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Etude Fondamentale et Application en Catalyse de Métaux de Transition Précoces Complexés à de Nouveaux Ligands Hémilabiles contenant des Hétéroéléments

Thibault Bagnol

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By Thibault BAGNOL

**Hemilabile Heteroelement Based Ligands for Early Transition
Metal Complexes, Fundamental Studies and Applications to
Catalysis**

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and Dr. Mathieu PUCHEAULT

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ABSTRACT

This thesis details the development of new hemilabile ligands using heteroelement chemistry to develop new precatalyst for hydrofunctionalization chemistry. These chelating molecules are studied with early transition metals from group 4 and 5 as titanium, zirconium and tantalum.

Synthesis of 1,3-*N,O*-chelating complexes containing boron atom have been synthesized using a new synthetic pathway based on electrophilic Friedel-Crafts reaction that involves amineborane complexes. Coordination chemistry with titanium is studied and shows unexpected reactivity with formation of another product.

1,3-*N,N*-chelating complexes containing boron were investigated through two different aspects, either using cyclic or acyclic boraamidines. A four step synthesis involving subsequent borylation and Suzuki-Miyaura cross-coupling reactions is developed, to obtain cyclic boraamidine. Acyclic boraamidines were synthesized using procedures from the literature. Coordination chemistry involving early transition metals was carried out, and catalytic hydroaminoalkylation examined.

Complementary to this work, another synthetic approach on order to obtain β -aminophosphine ligands was looked at. Hydroamination of alkynes has been reported several times in the literature using either aryl or alkyl alkynes. Besides, alkynes containing heteroelements such as phosphorus remains evasive. *N,P,N*-type ligands were synthesized and protonolysis reactions were carried out to achieve the formation of new *N,P,N*-metal complexes containing early transition metals like titanium and zirconium.

LAY SUMMARY

Catalysis chemistry is an important tool to synthesize new molecule containing diversity and complexity by decreasing the energy barrier between substrates and the desired product. The goal of a catalyst is to decrease the energy required to achieve the transformation with a good efficiency. Several transformations imply catalytic reactions to form valuable chemical products for pharmaceutical, agrochemical or industrial purposes. Development of new systems involving low cost and Earth abundant early transition metals such as titanium or tantalum are required to replace endangered late transition metal catalyst like palladium or platinum. This thesis focuses on the development of new catalysts containing boron atoms and early transition metals with good atom-economic reaction processes used in green chemistry.

PREFACE

All the work presented in this thesis has been completed under the supervision of my two supervisors Prof. Laurel L. Schafer and Dr. Mathieu Pucheault. I conducted all the experiments described in this thesis and I have written this document with the suggestions from my supervisors Prof. Laurel L. Schafer and Dr. Mathieu Pucheault.

The experiments of chapter two have been conducted at the University of Bordeaux (France) and the data will be published with the work done by Dr. Jean-Baptiste Charbonnier on the new synthetic pathway for the synthesis of compound containing boron atom.

Experiments presented in chapter three have been conducted at both Universities, University of Bordeaux (France) and University of British Columbia (Canada). The publication of the data obtained in this chapter will be considered after further studies.

The data from chapter four are under writing and are expected to be submitted to *ACS Catalysis*. It has been carried out with the collaboration of Han Hao, a *Ph.D.* student at the University of British Columbia (Canada).

RESUME

Les molécules organiques contenant du bore sont omniprésentes dans différentes applications chimiques, notamment dans des applications biomédicales et polymères, et en chimie organométallique comme agent de couplage. Les aminoboranes ont été développés pour le développement de nouvelles énergies durables pour le stockage de l'hydrogène. Ces dérivés sont des réactifs polyvalents et des travaux récents ont mis en évidence leur application en tant que ligands potentiels en chimie organométallique.

La chimie de coordination offre de nouvelles possibilités avec le développement de procédés catalytiques en synthèse organique *via* l'utilisation des métaux de transition, et plus précisément les métaux de transition précoces. En effet, les réactions catalytiques offrent de multiples avantages tel que l'activation de liaisons traditionnellement non réactives et elles peuvent également avoir un impact sur la régiosélectivité, la stéréosélectivité et la chimiosélectivité qu'elles peuvent soit améliorer soit inverser, permettant ainsi la formation de nouveaux produits. Les systèmes catalytiques favorisent la formation de produit en réduisant l'énergie nécessaire à la transformation chimique, et ils peuvent également réduire la quantité de sous-produits générés et être économiques en atome.

Les complexes métallocènes décrits dans les années 1950 constituaient l'une des premières familles de catalyseurs. Cependant, leurs synthèses ainsi que leurs modifications difficiles ont conduit à la mise au point de nouveaux systèmes catalytiques utilisant différents ligands facilement synthétisables. De nos jours, une grande variété de nouveaux catalyseurs a été rapportée *via* l'emploi de différents ligands tels que les amidinates, amidates et leurs dérivés. Contrairement aux métallocènes, ces ligands sont hémilabiles, facilement synthétisables et modifiables selon des voies de synthèse classique en chimie organique. Le chapitre 1 présente les différentes familles de 1,3-*N,N*- et 1,3-*N,O*-chélates souvent développés dans la littérature : les amidinates, guanidates, amidates, ureates, et pyridonates. Leurs applications en catalyse pour les réactions d'hydroamination et d'hydroaminoalkylation sont présentées permettant la création de liaisons carbone-azote et carbone-carbone.

L'amélioration de l'électrophilicité des 1,3-chélates a été rapportée en utilisant un hétéroélément pour remplacer le centre carboné. Ces complexes sont décrits dans la dernière section du chapitre 1 avec les différents hétéroéléments tel que le soufre, le phosphore et le bore observés dans la littérature. Leurs potentiels comparés aux 1,3-*N,N*- et 1,3-*N,O*-chélates contenant un atome de carbone central sont exposés, tout comme la présentation de leurs applications. Pour ces raisons, le développement de nouveaux ligands

chélatants utilisant la chimie des organoboranes pour des applications de catalyse semble intéressant. L'électropositivité de l'atome de bore pourrait avoir un impact sur le complexe métallique obtenu en améliorant sa réactivité pour les processus de catalyse. Peu d'exemples de 1,3-chélates contenant un atome de bore ont été rapportés dans la littérature et aucune application n'a été trouvée pour ces complexes. Cependant, Schafer a récemment rapporté que des complexes chélatants avec un atome de phosphore conduisent à une augmentation de la réactivité de tels complexes grâce au caractère électrophile du phosphore.

L'objectif du chapitre 2 est d'utiliser la propriété électrophile du bore pour développer de nouveaux ligands de type amidates ou amidinates contenant le motif 1,3-*N,O*- et 1,3-*N,N*-chélates. Récemment, le groupe Schafer à l'Université de la Colombie-Britannique (Canada) a publié un nouveau ligand phosphoramidate *O,P,N* utilisé en tant que complexe métallique pour l'hydrofonctionnalisation de liaison carbone-carbone insaturée. Grâce à la présence d'un centre électrophile induit par l'atome de phosphore, les complexes de type phosphoramidates peuvent effectuer l'hydroaminoalkylation à température ambiante. De plus, le groupe Schafer a également publié la synthèse de nouveaux complexes de type pyridonate contenant du tantale substitué par des fonctions chlore liées au centre métallique. Ces complexes présentent également une réactivité élevée pour l'hydroaminoalkylation. C'est pourquoi les alkoxyaminoboranes *O,B,N* semblent être un motif de choix pour imiter les 1,3-*N,O*-chélates grâce à la présence du bore à la place du carbone central dans le cas des ligands type amidates.

Ce chapitre est donc axé sur la synthèse de composés de type alkoxyaminoborane et leur application pour la formation de complexes métalliques de transitions précoces. Pour cela une nouvelle voie de borylation électrophile à partir du 2-hydroxy- ou du 2-amino-biphenyl a été étudiée pour obtenir les boroxarophénanthrènes ou borazarophénanthrènes. La borylation électrophile a été développée en utilisant une source alternative de bore pour éviter l'emploi d'halogénure de bore toxique tel que BCl_3 ou BBr_3 . C'est pourquoi les complexes amineboranes ont été utilisés avec l'addition d'une source de chlore comme AlCl_3 pour générer l'espèce électrophile *in situ*. Différents complexes amineboranes ont été étudiés, ainsi que différents solvants et sources chlorées. Cependant, un maximum de 66% de conversion a été obtenu. Il serait ainsi possible que des réactions secondaires comme la dimérisation et la trimérisation, conduisent à un intermédiaire non réactif vis-à-vis de la borylation électrophile.

La complexation du borazarophénanthrène obtenu a ensuite été étudiée avec des dérivés de titane, mais aucun complexe n'a été obtenu. Le diméthyltitanocène n'a pas fait l'objet d'une réaction de protonolyse avec le borazarophénanthrène comme envisagé. Il a réagi comme un organomagnésien ou un organolithien pour former un produit alkylé. Afin de résoudre ce problème, différentes sources de titane, telles que $Ti(OiPr)_4$ ou $Ti(NMe_2)_4$, ont été utilisées, mais sans réussite.

Le développement d'une nouvelle voie de synthèse pour obtenir les boroxaro- et borazaro-phénanthrènes a montré un succès limité. C'est pourquoi une nouvelle procédure a été considérée pour obtenir les composés désirés pour l'accès à de nouveaux ligands. La borylation de bromure d'aryle *ortho*-substitué a été réalisée avec des rendements variés. Par conséquent, cette transformation a été appliquée à différents bromures d'*ortho*-aryle. Les alkyles d'amines *N*-substituées ont été synthétisées en utilisant des procédures connues de la littérature puis impliquées en borylation. Un résultat limité a été obtenu avec l'impossibilité de former la molécule ciblée avec le motif *N,B,N*. La purification n'a pas permis d'isoler le produit souhaité, et dans certains cas une seule liaison carbone-bore s'est formée, ce qui est dû à un intermédiaire moins réactif défavorisant la formation de la deuxième liaison carbone-bore. La fonction amine a été protégée avec un groupement protecteur de type Boc, puis la réaction de borylation a été effectuée, mais le produit désiré n'a pas été formé.

Comme présenté dans les deux premiers chapitres, les 1,3-*N,O*-ligands, ont été largement utilisés en chimie organométallique pour le développement de nouveaux catalyseurs. Sur la base de ces précédents travaux, les dérivés de type boraamidine sont considérés comme des cibles attrayantes pour le développement de nouveaux 1,3-*N,N*-ligands. Ce type de ligands n'a jamais été appliqué pour la catalyse en chimie de synthèse. En raison du caractère électrophile du bore, le complexe boraamidinate devrait être plus réactif pour les réactions d'hydrofonctionnalisation. En effet, la littérature a décrit qu'un centre métallique électrophile augmenterait la réactivité pour la formation de liaison carbone-carbone ou carbone-azote. Dans le chapitre 3 la synthèse de 1,3-*N,N*-chélates contenant du bore est démontré avec deux cibles privilégiées pour la synthèse de boraamidinate cycliques ou acycliques. En raison d'un squelette plus stable, les boraamidines cycliques ont été étudiées en premier. En effet, les boraamidines acycliques sont généralement plus sujets à l'hydrolyse après contact avec de l'air ou de l'humidité, alors que les boraamidinates cycliques sont moins réactifs à l'hydrolyse et à l'oxydation due à l'impossibilité de rompre les liaisons bore-azote grâce à leur squelette aromatique carboné. C'est pour cela, que les composés pentacycliques ont été dans un premier temps développés pour la synthèse de

nouveaux 1,3-*N,N*-chélates contenant du bore. La première partie du chapitre 3, menée à l'Université de Bordeaux, présente la synthèse de nouveaux 1,3-*N,N*-chélates. Les boraamidines cycliques ont été synthétisés avec une nouvelle méthode de synthèse développée au cours de ce projet. La dernière étape de cyclisation électrophile pour former la liaison carbone-bore a conduit à un faible rendement. Malgré les différentes conditions de réaction les résultats obtenus étaient peu probants. Ces composés ont pu être employés en réaction de complexation avec du titane, mais aucun complexe boraamidinate n'a pu être isolé malgré toutes les tentatives.

Dans la deuxième partie du chapitre 3 la synthèse des boraamidines acycliques a été réalisée à l'Université de la Colombie-Britannique. Différents chloroaminoboranes ont été synthétisés en utilisant un procédé connu impliquant la réaction d'amine secondaire avec du dichlorophénylborane. Après isolement des aminochlorophénylboranes, l'addition d'amines primaires à une solution du dérivé de bore a été effectuée et le diamino-borane a été isolé avec succès. Les réactions de complexation ont été étudiées avec des métaux de transition des groupes 4 et 5. Les complexes de titane et de tantale ont été employés mais sans résultat. Dû aux limites avec les réactions de protonolyse, la métathèse a été exécutée avec une étape de déprotonation du ligand faite au-préalable. Cependant, l'isolation du sel du ligand n'a pas pu être caractérisée. C'est pourquoi la complexation a été faite en déprotonant *in situ*, suivie de l'addition du complexe métallique souhaité au mélange réactionnel. Malheureusement, aucun 1,3-chélate n'a pu être isolé par le biais de ce procédé, néanmoins la recristallisation a révélé la formation d'un complexe bis(titane) ponté avec deux groupes *tert*-butylamine. Ce résultat a permis de conclure que la formation d'un dimère de titane empêche la formation du 1,3-chélate souhaité. Le deuxième sous-produit formé au cours de cette réaction correspond à un composé cyclique de type borazine.

La catalyse d'hydroaminoalkylation a été développée en utilisant le ligand boraamidine ou boraamidinate *in situ* avec le complexe métallique. Les dérivés $\text{TiCl}_2(\text{NMe}_2)_4$, $[\text{TaCl}_2(\text{NMe}_2)_3]_2$ et $\text{Ta}(\text{NMe}_2)_5$ n'ont montré aucune réactivité pour cette réaction. Cependant, $\text{TaCl}_2(\text{CH}_2\text{SiMe}_3)_3$ a montré une forte activité pour l'hydroaminoalkylation avec une conversion complète à 130 °C pendant 18 heures. Mais, en dépit des progrès réalisés pour cette réaction d'hydroaminoalkylation à l'aide de ce système, le groupe Schafer a récemment publié un autre système permettant la transformation souhaitée avec une conversion complète en moins d'une heure.

Durant ces dernières années, les synthèses et les applications des dérivés aminophosphines ont été largement décrits dans la littérature. Différentes familles de *P,N*-ligands ont été mises en évidence à l'aide de différentes approches synthétiques pour obtenir la cible souhaitée. Ces ligands *P,N* présentent généralement des centres chiraux dans leur structure carbonée, ce qui justifie leur utilisation en catalyse asymétrique comme l'hydrogénation ou l'hydrosilylation. Plus récemment, ils ont été appliqués à des réactions de couplage pour la formation de nouvelles liaisons carbone-carbone. L'utilisation de ces ligands *P,N* découle de leur possibilité à avoir différents mode de coordination ainsi qu'à leur hémilabilité. Ces ligands peuvent présenter des coordinations monodentées ou bidentées au centre métallique lorsque l'azote et le phosphore sont liés au centre métallique. Certains groupes de recherche ont décrit la synthèse et l'application de nouveaux ligands *N,P,N*. Ces ligands offrent de nouvelles possibilités en synthèse organique en raison de leur mode de liaison tridentate. Fryzuk a notamment décrit l'activation de petites molécules organiques comme le dihydrogène ou le diazote en utilisant les ligands *N,P,N* coordonnés à un métal de transition précoce comme le titane ou le zirconium.

