

26
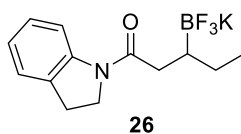
(Indolin-1-yl)-3-(trifluoro-l4-boraneyl)pentan-1-one, potassium salt (26). The title compound was prepared following a modified literature procedure.[XIII] To a solution of 1-(indolin-1-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-1-one **14** (150 mg, 0.46 mmol) in MeCN (2 mL) under nitrogen, was added saturated aq. KHF$_2$ (142 mg, 1.82 mmol, 0.4 mL). The resulting solution was stirred at ambient temperature for 2 h, before being concentrated *in vacuo* and azeotroped with MeOH. The crude product was placed under high vacuum overnight and then extracted with hot MeCN (3 × 10 mL), filtered and concentrated *in vacuo*. The resulting residue was rinsed with in Et$_2$O (2 mL) and sonicated for 30 minutes, before being filtered to afford the title compound as a colourless solid (123 mg, 87% yield). **^{1}H NMR** (600 MHz, DMSO) δ = 8.08 (d, *J* = 8.1 Hz, 1H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.15 − 7.00 (m, 1H), 6.98 − 6.86 (m, 1H), 4.24 − 3.94 (m, 2H), 3.25 − 2.96 (m, 2H), 2.43 − 2.28 (m, 1H), 2.10 − 1.75 (m, 1H), 1.39 − 1.01 (m, 2H), 0.80 (t, *J* = 7.5 Hz, 3H), 0.63 − 0.49 (m, 1H) ppm. **^{13}C NMR** (151 MHz, DMSO) δ = 174.6, 143.7, 131.6, 126.7, 124.5, 122.3, 115.9, 47.7, 38.0, 27.5, 23.9, 13.8 ppm. (*The carbon attached to boron was not observed due to quadrupolar relaxation*). **HRMS** calcd. for (C$_{13}$H$_{16}$BF$_3$KNO) [M-K]$^-$: 269.1317, found 269.1308.

27
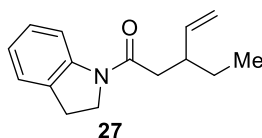
3-Ethyl-1-(indolin-1-yl)pent-4-en-1-one (27). The title compound was prepared following a modified literature procedure.[XIV] To a solution of (Indolin-1-yl)-3-(trifluoro-l4-boraneyl)pentan-1-one, potassium salt **26** (50.0 mg, 0.15 mmol) in THF (1.5 mL), was added vinylmagnesium bromide (0.87 mL, 0.7 M, 0.61 mmol) dropwise and the reaction was stirred at ambient temperature for 30 minutes. The reaction mixture was then cooled to −78 ºC, before a solution of iodine (155 mg, 0.61 mmol) in MeOH (2.0 mL) was added dropwise. The mixture was stirred at −78 ºC for a further 30

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minutes, before a solution of NaOMe (64.8 mg, 1.2 mmol) in MeOH (2.5 mL) was added dropwise. The solution was warmed to ambient temperature and stirred for another 1.5 h, before being diluted with pentane (10 mL) and washed with saturated aq. $Na_2S_2O_3$ (5 mL) and brine (5 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated in *vacuo*. Purification of the crude residue by FCC (hexane/EtOAc 90/10) afforded the title compound as an orange oil (33.5 mg, 96%). **^{1}H NMR** (600 MHz, CDCl$_3$) δ = 8.25 (d, *J* = 8.1 Hz, 1H), 7.21 – 7.10 (m, 2H), 7.07 – 6.93 (m, 1H), 5.81 – 5.63 (m, 1H), 5.15 – 4.95 (m, 2H), 4.16 – 3.95 (m, 2H), 3.26 – 3.07 (m, 2H), 2.78 – 2.33 (m, 3H), 1.71 – 1.32 (m, 2H), 0.95 – 0.85 (m, 3H) ppm. **^{13}C NMR** (151 MHz, CDCl$_3$) δ = 170.4, 143.2, 141.4, 131.2, 127.6, 124.6, 123.6, 117.3, 115.2, 48.3, 41.6, 41.2, 28.1, 27.5, 11.7 ppm. **HRMS** calcd. for ($C_{15}H_{19}NO$) [M+H]$^+$: 230.1545, found 230.1541.

4.5.5   *Control reactions with α,β-unsaturated amides*
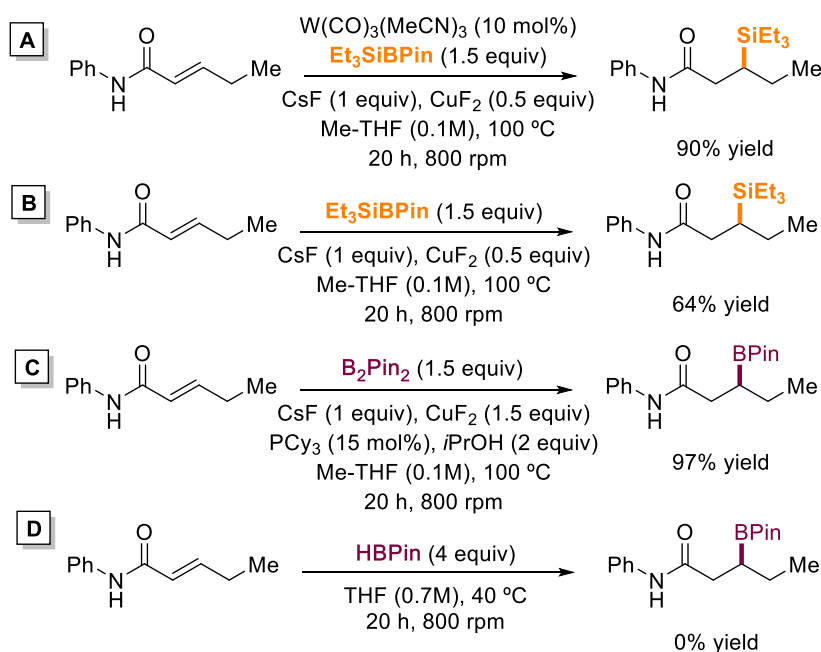
The control reactions for *B* showed that the reaction worked in good yield without the need of the W catalyst. This might point out to a mechanism similar to reaction *C*, where the tungsten promotes the isomerization of the double bond until the formation of the α,β-unsaturated amide allowing a 1,4-hydrosilylation or 1,4-hydroboration likely catalyzed by copper. As depicted, reaction *D* did not yield the product, leading to the conclusion that tungsten is involve in the borylative event or that intermediate is not involved through the catalytic cycle.

UNIVERSITAT ROVIRA I VIRGILI
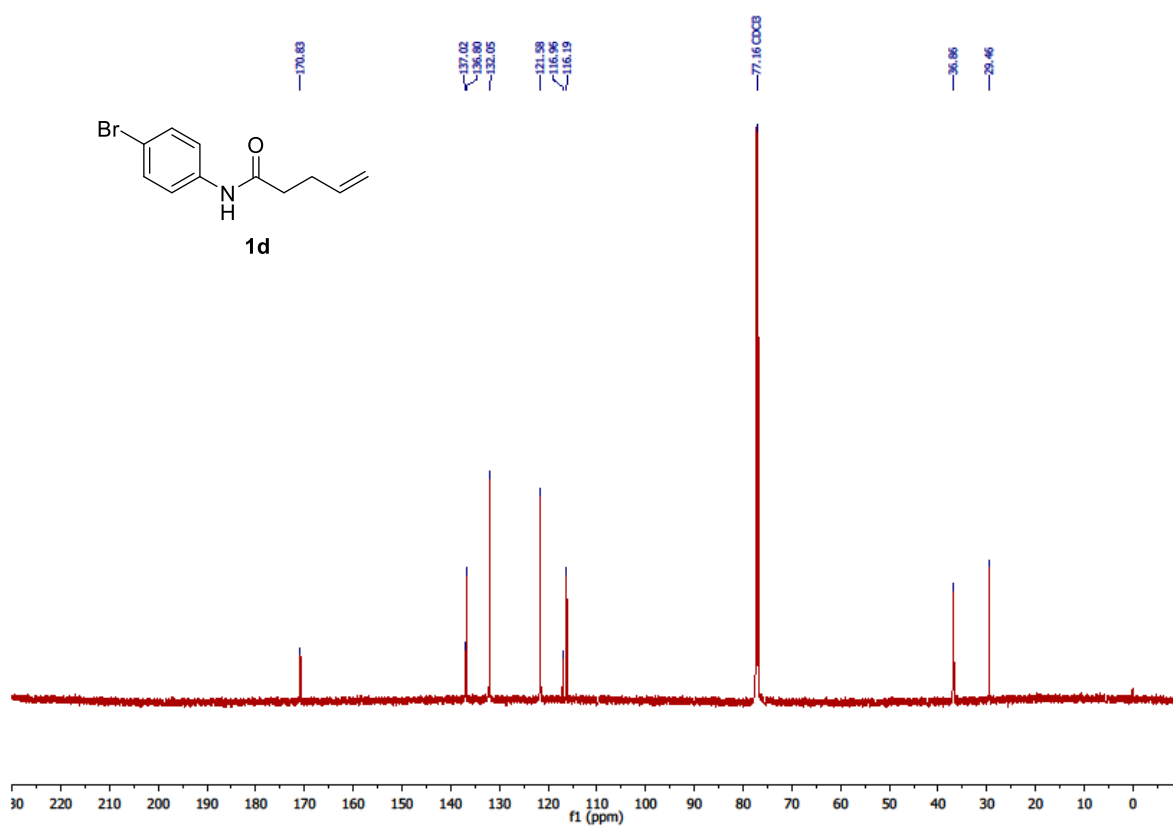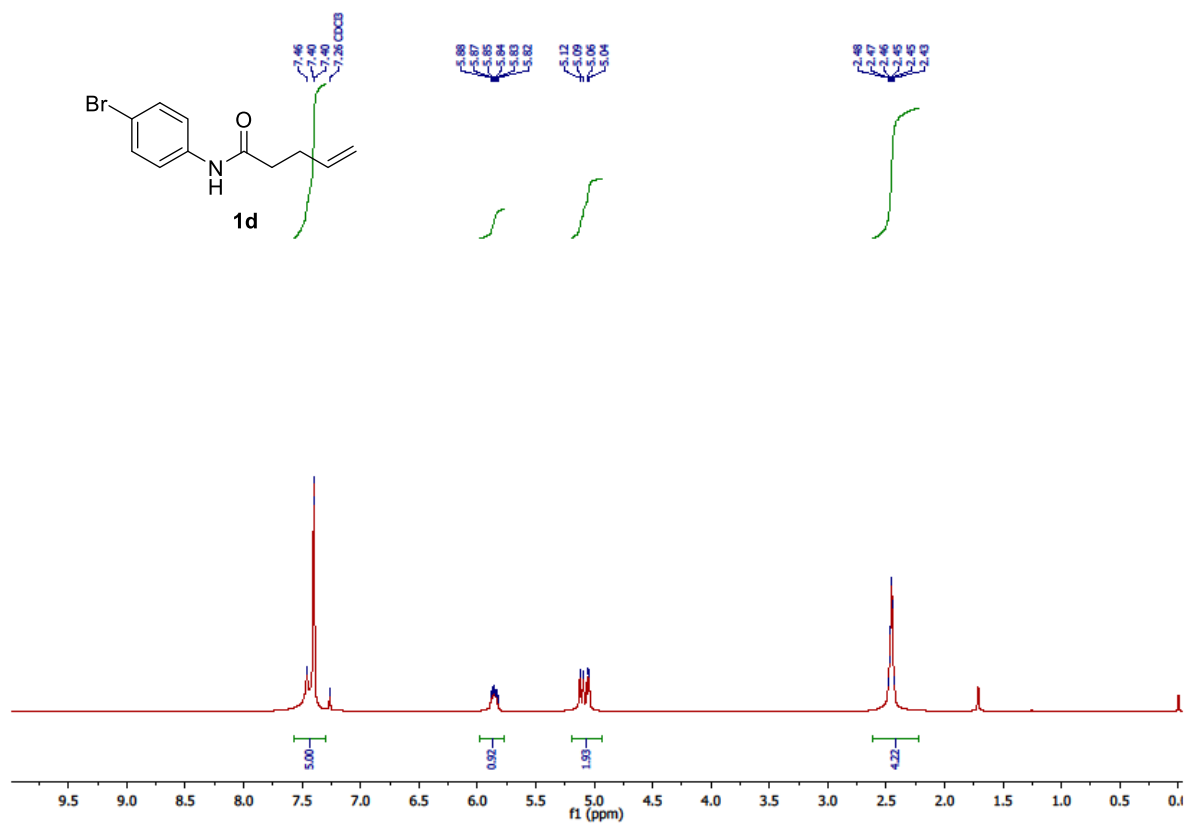Functionalization of Strong Sigma Bonds by Nickel and Tungsten Catalysis
Raúl Martín Montero

