INVESTIGATIONS OF NOVEL USES FOR BORON COMPOUNDS IN ORGANIC AND INORGANIC CHEMISTRY

by

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A thesis submitted to the Department of Chemistry

In conformity with the requirements for

the degree of Master's of Science

Queen's University

Kingston, Ontario, Canada

(September, 2011)

Abstract

Herein I describe a model study to determine the feasibility of organic hydride donors as a source of hydride in the regeneration of ammonia borane. Hydride transfer was observed in the model system comprised of Hantzsch ester and several analogues, as the organic hydride donor, and tris(pentafluorophenyl)boron, as the boron-based hydride acceptor akin to BBr_3. Side reactions could be minimized by varying the reaction conditions. We determined that a Lewis acid-base adduct was forming between the carbonyls of the donor and the hydride acceptor, that this adduct was dynamic in the case of Hantzsch ester and that it could be inhibited by bulkier ester groups or promoted by reducing the steric bulk at the carbonyl in the case of a methyl ketone. The thermodynamics of the hydride transfer reaction with an *N*-substituted analogue were probed via variable temperature NMR and compared to two differently substituted analogues.

In addition, the scope of the sp^2-sp^3 Suzuki-Miyaura cross-coupling previously developed in our lab was extended to include 2-(1,2-diaryl)ethane pinacolborane scaffolds. In order to access this asymmetric scaffold, reaction conditions for the cross-coupling of a primary boronic ester in the presence of a secondary one were developed. Yields achieved for the linear cross-coupling were in the 70 % range and varied from 42 % to 69 % for the secondary position. These latter yields are in the same range as the hydroborated styrene scaffolds described in our first account demonstrating the broad scope of these reaction conditions.

Acknowledgements

The close of this chapter of my life begs a reflection of who has helped me along the way. Although I cannot thank every single person who has encouraged me, I would like to say to everyone with whom I shared even just a late night laugh thank you for your support.

In particular I would like to thank you, Dr. Crudden. I cannot imagine a better lab to have worked in. You have taught me much more than I can describe- both personally and professionally- and have provided me with opportunities I could not have had anywhere else, not to mention encouragement and a positive outlook whenever we had a conversation.

I have been enriched by my various lab mates over the years. In particular I would like to thank Jonathan Webb for all his efforts to turn me into an inorganic chemist, I know it was not easy. A particular acknowledgement goes to Kevin McEleney. In addition to being a great resource, you were a great support in difficult times and I thank you.

I would like to thank Chatani-sensei and GCOE for the opportunity and funding with which to study abroad, Françoise Sauriol and Ruiyao Wang for their expertise and for always helping me with a smile. I would like to thank OGS and Queen's University for funding my research.

I would like to thank my current coworkers at Xerox Research Centre of Canada, Matthew, Adrien and Nan-Xing. I appreciate the chance you took hiring someone before graduation, as well as your excellent mentorship, I feel the transition from graduate school to the workplace was made all the easier thanks to your attention.

Finalement, j'aimerais remercier ma famille qui a su me supporter, de loin, tout au long de mes études. Je n'aurais rien pu accomplir sans vous, notamment cette dernière année. Votre soutient infaillible a été essential à ma réussite. Merci.

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List of Abbreviations

1,4-DHP	1,4-dihydropyridine
9-BBN	9-borabicyclo(3.3.1)nonane
AB	Ammonia borane
BCF	Tris(pentafluorophenyl)boron, $B(C_6F_5)_3$
br. d	Broad doublet
Bu	Butyl
CC	Cross-coupling
CPME	Cyclopentyl methyl ether
cod	1,5-cyclooctadiene
Cy	Cyclohexyl
d	Doublet
dba	Dibenzylideneacetone
DCE	Dichloroethane
DCM	Dichloromethane
dd	doublet of doublet
DHA, 9,10-DHA	Dihydroacridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
dmpe	1,2-bis(dimethylphosphino)ethane
DOE	Department of Energy
dppb	1,2-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
Et	Ethyl
FLP	Frustrated Lewis pair
GC	Gas chromatography
HSQC	Heteronuclear single-quantum correlation spectroscopy
LANL	Los Alamos National Labs
LDA	Lithium diisopropylamide
Me	Methyl
MOF	Metal organic framework
MS	Mass spectroscopy
NAD+/NADH	Nicotinamide adenine dinucleotide
NHC	N-heterocyclic carbene
NMR	Nuclear magnetic resonance
o, m, p	ortho, meta, para
OA	Oxidative addition
PB	Polyborazylene
Ph	Phenyl
PIM	Polymers with intrinsic microporosity

PNNL	Pacific Northwest National Laboratory
Pr, ^{i}Pr	propyl, *iso*propyl
*p*TSA	*para*-toluenesulfonic acid
QUINAP	(S) or (R)-(+)-1-(2-diphenylphosphino-1-naphthyl)isoquinoline
RE	Reductive elimination
SDS	Sodium dodecyl sulfate
STP	Standard temperature and pressure
t	triplet
TADDOL	trans-α,α'-(dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol)
TLC	Thin layer chromatography
^{t}Bu	*tert*-butyl
THF	Tetrahydrofuran
TM	Transmetallation
TS	Transition state
VT	Variable temperature
wt %	weight %

Preface

This thesis deals with broadening the scope of and breadth of two systems intrinsically dependent on boron. The first chapter describes the investigation of a new hydride donor applied to the regeneration of ammonia borane. Ammonia borane is a top candidate for hydrogen storage material in stationary and transportation applications, but few methods to regenerate the spent material currently exist, and none of them are viable at industrial scale. We investigated the possibility of using an NADH-based organic hydride donor to regenerate the B-H bonds of the spent storage material, thus providing new insights on this unusual system containing both a Lewis base and Lewis acid.

The second chapter describes efforts towards an orthogonal approach to 1,1,2-triarylethane scaffolds. The methodology described is based on a diborated styrene starting material which can be made to cross-couple with aryl halides, first at the primary then secondary positions in turn. Our investigations provide a straightforward and versatile approach to pharmaceutically active compounds difficult to attain by other means.

Chapter 1

Towards a Functional Application of Boron Lewis Acids in Inorganic Chemistry: The Production of a Borohydride from an Organic Donor and its Role in the Regeneration of Ammonia Borane

1.1 Introduction

1.1.1 Hydrogen Storage Materials

It has become a well-established fact that humanity's reliance on oil-based, non-renewable energy[1] sources must be shifted to renewable, non polluting alternatives.[2, 3, 4] One such energy carrier that has gained considerable attention is hydrogen gas, H_2[5, 6], which has a specific energy of 120 MJ kg^{-1} at STP, whereas that of petroleum is 44 MJ kg^{-1}.

Much effort has been invested in separating this simple molecule into its constituting protons and electrons for energy applications: energy transfer-efficient and non-polluting fuel cell technology has been used for many years, most notably by NASA since the 1960s in the space shuttles. While this technology is far from being commercially affordable on large scale at this time, it has already been integrated into vehicles. Two famous examples include the Chevy Sequel (2007) and the Honda FCX Clarity. Both of these vehicles use a polymer electrolyte fuel cell which, unfortunately, has a limited durability and which requires an expensive platinum catalyst hindering the widespread use of the technology.[7] Many research groups are currently working on developing less expensive fuel cells[8, 9] for everyday applications ranging from portable devices and stationary electronics to transportation. In parallel, many related fields have expanded: numerous new materials have been developed for the various membranes, electrolyte, charge

transport layers, etc. included in the cell, in addition to all the peripheral technologies like systems development, hydrogen (or fuel) storage[10] and, to a lesser extent in many cases, the regeneration of the spent storage material.

Despite its high specific energy, the energy density of hydrogen itself is low at 0.01 kJ L^{-1} (STP) compared to petroleum at 32 MJ L^{-1}; therefore, it is difficult to store efficiently due to its low molecular weight. Compression of hydrogen at 70 M Pa increases the energy density to 5.6 MJ kg^{-1} and enables the storage of 5 to 6 kg of hydrogen in a vehicle which is enough to travel approximately 500 km. Although the infrastructure required to attain such high pressures is not reducible to a scale needed for domestic purposes, compressed hydrogen is the actual state-of-the-art hydrogen storage method[11] for all current hydrogen-based motor vehicles. Unfortunately, there is a perceived danger linked to carrying a large amount of hydrogen since it is explosive and flammable.[12, 13] In addition, extremely high pressures required to store a practical amount of hydrogen on-board create a need for a mode of storage of hydrogen which would be more efficient as well as safer.

The DOE has issued guidelines concerning the efficiency of hydrogen storage systems as a whole (fuel and machinery), such that the target for 2010 was 6 wt% (2 kWh/kg or 1.5 kWh/L) for a vehicle travelling 500 km. Six weight % may seem low, however, because hydrogen is so light, any carrier or storage material adds a large amount of weight to the entire system. Sodium alanate is currently the only hydrogen storage material to achieve this goal.[14, 15] The guidelines for 2015 are a 9 wt% (3 kWh/kg or 2.7 kWh/L) target with an overall lower cost. To achieve this goal, many alternative hydrogen storage methods and materials have been investigated. Compression, as discussed above, does not seem to be a viable alternative at this time. Another so-called physical storage method that has received much attention is liquefaction of the hydrogen.

Although an energy density of 8.4 MJ kg^{-1} is achievable this way, most automotive companies have given the technology a 'no-go' as the liquefaction of the hydrogen takes up about 30 % of the total system energy and, much like a liquid nitrogen tank, unavoidable heat exchange with the outside causes boil-off gas which is an unacceptable loss of fuel as well as a very real explosion hazard. Physisorption of hydrogen gas has been investigated as an improved means of storage of a greater density of hydrogen at more reasonable temperatures and pressures. Physisorbents rely on low interaction strength to bind hydrogen then release it very easily upon heating. Many different types of sorbents are currently being investigated: zeolites[16], PIMs[17] (Polymers with Intrinsic Microporosity), MOFs[18, 19] (Metal Organic Frameworks) and carbon-based materials[20, 21] have all been shown to adsorb hydrogen to different degrees.[11] For these compounds generally, smaller pore sizes lead to stronger interactions with hydrogen. Higher surface areas, which typically stem from smaller pore materials, also lead to higher storage capacity. The best-performing cryoadsorbing PIM is composed of a triptycene monomer with a gravimetric density of 2.5 wt% H_2 at 1 MPa and -196 °C while some nanotubes can adsorb about 5 wt% at the same temperature. Although promising, these values do not take into account the cooling system that would be necessary for any practical applications of these materials and, thus, they remain unlikely hydrogen storage solutions.

By increasing the strength of the adsorption phenomenon, it is possible to store hydrogen at higher temperatures at the cost of the increased energy necessary to release hydrogen when the fuel is required. In this respect, metal hydrides[22, 23] provide a good alternative, with the downside being that binding hydrogen to heavier elements reduces the gravimetric density to around 2 wt% in even the most promising cases. There are some examples of metal hydrides in actual applications in which a counterweight is necessary and desired like fuel cell powered fork-lift

trucks. For widespread applications, only lightweight metals[24] have any chance of being optimised into a viable technology.

Currently, potential methods of chemical hydrogen storage include various complex hydrides[24-26] including alanates such as $NaAlH_4$ (7.4 wt%)[24, 27, 28] which is currently the compound with the highest gravimetric density and reasonable H_2 release conditions (typically achieved through doping). This is another factor that needs to be considered: the hydrogen release must be achievable at conditions and temperatures at which a fuel cell can function, typically 1 to 10 bar and 0 to 100 °C.[29]

While all previously mentioned hydrogen storage methods produce hydrogen in a satisfactory manner, they suffer from major drawbacks, notably a low weight percent in hydrogen (such that the DOE targets cannot be reached) and/or an energy intensive rehydrogenation of the spent material, which becomes an issue when chemical hydrogen carriers are used. In order to counteract the first of these drawbacks, one might favor elements of the first and second rows of the periodic table. These compounds are usually referred to as chemical hydrides and include cyclic organic compounds like naphthalene/decaline[30] and more useful higher anthracenes,[31, 32] amines,[33] polyboranes,[34] borohydrides[35] or the class of B-N compounds which includes amine boranes and ammonia borane,[36] NH_3:BH_3 (AB).[37-39 40, 41]

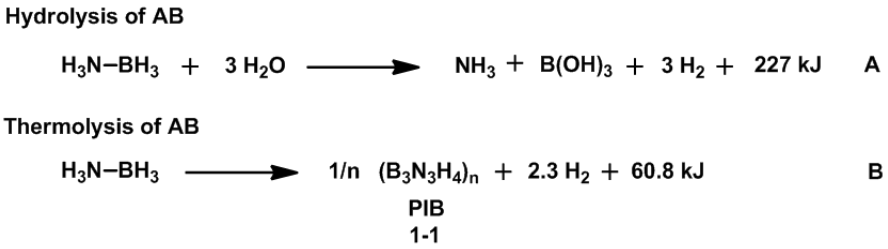
With a 19.6 wt% of hydrogen, ammonia borane provides considerable leeway for efficiency of hydrogen production and means of storage: for example, 1.95 kg of hydrogen is stored in every 10 kg of ammonia borane (19.5 wt %), while the same weight of $NaAlH_4$ can release only 0.74 kg of hydrogen (7.4 wt%). The category of amine boranes also encompasses hydrazine borane and hydrazinebis(borane) which have a storage capacity of about 13 wt%. Although these numbers seem promising, these hydrazine borane materials are often used as rocket propellants due to their

explosive nature. The downside of these chemical hydrides relates to difficulties regarding their regeneration: *covalent* bonds are being broken and therefore need to be regenerated. Despite this fact, these compounds have received an increasing amount of attention as they are currently the only class of storage materials which have gravimetric densities high enough for widespread practical applications.

1.1.2 Regeneration of Ammonia Borane

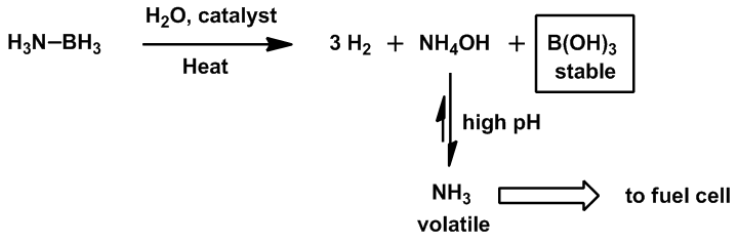
Interestingly, as early as 1953[41], researchers were interested in methods to extract hydrogen from ammonia borane (AB). Recent work has produced successful thermal,[42, 43] catalytic[44-46] and various other[47-49] methods of hydrogen release to varying degrees of success. Generally, AB can release hydrogen under two very different conditions: hydrolysis (solvolysis) or thermolysis (catalysed or not). These differ in terms of the ease of reaction as well as the dehydrogenation products formed. Hydrolysis generally provides a fast and efficient means of hydrogen release, depending on the conditions used such as metal[50, 51] or acid[52, 53] catalysis. In some cases, the catalyst is a heterogeneous solid[54] which is a promising development for on-board applications where H_2 will have to be available preferentially *only*, on demand. By having a flow reactor-type setup where the bulk of the AB is stored away from the initiating agent, this becomes achievable. The drawback to hydrolytic methods to release H_2 is the high stability of the resulting B-O bonds making the eventual rehydrogenation very energetically uphill and virtually impossible from an energy balance perspective (**Scheme 1-1, A**). In addition, the production of NH_4OH, which can equilibrate to NH_3 if the conditions are not strictly controlled, as well as the added weight of the solvent which reduces the overall gravimetric capacity, are problems that would need to be overcome. NH_3 in particular is a problem as this volatile compound will enter the hydrogen

stream causing depletion of the starting material and will likely poison the fuel cell catalyst (**Scheme 1-2**).



Scheme 1-1 Enthalpy of reaction for the two main conditions for AB dehydrogenation

When AB is activated thermally, the resulting products vary depending on the rate of heating,[55-57] catalyst[58] and solvent. It has been shown that the nucleation sites and/(or) templating effect of using mesoporous silica (SBA-15) reduces the onset temperature and improves the enthalpy of thermolysis relative to the parent AB.[49] Without water, only B-N bonds are formed making regeneration much more feasible (**Scheme 1-1, B)**.



Scheme 1-2 Production of ammonia under AB hydrolysis condition

During their studies of the dehydrogenation mechanism, Baker,[58-60] and others[58, 60-62] have identified the boron-nitrogen polymers resulting from catalytic decomposition, (**figure 1-1**) although full mechanistic studies for the various dehydrogenation mechanisms are ongoing.

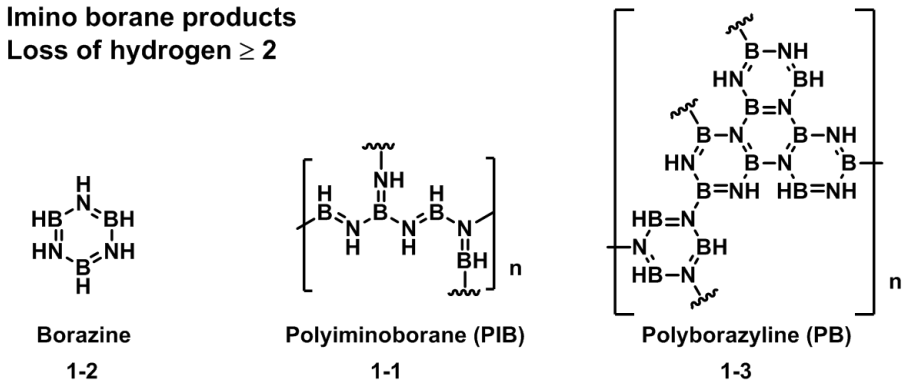


Figure 1-1 Common products of AB dehydrogenation

Some of the more notable hydrogen release conditions include the fastest catalysts $(POCOP)Ir(H)_2$[63] and $\{[C_5H_3(SiMe_3)_2]_2Ti\}N_2$[64] (used with amine borane) which produce insoluble powder after release of 1 equivalent of H_2 at 20 °C (and therefore are not viable at this point) and $Ni(1,5\text{-cod})_2$, 2 NHC[65] which can release almost all the stored H_2 after 3 hours at 60 °C. (POCOP: κ^3-2,6-$[OP(t\text{-Bu})_2]_2C_6H_3$ and NHC: *N*-heterocyclic carbene, in this case Ender's carbene: 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene) (**Figure 1-2**).

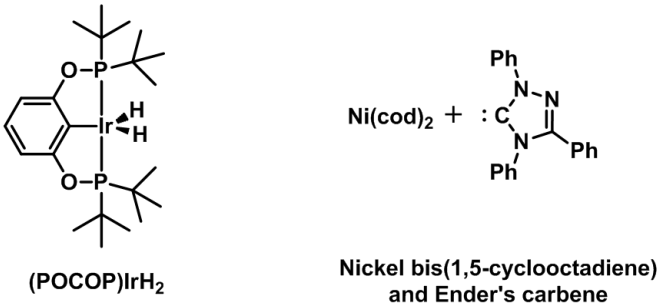


Figure 1-2 Two catalysts used for the dehydrogenation of AB

Ongoing work in this area includes developing cheap, robust and efficient catalysts which limit the formation of volatile byproducts, in particular borazine[34] **1-2**. It is important to note that the

final goal in this case is *not* the complete dehydrogenation of AB. Indeed, the loss of three equivalents of hydrogen produces boron-nitride polymer which has an enthalpy of formation of $\Delta H_{f,298K}$= - 59.97 ± 0.37 kcal/mol[66] (250.9 ±1.5 kJ/mol) and is, therefore, very difficult to convert back to the more energetic ammonia borane.

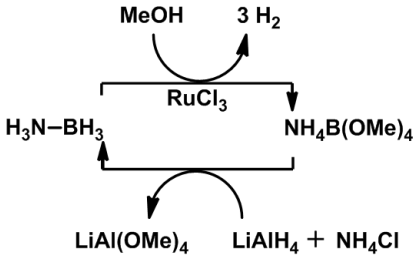
While work in the area of hydrogen storage and release is ongoing, our group and others have turned their attention to another necessary development associated with hydrogen as a renewable energy source: *regeneration of the spent fuel*. It has been determined that the addition of hydrogen gas directly onto the polymers, resulting from dehydrogenation of ammonia borane, is much too energy intensive to be a feasible option. The calculated enthalpy of formation of $B(OH)_3$ and 3 H_2 from AB and water[39, 67] is -227 kJ/mol and for the thermolysis[39, 68] is -60.8 kJ/mol. Regenerating AB form these products and hydrogen gas is then energetically uphill by the same values. In addition, the entropy of the system (H_2 gas to solid AB) is unfavourable making an indirect route necessary (**Scheme 1-3**).

Scheme 1-3 Main steps in the dehydrogenation/rehydrogenation by digestion of AB

In order to reach the DOE targets, at least two equivalents of H_2 will have to be released from any viable dehydrogenation method. Because there has not been a consensus on the hydrogen release conditions, the ideal regeneration pathway would be applicable to boron-nitrogen polymers, regardless of their structure. Currently, digestion of the spent AB by an acid is the favoured route as it requires low-energy and readily available reagents and is applicable to a wide variety of digestion products.[39] However, very recently, the use of hydrazine in order to directly regenerate the spent fuel has been reported.[69] Safety concerns would be the primary issue in this system,

which, as reported, employs anhydrous hydrazine. Digestion[70] of the polyiminoborane (PIB, **1-1**) or polyborazyline polymers (PB, **1-3**) and other dehydrogenation by-products with acid affords ammonia and a BX_3 species[39] (X depends on the nature of the acid used), as illustrated on the second arrow of **Scheme 1-3**.The drawbacks to this route are the additional synthetic step as well as the optimization of the acid: the resulting BX_3 species must be a compound that can be converted back into BH_3. Inorganic (metal) hydride sources such as Rh hydrides,[71] boron chloride-base adducts,[70] strong reducing agents like lithium aluminum hydride[72] and tin reagents[73] are currently the most efficient candidates for the reduction of BX_3, leaving much room for improvement since ideally the hydride source would be a non-toxic, industrially viable, easily reducible compound. Using strong reducing agents is not a viable option as they too need to be renewable: the high energy regeneration problem cannot be transferred from the ammonia borane by-products to the hydride source. It is important to note that currently no such hydride donor exists, contributing to the recent decline in interest in ammonia borane and hydrogen technology in general.

Despite these difficulties, a few examples of completed hydrogen storage-production-regeneration cycles have been published. The first notable AB dehydrogenation/regeneration cycle is the methanolysis[74] of AB by $RuCl_3$ catalysis (**Scheme 1-4**). A complete dehydrogenation was achieved in about one minute at ambient conditions.

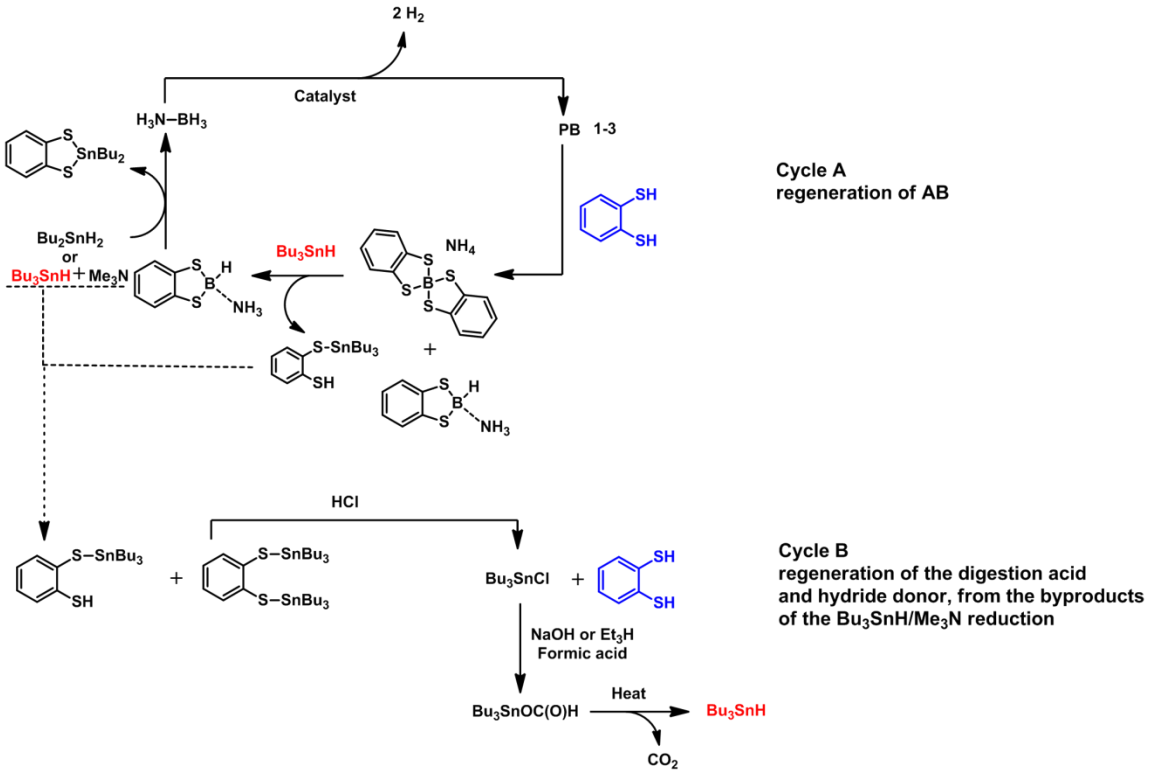


Scheme 1-4 AB regeneration cycle developed by Ramachandran

Methanol was chosen as the solvent despite the higher molecular weight (*versus* water) lowering the gravimetric density to 3.4 wt % as ammonia was found to contaminate the hydrogen stream under hydrolysis conditions. Using a strong reducing agent like $LiAlH_4$ and $NaBH_4$ directly to regenerate the hydride donor produced only low yields (10 %) of AB, as much of the material was being lost as NH_3. The regeneration of ammonium tetramethoxyborate $NH_4B(OMe)_4$was effected by adding a cold (-78 °C) solution of lithium aluminium hydride to a Parr reactor containing the dehydrogenated product in the presence of ammonium chloride as the ammonia source. The reaction takes 8 hours at room temperature and yields 81 % AB. Although this cycle is complete, it is far from being a viable method of ammonia borane regeneration since the method requires the use of $LiAlH_4$ which itself will require an energetic regeneration. In addition, the loss of 20 % of the hydrogen carrier for each cycle is unacceptable when we are considering the system as a renewable alternative to current fuel systems.

As mentioned above, acid digestion[70] seems an adequate first step for the digestion of the general class of boron-nitrogen polymers resulting from catalyzed thermolysis. Ideally, the acid chosen will produce a BX_3 compound from which BH_3 can be readily produced. The current hurdle to making this technology viable then would be regeneration of BH_3 from BX_3. Disproportionation (**Scheme 1-3,** last step) of the HBX_2 species to BX_3 and BH_3 is a known process[75, 76] and can further be driven by the addition of Lewis bases like NH_3 (or Et_3N *vide infra*) which will trap the desired boron species through a dative bond driving the formation, in this example, of ammonia borane. However, most hydride transfers to BX_3 actually result in $^-HBX_3$ which does not readily disproportionate. The cases where it does are few and far between and the factors influencing this transformation are still unknown. Four examples have been published as of 2011.

Los Alamos National Labs, in collaboration with the University of Alabama, has developed a regeneration procedure[73, 77] based on benzenedithiol as the acid and tin hydrides as the reducing agent as described in **Scheme 1-5**. DFT calculations indicated that the chelating *o*-benzenedithiol would be a favourable digestion acid with the B-S bonds formed still being weaker[78] than the analogous B-O bonds. The sulfur-tin affinity could also drive the regeneration of AB.



Scheme 1-5 AB regeneration cycle developed at LANL

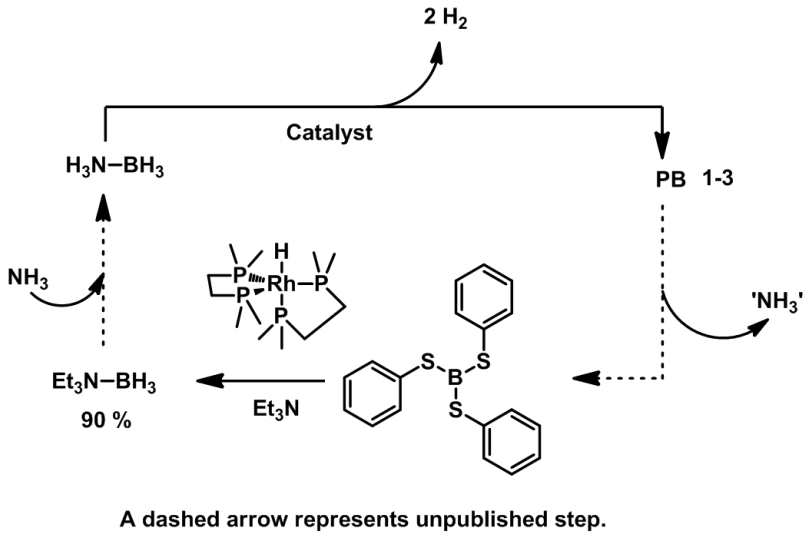
Treatment of polyborazylene (PB **1-3**, the most commonly encountered catalyzed thermolysis dehydrogenation product) with this acid produced a quantitative conversion of the polymer into two products: $(C_6H_4S_2)B\text{-}H\cdot(NH_3)$ and $[NH_4][B(C_6H_4S_2)_2]$. Treatment with Bu_3SnH causes the latter to be converted into the former and also serves to consume excess *o*-benzenedithiol

transforming it into $C_6H_4SH(S\text{-}SnBu_3)$. Different reducing agents were examined for the completion of the regeneration, but most either did not work or over reduced the boron species into borohydride. The digestion products were finally reduced to AB by Bu_2SnH_2, likely due to the strong bonds that form between *o*-benzenedithiol and the tin derivative. While Bu_3SnH could not reduce the digestion products on its own, further studies, prompted by the instability of Bu_2SnH_2, revealed that the addition of trimethylamine drives the reaction to AB.[77]

The regeneration of the metal hydride source and acid is afforded by decarboxylation of tin formate. Direct protonation of $C_6H_4SH(S\text{-}SnBu_3)$ and $C_6H_4(S\text{-}SnBu_3)_2$ with formic acid is thermodynamically unfavourable, but the desired formate can be obtained by first treating the tin species with HCl to give the desired $C_6H_4S_2H_2$ and Bu_3SnCl which can then be treated with formic acid in the presence of NaOH or Et_3N to afford only 60 % isolated yield of the initial Bu_3SnH. While, overall, this cycle is energetically favourable, the use of more than one equivalent of tin reagent for the formation of AB will undoubtedly not be feasible at a scale to provide enough fuel to solve the current energy crisis.

Another hydride donor capable of regenerating spent AB was developed by DuBois and his group at Pacific Northwest National Labs (PNNL). In addition, they have been attempting to create a scale of relative hydride donor and acceptor ability to help in the understanding prediction of successful hydride transfers.[79] Experimentally, the DuBois group found that $HRh(dmpe)_2$ was able to transfer a hydride to $BH_3{\cdot}THF$, to produce BH_4^-. In the presence of this rhodium hydride donor (3 eq) and triethylamine, $BF_3{\cdot}OEt_2$ accepts hydrides and disproportionates to $BH_3{\cdot}Et_3N$ in 20 hours. $HRh(dmpe)_2$ also transfers a hydride to the *o*-benzenedithiol digestion product $(C_6H_4S_2)B\text{-}H{\cdot}(NH_3)$ described in the example above but the reaction could not be driven past the

$[H_2B(S_2C_6H_4)]^-$ species. Finally, $B(SPh)_3$ was employed as a model digestion product. According to their calculations, the hydride transfer should be possible and it is observed (**Scheme 1-6**).



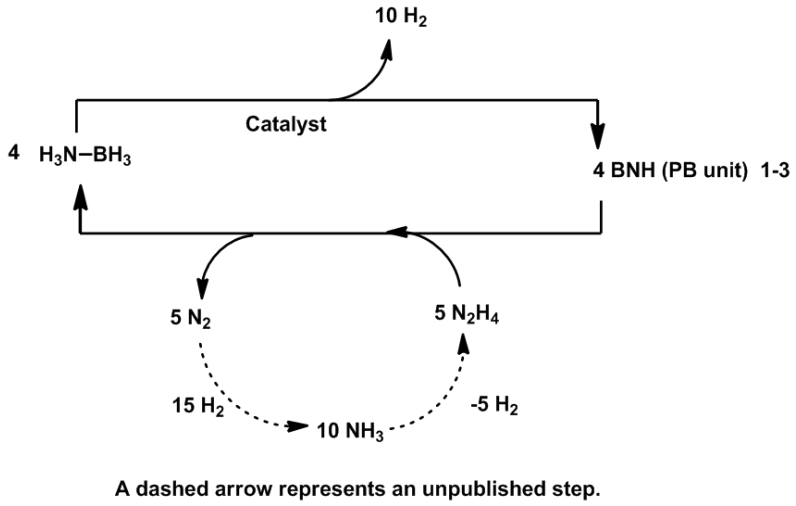
Scheme 1-6 AB regeneration cycle developed at PNNL

The publication does not specify whether spent AB can be digested with thiophenol to make the $B(SPh)_3$ species, but the hydride affinity and weak B-S bond strength of this intermediate would make it a good candidate. This has recently been captured in a patent issued to LANL.[80] Unfortunately, thiophenol is considered a hazardous substance and can cause health problems to those exposed to it. Practically speaking, however, phenol is not an alternative. In all comparable experiments with oxygen-bridged boronic esters, once the analogous $B(OPh)_4^-$ is formed, it has become non-reactive as the disproportionation with these species, although present, is much more difficult. No hydride exchange between $B(OPh)_4^-$ and the hydride donor is observed.