Différents groupes de ligands *P,N* ne présentant pas de liaison directe phosphore-azote ont été rapportés dans la littérature. Le premier groupe présente des dérivés de ferrocène publiés pour la première fois par Kumada en 1974. Ce sont les premiers dérivés appliqués dans des transformations asymétriques. Les ligands *P,N*-oxazoline représentent un autre exemple de groupe majeur utilisé dans le même but que les précédents ligands *P,N*-ferrocène. Les dérivés d'acides aminés chiraux ont également été largement utilisés en tant que ligands *P,N* contenant un centre stéréogénique pour la catalyse asymétrique. Cependant, plusieurs étapes réactionnelles sont généralement nécessaires pour modifier l'acide aminé d'origine. Les ligands MAP présentant une chiralité axiale sont une autre classe de ligands *P,N*, et ces derniers sont des ligands cycliques. Toutes ces différentes classes de *P,N*-ligands peuvent être combinées entre elles pour former des ligands hybrides.

Ces ligands nécessitent généralement plusieurs étapes de synthèse, entre deux à cinq, pour obtenir le ligand souhaité. Le complexe métallique est obtenu après une réaction de protonolyse ou de métathèse. Désymétriser les *P,N*-ligands est une méthode efficace pour prendre en charge une transformation spécifique au cours d'un cycle catalytique. Les deux hétéroéléments différents dans ces ligands permettent de stabiliser le centre métallique grâce à l'azote qui rend le métal plus réactif dû à son effet donneur et grâce au phosphore qui est accepteur. De plus, l'atome de phosphore peut être facilement modifié électroniquement et stériquement.

Une nouvelle approche pour la synthèse de ces ligands *P,N* et *N,P,N* a été développée en utilisant une réaction d'hydroamination avec un précatalyseur de titane mis

au point dans le laboratoire du groupe Schafer. Avant de réaliser l'hydroamination, les dérivés de phosphine d'alcynes ont été synthétisés par réaction de métathèse. Après, l'hydroamination a pu être effectué avec l'alcyne souhaité. La réduction des enamines intermédiaires par du NaBH_4 , et leur purification sur chromatographie sur colonne a permis d'obtenir les ligands P,N et N,P,N .

La chimie de coordination de ces ligands N,P,N a été développée avec du zirconium et du titane selon les travaux rapportés par Fryzuk. La recristallisation des produits à l'aide de HMDSO a permis la formation de cristaux qui ont été analysés par diffraction à rayons X, confirmant ainsi la formation d'un complexe métallique bipyramidal trigonal «déformé». Cette réaction a ensuite été utilisée avec d'autres complexes tels que $\text{Ti}(\text{NMe}_2)_4$ et $\text{ZrCl}_2(\text{NMe}_2)_2$ formant les produits souhaités, qui ont été confirmés par spectroscopie RMN (^1H , ^{31}P , $^{31}\text{P}\{^1\text{H}\}$, ^{13}C et 2D). Cependant aucune structure RX n'a été obtenue.

La réactivité vis-à-vis de l'activation de diazote a été tentée mais le produit obtenu n'a pas pu être isolé en raison de sa décomposition après concentration *in vacuo*. Les travaux futurs sur ces N,P,N -ligands pourraient être basés sur la réactivité de ces complexes pour ensuite activer de petites molécules tels que le diazote ou le dihydrogène.

La découverte d'une nouvelle approche de synthèse pour la formation de ligands N,P,N utilisant la réaction d'hydroamination offre de nouvelles possibilités pour la synthèse de ces ligands en les modifiant stériquement ou électroniquement. Dans la littérature, il existe déjà de nombreux exemples sur le développement de divers ligands P,N pour la catalyse asymétrique. Utiliser l'hydroamination pour la synthèse de ligand P,N asymétrique pourrait être une voie à explorer en s'appuyant sur des alcynes internes et terminales présentes sur la même molécule. En effet, comme indiqué dans ce chapitre, les amines primaires aliphatiques et aromatiques ne réagissent pas avec les mêmes conditions réactionnelles: un chauffage est nécessaire avec une amine aliphatique, tandis que l'amine aromatique peut subir une hydroamination à température ambiante. Les alcynes internes et terminales ont également démontré une réactivité différente: une température plus élevée et un temps de réaction plus long sont généralement nécessaires pour une alcyne interne, tandis que 70 °C ou une température ambiante pendant 18 heures sont nécessaires pour une alcyne terminale. Ainsi, en choisissant l'amine et l'alcyne voulues, des N,P,N -ligands asymétriques pourraient être facilement synthétisés. Le complexe métallique chiral avec le ligand N,P,N pourrait être alors obtenu après protonolyse avec la méthode décrite dans le chapitre 4.

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LIST OF ABBREVIATIONS

1D	one dimension
2D	two dimensions
A_N	nucleophilic addition
Boc	<i>tert</i> -butoxycarbonyl
Bp	boiling point
Bpin	4,4,5,5,-tetramethyl-1,3,2-dioxaborol
Bs	broad singlet
Cp	cyclopentadienyl
DABCO	1,4-diazabicyclo[2.2.2]octane
dan	1,8-diaminonaphtyl
DCM	dichloromethane
DICAB	dicyclohexylamine borane complex
DIMAB	dimethylamineborane complex
DIPAB	diisopropylamine borane complex
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EI	electron ionisation
e.g.	<i>exempli gratia</i>
equiv.	equivalent
ESI	electrospray ionization
FLP	frustrated Lewis pairs
GC/MS	gas chromatography/mass spectrometry
HMDSO	hexamethyldisiloxane
HPLC	high-performance liquid chromatography
i.e.	<i>id est</i>
IR	infrared spectroscopy
LDA	lithium diisopropylamide
MAO	methylaluminoxane
<i>n</i>-BuLi	<i>n</i> -butyllithium
NMR	nuclear magnetic resonance
<i>o</i>-DCB	<i>ortho</i> -dichlorobenzene
OLED	organic light-emitting diode

ORTEP	oak ridge thermal ellipsoid plot
PEG-400	polyethyleneglycol-400
Ph.D.	philosophiae doctor
pKa	acid dissociation constant
ppm	parts per million
<i>p</i>-TsOH	<i>p</i> -toluenesulfonic acid
r.t.	room temperature
S_E	electrophilic substitution
<i>t</i>-BuLi	<i>tert</i> -butyllithium
THF	tetrahydrofuran
THF-<i>d</i>₈	tetrahydrofuran- <i>d</i> ₈
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidine
TMSCI	trimethylsilyl chloride
TMSCN	trimethylsilyl cyanide
Tol	toluene
Tol-<i>d</i>₈	toluene- <i>d</i> ₈
UBC	University of British Columbia
USD	United States dollar
UV	ultraviolet
v:v	volume:volume

NOMENCLATURE

Organoborane compounds will be named according to the IUPAC nomenclature.

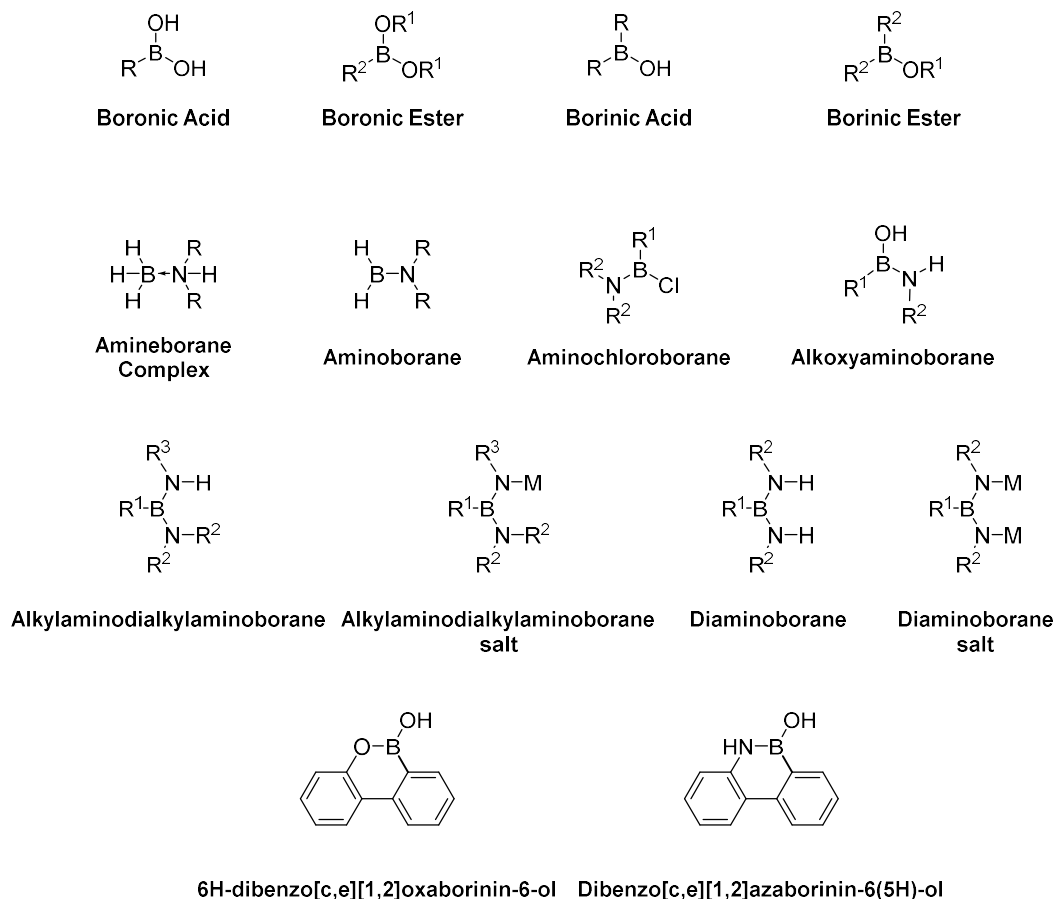


Figure 1: Organoboranes names according to IUPAC nomenclature.

In order to facilitate the comprehension of the reader, the last four organoborane compounds in Figure 1 won't be named only according to IUPAC nomenclature but will also be referred to as the names reported in literature precedent.

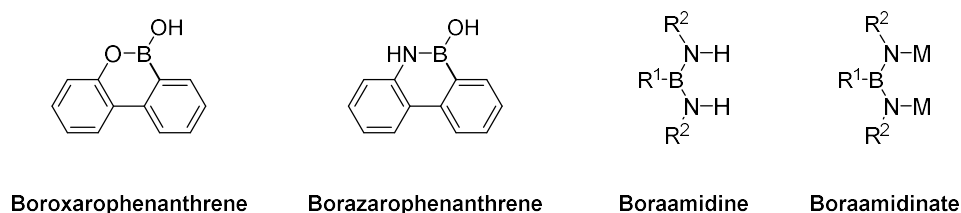


Figure 2: Organoboranes named according to literature precedent.

All the molecules drawn and described will be systematically numbered following their order of appearance in the present document while the first number corresponds to the chapter concerned.

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*This thesis is dedicated to Léonie, Thomas and Maxime
for their support and help over those three years in this accomplishment.*

GENERAL INTRODUCTION

Organic molecules containing boron functional groups are used extensively in a large variety of transformations relevant to biomedical¹ and polymer chemistry,²⁻³ as well as coupling reagents in organometallic chemistry.⁴ For example, aminoboranes have been used to address new possibilities in sustainable energy, and particularly hydrogen storage.⁵ Boranes are versatile reagents and recent work has highlighted their application as potential ligands in organometallic chemistry.⁶

Organometallic chemistry offers new possibilities by advancing developments in catalytic processes for the synthesis of small molecules containing amine moieties. Catalysts featuring transition metals, and early transition metals in particular are broadly applied in a range of industrially relevant transformations.⁷ Catalytic syntheses offer multiple advantages, such as activating traditionally unreactive bonds. They can also impact the regio-, stereo-, and chemo-selectivity of reactions by improving or changing selectivity trends. By using such controlled reactivity to advantage, new chemical products can be formed. Catalytic systems favour the formation of select products by decreasing the energy required for the desired transformation, and they can also reduce the amount of by-product generated and can even be 100% atom-economic.⁸

One of the first family of early transition metal catalysts were metallocene complexes that were described in the late 1950s.⁹ However, their challenging syntheses and modification led to the development of new non-cyclopentadienyl (Cp) catalytic systems using different ligands that are more easily tunable. Nowadays, a large variety of different catalysts have been reported using various ligands, including 1,3-chelating ligands like amidinates,¹⁰ amidates¹¹ and their derivatives. Such ligands are hemilabile, easily synthesized and modified using classic organic syntheses. Variable steric and electronic properties are more easily accessed using these ligands in comparison to Cp derivatives. 1,3-chelating ligands are introduced in the first section of this chapter, along with their different syntheses. The main applications of such ligands in catalytic hydrofunctionalization reactions are described in the second part of the chapter.

Enhanced electrophilicity of 1,3-chelating ligand was reported for heteroelement (P, S) incorporation into the ligand backbone.¹²⁻¹⁴ Complexes of these ligands are described in the last section of this chapter with the different heteroelements being highlighted. Also, their application in catalytic reactions is also presented. Enhanced electrophilicity has been noted to enhance reactivity in hydrofunctionalization reactions. For these reasons, the development of new chelating ligands using organoboranes sounds like an attractive approach for

generating a new family of electrophilic catalysts. The electropositive nature of the boron atom would impact the donor ability of the ligands which is anticipated to result in a metal complex with enhanced reactivity in catalysis processes. Few examples of 1,3-chelating ligands containing a boron atom have been reported in the literature.¹⁴⁻¹⁶ Furthermore, no application of such complexes in catalysis could be found.⁶

The first chapter will be centred on 1,3-*N,O*- and 1,3-*N,N*-chelates molecules reported in the literatures. Various chelating metal complexes will be enclosed as well as their applications in chemistry such as hydrofunctionalization reactions. 1,3-chelating ligands containing another heteroelement will then be introduced. The second chapter will study and enlighten the development of new potential 1,3-*N,O*-chelating metal complexes for catalytic purposes. A new synthetic approach using amineborane complexes will be presented. In this chapter the borinic acid synthesis will be described for the synthesis of new potential 1,3-*N,N*-chelating ligands. This study will introduce the third chapter in which potential cyclic and acyclic 1,3-*N,N*-chelating ligands will be synthesized through the use of a new synthetic approach developed in the Pucheault laboratory and the use of a reported procedure. Such potential ligands will then be tried for the hydroaminoalkylation catalysis throughout the use of group 4 and 5 metals. Lastly, the chapter four will enclose the study of a new synthetic approach for the synthesis of β -aminophosphine and bis(β -aminophosphine) ligands. This synthesis includes the use of a bis(amido)bis(amidate)titanium(IV) catalyst developed several years ago by the Schafer group. The last chapter will finally conclude on the entire research and the results.