W-catalyzed remote β-hydroboration of alkenes

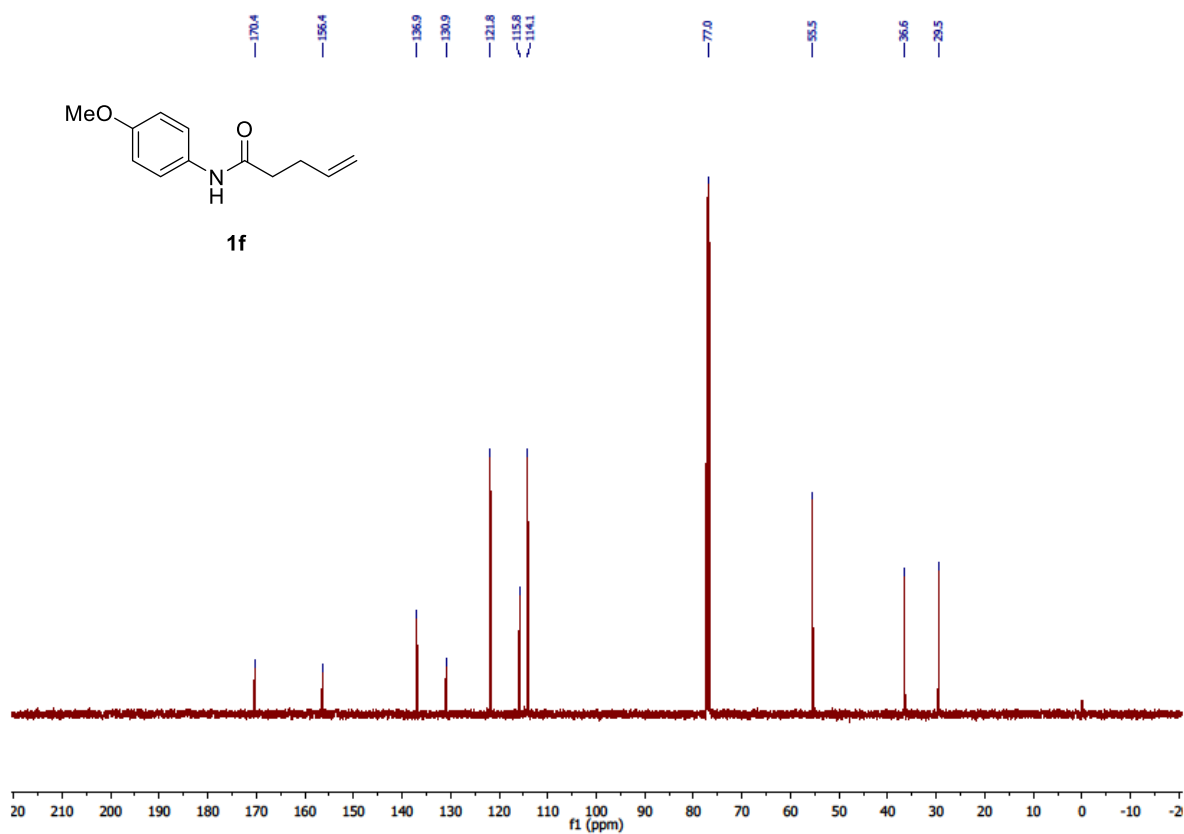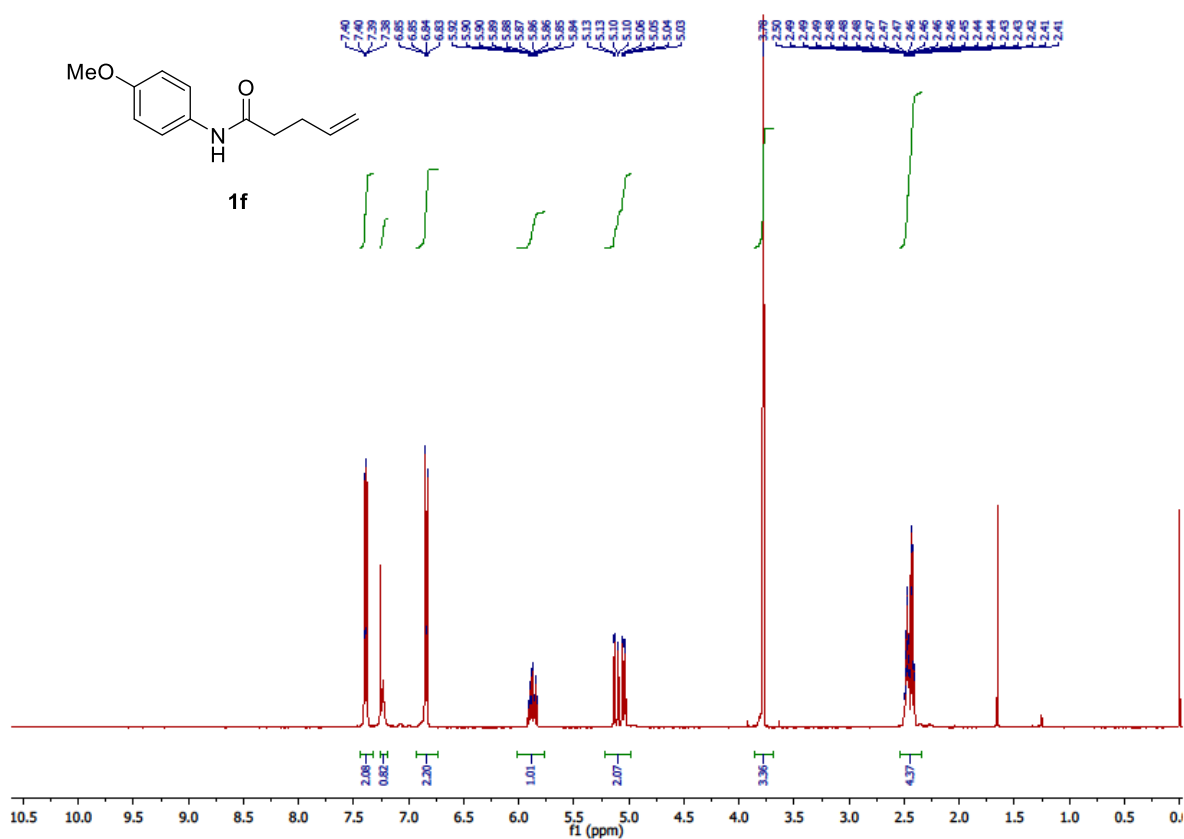### 4.5.6   Deuterium labeling experiments with DBpin
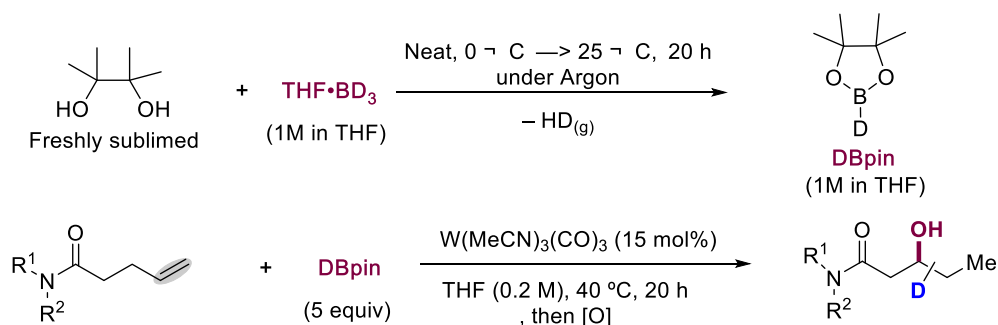
General Procedure F: freshly sublimed pinacol (118 mg, 1.00 mmol) was added to a solution of d3-borane-THF complex 1M (1 mL, 1.00 mmol) (commercial from Alpha Aesar) in a flame dried 6 mL screw top vial, under argon at 0 °C. The reaction mixture stirred in the glovebox and was allowed to warm up to room temperature overnight. The solution of deuterated pinacol borane was used as such, without further purification. Each experiment used freshly prepared DBpin.

To a freshly prepared DBpin solution (1M in THF) was added W(CO)$_3$(MeCN)$_3$ (11.4 mg, 15 mol%) followed by alkene (0.20 mmol). The vial was sealed inside the glovebox, then brought out and heated at 40 °C for 18 hours. The reaction was then allowed to cool to room temperature and 1 mL of 2M aq. K$_2$CO$_3$ was added to the reaction mixture followed by 30% H$_2$O$_2$ v/v (82 μL, 0.800 mmol). The reaction was stirred for 1 hour then diluted with diethyl ether and the organic layer separated, and evaporated to dryness. The crude material was purified by flash chromatography on silica gel using ethyl acetate/hexane (30/70) as eluent.

Quantitative ^{1}H NMR were conducted according to standard procedure outlined by Bruker. The integrations are given as they appear. For ^{13}C NMR or non-deuterated data see above.

Note: the boronic ester cannot accurately be integrated due to some overlapping signal. For this same reason d$_6$-dmso was the solvent of choice to prevent inaccurate integration by residual water.
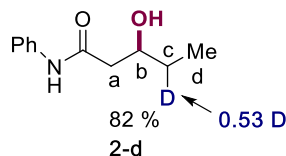
According to General Procedure F, W(CO)$_3$(MeCN)$_3$ (11.4 mg, 15 mol%) was added followed by alkene **1a** (35 mg, 0.20 mmol) and stirred at 40 °C for 18 hours. The oxidation to the alcohol was promoted by using H$_2$O$_2$ (30 % v/v) (82 μL, 0.80 mmol) with 1 mL aq. K$_2$CO$_3$ (2 M) affording the title compound as a white powder (32 mg, 82% yield) by using Hexane/EtOAc (70/30) as eluent. **^{1}H NMR** (600 MHz, DMSO) δ = 9.83 (s, 1.00H), 7.60 (d, *J* = 8.0 Hz, 2.03H), 7.28 (t, *J* = 7.8 Hz, 2.02H), 7.01 (t, *J* = 7.4 Hz, 1.05H), 4.68 (dd, *J* = 5.2, 3.0 Hz, 1.00H, **b**), 3.85 (p, *J* = 5.9 Hz, 1.00H), 2.37 (d, *J* = 6.5 Hz, 2.00H, **a**), 1.41 (dddt, *J* = 34.5, 19.7, 13.2, 7.2 Hz, 1.47H, **c**), 0.88 (d, *J* = 7.8 Hz, 3.02H, **d**) ppm.

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74 %
14-d
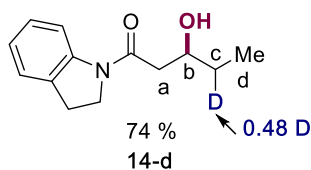
According to General Procedure F, W(CO)₃(MeCN)₃ (11.4 mg, 15 mol%) was added followed by alkene **1m** (40.2 mg, 0.20 mmol) and stirred at 40 °C for 18 hours. The oxidation to the alcohol was promoted by using H_2O_2 (30 % v/v) (82 uL, 0.80 mmol) with 1 mL aq. K_2CO_3 (2 M) affording the title compound as a white powder (32 mg, 74% yield) by using Hexane/EtOAc (70/30) as eluent. **¹H NMR** (600 MHz, DMSO) δ = 8.09 (d, *J* = 8.0 Hz, 0.98H), 7.33 – 7.04 (m, 2.13H), 6.97 (t, *J* = 7.4 Hz, 1.09H), 4.63 (dd, *J* = 5.1, 3.1 Hz, 1.00H, **b**), 4.11 (dq, *J* = 30.8, 9.5 Hz, 2.00H), 3.95 – 3.81 (m, 1.00H), 3.11 (t, *J* = 8.6 Hz, 2.00H), 2.59 – 2.37 (m, 2.49H, **a**), 1.54 – 1.32 (m, 1.52H, **c**), 0.90 (dd, *J* = 8.8, 7.3 Hz, 3.08H, **d**) ppm.

4.5.7   *References of experimental procedures*

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4.5.8   X-Ray of compound 14

Table 1. Crystal data and structure refinement for **14**.

Report date	2020-09-21
Identification code	engle265
Empirical formula	C19 H28 B N O3
Molecular formula	C19 H28 B N O3
Formula weight	329.23
Temperature	100.0 K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P 1 21/c 1
Unit cell dimensions	a = 10.5238(3) Å α= 90°.
	b = 14.0554(3) Å β= 96.2420(10)°.
	c = 25.2685(6) Å γ = 90°.
Volume	3715.46(16) Å^3
Z	8
Density (calculated)	1.177 Mg/m^3
Absorption coefficient	0.614 mm^{-1}
F(000)	1424
Crystal size	0.18 x 0.15 x 0.085 mm^3
Crystal color, habit	colorless plate
Theta range for data collection	3.519 to 58.031°.
Index ranges	-11<=h<=11, 0<=k<=15, 0<=l<=27
Reflections collected	45664
Independent reflections	5245 [R(int) = 0.0627]
Completeness to theta = 58.031°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.751 and 0.504
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5245 / 0 / 444
Goodness-of-fit on F^2	1.126
Final R indices [I>2sigma(I)]	R1 = 0.0505, wR2 = 0.1257
R indices (all data)	R1 = 0.0591, wR2 = 0.1308
Largest diff. peak and hole	0.304 and -0.202 e.Å^{-3}
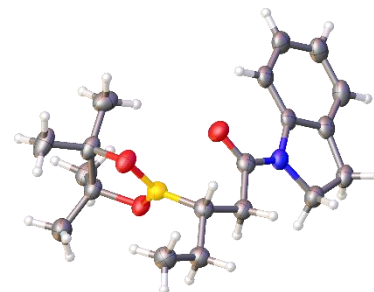
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Anisotropic displacement parameters ($Å^2$x 10^3) The anisotropic displacement factor exponent takes the form: $-2\pi^2[$ $h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}$]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	30(1)	46(1)	46(1)	0(1)	5(1)	-6(1)
O(1')	29(1)	44(1)	49(1)	1(1)	2(1)	1(1)
O(2')	27(1)	35(1)	47(1)	1(1)	5(1)	-3(1)
O(2)	32(1)	28(1)	57(1)	-10(1)	9(1)	-3(1)
O(3)	27(1)	29(1)	50(1)	-3(1)	6(1)	-3(1)
O(3')	30(1)	30(1)	48(1)	8(1)	2(1)	-7(1)
N(1')	28(2)	28(1)	39(2)	2(1)	2(1)	-2(1)
N(1)	30(2)	25(1)	43(2)	-1(1)	2(1)	1(1)
C(1')	49(2)	59(2)	41(2)	9(2)	5(2)	-9(2)
C(1)	48(2)	45(2)	44(2)	-3(2)	3(2)	0(2)
C(2')	46(2)	48(2)	43(2)	0(2)	4(2)	-10(2)
C(2)	40(2)	36(2)	43(2)	1(1)	5(2)	-1(2)
C(3)	35(2)	27(2)	41(2)	-2(1)	2(2)	-2(1)
C(3')	35(2)	34(2)	43(2)	2(1)	2(2)	-4(2)
C(4)	33(2)	26(2)	46(2)	-1(1)	6(2)	-1(1)
C(4')	29(2)	35(2)	46(2)	5(1)	2(1)	-6(1)
C(5')	30(2)	23(2)	44(2)	3(1)	1(2)	-6(1)
C(5)	34(2)	22(2)	44(2)	-1(1)	2(2)	0(1)
C(6)	33(2)	33(2)	49(2)	-2(2)	6(2)	1(2)
C(6')	28(2)	34(2)	46(2)	2(1)	7(2)	-2(1)
C(7')	27(2)	30(2)	45(2)	3(1)	3(1)	-3(1)
C(7)	28(2)	28(2)	56(2)	-3(1)	0(2)	1(1)
C(8')	25(2)	23(2)	42(2)	1(1)	4(1)	2(1)
C(8)	35(2)	22(2)	48(2)	-3(1)	-1(2)	5(1)
C(9')	24(2)	31(2)	47(2)	1(1)	0(2)	3(1)
C(9)	37(2)	35(2)	52(2)	-7(2)	-7(2)	8(2)
C(10')	36(2)	31(2)	42(2)	-2(1)	4(2)	4(2)
C(10)	46(2)	40(2)	45(2)	-4(2)	0(2)	13(2)
C(11')	33(2)	26(2)	44(2)	-2(1)	9(2)	-4(1)
C(11)	40(2)	30(2)	47(2)	-2(1)	7(2)	10(2)
C(12)	32(2)	24(2)	47(2)	-1(1)	1(2)	7(1)
C(12')	24(2)	22(2)	50(2)	-1(1)	3(1)	-2(1)
C(13)	31(2)	20(2)	42(2)	-1(1)	0(2)	7(1)
C(13')	29(2)	18(1)	40(2)	0(1)	1(1)	-1(1)

C(14')	23(2)	30(2)	47(2)	-1(1)	4(1)	-3(1)
C(14)	29(2)	31(2)	56(2)	-12(2)	9(2)	0(1)
C(15)	28(2)	31(2)	47(2)	-3(1)	5(1)	0(1)
C(15')	28(2)	25(2)	46(2)	4(1)	2(1)	-7(1)
C(16')	30(2)	32(2)	64(2)	8(2)	3(2)	0(2)
C(16)	53(2)	32(2)	64(2)	-1(2)	24(2)	-5(2)
C(17)	27(2)	48(2)	86(3)	-23(2)	6(2)	-4(2)
C(17')	41(2)	45(2)	59(2)	-12(2)	4(2)	1(2)
C(18)	35(2)	30(2)	60(2)	-7(2)	6(2)	-7(2)
C(18')	40(2)	34(2)	54(2)	1(2)	10(2)	1(2)
C(19')	28(2)	30(2)	64(2)	4(2)	-4(2)	-1(2)
C(19)	42(2)	49(2)	55(2)	6(2)	8(2)	7(2)
B(1)	34(2)	31(2)	37(2)	-1(2)	4(2)	-7(2)
B(1')	33(2)	34(2)	36(2)	2(2)	1(2)	-2(2)

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Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2x $10^{\ 3}$)for Engle265.