The initial species formed immediately after mixing $B(SPh)_3$ and $HRh(dmpe)_2$ are $[HB(SPh)_3]^-$ and the partially disproportionated product $[H_2B(SPh)_2]^-$. Surprisingly, a small amount of $[B(SPh)_4]^-$ is observed, presumably formed from a small amount of quickly disproportionating

starting material whereby volatile BH_3 is lost. Heating to 50 °C drives the reaction exclusively to $[H_2B(SPh)_2]^-$ and $[H_3B(SPh)]^-$ in a 3:1 ratio. Since the hydride source was not depleted at this point, the reaction was heated to 50 °C for a total of 20 hours. The major reaction product was the desired $[H_3B(SPh)]^-$ with a small amount of dmpe-$(BH_3)_2$, resulting from decomposition of the metal complex, as well as over-reduced BH_4^-. This demonstrated the reasonable hydride donor ability of the rhodium hydride, as well as the importance of choosing the BX_3 species with low heterolytic B-X bond strength. In order to drive the reaction to completion in milder conditions, the reaction was run in the presence of excess triethylamine, at room temperature. The triethylamine-borane was observed this time in over 90 % yield, with only trace amounts of dmpe-$(BH_3)_2$, and the remaining mass balance consisting of BH_4^-. A simple substitution of ammonia for the triethylamine would yield the desired ammonia borane. Unfortunately, the procedure has not been attempted on anything larger than an NMR-scale, nor have any intermediates or products been isolated at this time, placing a legitimate doubt on the feasibility of the process. The regeneration of acid and Rh complex has not been published. The donor was initially formed from the reaction of $[Rh(dmpe)_2](CF_3SO_3)$ which gives an equilibrium with the dihydride when exposed to a hydrogen atmosphere.[81] Treating the dihydride product with a strong base like ^{t}BuOK causes deprotonation of the hydride donor and regenerates $HRh(dmpe)_2$. It is as yet unknown if this can be accomplished directly with the product of hydride transfer $[Rh(dmpe)_2][SPh]$. Needless to say, the use of triflic acid on industrial scale to regenerate the digestion acid HSPh and replace the metal counterion to yield $[Rh(dmpe)_2](CF_3SO_3)$, in addition to the high cost of rhodium, makes this regeneration method far from a commercial process. Finally, a very different approach has recently been described[69] by the aforementioned researchers at Los Alamos National Labs. Based on a study of the viability of their own

regeneration procedure at process scale, they found that the most energy and cost consuming aspect was the high molecular weight of the tin hydride, more specifically its transportation, not to mention its toxicity. Their efforts to find a light weight, atom economical reductant, led them to consider hydrazine (N_2H_4) which can regenerate AB releasing N_2 as the only by-product (**Scheme 1-7**).



Scheme 1-7 Recent AB regeneration cycle developed at LANL

Their first attempts at reducing PB **1-3** in THF led to the complete consumption of the starting material and the production of the hydrazine-borane adduct instead of the desired AB. It was found that by gently heating the reaction to 40 °C in a supersaturated environment of NH_3, AB could be isolated in 95 % yield. The reaction is performed on a 100 mg scale (a 75 mL stainless steel pressure reactor was used as large amounts of gas are involved) the PB **1-3** and hydrazine are added to cooled liquid NH_3 and the sealed reactor is then heated to 40 °C for 24 h. The reactor needs to be cooled to -77 °C once again, before it is opened, but AB can be isolated from the reaction mixture by distillation of the starting material and solvent. Future work will consist of

developing a regeneration cycle for the hydrazine instead of being forced to rely on the current production method which is the Olin-Rashig process.[82] On site regeneration of the reducing agent will be the most efficient method of procuring the material. Despite this being a very elegant method of AB regeneration, like all other AB regeneration processes, there are significant hurdles to the industrial applicability of this process. Hydrazine is an explosive substance (particularly if heated) and has been shown to cause toxic effects in animals and possibly, in humans.[83] Its use is being controlled[84] to minimize its concentrations in the environment, which may hinder any industrial process which relies on very large quantities of it, particularly in a case like this where off-site plants will have to be frequent to minimize travel costs to and from the regeneration site. Given the difficulties with the state-of-the-art regeneration methods described above, our group embarked on a study of alternative *organic* hydride donors.

1.1.3 Proposed Hydride Acceptor

The first goal of the project was a model study to answer the question: can we transfer a hydride from an organic hydride donor to a BX_3 compound? (Please note: the expression 'hydride transfer' is used frequently in this thesis. Please be aware that it is used to express a net result and not a mechanistic implication. Jonathan Webb, a fellow Crudden group member has undertaken the study of the transfer mechanism independently: the mechanistic analysis of the system is consistent with a single electron transfer pathway although the possibility of a concerted reaction proceeding through an asynchronous transition state cannot be ruled out.) In order to simplify our studies, we focused on a hydride acceptor which would not disproportionate, in order to directly observe and study the hydride transfer directly. For that, we required a strong Lewis acid with strong B-carbon instead of B-halide bonds.

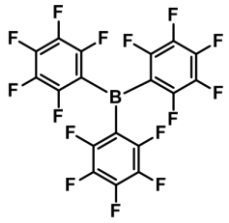
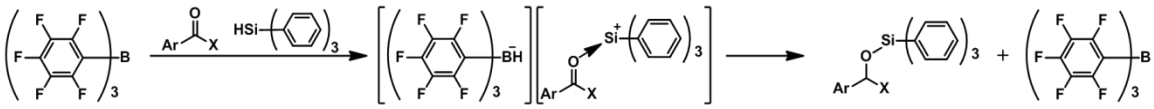


Figure 1-3 Tris(pentafluorophenyl)boron, $B(C_6F_5)_3$

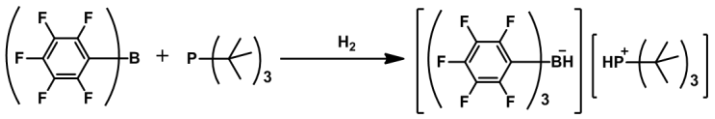
Tris(pentafluorophenyl)boron[85] (BCF) (**Figure 1-3**) was deemed an ideal candidate. Its Lewis acidity is comparable[86-91] to BF_3 and BCl_3 but it is much more stable[92] and, thus, easier to handle. Most importantly, the use of BCF, with its boron-carbon bonds that are strongly resistant to disproportionation, would permit us to examine only the first step in the reaction, the hydride transfer, without complications due to disproportionation.

BCF is sterically hindered and, therefore, will not easily form dative bonds with Lewis bases present on the hydride donor. In addition, BCF has an unusually high hydride affinity due to its soft character.[93] Transfer of hydrides, some organic, to BCF, has been observed in select cases. Piers[94] observed a silicon hydride transfer to BCF in his study of this molecule as a catalyst for the hydrosilation of carbonyl compounds[95] (**Scheme 1-8**).



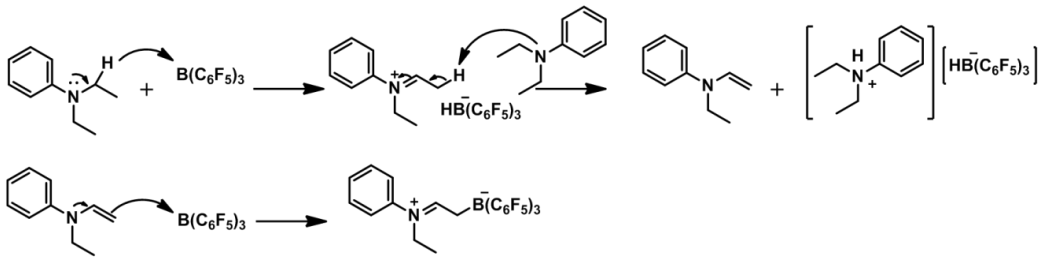
Scheme 1-8 Hydrosilation mechanism

The particular Frustrated Lewis Pairs (FLP) chemistry[96] often involves cleavage of H_2 by a hindered Lewis acid and Lewis base coexisting without adduct formation (**Scheme 1-9**).



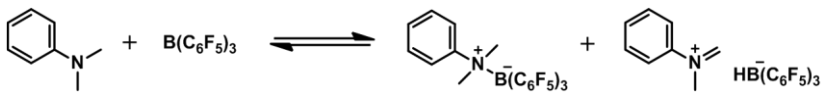
Scheme 1-9 Hydrogen activation by an FLP system

BCF is often the Lewis acid of choice resulting, in this example, in a readily characterized borohydride. Finally, there are a few examples of a C-H α to a nitrogen transferring a hydride to BCF. The first example was reported by Basset[97]: upon mixture of BCF and Et_2NPh, no adduct formation was observed. The reaction products including a diagnostic boron species were borohydride, a tetravalent boron species and starting material. Using multinuclear and 2D NMR, the authors were able to determine the structure of the two products as $[HNEt_2Ph]^+[HB(C_6F_5)_3]^-$ and $PhEtN{=}CHCH_2\text{-}B(C_6F_5)_3$. The proposed mechanism is described in **Scheme 1-10**.



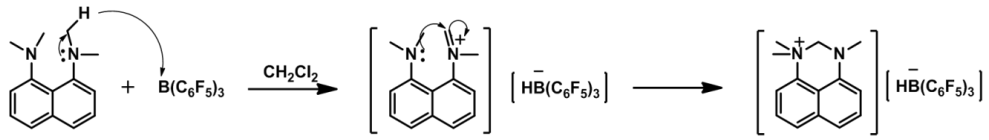
Scheme 1-10 Mechanism of hydride transfer from a C α to a N atom

The position of the abstracted hydride was confirmed by observing the effect of BCF on the Me_2NPh analogue which cannot isomerize to the enamine. In this case, the iminium ion was characterized confirming the proposed mechanism[97] (**Scheme 1-11**).



Scheme 1-11 Hydride transfer product observed in an *N*-methylated system

Other groups have observed similar reactivity between BCF and Et_3N in dichloromethane.[98] Bulky amines like $^{i}Pr_2NH$ and $^{i}Pr_2NEt$ and finally, 1,8-bis(dimethylamino)naphthalene[98] (or proton sponge$^{(R)}$) also react to transfer hydrides to boron, in the latter case yielding a cyclic structure as described in **Scheme 1-12**.



Scheme 1-12 Hydride transfer from 1,8-bis(dimethylamino)naphthalene to BCF

In all of these cases, the net transfer of hydride is only 50 % with regards to the amines (or hydride), as the iminium resulting from hydride transfer is attacked by another equivalent of amine.

1.1.4 Proposed Hydride Donor

The ideal hydride donor would be readily available, inexpensive, recyclable (essential for a 'renewable' aspect of the fuel) and, preferably, non-toxic. Although it may seem redundant to use a hydride to regenerate a spent material and not as a storage material directly, the energy intensive regeneration associated with light meal hydrides, in addition to the higher weight percent of hydrogen in AB make it a better choice as a storage material for mobile applications. The issues regarding metal hydrides as the regenerating species, discussed previously, explain why our attention turned to organic hydride donors.

In nature the NAD+/NADH[99] is the most commonly encountered redox pair (**Figure 1-4**).

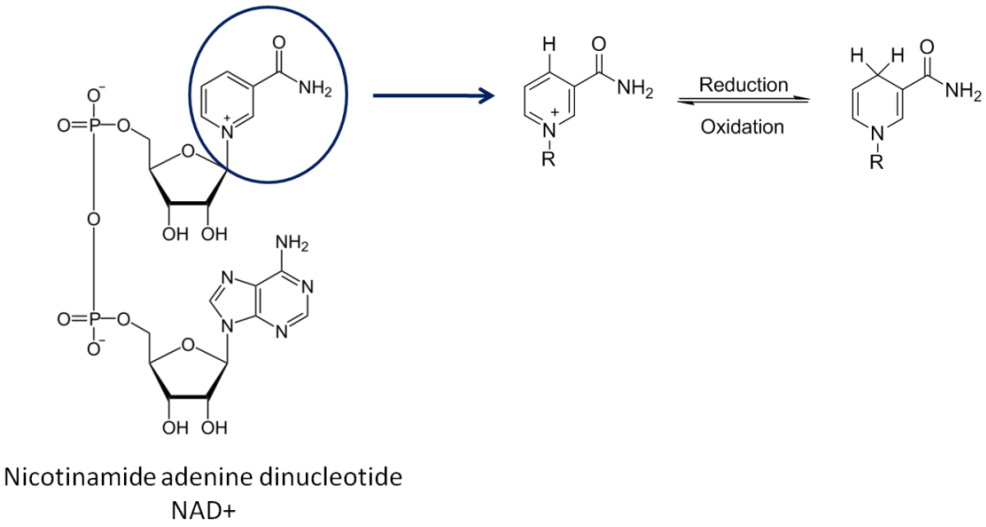


Figure 1-4 'Nature's reducing agent'

This species is found in most living organisms and has a low redox barrier between the 1,4-dihydropyridine and pyridinium forms while remaining a strong reducing agent.[100] The driving force for the loss of hydride is the aromatization of the pyridine ring, but the positive charge of the resulting pyridinium facilitates reduction. 1,4-DHPs belong to a class of compounds which are calcium channel blockers so quite a bit of work has been invested into their synthesis[101] and use as pharmaceutical agents.[102-111] Previous work[112] resulted in many highly substituted analogues at every position, in particular the 3 and 4 carbons. Another area of research which has arisen from this class of compounds involves the use of 1,4-DHPs as stoichiometric non-metallic reducing agents. Efforts have concentrated around one particular analogue: diethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, Hantzsch ester[101] (**1-4**, **Figure 1-5**) which has the advantages of being bench stable, commercially available and readily synthesized, soluble in organic solvents, and more hydridic than NADH itself.[113]

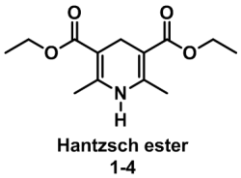
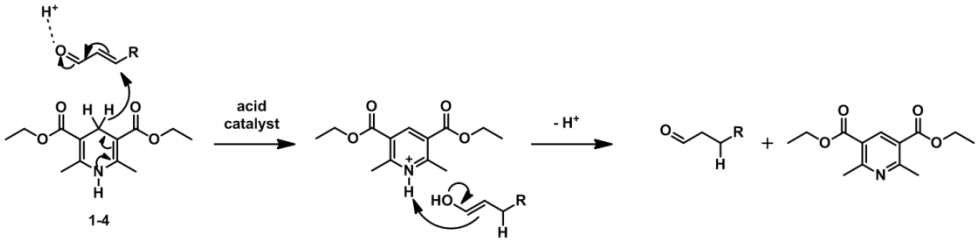


Figure 1-5 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate

A recent review[114] discusses the scope of the metal-free reduction using Hantzsch ester in which first a hydride is transferred followed by the pyridinium proton, producing a net addition of a hydrogen molecule.[115] More notable examples include reductive amination (both racemic and enantioselective) as well as reduction of α,β-unsaturated carbonyl olefins[101] (**Scheme 1-13**).

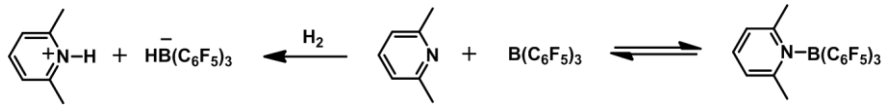


Scheme 1-13 Metal-free reduction of an α, β-unsaturated aldehyde

These reductions generally require an acidic or iminium catalyst but proceed at room temperature in good yield. Even industrial processes have been developed for this chemistry: in one reported case, the desired reductive benzylation of malonitrile was accomplished through a ball milling process of the neat reagents.[116]

Thus we embarked on the study of NADH analogues as hydride donors for the regeneration of borane from digestion products of spent AB.[117] Hantzsch ester was chosen as the starting point. Our system required no substitution at the 4 position, so this choice reduced molecular waste which would have been encountered with numerous other published analogues. Being substituted

at both the 3 and 5 positions avoids possible decomposition by electrophilic attack[118] at the 5 position, possibly by the pyridinium proton formed as a result of hydride transfer.[119] Given the precedent of the pyridinium proton being transferred to organic molecules when 1,4-DHPs are used as metal-free reducing agents,[101] there was a concern that dehydrogenation could occur between the hydride and acidic pyridinium proton, yielding hydrogen gas and readily identifiable pyridine. To inhibit this side reaction, analogues considered from the start were *N*-substituted Hantzsch esters *vide infra*. Substitution at the 2 and 6 positions flanking the nitrogen was deemed essential to inhibit adduct formation with BCF, as the BCF-pyridine adduct is very stable and has been known as long as BCF itself.[85, 120] During the course of our work, the Stephan group published an FLP paper involving 2,6-lutidine and BCF[121] which showed that although adduct formation at the moderately hindered nitrogen is observed, it is reversible and this system is even able to activate hydrogen (**Scheme 1-14**).



Scheme 1-14 Lutidine- BCF activation of H_2

In addition, some studies have shown that the 2,6-substituted analogues are more stable towards irradiation[122] making for more robust compounds than the unsubstituted analogues. Although the carbonyl groups stabilising the 1,4-dihydropyridine structure of Hantzsch ester are potential sites for complexation with BCF, we accepted this potentiality for our initial study based on the significant data present in the literature on this compound, and its ease of synthesis. If these groups proved to be a problem, we planned to design and synthesize more suitable hydride donors.

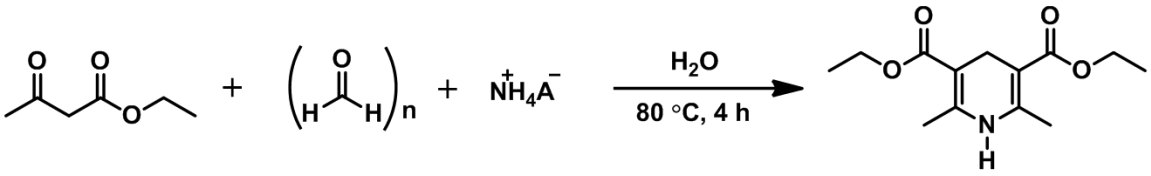
1.2 Results and Discussion

1.2.1 1,4-Dihydropyridines

Hantzsch Ester

The most readily available NAD/NADH+ analogue is diethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, Hantzsch Ester. Like all 1,4-DHPs, the methylene hydrogens are in a doubly allylic position with the electron rich nitrogen, but the advantages of Hantzsch ester are its stability, commercial availability, synthetic feasibility and solubility in organic solvents *vide supra*. Unfortunately, its high price -and the questionable purity of the received material- led us to investigate a protocol for its synthesis in house. Based on the methodology of Zolfigol and Safaiee[123-125] we carried out a short optimization of the ammonia source (**Table 1-1**).

Table 1-1 Optimization of reaction conditions for the synthesis of Hantzsch ester



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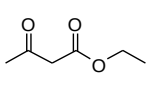
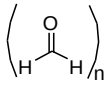
Entry			*Ammonium counter ion (eq)*	*Solvent*	*Time (h)*	*Crude Yield (%)*
1	2	1	formate (2)	neat	2.5	17
2	2	1	acetate (1.5)	1 M H_2O	50 min	57
3	3	1	acetate (4)	1 M H_2O	4	81

Contrary to the published procedure, we determined that neat conditions were unsuitable for the synthesis but that just enough water to make an easy-stirring suspension once the product

precipitates, gave high yields. Based on other published procedures,[125, 126] ammonium acetate as the ammonia source was shown to give high yields therefore a thorough investigation was not undertaken. The workup calls for a filtration of the product from the reaction mixture. We found that the ideal washing solvent is ether, as it solubilises the pyridine much better than the desired 1,4-dihydropyridine, thus eliminating the need for flash chromatography. Once satisfied the gram-scale synthesis and purification of the hydride donor could be achieved with very little time, effort, or cost, we undertook the study of the hydride transfer to BCF. The first challenge was to determine a suitable solvent for the reaction, work which Jonathan Webb undertook. Hydride transfer was observed in chloroform, but the reaction products decomposed over short periods of time resulting in several species as described in **Figure 1-6**.

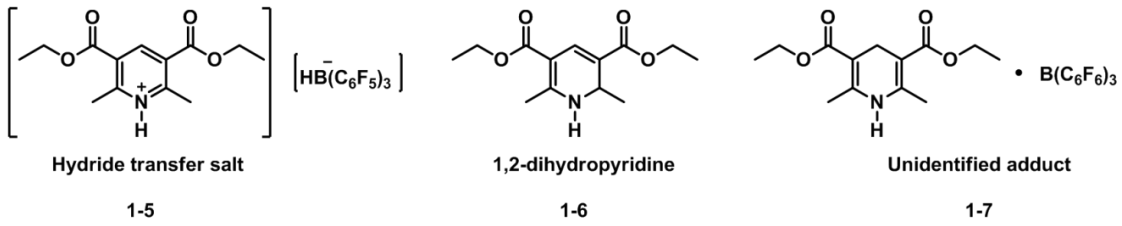


Figure 1-6 Products of the reaction of Hantzsch ester and BCF

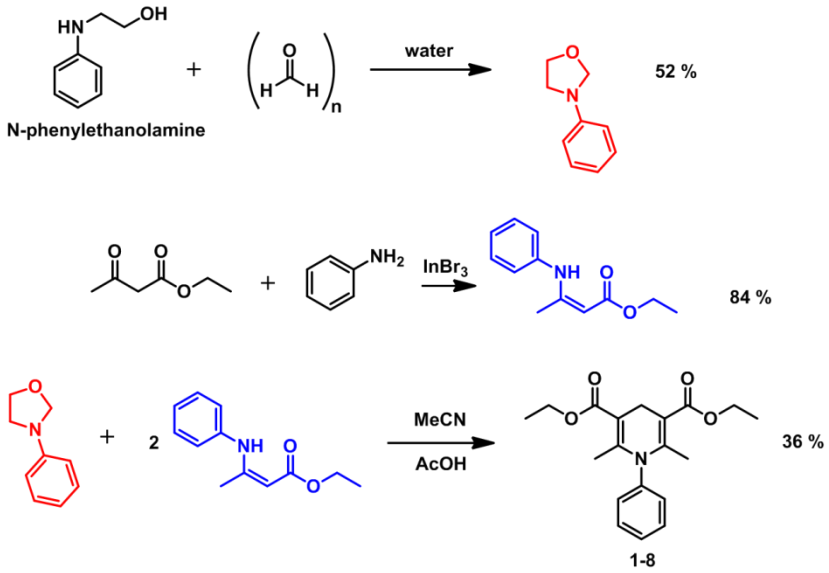
Deuterated benzene, bromobenzene d_5, THF-d_6, and dichloroethane were found to give the same multiple species which Jonathan Webb identified, including the hydride transfer salt (desired product, **1-5**) as seen in the ^{1}H and ^{11}B NMR spectra, a boron based Lewis adduct (**1-7**) seen only in the ^{11}B NMR spectrum and based on the ^{1}H NMR spectrum, 1,2-dihydropyridine (**1-6**), resulting from the reversible transfer of hydride.[127-130] The presence of 1,2-DHP confirmed the statement by Kellog that '*In any reaction whereby pyridinium salt is generated during the reaction in the presence of unconsumed 1,4-DHP, exchange and isomerisation may be complicating factors especially in the case that the substrates to be reduced are only sluggishly*

reactive.'[115] In the end, deuterated methylene chloride was found to favour the rapid formation of the desired salt thereby limiting the formation of the 1,2-Hantzsch ester and reducing the amount of adduct formation, provided it was dried and distilled over CaH_2 and kept at -25 °C over molecular sieves in the presence of CaH_2 in the glovebox. Reactions were prepared in the glovebox by combining a solution of BCF with a solution of 1,4-DHP, in an NMR tube in the dark. Immediately upon mixing, the color changes from clear to bright yellow. NMR data confirm the transfer of hydride from Hantzsch's ester to BCF (**1-5**). Although I carried out the work for the synthesis of Hantzsch's ester, the hydride transfer was initially studied by Jonathan Webb on this donor. The other analogues offer comparable results, and so the discussion of Hantzsch ester specifically will be addressed only as needed in the discussions of the other compounds.

N-phenyl Hantzsch Ester

Initially, there was a concern as to whether or not the methyl groups flanking the nitrogen of Hantzsch ester would provide enough steric hindrance to inhibit the formation of a Lewis acid-base adduct with the BCF. Accordingly, the synthesis of *N*-substituted analogues was undertaken at the same time. In view of the preliminary results with Hantzsch ester, we also postulated that the increased steric bulk would make the formation of the 1,2-dihydropyridine more difficult. As mentioned previously, this was also a solution in case dehydrogenation was observed. Unfortunately, the condensation procedure used for the synthesis of Hantzsch ester was not applicable to substituted amines or their salts. Indeed, reaction with aniline, aniline hydrochloride, aniline acetate, as well as changing the formaldehyde source to a solution and increasing the heat gave either no reaction or a complex mixture with no diagnostic peaks. In the case of *N*-phenyl

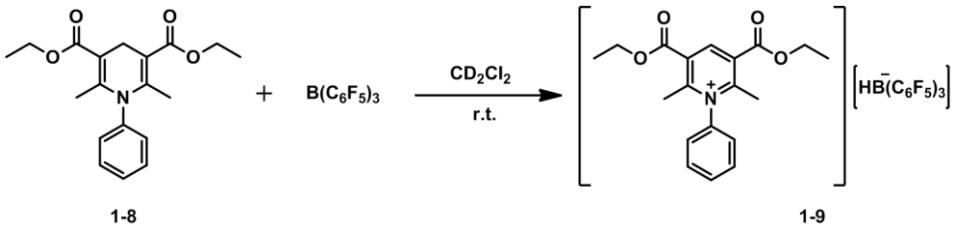
Hantzsch ester **1-8**, pre-condensation of the aniline and ethyl acetoacetate[131, 132] was not a viable route either. The synthesis of the Micheal acceptor through reaction of ethyl acetoacetate and paraformaldehyde was also unsuccessful due to self-condensation. Fortunately, *N*-phenyl Hantzsch ester **1-8** is known in the literature[133, 134] and the procedure, which calls for pre-condensation of the aniline[135, 136] and ethyl acetoacetate, as well as protection of the paraformaldehyde in the form of an oxazolidine[136], was followed to completion albeit with the expected low yield of 36 % and notable molecular waste (**Scheme 1-15**).



Scheme 1-15 Synthetic route followed to obtain *N*-phenyl Hantzsch ester

Based on our previous studies, CD_2Cl_2 was chosen as the solvent for the reaction of *N*-phenyl Hantzsch ester and BCF. Hydride transfer was immediately observed as in the case of unsubstituted Hantzsch ester, **1-4** (**Scheme 1-16**). Interestingly, the ^{11}B NMR spectrum shows two peaks (at -23.3 (d) and 1.6 (broad) ppm), and the ^{1}H NMR spectrum shows evidence of two species as well. The major peak at -23.3 ppm in the ^{11}B NMR spectrum corresponds to the

borohydride salt **1-9**, as expected, but the second does not correspond to free BCF which is observed at 60 ppm, see **Figure 1-7**.



1-8 1-9

Scheme 1-16 Reaction of *N*-phenyl Hantzsch ester and BCF

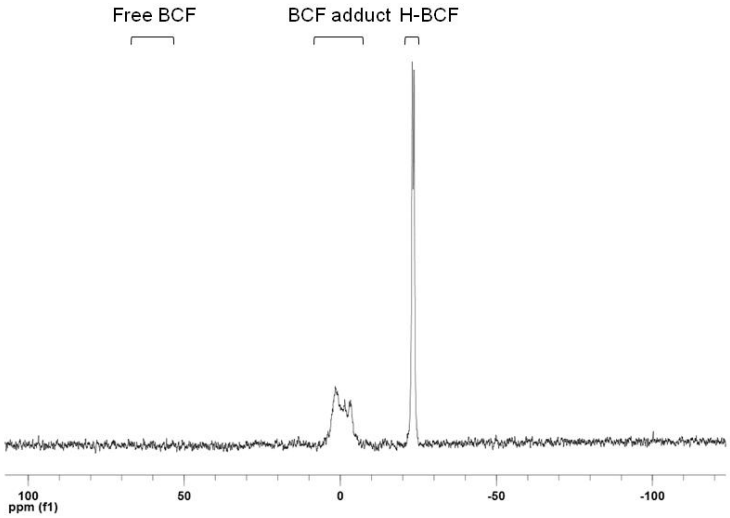


Figure 1-7 ^{11}B NMR spectrum obtained for the reaction of *N*-phenyl Hantzsch ester and BCF

This result was also observed with Hantzsch ester **1-4** and had led us to consider the formation of an adduct between BCF and the 1,4-DHP (**1-7**). Adduct formation with the *N*-phenyl substituted analogue was an indication that the carbonyls, and not the hindered nitrogen were interacting with

the Lewis acid. Stephan has shown that when the steric and electronic factors are adequate (high and low respectively) these adducts can be reversible (**Scheme 1-14**); thus, adduct formation does not inhibit reactions that require free BCF in solution.[121] The two same boron peaks were also observed by Jonathan Webb with an *N*-methylated analogue implying a similar equilibrium in that case as well.

A crystal suitable for X-ray crystallography was grown from slow diffusion of pentane into a solution of reagents in dichloromethane, **Figure 1-8**. The crystal shows the borohydride and aromatic pyridinium ring with the *N*-phenyl group lying in the perpendicular plane.

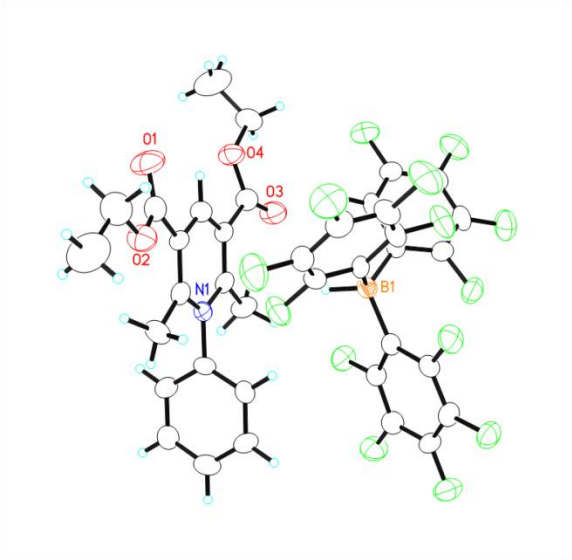
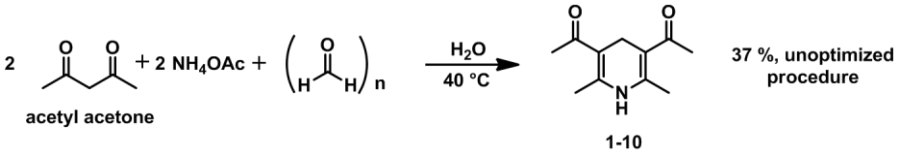


Figure 1-8 Crystal structure of the borohydride salt formed from *N*-phenyl Hantzsch ester and BCF (1-9)

Having successfully transferred a hydride from two Hantzsch ester *N*-analogues to BCF in 90 % yield, we set out to study the effect of the hindrance at the carbonyls to gain an understanding of the system in the goal of designing a better hydride donor. With this goal in mind, two additional 1,4-DHP analogues were studied: a diketone (**1-10**) and a di-*tert*-butyl ester (**1-14**).

1,4-dihydro-2,6-dimethylpyridine-3,5-diacetyl

This analogue of Hantzsch ester presents very little steric hindrance to the carbonyl groups, but keeps the nitrogen environment intact. This compound is known in the literature[137-139],



Scheme 1-17 Synthesis of diketone Hantzsch ester

but the reaction conditions for the synthesis of Hantzsch ester were applied to acetylacetone (**Scheme 1-17**) successfully in 37 %, using an unoptimized procedure: sufficient quantities were made on the first try for all subsequent experiments.

The reaction with BCF gave an interesting product (**Figure 1-9**). Indeed, no hydride transfer was observed in CD_2Cl_2 (nor $CDCl_3$ or C_6D_6) but all solvents gave similar results. The ^{11}B NMR spectrum shows no borohydride peak nor free BCF either, only one peak at -1.06 ppm (Note: peak position varied from approximately 1.5 to -1.5 ppm) implying an adduct (**1-11**) with a similar structure as that observed previously. The ^{1}H NMR spectrum at room temperature shows a broadening of the methyl peaks and the NH indicating that any adduct present is dynamic. Upon cooling the reaction mixture to 0 °C, a decoalescence of the four methyl peaks is observed, indicating a non-symmetric adduct, **Figure 1-9**.