1 CHAPTER I: 1,3-CHELATING LIGAND COMPLEXES WITH EARLY TRANSITION METALS: SYNTHESSES AND APPLICATIONS FOR HYDROFUNCTIONALIZATION

1.1 1,3-*N,O*- and 1,3-*N,N*-chelating metal complexes

In 1954, Wilkinson and co-workers reported the first examples and syntheses of bis-Cp (LX type ligand) complexes with titanium, zirconium and vanadium.¹⁷⁻¹⁸ These complexes were used in catalysis, such as the Ziegler-Natta polymerization of olefins¹⁹ and in hydroamination.²⁰ Even if Cps are attractive ligands, the synthesis of Cp ligand derivatives with varied steric and electronic properties remains laborious.²¹ In the contrary to Cp ligands, hemilabile ligands as 1,3-chelating ligands are another class of LX type ligands and they can offer the same reactivity and even greater through simplified syntheses than Cp ligands.¹⁰⁻¹¹ The development of 1,3-chelating ligands, like amidinates, guanidinates, amidates and their derivatives, as hemilabile ligands offers other more readily modified ligand motifs than Cp ligands. Their electronic and steric properties, as well as their straightforward tunability, make them interesting compounds to replace Cp ligands in catalysis.²² 1,3-chelating ligands include 1,3-*N,N*- and 1,3-*N,O*-ligand families and are known as amidinate and amidate ligands respectively (Figure 3, Figure 4).

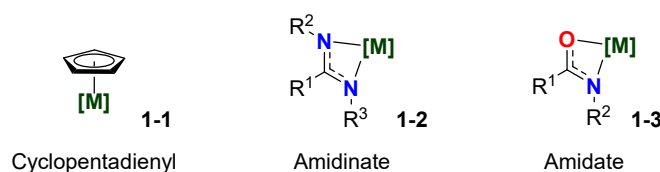


Figure 3: Representation of cyclopentadienyl, 1,3-*N,N*- and 1,3-*N,O*-chelating metal complexes.

Amidates, guanidinates and their derivatives can bind to the metal centre in different ways (Figure 4):¹⁰ κ_1 -*N* coordination mode **1-5**, μ_2 -*N,N* coordination mode **1-6** and κ_2 -*N,N* coordination mode **1-2** and **1-4**.¹⁰ There are few examples of κ_1 -*N* coordination mode reported in the literature because of severe steric hindrance due to bulky substituents, which are usually present in ligand frameworks (Figure 4, **1-5**).^{10, 22-23} However, there are plenty of articles depicting bridging and chelating coordination modes with transition metals (Figure 4).²⁴⁻³¹ Electronic and steric effects of the substituents on the N-C-N unit of amidinates and guanidinates are the factors influencing the observed coordination modes. Chelate formation is favoured with bulky substituents on the central carbon centre, and a bridging coordination

mode is observed with small substituents (Figure 4, **1-2**).³² The same substituent-phenomenon is noticed on nitrogen atoms and leads to either the chelate or the bridging coordination mode (Figure 4, **1-6**).³² In the chelate coordination mode, both nitrogen atoms are equally bound to the metal centre, but in some cases, one nitrogen atom is anionically bound to the metal centre and the lone pair of the other nitrogen atom is involved in the coordination (Figure 4, **1-4**).³³⁻³⁴ 1,3-*N,O*-chelate complexes like amidates (Figure 4), ureates and pyridonates, share similar bridging and chelate coordination binding modes to 1,3-*N,N*-chelates **1-3** and **1-9**. Due to their structural properties and substituent effects, 1,3-*N,O*-chelates have two very different κ_1 -binding possibilities: $\kappa_1\text{-N}$ or $\kappa_1\text{-O}$ (Figure 4, **1-7**, **1-8**). Those coordination mode differences have played an important role in reaction mechanisms like hydroamination and hydroaminoalkylation reactions.^{10-11, 35} A detailed description of principles 1,3-*N,O*- and 1,3-*N,N*-chelates will be disclosed in the following section (Figure 4, **1-10**, **1-11**, **1-12**). In the second section the use in the hydroamination (formation of a C-N bond) and the hydroaminoalkylation (formation of a C-C bond) reactions of such 1,3-*N,O*- and 1,3-*N,N*-chelating metal complexes will be presented. In the third part, 1,3-*N,O*- and 1,3-*N,N*-chelating metal complexes containing another heteroelement will be explored.

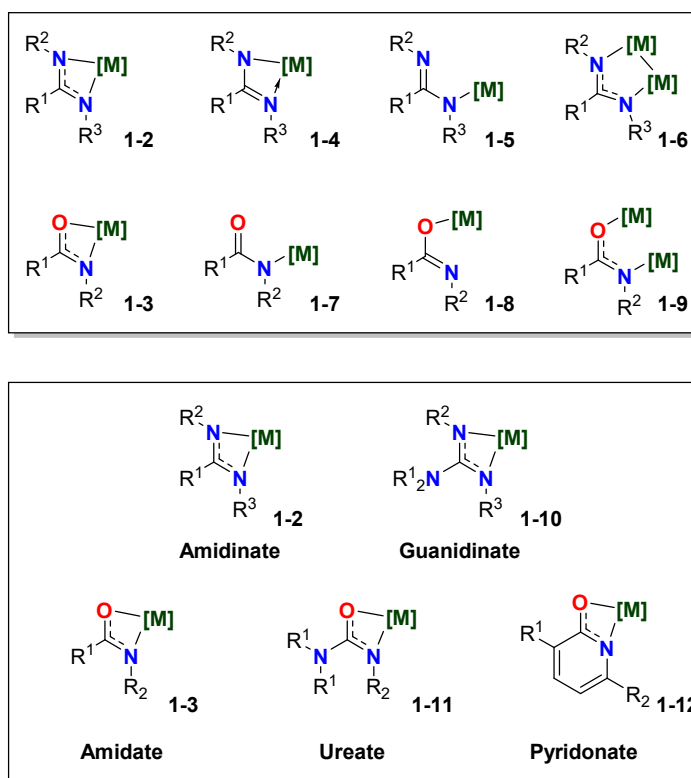
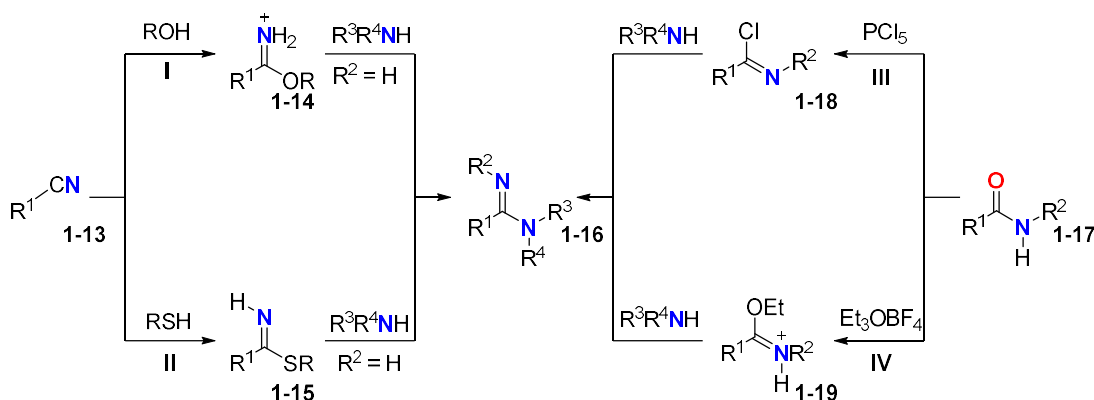


Figure 4: 1,3-*N,N*- and 1,3-*N,O*-ligands coordination modes and representation of the different ligands.^{10-11, 35}

1.1.1 1,3-*N,N*-chelating metal complexes: amidinates and guanidinates

1.1.1.1 1,3-*N,N*-chelating metal complexes: amidinates

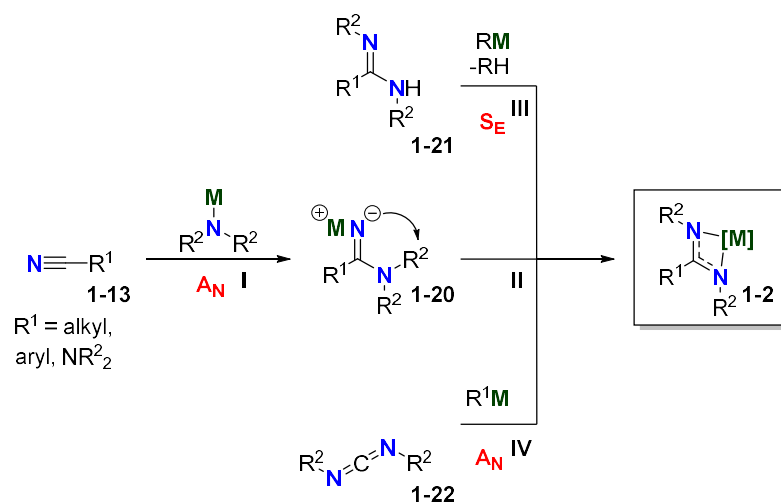
Amidines were first synthesized by Gerhardt in 1858 by reaction of anilines with *N*-phenylbenzimidyl chloride.³⁶ The first use of amidine as a ligand for coordination chemistry was reported in 1973 by Sanger.³⁷ The author described the first *N*-silylated benzamidine derivative as its lithium salt prepared by the addition of lithium bis (trimethylsilyl) amide to benzonitrile.³⁸⁻⁴⁰ The most common methods to prepare amidines are from nitriles and amides. Alternative methods include iminium cations as intermediates, that can then react with a secondary amine nucleophile.⁴¹ The Pinner reaction (I) was first employed to prepare amidines **1-16** from nitriles **1-13** in presence of an alcohol and an acid (Scheme 1). Modification of Pinner reaction (II) by replacing the alcohol by a thiol in order to form the thioamide ester **1-15** intermediate was the second approach to generate amidine **1-16** from nitriles **1-13**.⁴¹ The interest of this last approach is to form a better leaving group which favored the formation of the desired product. The production of amidines **1-16** from corresponding amides **1-17** can be realized in presence of either phosphorus pentachloride (III) or triethyloxonium tetrafluoroborate (IV). They both activate the amide **1-17** to form highly reactive imidic ester intermediates **1-18** and **1-19**.⁴¹



Scheme 1: Most common methods for amidine synthesis using nitriles or amides as starting materials.⁴¹

Amidinate metal complexes are generally synthesized through three pathways:¹⁰

- the nucleophilic addition of amide substrate onto the carbon of the nitrile derivatives (I, II);⁴²
- N-H deprotonation to form the anionic chelate (III);⁴²
- alkyl/aryl-metal nucleophilic addition onto *N,N*-disubstituted carbodiimide (IV).⁴²



Scheme 2: Main reaction pathways for the formation of 1,3-*N,N*-chelating metal complexes.⁴²

The first amidinate metal complexes were reported to have a bridging coordination mode with the early transition metal molybdenum (Figure 5, **1-23**).¹⁰ The first titanium metal complex was synthesized from *N*-silylated amide complexed to titanium(IV).²⁸ Since then other early transition metals such as zirconium and tantalum amidinate complexes have been reported (Figure 5, **1-24**, **1-25**).^{10, 34} Amidinates have largely been developed for olefin polymerization catalysis with various different metals such as aluminium,⁴³⁻⁴⁴ nickel⁴⁵⁻⁴⁷ or lanthanides.⁴⁸ Moderate polymerization activity of propylene and ethylene has been demonstrated with early transition metal amidinate precatalysts like titanium, zirconium and hafnium.⁴⁹⁻⁵⁰ The first stereospecific living Ziegler-Natta polymerization of α -olefin was achieved by using such titanium amidinate complexes with MAO as cocatalyst.⁵¹⁻⁵⁴ The polymerization of polar monomers like methyl methacrylate or ϵ -caprolactone were also reported, but only with lanthanide metals and not with early transition metals.⁵⁵

More recently, 1,3-amidinate ligands have been developed for hydroamination or hydroaminoalkylation reactions with early transition metals. These reactions consist in the formation of new carbon-nitrogen (C-N) or carbon-carbon (C-C) bonds respectively. C-N bond results from hydroamination reaction, and the product formed are either branched or linear products. Hydroaminoalkylation reaction forms C-C bond and the product obtained can also be linear or branched. Compared to 1,3-*N,O*-chelating ligands, 1,3-amidinate ligands were described as catalysts being less reactive for hydroamination with group 4 metals (Figure 5, **1-26**).⁵⁶ Directly derived from 1,3-*N,N*-amidinates, formamidinates complexed with titanium were recently revealed by Doye and co-workers as highly reactive catalyst for hydroaminoalkylation reaction (Figure 5, **1-27**).⁵⁷ The particular advantage of this ligand is the ease of preparation as well as the low cost of synthesis.⁵⁸ Resulting catalysts have been

reported to exhibit high activity for intermolecular hydroaminoalkylation reaction of unactivated and sterically hindered disubstituted olefins.^{57, 59} Amidinates are versatile ligands in the development of catalysts for organic synthesis. Their enhanced properties in terms of variable chelating modes to the metal, as well as their capacity to bear unsymmetrical substituted groups on nitrogen atoms leading to the generation of chiral complexes ($R^1 \neq R^2 \neq R^3$)²² make them a great alternative to Cp ligands.