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	x	y	z	U(eq)
H(1'A)	5443	3291	4983	74
H(1'B)	5767	2548	4537	74
H(1'C)	6596	2554	5106	74
H(1A)	9633	3589	4634	68
H(1B)	8627	3846	5044	68
H(1C)	9219	2798	5038	68
H(2'A)	3970	1997	4919	55
H(2'B)	5129	1274	5059	55
H(2A)	10676	4464	5350	47
H(2B)	11264	3415	5346	47
H(3)	9987	2952	6026	42
H(3')	4407	2691	5779	45
H(4A)	12086	3393	6296	42
H(4B)	11715	4499	6291	42
H(4'A)	6247	1190	5983	44
H(4'B)	6559	2307	5998	44
H(6A)	13476	4747	6982	46
H(6B)	13806	3628	6999	46
H(6'A)	8351	2148	6683	43

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H(6'B)	8097	1020	6633	43
H(7'A)	9249	777	7421	41
H(7'B)	9580	1896	7451	41
H(7A)	14950	3829	7792	45
H(7B)	14579	4942	7784	45
H(9')	9022	1389	8528	41
H(9)	14289	4237	8869	51
H(10')	7313	1617	9043	44
H(10)	12560	3899	9347	53
H(11')	5270	1915	8629	41
H(11)	10550	3581	8901	47
H(12)	10222	3588	7967	41
H(12')	4867	1976	7701	39
H(16D)	3116	-1233	6399	63
H(16E)	1672	-972	6484	63
H(16F)	2829	-381	6790	63
H(16A)	6604	3744	6962	73
H(16B)	6536	4847	7115	73
H(16C)	7893	4332	7117	73
H(17A)	5755	4686	5685	81
H(17B)	5230	5172	6191	81
H(17C)	5279	4037	6145	81
H(17D)	2181	-76	5178	73
H(17E)	1391	-871	5456	73
H(17F)	2895	-1000	5433	73
H(18A)	8224	5943	7068	63
H(18B)	7001	6477	6775	63
H(18C)	8408	6803	6668	63
H(18D)	2312	1171	6823	63
H(18E)	963	635	6786	63
H(18F)	1023	1739	6635	63
H(19D)	-185	1389	5772	62
H(19E)	-182	257	5844	62
H(19F)	408	724	5347	62
H(19A)	8107	6541	5699	73
H(19B)	6630	6345	5756	73
H(19C)	7444	5583	5465	73

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W-catalyzed remote β-hydroboration of alkenes

4.5.9 ^{1}H NMR, ^{13}C NMR & ^{19}F NMR spectra

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W-catalyzed remote β-hydroboration of alkenes