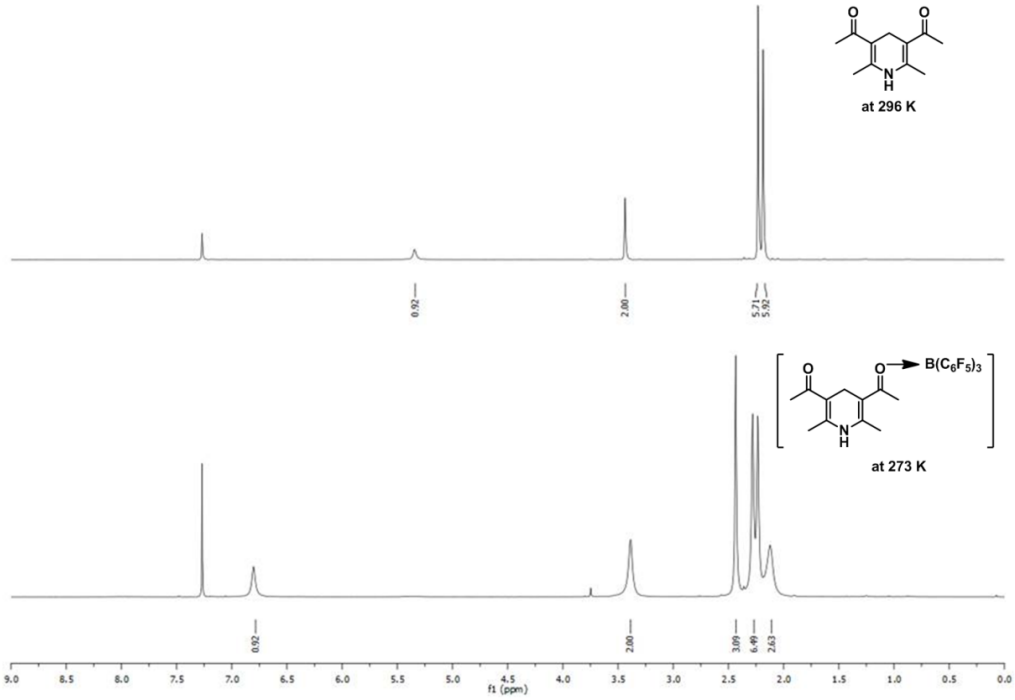


Figure 1-9 ^{1}H NMR spectrum of the diketone Hantzsch ester before and after reaction with BCF

This eliminates the possibility of adduct formation at the nitrogen which would be symmetrical with regards to the four methyl peaks thus confirming the BCF-*carbonyl* binding theory as described in **Figure 1-10**.

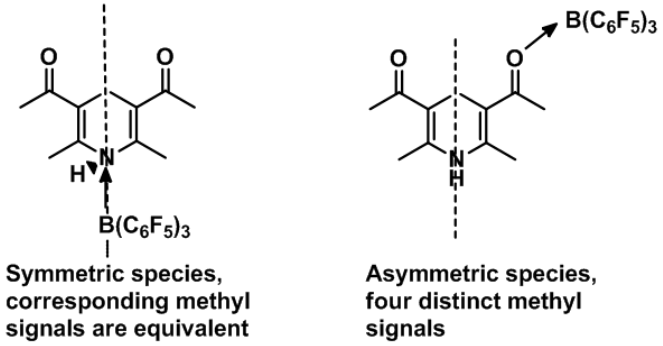
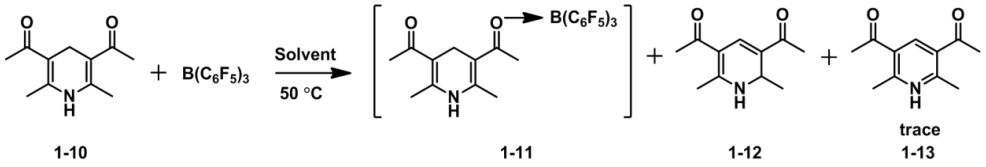


Figure 1-10 A comparison of N vs. O binding products

In $CDCl_3$, this adduct is not stable over time, producing noticeable amounts of Hantzsch pyridine **1-13** and 1,2-dihydropyridine **1-12** when left in solution. Having proved that the equilibrium between the diketone Hantzsch ester analogue **1-10** and BCF was dynamic, through variable temperature (VT) NMR studies, we attempted to heat the reaction mixture (in all three solvents) hoping to increase the amount of free BCF in solution, thereby driving the reaction to hydride transfer instead of adduct formation. Heating the reaction to 57 °C for four hours did not induce a clean hydride transfer but only produced the 1,2-dihydropyridine and a trace amount of dehydrogenation product (**Scheme 1-18**).



Scheme 1-18 Identified products observed after heating a solution of 1-10 and BCF

As discussed previously, Hantzsch ester will transfer a hydride to its pyridinium to yield the 1,4- or 1,2-dihydropyridine, as studied by Kellogg[127] (**Section 1.2.1**) and observed for our system. In our case however, given the much milder reaction conditions, we suspected that the $HB(C_6F_5)_3^-$ species may be involved in the transfer as there are many examples of hydride transfer from $HB(C_6F_5)_3^-$ once it is formed: these include the hydrosilation previously discussed, FLP examples like the reduction of imines, and one transfer to an aromatic compound.[140] Another report of a reversible hydride transfer from the organic hydride donor to BCF[141] has been published for the reaction of diisopropyl amine with BCF at 110 °C. Interestingly, in this system no adduct formation was observed between the amine and BCF.

Finally, in order to absolutely confirm the regioselectivity of the binding of BCF to our 1,4-DHP analogue, a crystal was grown from slow diffusion of pentane into a solution of methylene chloride (**Figure 1-11**).

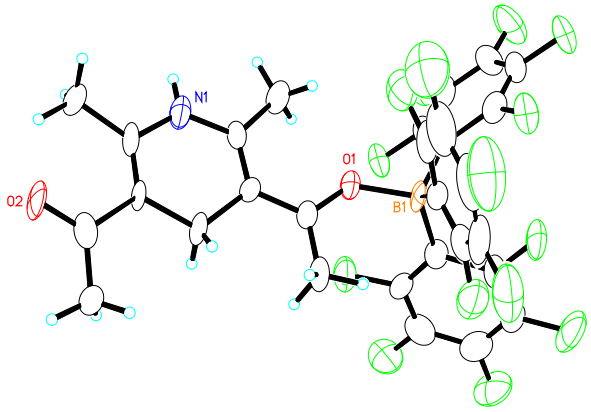


Figure 1-11 Crystal structure isolated from a mixture of diketone Hantzsch ester and BCF (1-11)

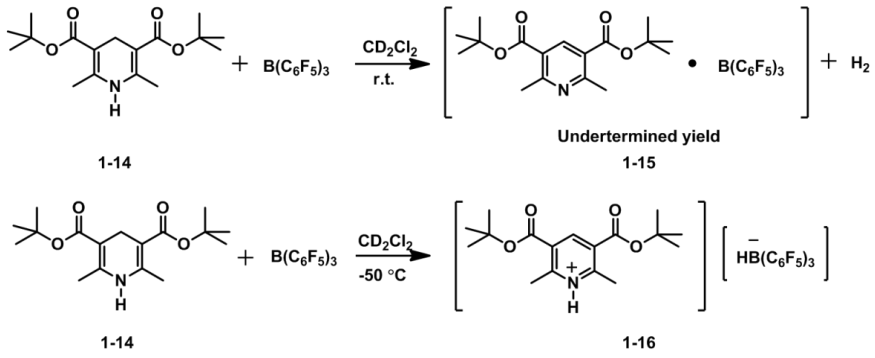
From the crystal structure, we can confirm without a doubt that the binding of BCF to carbonyl oxygen occurs, at least in the solid state. Although this does not demonstrate the complete absence of N-B adduct as was observed by Stephan, the combined results of the VT NMR studies and the crystal structure do indicate that, in our system, the carbonyls have a greater effect which is consistent with the high oxygen affinity[120] of BCF. To probe this effect further, we studied the 1,4-dihydro-2,6-dimethylpyridine-3,5-*tert*-butyldicarboxylate in which the *tert*-butyl groups cause a significantly more hindered environment for the carbonyl groups.

Studies of the Hydride Transfer from *tert*-Butyl Hantzsch Ester 1-14 to BCF

The first attempt at the synthesis of this compound **1-14** was carried out using the same procedure as Hantzsch ester, with the substitution of tert-butyl acetoacetate for the ethyl acetoacetate. Only about 20 % of product was isolated, the mass balance consisting of starting material and the corresponding pyridine which is difficult to separate from the desired product. The next attempt was following a procedure found in *synlett* which used formaldehyde in its pure form, *p*TSA (*para*-toluene sulfonic acid) as a catalyst as well as SDS (sodium dodecyl sulfate) and sonicated overnight.[137] The TLC (thin layer chromatography) showed some product, but it was difficult to isolate as only an oil had separated from the solution and all attempts at crystallizing the product were unsuccessful. In a final attempt to synthesize the product, *p*TSA was added to the initial moderately successful conditions as a catalyst. Although the starting material was almost entirely consumed, the major product was the pyridine in a 2.25:1 ratio with the 1,4-dihydropyridine. Preliminary attempts at reduction of the corresponding pyridine gave fairly low yields and required multiple purifications. In view of the difficulty we were experiencing with its synthesis, this 1,4-DHP **1-14** was purchased through Aldrich.

Combining the tert-butyl Hantzsch ester **1-14** with BCF in $CDCl_3$ produced an insoluble solid precipitate that could not be characterized. By changing the solvent to CD_2Cl_2, solubility was increased somewhat, but not dramatically, and no hydride transfer was observed. Analysis of the multiple products remaining in solution by ^1H NMR was difficult, however, characteristic peaks around 9 ppm diagnostic of the dehydrogenation product (pyridine, **1-15**) were observed. The proposed dehydrogenation was further confirmed by the absence of borohydride peak in the ^{11}B NMR spectrum. These results were not unexpected as, under these conditions, the most reasonable dehydrogenation pathway goes through the borohydride. We were confident that the

hydride was being, at least partially, transferred but subsequently being lost as hydrogen (**Scheme 1-19**).



Scheme 1-19 Reaction of ^{t}Butyl Hantzsch ester and BCF at room temperature and upon cooling

A new methodology was developed to permit the low temperature study of these reactions, in order to stop the unwanted precipitation reaction, as well as dehydrogenation. By layering the reagent solutions one over the other, freezing the solvent between each addition, and keeping the layers in a dry ice/acetone solution for transportation, we were able to eliminate any possibility for reaction at room temperature. The J-Young tube containing the frozen reagent layers was warmed to – 50 °C in the NMR. At this temperature, most of the species are not in solution so it is necessary to eject the tube, quickly shake it, and return it to the NMR. The spectra obtained this way were reproducible as the time spent out of the NMR environment was too short to cause a significant temperature shift. Under these careful conditions, it was possible to observe hydride transfer product, **1-16**, as this procedure strikes a balance between the reactivity of the hydride transfer (the salt of which is soluble) while denying the system the energy necessary for the side reaction, causing the insoluble solid to crash out of solution. The borohydride **1-16** can be observed at temperatures up to -30 °C, but tends to decompose faster at higher temperatures. For

this reason, it was difficult to acquire a ^{13}C NMR spectrum since it is impossible to sustain temperatures lower than – 25 °C overnight. Characterization was accomplished through an HSQC (Heteronuclear single-quantum correlation spectroscopy) spectrum which could be run in a much shorter time frame. No adduct formation was observed with this analogue confirming that it is the carbonyl group which binds to BCF. The increased reactivity at low temperature can be caused by a number of factors: for instance a higher amount of free BCF in solution, as well as an increased hydride donor ability. In the case of ^{t}butyl Hantzsch ester **1-14**, it is possible that the bulky side chains are forcing the carbonyls out of the plane of the nitrogen atom decreasing the stabilisation afforded by conjugation which, in turn, could result in a higher hydride donating ability. A comparative computational study of the hydride donating ability and the factors influencing it for several Hantzsch ester analogues has been undertaken by the Crudden lab in order to gain understanding of the relative hydride-donating abilities of the different analogues.

With the study of these analogues, we were able to show that Hantzsch ester **1-4** and its derivatives can transfer a hydride to BCF in good yield, with the mass balance consisting of a Lewis acid- base adduct. The main site of adduct formation is the carbonyl oxygen, not the nitrogen. When adduct formation is inhibited by rendering the carbonyls inaccessible, the yield of hydride transfer increases to quantitative even at extremely low temperature. On the other hand, more basic analogues, such as vinylogous amide (**1-10**), show no evidence of hydride transfer and, instead, react completely by adduct formation. Clearly the proof-of-concept was successful: 1,4-dihydropyridines have been shown to be adequate hydride donors for BCF. The next stage of the project was to design hydride donors which did not possess carbonyl groups to inhibit adduct formation. In addition, in the final iteration of our approach, BH_3 is the desired product and, thus, it is necessary to have a hydride donor which does not possess an easily

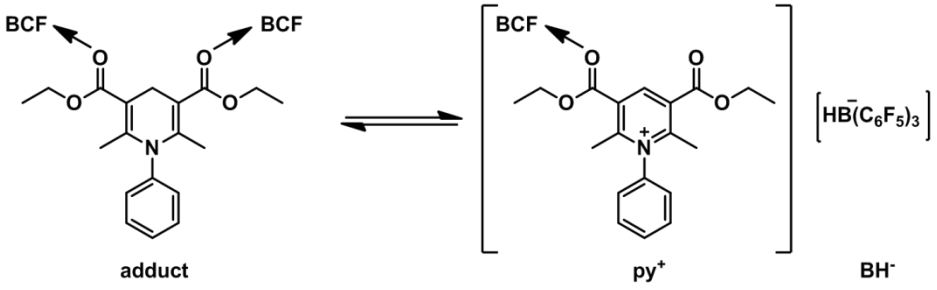
reducible functional group. Finally, in view of the recent reports of the regeneration of AB directly from its dehydrogenation product PB (**1-3**) with the hydrazine system[69], compounds containing both hydride and proton, like our 1,4-DHPs have great potential as they could make the acid digestion step of the regeneration cycle obsolete if a hydride donor capable of hydrating PB (**1-3**) can be developed.

1.2.2 Effect of the substitution of nitrogen

To gain additional insight about the system at hand, a comparative study of *N*-substituted analogues was undertaken. Nitrogen influences the hydricity of 1,4-dihydropyridines by providing the 'push' in the hydride loss and, with its lone pair, can potentially interact with BCF. Although we have seen no evidence of the latter in any of our studies, despite a precedent published by Stephan[121], the former is most certainly affected by the electronic characteristics of the substituent. During the initial hydride transfer studies we were able to determine that unreacted starting material was being trapped in the form of a dynamic Lewis acid-base adduct (**Figure 1-9**); therefore, we postulated that varying the stoichiometry of reagents would increase the proportion of desired salt **1-9**. As expected, increasing the amount of hydride donor increased our yield of (**1-9**) from 90 % (for a 1:1 ratio) to > 95 % conversion (for a 1.5:1 ratio of 1,4-DHP: BCF) of the BCF into borohydride at 296 K. This bodes well for our long-term goals, as the regeneration of borane will ultimately require a three-fold excess of the hydride donor. Excess BCF, however, did not have much effect on the yield of the reaction: at 253 K, the yield of the stoichiometric reaction is 41 % with respect to the limiting reagent while adding a total of 4.5 equivalents of BCF under identical reaction conditions gives a comparable yield of 31 %. Comparable trends were reported by Jonathan for both Hantzsch ester **1-4** and the *N*-methyl

analogue. Interestingly, under excess BCF conditions, the yield of salt increases with temperature for all three analogues; in addition, the yield was reproducible for any given temperature. That is, the reaction could be heated to a certain temperature and yield then cooled to a lower temperature and yield and back again. This fast equilibrium gave us an exclusive insight into the thermodynamics of the reaction and a powerful tool by which to compare the hydricity (and inversely, hydride affinity) of the *N*-substituted analogues. In order to have a system we could study, we needed to be able to know which species were present at any given time which could be difficult as there are two carbonyl groups and, ultimately, two adduct formation sites. Gross excess of BCF was deemed the most simple case in which the carbonyls are all involved in dative bonds with BCF yet there is still enough hydride acceptor to enable the hydride transfer. Multiple binding at the carbonyls was confirmed by Jonathan Webb who performed a detailed binding study of the less hydridic 4-phenyl substituted Hantzsch ester at different concentrations of BCF. Jonathan was able to determine that binding at the nitrogen was not occurring under the reaction conditions.

Reactions with gross excess (4.5 equivalents) of BCF were prepared at two different concentrations. The yields at the various temperatures were measured and Van't Hoff plots were traced (**Figure 1-12**) based on the following equilibrium (**Scheme 1-20**):



Scheme 1-20 Equilibrium conditions during the Van't Hoff studies

Given the following equation for the equilibrium constant $K_{eq}=[py^{+}][BH^{-}]/[adduct]$, it is possible to calculate K_{eq} by ^{1}H NMR: the pyridinium presents an aromatic peak as well as distinct aliphatic signals for the ester groups and its concentration is equal to that of borohydride. The adduct peaks present are easily identifiable in the NMR spectrum and, importantly, there are no additional peaks, so the mass balance for all components is accounted for.

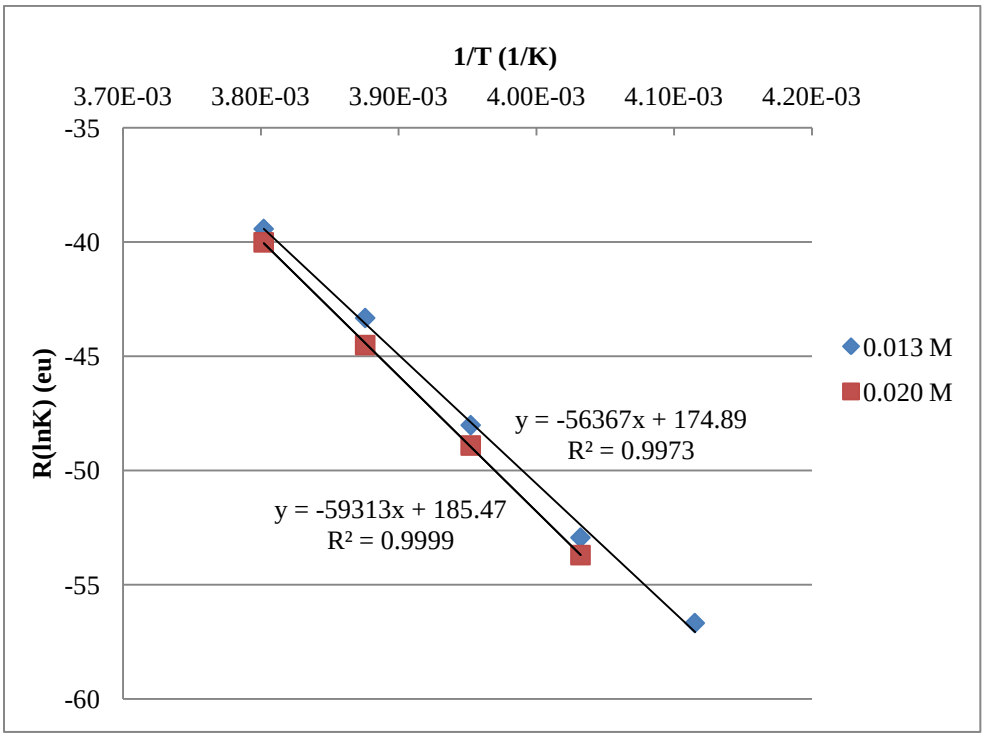


Figure 1-12 Van't Hoff plots for the reaction of *N*-phenyl Hantzsch ester with a 4.5-fold excess of BCF at two different concentrations of limiting reagent

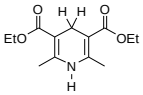
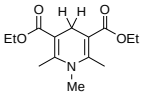
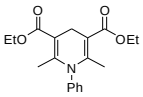
Based on $R(lnK)= \Delta H^{o}(1/T)+ \Delta S$ we can easily determine that this system has the following thermodynamic parameters:

ΔH_{rxn}^{253K} = 57. 8 kJ/mol or 13.8 kcal/mol ΔS_{rxn} = 180.1 J/mol or 43.0 cal/mol

ΔG^{253K}= 12.3 kJ/mol or 2.9 kcal/mol

A comparative table describing the results from all three analogues is included below.

Table 1-2 Thermodynamic data for three *N*-substituted Hantzsch ester analogues

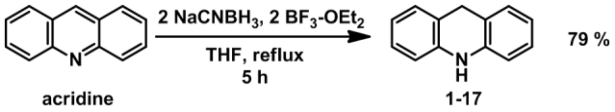
Compound	ΔH_{RXN}^{253K} *(kJ/mol)*	ΔS_{RXN} *(J/mol)*	ΔG_{RXN}^{253K} *(kJ/mol)*	K_{eq}^{253K}
	31	87	9	$1 \cdot 10^{-2}$
	38	133	5	$6 \cdot 10^{-2}$
	57	180	12	$2 \cdot 10^{-3}$

By comparing the data for these three analogous compounds, we can see the enthalpy of the reaction increases slightly with the bulk of the substitution on nitrogen, and that the entropy term varies following the same trend resulting in a Gibbs free energy in the same range for all three compounds. Based on this limited study, the bulk of the substitution at nitrogen is not a highly influential factor on the Gibbs free energy at the temperature studied.

1.2.3 9,10-Dihydroacridine

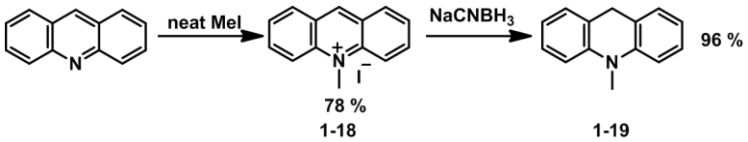
We next turned our attention to 9,10-dihydroacridine (9,10-DHA, **1-17**). Studies on the 9,10-dihydroacridine scaffold, in particular the *N*-methyl analogue, are fairly common in the literature. Along with the less stable 1-benzyl-1,4-dihydronicotinamide and Hantzsch ester (**1-4**) it is an NADH analogue commonly used in the study of the hydride transfer mechanism.[142] Its hydride donating ability is inferior to that of Hantzsch ester[143] **1-4** promising a more thermoneutral process should the hydride transfer be successful. This donor also has the advantage of containing no carbonyl groups. Methods to synthesize 9,10-DHA **1-17** from acridine include various metal catalyzed hydrogenations[144-147] which have varying degrees of selectivity as well as a surprising non-metal H_2 activation using BCF.[140] The most selective, high yielding and simple method was a

reduction using sodium cyano borohydride ($NaCNBH_3$) and $BF_3{\cdot}OEt_2$[148a] (**Scheme 1-21**). This reduction was not considered a part of a viable regeneration strategy, but merely a cheap and efficient way to achieve a target compound for a preliminary investigation of its hydride donating properties.



Scheme 1-21 Selective reduction of acridine

The desired 9,10-DHA **1-17** was isolated in 79 % yield. Similarly, the *N*-methylated analogue **1-19** was isolated in high yield by reduction of the *N*-Me acridinium **1-18** with $NaCNBH_3$, without the need for Lewis acid (**Scheme 1-22**).



Scheme 1-22 Synthesis of N-methyl-9,10-dihydroacridine from acridine

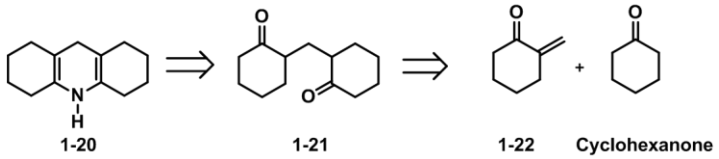
Unfortunately, no hydride transfer is observed for the treatment of both 9,10-DHA, **1-17**, and the methyl substituted analogue **1-19** with BCF at room temperature: the ^{11}B NMR spectrum shows the major species to be free BCF (58 ppm) with a small amount of adduct (peak at -3 ppm). Upon heating in $CDCl_3$, the adduct peak can be increased at the expense of the free BCF peak: the proton NMR spectrum shows small amounts of a different product. A control reaction of acridine and BCF also gave similar peaks in both spectra so it is possible that the fully aromatic acridine is being formed under the reaction conditions and the acridine-BCF adduct, also described by Stephan,[140] is what we are observing at -3 ppm. Heating the reaction overnight does not produce a

borohydride in the ^{11}B NMR spectrum so an optimization of the reaction conditions involving solvent, reaction time and temperature was undertaken, to no avail. We subsequently focused our efforts on the alkylated 1,4-dihydropyridines as these results indicate that the 9,10-dihydroacridine scaffolds are not strong enough hydride donors to afford the transfer, providing an idea of the lower limit of the required donating ability required by our system.

1.2.4 Alkylated 1,4-Dihydropyridine

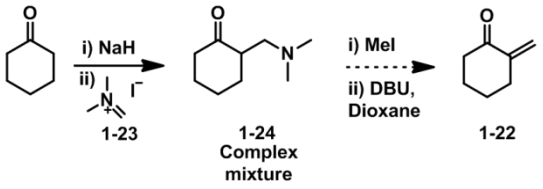
The rational design of the following compounds was to keep the structure of the analogue we were designing as close as possible to that of the initial Hantzsch ester-based compounds while replacing the ester groups with alkyl groups.

The retrosynthetic analysis for the aliphatic 1,4-DHP (**1-20**) was fairly straightforward and is shown in **Scheme 1-23**.



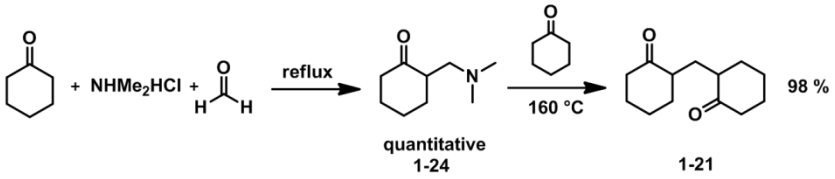
Scheme 1-23 Retrosynthetic analysis of 1,2,3,4,5,6,7,8,10-decahydroacridine

The carbonyls of diketone (**1-21**) should be readily condensed into a cyclic structure[149] with a previously proven ammonia source, ammonium acetate. To obtain the known dicarbonyl compound (**1-21**)[150], we proposed a two-step procedure involving the addition of Eschenmoser's salt[151] **1-23** to cyclohexanone (**Scheme 1-24**) followed by addition of a second cyclohexanone to the Michael acceptor(**1-22**) formed.



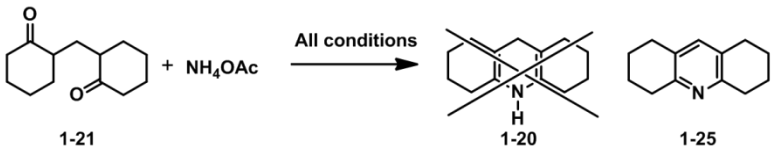
Scheme 1-24 Reaction of Eschenmoser salt with cyclohexanone

The deprotonation of cyclohexanone with NaH, followed by the addition of Eschenmoser's salt **1-23,** yielded an unidentifiable mixture upon workup. Using LDA as a base was not a suitable solution, so the methodology was changed to a published procedure (**Scheme 1-25**):[152] cyclohexanone was refluxed in the presence of dimethylamine hydrochloride and formaldehyde to yield desired amine (**1-24**) in 47 % yield. Heating this compound in a sealed tube in the presence of cyclohexanone at 160 °C yielded the desired diketone **1-21** in 98 % yield. The yield can be increased to quantitative in the first step by changing the workup and adding KOH pellets instead of a large amount of KOH solution as described in the publication.



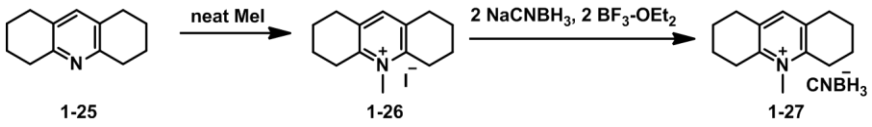
Scheme 1-25 Synthetic route to 2,2'-methylenedicyclohexanone

The final step was the cyclization **Scheme 1-26**. The diketone and ammonium acetate were taken up in THF with acetic acid, but the product of this reaction is the fully aromatized pyridine **1-25**. Various reaction conditions were attempted, including changing the acid to *p*TSA and formic acid, as well as running the reaction at low temperature or adding molecular sieves in the absence of acid catalyst. In all cases, pyridine **1-25** was the only product observed.



Scheme 1-26 Cyclization of 2,2'-methylenedicyclohexanone

As an alternate route, the synthesis of *N*-methyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine was attempted. The tetraalkylpyridine **1-25** was methylated on nitrogen and the resulting pyridinium **1-26** was exposed to $NaCNBH_3$ (**scheme 1-27**). Unfortunately, the only reaction observed was the salt metathesis between the pyridinium iodide **1-26** and the reducing agent, yielding **1-27**. Stronger reducing agents such as $NaBH_3$ and $Na(OMe)_3BH$ were ineffective on either the pyridine **1-25** or the more activated methyl pyridinium **1-26** (formed with methyl iodide).



Scheme 1-27 Methylation and reduction of 1,2,3,4,5,6,7,8-octahydroacridine

It was very apparent that the conjugation afforded by the carbonyls is important in adding stability to the dihydropyridine form of Hantzsch ester **1-4** and its derivatives. Given the difficulties encountered synthesizing **1-20**, we considered other routes to similar unfunctionalized analogues.

We persevered notably, because unsubstituted 1,4-dihydropyridine has been reported.[153] Although it was deemed too unstable for our intended purpose, this precedent showed that given the correct methodology, the synthesis of an unfunctionalized 1,4-DHP should be attainable. The

most significant feature of the published procedure, compared to ours, is that 1,4-DHP is not subjected to acidic conditions.

Of interest to us is that the paper also describes the reduction of the *N*-carbamate to the methyl group by treatment with lithium aluminium hydride and sodium hydroxide quench (**Figure 1-13**).

Our next strategy was to reduce the esters from Hantzsch ester. We postulated the reduction could take place as the molecule consists essentially of two vinylogous carbamates (**Figure 1-13**) and the tetraalkylated double bonds would be more stable than those of *N*-methyl-1,4-dihydropyridine, the product of the treatment of **1-28** with $LiAlH_4$ (**Figure 1-13**).

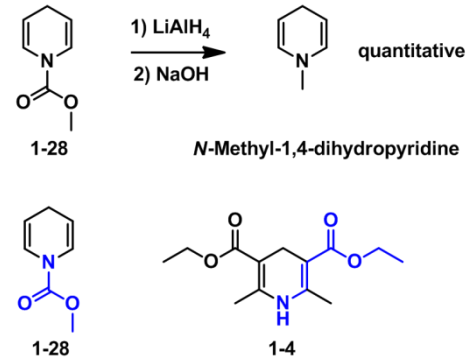
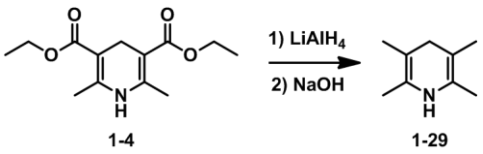


Figure 1-13 Reduction of *N*-carbomethoxy-1,4-dihydropyridine and comparison between 1-28 and Hantzsch ester

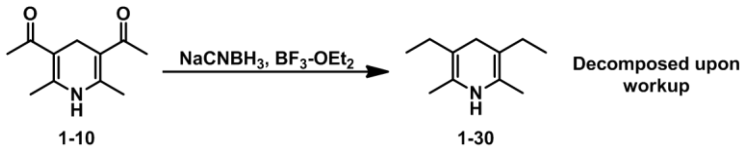


Scheme 1-28 Attempted reduction of Hantzsch ester with $LiAlH_4$

The reduction (**Scheme 1-28**) was attempted several times with different sources of $LiAlH_4$ but the reaction either yielded starting material or a complex mixture of products. One reaction

showed aromatization of the starting material. However, it is possible that with ultra-high purity $LiAlH_4$, the reduction could be feasible.

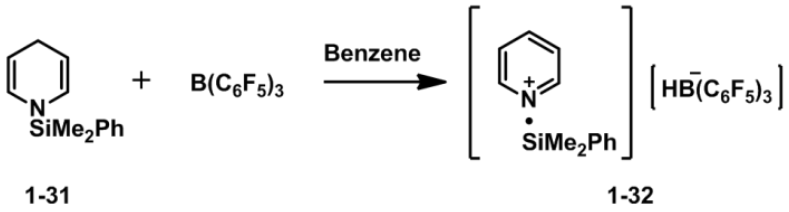
Our second route to a fully alkylated 1,4-DHP followed a literature procedure for the selective reduction (of the carbonyl) of α,β- unsaturated ketones.[148b] By treating the 1,4-dihydro-2,6-dimethylpyridine-3,5-diacetyl **1-10** with $NaCNBH_3$ and $BF_3{\cdot}Et_2O$, we hoped to obtain the desired alkylated 1,4-DHP **1-30**, **Scheme 1-29**.



Scheme 1-29 Reduction of diketone Hantzsch ester

Anticipating that the product would be fairly unstable in air, an aliquot of the reaction mixture was quickly dried in vacuo to take an ^1H NMR without work up. Gas was observed in the tube upon dissolution in $CDCl_3$. The spectrum showed a pyridine peak and the significant t and q ($-CH_2CH_3$) of the desired product, so the reaction mixture was worked up. After an aqueous alkaline workup no trace of the significant peaks was present in the ^1H NMR spectrum. The product obviously decomposed upon work up but due to the toxic by-products that could be produced from the reagents in case of an improper workup, our options to improve it were limited. The reaction did not work without $BF_3{\cdot}Et_2O$ and an attempt at using a Schlenk filter to remove the sodium cyano borohydride salts was unsuccessful as the salts are very fine. This reduction strategy, however promising, was abandoned due to the technical difficulties of the procedure and instability of the product. New, more achievable targets were designed.

A publication released after I had left the lab reported a selective 1,4-hydrosilation of pyridine to give a stable product. [154] In the same report, Nikonov *et. al*. also describe the hydride transfer from this compound to BCF in benzene (**Scheme 1-30**) and this salt could convert to the pyridine-BCF adduct upon standing in DCE. Jonathan Webb obtained a sample and tried to observe more than one hydride transfer, not to BCF which does not disproportionate, but to a more realistic BX_3 compound $B(SPh)_3$. Unfortunately, more than one hydride transfer was not observed, providing us with further incentive to pursue this route with less functionalized substrates.



Scheme 1-30 Reaction of N-silated-1,4-DHP and BCF

1.2.5 Other Non-Oxygenated Hydride Donors

The difficulty of isolating (and subsequently handling) alkylated 1,4-DHPs not only made these compounds difficult to synthesize and store, but limited their potential usefulness as hydride donors as well. We thus turned to phenylated derivatives like **1-33** which could enable conjugation without adding a reactive functional group (**Figure 1-14**).