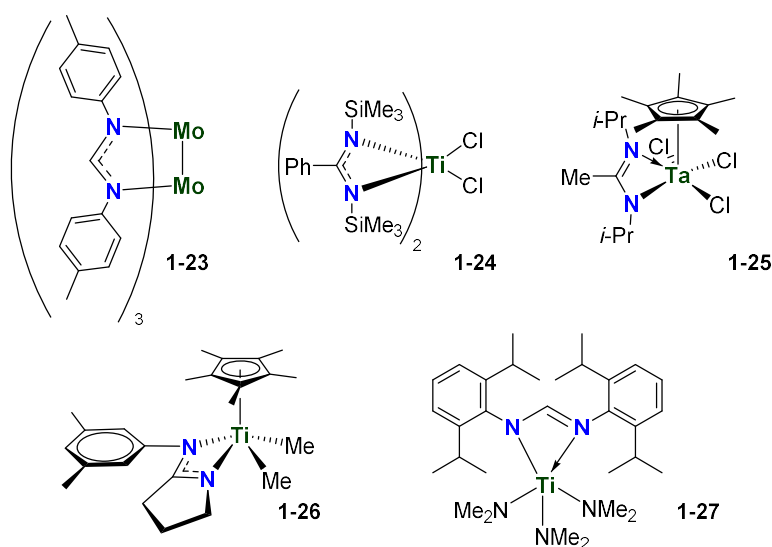


Figure 5: Examples of 1,3-N,N-amidinate ligands reported in the literature complexed to early transition metals.^{10, 34, 50, 56-57, 59}

1.1.1.2 1,3-N,N-chelating metal complexes: guanidates

Guanidinate ligands are similar to amidinate ligands in that they share electronic and steric properties; and metal complexes are formed using the same reactions.¹⁰ The first guanidinate was reported in 1970 by Lappert and co-workers.⁶⁰ Even if some guanidines are commercially available, the synthesis of guanidines is usually easy and straightforward.⁶¹ The most successful synthesis of guanidine **1-29** is an addition-elimination reaction (I) of a primary amine on an activated guanidine precursor **1-28** (Scheme 3).⁶¹ An example of this approach (II) uses a thiourea as starting material **1-31**. A stoichiometric amount of HgCl₂ Lewis acid is first employed to desulfurize and to convert thiourea into an electrophilic carbodiimide intermediate, which reacts with a primary amine **1-30** (Scheme 3).⁶² Recent synthetic systems describe a greener approach to synthesize guanidines: the use of a metal-catalysed system with ZnO⁶³ or the use of polymer-supported reagents to facilitate the removal of undesired chemicals that are starting material, solvents and by-products.⁶⁴

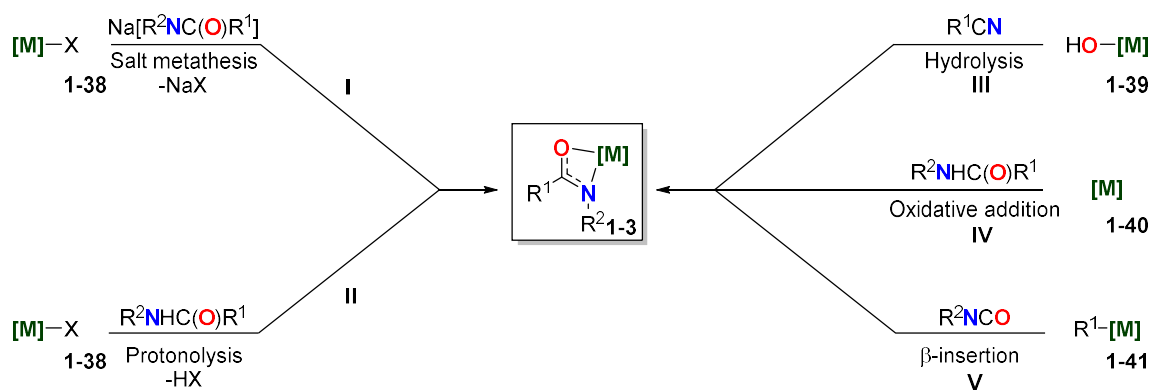
coordinate with main group elements or transition metals, as 1,3-chelates.¹⁰ But, such delocalisation results in the enhancement of the ligand with basicity, and the ligand has the ability to stabilize metals with higher oxidation states in comparison to amidinate variants.¹⁰ Like 1,3-*N,N*-amidinates, guanidinate have been applied to olefin polymerizations with metals like calcium,⁶⁹ lanthanides,⁴⁸ or zirconium.⁷⁰ 1,3-*N,N*-guanidinate early transition metals have also been used for intramolecular hydroamination of alkene like their amidinate congener. However their catalytic activity was reported to be lower than both amidinate ligands and 1,3-*N,O*-chelates (Figure 6).^{67, 71-73}

1.1.2 **1,3-*N,O*-chelating metal complexes: amidates, ureates, pyridonates**

1,3-*N,O*-chelating complexes can be synthesized with the desired proligand in hand (*i.e.* amide, pyridone, urea),⁷⁴ and several pathways are possible to obtain the desired metal complexes:⁷⁴

- salt metathesis reaction, requiring an initial deprotonation of the ligand prior to the complexation to the metal centre (path I, Scheme 4) with subsequent elimination of salt, which acts as a driving force for the reaction;
- protonolysis reaction, involving the reaction of the proligand with a metal complex with basic ligands (path II, Scheme 4); this reaction can be in equilibrium between the resulting complex and the proligand depending on their respective pKas;
- nitrile hydrolysis with a metal alkoxide moiety (path III, Scheme 4);⁷⁴
- oxidative addition onto the nitrogen-hydrogen amide bond (path IV, Scheme 4);
- isocyanate insertion into the metal alkyl/aryl/amide bond (path V, Scheme 4),⁷⁵ the insertion reaction onto the metal-element bond is in equilibrium between the 1,3-*N,O*-chelate and the starting materials.⁷⁵

Of these routes salt metathesis and protonolysis reactions are generally preferred to obtain early transition metal 1,3-*N,O*-chelated complexes.⁷⁴



Scheme 4: Generals 1,3-*N,O*-chelating metal complexes synthesis routes.^{35, 74}

1,3-*N,O*-chelated complexes can adopt five different geometric isomeric forms upon formation of monomeric bis(amidate) complexes (Figure 7). These variable bonding modes highlight the challenge in rigorously characterizing this class of complexes in solution phase as the various isomers can display complex equilibria.¹¹ Furthermore, such 1,3-*N,O*-ligands are also known to adopt a κ^1 -*O*-bound bonding motif.¹¹ Such dynamic behaviour points toward the opportunity with these ligands for adopting variable metal coordination modes to accommodate incoming substrates or stabilize reactive species upon elimination of product for catalytic turnover.

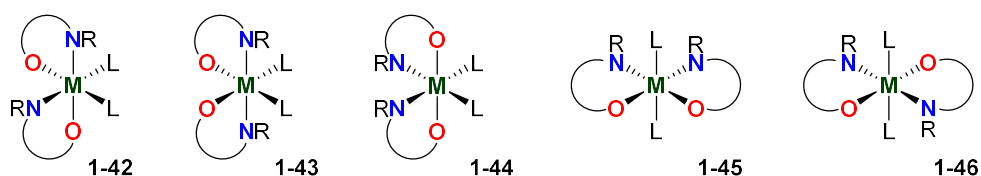


Figure 7: Different coordination modes for 1,3-*N,O*-chelating metal complexes with L = chloro, alkyl or amido.^{11, 76}

1.1.2.1 1,3-*N,O*-chelating metal complexes : amidates

Amide proligands are generally prepared from acyl chlorides by substitution of chloride with amine.⁷⁷ Amidate ligated complexes were originally obtained by reacting organometallic compounds with isocyanate.⁷⁸ Nowadays, the generation of a diverse family of complexes take advantage of the tunable ligand set that is installed by either a protonolysis or salt metathesis reaction.⁷⁴ The first amidate metal complexes were reported by Cotton and co-workers in 1970, with transition metals like cobalt, platinum,⁷⁹ rhodium⁸⁰ and molybdenum as bridged metal complexes (Figure 8, **1-47**).⁸¹ Based on the isocyanate insertion reaction, different amidate metal complexes were prepared using early transition metals from group 4 (Ti, Zr)⁸²⁻⁸⁴ and group 5 (Ta, Nb)⁷⁸ (Figure 8, **1-48**, **1-49**, **1-50**). Different

complexes were then isolated and characterized, however their reactivity and application in catalysis remained unexplored until the early 2000s. They regained interest in 2001 when Arnold reported the first titanium amidate complex (Figure 8, **1-51**).⁸⁵ This metal complex possesses two titanium centres coordinated to two bridging amidate moieties, and exhibits moderate activities as an ethylene polymerization catalyst.⁸⁵ That same year Lin and co-workers isolated a mono-amidate complex coordinated to aluminium (Figure 8, **1-52**), and showed that the amidate complex can adopt multiple coordination modes as presented in the introduction of this section (Figure 7).⁸⁶

In 2001 Odom and co-workers published the use of tetrakis(dimethylamido)titanium(IV) as a catalyst for the hydroamination of alkynes.⁸⁷ This simple commercially available complex was the first non-Cp based precatalyst used for this reaction.⁸⁸⁻⁹² The work of Bergman and co-workers later highlighted the potential of the first bis(sulfonamide) titanium precatalyst for the hydroamination of alkynes and allenes.⁹³ Based on these works, Schafer and co-workers developed the first amidate titanium complex for *intra*- and *inter*-molecular hydroamination catalysis of alkynes (Figure 8, **1-53**, **1-54**).⁹⁴⁻⁹⁵ These 1,3-*N,O*-amidates metal complex exhibit various advantages:

- they can easily be synthesized using amide chemistry and be tuned sterically or electronically by varying substituents,⁹⁵⁻⁹⁶
- they are bidentate ligands that adopt different coordination mode, which is not possible for Cp-based ligands,⁸⁶
- they are suitable precatalyst for *intra*-molecular hydroamination of alkenes,⁹⁷⁻⁹⁸ allenes,⁹⁹ and alkynes and *inter*-molecular hydroamination of alkynes,^{11, 94-95, 100-102}
- they can easily be tuned to achieve asymmetric hydroamination reaction of aminoalkenes;^{98, 103-106}
- they can preferentially form either the branched or the linear product depending of the substituents on the 1,3-chelate ligand.¹⁰⁷

As recently reported by Schafer and co-workers, 1,3-*N,O*-amidate complexes of tantalum showed high reactivity for a different hydrofunctionalization reaction, hydroaminoalkylation.¹⁰⁸⁻¹¹⁰ The initial report of this transformation shows that Cp or alkoxide early transition metal complexes have reduced catalytic activity for this reaction,¹¹¹ whereas the generation of an electrophilic complex increases the activity of the catalytic species.¹¹² Similar electronic effects have also been observed in early transition metal catalysed hydroamination reactions.¹¹⁰ Titanium amidate metal complexes with high reactivity for ethylene polymerization to access high molecular weight polymers were published by

Schafer and coworkers.¹¹³ Zirconium amidate complexes were also reported as olefin polymerization catalysts (Figure 8, **1-54**).¹¹³

The reaction between bis(amidate)bis(amido)titanium(IV) and a primary amine forms a bis(amidate) imido complex. Mechanistic investigations propose that this imido complex is a key reactive intermediate for the hydroamination reaction (Figure 8, **1-55**).¹¹⁴ As previously mentioned, tantalum amidate complexes have been used for hydroaminoalkylation catalysis. In this case the amidate ligand supports the formation of tantallaziridine as a key reactive intermediate for the hydroaminoalkylation reaction (Figure 8, **1-56**).^{108, 115} Amidate ligand complexes have thus been great catalysts and useful systems for stoichiometric investigations to confirm the formation of isolable reactive intermediates for both hydroamination and hydroaminoalkylation reactions.¹¹⁴

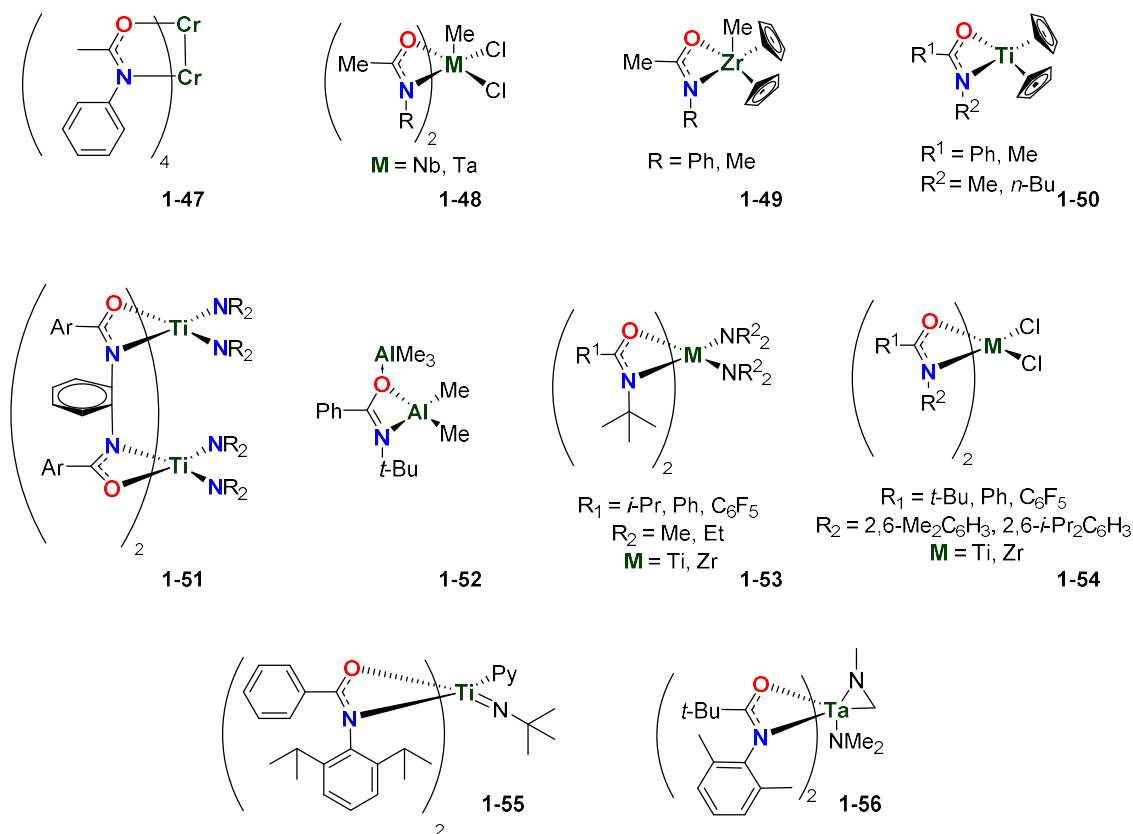
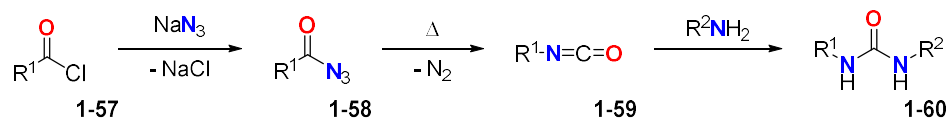


Figure 8: Example of different amidate metal complexes reported in the literature.^{78, 81-82, 84-86, 94, 109, 114, 116}

1.1.2.2 1,3-*N,O*-chelating metal complexes: ureates

Ureate complexes are synthesized from their corresponding ureas, which can be obtained using isocyanate chemistry.⁶⁰ Isocyanate **1-60** compounds are moisture sensitive and they are usually generated *in situ* by a Curtius rearrangement.¹¹⁷ For example, an

isocyanate is obtained in the reaction of an acyl chloride **1-57** with an azide (Scheme 5), which then reacts with a secondary amine to give the corresponding urea **1-60**.¹¹⁷ Since the synthesis of isocyanate intermediates is laborious, the generation of diverse ureate metal complexes remains complicated. Lappert and co-workers reported the first examples of ureate metal complexes by the insertion of an isocyanate into the metal-amido bond.⁷⁵ However, the isocyanate approach is not the most relevant route for the synthesis of ureate metal complexes.⁶⁰ In order to avoid the isocyanate intermediate, Randad and Majer described in 1994 a one-pot synthesis of urea from the addition of triphosgene to a primary or secondary amine.¹¹⁸ This approach allows for the generation of a diverse array urea ligands. Such ureas can then be deprotonated and installed onto a metal centre by protonolysis or salt metathesis.