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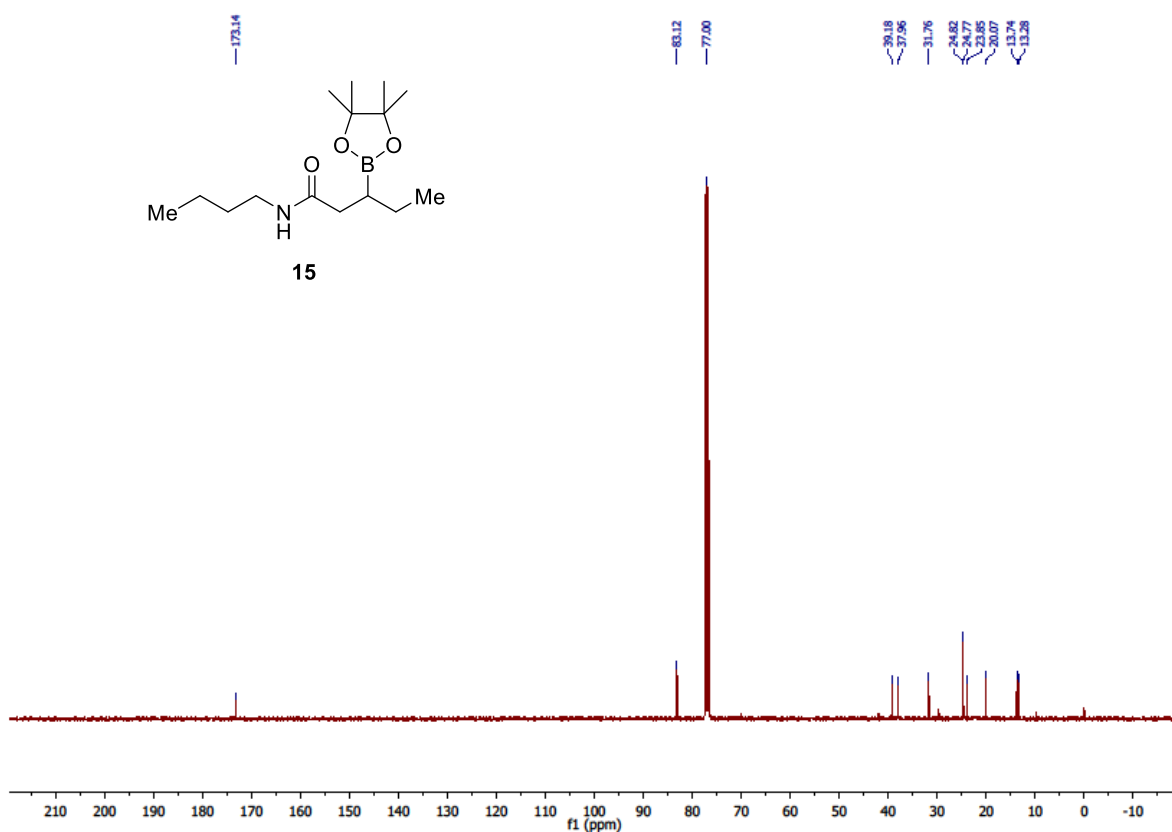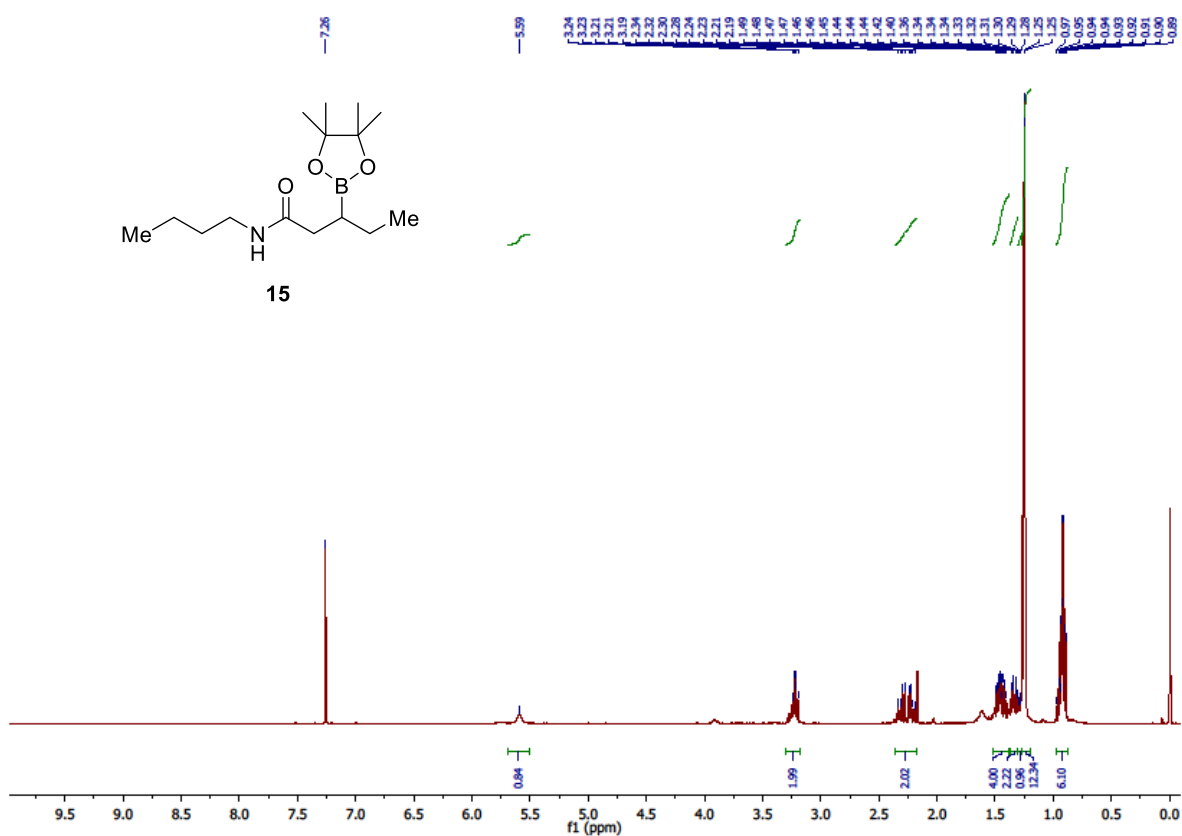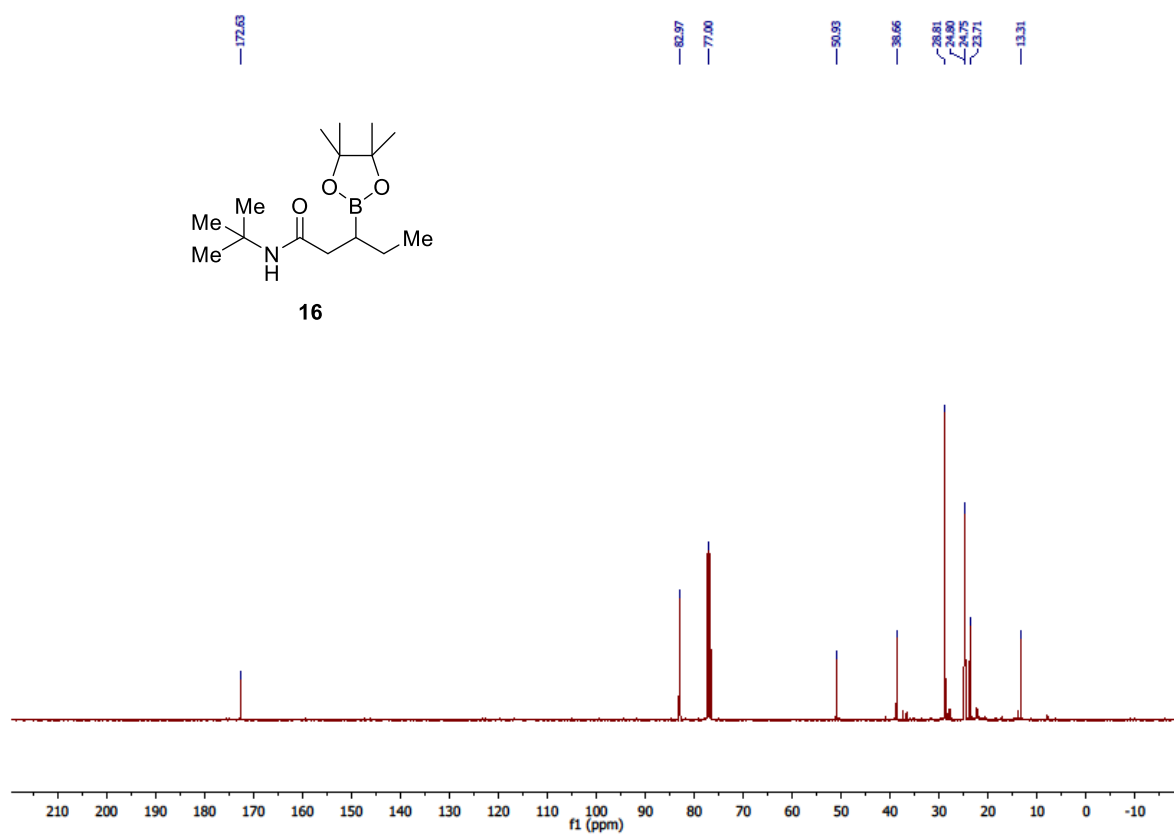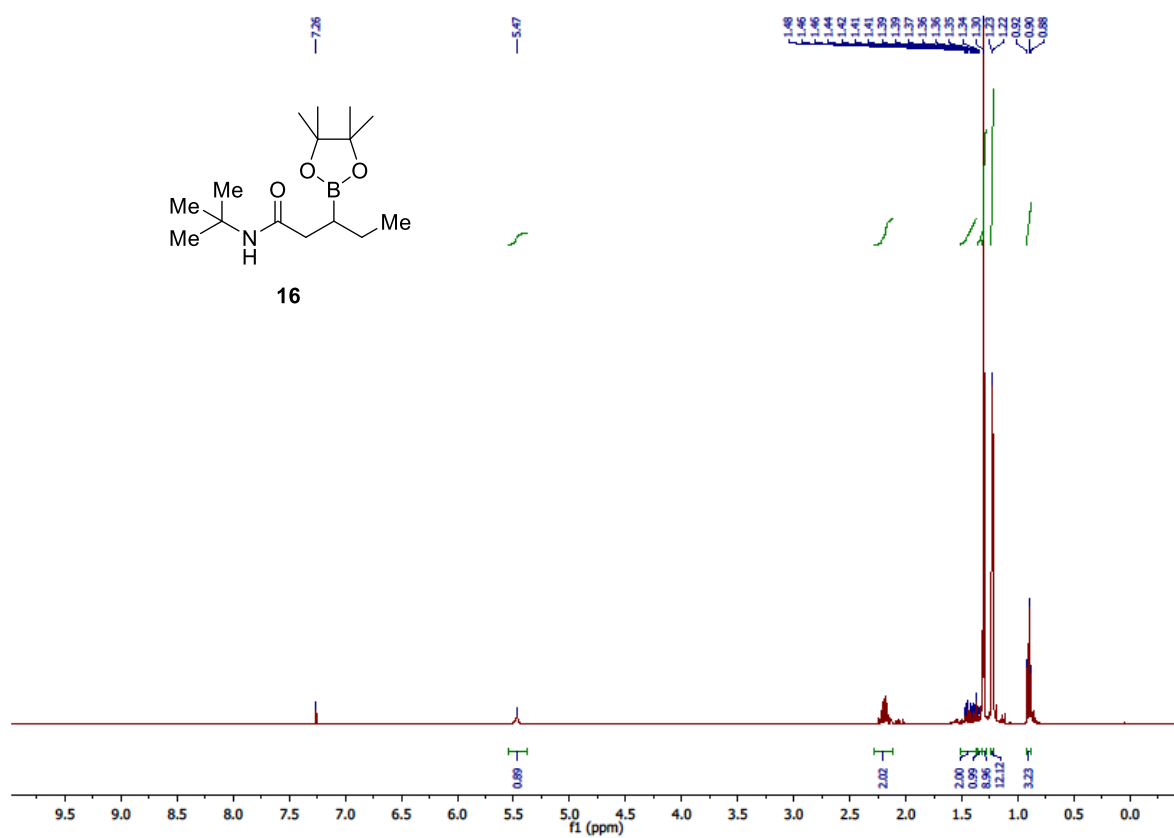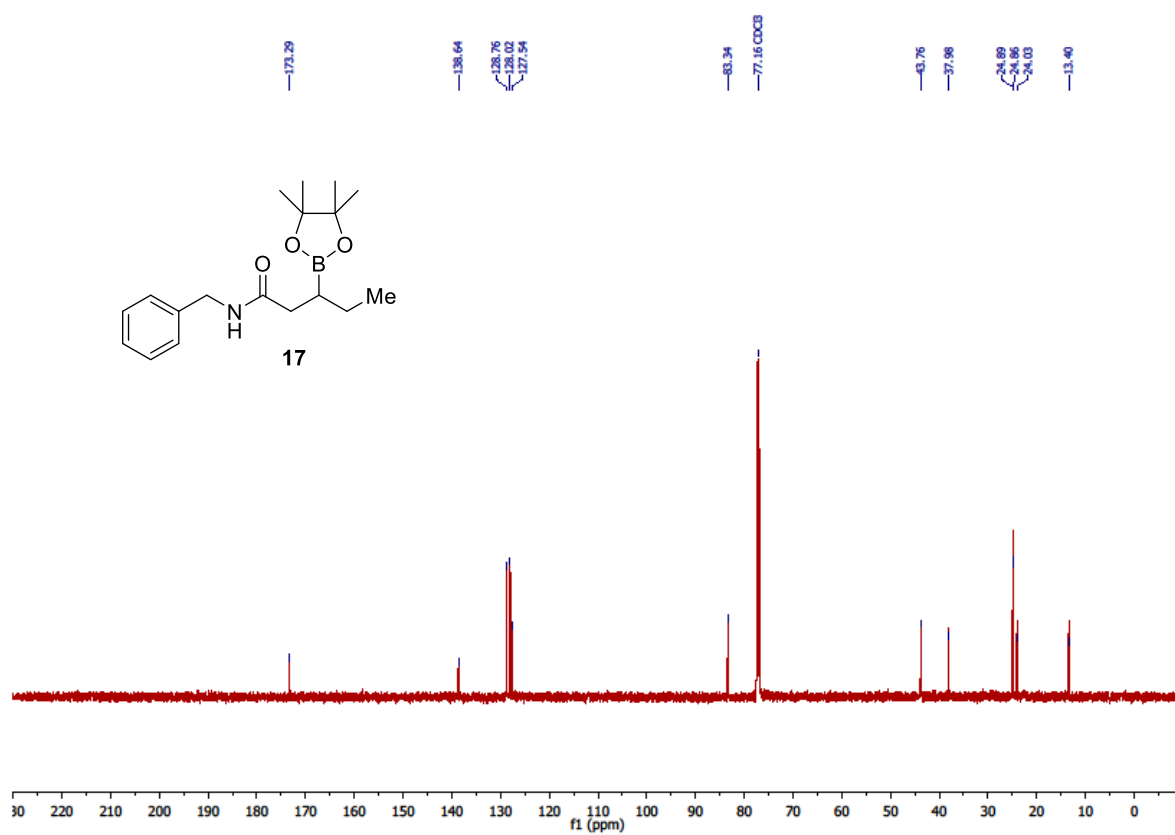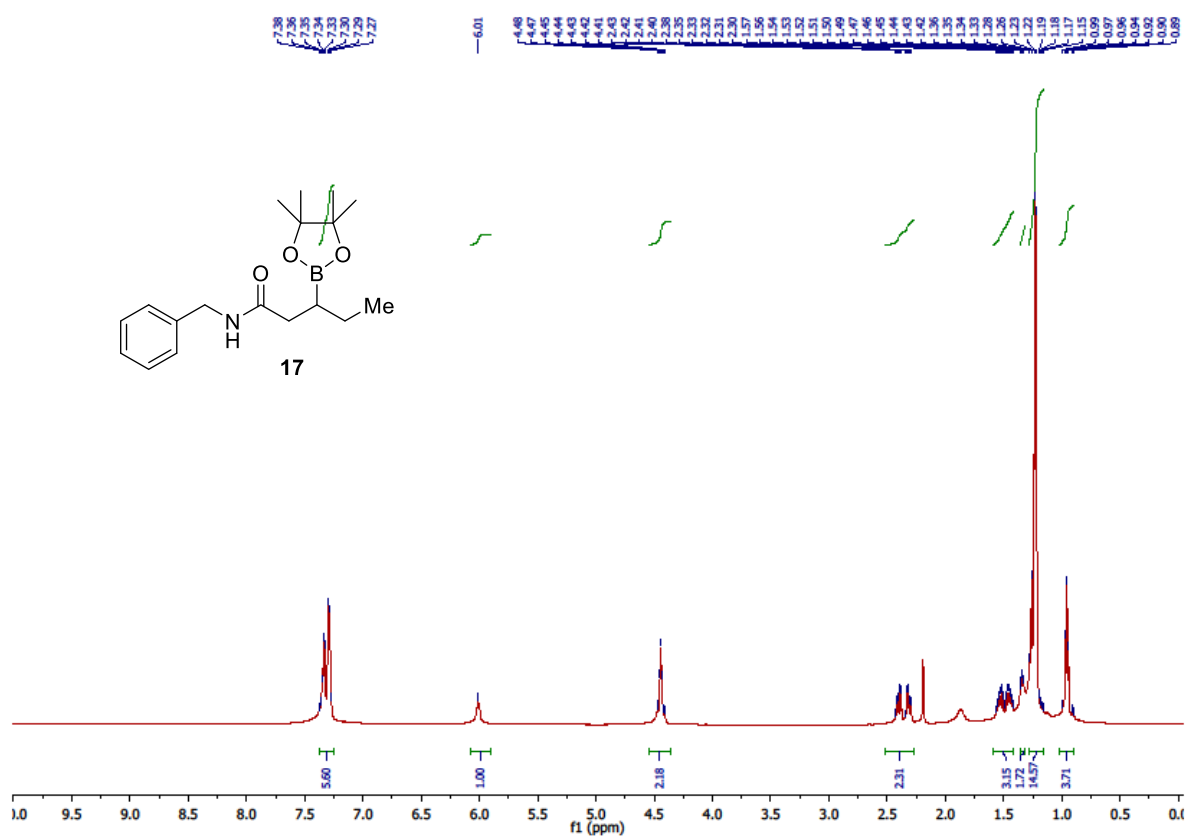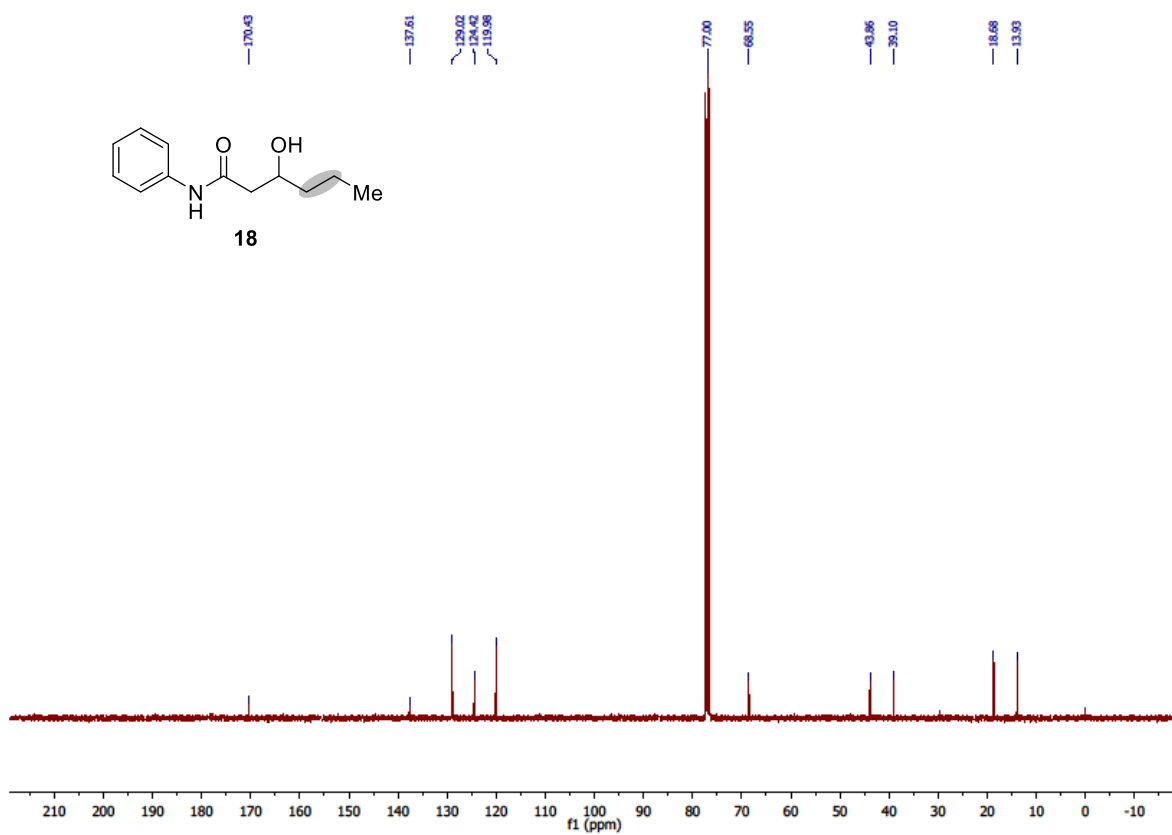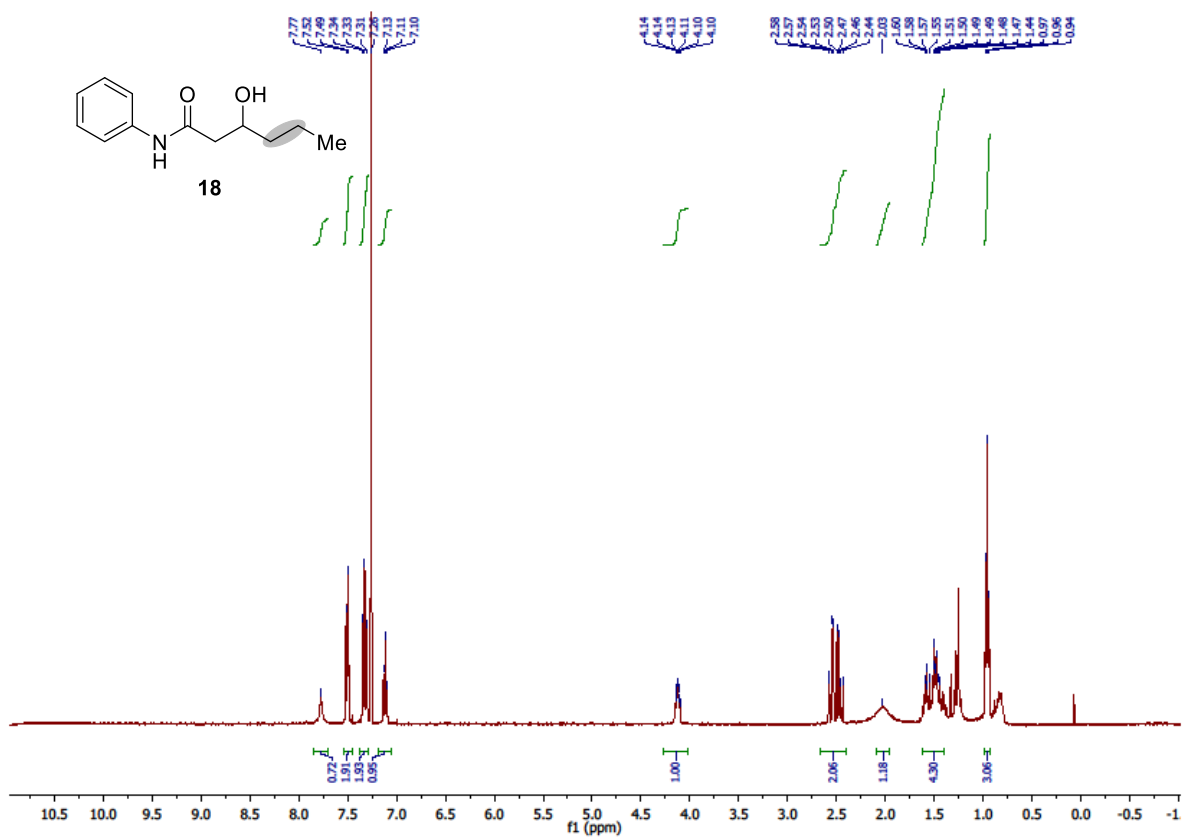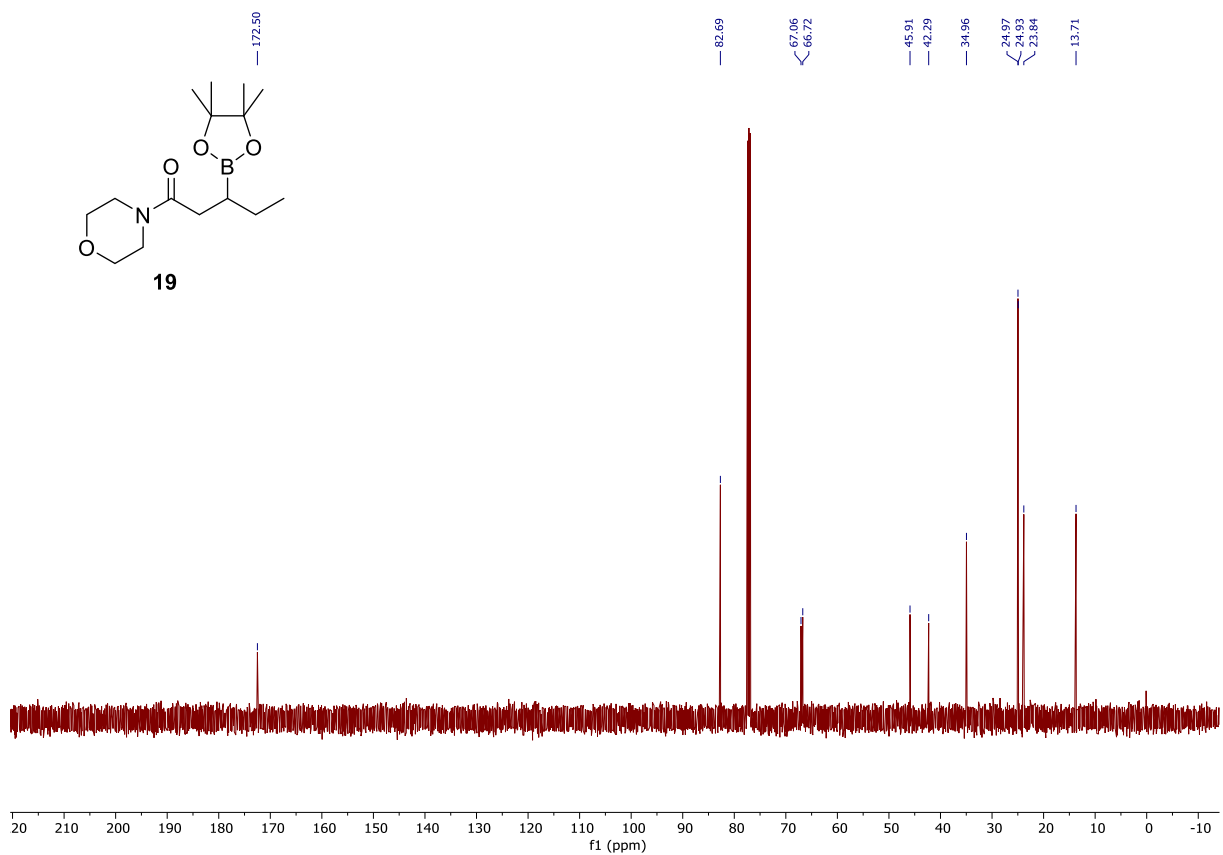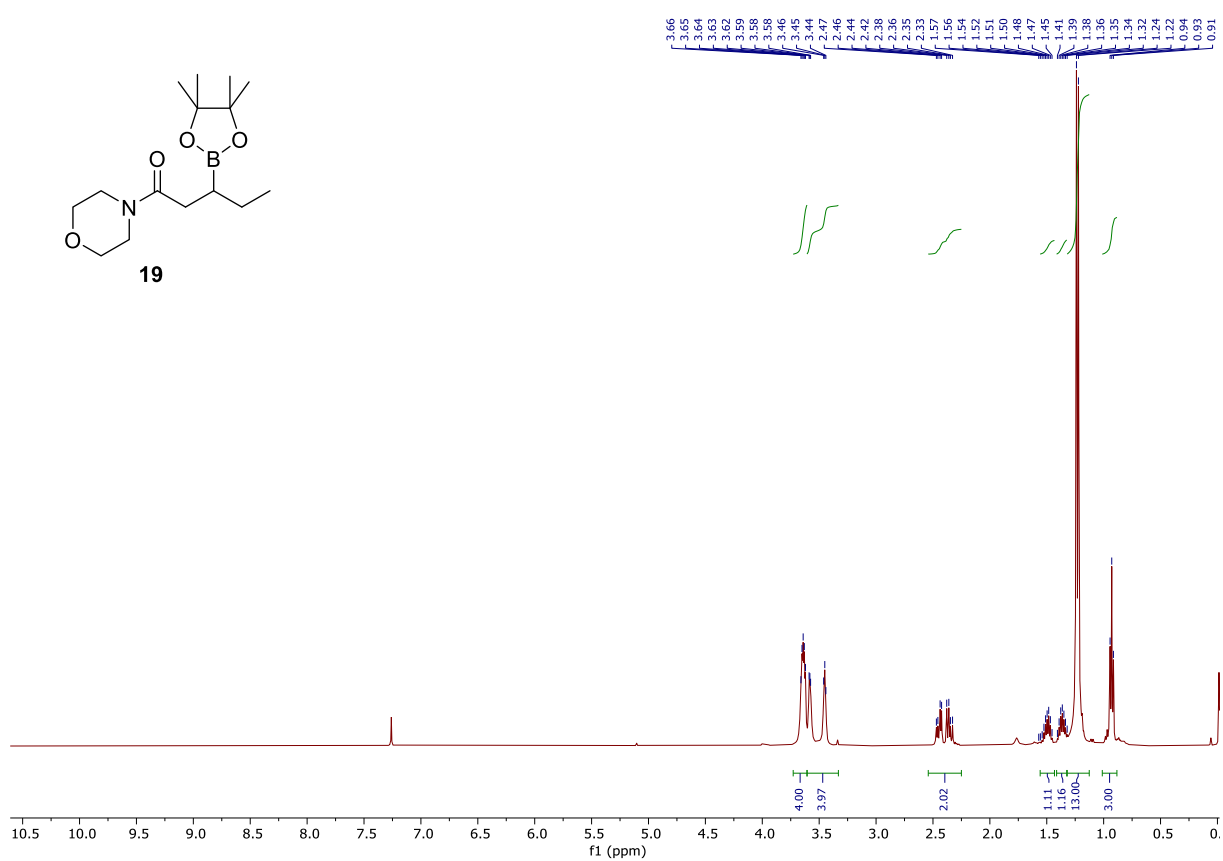*W-catalyzed remote β-hydroboration of alkenes*