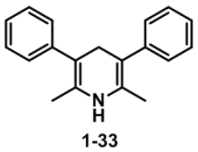
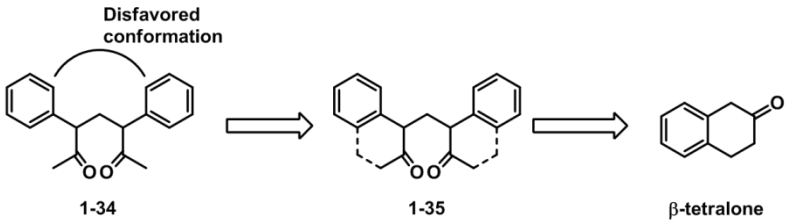
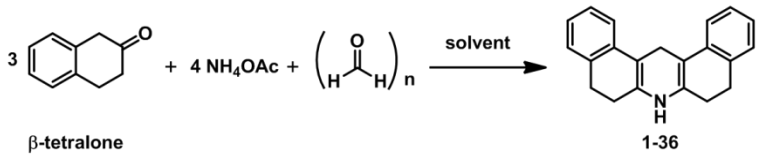


Figure 1-14 2,6-dimethyl-3,5-diphenyl-1,4-dihydropyridine

The phenyl substituents of **1-33** would be able to provide increased stability through conjugation while remaining inert to adduct formation and reducing agents. The synthetic strategy was based on the synthesis of Hantzsch ester: phenyl acetone was heated in the presence of ammonium acetate and paraformaldehyde in THF from Na/benzophenone ketyl. Wary of the decomposition of the product in aqueous acid, a drying agent was added to the reaction mixture. However, neither $NaSO_4$, $MgSO_4$, nor 4 Å molecular sieves, promoted the production of the desired product. Postulating that the bulky phenyl rings were twisting the condensed product and inhibiting cyclization, see **1-34**, we developed a new synthetic strategy in which the phenyl groups are forced into a more reactive conformation (**Scheme 1-31)**.



Scheme 1-31 Rational design of a better carbonyl-free 1,4-dihydropyridine



Scheme 1-32 Tetralone-based synthesis of phenyl substituted 1,4-DHP 1-36

Conveniently, the starting material required was β-tetralone so no additional synthesis was required. Due to time constraints and prioritization, the reaction was attempted once with three different solvents systems: neat, in water, in acetonitrile, in parallel **Scheme 1-32**. Unfortunately, the characteristic peaks in the aliphatic region could not be absolutely confirmed the NMR spectrum of the neat conditions due to side reactions, but this spectrum seemed promising. The

reaction run in water changed color when the water was removed by decantation and the mixture was discarded. Fearing sensitivity to air, the final reaction mixture was diluted with ether and dried over a strong stream of Ar which yielded some crystals. These were taken into the glovebox. A GC-MS was run and showed clean reaction: the pyridine of the cyclized product (aromatized **1-36**). The presence of this compound indicates that the desired product was formed. Observation of the pyridine rather than the 1,4-DHP is not surprising since the 1,4-dihydropyridine is a sensitive compound and it is expected to degrade upon entering the mass spectrometer. This is very exciting as it suggests that the non-substituted 1,4-DHP has been synthesized and can tolerate a careful workup.

1.3 Conclusions and Future Work

We have demonstrated that 1,4-dihydropyridine based hydride donors are capable of transferring a hydride to BCF. The substitution on nitrogen influences the entropy of the transfer such that a bulkier group will favor disorder in the final product. On the other hand, the presence of the carbonyl groups slows the reaction by trapping the hydride donor as a reversible Lewis acid-base adduct with BCF. The two extremes of this effect are the methyl 3,5- dimethylketone analogue **1-10** which forms a dynamic adduct exclusively with no evidence of hydride transfer **1-11** whereas the *t*-butyl ester **1-14** reacts to transfer hydride even at – 50 °C, without adduct formation. Increasing the hydride affinity of the hydride donor in the case of the 9,10-dihydroacridine resulted in an unreactive system. Attempts to synthesize a stable alkylated 1,4-dihydropyridines were mostly unsuccessful due to the reactivity of the resulting compounds. This was promising as it does indicate a low hydride affinity; however, excessively reactive species were not pursued as they would not make industrially viable candidates. A stable, carbonyl-free 1,4-DHP with phenyl groups conjugated to the nitrogen appered to be a promising route, but this product (**1-36**) could

not be pursued due to lack of time. Future work should include the optimization of the synthesis and workup conditions for this compound, as well as the evaluation of its hydride donation properties. Being free of a carbonyl, it can potentially be used as a regenerating species and, therefore the production of borane from three equivalents of it with $B(SPh)_3$ should be investigated, as should the investigation of the regeneration of AB directly from its dehydrogenation product PB **1-3** which could make use of the inherent hydride and proton groups present in this class of compounds.

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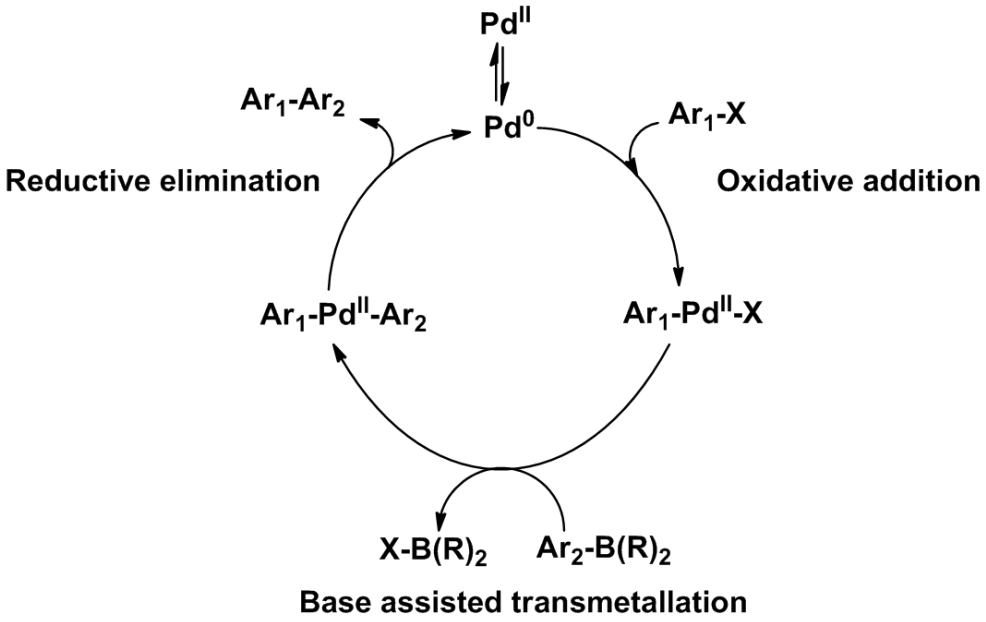
Chapter 2

Orthogonal Cross-Coupling Reactions as a Direct Route to 1,1,2-Triarylethane Scaffolds

2.1 Cross-Coupling Reactions

2.1.1 Brief Overview of the Suzuki-Miyaura Cross-Coupling Reaction

The Suzuki-Miyaura cross-coupling[1, 2] reaction is one of the most common methods for aromatic carbon-carbon bond formation[3-7], both in the pharmaceutical industry[8] and academia. In brief, an activated aryl halide, or triflate and an organo boron compound are joined together through metal catalysis enabling transformations which, otherwise, would require multiple steps or be impossible by other means. As can be seen from the catalytic cycle[9] (**Scheme 2-1**) the first step is **oxidative addition** (OA) of the palladium catalyst into the halogen-carbon bond of the activated electrophile followed by the **transmetallation** (TM) (facilitated by base) of the boron-activated second aryl ring. Finally, **reductive elimination** (RE) releases the active catalyst and gives the cross coupled biaryl product. Most cross-coupling[10] reactions share the same catalytic cycle but differ by the nature of the organometallic transmetallating species. Because of the ease of reaction and the low toxicity of the boron-containing byproducts[11], especially in comparison to the Stille coupling where the transmetallating agent is tin, much effort has been invested in the optimization and broadening of the scope of the Suzuki-Miyaura cross-coupling reaction.



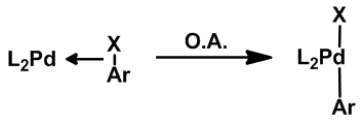
Scheme 2-1 Suzuki-Miyaura cross-coupling catalytic cycle

Indeed, in the 11 years since the publication of Miyaura and Suzuki's integral review on the subject, it has been cited over 5000 times with many new papers being published on the subject each week. Initial advances included developing broad-scope reaction conditions so that each class of compounds did not have to be optimized.[12, 13]

Much mechanistic investigation was undertaken in order to understand each step[14, 15] in the mechanism and the factors influencing it. Oxidative addition[16] is the first step of the catalytic cycle but is normally preceded by the formation of the active catalyst. The readily available, stable Pd^0 species that can be purchased are 18 electron precatalysts and as such, will not undergo OA. Indeed, Pd^0 species with 14 or even 12 valence electrons are thought to be the active catalyst.[7, 17-21] These are fleeting species when triphenylphosphine (PPh_3) is used as a ligand and have never been isolated. However, the use of bulky ligands which inhibit the formation of a coordinatively saturated metal center has enabled the isolation of 14 electron species.[22, 23] There is

also evidence for the 12 electron species[24], but these are thought to be so reactive that they would react either with a ligand or the halide substrate as soon as they are formed.

Another requirement for OA is a vacant 2 electron site as the breaking of the C-X bond and the creation of two new palladium bonds will not take place on a coordinatively saturated metal centre. The mechanism of OA can go through one of several pathways depending on the nature of the halide and the metal. The OA of an aryl halide to Pd^0 species is thought to go through a concerted (three-centered) addition, with initial formation of an associative complex between the metal and C-X bond which is cleaved by the strong backbonding of the metal into the σ* orbital of C-X and which will give the *trans* isomer once the bond is broken[24] (**Scheme 2-2**).



Scheme 2-2 Mechanism of Oxidative Addition

Because the metal centre is being oxidized, this transformation is favored by strongly electron donating ligands. Many groups have developed catalysts to favor the OA.[25-28] In particular, those developed by Buchwald[29-31] consistently present an ortho-aromatic ring providing the active catalyst with an intramolecular π-system which stabilizes the 12 electron species, while ensuring the presence of the vacant coordination site required for the complexation of the electrophile (**Figure 2-1**).

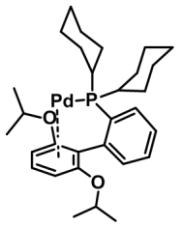


Figure 2-1 Pd^0 mono-ligated to Ruphos

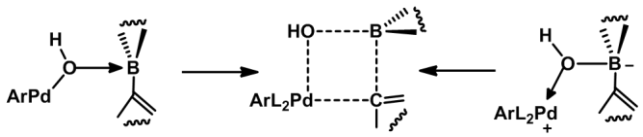
The net result is a relatively stable, very reactive, catalytic species which presents the ideal precursors to reactivity: low electron count with only one electron-donating ligand present. In addition, the steric bulk of these ligands generally increases the speed of RE which is an important factor in more difficult cross-couplings *vide infra*.

Bidentate ligands[32-34] are also commonly used in difficult cross-couplings as they possess the steric bulk necessary to inhibit the coordination of all the vacant sites on the metal, and present the advantage of being locked in the *cis*-configuration lowering the activation barrier to RE.[35]

Finally, independently of the catalyst, the ease of OA is increased with decreasing carbon-halogen bond strength such that the ease of reactivity follows the following trend: I > Br > OTf > Cl >>> F.[13]

The other reagents needed for the reaction, namely base and water, facilitate the transmetalation (TM) step. There is no doubt that, in the presence of water and base, the organoboron is quaternized into a borate salt $[R\text{-}B(Y)_2(OH)]^- X^+$ where Y is OH, OR or alkyl[36-38], causing the higher electron density on boron to be transmitted to the organic group, making it more nucleophilic towards the Pd^{II} metal centre. While it is certain that this species is present in the reaction mixture, there is still some debate as to whether it is the main contributer. It has been shown[39-41] that oxygen-containing bases can replace the halide on the metal centre at this step. It is possible to envisage a boron complex empty p orbital interacting with these lone pairs and,

thus, being brought in close proximity to the metal centre (lowering the degrees of freedom in the TS) and the transmetalation occurring in a pseudo-intramolecular fashion[42] (**Scheme 2-3**).



Scheme 2-3 Possible mechanisms for Transmetallation

To increase this possibility, silver salts, like $AgSdF_6$, Ag_2O and thalium bases and salts[43], as well as gold and platinum salts, have been successfully added to difficult reactions with the rationale that the Ag or other cation will abstract the halide from palladium and crash out of the solution, leaving an activated cationic metal center to react with the anionic base or borate species formed. Regardless of the activated species, in both these cases the net intermediate is the same: a four-membered ring where the oxaphilic boron is linked to the palladium center, through an oxygen atom, bringing the organic group on boron closer to the transition metal for a pseudo-intramolecular transmetallation. Some studies[42] have linked the activated species to the Lewis acidity of the borane. Boranes like R-9-BBN or $R\text{-}BSia_2$ (Sia= $CH(CH_3)CH(CH_3)_2$) are strong Lewis acids in comparison to boronic acids and esters in which the oxygen lone pairs donate into the empty p orbital so it is likely that, in the former case, the boronate is formed then complexes to palladium whereas, in the latter, bases that interact well with palladium are favorable as it will most likely be the activated species. Recent studies by Hartwig[44] and Amatore[45] argue that the role of hydroxide is to make a reactive palladium hydroxo complex and that any four-coordonate borate species present actually inhibit reactivity. The amount of base therefore should be carefully optimized. An alternative mechanism for TM can explain the use of fluoride bases such as CsF. Here it has been shown that the alkyl$BF_3^-X^+$ species are formed *in situ.*[46] Genet[47, 48] and

Molander[49-51] have developed facile methodologies to make and isolate these organometallic species as they are bench stable (unlike the analogous alkylboranes) and extremely reactive in the Suzuki-Miyaura cross-coupling reaction. Although these species decompose further into the boronic acids under aqueous reaction conditions[52], they tend to provide cleaner Suzuki-Miyaura cross-coupling reactions than the boronic acids, as the absence of boronic acid in the early stages of the catalytic reaction avoids the formation of side-products.

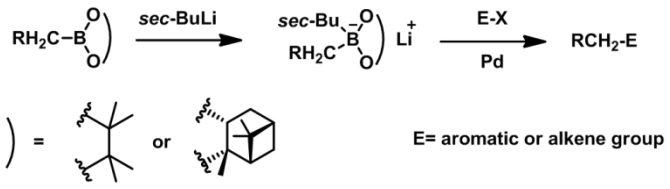
The final step, reductive elimination (RE) of the two organic groups,is generally thermodynamically favored.[9] The reverse of the oxidative addition, it is considered to go through three-centered, concerted TS. The mechanism is thought to vary with the nature of the species being eliminated.[53] In a typical Suzuki-Miyaura cross-coupling between two aromatic components, the organic species must be in a *cis* position to each other, therefore, an isomerization from the TM product (which is *trans*)[54] should occur. In order to facilitate this transformation, bidentate ligands, in particular, dppf, are used as they can lock the two organic groups in a *cis* position favoring the RE.[35] In the case where an alkyl group is to be eliminated, the ease of the RE step becomes a concern as it will be competing with the non-productive β-hydride elimination pathway. The two species involved in an alkyl-aryl cross-coupling are generally an aryl halide and an alkyl organometallic. Cross-couplings of alkyl halides with aromatic organo boron compounds have been reported[55-58], but are much rarer due to the difficulty of OA (in fact the catalyst used is often Ni, not Pd) and the ease of β-hydride elimination.[59, 60] Alkyl-alkyl cross-couplings have been reported only since 2007.[61] Recent computational studies have shown[62] that the L_2PdR_2 species (where R is an alkyl) likely dissociates into the $LPdR_2$ species before reductive elimination can occur. Should this be the case, bidentate ligands could hinder the reductive elimination of alkyl substrates. It is important to note

that each step of the Suzuki-Miyaura Cross-coupling proceeds with retention of chemistry at the carbon[3, 9, 42, 63] (OA proceeds with inversion in the case of allyl and benzyl halides since OA will proceed via an S_N2 mechanism in these cases). Because any chirality initially present will remain in the product, the development of cross-coupling conditions for aliphatic, more specifically chiral, secondary substrates is a feasible and potentially useful transformation. However, key challenges remain facilitating oxidative addition or transmetallation of alkyl electrophiles or organometallics, and accelerating reductive elimination relative to β-hydride elimination.

2.2 Secondary cross-coupling reactions

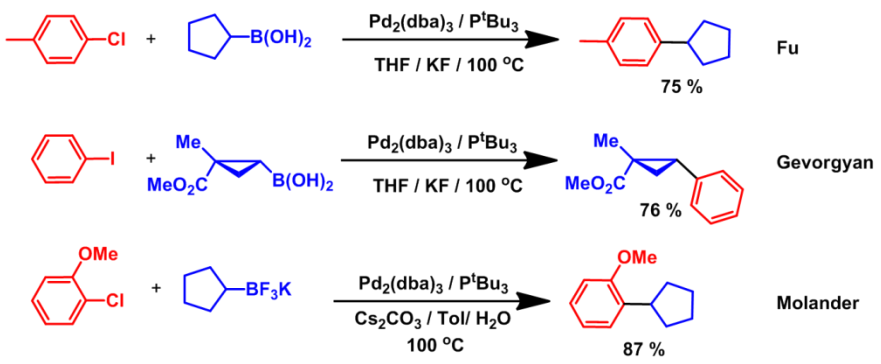
Compared to the prevalence of the cross-coupling of aromatic and unsaturated organoboron species, the cross-coupling of saturated boron species is much rarer. This is due partially to additional pathways to side products during the catalytic cycle. These side reactions stem from the fact that these species possess β-hydrogens which are prone to β-hydride elimination once the organopalladium species is formed.

Another issue with alkylboranes is a more difficult TM. In particular, secondary sp^3 boronic esters demonstrate an extremely difficult transmetallation[64, 65, 13] H9-BBN and $HBSia_2$ are often used to hydroborate alkenes to the aliphatic borane and the secondary alkyl groups are virtually never transferred. In a competition experiment (**Scheme 2-4**) where two alkyl groups, one primary, the other secondary are on the same boronic ester 'ate' complex, the primary alkyl groups are preferentially transferred.[66]



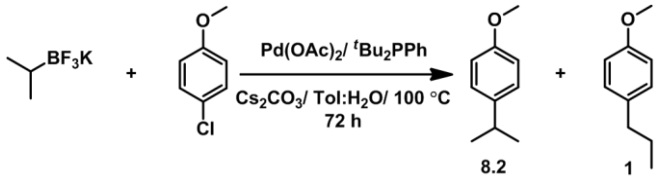
Scheme 2-4 Transfer of a primary alkyl chain in the presence of a secondary

Addressing the specific issues of the difficult TM, in addition to the relative ease of β-hydride elimination, enabled our lab to develop reaction conditions for the cross-coupling of secondary sp^3 boronic esters.[67] At the time this project was undertaken, previous reports of the cross-coupling of secondary boronic esters were few and far between. The first report by Fu[13] describes the cross-coupling of cyclopentylboronic acid with 4-chlorotoluene with 75 % yield, but as one reaction among many tables of aryl boronic acids used to demonstrate new versatile catalytic conditions. Following suit, Gevorgyan[68] reports the enantioselective cross-coupling of a tertiary cyclopropane boronic ester. This was a promising result, but the reaction conditions were applicable only to highly strained cyclopropane systems until Molander[69, 70] and van den Hoogenband[70] successfully cross-coupled cyclopentyl- and cyclohexyltrifluoroborates respectively (**Scheme 2-5**).



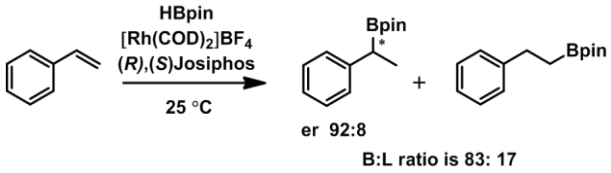
Scheme 2-5 Examples of Suzuki-Miyaura cross-couplings with a secondary boronic acid or trifluoroborate salt

When considering the broad-scope application of the reaction of secondary boronic ester, a more in-depth analysis of these results is in order. In the case of the cyclopropane system, the high ring strain causes the reactivity of the carbons to be more like that of sp^2 carbons, resulting in a more facile transmetallation. In addition, β-hydride elimination cannot occur, as the corresponding cyclopropene ring is highly strained and unfavored. The potassium tetrafluoroborate salts used by Molander are well-suited for this transformation, but by using a symmetric cyclopentane ring masks the β-hydride elimination product, as all resulting products of direct Suzuki-Miyaura and Mizoroki-Heck (elimination-addition reaction sequence) are identical. When the organometallic is changed to a non-symmetric[69] or acyclic[28] boron species, these side products become apparent (**Scheme 2-6**).



Scheme 2-6 Product distribution of the cross-coupling of a secondary acyclic potassium trifluoroborate salt

In 2004, our group developed a methodology for the regio- and enantioselective hydroboration of styrene,[71] based on groundbreaking work from Hayashi and Ito[72] (**Scheme 2-7**)



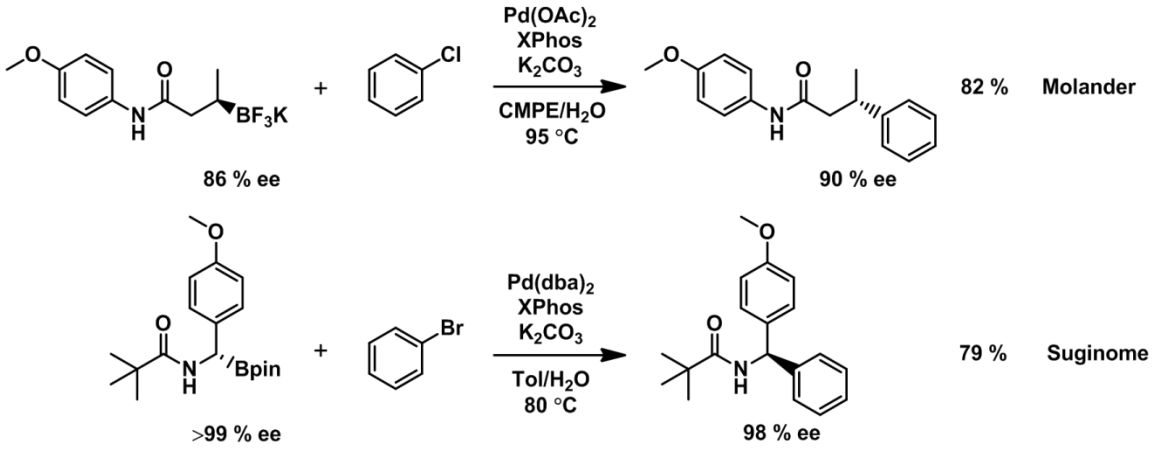
Scheme 2-7 Regio- and enantioselective hydroboration of styrene

With convenient access to chiral boronic esters[73], we were enthusiastic to employ these compounds in Suzuki-Miyaura reactions, not only to expand the scope of the coupling reaction, but also to illustrate additional transformations of the boronic ester, which was previously only useful for the conversion to the alcohol, carboxylic acid or amine.[74] A broad scope cross-coupling methodology, in which the chiral centre is preserved, would be a very useful way to use these building blocks. Following a lengthy optimization study spearheaded by Dr. Imao, the reaction conditions found to affect this transformation were: $Pd_2(dba)_3$ (8 mol%); PPh_3 (8 to 12 eq *vs.* Pd); Ag_2O (1.5 eq) in the presence of a slight excess of boronic ester[67] (**Scheme 2-8**).

Scheme 2-8 Cross-coupling of a secondary boronic ester with retention of configuration

Not only did these reaction conditions provide the desired cross-coupling product, the stereochemistry was retained in very high amount, over 90 % in all cases. Without having fully elucidated the reaction mechanism, notably how the excess ligand is affecting RE (this is ongoing work in our lab), we employed silver oxide to aid in the transmetallation[46, 75, 76] and excess

triphenylphosphine, which has the potential to inhibit β-hydride elimination by filling any vacant sites on the palladium. Following our publication, Molander[77] and Suginome[78, 79] reported the cross-coupling of potassium trifluoroborate salts and pinacol esters, respectively which proceeded with inversion of configuration.



Scheme 2-9 Recent examples of sp^2-sp^3 cross-coupling reactions

The key to these similar but different systems is the carbonyl in the γ position relative to the boron (**scheme 2-9**) limiting the substrate scope considerably, in addition to making the synthesis of more complicated boron species difficult.

2.3 Description of the Project

With the goal of broadening the reaction scope of the secondary cross coupling reaction, we set out to examine the effect of introducing additional aryl groups to the β-carbon of the hydroborated product.

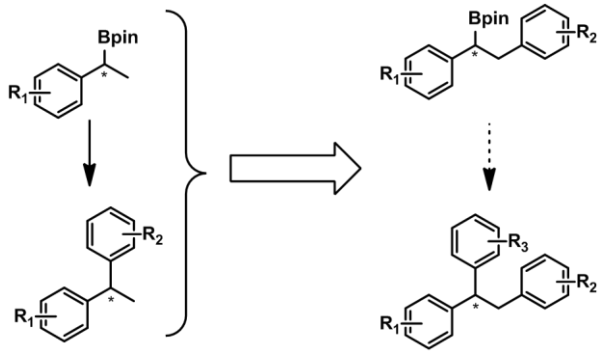


Figure 2-2 Proposed substrates for the evaluation of the reaction scope

This particular sunstrate was chosen as it would expand the scope of the product, give information as to the amount of steric bulk tolerated by the system already developed, and provide access to compounds with important biological properties. The resulting 1,1,2-triarylethane scaffold is found in several natural products and medicinal compounds, for example CDP-840, which was synthesized by Merck-Frosst[80] as a promising phosphodiesterase-IV inhibitor (compound **2-1, Figure 2-3**).

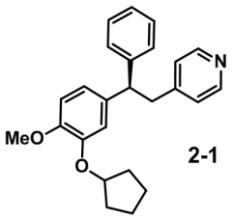


Figure 2-3 CDP-840

Finally, a more long-term goal was to apply this methodology to the synthesis of polyaromatic materials through iterative couplings of a diborated stilbene or derivative (**Figure 2-4**), which could eventually lead to interesting chiral materials.

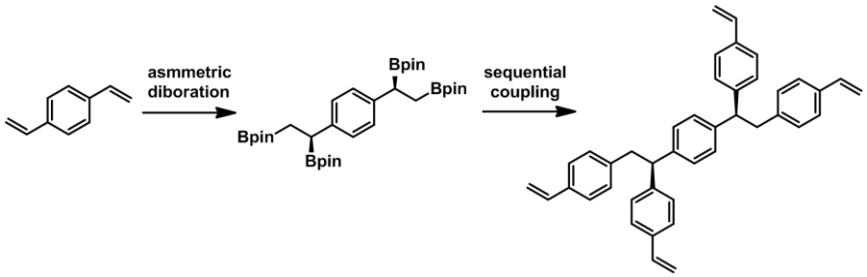
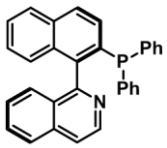


Figure 2-4 Long-term potential application of the research

2.3.1 Evaluation of Alternate Routes

The most direct route to the targeted internal pinacolate **2-4** (**Scheme2-11**) is the hydroboration of stilbenes. Crudden et al.[81] have shown that the rhodium ($[Rh(cod)_2]BF_4$ and dppb) catalyzed hydroboration of unsymmetrical stilbenes regioselectively places the boron towards the substituted ring (in a maximum of 3 to 1 ratio) independently of whether the substituent is electron withdrawing or electron donating. In addition, Brown et al.[82] have achieved high regio- and enantioselectivities using a Rhodium catalyst and QUINAP [(S)- or (R)-(+)-1-(2-Diphenylphosphino-1-naphthyl)isoquinoline] ligand (**Figure 2-5**).

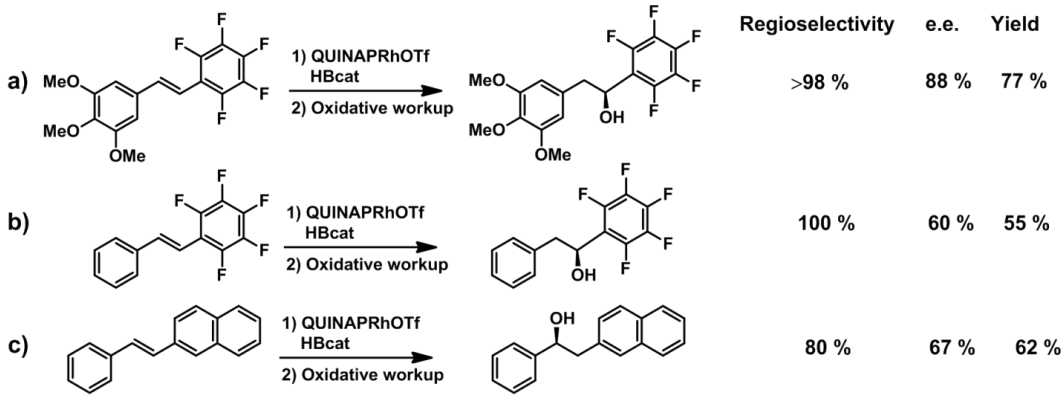


(R)-Quinap

Figure 2-5 Ligand used in the regio- and enantioselective hydroboration of stilbene

The regioselectivity consistently favors boron proximal to the electron deficient ring in varying ratios depending on the difference in electronegativity of the aryl rings. Although the catalytic system is useful in stilbenes with drastically different aryl groups (**Scheme 2-10 a**), the regio- and

enantoselectivities crash when the aryl groups flanking the double bond are less dramatically substituted, limiting the scope of this reaction (**Scheme 2-10 b and c**).

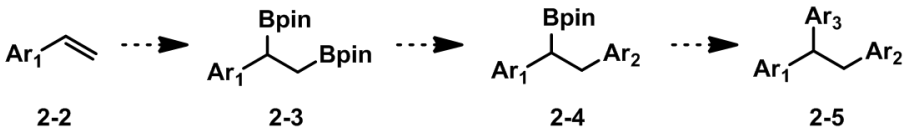


Scheme 2-10 Examples of selective hydroborations of substituted stilbenes as reported by Brown

An alternate method for the synthesis of 2-(1,2-dirayl)ethane pinacolborane would be the enantioselective reduction of a vinyl boronate. However, we thought the scope was too limited or the number of steps too high to be synthetically practical. In order to have a truly versatile methodology to 1,1,2-triarylethanes which include a wide variety of aryl groups at all three aromatic positions, we decided to investigate the orthogonal cross coupling of a diborated styrene.

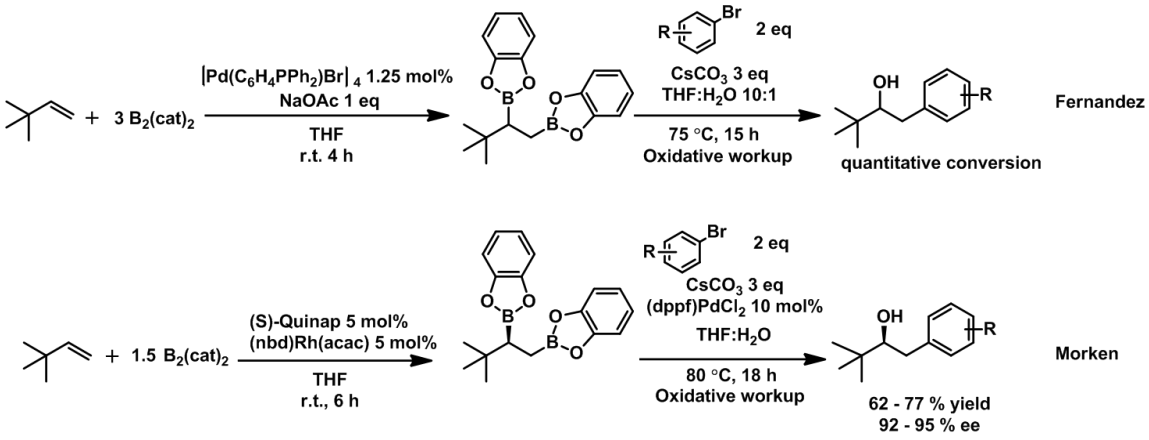
We proposed a successive cross-coupling of the linear and branched boronic esters, **Scheme 2-11,** which would provide access to the desired 1,1,2-triarylethane **2-5** as well as a challenging intramolecular test of the linear vs. branched selectivity for the new conditions. The particularity of the reaction conditions of the existing cross-coupling of the secondary boronic ester caused certain restrictions on the systems we could use for the linear position. For example, in order to minimize the number of synthetic steps, we opted for the pinacolatoboron species at both linear

and branched positions. These compounds have the added advantage of being bench-stable, as opposed to their more reactive catecholborane counterparts.