Scheme 5: Urea synthesis involving isocyanate intermediate.¹¹⁷

Various ureate metal complexes have been reported with early to late transition metals. A large majority of ureate complexes have been obtained with late transition metals, such as κ_1 -*N*-platinum ureate, κ_1 -*N*-rhenium ureate, or κ_2 -*N,O*-molybdenum or tungsten complexes (Figure 9, **1-63**).^{60, 119-124} Although ureates and amidates are similar, ureates can have additional coordination modes.¹²⁵ Indeed, ureates display a second electron-donating amino moiety in equilibrium between two mesomeric forms, and are related to guanidinate chelating complex (Figure 9, **1-61**, **1-62**).¹⁰ Therefore, different ureate derivatives can form depending upon the coordination mode of the chelate. For example the mesomeric forms can result in a κ_2 -*N,N* mode, which was confirmed by Richeson and co-workers who reported a ureate tungsten complex (Figure 9, **1-64**).^{60, 121, 126} According to the authors, the rigidity of the ligand forces the coordination through the nitrogen atom rather than the oxygen centre.¹²⁶

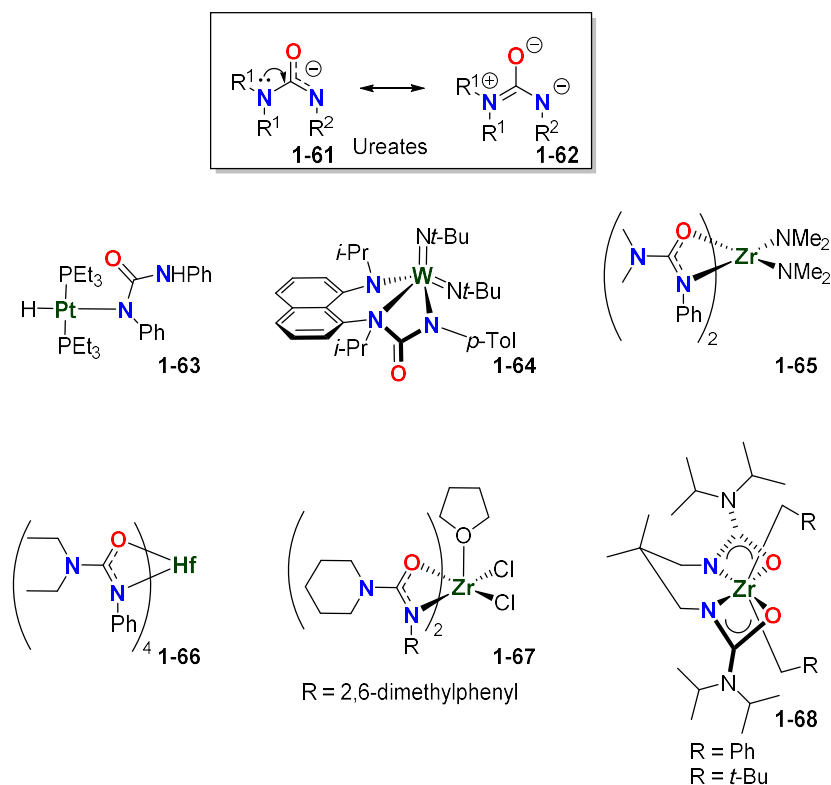


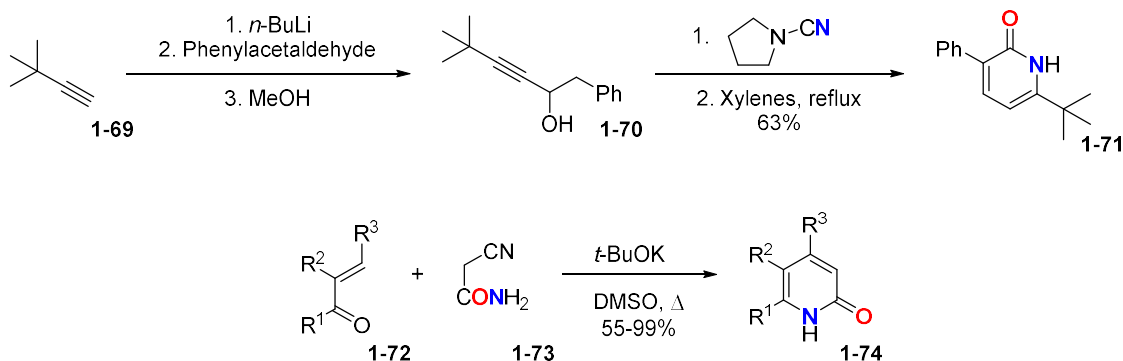
Figure 9: Examples of early and late transition metal ureate complexes reported in the literature.^{119-120, 122, 126-127}

However, κ_2 -*N,O* ureate complexes of early transition metals were also reported in the early 2000s by Xie and co-workers¹²⁰ and Huang and co-workers,¹¹⁹ who exposed respectively complexes of bis(ureate) zirconium¹²⁰ and tetrakis(diethylamido) hafnium (Figure 9, **1-65**, **1-66**).¹¹⁹ Based on their work, Schafer and co-workers developed new bis(ureate) zirconium complexes and new tether ligands to reduce the prevalence of solution-phase isomerization equilibria (Figure 9, **1-68**).¹²⁷ A notable reaction that can be accomplished using a tethered zirconium ureate complex includes alkyne dimerization to afford selective *Z*-enynes.¹²⁸ Generally ureate complexes have similar or better reactivity than amidate catalysts for hydroamination¹²⁹⁻¹³¹ and hydroaminoalkylation (Figure 9).¹³²⁻¹³³

1.1.2.3 1,3-*N,O*-chelating metal complexes: pyridonates

The last class of 1,3-*N,O*-ligands are 2-pyridone derivatives. These ligands are synthesized, as described by Overman and co-workers, in two straightforward reactions (Scheme 6).¹³⁴ The first approach involves the lithiation of the terminal alkyne **1-69** with *n*-BuLi, followed by the addition of phenylacetaldehyde and subsequent quench with methanol. The resulting propargylic alcohol **1-70** is treated with 1-cyanopyrrolidine and is then refluxed in xylene to give 3,6-pyridone derivatives (Scheme 6, **1-71**). More recent research has illustrated the synthesis of substituted 6-pyridones (**1-71**) and their easily modified structure

using enone (**1-72**) and cyanoacetamide (**1-73**) in the presence of potassium *tert*-butoxide in DMSO (Scheme 6).¹³⁵



Scheme 6: 2-pyridone syntheses pathways described in the literature.¹³⁵

The first pyridonate metal complexes were reported by Cotton and co-workers in 1978,¹³⁶ and revealed dimeric complexes of chromium, molybdenum and tungsten after reaction of four equivalents of methyl pyridone with one equivalent of $M(\text{CO})_6$ where $M = \text{Cr}, \text{Mo}$ or W (Figure 10, **1-77**). Some examples of bridging or chelate coordination modes of pyridonate complexes have also been reported with late transition metals of Groups 8¹³⁷⁻¹³⁸ and 9.⁹⁶⁻⁹⁷ Compared to the other families of 1,3-*N,O*-chelates, the enhanced thermal and chemical stability of pyridonate complexes are attractive features for their on-going development.

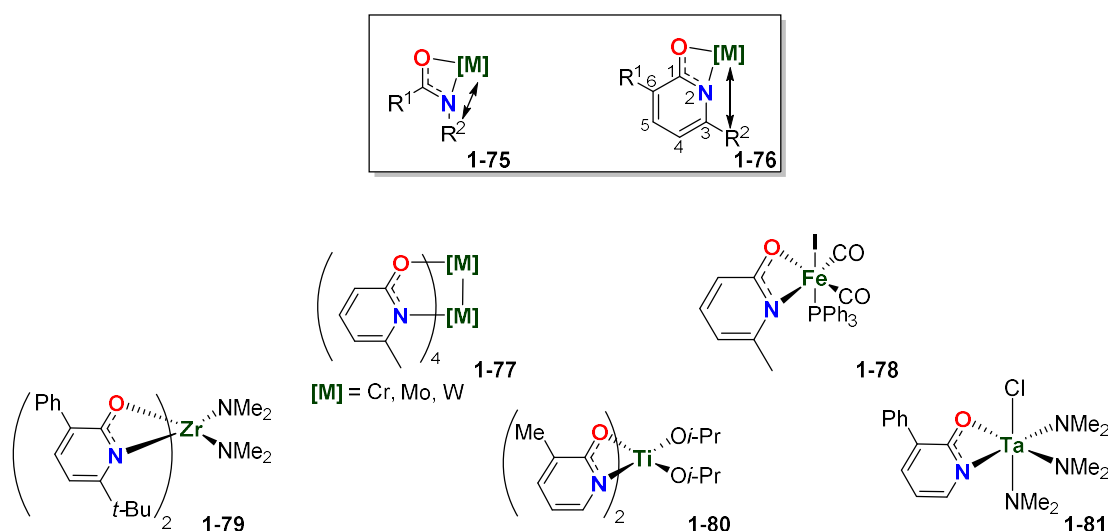


Figure 10: Examples of pyridonate early and late transition metal complexes.¹³⁷⁻¹⁴²

The electronic withdrawing effects of the pyridonate ligand result in a more electrophilic complex when compared to the amidate derivatives.¹⁴³ As mentioned previously,

enhancement of the electrophilicity of the metal centre is advantageous for high catalysis activity. Furthermore, pyridonates can bear substituents on position three and six, which are more distant from the metal centre, and thus offer new steric profiles to be explored in catalysis (Figure 10, **1-75**, **1-76**).¹⁴¹ Indeed since the early transition metal hydroamination of sterically hindered aminoalkenes is known to be limited by large steric bulk around the metal centre,¹⁴¹ pyridonate complexes have been examined as a new catalyst family for that reaction.¹⁴¹

Their catalytic behaviours are correlated with the influence of electronic and steric hindrance of the pyridonate ligands. When κ_1 -species are involved in catalytic cycles, they exhibit more reactivity than amidate ligated variants. This was confirmed through both experimental and computational modelling.⁷⁶ Such properties were reported for hydroaminoalkylation,¹⁴¹ and various pyridonate complexes of early transition metals, such as titanium and tantalum, were developed to catalyse this reaction (Figure 10, **1-79**, **1-81**).^{13,}

139, 144

The high reactivity of early transition metal pyridonate **1-80** complexes have also been studied for ring-opening polymerization catalysis involving ϵ -caprolactone and *rac*-lactide to afford homopolymers, block and random copolymers (Figure 11, **1-82**, **1-83**, **1-84**).^{140, 145} These 1,3-*N,O*-pyridonate titanium complexes show competitive results compared to other reported titanium catalyst.¹⁴⁶⁻¹⁴⁹

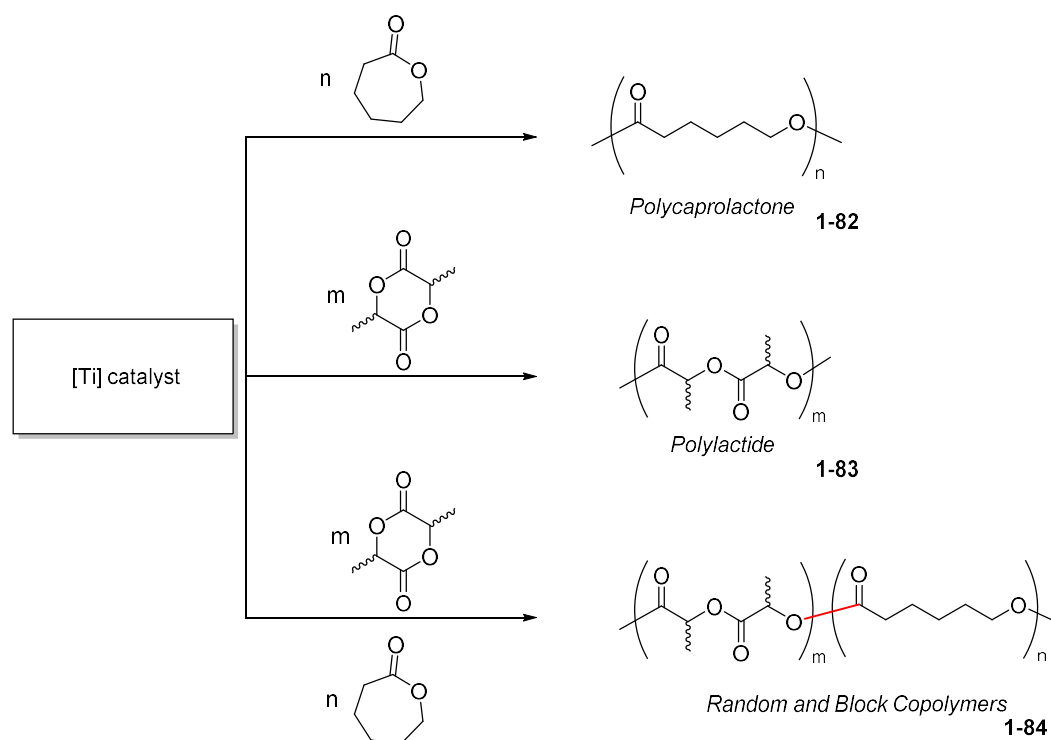


Figure 11: Polymer application of 1,3-*N,O*-chelating titanium complexes.^{140, 145}

To conclude a variety of 1,3-*N,O*- and 1,3-*N,N*-chelated early transition metal complexes have been synthesized and applied in catalysis. According to their structures, they have tunable properties, such as electronic features, steric hindrance and variable coordination modes, to offer new catalysis opportunities for hydroamination and hydroaminoalkylation reactions.