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W-catalyzed remote β-hydroboration of alkenes

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W-catalyzed remote β-hydroboration of alkenes

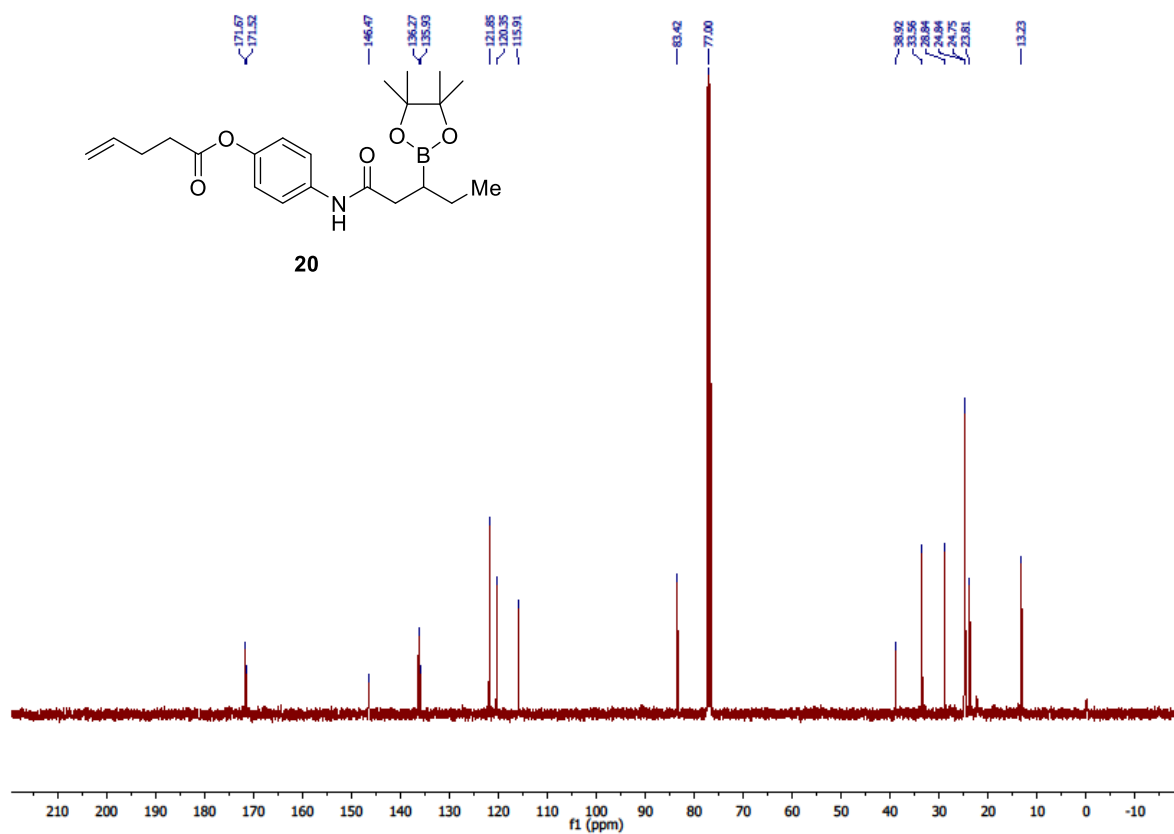*Chapter 4*

W-catalyzed remote β-hydroboration of alkenes

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W-catalyzed remote β-hydroboration of alkenes

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W-catalyzed remote β-hydroboration of alkenes

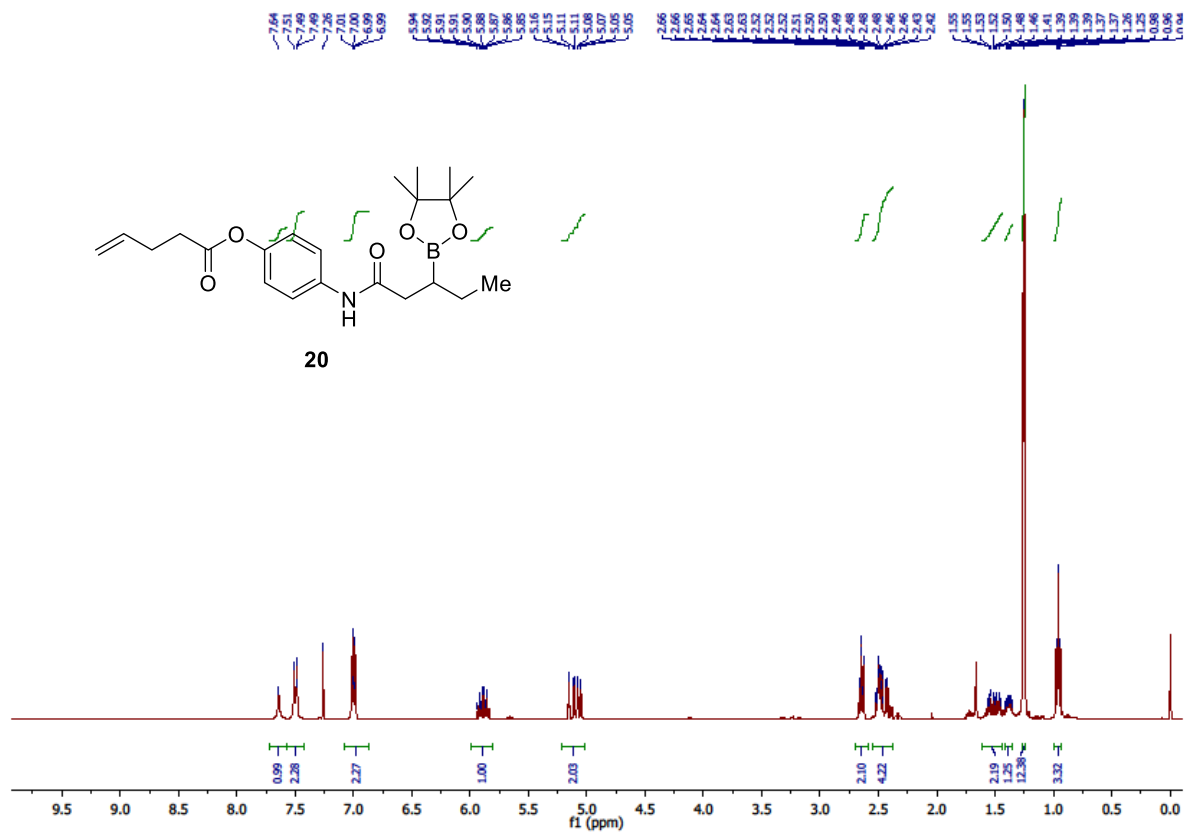*Chapter 4*

W-catalyzed remote β-hydroboration of alkenes

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W-catalyzed remote β-hydroboration of alkenes

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W-catalyzed remote β-hydroboration of alkenes

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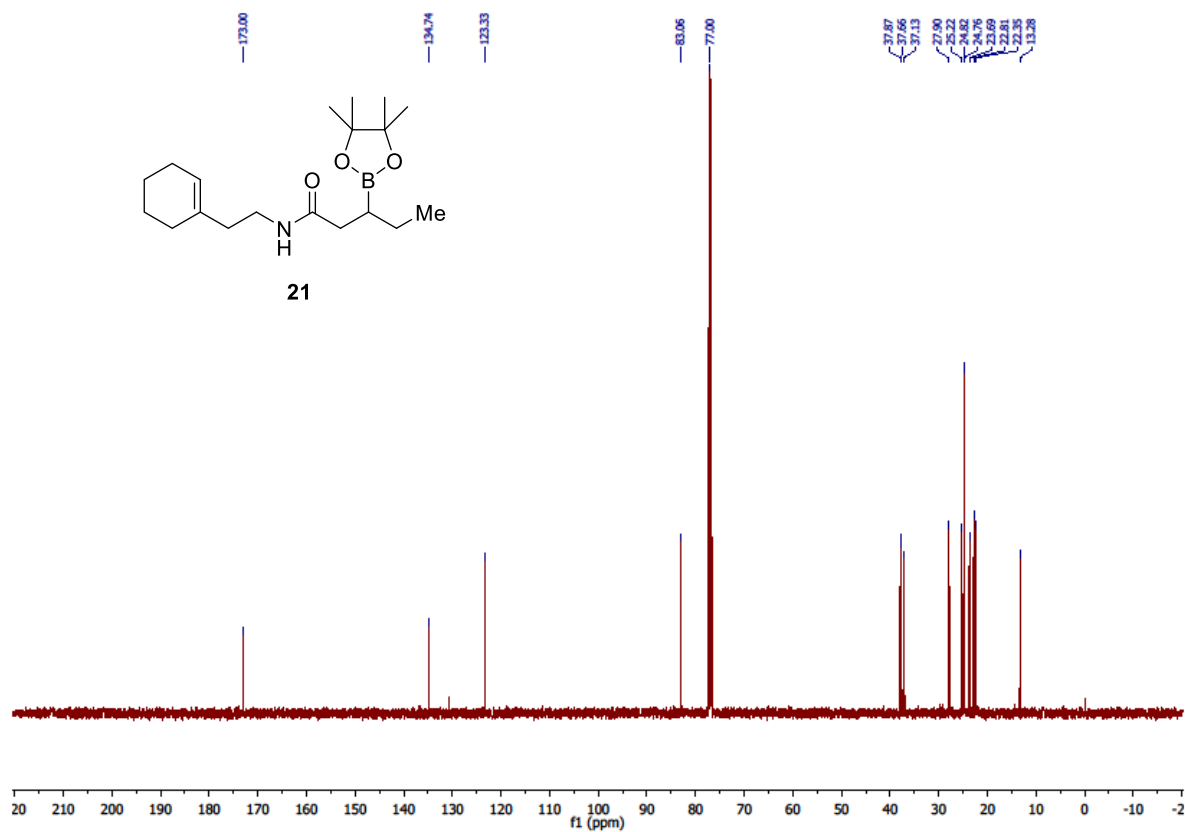*W-catalyzed remote β-hydroboration of alkenes*

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W-catalyzed remote β-hydroboration of alkenes

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W-catalyzed remote β-hydroboration of alkenes