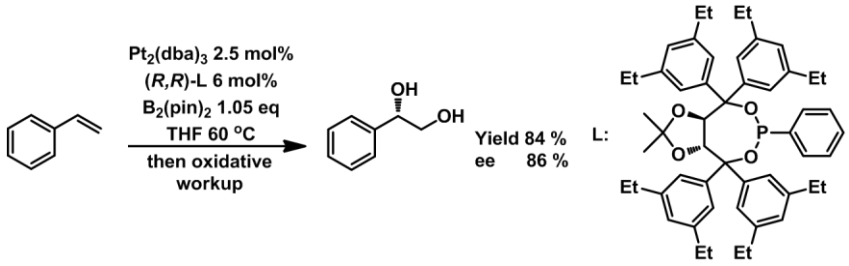
Scheme 2-11 Proposed orthogonal cross-coupling strategy

In order for the linear cross-coupling to be compatible with the secondary, both sets of reaction conditions would have to absolutely inhibit β-hydride elimination as this would cause the racemization of the chiral center at the branched position, rendering our efforts to put it there useless. Diboration of styrene is the most straightforward method of achieving the desired diborated species. Happily, there are many examples of such a transformation in the literature: Morken[83-95], Fernandez[96-102], and others, have achieved this transformation with palladium and a variety of methods using other metals such as Rh[90, 103, 104], Ir[105], Pt[106, 107, 108, 109], Ag[110], Au[111] and Cu[112] and either B_2pin_2 or B_2cat_2. Of particular interest to us are recent reports by Fernandez[113], and Morken[92] (enantioselectively), using B_2cat_2 in which styrene is successively diborated, made to cross couple at the linear position then oxidized in a one pot procedure to yield a diarylated alcohol (**Scheme 2-12**).



Scheme 2-12 One-pot diboration, cross-coupling and oxidation sequences

Our secondary cross-coupling conditions could replace the oxidation in these procedures to give scaffolds difficult to attain by other means. However, in order to use our stereoretentive secondary cross-coupling methodology to its full potential, the initial diboration of styrene needs to be enantioselective. Fortunately, methods have recently been developed to obtain this product. Morken[84] described a TADDOL-based ligand which affords the diborated styrene with good enantioselectivity (**Scheme 2-13**).

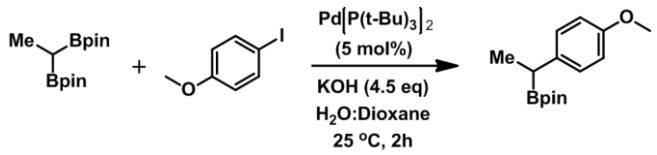


Scheme 2-13 Recent example of an enantioselective diboration

An alternate route to diborated compound **2-3** is the reduction of a vinyl (bis)boronate[118] for example, as described by Andersson et al.[114] The first challenge then was to develop a

methodology for the selective cross-coupling of the linear pinacolate in the presence of the branched species. Although the cross-coupling of alkyl boronates is an established field,[115, 116] reports of this transformation using boronic acids[13, 27, 28, 117] are scarce and, even more rare, are reports of the linear cross-coupling of alkyl boronic esters. We found only one example of linear alkyl cross-coupling using the pinacol ester.

This example is a particular substrate which contains geminal pinacol esters[120] enabling the ate complex of one of them to form readily in strongly basic conditions, favoring TM (**Scheme 2-14**). The second boronic ester remains unreactive under the developed conditions. Unfortunately, the scope is limited to geminal Bpin groups. When a 1,2-Bpin hydrocarbon such as (n-C_6H_{13})CHBpinCH_2Bpin is submitted to the same reaction conditions, no reaction is observed.

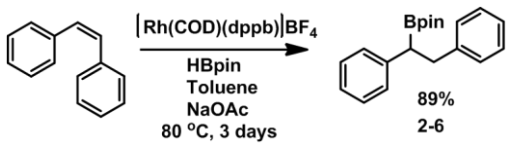


Scheme 2-14 Cross-coupling of an alkyl boronic pinacol ester

Even the use of thallium salts, usually helpful in difficult cases, does not improve the reactivity of the linear pinacol esters.[27] The usual procedure[121, 122] for the use of boronic esters like pinacolates is their treatment with KHF_2 which makes the trifluoroborate salts that cross-couple more readily.[123] As described earlier, this methodology is not appealing for a system like ours as the added synthetic step is not selective and, more importantly, the secondary cross-coupling procedure developed is inert to trifluoroborate salts. Based on the precedent set by Fernandez and Morken with cathecolboranes, and motivated by the potential usefulness of a transformation enabling the regioselective cross-coupling of a primary pinacol boronic ester in the presence of a typically more reactive secondary boronic ester which could also be used in a cross-coupling

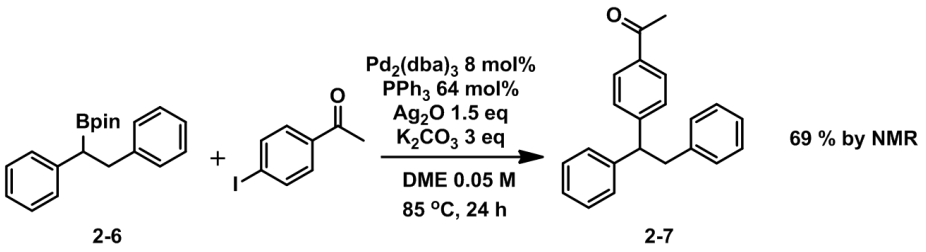
reaction, we undertook the optimization of reaction conditions for the selective cross-coupling of linear alkyl pinacol boranes. Additional aspirations were to afford both cross-couplings in a one-pot system in which the reaction conditions of the linear cross coupling would be compatible with that of the secondary. All that would be necessary would be the addition of the second aryl halide electrophile and silver oxide at the second step.

To confirm that the additional substituent would be compatible with the arylation conditions developed by our group, we first hydroborated *cis*-stilbene (**Scheme 2-15**).



Scheme 2-15 Hydroboration of cis-stilbene

A report by Shibata[124] described an acceleration of the reaction by using $[Rh(OAc)(cod)]_2$ and dppb as a ligand. They found that the OAc group was essential to the increased reactivity. We opted to try the reaction with a rhodium catalyst, $[Rh(cod)(dppb)]BF_4$ we had previously prepared. After a short optimization of the nature of the base (NaOAc was, by far, the best, although not in reaction times comparable to the publication) and reaction time, we could obtain the desired cross-coupling reagent in 89 % yield. Cross-coupling of this racemic compound under the enantioretentive conditions previously described by us, provided the desired product in 69 % yield, by NMR spectroscopy (**Scheme 2-16**).

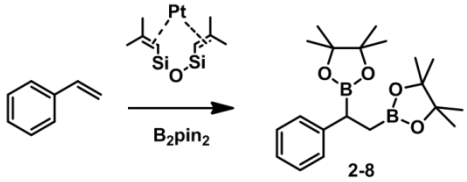


Scheme 2-16 Secondary cross-coupling of 2-(1,2-diphenyl)ethane pinacol borane

With the feasibility of the cross-coupling on **2-6** confirmed, we began a study of the coupling of unsymmetrical diboron species such as **2-8**.

2.4 Linear Cross-Coupling Methodology development

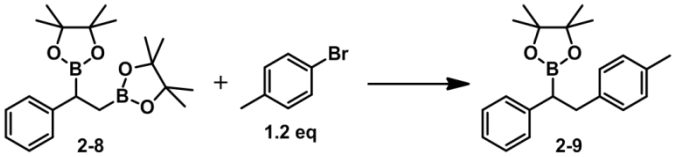
The diboration of styrene was accomplished using a modification of a published procedure[125] giving the desired product in 74 % isolated yield (**Scheme 2-17**).



Scheme 2-17 Diboration of styrene

We opted to use the racemic mixture of diborated styrene to minimize cost and efforts during the optimization studies. The reaction conditions chosen as a starting point were based on typical conditions found in the literature for other related linear cross couplings : bromotoluene (1.2 eq); catalyst (10 mol%); ligand (45 mol%); base (3 eq); THF (0.2 M): H_2O (0.01 M), 80 °C for 20 hours. The first optimization point was the catalyst (**Table 2-1**).

Table 2-1 Initial optimization of the catalyst



Entry[a]	*Catalyst*	*Ligand (vs. Pd)*	*Base*	*Solvent (20:1)*	*GC yield %*
1	$Pd(OAc)_2$	PPh_3	K_2CO_3	$THF:H_2O$	17
2	**$Pd(OAc)_2$**	**PCy_3**	**K_2CO_3**	**$THF:H_2O$**	**11**
3	$Pd(PPh_3)_4$	PPh_3 (1 eq)	K_2CO_3	$THF:H_2O$	3
4	$Pd_2(dba)_3$	PPh_3	K_2CO_3	$THF:H_2O$	4
5	$Pd_2(dba)_3$	PCy_3	K_2CO_3	$THF:H_2O$	4
6	$PdCl_2(dppf)$	---	Cs_2CO_3	THF	0
7	$PdCl_2(dppf)$	---	KOAc	THF	16

Reaction conditions (8 mg scale): catalyst (10 mol %), ligand (45 mol%), base (3 eq), solvent (0.2:0.01 M), 80 °C, 20 h.

Palladium acetate clearly gave superior results compared to tetrakis(triphenylphosphine)palladium and palladium dibenzylidene acetone with both triphenylphosphine and tricyclohexylphosphine (compare entries 1 and 2 with entries 3 to 5). Although PPh_3 gave a slightly superior yield, it contained more by-products than the PCy_3, which was the best performing ligand in this study. The reaction conditions used in entry 6 are fairly common for couplings at the linear substituent.[115] Indeed, the dppf ligand facilitates the reductive elimination of product, which is considered to be the difficult step in the catalytic cycle with these primary aliphatic substrates. We were surprised to see no desired product in this reaction, the majority of product being homocoupled aryl halide. Changing the base to a different one we had on hand (entry 7) did increase the yield to 16 %. However, there is minimal versatility in the

reaction conditions (the ligand cannot be changed) which leaves little room for further optimization. We next scanned a number of bases to use for the ligand optimization. Once the ligand optimization would be performed, we planned to go back and further optimized the nature and number of equivalents of base as well as solvent and temperature. In order to gain time by limiting the workup and analysis steps for the preliminary scans, reactions were analyzed qualitatively. Samples were run on the GC-MS, without an internal standard, and were analyzed for: presence of desired cross-coupling product (23.4 min), presence of starting material (aryl halide, 7.4 min, diborated styrene, 22.5 min), cleanliness of the reaction, nature of by-products. Although these were not isolated and characterized, based on the molecular weight and possible side reactions of this well-known reaction, we were able to determine within reasonable doubt, what species were being formed. A brief summary of the most common species observed and their possible modes of formation are outlined below whereas tables of the results can be found in appendix B.

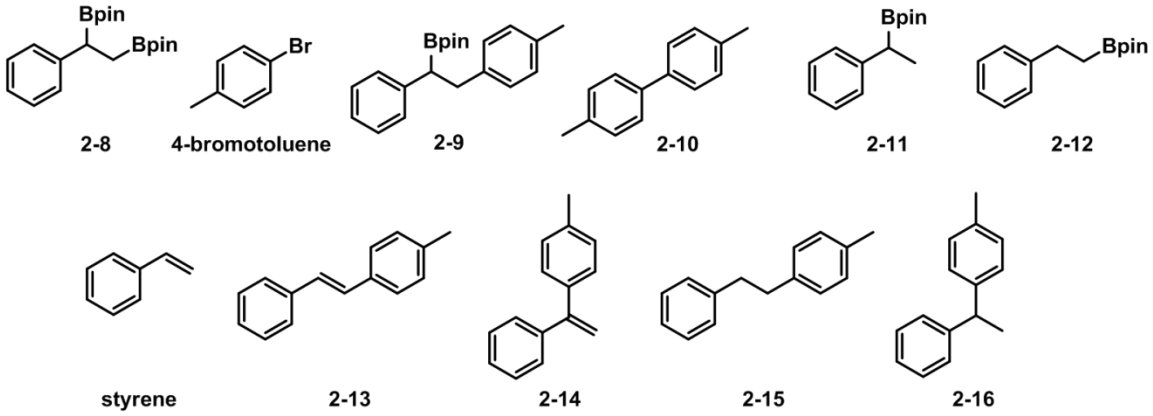


Figure 2-6 Common species observed during our optimization studies

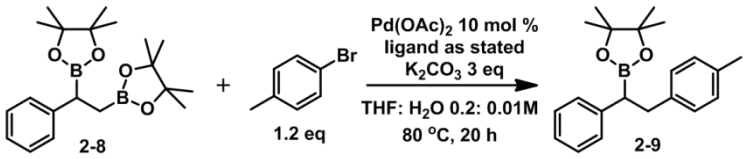
Both starting materials were straightforward to identify. For the formation of the desired product, 1,2-diaryl-1-Bpin-ethane **2-9,** the linear boronic ester couples leaving the branched position

intact. 4,4'-dimethylbiphenyl **2-10** is the arylhalide homocoupling product. The largest quantities were found under reaction conditions where styrene, derived from the diboronic ester, was also observed. 1- aryl-1 or 2-pinacolborane-ethane **2-11** and **2-12** result from a single protodeboration of the starting diborated styrene and both isomers are indistinguishable by GC-MS. When this species is the major product, there is generally a large amount of 4-bromotoluene left implying very little, if any cross-coupling occurred. Styrene was a fairly common side product, resulting from the hydrolysis of one Bpin, and the β-hydride elimination of the other. 4-methyl stilbene (phenyl-tolyl stilbene) **2-13** can result from several different pathways. It could be the product of a linear cross-coupling followed by β-hydride elimination from the secondary position, or the reverse order, in which an alkenylboronic ester was the cross-coupling species. In this case, it is possible that the isomer **2-14** may be the species observed, as the β-hydride elimination of the linear boronic ester would result in a secondary alkenylboronic ester, which would likely cross-couple under the reaction conditions. 4-methyl stilbene **2-13** may also be the product of a Heck reaction on styrene. Another notable side product observed was 1,2-diarylethane **2-15**. This constitutes the product of a cross-coupling at the linear position in addition to protodeboration of the branched boronic ester. The order of these transformations cannot be confirmed; however, given the difficulty of cross-coupling at the secondary boronic ester and the absence of Ag_2O in the reaction mixture, it is highly improbable that the isomer **2-16** was formed.

In order to determine suitable optimization conditions, we investigated three different bases using the previous reaction conditions (**Table 2-1**, entry 2): bromotoluene (1.2 eq); $Pd(OAc)_2$ (10 mol%); PCy_3 (45 mol%); base (3 eq); THF (0.2 M): H_2O (0.01 M), 80 °C for 20 hours. Cesium carbonate showed very little product. Major species after the reaction included 4-methylstilbene **2-13**, starting materials and 1-phenyl-2-tolylethane **2-15**. Sodium acetate showed very little

reactivity and mostly starting material was observed after the reaction. Potassium carbonate remained the most promising base examined, showing distinctly more desired product than the other two. The major peak was 4-methylstilbene **2-13**. The mass balance consisted of starting material, indicating that this was the cleanest reaction as well.

The following ligand optimization (**Scheme 2-18**) was performed using potassium carbonate as the base, with ligand loadings corresponding to 5 equivalents per palladium for monodentate ligands, and just fewer than two equivalents per palladium for bidentate ligands.



Scheme 2-18 Reaction conditions used in the qualitative ligand scan reactions

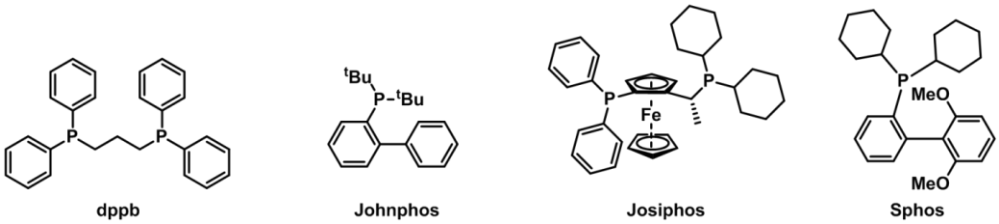
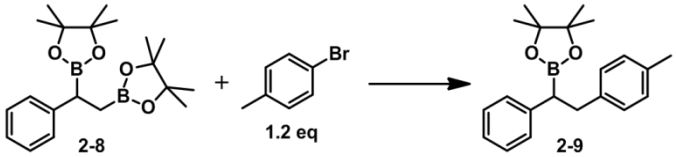


Figure 2-7 Trivial names for ligands used in the qualitative ligand scan

Di*tert*butoxyphenyl phosphine, $PPh(O^tBu)_2$ (50 mol%) did not seem to be electron rich enough to afford the desired transformation as the starting materials were the only species present at the end of the reaction. Diphenylphosphinebutane (dppb, 17 mol%), triphenylphosphine, PPh_3 (50 mol%) and Josiphos (17 mol%) gave homocoupling **2-10** as the major product, with 4-methylstilbene **2-13** and small amounts of the desired cross-coupling product **2-9**, amongst others, being observed in all three cases as well. Sphos (50 mol%) and Johnphos (50 mol%) gave the cleanest reactions,

albeit showing small amounts of desired product **2-9.** However, major species were starting materials in the case of these ligands, not side products. By comparing the GC-MS spectra, tricyclohexylphosphine from the initial scans (**Table 2-2**, Entry 2) still provided the cleanest reaction conditions yet. Encouraged by the ability to limit side reactions by changing the ligand, we set out to further probe the reaction. Because 4-Me stilbene **2-13** was a fairly common side product, a very bulky ligand (tri*tert*butylphosphine salt, 50 mol%) was used with the goal of limiting transmetalation of the secondary boronic ester once the primary cross-coupling had taken place, although there are other potential pathways to this product. This ligand was used with both $Pd(OAc)_2$ and $Pd_2(dba)_3$ and, in both cases, homocoupling of the aryl iodide to give compound **2-10** seemed favored instead of the desired linear cross coupling. Next, the solvent was examined. For this study, we employed the last optimal reaction conditions (**Table 2-1**, entry 2): 10 mol% $Pd(OAc)_2$, 45 mol% PCy_3, 3 eq K_2CO_3, 0.2:0.01 M of solvents at 80 °C for 20 h. A mixture of DMF:H_2O caused a large increase in protodeboration products (**2- 11, 2-12, 2-15**) whereas using a mixture of Tol:H_2O resulted in a more difficult reaction: the major species after reaction were starting materials and stilbene **2-13** with a small amount of product **2-9**. Anhydrous conditions (0.2 M THF) resulted in a complete inhibition of reaction. Finally, we attempted the reaction with a more reactive aryl halide: $CH_3(C_6H_4)I$ at a lower temperature (60 °C) in the hopes of reducing the amount of side products observed, to no avail; starting materials appeared to be the major species with 4,4.-dimethylbiphenyl **2-10** with stilbene **2-13** being the other species observed. The results of these basic screening studies pointed to the use of the electron rich ligands in THF/water mixtures (**Table 2-1**) and, thus, a variety of electron rich ligands were employed in a quantitative screen (**Table 2-2**)

Table 2-2 Ligand Optimization



Entry[a]	*Catalyst*	*Ligand*	*Eq. vs. Pd*	*GC yield %*
1	$Pd(OAc)_2$	dppf	2	5
2	$Pd(OAc)_2$	dppb	2	4
3	$Pd(OAc)_2$	Davephos	4.5	2
4	$Pd(OAc)_2$	Johnphos	4.5	18
5	$Pd(OAc)_2$	cyclohexyl Johnphos	4.5	14
6	$Pd(OAc)_2$	Xphos	4.5	38
7	$Pd(OAc)_2$	Sphos	4.5	55
8	$Pd(OAc)_2$	Ruphos	4.5	62
9	$Pd(OAc)_2$	Ruphos (2.5 eq)	2.5	49

Reaction conditions (8 mg scale): $Pd(OAc)_2$ (10 mol %), ligand (eq *vs.* Pd), K_2CO_3 (3 eq), THF:H_2O (0.2:0.01 M), 80 °C, 20 h.

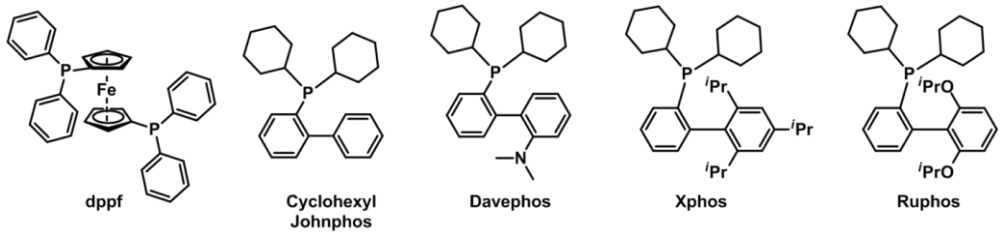
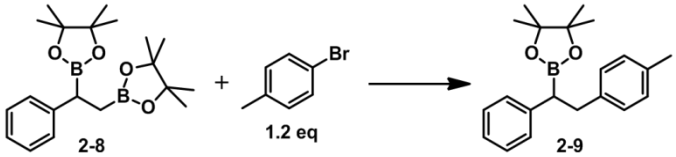


Figure 2-8 Trivial names for ligands used in the ligand optimization study

The use of electron rich ligands showed a general increase in the observed yields. The phenyl based phosphines used in entries 1 and 2, as well as the amine-containing ligand Davephos

(entry 3), were inadequate at catalyzing the reaction. Johnphos and cyclohexyl Johnphos (entries 4 and 5) gave similar yields of 18 and 14 % respectively. The major difference noted was with the other Buchwald ligands: Xphos 38 %, Sphos 55 %, Ruphos 62% (entries 6, 7 and 8). Because the catalyst loading was particularly high for Buchwald ligands, we reduced the number of equivalents of Ruphos 2.5 *versus* palladium corresponding to a net 1.5 equivalents as one equivalent of phosphine ligand is involved in the reduction of the Pd^{II} precatalyst to the Pd^{0} active catalyst.[19] Although the yield did decrease from 62 % to 49 %, this was not judged to be very significant considering the scale of the reaction with: 0.022 mmol of limiting diborated stilbene, 62 % corresponds to 0.014 mmol of product whereas 49 % corresponds to 0.011 mmol. With a few higher performing ligands in hand, we undertook the optimization of solvent and base. We started with the optimization of the Xphos ligand, **Table 2-3**.

Table 2-3 Optimization of solvent and base for Xphos ligand



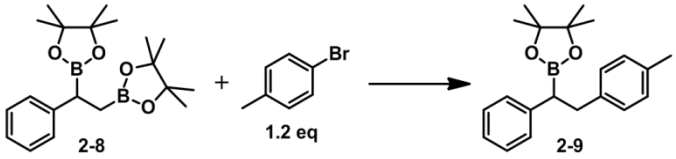
Entry	*Catalyst*	*Ligand (vs Pd)*	*Base*	*Solvent (10:1)*	*GC yield %*
1	$Pd(OAc)_2$	X-phos	K_2CO_3	DME: H_2O	38
2	**$Pd(OAc)_2$**	**X-phos**	**K_2CO_3**	**dioxane: H_2O**	**57**
3	$Pd(OAc)_2$	X-phos	K_3PO_4	THF:H_2O	45
4	**$Pd(OAc)_2$**	**X-phos**	**K_3PO_4**	**DME: H_2O**	**58**
5	$Pd(OAc)_2$	X-phos	K_3PO_4	dioxane: H_2O	27
6	$Pd(OAc)_2$ (5 mol%)	Xphos (2.5)	K_3PO_4	DME: H_2O	27

Reaction conditions (8 mg scale): $Pd(OAc)_2$ (10 mol %), XPhos (50 mol%), Base (3 eq), Solvent (0.2:0.01 M), 80 °C, 20 h

Changing the organic solvent from THF (**Table 2-2**, entry 6) to DME (**Table 2-3**, entry1) with potassium carbonate as the base gives a comparable yield (38 %). However, changing the organic solvent to dioxane increases it to 57 % (entry 2). The effect of solvent varies depending on what base is employed. With tripotassium phosphate as a base, the highest yield is obtained with DME and H_2O (58 %) whereas THF:H_2O and dioxane:H_2O as organic solvents yield 45 % and 27 % respectively. When the ligand loading was reduced to 2.5 equivalents per palladium, the yield decreases significantly (entry 6). In addition, the base was changed to triethylamine in the presence of the three solvent systems and no reaction was observed.

The effect of base and solvent was also optimized with Sphos as the ligand (**Table 2-4**). Given that Ruphos gave equivalent yields at a lower loading, this study was performed at 2.5 equivalent *versus* palladium loading from the start.

Table 2-4 Optimization of solvent and base for Sphos ligand



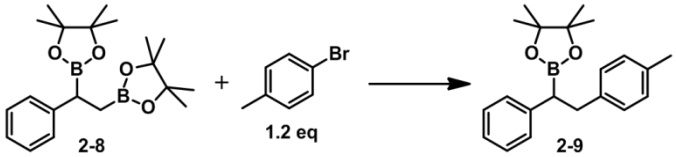
Entry	*Catalyst*	*Ligand vs Pd*	*Base*	*Solvent (20:1)*	*Products*	*GC yield %*
1	$Pd(OAc)_2$	Sphos	K_2CO_3	1,4-dioxane: H_2O	SM boronic ester, no Br	16
2	$Pd(OAc)_2$	Sphos	K_3PO_4	THF: H_2O		11
3	$Pd(OAc)_2$	Sphos	K_3PO_4	1,4-dioxane: H_2O	Both SM present	17
4	$Pd(OAc)_2$	Sphos	K_3PO_4	DME:H_2O		NR

Reaction conditions (8 mg scale): $Pd(OAc)_2$ (10 mol %), SPhos (25 mol%), Base (3 eq), Solvent (0.2:0.01 M), 80 °C, 20 h

Unfortunately, all yields were distinctly inferior to that of potassium carbonate in THF and water at a higher ligand loading (**Table 2-2**, entry 7, 55 % yield). As a result, efforts were stopped entirely in the case of this ligand.

Finally, the effect of base and solvent was studied with the highest performing ligand yet, Ruphos. The ligand loading was further reduced to two equivalents *versus* palladium for this study.

Table 2-5 Optimization of solvent and base for Ruphos ligand



Entry	*Catalyst*	*Ligand (eq vs Pd)*	*Base*	*Solvent (20:1)*	*GC yield %*
1	$Pd(OAc)_2$	Ruphos	K_2CO_3	DME: H_2O	55
2	$Pd(OAc)_2$	Ruphos	K_2CO_3	1,4-dioxane: H_2O	46
3	$Pd(OAc)_2$	Ruphos	K_3PO_4	THF:H_2O	32
4	$Pd(OAc)_2$	Ruphos	K_3PO_4	DME: H_2O	54
5	$Pd(OAc)_2$	Ruphos	K_3PO_4	1,4-dioxane: H_2O	32
6	$Pd(OAc)_2$ (5 mol%)	Ruphos (2.5)	K_3PO_4	DME: H_2O	5
7	$Pd_2(dba)_3$	Ruphos (2.5)	K_2CO_3	DME: H_2O	40

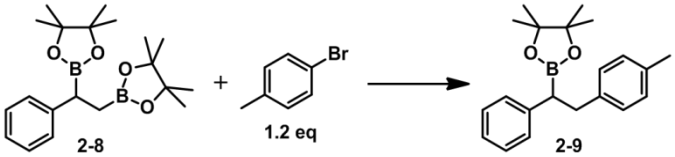
Reaction conditions (8 mg scale): catalyst (10 mol %), RuPhos (20 mol%) or as indicated, Base (3 eq), Solvent (0.2:0.01 M), 80 °C, 20 h

By comparing the results in this table to those in **Table 2-3,** it is clear that the yields for Ruphos are consistently higher than those of Xphos, despite the lower Ruphos loading. In this particular study, yields are comparable when potassium carbonate is the base: 49 % with THF: H_2O

(see **Table 2-2**, entry 9) compared to 55 % and 46 % for DME and 1,4-dioxane and water respectively. The yields were lower when tripotassium phosphate was used as the base: 32 % in THF or 1,4-dioxane (entries 3 and 5) and slightly higher, 54 % in DME (entry 4). Finally, a lower catalyst loading (entry 6) showed a dramatic decrease in yield and changing the palladium source to Pd^0 decreased the yield to about 40 % (entry 7). The choice of the ligand between Xphos and Ruphos was decided based on the catalyst loading which was significantly lower in the case of Ruphos. The base and solvent chosen were potassium carbonate and DME as they are the most compatible with the secondary cross coupling step, in preparation for a one-pot cross-coupling procedure as well as high-yielding for this transformation.

In most cases described above, protodeboration to give **2-15** is a major byproduct. In order to try to limit this, anhydrous reaction conditions were reexamined with bases that are soluble in organic solvents (**Table 2-6**). Potassium *tert*-butoxide is soluble in toluene and partially soluble in various other organic solvents.

Table 2-6 Study of various anhydrous reaction conditions



Entry	*Catalyst*	*Ligand*	*Base*	*Solvent*	*Products*
1	$Pd(OAc)_2$	Ruphos	KO^{t}Bu	THF	diaryl ethane **2-15**, protodeboration products **2-11**, **2-12**, styrene, phenyl ethane.
2	$Pd(OAc)_2$	Ruphos	KO^{t}Bu	DME	protodeboration products **2-11**, **2-12**
3	$Pd(OAc)_2$	Ruphos	KO^{t}Bu	Toluene	Same products as A, different distribution.
4	$Pd(OAc)_2$	Ruphos	$CsCO_3$	THF	No reaction
5	$Pd(OAc)_2$	Ruphos	$CsCO_3$	DME	No reaction
6	$Pd(OAc)_2$	Ruphos	$CsCO_3$	Toluene	No reaction
7	$Pd(OAc)_2$	Ruphos	KO^{t}Bu	DME: H_2O	trace

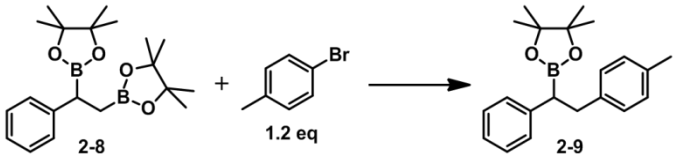
Reaction conditions (8 mg scale): $Pd(OAc)_2$ (10 mol %), RuPhos (25 mol%), Base (3 eq), solvent (0.2 M), 80 °C, 20 h

Based on these results, potassium *tert*-butoxide seemed to be an inappropriate base. All starting material is consumed, but the only evidence of the desired product is the protodeborated side product 1-phenyl-2-tolylethane (diaryl ethane, **2-15**), which we were trying to avoid. Other side products included homocoupling of the aryl bromide **2-10** and various deborated products like styrene and ethylbenzene, as well as monoborated ethylbenzene **2-11** or **2-12** (it is impossible to confirm the position of the boronic ester by GC-MS). In DME, the GC-MS indicated mono-borated ethylbenzene **2-11** or **2-12**. No reaction was observed in any solvent using cesium carbonate as a base in the absence of water. Given that some reactivity was observed under

anhydrous conditions with potassium *tert*-butoxide, we tried adding water to the reaction to see the results, but only trace product was observed (entry 7).

Returning to the system that worked the best, potassium carbonate was further optimized in terms of its loading and concentration (**Table 2-7**).

Table 2-7 Optimization of base loading and reaction concentration



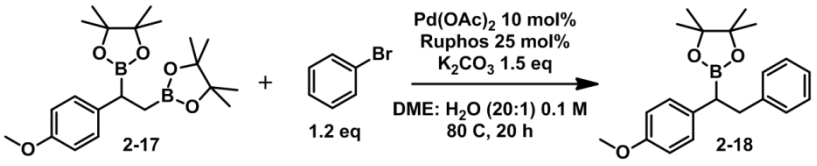
Entry	*Catalyst*	*Ligand*	*Base (eq)*	*Solvent (20:1)*	*GC yield %*
1	$Pd(OAc)_2$	Ruphos	K_2CO_3 (3)	DME 0.04M: H_2O (10:1)	58
2	$Pd(OAc)_2$	Ruphos	K_2CO_3 (1.5)	DME: H_2O	80

Reaction conditions (8 mg scale): $Pd(OAc)_2$ (10 mol %), RuPhos (25 mol%), Base (as indicated), solvent (0.2 M or as indicated)), 80 °C, 20 h

Diluting the reaction gave a comparable yield of product and a significant amount of starting material was present at the end of the reaction (entry 1). Lowering the concentration appears to limit the amount of side products without affecting the yield. It may be advantageous to dilute the reaction mixture and increase the reaction time by 6 to 12 hours. By diminishing the base loading from 3 to 1.5 equivalents (entry 2), we dramatically increased the yield from around 60 % to 80 %. A more through base equivalent study (from 1 to 3 eq) was undertaken. Although yields were below 80 %, 1 to 2 equivalents of base consistently gave yields in the 70 % range. Subsequent reactions were run at 1.5 to 1.7 equivalents of base.

With suitably optimized conditions in hand, we scaled the reaction of the linear cross-coupling successfully. The reaction on a 500 mg scale gave a 69 % isolated yield (85 % NMR yield) on the first try. Due to time constraints, the scope of this cross-coupling was not thoroughly evaluated.

We were, however, able to isolate 35 % product using boronic ester **2-17** on 30 mg scale (**Scheme 2-19**).

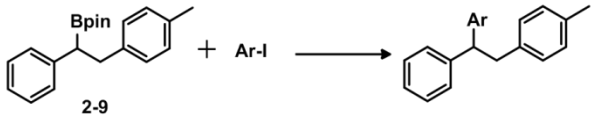


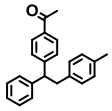
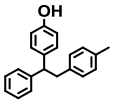
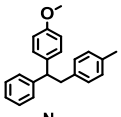
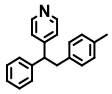
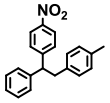
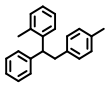
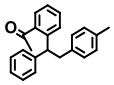
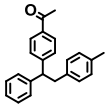
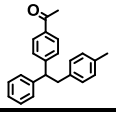
Scheme 2-19 Optimized linear cross-coupling conditions applied to a functionalized diborated starting material

2.5 Evaluation of the Scope of the Secondary Cross-Coupling Conditions

The next step was to examine the scope of the secondary cross-coupling on the 1,2-diarylethane scaffold. The conditions previously described in **Scheme 2-16** were based on those published in our previous paper.[67] These reaction conditions have been further optimized by Crudden group student, Martins Oderine, notably to include potassium carbonate as a base. This does not increase the yield of the transformation so much as the stereofidelity of the reaction, as well as broaden the scope to include aryl bromides (in which case the solvent should be toluene or DME). There was one caveat to the use of these reaction conditions. While the published procedure was almost fully selective for the secondary position in competition experiments, the addition of base erodes this selectivity. This was also a consideration when deciding which boronic ester to attempt to couple first. In other words, if the selectivity for the coupling of the second boronic ester, in the presence of the primary, is eroded with potassium carbonate, it is important to perform the coupling on the primary ester first, as we have done (**Table 2-8**).