1.2 Applications as catalysts in hydrofunctionalization reactions

Since the last century, group 4 metal complexes have been widely used in catalysis due to their useful reactivity, abundance in the Earth's crust and their low cost.^{93-95, 150} Notably, they have been used in various organic transformation as for instance in aldol additions.¹⁵¹ Mukaiyama developed in 1973 the catalytic aldolisation between a silyl enol ether and an aldehyde, using titanium(IV) tetrachloride as active catalytic species.¹⁵¹ Prior to this discovery, titanium(IV) tetrachloride has been largely reported for the Ziegler's polymerization of ethylene.¹⁵² Propene polymerization was further reported by Natta,¹⁵³ and the next decades several research groups promoted various catalytic systems with either titanium or zirconium metals for ethylene, propene or styrene polymerisations.¹⁵⁴⁻¹⁵⁵ In the 1990s the groups of Bergman, Livinghouse and Doye found that group 4 metal complexes, notably zirconium and titanium complexes, could also be useful for hydrofunctionalization catalysis. Hence, they reported first the possibility of group 4 and 5 metals for the hydroamination reaction and later for the hydroaminoalkylation reaction.⁹⁰⁻⁹²

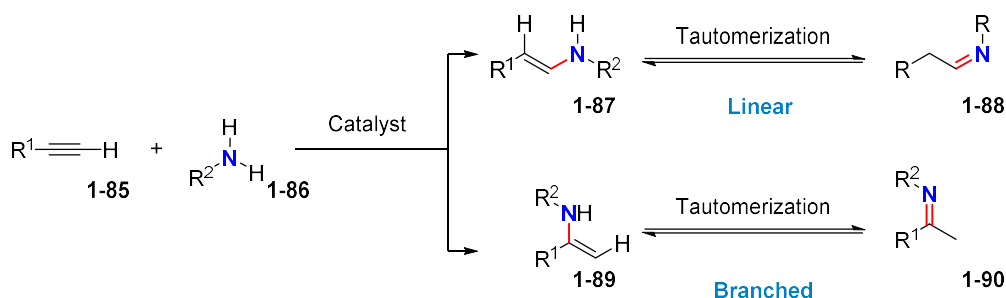
1.2.1 *Early transition metal complexes: application in hydroamination*

1.2.1.1 *General features of the hydroamination*

Hydroamination has become widely explored for the synthesis of molecules containing nitrogen.^{100-101, 107} Hydroamination of alkynes with late and early transition metals is generally easier compared to alkene hydroamination because olefins have lower reactivity due to less electron density on the unsaturated carbon-carbon bond.¹⁰⁷ However, recent studies have shown that 1,3-chelated complexes of group 4 metals (Ti and Zr) exhibit tremendous activity in alkene hydroamination due to their electrophilic properties.¹⁰⁷

The hydroamination reaction consists of an addition of nitrogen and hydrogen atoms across an unsaturated carbon-carbon bond such as an alkyne, alkene, allene, and dienes (Scheme 7). In the case of alkyne substrates, the resulting enamine **1-87** and **1-89** molecule can tautomerize to the imine product **1-88** and **1-90** (Scheme 7).¹⁰⁰ Late transition metals

generally proceed with branched regioselectivity whereas early transition metals follow either linear or branched regioselectivity, depending on the metal complex and the substrate used.¹⁰⁷



Scheme 7: Hydroamination reaction general equation.¹⁰²

The alkyne hydroamination mechanism was first studied by Bergman in 1992 using kinetic experiments while monitoring the reaction by NMR spectroscopy (Figure 12).¹⁵⁰ The mechanism proposed by the authors is applicable to early transition metals of group 4 and 5. The mechanism starts with the reaction between the early transition precatalyst **1-91** and the primary amine to form the reactive metal imido species **1-92**. After coordination of the alkyne to the metal catalyst there is a reversible [2+2]-cycloaddition to form an azametallacyclobutene **1-94**. Subsequent protonation of the metal-carbon bond of this intermediate by another equivalent of primary amine forms the enamide-amide complex intermediate (Figure 12, **1-95**). This precatalyst species can then be regenerated by α -elimination to form the hydroamination product **1-96**. The latter enamine product can then tautomerize to form the more stable imine derivative (Figure 12, **1-97**).¹⁰¹

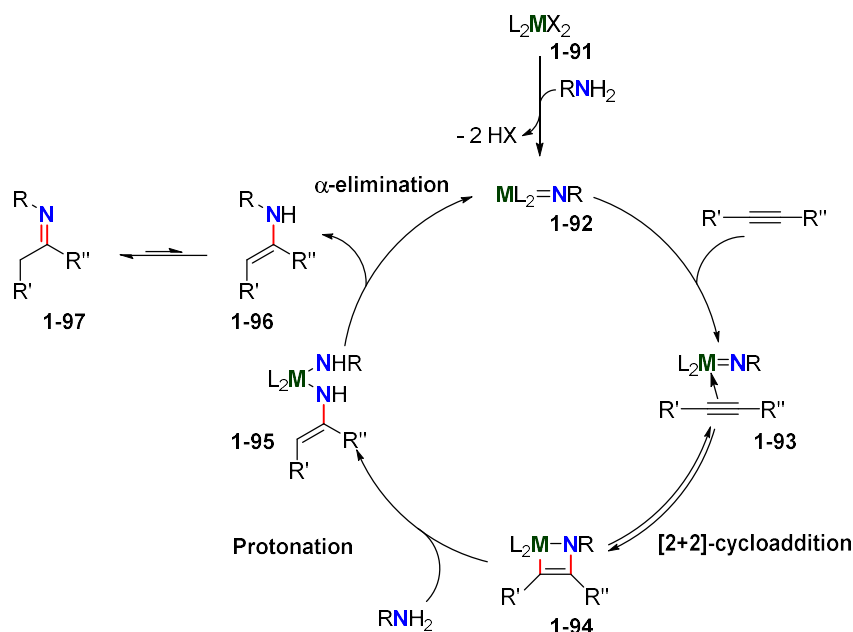
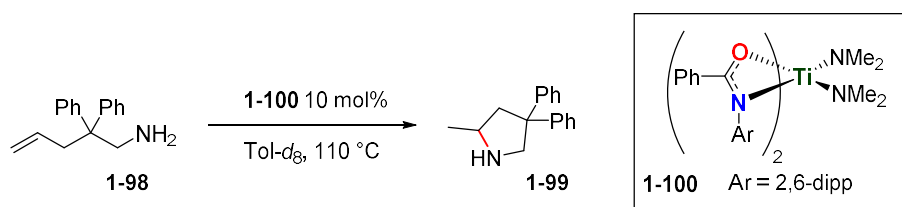


Figure 12: Proposed simplified alkyne hydroamination mechanism with group 4 and 5 transition metal catalysts.¹⁵⁰

1.2.1.2 Hydroamination application in synthesis using 1,3-N,O-chelating metal complex pre-catalysts

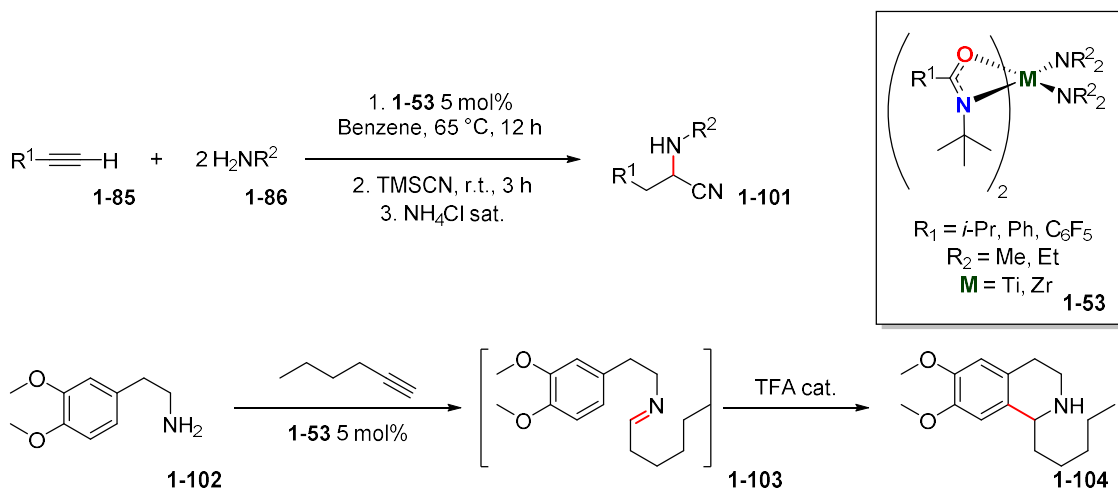
As previously mentioned, the hydroamination of olefins is more challenging and the substrate scope is more restricted. High negative entropy is generally observed for *inter*-molecular hydroamination reaction of olefins, which is not in favour for the reaction to proceed. However, aminoalkenes as **1-98** have lower entropic impact and allow the reaction to work well *via intra*-molecular hydroamination reaction to form products **1-99** (Scheme 8).⁹⁷ ¹⁰⁷ Based on this reactivity, asymmetric hydroamination was reported by using group 4 metal catalysts containing chiral ligands, the cyclization of aminoalkenes could be achieved with high enantioselectivities.^{98, 156-157}



Scheme 8: *Intra*-molecular hydroamination reaction of aminoalkene catalyzed by 1,3-N,O-chelating metal complexes.⁹⁷

Alkynes have shown high potential in synthetic chemistry by the hydroamination of terminal alkyne for the formation of bicyclic nitrogen-containing skeletons. Hydroamination has been applied for both the total synthesis of alkaloids, and the synthesis of isoquinolines

through intermolecular hydroamination of alkynes followed by Pictet-Spengler cyclization catalyzed with acid (Scheme 9, **1-104**).^{95, 158} The aldimine intermediate formed during the hydroamination mechanism can also be used in a one-pot synthesis when reacted in presence of TMSCN to realize a tandem hydroamination, Strecker reaction (Scheme 9, **1-101**).¹⁰²

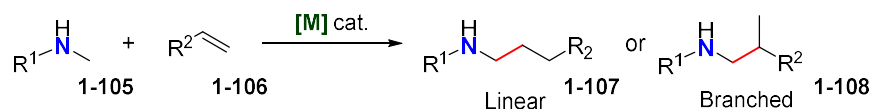


Scheme 9: Application of hydroamination reaction in multistep reaction sequences.^{95, 102, 159}

1.2.2 1,3-chelating early transition metal complexes: application for hydroaminoalkylation

1.2.2.1 Introduction on hydroaminoalkylation reaction

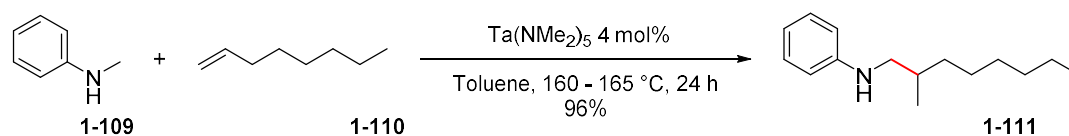
Hydroaminoalkylation was reported for the first time in 1980 and 1983 by Maspero and Nugent for the α -alkylation of dimethylamine with olefins in the presence of pentakis(dimethylamido)niobium(V) or pentakis(dimethylamido)tantalum(V) as catalyst.¹⁶⁰⁻¹⁶¹ Harsh conditions were often required with 160 to 200 °C for 24 to 150 hours needed to obtain at least 38% of the desired product. Hydroaminoalkylation could result in two different products; the linear or the branched product (Scheme 10, **1-107**, **1-108**).¹⁶² Regioselectivity in this reaction can be influenced by choosing carefully the desired starting amine **1-105**, olefin **1-106** and catalyst. For example, late transition metals generally produced linear amines for both electronic and steric reasons.¹⁶³ The most common product is the branched amine product with early transition metal catalysts such as titanium or tantalum.^{112, 164}



Scheme 10: α -alkylation of disubstituted amines in presence of olefin catalyzed by early transition metals.¹⁶²

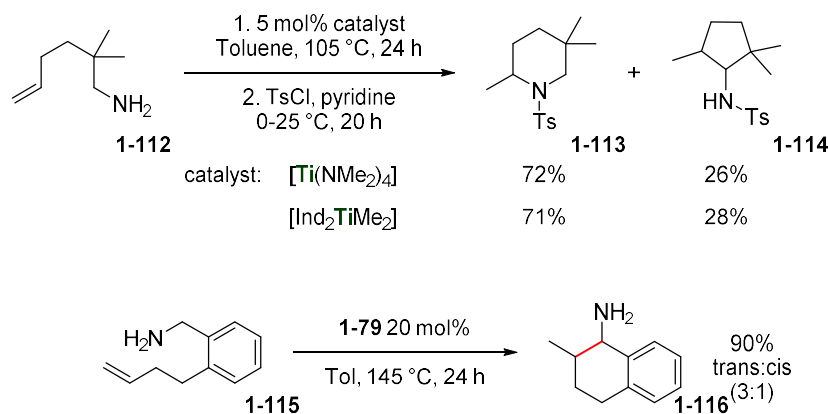
The first report of hydroaminoalkylation catalysis with late transition metals was in 1998 by Jun and co-workers where they report the use of $\text{Ru}_3(\text{CO})_{12}$.¹⁶⁵ Chatani and co-workers extended the scope of metals by using iridium catalyst for this transformation.¹⁶⁶ Using late transition metals, the hydroaminoalkylation mechanism goes through a metal-hydride insertion mechanism¹⁶⁶ and requires the use of directing or protecting groups on the nitrogen.¹⁶⁷ This reaction was then reinvestigated in 2007 by Herzon in Hartwig through the use of early transition metals.¹¹¹⁻¹¹² Contrary to late transition metals, no protecting groups or directing groups are required for the transformation, thus having various economic and environmental advantages. Such catalyze involve another mechanism processing through a metallaziridine mechanism presented (*vide infra*) instead of a metal-hydride insertion process.¹⁶²

Herzon and Hartwig described an efficient synthesis for the α -functionalization of amine **1-109** with unactivated olefins **1-110** using pentakis(dimethylamido)tantalum(V).¹¹¹⁻¹¹² They managed to achieve the hydroaminoalkylation reaction at lower temperatures in high yield in a shorter time due to the use of an activated *N*-methylaniline amine substrate. The branched hydroaminoalkylation product **1-111** from *N*-methylaniline and 1-octene was obtained in 96% within 24 hours in toluene at 160-165 °C with 4 mol% $\text{Ta}(\text{NMe}_2)_5$ catalyst loading (Scheme 11).¹¹¹



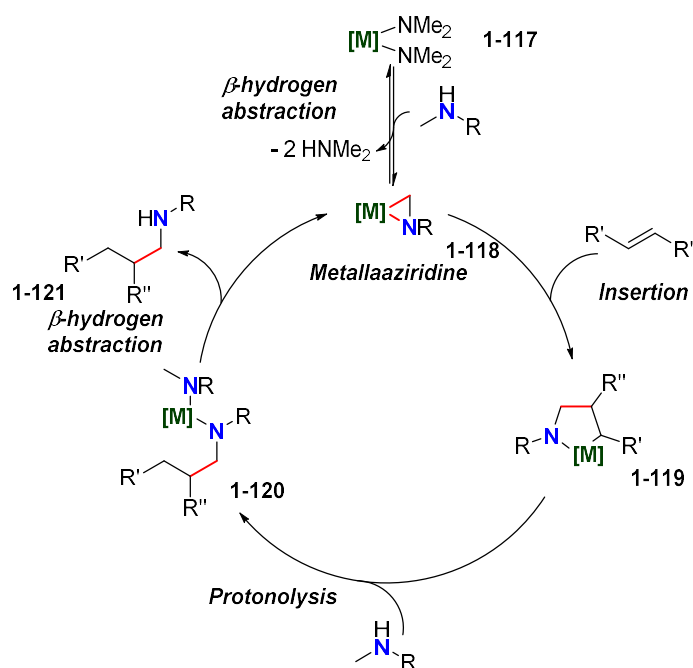
Scheme 11: Alkylation of *N*-methylaniline with 1-octene using pentakis(dimethylamido)tantalum(V) catalyst.