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W-catalyzed remote β-hydroboration of alkenes
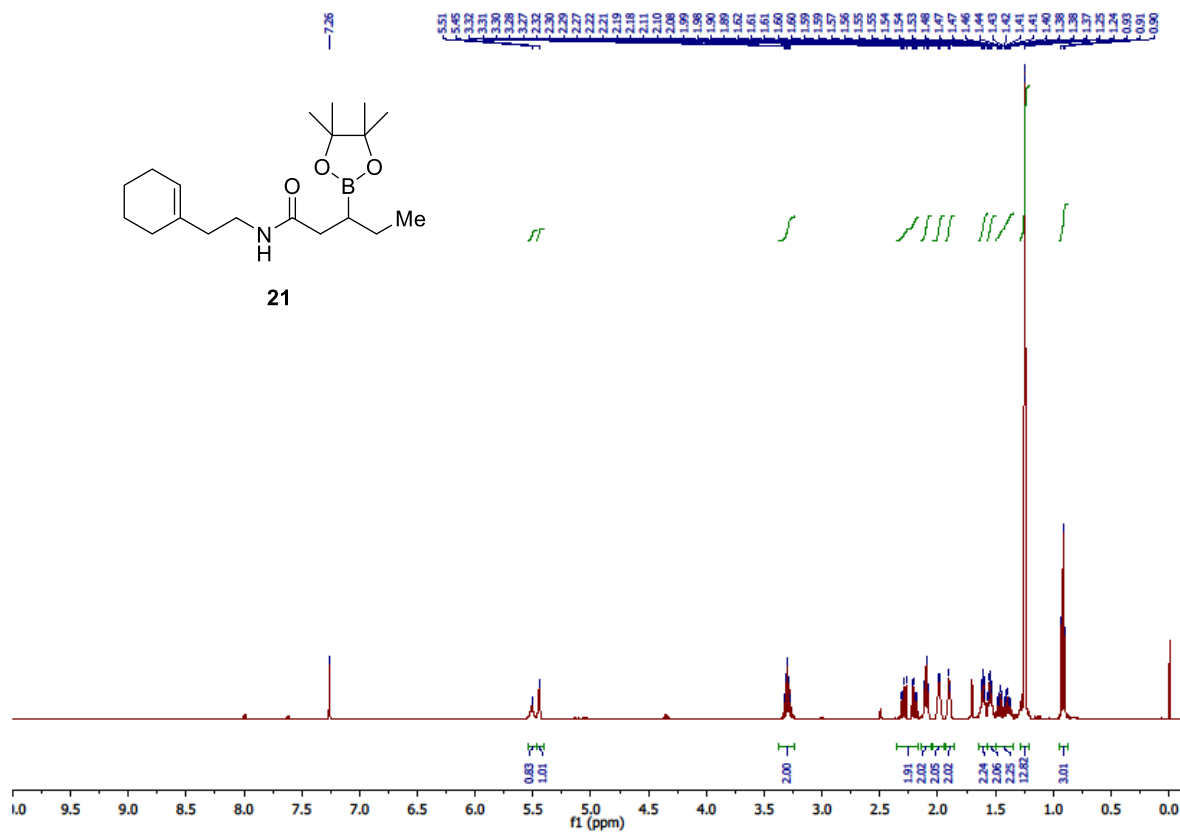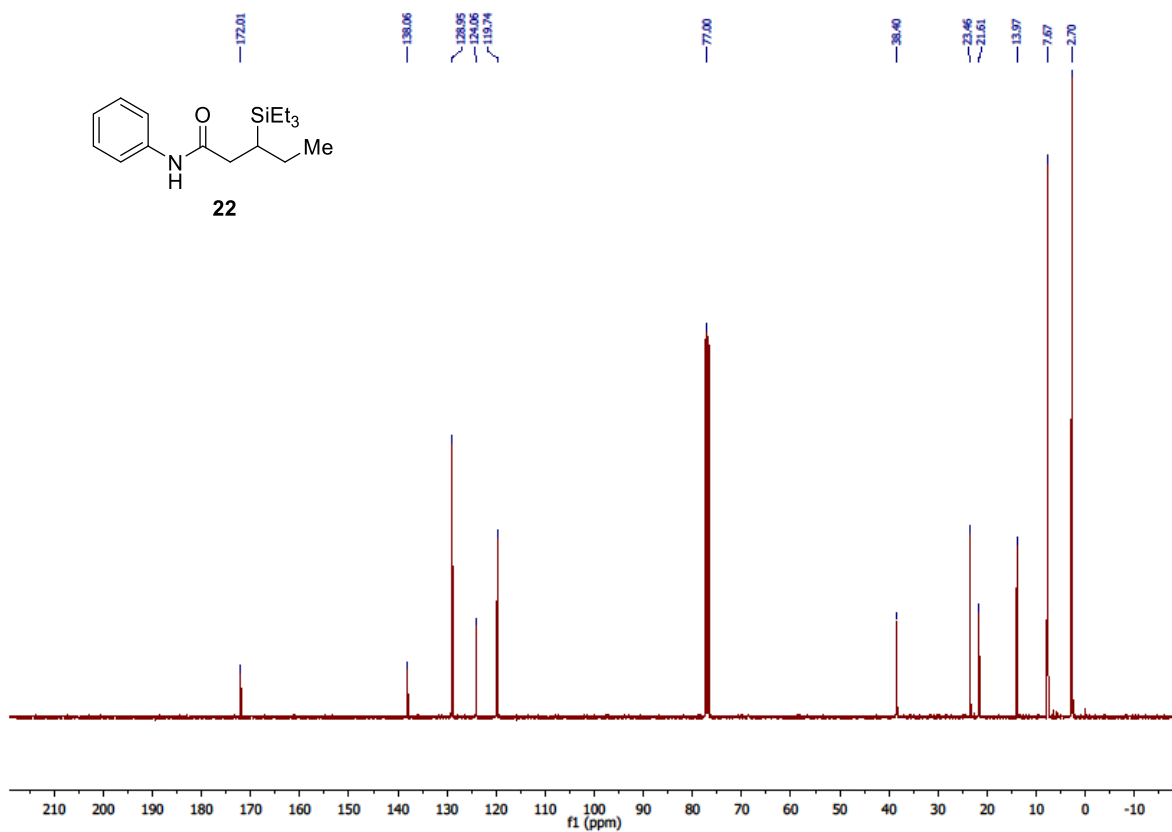
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W-catalyzed remote β-hydroboration of alkenes

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W-catalyzed remote β-hydroboration of alkenes

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W-catalyzed remote β-hydroboration of alkenes

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W-catalyzed remote β-hydroboration of alkenes

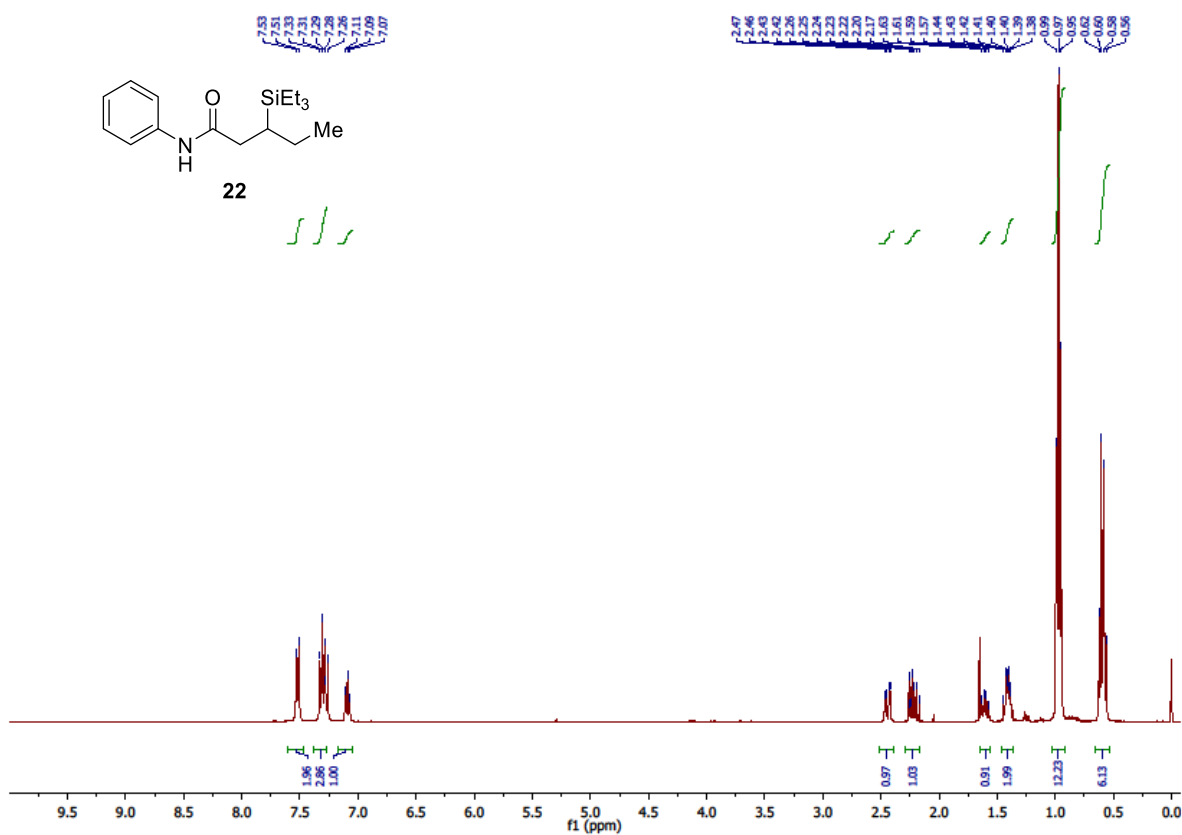*Chapter 4*

W-catalyzed remote β-hydroboration of alkenes

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W-catalyzed remote β-hydroboration of alkenes
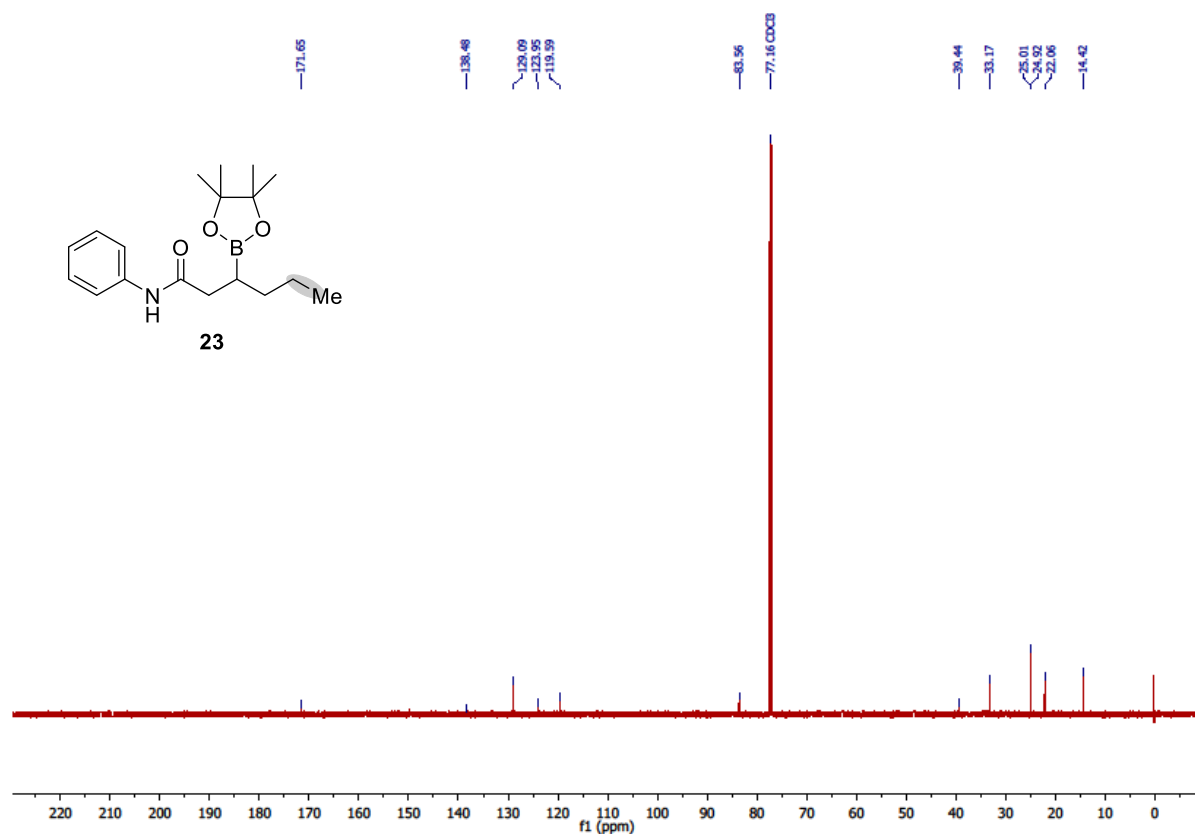
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W-catalyzed remote β-hydroboration of alkenes
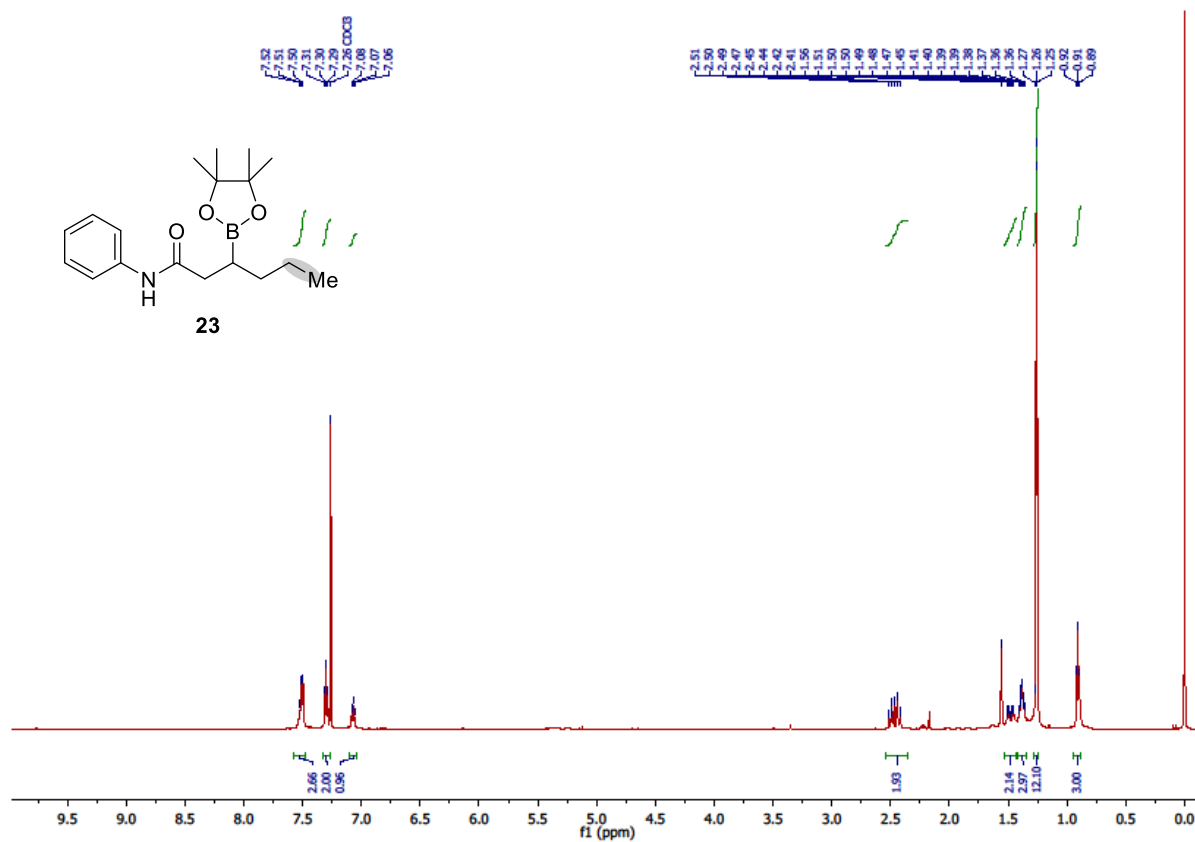
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W-catalyzed remote β-hydroboration of alkenes