Table 2-8 Cross-coupling of the secondary boronic ester



Entry	*Aryl Halide*	*Product*	*Product no.*	*Yield % (NMR)*
1	*p*-$CH_3CO(C_6H_4)I$		2-19	64 (72)
2	*p*-$HO(C_6H_4)I$		2-20	0
3	*p*-$MeO(C_6H_4)I$		2-21	67 (69)
4	4-NC_5H_4I		2-22	61 (68)
5	*p*-$NO_2(C_6H_4)I$		2-23	42 (31)
6	*o*-$Me(C_6H_4)I$		2-24	(68)
7	*o*- $CH_3CO(C_6H_4)I$		2-25	no reaction
8	*p*-$CH_3CO(C_6H_4)Br$		2-19	(45)
9	*p*-$CH_3CO(C_6H_4)Br$ in toluene*		2-19	39 (65)

Reaction conditions: $Pd(PPh_3)_4$ (8 mol%), PPh_3 (32 mol%) K_2CO_3 (3 eq), Ag_2O (1.5 eq), DME (0.05 M), 85 °C, 36 h

*Toluene has been shown to be the ideal case for the cross-coupling of an aryl bromide in the presence of K_2CO_3

These yields are comparable to those obtained for the 1-arylethane-1-pinacolatoboron compound we previously published which ranged from 48 to 86 % yield. This is very promising, as it not only indicates the broad scope of our reaction conditions for the cross-coupling of secondary

boronic esters, but also provides easy and straightforward access to a class of products very difficult to obtain in any other way. Only in the case of a very electron-deficient nitro group substituted aryl iodide (entry 5), was a significantly lower yield observed. The reaction conditions were not applicable to 4-iodophenol but a methyl ether was tolerated (entries 2 and 3). Ketones (entries 1, 8 and 9) and heterocycles (entry 4) are also adequate substrates as are electroneutral groups (entry 6). In addition, 2-acetoxyidobenzene was not suitable for cross-coupling (entry 7) probably due to the oxygen chelating to the palladium after oxidative addition and inhibiting transmetallation by blocking a vacant site (**Figure 2-9**).

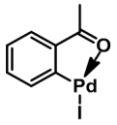
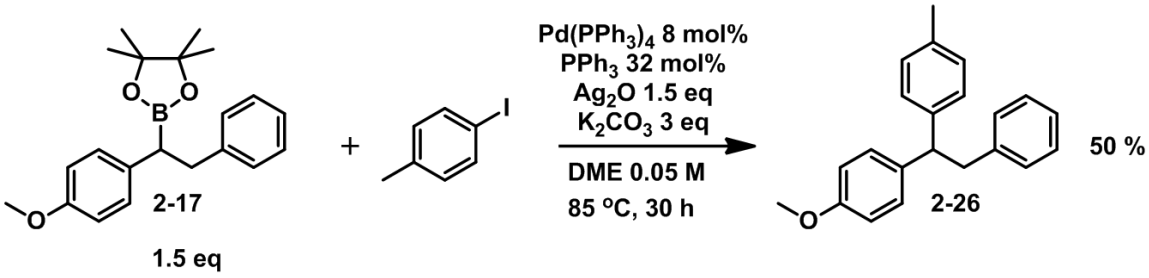


Figure 2-9 The chelating effect of the *o*-acetyl group

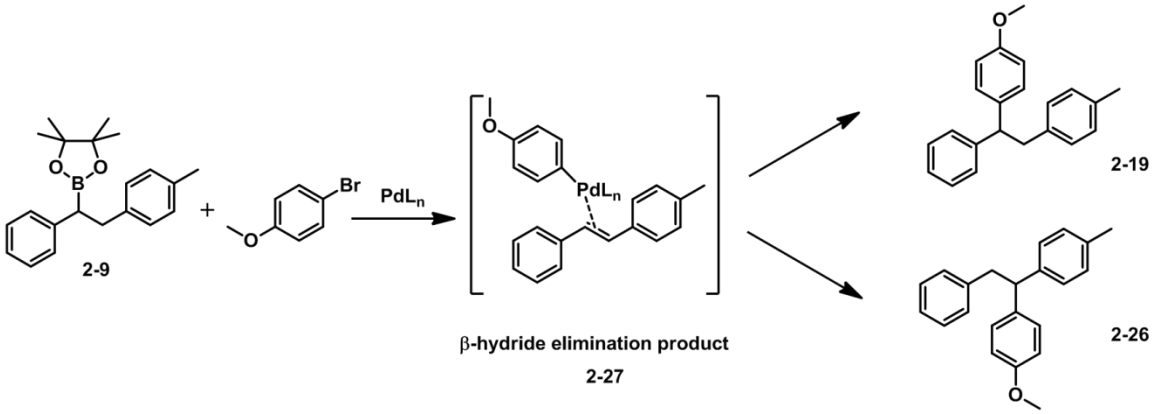
The final compound we synthesized was triarylethane **2-26** in 50 % yield (**Scheme 2-20**).



Scheme 2-20 Secondary cross-coupling using a different boronic ester

In order to probe the stability of the intermediate organopalladium species towards β-hydride elimination, we prepared compound **2-26**, which is the regioisomer of **2-19** (**Scheme 2-21**). Intermediate **2-27** is the product of β-hydride elimination and once formed will produce both

products **2-19** and **2-26**. Although compound **2-26** was not synthesized in a large enough quantity to be fully characterized, we were able to analyze the crude spectrum of **2-19** and did not find any peaks corresponding to **2-26**.



Scheme 2-21 Effect of transmetallation on the product distribution for the secondary cross coupling

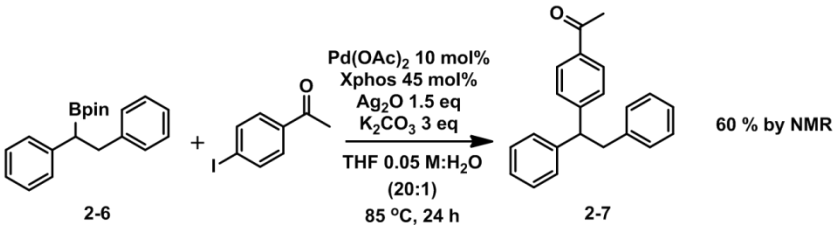
This is a very good indication that the β-hydride elimination-addition mechanism and the resulting scrambling of products (and potential effects on any inherent chirality) is not taking place without the use, for the time being, of enantioenriched starting material.

2.6 Efforts Towards a One-Pot Reaction Sequence

Pinacolates are generally air- and bench-stable, our reagents being no exception. It is possible to make, isolate, and store the 1,2-diarylethane-1-boronates **2-4** synthesized through the previous procedure. In some instances, for example, while making a library of pharmaceutical compounds, it may be more useful to have a one-pot procedure for both the linear and secondary cross-couplings. This is also an advantage regarding cost and environmental concerns as the solvent, energy, and silica gel necessary for the work up, purification, and drying of the intermediate

material become unnecessary. During the course of the optimization of the linear cross-coupling, the end goal of achieving the cross-coupling of the secondary boronic ester in the same pot was always a consideration. The solvent (DME), base and metal catalyst used are the same. In addition, the linear cross-coupling was optimized with the aryl bromide not only because the scope is broader with a less reactive substrate, but also because any residual starting material would present less competition to the aryl iodide added in the second step. Despite these similarities, there were some issues to overcome as well. The stoichiometry of the reagents is not the same in both cross-couplings. More importantly, however, the effect that water and the different phosphine ligand could have on the secondary cross-coupling was unknown.

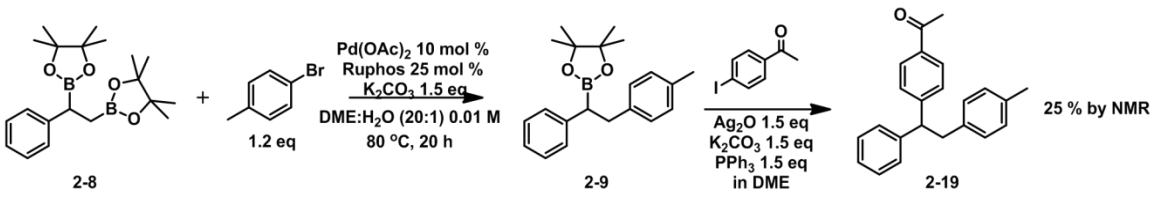
In order to determine the feasibility of combining both cross-coupling reactions sequentially, the reaction conditions of the secondary cross-coupling were changed to reflect the differences with the conditions for the linear cross-coupling. We ran the reaction in the presence of water and silver oxide with Xphos in THF (the most promising ligand and solvent at the time this reaction was run) (**Scheme 2-22**).



Scheme 2-22 Pseudo one-pot reaction conditions

We were delighted to discover a 60 % yield by NMR. To determine the feasibility of the one-pot procedure, preliminary experiments were run: cooling the reaction mixture before the addition of silver oxide, triphenylphosphine (the additional equivalents of ligand were added as PPh_3 as it is closer to the original conditions and much more economical), potassium carbonate and 4-

iodoacetophenone resulted in no conversion of the 1,2-diaryl-1-pinacolatoethane **2-9**. We concluded that cooling the reaction mixture killed the catalyst and that the addition should be performed into the hot reaction mixture via a septum cap (**Scheme 2-23**).



Scheme 2-23 Orthogonal cross-coupling of diborated styrene

This was attempted once with a 25 % yield. This may appear low but it should be noted that both linear and secondary cross-coupling reactions were unoptimized at the time. Additional precautions can be taken: for example, the slow addition of the reagents for the second step to avoid a temperature change in particular when the reaction is done on such small scale.

2.7 Conclusions and Future Work

The progress towards the orthogonal cross-coupling of adjacent boronic esters was noteworthy. The linear cross-coupling reaction has been developed and optimized to about 70 % yield and seems to be applicable to various substrates. In addition, the previously developed secondary boronic ester cross-coupling conditions are applicable to 2-(1,2-diaryl)ethane pinacolboranes like **2-9,** with little loss of yield demonstrating a broader scope of reactivity. Preliminary results indicate that it may be possible to combine these two reactions in one-pot to increase productivity and decrease the amount of waste generated during the process.

The majority of the reaction optimization has been performed on very small scales, therefore additional optimization may be required to obtain the direct cross-coupling of linear pinacol

boranes in yields analogous to trifluoroborate salts. The scope of the reaction should be determined with regard to both the aryl halides tolerated and the nature of the substitution on the diborated styrene. In addition, it should be determined whether the reaction can be performed enantiospecifically when enantiomerically enriched reagents are employed. Finally, despite the positive preliminary results, the secondary cross-coupling should be optimized to tolerate water in order to permit a one-pot procedure.

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Chapter 3

Conclusions

Borohydrides are generally the go-to compounds for the reduction of olefins and carbonyls, amongst others. In the first topic of study, however, we reported the successful transfer of a hydride from an organic compound to BCF, a boron-based Lewis acid analogous to the BX_3 species produced during the first step of regeneration of spent ammonia borane. The donors, all Hantzsch ester (**1-4**) derivatives, are stable analogues of a redox agent commonly encountered in nature: NADH. The hydride transfer was easily monitored by ^{11}B NMR spectroscopy and was observed in over 90% yield for the *N*-phenylated analogue, **1-8**. We determined that the mass balance consisted of an adduct at the carbonyl by studying a second analogue, a 3,5-diketone analogue of Hantzsch ester, **1-10**. This compound does not transfer a hydride to BCF, even upon heating, however, a dynamic adduct between the carbonyl and BCF can be observed at room temperature, and the carbonyl-bound Lewis acid-base adduct (**1-11**) can be observed by NMR spectroscopy at low temperature. At the opposite end of the spectrum, a 3,5-*tert*-butyl ester analogue of Hantzsch ester (**1-14**) shows a significantly increased reactivity, transferring a hydride in very high yield at -30 °C. Although, at this time, the cause of the increased reactivity can be linked to an increase in the hydride donating ability as much as the increased concentration of free BCF in solution, it is clear that the carbonyl groups present in these donors have an influence on the reactivity. Non-functionalized hydride donors, all with the 1,4-DHP scaffold, were designed and synthesized. 9,10-dihydroacridine (**1-17**) and its *N*-methylated analogue (**1-19**) are not hydridic enough to transfer a hydride to BCF indicating a lower limit to the donor strength necessary for a viable system. Completely unfunctionalized 1,4-DHPs (**1-20**, **1-29**, **1-30**, **1-33**)

were difficult to synthesize and isolate limiting their usefulness as donors on an industrial scale. Efforts towards a 3,5-phenylated (**1-36**) analogue were promising: however, further work towards its synthesis should be undertaken. With this successful model study and promising results towards the synthesis of a second-generation hydride donor, the next step remains to determine whether 1,4-DHP donors can yield more than one hydride to BX_3 species that undergo disproportionation ($B(SPh)_3$ for example). Given that the intrinsic structure of 1,4-DHPs posses a hydride and proton group, it will be very interesting to attempt the regeneration of PB (**1-3**) directly with these species. Finally, if these results are positive, a regeneration of the hydride donor should be undertaken.

Our studies towards broadening the scope of the Suzuki-Miyaura cross-coupling reaction led to the development of reaction conditions enabling the selective coupling of a primary boronic ester in the presence of an adjacent secondary boronic ester. The new methodology enables the transformation of bench-stable di-pinacolates (**2-3**) into asymmetric stilbenes (**2-4**) which can be further functionalized into various 1,1,2-triaryl ethanes (**2-5**). These are pharmaceutically active compounds and are difficult to make by other means. Our previously developed methodology for the cross-coupling of secondary boronic esters was applicable to the stilbene scaffold indicating that these conditions, which notably include Ag_2O, have a broad reaction scope. Efforts were made to accomplish both transformations in a one-pot procedure. A control experiment using hydroborated stilbene as a substrate demonstrated that the secondary cross-coupling could be run in the presence of water and a different ligand, making it compatible with the primary cross-coupling conditions. The one-pot reaction was attempted several times and, although further optimization of both steps is necessary, the results are very promising. In addition, because the

Suzuki-Miyaura cross-coupling steps occur with retention of configuration, this methodology should be applicable to enantioenriched reagents without erosion of ee.

Chapter 4

Experimental Procedures

4.1 General

All hydride transfer and cross-coupling reactions were setup in the glovebox. Solvents therein were either obtained from the alumina-dried purification system (innovative Technologies SPS) or dried over adequate drying agents (pentane: P_2O_5; hexanes: Na; THF: Na ketyl; Et_2O, CH_2Cl_2, toluene, trifluorotoluene, CD_2Cl_2 , 1,2-dichloroethane and DME: CaH_2; $CDCl_3$: Na_2SO_4) for 24 h and distilled into a Schlenk flask. All solvents were degassed a minimum of three freeze-pump-thaw cycles and stored over 4 Å molecular sieves. Water was used outside the glovebox and degassed by bubbling argon through the liquid for one hour. All reagents were purified by literature precedent when necessary. BCF was purchased from Strem and sublimed before use. All styrenes were distilled, and passed through dried activated neutral alumina immediately before use. B_2pin_2 was recrystallized before use. All solids and most oils made in-house were dried in a vacuum desiccator in the presence of P_2O_5 over a weekend, under dynamic vacuum, if tolerated by the material. Thin Layer Chromatography was performed on aluminum backed silica plates and visualized by UV (254, 365 nm), I_2 and appropriate indicator, generally ceric ammonium molybdate (CAM). All column chromatography was performed using flash grade silica (Silicycle, 50 μm particle size, 60 Å porosity) and reagent grade solvents. All NMR yields were determined using hexamethylbenzene as the internal standard. The internal standard for the GC yields was octadecane. All GC spectra were obtained using an Agilent 685chromatograph with FID detector loaded with an HP-5 (L=30 m, ID= 0.32 mm) and operating with splitless injection using helium as the carrier gas. The method used was CHRIS1. All GC-MS spectra

were obtained using an Agilent Technologies 5975CVL-MSD (triple axis detector), the capillary measures 30m by 250 μm by 0.25μm nominal, 250 inlet, splitless detector. Samples were run using method BEN1 which has an 8 °C/min ramp from 45 to 280 °C. NMR was run on four Bruker machines: 300, 400, 500 and 600 as indicated. Low temperature glovebox experiments were performed under N_2 atmosphere, using the cold temperature accessory cooled with liquid N_2.

4.2 1,4-dihydropyridine Project

*Hantzsch Ester (**1-4**)*

Ethylacetoacetate (3.78 mL, 30 mmol), paraformaldehyde (0.30 g, 10 mmol) and ammonium acetate (3.08 g, 40 mmol) were weighed into a round bottom flask, purged with Ar gas and suspended in water (10 mL). The suspension was stirred at 80 °C for 5 hours. The reaction mixture was cooled to room temperature then to 0 °C. A yellow solid precipitates. The solid was filtered and washed with cooled Et_2O then dried under vacuum. The solid was recrystallized from a water/MeOH mixture to yield 2.05 g (80 %) of a bright yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ: 1.27 (t, $^3J_{H\text{-}H}$ = 7.1 Hz, 6 H, CH_2CH_3), 2.18 (s, 6 H, CH_3), 3.25 (s, 2 H, CH_2), 4.16 (q, $^3J_{H\text{-}H}$ = 7.1 Hz, 4 H, CH_2CH_3), 5.09 (br. s, 1 H, NH). The collected spectra were consistent with literature reports: Arguello, J.; Nunez-Vergara, L. J.; Strum, J.C.; Squella, J. A. *Electrochimica Acta*, **2004**, *49* (27), 4849- 4856.

Diethyl-2,6-dimethyl-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (N-phenyl Hantzsch Ester) (1-8)

3-phenyloxazolidine

Paraformaldehyde solution (37 wt% solution in water, 4.5 mL, 60 mmol) and *N*-(2-hydroxyethyl) aniline (5 mL, 40 mmol) were combined in a round bottom flask and the thick solution was stirred at room temperature overnight. The reaction mixture was cooled to 0 °C before quickly filtering the beige solid through a Buchner funnel. The product has a melting point around room temperature and thus is a waxy solid. The product was dissolved in a small amount of DCM and precipitated with pentane in an ice bath to yield 3.08 g (52 %) of a readily melting solid. This procedure was based on the procedure developed by Kon, G. A. R.; Roberts, J. J. *J. Chem. Soc.*, **1950**, 978- 982 and our characterization consistent with the reports therein. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ: 3.41 (t, $^{3}J_{H\text{-}H}$ = 6.4 Hz, 2 H), 4.16 (t, $^{3}J_{H\text{-}H}$ = 6.3, 2 H), 4.87 (s, 2 H), 6.53 (apparent d, $^{3}J_{H\text{-}H}$ = 7.9 Hz, 2 H), 6.77 (apparent t, $^{3}J_{H\text{-}H}$ = 7.4 Hz, 1H), 7.25 (apparent t, $^{3}J_{H\text{-}H}$ = 7.9 Hz, 2 H).

(Z)-ethyl-3(phenylamino)but-2-enoate

Ethylacetoacetate (1 mL, 7.9 mmol), aniline (0.70 mL, 7.9 mmol) and indium bromide (3 mg, $8.0\text{x}10^{-3}$ mmol) were combined in an Ar-purged round bottom flask and stirred at room temperature overnight. The reaction mixture was purified by heating to 75 °C under high vacuum for 4 hours, the residue was then dissolved in EtOAc and passed through a pad of celite to remove the $InBr_3$. The solution was concentrated to obtain 1.37 g (84 %) of product. This procedure was based on the procedure developed by

Braibante, M. E. F.; Braibante, H. S.; Missio, L.; Andricopulo, A. *Synthesis*, **1994**, 898 and our spectra are consistent with those reported therein. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ: 1.28 (t, $^{3}J_{H\text{-}H}$ = 7.1 Hz, 3 H, CH_2CH_3), 1.99 (s, 3 H, CH_3), 4.14 (q, $^{3}J_{H\text{-}H}$ = 7.1 Hz, 2 H, CH_2CH_3), 4.68 (s, 1 H, C=CH), 7.02- 7.20 (m, 3 H Ar), 7.26- 7.40 (m, 2 H, Ar), 10.37 (br. s, 1 H, NH)

*Diethyl-2,6-dimethyl-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (N-phenyl Hantzsch Ester) (**1-8**)*

(Z)-Ethyl-3(phenylamino)but-2-enoate and 3- phenyloxazolidine were combined in a round bottom flask and dissolved in acetonitrile. Acetic acid was added to this stirring solution. The reaction mixture was stirred at room temperature for 3 hours. The solution went from colorless to yellow. The reaction mixture was quenched by adding cold saturated aqueous sodium bicarbonate solution until the pH reaches 7. The reaction mixture turned bright orange and the phases separated. The aqueous phase was extracted with chloroform (2x), the combined organic phases were washed with brine (2x), dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash chromatography, the column was pre-treated with Et_3N, loaded with 10 % EtOAc/Hex and eluted with 25 % EtOAc/Hex. The separation of the product was difficult and the pure product was only isolated as 61 mg (36 %). The procedure was described in: Singh, H.; Singh, K. *Tetrahedron*, **1989**, *45*(12), 3967-3989 and our recorded spectra are consistent with the reports therein. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ: 1.27 (t, $^{3}J_{H\text{-}H}$ = 6.9 Hz, 6 H, CH_2CH_3), 1.90 (s, 6 H, CH_3), 3.37 (s, 2 H, CH_2), 4.18 (q, $^{3}J_{H\text{-}H}$ = 6.9 Hz, 4 H, CH_2CH_3), 7.13- 7.41 (m, 5 H, NPh).

Attempts to improve the yield

Sodium bicarbonate was replaced by DABCO in the hope that a more sterically hindered base would not cause decomposition of the product, but no improvement was noted. Molecular sieves were added in case the product was sensitive to water but no improvement was noted.

The purification was improved by changing the chromatography conditions: the crude mixture was loaded onto a column prepared with the elution solvent 95 % DCM/Hex (no pre-treatment of the silica with Et_3N). Separation remained difficult but the co-eluting impurity could easily be removed by drying the product on high vacuum at 50 °C to give a pure product. No exact yield was obtained for this purification procedure as multiple batches had been combined and columned several times under various conditions.

Hydride transfer from N-phenyl hantzsch ester to BCF (1-9)

$B(C_6F_5)_3$ (8.6 mg, 0.015 mmol) was weighed in a glovebox , dissolved in CD_2Cl_2 (0.25 mL) and added, in the dark, to a suspension of *N*-phenyl Hantzsch ester **1-8** (5.0 mg, 0.015 mmol) frozen in CD_2Cl_2 (0.25 mL) in an NMR tube. On warming, a bright yellow solution formed. The solution was characterized by VT multi-nuclear NMR. Anal. Calcd for $C_{37}H_{23}BF_{15}NO_4$: C, 52.82%; H, 2.76%; N, 1.67%. Found: C, 53.25%; H, 2.68%; N, 1.67%. ^{1}H (400 MHz, CD_2Cl_2, 243 K) δ: 1.43 (t, 6 H, $^3J_{H\text{-}H}$ = 5.0 Hz, OCH_2CH_3), 2.76 (s, 6 H, CH_3), 3.45 (br m, 1 H, B-*H*), 4.51 (q, 4 H, $^3J_{H\text{-}H}$ = 5.0 Hz, OCH_2CH_3), 7.24 (d, 2 H, $^3J_{H\text{-}H}$ = 4 Hz, *ortho*-Ar*H*), 7.79 (ov m, 3 H, *meta* & *para*-Ar*H*), 9.32 (s, 1H, *para-H*). ^{13}C NMR (150 MHz, CD_2Cl_2 258 K) δ: 13.8, 21.5, 64.2, 124.6, 129.4, 129.5,

129.9, 132.2, 132.5, 136.3 (dm, $^{1}J_{C\text{-}F}$ = 244 Hz, *C*-F), 136.9 (dm, $^{1}J_{C\text{-}F}$ = 238 Hz, *C*-F), 138.2, 147.6 147.8 (dm, $^{1}J_{C\text{-}F}$ = 244 Hz, *C*-F), 161.5, 162.0; ^{19}F NMR (376 MHz, CD_2Cl_2, 253 K) δ: -135.3 (br m, 6 F, *ortho*-C_6F_5), -164.3 (br m, 3 F, *para*-C_6F_5), -167.3 (br m, 6 F, *meta*-C_6F_5); ^{11}B (168 MHz, CD_2Cl_2, 298K) δ: -23.3 (d, $^{1}J_{B\text{-}H}$ = 93 Hz, *B*-H).

1,1'-(2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)diethanone (diketone Hantzsch ester) (1-10)

Acetyl acetone (6.0 mL, 58 mmol), paraformaldehyde (0.86 g, 29 mmol) and ammonium formate (3.6 g, 58 mmol) were weighed into an argon-purged round bottom flask and suspended in water (20 mL). The suspension was stirred at 40 °C overnight. The reaction mixture was cooled to room temperature then to 0 °C. The yellow solid was filtered, and rinsed with cold EtOAc. The crude solid was dissolved in DCM and MeOH (3:1) then precipitated with hexanes. This solution was cooled to -5 °C, the bright yellow crystals filtered and then washed with cold DCM. Much product was lost during the purification (probably dissolved in the MeOH) and the product showed a significant amount of oxidized side-product (1,1'-(2,6-dimethyl-pyridine -3,5-diyl)diethanone) which would likely explain the low yield. The solid was transferred to a Buchner funnel and washed with a large amount of Et_2O to give 3.60 g (32 %) of clean desired product. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ: 2.17 (br. s, 6 H, C*H*$_3$), 3.42 (s, 6 H, COC*H*$_3$), 3.42 (s, 2 H, C*H*$_2$), 5.24 (br.s, 1 H, N*H*). The collected spectra were consistent with literature reports: Memarian, H. R.; Sadeghi, M. M.; Momeni, A. R.; Döpp, D. *Monatschefte für Chemie*, **2002**, *133*, 661-667.

Hydride transfer from diketone Hantzsch ester to BCF (1-11)

$(C_6F_5)_3$ (25 mg, 0.05 mmol) was weighed in a glovebox, dissolved in CD_2Cl_2 (0.25 mL) and added, in the dark, to a suspension of diketone Hantzsch ester **1-10** (9 mg, 0.05 mmol) in CD_2Cl_2 (0.25 mL) in an NMR tube. The solution was characterized by VT multi-nuclear NMR. X-ray quality crystals were grown from 1,2-DCE layered with pentane at -25 ˚C. Anal. Calcd for $C_{32}H_{21}BF_{15}NO_4 \cdot 0.5CH_2Cl_2$: C, 49.39%; H, 2.14%; N, 1.99%. Found: C, 49.22%; H, 2.03%; N, 1.96%. ^{1}H (600 MHz, CD_2Cl_2, 273 K) δ: 2.10 (s, 3 H, C*H*$_3$), 2.21 (s, 3 H, C*H*$_3$), 2.28 (s, 3 H, C*H*$_3$), 2.45 (s, 3 H, C*H*$_3$), 3.34 (s, 2 H, C*H*$_2$), 7.10 (s, 1 H, *NH*). ^{13}C NMR (125 MHz, CD_2Cl_2 273 K) δ: 19.1, 23.9, 25.3, 27.0, 30.4, 105.9, 116.6, 119.6 (br m, *C*-B), 137.3 (dm, $^1J_{C\text{-}F}$ = 246 Hz, *C*-F), 139.3, 140.2 (dm, $^1J_{C\text{-}F}$ = 253 Hz, *C*-F), 148.0 (dm, $^1J_{C\text{-}F}$ = 240 Hz, *C*-F), 164.7, 197.9, 198.5; ^{19}F NMR (376 MHz, CD_2Cl_2, 250 K) δ: -134.0 (br m, 6 F, *ortho*-C_6F_5), -155 (br m, 3 F, *para*-C_6F_5), -163.3 (br m, 6 F, *meta*-C_6F_5); ^{11}B (168 MHz, CD_2Cl_2, 273K) δ: -2.0 (br s, *B*-O).

Hydride transfer from di-tert-butyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate to BCF (1-16)

$B(C_6F_5)_3$ (10.0 mg, 0.02 mmol) was weighed in a glovebox, dissolved in CD_2Cl_2 (0.25 mL) and was added in the dark, to a suspension of *tert*-butyl Hantzsch ester **1-14** (6.0 mg, 0.02 mmol) dissolved in CD_2Cl_2 (0.25 mL) in an NMR tube. The solution immediately turned bright yellow then became foggy and a large amount of solid crashed out of solution. Our attempts at characterizing the solid were unsuccessful. The reaction was studied at low temperature.

$B(C_6F_5)_3$ (9.7 mg, 0.02 mmol) was weighed in a glovebox, dissolved in CD_2Cl_2 (0.25 mL) and was added in the dark, to a suspension of *tert*-butyl Hantzsch ester **1-14** (5.5 mg, 0.02 mmol) frozen in CD_2Cl_2 (0.25 mL) in an NMR tube. A bright yellow heterogeneous solution formed on warming to -50 ˚C. The yellow precipitate dissolved on shaking and the solution was characterized by VT multi-nuclear NMR. ^{1}H (600 MHz, CD_2Cl_2, 233 K) δ: 1.58 (s, 18 H, OC(C*H*$_3$)$_3$), 2.90 (s, 6 H, C*H*$_3$), 3.50 (br m, B-*H*), 9.28 (s, 1 H, *para-H*), 12.81 (br s, 1H, N*H*); Partial ^{13}C (150 MHz, CD_2Cl_2, 223 K HSQC and HMBC) δ: 25.1 (s, C*C*H$_3$), 27.5 (s, OC(*C*H$_3$)$_3$), 85.7 (s, O*C*(CH$_3$)$_3$), 127.9 (s, py*C*), 149.2 (s, py*C*H), 158.4 (s, py*C*), 160.4 (s, *C*OO^{t}Bu); ^{19}F NMR (376 MHz, CD_2Cl_2, 233 K) δ: -134.7 (d, 6 F, $^3J_{F\text{-}F}$ = 22 Hz, *ortho*-C$_6$*F*$_5$), -162.5 (t, 3 F, $^3J_{F\text{-}F}$ = 20 Hz, *para*-C$_6$*F*$_5$), -66.2 (t, 6 F, $^3J_{F\text{-}F}$ = 20 Hz, *meta*-C$_6$*F*$_5$); ^{11}B (168 MHz, CD_2Cl_2, 240K) δ: -24.6 (d, $^1J_{B\text{-}H}$ = 74 Hz, *B*-H). This product decomposes upon heating to -30 °C for prolonged periods of time.

9,10-dihydroacridine (1-17)

Sodium cyanoborohydride (1.3 g, 5.5 mmol) was dissolved in dry THF (18 mL) in a flame-dried round bottom flask. Boron trifluoride etherate (1.9 mL, 5.5 mmol) was added to this solution followed by acridine (0.80 g, 4.4 mmol). The reaction mixture was stirred at reflux (70 °C) for 5 hours and quenched with a 30 % aqueous ammonia solution (20 mL). The reaction mixture was poured into a separatory funnel containing Et_2O and the phases separate. The aqueous phase was washed with Et_2O (4 x). The combined organic phases were washed with water then brine, dried over $MgSO_4$, filtered, and

concentrated. The crude product was dry-loaded onto a Et_3N pre-treated column prepared with the elution solvent (10 % EtOAc/Hex) to produce 630 mg (79 %) of white solid. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ: 4.05 (s, 2 H), 5.94 (br. s, 1 H), 6.66 (d, $^3J_{H\text{-}H}$ = 7.9 Hz, 2 H), 6.84 (apparent t, $^3J_{H\text{-}H}$ = 7.4 Hz, 2 H), 7.00 - 7.17 (m, 4 H). The collected spectra were consistent with literature reports: Sakanishi, K.; Ohira, M.; Mochida, I. Okazaki, H.; Soeda, M. *J. Chem. Soc. Perkin Trans.II*, **1988**, 1769- 1773.

N-Me-9,10-dihydroacridine (1-19)

*N-Methyl acridinium Iodide (**1-18**)*

Acridine (0.40 g, 2.2 mmol) and iodomethane (4 mL, 64 mmol) were combined in an oven-dried sealed tube. The reaction mixture was stirred at 85 °C overnight then cooled to room temperature. The MeI was removed *in vacuo* to give 0.70 g (77 %) of bright red, irritating solid. The reduction was performed on the crude product.

*N-Methyl-9,10-dihydroacridine (**1-19**)*

Sodium cyanoborohydride (0.41 g, 1.7 mmol) was dissolved in dry THF (5 mL) in a flame-dried round bottom flask. *N*-methyl acridinium iodide (0.35 g, 0.86 mmol) was added to this solution. The reaction mixture was stirred at reflux (75 °C) for 4 hours and quenched with a 30 % aqueous ammonia solution (10 mL). The reaction mixture was poured into a separatory funnel containing Et_2O and the phases separated. The aqueous phase was washed with Et_2O (4 x). The combined organic phases were washed with water then brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography on a Et_3N pre-treated column prepared with the elution

solution 5 % EtOAc/Hex. The crude reaction mixture was loaded with benzene and it eluted quickly but yielded pure product: 0.17 g (quantitative yield) of white crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 2.81 (s, 3 H), 3.67 (s, 1 H), 6.58 (apparent d, J_{H-H}= 8.1 Hz, 2 H), 6.90 (apparent t, 2 H), 6.99 (apparent d, J_{H-H} =7.1 Hz, 2 H), 7.11 (apparent t, J_{H-H} =7.2 Hz, 2 H). The collected spectra for these compounds were consistent with literature reports: Colter, A. K.; Saito, G.; Sharom, F. J. *Can. J. Chem.*, **1977**, *55*(14), 2741-2745.