Doye observed in 2008 a C-H activation process using tetrakis(dimethylamido)titanium(IV) for intramolecular alkene hydroamination (Scheme 12). The same year, Schafer disclosed the first bis(pyridonate) zirconium dimethylamido complex showing catalysis activity for intramolecular α -alkylation.¹⁶⁸ In this reaction a substrate containing both a primary amine and terminal olefin reacted in the presence of a zirconium precatalyst to form bicyclic framework substituted primary amine **1-116** in high yield (Scheme 12).

Scheme 12: First α -functionalization of amine with titanium-catalyst.¹⁶⁹⁻¹⁷⁰

1.2.2.2 Hydroaminoalkylation mechanism

In 1983, Nugent proposed a catalytic mechanism based on kinetic experiments. This reaction proceeds through a metallaziridine as a key intermediate (Scheme 13).¹⁶⁰ The mechanism consists of amine elimination achieved by β -hydrogen abstraction to form the metallaziridine intermediate (Scheme 13, **1-118**). Insertion of the olefin into the metal-carbon bond then occurs to give a 5-membered metallacycle (Scheme 13, **1-119**). A second equivalent of secondary amine subsequently reacts with the 5-membered metallacycle to form the intermediate **1-120**. A second β -hydrogen abstraction releases the desired product **1-121** and reforms the metallaziridine (Scheme 13, **1-118**). Group 5 metal complexes generally follow this hydroaminoalkylation reaction mechanism.¹⁷¹

Scheme 13: Hydroaminoalkylation reaction mechanism involving group 4 or 5 transition metals.¹⁶⁰

Hydroaminoalkylation offers high reactivity for the formation of α -methylated secondary amine when reacting with olefins, but there are still challenges to overcome. To date, the alkylation of secondary carbons with internal or *gem*-disubstituted alkenes have not been reported with any catalysts. Moreover, intermolecular hydroaminoalkylation of primary amines is still unknown, whereas intermolecular hydroaminoalkylation of tertiary amines is relatively recent but limited to cationic scandium and late transition metals.^{163, 172-174} Furthermore, hydroaminoalkylation of substituted α,β -disubstituted amines and 1,2-disubstituted olefins are still difficult due to steric effects, with inhibition of the alkene insertion step and the more challenging formation of the metallaziridine intermediate. However, recently catalysts were reported for such transformations such as tantalum amidate,^{13, 108} titanium sulfonamide amidate,¹⁷⁵ or tantalum phosphoramidates.^{12, 171} Thanks to the phosphorus centre high reactivity was reported for the latter, and for this reason research has focused on developing other heteroelement based 1,3-chelated catalysts.

1.3 1,3-chelating metal complexes containing another heteroelement atom

Different isoelectronic chelating ligands based on 1,3-*N,N*- and 1,3-*N,O*-chelating backbones have been reported in the literature (Figure 13).¹⁰ Those ligands contain a heteroelement instead of the carbon centre typically present in amidinate and amidate derivatives. Sulfur, phosphorus and boron have been described as new 1,3-*N,N*- and 1,3-*N,O*-chelating ligands and are respectively called diiminophosphinate **1-122**,¹⁷⁶⁻¹⁷⁷ diiminosulfinate **1-123**,¹⁷⁸ boraamidinate **1-124**,¹⁷⁹ phosphoramidate **1-125**¹² and sulfonamidate **1-126**.¹⁸⁰⁻¹⁸² These anions have been reported as ligands complexed to main-group elements or transition metals to give more electrophilic metal complexes that display increased catalytic reactivity.^{179, 183-187}

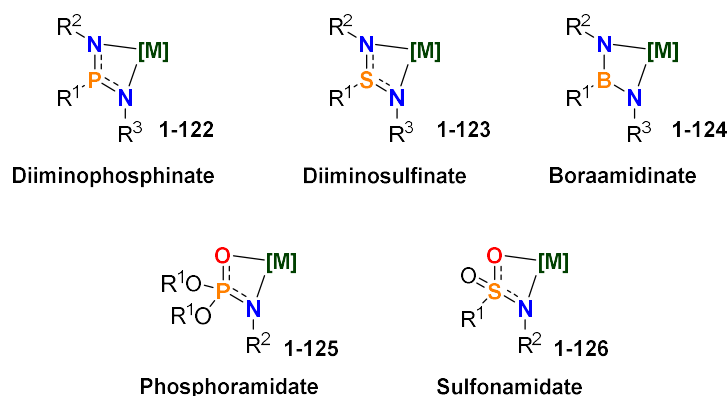
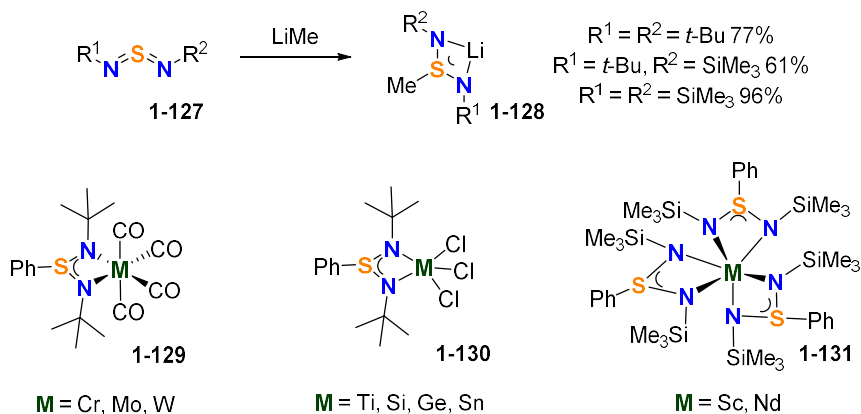


Figure 13: Isoelectronic heteroelement based 1,3-*N,N*- or 1,3-*N,O*-chelating metal complexes.^{179, 183-187}

1.3.1 Heteroelement based ligands containing a sulfur atom

1.3.1.1 1,3-*N,N*-chelating metal complexes containing a sulfur atom: diiminosulfinate

1,3-*N,N*-chelating ligands containing sulfur atoms instead of carbon atoms are obtained using sulfurdimine starting materials. Organolithium or organomagnesium reagents react with the electrophilic sulfur atom to form the diiminosulfinate anion (e.g. **1-128**, Scheme 14).^{184, 188} This anion is then used to synthesize the desired 1,3-*N,N*-chelated complexes. Vrieze and co-workers presented the first diiminosulfinate chelate complex in 1976 using group 6 metals (Cr, Mo, W) (Scheme 14, **1-129**).¹⁸⁹⁻¹⁹⁰ Roesky and co-workers applied the chemistry of diiminosulfinate to other elements and they isolated a diiminosulfinate titanium complex **1-130**, but its geometry has not been determined due to the absence of X-ray structure (Scheme 14, **1-130**).¹⁹¹ More recently homoleptic octahedral diiminosulfinate lanthanide complexes have been disclosed by Edelmann (Scheme 14, **1-131**).¹⁹² Despite the presence of various examples of diiminosulfinate complexes reported in the literature with lanthanide and transition metals, no application of these systems for hydrofunctionalization reactivity has been reported.



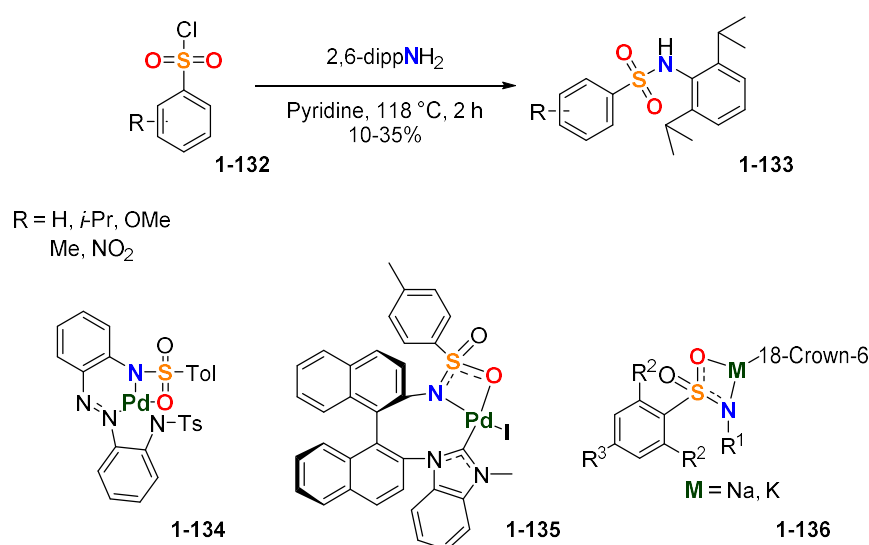
Scheme 14: General diiminosulfinate synthesis and examples of diiminosulfinate metal complexes with transition metals and lanthanides.^{184, 188, 191-192}

1.3.1.2 1,3-*N,O*-chelating metal complexes containing a sulfur atom: sulfonamidates

Sulfonamidate complexes are another class of 1,3-*N,O*-chelates containing a sulfur atom instead of a carbon atom. Their utilization as chelating agents in chemistry are elusive and only a few examples have been reported.¹⁸⁰⁻¹⁸² Synthesis of sulfonamides requires the use of amine substrates, and primary amines in particular. Secondary amines are not

suitable substrates; no anionic ligands formation occurs since resulting sulfonamides cannot be deprotonated. Therefore, in this section we will limited our bibliographic research to sulfonamides that can be deprotonated, and the common synthetic approach to synthesize them goes through the addition of primary amines onto sulfonyl chlorides **1-132** (Scheme 15).¹⁸² In the examples presented, poor yields are obtained, between 10 to 35%, depending on phenyl ring substituents (Scheme 15, **1-133**).¹⁸²

Only a few examples of sulfonamide complexes with late transition metals and main group elements have been described by Sanford¹⁸¹ and Shi and co-workers in 2007-2008 (*vide infra*).¹⁸⁰ Sanford and co-workers isolated a new complex with palladium(II) (Scheme 15, **1-134**) and the X-ray crystallography reveals a square planar geometry of palladium(II) complexed to a 1,3-*N,O*-sulfonamide. The authors proposed that the formation of the five-membered sulfonamide ring **1-134** goes through insertion and decoordination/recoordination steps followed by C-H activation, and reactivity of complex **1-134** remains unknown. Shi and co-workers reported *N*-heterocyclic carbene sulfonamide palladium complexes and examined their application for Suzuki-Miyaura cross-coupling (Scheme 15, **1-135**).¹⁸⁰ However, the benefit of having a sulfur atom in the ligand framework in term of catalytic activity in the Suzuki-Miyaura cross-coupling reaction was not described by the authors.¹⁸⁰ Recently, 1,3-*N,O*-sulfonamide complexes with main group elements such as potassium and sodium have been reported by Wu and co-workers (Scheme 15, **1-136**).¹⁸² The authors examined the chelating effect of such complex with either sodium or potassium to study ring-opening polymerisation of *rac*-lactide. Indeed, sulfonamide complexes tend to slow down the polymerisation, which allowed Wu and co-workers to investigate the mechanism of this reaction.¹⁸²

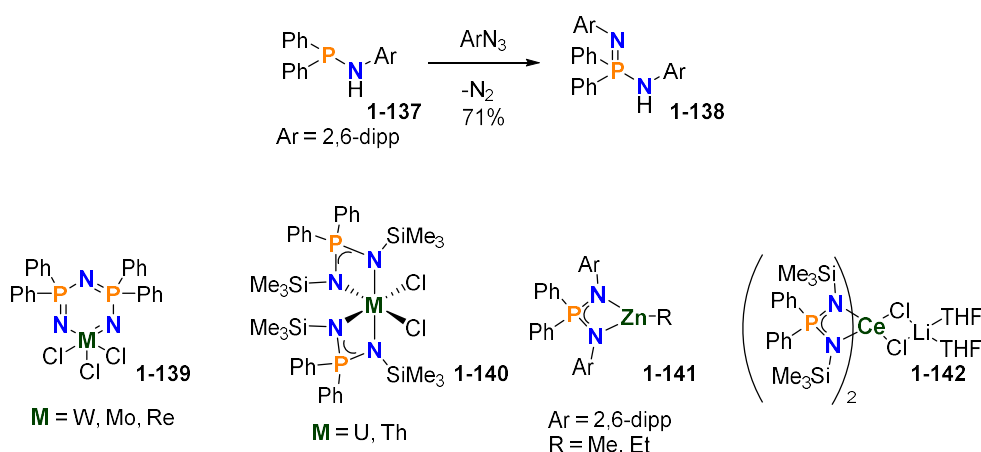


Scheme 15: Sulfonamide synthesis pathway and reported chelating metal complexes.¹⁸⁰⁻¹⁸²

1.3.2 Heteroelement based ligands containing a phosphorus atom

1.3.2.1 1,3-*N,N*-chelating metal complexes containing a phosphorus atom: diiminophosphinates

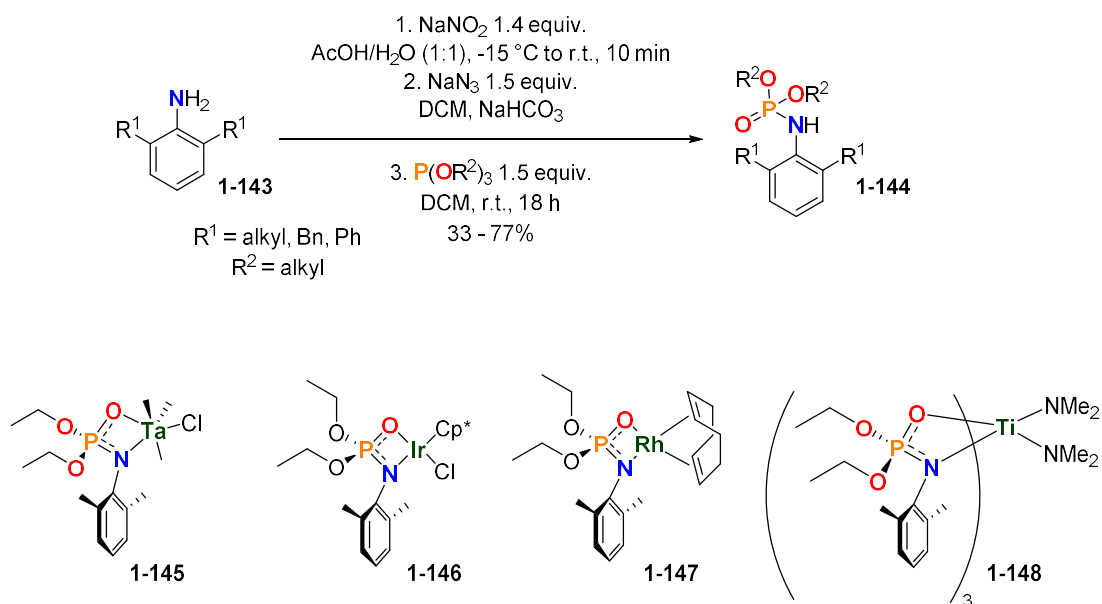
Diiminophosphinate ligands are precursors for 1,3-*N,N*-chelate complexes containing a phosphorus atom. They are generally prepared by a Staudinger reaction of a phosphineamine with 2,6-diisopropylphenyl azide (Scheme 16, **1-138**). Few diamidophosphine ligands have been described in the literature. Preliminary work in 1980s by Roesky and co-workers reported the synthesis and application of diiminophosphinate anions for the synthesis of cyclic metallaphosphazenes with different transition metals like tungsten, molybdenum and rhenium. However, these ligands were not employed as 1,3-*N,N*-chelates (Scheme 16, **1-139**).^{176, 193-197} More recent work highlights the preparation and chelation of diiminophosphinate with different metals but not with early or late transition metals.¹⁹⁸⁻²⁰⁰ Lanthanide,¹⁹⁸ groups 12 (Zn)¹⁹⁹ and 13 (Al, Ga, In, Tl)^{183, 200} metals were chelated by 1,3-*N,N*-diiminophosphinate ligands using a protonolysis or salt metathesis reaction. Diiminophosphinate aluminium chelates were recently applied toward ring-opening polymerization catalysis of ϵ -caprolactone with high activity (Scheme 16, **1-140**, **1-141**, **1-142**).²⁰⁰ No examples of such diiminophosphinate chelates were reported with early transition metals.