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W-catalyzed remote β-hydroboration of alkenes
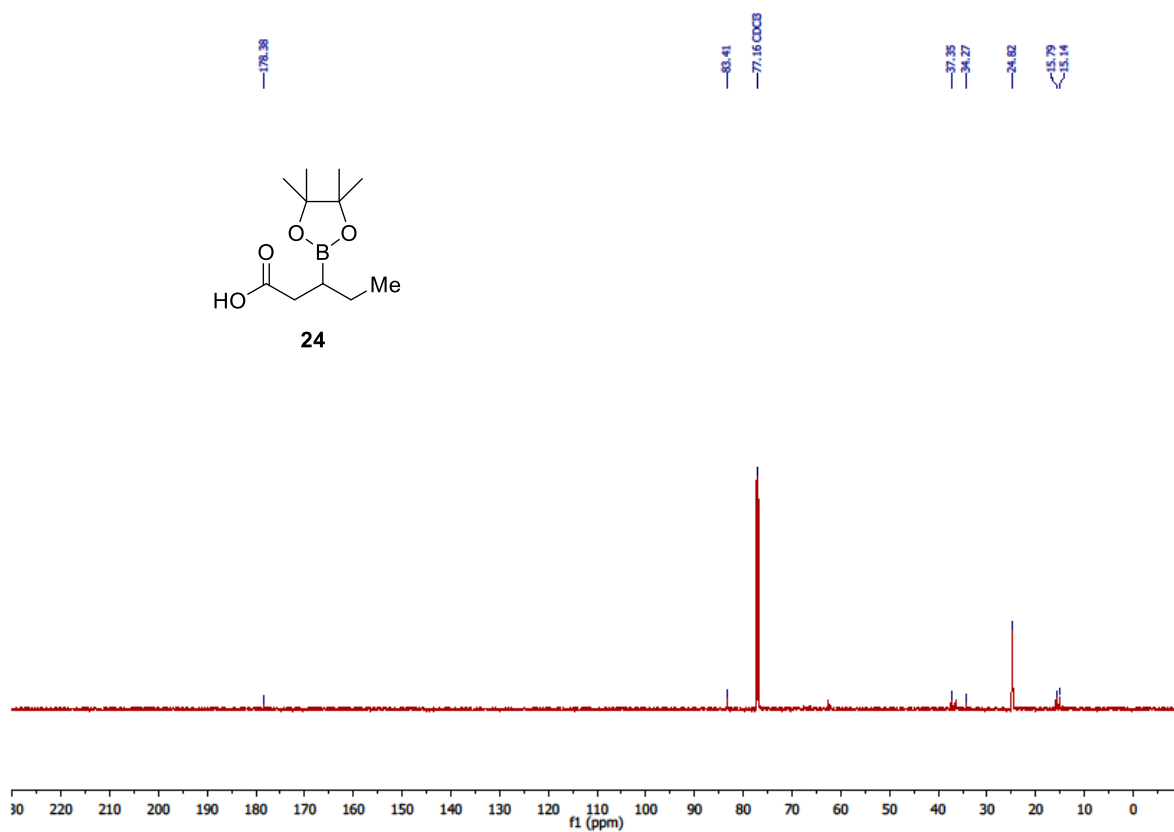
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W-catalyzed remote β-hydroboration of alkenes

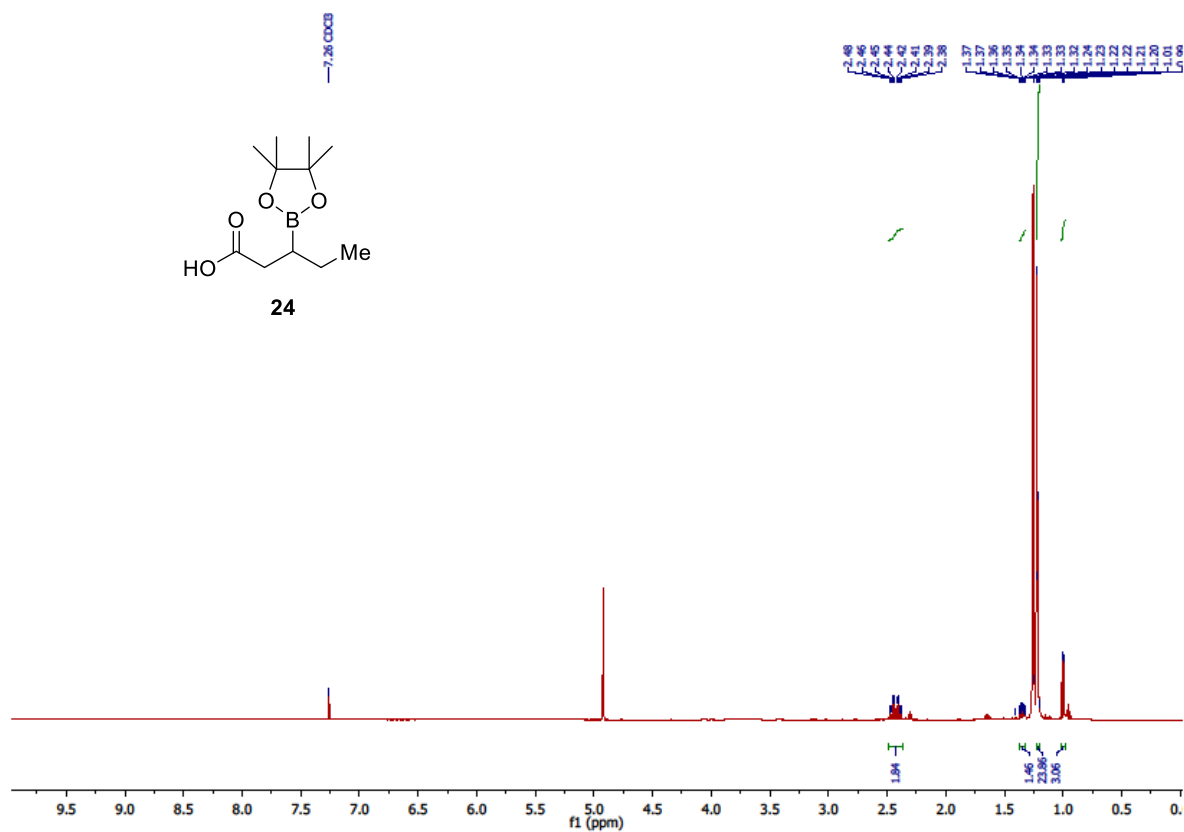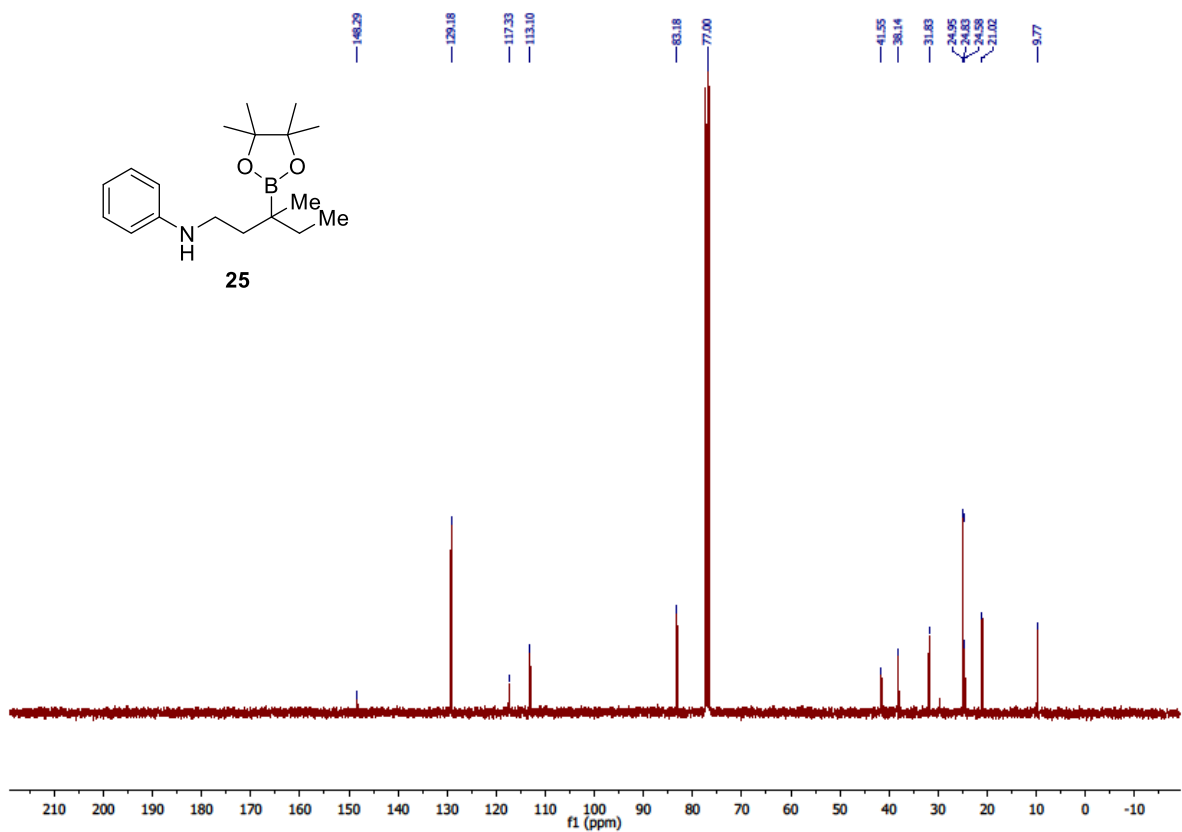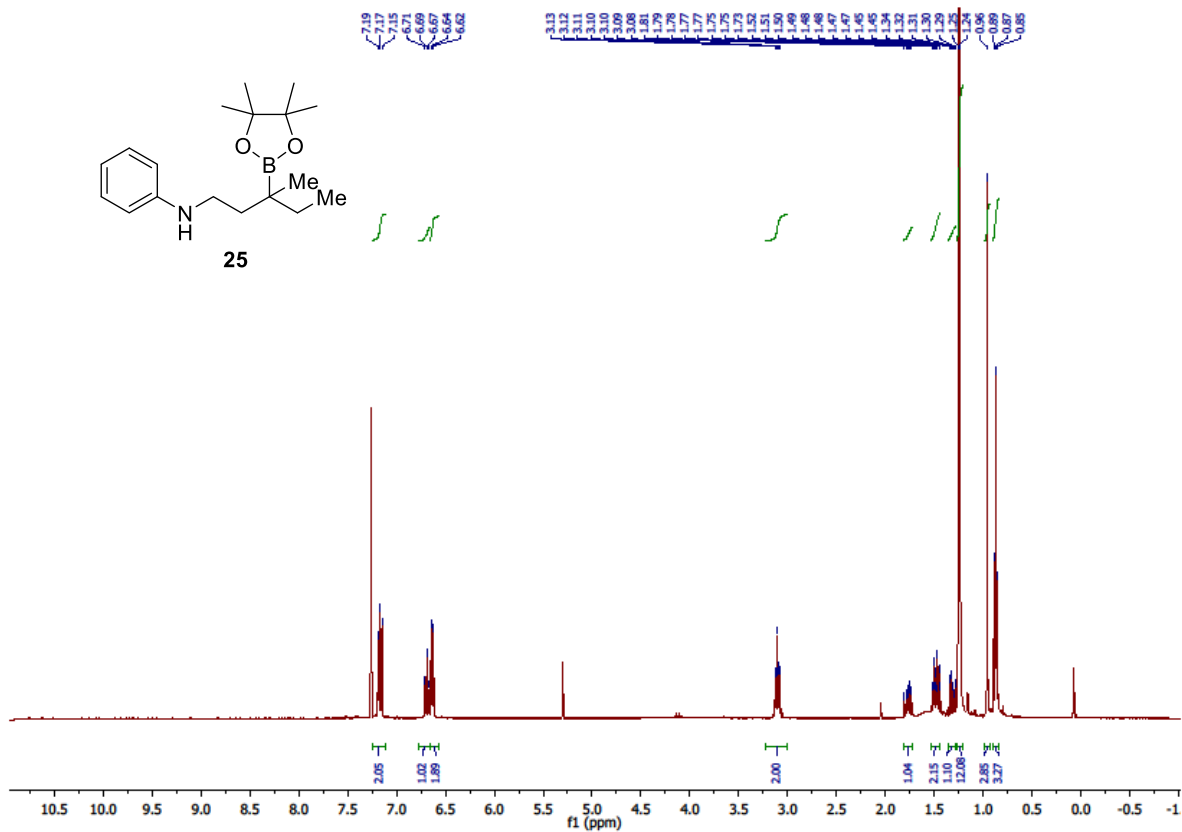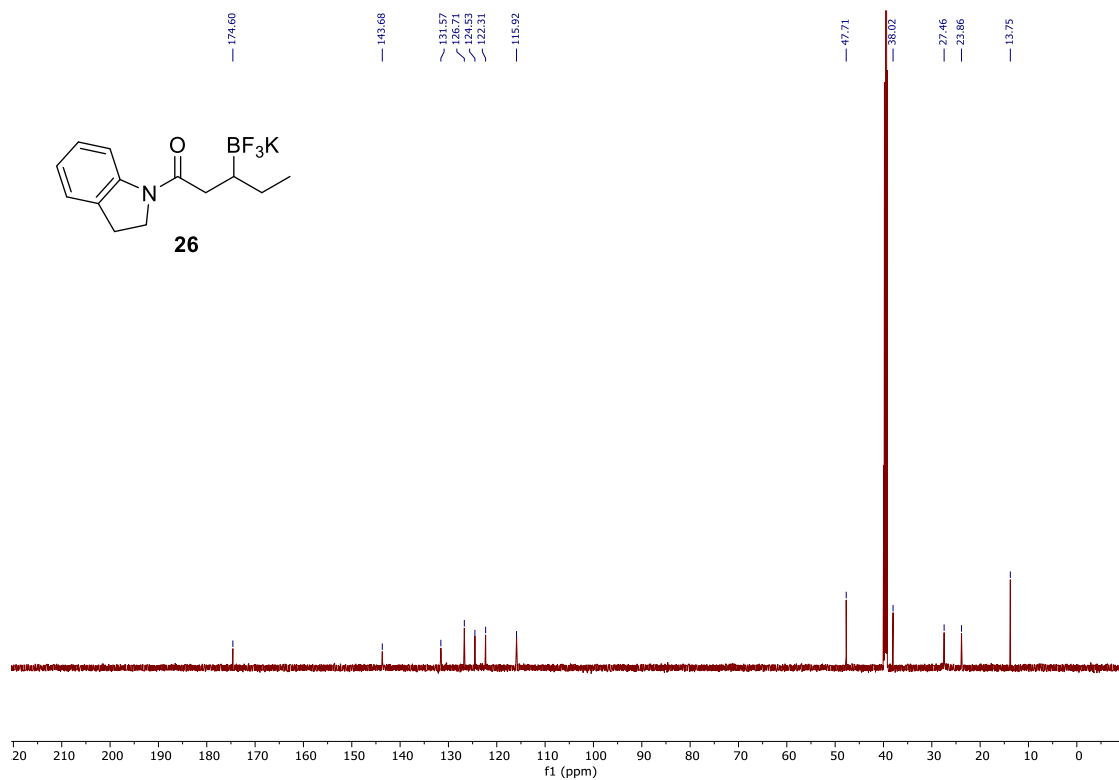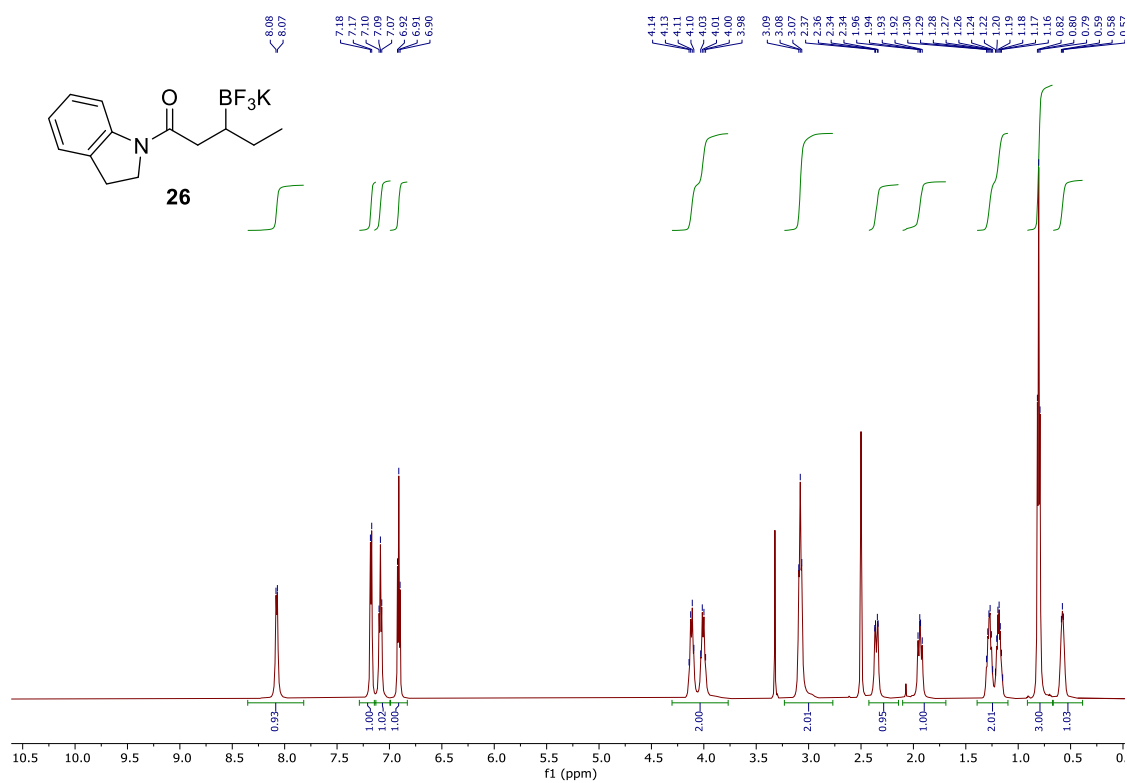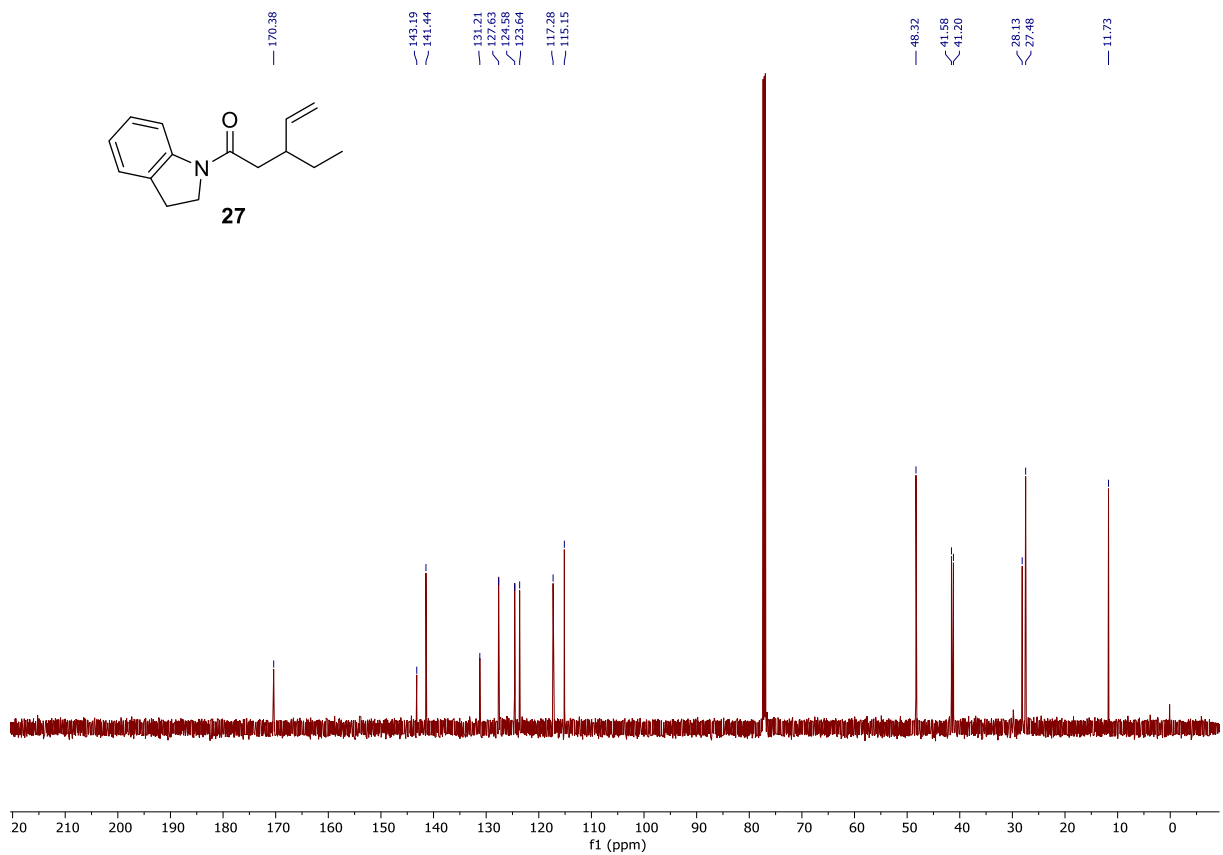*Chapter 4*