Reaction of 9,10-dihydroacridine with BCF

$B(C_6F_5)_3$ (15.7 mg, 0.03 mmol) was weighed in a glovebox, dissolved in 1,2-dichloroethane (DCE) (0.25 mL), and added in the dark to a solution of 9,10-dihydroacridine **1-17** (5.0 mg, 0.03 mmol) dissolved in DCE (0.25 mL) in an J-Young tube. ^{11}B NMR: free BCF is observed initially at 60 ppm but is replaced by a wide peak centred at 0 ppm upon heating at 75 °C overnight in a sand bath. No hydride transfer was observed.

$B(C_6F_5)_3$ (31.5 mg, 0.06 mmol) was weighed in a glovebox, dissolved in CD_2Cl_2 (0.25 mL), added, in the dark to a solution of 9,10-dihydroacridine **1-17** (5.0 mg, 0.03 mmol) and dissolved in CD_2Cl_2 (0.25 mL) in an NMR tube. No reaction was observed upon standing several hours.

Reaction of N-methyl-9,10-dihydroacridine with BCF

$B(C_6F_5)_3$ (14.6 mg, 0.03 mmol) was weighed in a glovebox, dissolved in α,α,α-trifluorotoluene (0.25 mL), added, in the dark, to a solution of *N*-methyl-9,10-

dihydroacridine **1-19** (5.0 mg, 0.03 mmol) and dissolved in α,α,α-trifluorotoluene (0.25 mL) in a J-Young tube. Initial ^{11}B NMR showed free BCF at 60 ppm, but this gradually transformed to a peak at 6.3 ppm upon heating at 55 °C for 5.5 h. No hydride transfer was observed.

$B(C_6F_5)_3$ (29.4 mg, 0.06 mmol) was weighed in a glovebox, dissolved in CD_2Cl_2 (0.25 mL), added, in the dark, to a suspension of *N*-methyl-9,10-dihydroacridine **1-19** (5.0 mg, 0.03 mmol), and dissolved in CD_2Cl_2 (0.25 mL) in an NMR tube. No reaction was observed upon standing several hours.

1,2,3,4,5,6,7,8,9,10-decahydroacridine (1-20)

*2-((dimethylamino)methyl)cyclohexanone (**1-24**)*

Cyclohexanone (20 mL, 194 mmol), dimethylamine hydrochloride (7.9 g, 97 mmol) and formaldehyde (37 % solution in water, 19.5 mL, 241 mmol) were measured into a round bottom flask and stirred at reflux (130 °C) for 2 hours. The mixture was cooled to room temperature before the addition of a sodium chloride aqueous solution (3.4 g in 8.8 mL H_2O). The mixture was stirred an additional 30 minutes then transferred to a separatory funnel containing Et_2O, the phases separate. The aqueous phase was extracted with Et_2O (x 8) to remove unreacted cyclohexanone. KOH pellets were added to the aqueous phase until the pH reached 12. The product was extracted from the aqueous phase with Et_2O (x 6). The combined organic phases were washed once with water then brine, and subsequently dried over $MgSO_4$, filtered and concentrated. The next step was performed on the crude material (quantitative yield).

*2,2'-methylenedicyclohexanone (**1-21**)*

Two equal batches were prepared then combined after heating.

2-((dimethylamino)methyl)cyclohexanone (7.8 g, 50 mmol) and cyclohexanone (15.5 mL, 150 mmol) were combined in a sealed tube then heated to 170 °C for 6 hours. The reaction mixture goes from colorless to deep red within 1.5 h. The two reaction mixtures were combined into a round bottom flask, concentrated *in vacuo*, and dried over high vacuum. The crude product was distilled under vacuum to remove the cyclohexanone (the product remains in the initial flask up to 180 °C). The distilled mixture was recrystallized out of 20 mL of hexanes cooled to – 40 °C for 48 hours. The solid-oil product was filtered and quickly rinsed with a small amount of cold hexanes to obtain 10.26 g (98 %) of low-melting beige solid. This compound and its precursor were synthesized following the procedure described in: Gan, X. M.; Parveen, S.; Smith, W. L.; Duesler, E. N.; Paine, R. T. *Inorg. Chem.* **2000**, *39*, 4591-4598 and our spectra match those reported therein. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 1.01- 2.48 (m, 20 H).

*Representative example of an attempt at the synthesis of 1,2,3,4,5,6,7,8,9,10-decahydroacridine (**1-20** obtained **1-25**)*

2,2'-methylenedicyclohexanone **1-21** (50.0 mg, 0.24 mmol) and ammonium acetate (130.0 mg, 1.68 mmol) were weighed into a round bottom flask and purged with Ar. Acetonitrile (1.2 mL) and *p*-toluenesulfonic acid (91.3 mg, 0.48 mmol) were added and the reaction mixture was stirred at 60 °C for 5 hours. The reaction was quenched with saturated $NaHCO_3$ solution (pH= 7) and transferred to a separatory funnel. The phases

separated. The aqueous phase was extracted with EtOAc (x 4). The combined organic phases were washed with water then brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (as recrystallization was difficult) in a column pre-treated with Et_3N prepared with the elution solvent 20 % EtOAc/Hex to obtain a white solid, the aromatized product (**1-25**). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ: 1.70 - 1.81 (m, 4 H), 1.81 - 1.93 (m, 4 H), 2.68 (t, $^3J_{H\text{-}H}$ = 6.2 Hz, 4 H), 2.84 (t, $^3J_{H\text{-}H}$ = 6.3 Hz, 4 H), 7.02 (s, 1 H, Ar-C*H*). The collected spectra were consistent with literature reports: Potmischil, F.; Marinescu, M.; Nicolescu, A.; Deleanu, C. *Magn. Reson. Chem.*, **2009**, *47*, 1031-1035

Representative example of a reduction of Hantzsch ester with $LiAlH_4$

$LiAlH_4$ (1 M solution in Et_2O, 0.22 mL, 0.22 mmol) was dissolved in dry THF (9 mL) in a flame-dried round bottom flask and cooled to – 20 °C. Hantzsch ester **1-4** (40 mg, 0.16 mmol) was added carefully in several portions. The color changed from colorless to yellow-orange to clear again towards the end of the addition. Once the addition was finished, the ice from the ice bath was removed and the reaction temperature was allowed to rise slowly for 1.5 h after which the water bath was removed and the reaction was stirred at room temperature for 6 h. The reaction was quenched by first cooling the reaction mixture to 0 °C, adding 12 μL H_2O followed by 12 μL 15 % NaOH aqueous solution then 36 μL H_2O. The reaction mixture was warmed to room temperature and stirred for 1 hour, dried over $MgSO_4$ and the liquid removed via cannula filter. Used high vacuum to remove the solvent and brought the residue into the glovebox to prepare the

NMR tube in inert atmosphere. ^{1}H NMR showed a complex mixture and the desired product could not be identified.

Attempt at reduction of 1,1'-(2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)diethanone (1-10) using $NaCNBH_3$

1,1'-(2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)diethanone **1-10** was dissolved in dry THF (5 mL) in a flame-dried round bottom flask. $NaCNBH_3$ (0.35 g, 0.86 mmol) was added to this solution. The reaction mixture was stirred at room temperature for 3 hours, after which an aliquot was collected and dried under high vacuum. The residue was taken up in $CDCl_3$ and bubbles were observed in the NMR tube. The ^{1}H NMR showed the significant q and t of the ethyl peaks in the desired product. The reaction mixture was quenched with $NaHCO_3$ to pH= 7 and transferred to a separatory funnel containing Et_2O. The phases separated. The aqueous phase was extracted with Et_2O (4 x) and DCM (x 1). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. NMR of the crude reaction mixture showed decomposition.

5,6,7,8,9,14-hexahydrodibenzo[a,j]acridine (1-36)

Three reactions were set up in tandem:

β-tetralone, ammonium acetate, and paraformaldehyde were weighed into a vial equipped with a septum and degassed. Solvent was added as follows: A, water; B, no solvent; and C, acetonitrile. The reaction vials were capped with a Teflon lined (green) cap, sonicated about 10 s and the reaction was stirred at 80 °C for 5 h. The solution changed from colorless to yellow or yellow-green. The workups were varied as follows:

A. Water was decanted from the solid. Observed a color change. Discarded the reaction mixture as better results were observed with B and C.

B. A ^{1}H NMR was taken of the reaction mixture directly. Although the spectrum is not clean but starting material peaks seem small and the integration of the aromatic peaks may correspond to aromatized desired product. There is also a peak which could correspond to a methylene, indicating the desired 1,4-DHP may also be present. The reaction should be tried again on larger scale and purified.

C. The reaction mixture was diluted with Et_2O but no precipitation was observed. The reaction mixture was dried under a strong flow of argon. Crystals formed and were brought into the glovebox. A small amount of solid was dissolved in acetonitrile and analyzed by GC-MS. The GC-MS spectrum shows two peaks and the larger of the two has a mass ion peak at 283.1. Desired product is 285.15 g/mol and the corresponding pyridine is 283.14 g/mol.

No further characterization was possible, but these results were very promising. Reaction C should be reproduced in a more controlled environment and an optimization of reaction conditions undertaken.

Van't Hoff studies (Figure 1-12)

$B(C_6F_5)_3$ (3.6 mg, 0.0098 mmol) was weighed in a glovebox, dissolved in CD_2Cl_2 (0.4 mL) and added, in the dark, to a suspension of *N*-phenyl Hantzsch ester (22.5 mg, 0.044 mmol) frozen in CD_2Cl_2 (0.35 mL) in an NMR tube. The two frozen layers were

warmed to -20 °C in an NMR. The reaction was monitored for 30 minutes to insure a complete reaction. Note: the pulse delay was changed to 10 s to insure a more reliable area for all peaks. The reaction mixture was cooled to -30 °C and a 5 minute delay was instituted for equilibration of the reaction before acquiring the spectrum. The reaction mixture was warmed to -10 °C in 5 °C increments following the same procedure.
This procedure was repeated to insure more accurate thermodynamic values, but the concentration was changed to confirm the equilibrium state.
The K_{eq} was calculated based on the average yield of reaction of four significant peaks in the NMR for each temperature. The reported values are an average of both experiments.

4.3 Cross-Coupling Project

2-(1,2-diphenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane or pinacol(1,2-diphenylethyl)boronate via hydroboration of stilbene (2-6)

In the glovebox, [Rh(cod)dppf]BF_4 (15.9 mg, 0.02 mmol) was stirred with *cis*- stilbene (80.0 mg, 0.44 mmol) and NaOAc (18.0 mg, 0.22 mmol) in THF (2 mL) for 1.5 h. This suspension was transferred to a sealed tube containing HBpin and was stirred at 70 °C for three days. The reaction mixture was concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography, by dry loading the crude material onto a column prepared with the elution solvent 2.5 % EtOAc/Hex, to yield 120.4 mg (89 %) of white solid. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ: 1.11 (s, 6 H, *pinacol*), 1.12 (s, 6 H, *pinacol*), 2.69 (dd, $^3J_{H\text{-}H}$ = 9.79, 1 H, 6.85 Hz, BC*H*), 2.97 (dd, $^3J_{H\text{-}H}$ = 13.44, 6.72 Hz, 1 H, CH_2), 3.16 (dd, $^3J_{H\text{-}H}$ = 13.41, 9.76 Hz, 1 H, CH_2), 7.14-7.27 (m, 10 H, *Ar*). The collected

spectra were consistent with literature reports: Hirokami, M.; Shibata, T. *Organometallics*, **2008**, *27*, 5390-5303.

Representative example of Diboration of styrene

In the glovebox, styrene (0.78 mL, 6.80 mmol) and B_2pin_2 (1.0 g, 3.90 mmol) were dissolved in toluene (15.5 mL). The round bottom flask was equipped with a septum and taken out. Platinum-1.3-divynyl-1,1,3,3- tetramethyldisiloxane complex in xylene (1.1 mL, 0.1 M, 0.11 mmol) was added via syringe. A color change from clear to yellow to brown was observed within 2 minutes. The reaction mixture was stirred at 50 °C for 3 h. Upon completion of the reaction, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (a long column was used) on a column loaded with the elution solvent 10 % EtOAc/Hex to yield 1.04 g (74 %) of white solid. This procedure was based on the work of Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.*, **1997**, 689-690.

1-phenyl-1,2-di(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)ethane (2-8)

Synthesized as described above: styrene (710 mg, 6.8 mmol), bisboronpinacolate (1.0 g, 3.9 mmol), platinum^0-1,3-divinyl-1,1,3,3,-tetramethyldisiloxane complex (1.1 mL, 0.1 M, 0.15 mmol), toluene (16 mL), 50 °C for 3 hours. The reaction yielded 1.04 g (74 %) of white solid. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 1.10 (dd, 1 H, $J_{H\text{-}H}$= 16.00, 5.64 Hz, C*H2*), 1.16 (s, 6 H, *branched pinacol*), 1.18 (s, 6 H, *branched pinacol*), 1.19 (s, 12 H, *linear pinacol*), 1.37 (dd, 1 H, $^3J_{H\text{-}H}$ = 15.96, 11.10 Hz, C*H2*), 2.51 (dd, 1 H, $^3J_{H\text{-}H}$ = 11.05, 5.64 Hz, C*H*), 7.08 (m, 1 H, C*H p*), 7.21 (br. d, 4 H, $J_{H\text{-}H}$= 4.40 Hz, C*H o,m*). The

collected spectra were consistent with literature reports: Girrane, A.; Corma, A.; Garcia, H. *Chem. A Eur. J.*, **2011**, *17*(8), 2467-2478.

1-(4-methoxyphenyl)-1,2-di(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)ethane (2-17)

Synthesized as described above: 4-methoxystyrene (200.0 mg, 1.5 mmol), bisboronpinacolate (217.6 g, 0.86 mmol), platinum^0-1,3-divinyl-1,1,3,3,-tetramethyldisiloxane complex (0.45 mL, 0.1 M, 0.045 mmol), toluene (3.4 mL), 50 °C for 3 hours. The reaction yielded 207 mg (62 %) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 1.07 (dd, 1 H, $J_{H\text{-}H}$= 15.96, 5.76 Hz, C*H*$_2$), 1.16-1.20 (m, 24 H, *pinacol*), 1.32 (dd, 1 H, $^3J_{H\text{-}H}$ = 15.92, 10.93 Hz, C*H*$_2$), 2.44 (dd, 1 H, $^3J_{H\text{-}H}$ = 10.93, 5.72 Hz, C*H*), 3.75 (s, 3 H, OC*H*$_3$), 6.77 (m, 2 H, C*Ho*), 7.12 (m, 2 H, C*Hm*). The collected spectra were consistent with literature reports: Marder, T.B. *Science of Synthesis*, **2004**, *6*, 117- 137.

Typical optimization study procedure

Please note: these reactions were done on very small scale. In order to have comparable results, reagents which were identical (except base, which was insoluble in reaction solvents) were weighed in bulk, dissolved and added to the reaction vials via syringe. For example, a base optimization study was carried out as follows:

Ruphos (4.46 mg, 0.01 mmol) and potassium carbonate (5.8 mg, 0.04 mmol; 7.6 mg, 0.05 mmol; 9.3 mg; 0.07 mmol; 4.0 mg, 0.03 mmol) were weighed into vials named respectively A, B, C and D. In a separate vial were weighed 1-phenyl-1,2-di(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)ethane **2-8** (60 mg, 4 x 0.04 mmol), bromotoluene

(43.0 mg, 4 x 0.06 mmol), $Pd(OAc)_2$ (3.76 mg, 4 x 0.004 mmol) and the internal standard, octadecane (10.01 mg, 0.01 mmol). These solids were dissolved in DME (1.6 mL) and 0.4 mL of this solution was distributed among the vials A to D. The vials were capped with septum vial caps, removed from the glovebox and water (20 μL) was added carefully. All vials were sonicated about 30 s before being stirred at 80 °C for 20 h in the vial adapter of the starfish. The reaction mixture was cooled, diluted with diethylether, dried over $MgSO_4$, and filtered through a celite plug. Took up an aliquot and took a GC-MS spectrum for determination of species present as well as a GC spectrum to determine the yield. Formula obtained from the calibration curve $\frac{nprod}{nIS} = 1,0774 \frac{Aprod}{AIS}$ where R^2=1.000.

Although quantities are small this provides a method in which the comparison of yields within a study is reliably comparable.

Example of a synthesis-scale linear cross coupling reaction

In a glovebox, 1-phenyl-1,2-di(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)ethane **2-8** (500.0 mg, 1.39 mmol), bromotoluene (286.6 mg, 1.6 mmol), $Pd(OAc)_2$ (31.2 mg, 0.14 mmol), Ruphos (162.1 mg, 0.35 mmol), potassium carbonate (287.5 mg, 2.1 mmol) and internal standard (octadecane, weighed precisely) were dissolved in DME (13.9 mL). The sealed tube was capped with a septum, removed from the glovebox and brought into a glove bag where the water (0.7 mL) was carefully added and the septum replaced with a cap. The reaction mixture was sonicated about 30 s before being stirred at 80 °C for 21 h. The reaction mixture was cooled to room temperature then dried over $MgSO_4$ (no heat or

bubbles were observed), and filtered through a celite plug rinsing with ether. The foggy yellow solution was transferred to a separatory funnel and washed twice with brine. An aliquot was taken to determine yield by GC and the remainder of the yellow crude mixture was concentrated *in vacuo*. The crude product was purified by flash chromatography using a column loaded with 6 % EtOAc/Hex and eluted with 10 % EtOAc/Hex. Isolated 0.311 g (69 %) of white solid.

1-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)-2-tolylethane (2-9)

Followed the procedure described above: 1-phenyl-1,2-di(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)ethane **2-8** (500.0 mg, 1.39 mmol), bromotoluene (286.6 mg, 1.6 mmol), $Pd(OAc)_2$ (31.2 mg, 0.14 mmol), Ruphos (162.1 mg, 0.35 mmol), potassium carbonate (287.5 mg, 2.1 mmol), internal standard (octadecane, weighed precisely), DME (13.9 mL), water (3.7 mL), 80 °C for 21 hours. The reaction mixture was worked up and purified to yield 311 mg (69 %) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 1.15 (s, 6 H, *pinacol*), 1.15 (s, 6 H, *pinacol*), 2.32 (s, 3 H, C*H*$_3$), 2.69 (dd, $^3J_{H\text{-}H}$ = 9.5, 6.9 Hz, 1 H, C*H*), 2.95 (dd, $^3J_{H\text{-}H}$ = 13.4, 6.8 Hz, 1 H, C*H*$_2$), 3.16 (dd, $^3J_{H\text{-}H}$ = 13.4, 9.6 Hz, 1 H, C*H*$_2$), 7.05 (d, $J_{H\text{-}H}$ = 8.1 Hz, 2 H, *p*-*C*H$_3$(C$_6$*H*$_4$)), 7.10 (d, *J*=8.1 Hz, 2 H, *p*-H$_3$(C$_6$*H*$_4$)), 7.17 (m, 1 H, C*Hp*), 7.27- 7.29 (m, 4 H, C*Ho,m*); ^{13}C NMR (125 MHz, $CDCl_3$ 298 K) δ: 20.98, 24.52, 24.56, 38.32, 83.35, 125.30, 128.27, 128.39, 128.68, 135.05, 138.63, 142.68 (one quaternary C does not appear); ^{11}B NMR (160 MHz, $CDCl_3$, 298 K) δ: 32.61; UV spectrum, film prepared from CH_2Cl_2 (wavenumber): 3024,

2978 (m), 2928, 2862, 1365 (s), 1326 (s), 1142 (s), 701 (m); HRMS calcd. for $C_{21}H_{27}BO_2$ (M+) 322.2104, found (M+) 322.2112

1-(4-methoxyphenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)-2-phenylethane (2-18)

Followed the procedure described above***:*** 1-(4-methoxyphenyl)-1,2-di(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)ethane **2-17** (3.00 mg, 0.077 mmol), bromotoluene (15.8 mg, 0.093 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0077 mmol), Ruphos (8.9 mg, 0.0.019 mmol), potassium carbonate (15.9 mg, 0.12 mmol), internal standard (octadecane, weighed precisely), DME (0.7 mL), water (0.03 mL), 80 °C for 21 hours. The reaction mixture was worked up and purified to yield 9.4 mg (35 %) of white solid.^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 1.13 (s, 6 H, *pinacol*), 1.13 (s, 6 H, *pinacol*), 2.29 (s, 3 H, C*H*$_3$), 2.54 - 2.66 (m, 1 H), 2.88 (dd, $^3J_{H\text{-}H}$ = 13.4, 7.1 Hz, 1 H), 3.08 (dd, $^3J_{H\text{-}H}$ = 13.4, 9.6 Hz, 1 H), 3.78 (s, 3 H, OC*H*$_3$), 6.84 (apparent d, $^3J_{H\text{-}H}$ = 12 Hz, 2 H, *p*OCH_3(C_6H_4)), 7.02 (d, $^3J_{H\text{-}H}$ = 8.0, 2 H, *p*CH_3(C_6H_4)), 7.06 (d, $^3J_{H\text{-}H}$ = 8.0, 2 H, *p*CH_3(C_6H_4)), 7.15 (apparent d, $J_{H\text{-}H}$= 8.0, 3 H, *p*OCH_3(C_6H_4))

Typical procedure for the secondary cross-coupling reaction

In the glovebox, 1-phenyl-1-Bpin-2-*p*tolylethane **2-9** (25.0 mg, 0.07 mmol), 4-iodoacetophenone (12.3 mg, 0.05 mmol), $Pd(PPh_3)_4$ (4.6 mg, 0.004 mmol), PPh_3 (4.2 mg, 0.016 mmol), Ag_2O (18.4 mg, 0.07 mmol), K_2CO_3 (19.3 mg, 0.14 mmol) were diluted/suspended in DME (1 mL). The reaction vial was capped, taken out of the glovebox, sonicated for 30 s and stirred at 80 °C for 36 h. The crude reaction mixture was diluted with diethyl ether and filtered through a short pad of celite into a pre-weighed

vial. The reaction mixture was concentrated *in vacuo*, weighed, then a known amount of external standard (HMB) was added to the vial. The contents of the vial were dissolved in $CDCl_3$, and an NMR was acquired. The NMR yield was determined and the crude product was purified by prep-TLC using an adequate solvent mixture, usually 5 to 10 % EtOAc/Hex.

1-(4-(1-phenyl-2-(p-tolyl)ethyl)phenyl)ethanone (2-19)

Followed the procedure described above: 1-phenyl-1-Bpin-2-*p*tolylethane **2-9** (25.0 mg, 0.07 mmol), 4-iodoacetophenone (12.3 mg, 0.05 mmol), $Pd(PPh_3)_4$ (4.6 mg, 0.004 mmol), PPh_3 (4.2 mg, 0.016 mmol), Ag_2O (18.4 mg, 0.07 mmol), K_2CO_3 (19.3 mg, 0.14 mmol), DME (1 mL), 80 °C, 36 h. The reaction mixture was worked up and purified to yield 10 mg (64 %) of product. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 2.27 (s, 3 H, C*H*$_3$), 2.56 (s, 3 H, COC*H*$_3$), 3.35 (m, 2 H, C*H*$_2$), 4.29 (t, $^3J_{H\text{-}H}$ = 7.7 Hz, 1 H, C*H*), 6.90 (d, $^3J_{H\text{-}H}$ = 8.0 Hz, 2 H), 6.98 (d, $^3J_{H\text{-}H}$ = 8.0, 2 H), 7.16 - 7.32 (m, 5 H), 7.43 - 7.59 (m, 2 H), 7.64 - 7.72 (m, 1 H), 7.84 (d, $J_{H\text{-}H}$ = 8.1 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, 298 K) δ: 20.97, 26.52, 41.31, 53.10, 77.20, 126.49, 127.94, 128.31, 128.49, 128.81, 128.86, 135.22, 135.50, 136.51, 143.68, 150.11, 197.80; HRMS calculated for $C_{23}H_{22}O$ (M+) 314.1671, found (M+) 314.1675.

1-*methoxy-4-(1-phenyl-2-(p-tolyl)ethyl)benzene (2-21)*

Followed the procedure described above: 1-phenyl-1-Bpin-2-*p*tolylethane **2-9** (15.0 mg, 0.047 mmol), 4-iodoaniline (7.3 mg, 0.031 mmol), $Pd(PPh_3)_4$ (2.9 mg, 0.0025 mmol), PPh_3 (2.6 mg, 0.01 mmol), Ag_2O (12.4 mg, 0.047 mmol), K_2CO_3 (12.9 mg, 0.09 mmol),

DME (0.6 mL), 80 °C, 36 hours. The reaction mixture was worked up and purified to yield 9.2 mg (98 %) of product. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 2.28 (s, 3 H, CC*H*$_3$), 3.30 (d, 2 H, $^{3}J_{H\text{-}H}$ = 7.6 Hz, C*H*$_2$), 3.77 (s, 3 H, OC*H*$_3$), 4.18 (t, 1 H, $^{3}J_{H\text{-}H}$ = 7.7 Hz, C*H*), 6.80 (d, 2 H, $^{3}J_{H\text{-}H}$ = 8.6 Hz, *Ar*), 6.93 (d, 2 H, $J_{H\text{-}H}$= 7.8 Hz, *Ar*), 7.00 (d, 2 H, $J_{H\text{-}H}$= 7.8 Hz, *Ar*), 7.12-7.27 (m, 7 H, *Ar*); ^{13}C NMR (125 MHz, $CDCl_3$ 298 K) δ: 21.01, 41.86, 52.27, 55.19, 113.70, 126.04, 127.96, 128.31, 128.75, 128.92, 128.97, 135.22, 136.76, 137.26, 145.03, 157.88; UV spectrum film prepared from CH_2Cl_2 (wavenumber): 3024, 2921 (s), 2852 (m), 1610, 1511 (s), 1452 (m), 1248 (s), 1178 (m), 1036 (m); HRMS calculated for $C_{22}H_{22}O$ (M+) 302.1671, found (M+) 302.1675.

4-(1-phenyl-2-(p-tolyl)ethyl)pyridine (2-22)

Followed the procedure described above: 1-phenyl-1-Bpin-2-*p*tolylethane **2-9** (15.0 mg, 0.047 mmol), 4-iodopyridine (6.3 mg, 0.031 mmol), $Pd(PPh_3)_4$ (2.9 mg, 0.0025 mmol), PPh_3 (2.6 mg, 0.01 mmol), Ag_2O (12.4 mg, 0.047 mmol), K_2CO_3 (12.9 mg, 0.09 mmol), DME (0.6 mL), 80 °C, 36 hours. The reaction mixture was worked up and purified to yield 5.2 mg (61 %) of product. ^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ: 2.28 (s, 3 H, C*H*$_3$), 3.32 (m, 2 H, C*H*$_2$), 4.20 (t, $^{3}J_{H\text{-}H}$ = 7.7 Hz, 1 H, C*H*), 6.89 (m, *J*= 7.7 Hz, 2 H), 6.99 (m, *J*= 7.6 Hz, 2 H), 7.11 (d, *J*=v5.8 Hz, 2 H), 7.18 - 7.25 (m, 3 H), 7.27 - 7.33 (m, 2 H), 8.41 - 8.51 (m, 2 H) ; ^{13}C NMR (125 MHz, $CDCl_3$ 298 K) δ: 20.98, 40.93, 52.59, 123.46, 126.77, 128.01, 128.61,128.82, 128.95, 135.71, 136.13, 142.78, 149.73, 153.31; UV spectrum film prepared from CH_2Cl_2 (wavenumber): 3024 (m), 2921 (m), 2853 (m),

1596 (s), 1514 (m), 1493 (m), 1451 (m), 1413 (m), 813 (s), 699 (s); HRMS calculated for $C_{20}H_{19}N$ (M+) 273.1517, found (M+) 273.1520.

1-methyl-4-(2-(4-nitrophenyl)-2-phenylethyl)benzene (2-23)

Followed the procedure described above: 1-phenyl-1-Bpin-2-*p*tolylethane **2-9** (15.0 mg, 0.047 mmol), 4-iodonitrobenzene (7.7 mg, 0.031 mmol), $Pd(PPh_3)_4$ (2.9 mg, 0.0025 mmol), PPh_3 (2.6 mg, 0.01 mmol), Ag_2O (12.4 mg, 0.047 mmol), K_2CO_3 (12.9 mg, 0.09 mmol), DME (0.6 mL), 80 °C, 36 hours. The reaction mixture was worked up and purified to yield 3.7 mg (38 %) of product.^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ: 2.28 (s, 3 H, CH_3), 3.30 (apparent dd, $^3J_{H\text{-}H}$ = 13.6, 6.8 Hz, 1 H, CH_2), 3.41 (apparent dd, $^3J_{H\text{-}H}$ = 13.6, 6.8 Hz, 1 H, CH_2), 4.34 (t, $^3J_{H\text{-}H}$ = 7.8 Hz, 1 H, C*H*), 6.89 (d, $J_{H\text{-}H}$ = 7.8 Hz, 2 H), 7.00 (d, $J_{H\text{-}H}$ = 7.6 Hz, 2 H), 7.20 - 7.25 (m, 3 H), 7.29 - 7.35 (m, 4 H), 8.09 (apparent d, $J_{H\text{-}H}$ = 8.7 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$ 298 K) δ: 21.01, 41.33, 53.04, 123.61, 126.87, 127.93, 128.73, 128.80, 12.98, 129.03, 135.83, 136.00, 142.97, 146.45, 152.14; UV spectrum film prepared from CD_2Cl_2 (wavenumber): 3026 (w), 2922 (m), 2853 (w), 1599 (w), 1518 (s), 1345 (s), 1108 (w), 1019 (w), 855 (m), 808 (m), 743 (m), 701 (m), HRMS calculated for $C_{21}H_{19}NO_2$ (M+) 317.1416, found (M+) 317.1420.

1-methyl-2-(1-phenyl-2-(p-tolyl)ethyl)benzene (2-24)

Followed the procedure described above: 1-phenyl-1-Bpin-2-*p*tolylethane **2-9** (12.0 mg, 0.037 mmol), 2-iodotoluene (5.4 mg, 0.025 mmol), $Pd(PPh_3)_4$ (2.3 mg, 0.002 mmol), PPh_3 (2.1 mg, 0.008 mmol), Ag_2O (9.7 mg, 0.037 mmol), K_2CO_3 (10.2 mg, 0.074 mmol),

DME (0.5 mL), 80 °C, 36 hours. The reaction mixture was worked up and purified to yield 2.38 mg (33 %) of product.^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 2.14 (s, 3 H, C*H*$_3$), 2.17 (rotomer), 2.28 (s, 3 H, C*H*$_3$), 2.31 (rotomer), 3.30 (apparent d, 2 H, $^{3}J_{H\text{-}H}$ = 7.2, 2 H, C*H*$_2$), 4.41 (t, 1 H, $J_{H\text{-}H}$= 7.6, C*H*), 6.90 (d, 2 H, $J_{H\text{-}H}$= 7.9 Hz, p-*Ar*), 6.97 (d, 2 H, $J_{H\text{-}H}$= 7.8 Hz, p-*Ar*), 7.09- 7.22 (m, 8 H, *Ar*), 7.41 (apparent d, 1 H, $J_{H\text{-}H}$= 7.8 Hz, *Ar*); ^{13}C NMR (125 MHz, $CDCl_3$ 298 K) δ: 20.12, 21.30, 42.33, 48.95, 126.27, 126.37, 127.29, 128.45, 128.68, 129.02, 129.21, 130.69, 135.58, 136.62, 137.51, 142.91, 144.35; UV spectrum film prepared from CD_2Cl_2 (wavenumber): 3022 (s), 2923 (s), 2857 (s), 1514 (m), 1491 (m), 1450 (m), 1030 (m), 799 (m), 761 (m), 733 (m), 699 (s); HRMS calculated for $C_{22}H_{22}$ (M+) 287.1721, found (M+) 286.1723.

Verification of the feasibility of one-pot reaction conditions

Note: this reaction was run before Ruphos was chosen as the most appropriate ligand and DME as the appropriate solvent. In the expectancy of one-pot reaction conditions, we varied the reactions for the cross-coupling of the secondary boronic ester to match those encountered for a one-pot reaction. In order to do this, we attempted a secondary cross-coupling with a palladium source matching the linear cross-coupling conditions, Xphos instead of PPh_3, and in the presence of water.

In the glovebox, 2-(1,2-diphenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **2-6** (10.0 mg, 0.032mmol), 4-iodoacetophenone (12.0 mg, 0.049 mmol), $Pd(OAc)_2$ (0.71 mg, 0.0032 mmol), XPhos (6.53 mg, 0.014 mmol), Ag_2O (12.9 mg, 1.5 mmol), K_2CO_3 (13.26 mg, 0.096 mmol) were diluted/suspended in THF (0.2 mL). The reaction vial was

capped with a septum cap, taken out of the glovebox and water (0.01 mL) carefully added. The reaction mixture was sonicated for 30 s then stirred at 80 °C for 36 h. The crude reaction mixture was diluted with Et_2O, dried over $MgSO_4$, and filtered through a short pad of celite into a pre-weighed vial. The crude reaction mixture was concentrated and dried. The residue was weighed and to a known amount of external standard (hexamethyl benzene) was added to it. The contents of the vial were dissolved in $CDCl_3$, and an NMR was acquired. Based on the average of yield calculated the product's significant peaks at 3.48 and 3.13 ppm, a 50 % yield was obtained. The product was not isolated but one-pot reaction conditions were pursued once the steps were further optimized as the cross-coupling of the secondary position in the same pot as the primary had been confirmed.

Attempts at the one-pot reaction

In the glovebox, 1-phenyl-1,2-di(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)ethane **2-8** (12 mg, 0.030 mmol), bromotoluene (6.8 mg, 0.040 mmol), $Pd(OAc)_2$ (0.67 mg, 0.003 mmol, 10 mol%), Ruphos (3.5 mg, 0.0075 mmol, 25 mol %, bidentate), K_2CO_3 (7.0 mg, 0.052 mmol, 1.7 eq.), were dissolved/suspended in DME (0.3 mL). The vial was capped with a septum cap and removed from the glovebox. Water (0.015 mL) was added carefully via syringe and the reaction mixture was sonicated for about 30 s then stirred at 80 °C for 20 h.

Ag_2O (11.86 mg, 0.045 mmol) and 4-iodoacetophenone (6.6 mg, 0.027 mmol) were suspended in DME (0.15 mL), then slowly added, via syringe, to the hot reaction mixture

and stirred at 80 °C for 24 h. The crude reaction mixture was diluted with diethyl ether, dried over $MgSO_4$ and filtered through a short pad of celite into a pre-weighed vial. The crude reaction mixture was concentrated and dried, the reaction residue was weighed, and a known amount of external standard (hexamethyl benzene) added to the vial. The contents of the vial were dissolved in $CDCl_3$, and an NMR was acquired. The NMR yield was determined to be 25 %. The product was not isolated due to the low yield.

Variations: The first one-pot reaction was cooled before the addition of the silver and aryliodide and no conversion from the linear cross-coupled product was observed. It was thought that the catalyst had decomposed on cooling.

Two other variations to the second step were undertaken: in the first, an additional 1.5 eq of PPh_3 ligand was added to the reaction mixture at the second step and for the second variation, both 1.5 eq PPh_3 and 1.3 eq K_2CO_3 (to better match the secondary cross-coupling conditions previously optimized) were added. Unfortunately, issues were encountered with trying to add the insoluble bases to the reaction vessel, compounded by the fact that the temperature, in the small volume of solution in the reaction vessel was bound to change upon addition (even slow) of an equal volume of room temperature solvent. Having seen no improvement in the yield, but having demonstrated the feasibility of the one-pot reaction procedure, it was decided to wait until both steps were further optimized before further attempts could be made on larger scale. Heating the suspension of reagents for the secondary cross-coupling before addition into the linear reaction vessel should also be attempted.

Notes on the synthesis of the TADDOL-based ligand used by Morken for the enantioselective diboration of styrene (Scheme 2-11)

The procedure followed was almost identical to those included in the supplemental information of the paper (Kilman, L. T.; Mlynarski, S.N.; Morken, J. P. *J. Am. Chem. Soc.*, **2009**, 131, 13210-13211, supplementary information p.3) however, (4R, 5R)dimethyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate was used with the Grignard reagent, not (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxilic acid.

In addition, the purification procedures for the phosphine ligand used as described (flash chromatography 1-50 % EtOAc/Hex) resulted in decomposition of the product. The authors were contacted and it seems a silica plug with polar solvent was used. This aspect of the project was not pursued due to time constraints and the crude ligand was left for the following person on the project.

Appendix A

Crystal Structure Coordinates

Table A 1 Atomic coordinates and equivalent isotropic displacement parameters (Å^2) for the N-Phenyl hantzsch Ester-BCF adduct (1-9)

Label	Xfrac + ESD	Yfrac + ESD	Zfrac + ESD	Uequiv
N1	0.7394(2)	0.4935(3)	0.12702(15)	0.0295
O1	0.9852(2)	0.3749(3)	0.03701(15)	0.0641
O2	0.8419(2)	0.3714(3)	-0.02141(14)	0.0489
O3	0.9521(2)	0.6666(3)	0.26256(14)	0.0514
O4	1.0519(2)	0.5594(3)	0.21966(13)	0.0458
C1	0.7647(3)	0.4449(4)	0.07759(19)	0.0333
C2	0.8592(3)	0.4426(4)	0.07788(19)	0.0302
C3	0.9221(3)	0.4907(4)	0.1264(2)	0.0379
C4	0.8950(3)	0.5427(4)	0.17481(19)	0.0314
C5	0.8008(3)	0.5440(4)	0.17494(19)	0.0317
C6	0.6886(3)	0.3966(4)	0.02876(18)	0.0418
C7	0.9038(4)	0.3934(5)	0.0294(2)	0.0408
C8	0.8796(4)	0.3233(5)	-0.0707(2)	0.061
C9	0.7986(4)	0.2710(6)	-0.1150(2)	0.0874
C10	0.9680(3)	0.5989(5)	0.2244(2)	0.039
C11	1.1321(3)	0.6026(5)	0.2650(2)	0.0528
C12	1.2052(4)	0.5057(6)	0.2686(3)	0.0965
C13	0.7621(3)	0.5901(4)	0.22556(18)	0.0437
C14	0.6388(3)	0.4970(5)	0.12695(19)	0.0324
C15	0.5883(3)	0.6005(4)	0.10388(18)	0.0353
C16	0.4944(3)	0.6024(5)	0.10338(18)	0.0401
C17	0.4535(3)	0.5017(5)	0.12513(19)	0.0419
C18	0.5060(3)	0.3987(5)	0.14826(19)	0.0412
C19	0.6000(3)	0.3953(5)	0.14944(19)	0.0394
B1	0.7774(4)	0.9050(5)	0.0929(2)	0.0326
C20	0.6743(3)	0.9655(4)	0.08902(19)	0.031
C21	0.6213(3)	0.9329(4)	0.12879(19)	0.0334

C22	0.5330(3)	0.9750(5)	0.1277(2)	0.0381
C23	0.4938(3)	1.0637(5)	0.0867(2)	0.0373
C24	0.5440(3)	1.1029(5)	0.04653(19)	0.0364
C25	0.6305(3)	1.0542(4)	0.0479(2)	0.033
C26	0.8598(3)	0.9821(4)	0.13795(18)	0.0308
C27	0.9433(3)	0.9232(4)	0.1623(2)	0.0355
C28	1.0157(3)	0.9755(5)	0.2032(2)	0.0374
C29	1.0080(4)	1.0959(5)	0.2225(2)	0.0423
C30	0.9273(4)	1.1606(5)	0.2007(2)	0.0393
C31	0.8565(3)	1.1034(5)	0.1597(2)	0.036
C32	0.8021(3)	0.8842(4)	0.02752(19)	0.0313
C33	0.7763(3)	0.7747(5)	-0.0042(2)	0.0349
C34	0.8002(3)	0.7449(5)	-0.0571(2)	0.0404
C35	0.8524(3)	0.8284(5)	-0.0809(2)	0.0414
C36	0.8783(3)	0.9386(5)	-0.0523(2)	0.042
C37	0.8536(3)	0.9645(5)	0.0003(2)	0.0379
F21	0.65747(17)	0.8511(2)	0.17383(10)	0.0454
F22	0.48498(17)	0.9311(3)	0.16695(11)	0.0522
F23	0.40796(18)	1.1095(3)	0.08542(11)	0.056
F24	0.50573(17)	1.1912(2)	0.00554(11)	0.0493
F25	0.67341(17)	1.0977(2)	0.00552(10)	0.0474
F27	0.95835(16)	0.8040(2)	0.14355(11)	0.0471
F28	1.09467(18)	0.9089(3)	0.22418(12)	0.0599
F29	1.07904(18)	1.1505(3)	0.26145(11)	0.0585
F30	0.91798(19)	1.2788(3)	0.21890(11)	0.0586
F31	0.77994(18)	1.1772(2)	0.13946(11)	0.0502
F33	0.72388(18)	0.6871(2)	0.01641(11)	0.0511
F34	0.7725(2)	0.6354(3)	-0.08513(12)	0.064
F35	0.8765(2)	0.8015(3)	-0.13272(11)	0.0633
F36	0.92886(19)	1.0227(3)	-0.07600(11)	0.0638
F37	0.88050(18)	1.0787(3)	0.02509(11)	0.0543

Table A 2 Atomic coordinates and equivalent isotropic displacement parameters (Å^2) for the Diketone Hantzsch ester-BCF adduct (1-11)

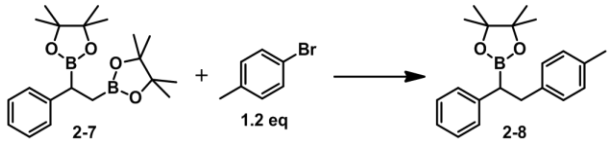
Label	Xfrac + ESD	Yfrac + ESD	Zfrac + ESD	Uequiv
B1	0.3202(3)	0.73788(17)	0.3543(2)	0.0321
N1	0.3904(2)	0.68140(14)	0.11586(16)	0.0409
O1	0.31703(14)	0.72025(10)	0.28303(12)	0.0349
O2	0.31753(17)	0.79515(11)	-0.04934(13)	0.0471
C1	0.3648(2)	0.68958(16)	0.17052(19)	0.0364
C2	0.3054(2)	0.73266(15)	0.16895(18)	0.0322
C3	0.2652(2)	0.76732(16)	0.10552(17)	0.0372
C4	0.3050(2)	0.75510(15)	0.05067(17)	0.0327
C5	0.3643(2)	0.71363(16)	0.05668(18)	0.0367
C6	0.4073(3)	0.65019(16)	0.2281(2)	0.0459
C7	0.2839(2)	0.74813(15)	0.22623(18)	0.0324
C8	0.2238(2)	0.79670(15)	0.22227(19)	0.0389
C9	0.2741(2)	0.78982(16)	-0.01067(19)	0.0383
C10	0.1850(2)	0.81937(18)	-0.0264(2)	0.0478
C11	0.4081(3)	0.69503(19)	0.0071(2)	0.0527
C12	0.2212(2)	0.73574(15)	0.36347(19)	0.0351
C13	0.2127(3)	0.75141(16)	0.4246(2)	0.0423
C14	0.1336(3)	0.74898(17)	0.4383(2)	0.0491
C15	0.0579(3)	0.72824(17)	0.3915(2)	0.05
C16	0.0617(2)	0.70945(17)	0.3309(2)	0.0465
C17	0.1421(2)	0.71349(16)	0.3182(2)	0.0392
C18	0.3789(2)	0.68834(15)	0.40484(17)	0.0316
C19	0.4450(2)	0.69561(15)	0.46750(18)	0.0343
C20	0.4875(2)	0.65263(16)	0.50998(18)	0.0366
C21	0.4641(2)	0.59957(17)	0.4914(2)	0.0458
C22	0.3982(3)	0.58956(16)	0.4302(2)	0.043
C23	0.3578(2)	0.63331(15)	0.38920(19)	0.0345
C24	0.3711(2)	0.79865(16)	0.36799(18)	0.0384
C25	0.3366(3)	0.84928(18)	0.3762(2)	0.0475
C26	0.3824(3)	0.89950(18)	0.3855(2)	0.0567
C27	0.4690(4)	0.8994(2)	0.3854(2)	0.0594
C28	0.5081(3)	0.8505(2)	0.3757(2)	0.0567
C29	0.4593(3)	0.80194(17)	0.36717(19)	0.0421

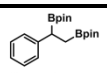
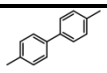
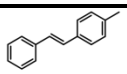
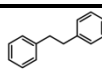
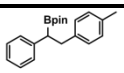
F13	0.28644(15)	0.77201(10)	0.47417(11)	0.0552
F14	0.13077(17)	0.76743(11)	0.49915(13)	0.0706
F15	-0.02074(16)	0.72654(11)	0.40385(15)	0.074
F16	-0.01177(14)	0.68697(10)	0.28497(13)	0.0637
F17	0.13986(13)	0.69416(9)	0.25685(11)	0.0477
F19	0.47374(13)	0.74706(9)	0.49082(11)	0.0463
F20	0.55253(14)	0.66397(9)	0.56987(11)	0.0539
F21	0.50393(17)	0.55726(10)	0.53267(13)	0.0734
F22	0.37272(16)	0.53654(9)	0.41129(12)	0.0631
F23	0.29055(12)	0.61966(8)	0.33049(10)	0.0412
F25	0.24870(15)	0.85364(9)	0.37473(12)	0.0576
F26	0.34378(19)	0.94675(10)	0.39434(13)	0.0732
F27	0.5162(2)	0.94705(11)	0.39494(14)	0.0888
F28	0.59345(18)	0.85004(12)	0.37409(15)	0.0854
F29	0.50190(13)	0.75489(10)	0.35828(11)	0.0514

Appendix B

Qualitative Data from the Preliminary Optimization Studies

Table B 1 Preliminary optimization of ligand

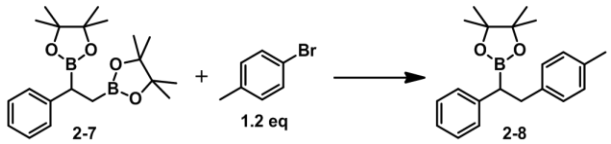


Ligand	 diborated styrene 2-8	 4,4'-dimethylbiphenyl 2-10	 styrene	 4-methylstilbene 2-13	 1-phenyl-2-tolylethane 2-15	 Desired product 2-9	 4-Bromotoluene
dppb (1.7eq *vs* Pd)	s	m	m	t	___	t	___
PPh_3 (5 eq *vs* Pd)	s	m	m	___	___	t	___
Johnphos (5 eq *vs* Pd)	s	t	___	t	t	m	___
Josiphos (1.7 eq *vs* Pd)	s	m	t	m	___	t	___
Sphos (5 eq *vs* Pd)	___	___	___	___	m	m	s
$(OtBu)_2PPh_3$ (5 eq *vs* Pd)	s	___	t	___	___	___	s

Strong peak: s, Medium peak: m, Trace peak: t

a) Reaction conditions (8 mg scale): catalyst (10 mol %), ligand (45 mol%), base (3 eq), solvent (0.2:0.01 M), 80 °C, 20 h.

Table B 2 Preliminary optimization of ligand and solvent



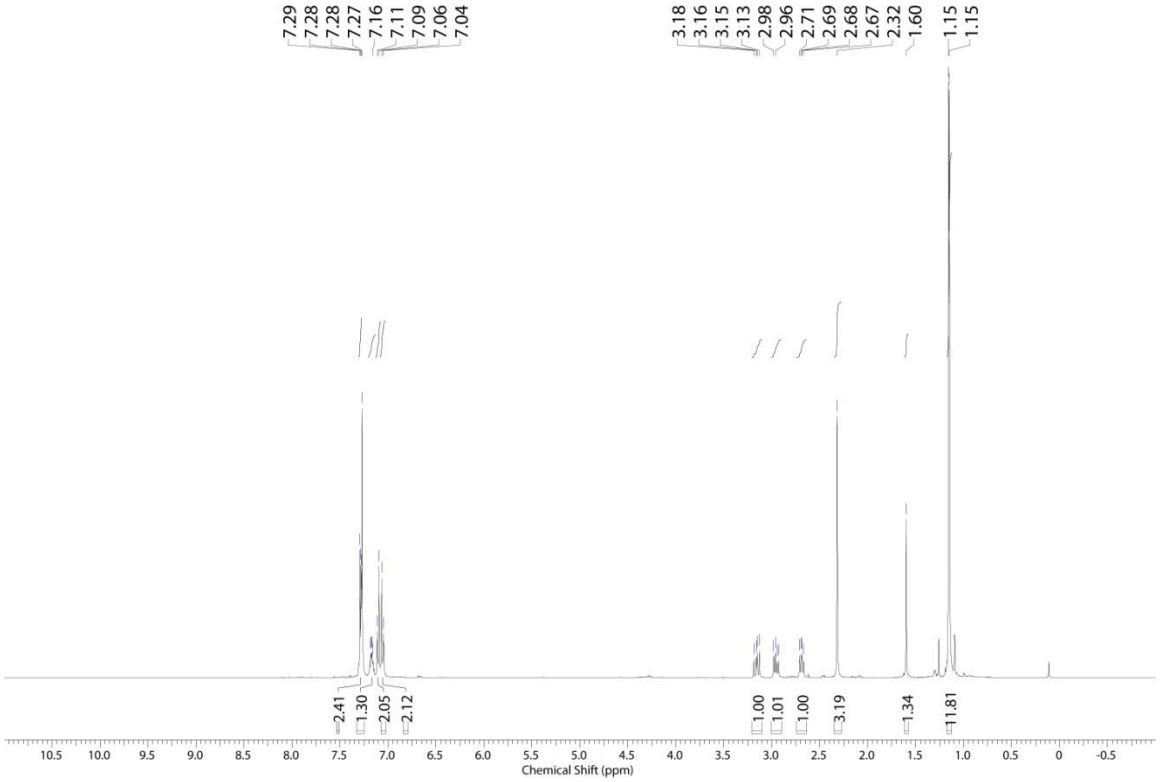
Entry	*Catalyst*	*Ligand vs Pd*	*Base*	*Solvent (20:1)*	*Other*	*Products*
1	$Pd_2(dba)_3$	Cy_3P	K_2CO_3	THF:H_2O		styrene, diarylethane, stilbene
2	$Pd(OAc)_2$	Cy_3P	K_2CO_3	THF:H_2O	IPhMe, 60 ^oC	SM, stilbene, dimethylbiphenyl (homocoupling)
3	$Pd_2(dba)_3$	$^tBu_3PHBF_4$	K_2CO_3	THF:H_2O		PRODUCT, diborated stilbene are major (still a lot of SM) diarylethane, dimethylbiphenyl
4	$Pd(OAc)_2$	$^tBu_3P$	K_2CO_3	THF:H_2O		diborated styrene, PRODUCT, diarylethane
5	$Pd(OAc)_2$	Cy_3P	K_2CO_3	DMF:H_2O		protodeboration, SM, stilbene, dimethylbiphenyl
6	$Pd(OAc)_2$	Cy_3P	K_2CO_3	Tol: H_2O		SM, stilbene, PRODUCT
7	$Pd(OAc)_2$	Cy_3P	K_2CO_3	THF	Anhydrous	No reaction

Reaction conditions (8 mg scale): catalyst (10 mol %), ligand (45 mol%), base (3 eq), solvent (0.2:0.01 M), 80 °C, 20 h.

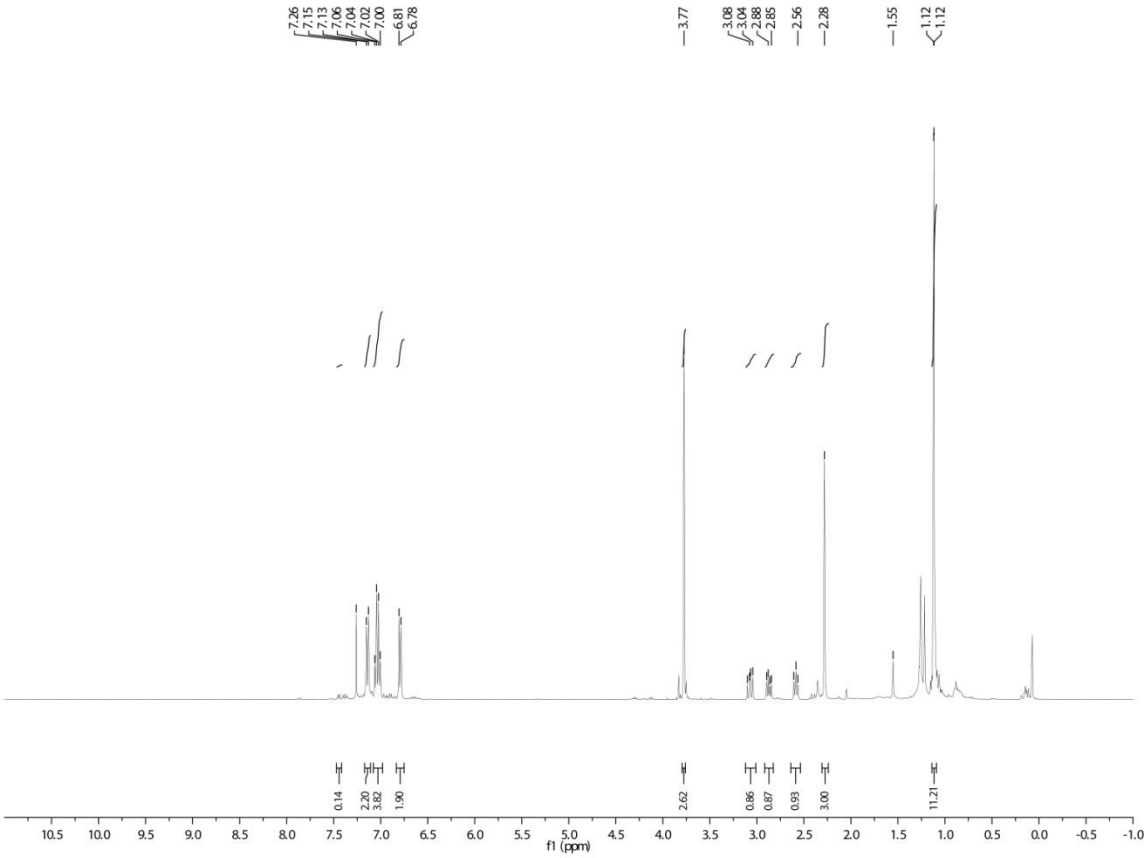
Appendix C

Supplementary ^{1}H NMR

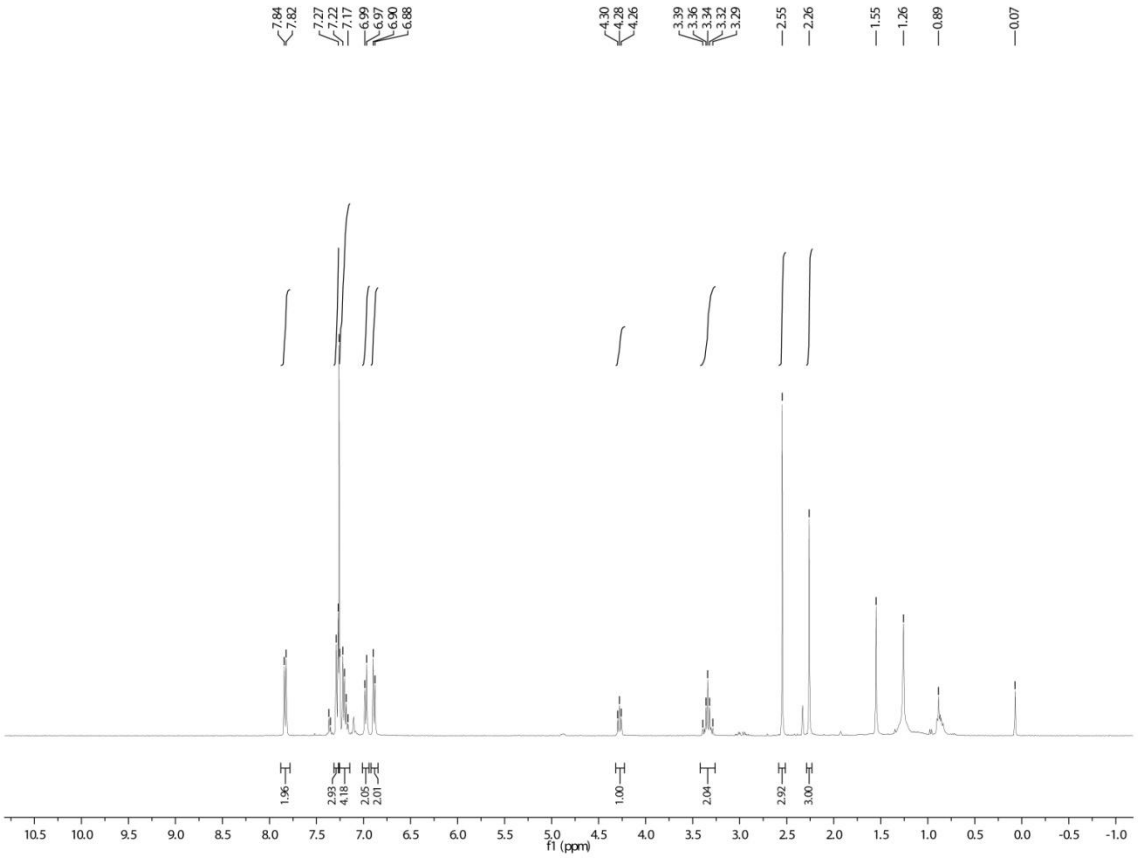
1-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)-2-tolylethane (2-9)



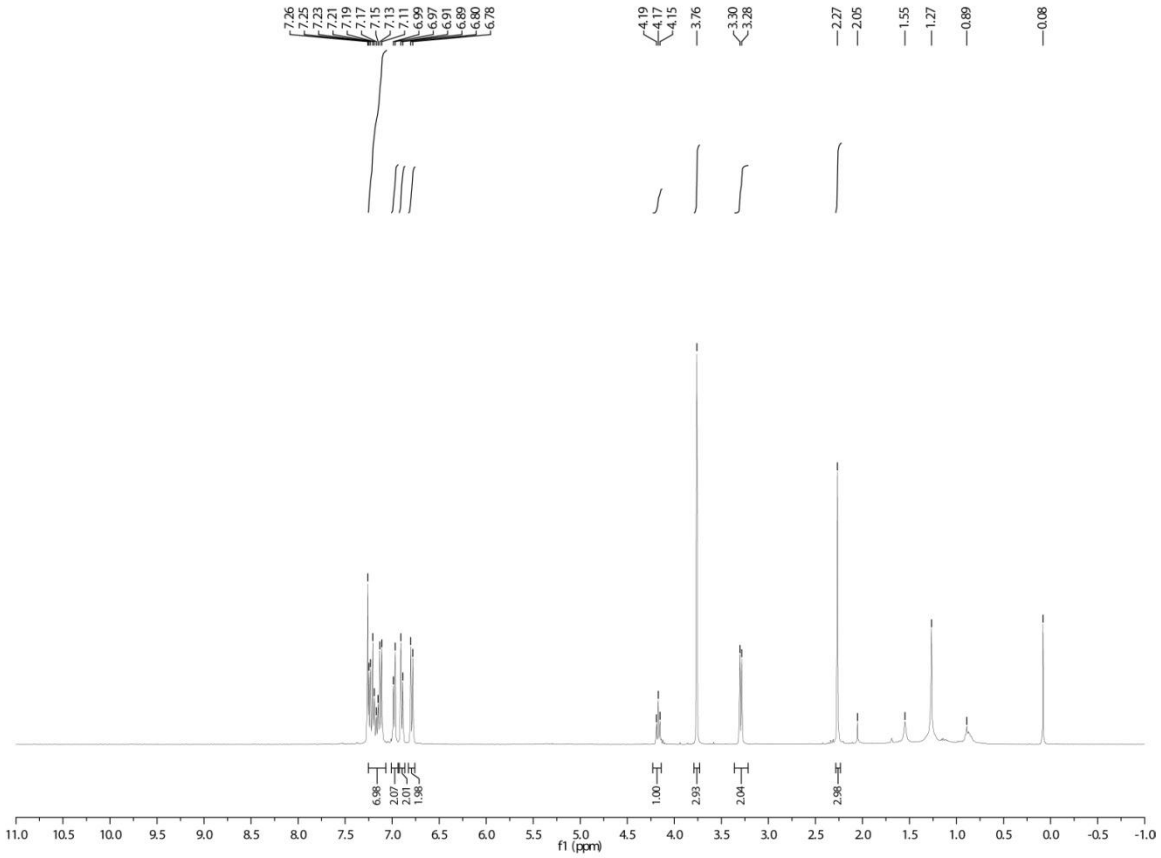
1-(4-methoxyphenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)-2-phenylethane (2-18)



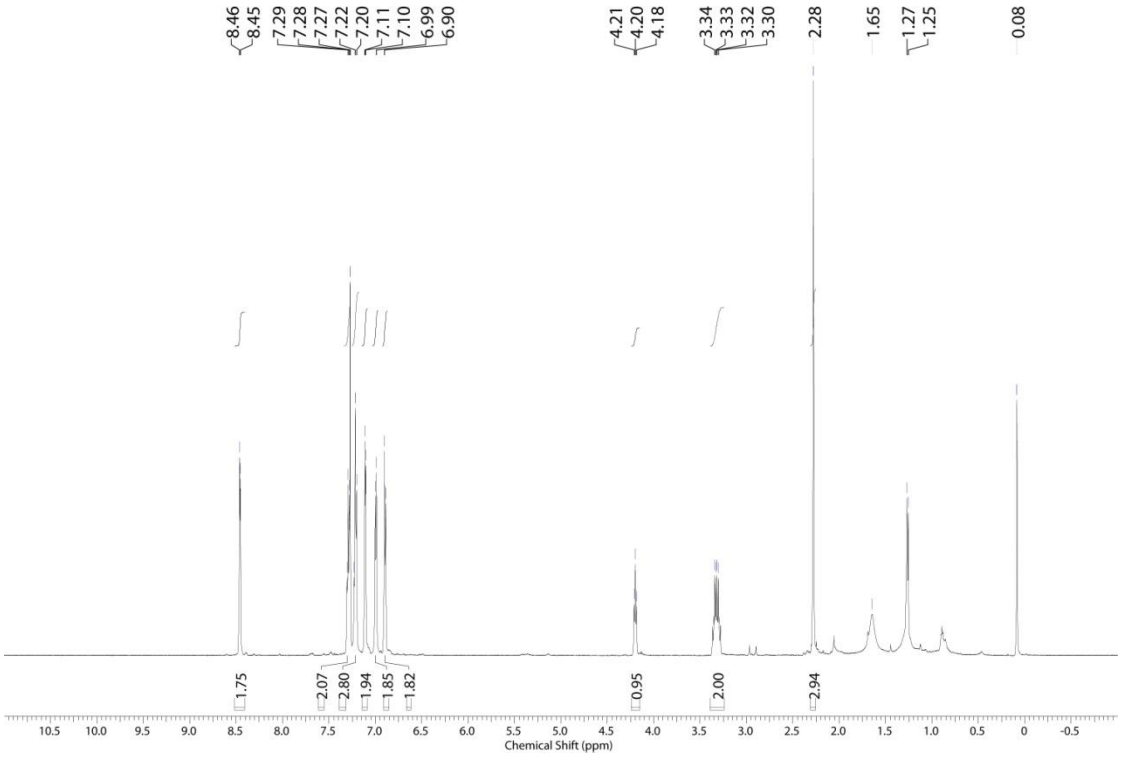
1-(4-(1-phenyl-2-(*p*-tolyl)ethyl)phenyl)ethanone (2-19)



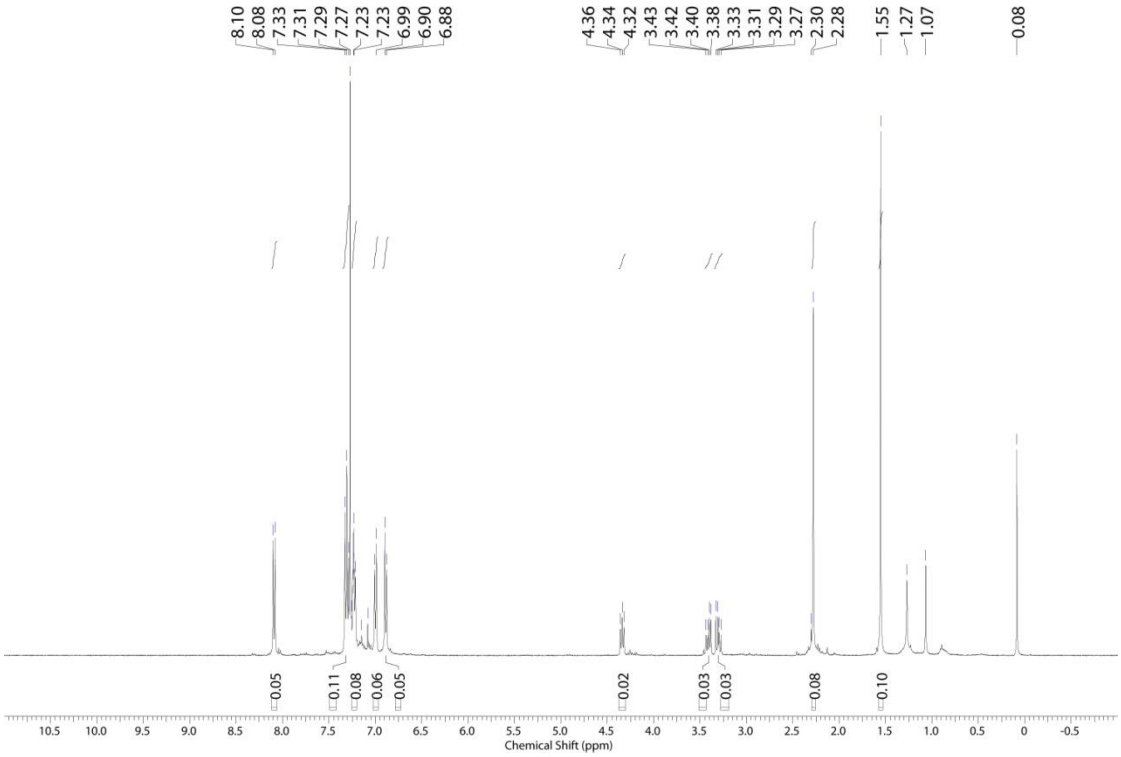
1-methoxy-4-(1-phenyl-2-(*p*-tolyl)ethyl)benzene (2-21)



4-(1-phenyl-2-(*p*-tolyl)ethyl)pyridine (2-22)



1-methyl-4-(2-(4-nitrophenyl)-2-phenylethyl)benzene (2-23)



1-methyl-2-(1-phenyl-2-(*p*-tolyl)ethyl)benzene (2-24)