W-catalyzed remote β-hydroboration of alkenes

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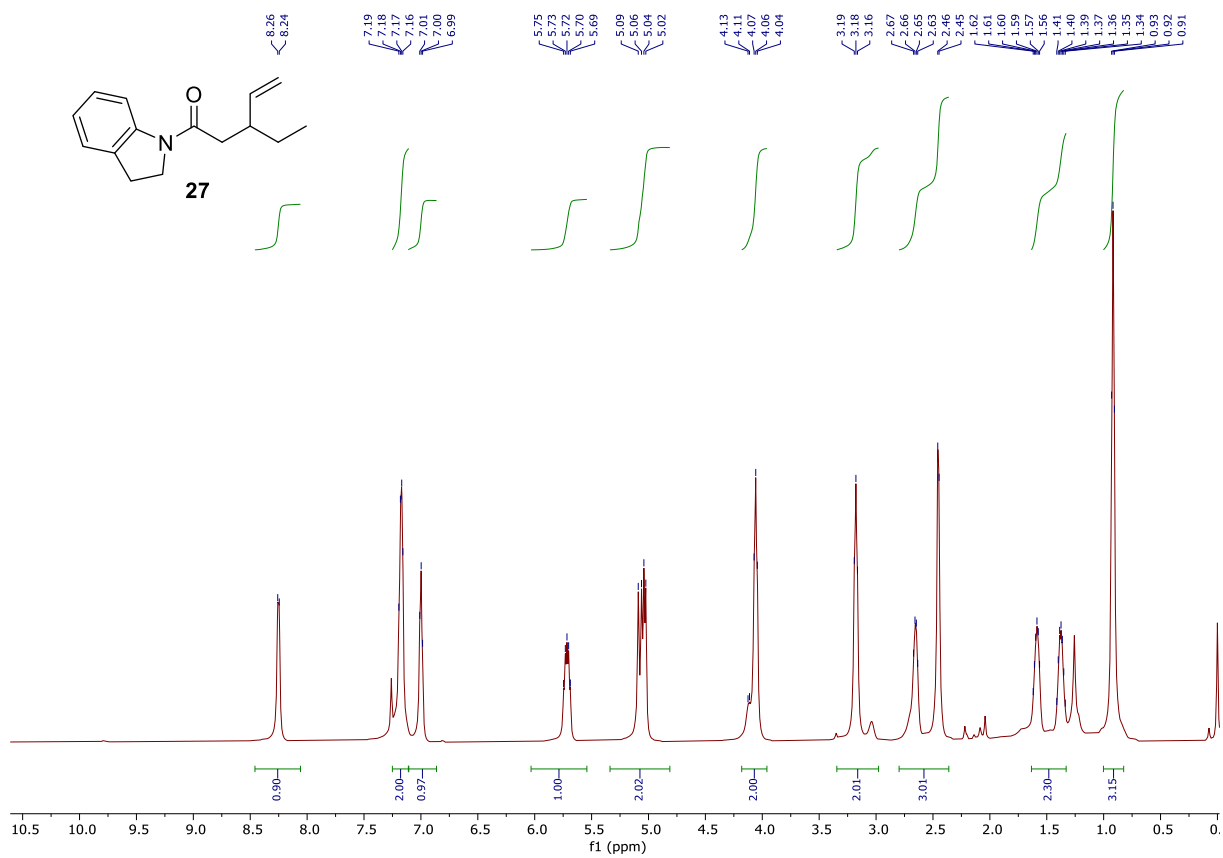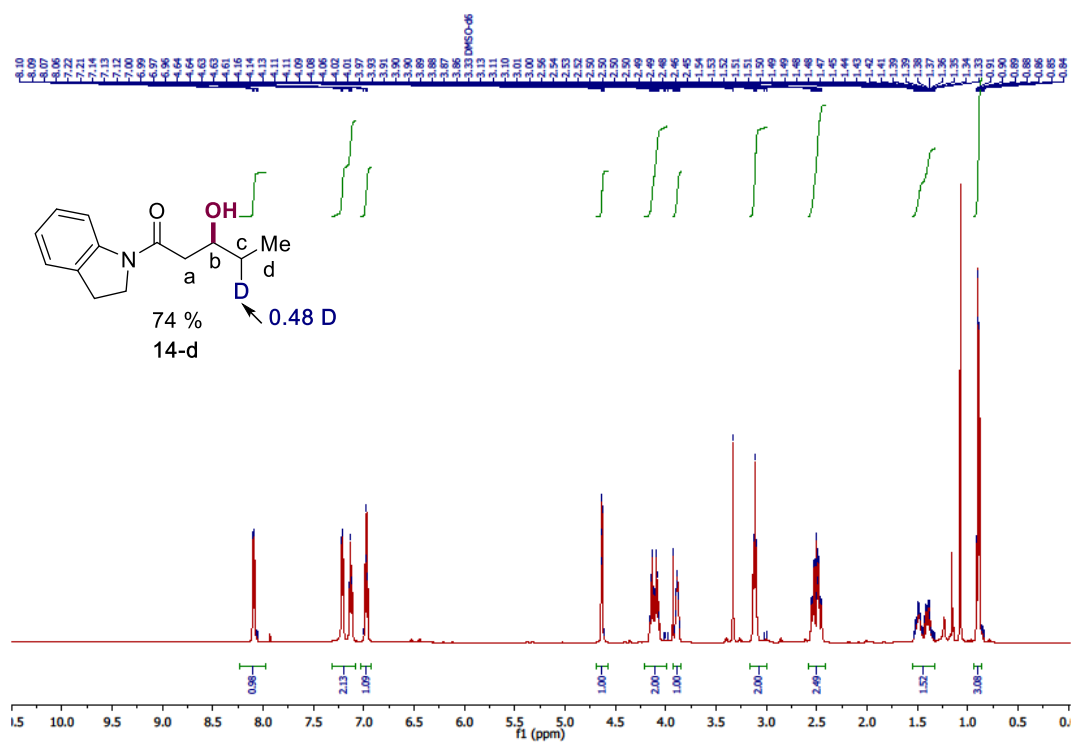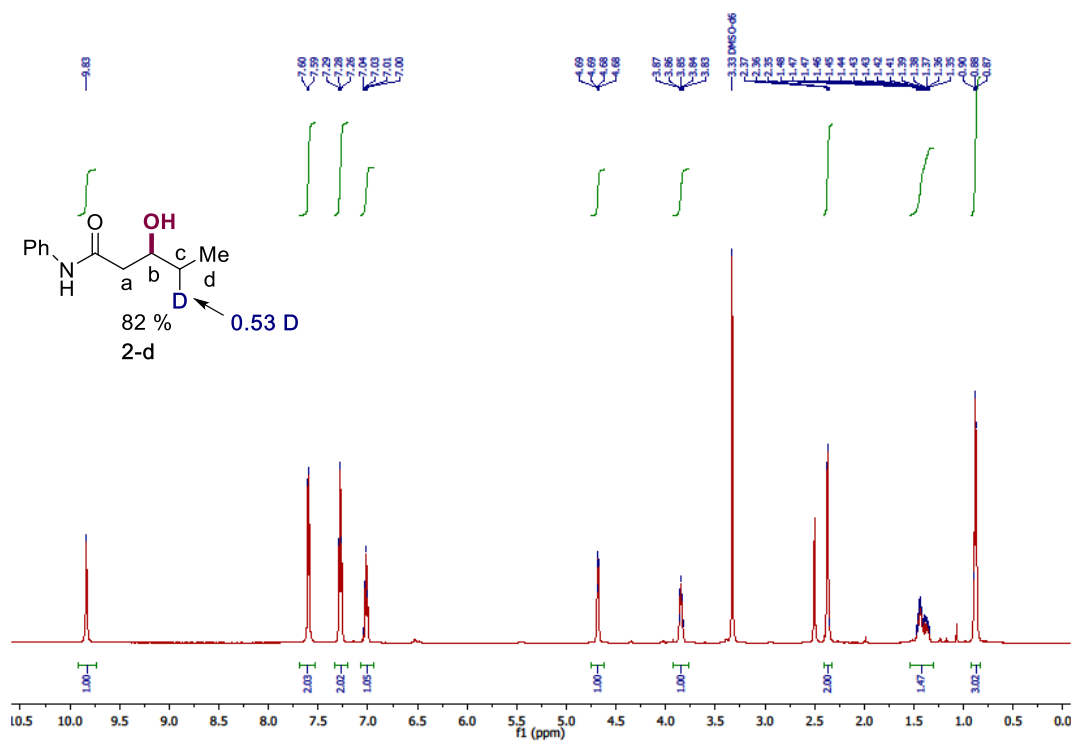Functionalization of Strong Sigma Bonds by Nickel and Tungsten Catalysis
Raúl Martín Montero

W-catalyzed remote β-hydroboration of alkenes

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Chapter 5.

General Conclusions

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Functionalization of Strong Sigma Bonds by Nickel and Tungsten Catalysis
Raúl Martín Montero

General conclusions

To conclude this doctoral dissertation, it would be useful to highlight the main features found in this PhD thesis.

In *Chapter 2*, we met the goal of establishing the first stereospecific borylation of secondary benzyl pivalates. Mild conditions and exquisite stereospecificities generated a reliable and robust method, setting the basis for future C–Heteroatom bond formations through C–O bond scission. In addition, the incorporation of an enantioenriched boryl unit afforded a series of stereospecific derivatizations that might be expanded beyond Suzuki-Miyaura cross-couplings reactions. Two mechanistic pathways have been proposed, although further studies are necessary to determine the full picture of the protocol.

In *Chapter 3*, we developed a catalytic reductive deamination of alkyl pyridinium salts with a diverse set of aryl halides. The transformation could be executed for a wide number of alkyl amines and aryl bromides bearing multiple functional groups. Particularly noteworthy was the ability to extend this technology to primary alkyl amines, counterparts that are difficult to reach otherwise, or the application to advanced bioactive compounds. Cyclic voltammetry experiments of the substrates and the nickel oxidative addition complexes allowed for unravelling an unusual mechanistic manifold that might have consequences within the general area of deaminative protocols.

In *Chapter 4*, we have described the implementation of tungsten catalysts for triggering a remote hydroboration of sp^3 C–H bonds of carbonyl compounds possessing alkenes on the side chain. The protocol could be conducted under mild conditions and tolerated a wide number of different carbonyl counterparts, including amides or carboxylic acids. The transformation showed an exquisite regio- and chemoselectivity profile at the β position of the carbonyl group.

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