Scheme 16: Staudinger reaction for the synthesis of diiminophosphine ligands and examples of diiminophosphinate metal complexes.^{183, 193, 195, 198-199}

1.3.2.2 1,3-*N,O*-chelating metal complexes containing a phosphorus atom: phosphoramidates

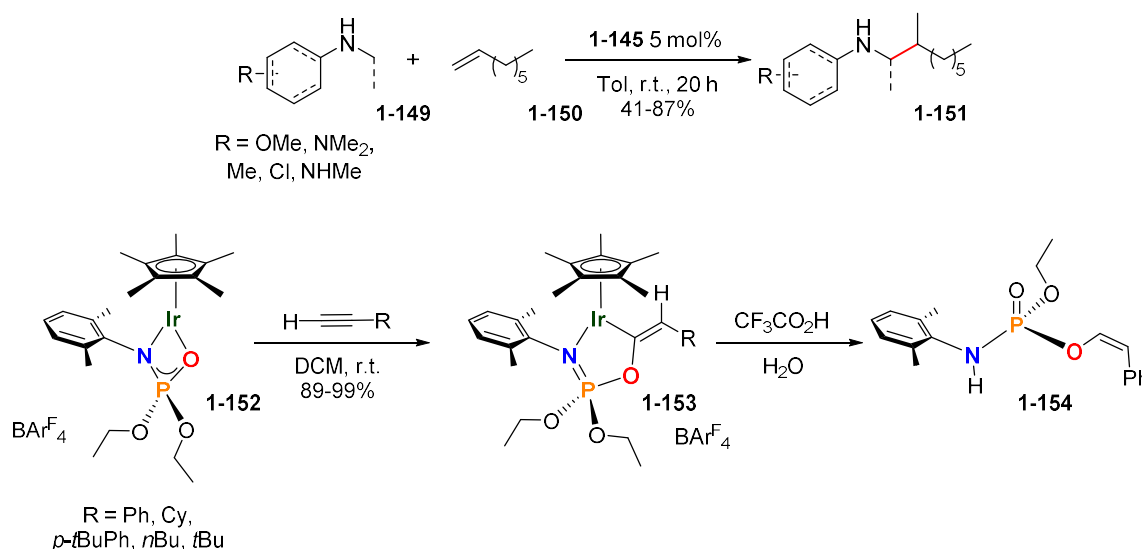
Phosphoramidates are a class of 1,3-*N,O*-chelating ligands that can be synthesized *via* generation of a diazonium intermediate from the corresponding aniline, with addition of sodium azide and phosphite ester (Scheme 17, **1-144**).²⁰¹ This Staudinger-phosphite type reaction is involved for the formation of phosphoramidate in a similar fashion to diiminophosphinate.



Scheme 17: Staudinger-phosphite reaction pathway for phosphoramidate synthesis and examples of different transition metal phosphoramidate complexes.^{12, 202-203}

Since 2013, the Schafer group has reported different phosphoramidate complexes with both early and late transition metals, through either salt metathesis or protonolysis reactions.^{12, 204} Tantalum and titanium phosphoramidate complexes were reported for their reactivity in hydroaminoalkylation catalysis (Scheme 17, **1-145**, **1-148**).^{12, 202} The tantalum complexes are the first catalysts reported for hydroaminoalkylation at room temperature to give moderate to high yields. The electron-withdrawing property of the phosphoramidate ligand accounts for the higher reactivity compared to common 1,3-*N,O*-chelates. Titanium based phosphoramidate complexes have been recently reported for hydroaminoalkylation catalysis, but longer reaction times (24-164 hours) and higher temperatures (130 °C) are required.²⁰² Phosphoramidate complexes of late transition metals have also been described for C-H activation and O-phosphoramidation (Scheme 17, **1-146**, **1-147**).^{203, 205} After chloride abstraction from **1-146** using $\text{Na}[\text{BAr}^{\text{F}}_4]$, the resulting phosphoramidate iridium(III) further reacts with terminal alkynes. Upon acidic treatment and workup the desired (*Z*)-vinyloxy

phosphoramidate (Scheme 18, **1-154**) could be isolated.²⁰³ Because of the complex geometry, the presence of the N-M-O bite angle of 70° increases the metal complex reactivity during O-phosphoramidation.²⁰⁴



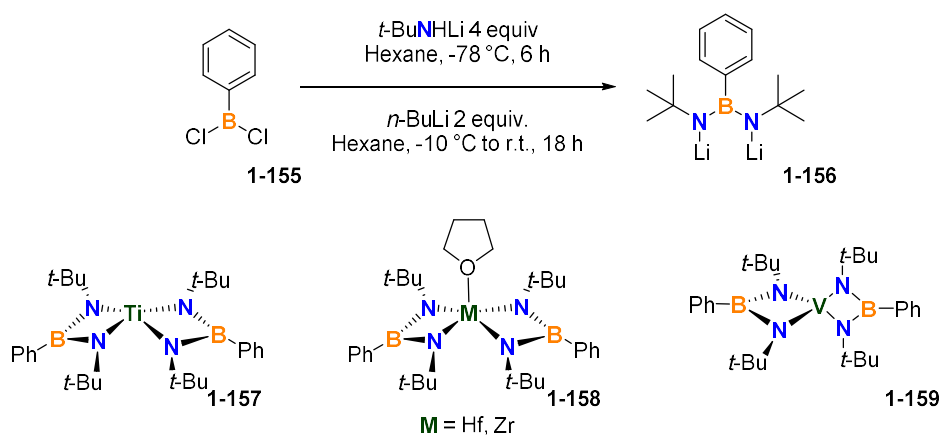
Scheme 18: Examples of phosphoramidate metal complexes and their application in organic synthesis.^{12, 205}

1.3.3 Heteroelement based ligands containing a boron atom

The only reported chelating ligand containing boron instead of a carbon centre is a 1,3-*N,N*-chelate; no 1,3-*N,O*-chelate has been reported. Boraamidinate anions present two negative charges located on the nitrogens, which is in contrast to the monoanionic 1,3-chelating ligands discussed.¹⁰ They also exhibit strong electron-donating properties that make boraamidinate ligands suitable for stabilizing metals of high oxidation states.²⁰⁶ The first reported dianionic boraamidinate was in 1979, and it was complexed to tin¹⁷⁹ using a salt metathesis reaction (Scheme 19).¹⁸⁶ The requisite boraamidinate lithium salts can be synthesized by addition of lithium amide to a dichlorophenylborane **1-155** solution followed by addition of *n*-butyllithium.¹⁸⁶ Limited modifications of the resulting chelating ligand are possible by using different chloroborane derivatives in this synthetic pathway.

The first early transition boraamidinate complexes were reported with titanium and zirconium,¹⁸⁷ then other group 4 (Hf) and 5 (V) metals were also used (Scheme 19, **1-157**, **1-158**, **1-159**).¹⁵ Examples of boraamidinate complexes with other transition metals (gallium, indium¹⁶ and molybdenum²⁰⁷) and lanthanides^{206, 208} have been reported in the literature. While a variety of boraamidinate complexes have been reported, limited applications of these complexes in reactivity have been reported. The only example reported to date is the ring-opening polymerization of *rac*-lactide with a boraamidinate magnesium complex.¹⁴

Thus there are many opportunities to explore 1,3-chelating ligands containing a boron atom in the ligand backbone. Furthermore, the development and investigation of *O,B,N* and *N,B,N* motifs as 1,3-chelating ligand and as reagents/catalysts have yet to be investigated.



Scheme 19: General boraamidinate synthesis and examples of different early transition boraamidinate metal complexes.^{15, 179, 187}

1.4 Conclusion: scope of thesis

1,3-*N,N*- and 1,3-*N,O*-chelating ligands can be prepared by straightforward ligand syntheses. Metal complexes are then typically obtained by either protonolysis or salt metathesis reaction. 1,3-*N,O*-chelating early transition metal complexes have been further applied toward hydrofunctionalization reactions and polymer syntheses. Most importantly, they can be used to create new catalysts that prepare carbon-nitrogen and carbon-carbon bonds with a 100% atom-economic process.

The central focus of this thesis is inspired from previous works on heteroelement based 1,3-chelating ligands for the development of new hemilabile ligands containing a heteroelement. Indeed, the replacement of carbon by a heteroelement has revealed new properties and due to enhanced electrophilicity, the resulting metal complexes can display enhanced reactivity in comparison to the parent amidate and amidinate type catalysts. The work reported in chapter two focuses on the development of new potential 1,3-*N,O*-chelating complex containing a boron centre instead of a carbon atom. A novel synthetic approach for generating a chelating boron containing ligand with the *O,B,N* motif has been developed based on the borazarophenanthrene backbone and its synthesis. The optimized synthesis involves the use of amineborane complexes instead of boron halides, and complexation reactions have then been studied with early transition metals.

In chapter three, syntheses of potential 1,3-*N,N*-chelating ligands containing boron are developed. An initial synthetic approach showed the synthesis of cyclic boraamidine

derivatives and the second approach involved the synthesis of acyclic boraamidine compounds. Both types of boraamidine proligands were then been studied for complexation reactions with early transition metals such as titanium, zirconium and tantalum. Further application of these potential ligands in hydroaminoalkylation reactions has been examined using tantalum complexes.

The fourth chapter presents the development of a new synthetic approach to prepare *P,N*- and *N,P,N*-ligands *via* a hydroamination reaction that is regioselectively mediated by a 1,3-*N,O*-chelated titanium complex. This synthesis utilized phosphine alkynes as a new class of substrates for the hydroamination reaction. Coordination chemistry investigations using these new ligands has been investigated with group 4 metals to give new *N,P,N*-chelates.

The fifth chapter summarizes all the work presented in this thesis, as well as it discusses about future works for future student in the Schafer and Pucheault laboratories. Despite all the unexpected results we managed to identify relevant strategies for the development of chelates with heteroelement atoms. Based on the results, and preliminary results, we suggested various research axis that will be important for the organic community to consider when designing 1,3-chelating molecules with heteroelements as ligands with early transition metals for catalytic purposes.

2 CHAPTER II: TOWARD NEW POTENTIAL BORON LIGANDS MOTIFS: SYNTHESIS OF 1,3-*N,O*- AND 1,3-*N,N*-CHELATING METAL COMPLEXES

2.1 Synthesis of potential 1,3-*N,O*-chelating metal complexes containing boron throughout boronic acid derivatives

2.1.1 Introduction

The opportunity to use the electrophilicity of boron to develop new potential derivatives of 1,3-*N,O*- and 1,3-*N,N*-chelating ligands like amidates **2-1** or amidinates have been underexplored. Recently, the Schafer group reported new phosphoramidate *O,P,N*-ligands as versatile complexes for hydrofunctionalization reaction.²⁰⁹ Thanks to their electrophilic oxidized phosphorus centre, these phosphoramidate metal complexes catalyse hydroaminoalkylation at room temperature.^{12, 202} Changing the central carbon atom within a 1,3-*N,O*-amidate or pyridonate complex with a boron moiety should potentially offer new features for catalysis. Enhancement of the electrophilicity of such 1,3-*N,O*-chelating ligands is expected to result from the electrophilicity of the boron atom. The Schafer group also published the synthesis of new tantalum pyridonate complexes containing chloride bound to the metal centre which also showed high reactivity in the case of hydroaminoalkylation as well due to the increase of electrophilicity.¹³ Thus, to retain the 1,3-chelating motif while accessing new heteroatom containing ligand sets that can stabilize the anionic charge effectively, boroxaaminoborane **2-5** (*O,B,N*) seems to be an attractive motif (Figure 14).

This project is focused on the synthesis of alkoxyaminoboranes **2-6** and their application towards the formation of potential early transition metal complexes **2-5**. Different synthetic pathways will be envisioned and applied to obtain the desired molecule. Cyclic alkoxyaminoborane derivatives have also been targeted due to their stability compared to acyclic alkoxyaminoborane which can be more prone to hydrolysis. Methodology will be developed to determine the best system for the formation of the desired alkoxyaminoboranes and their use as potential ligands.

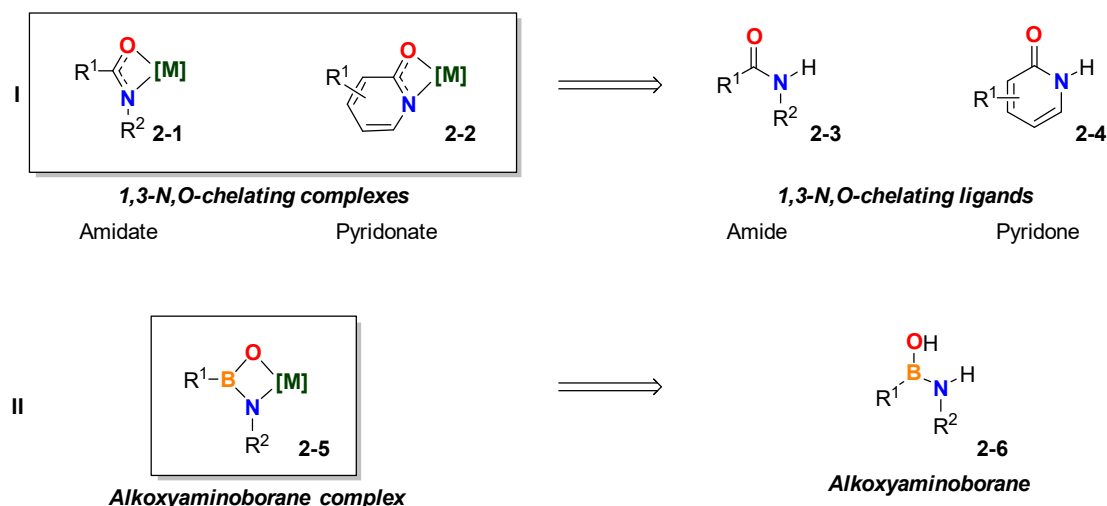
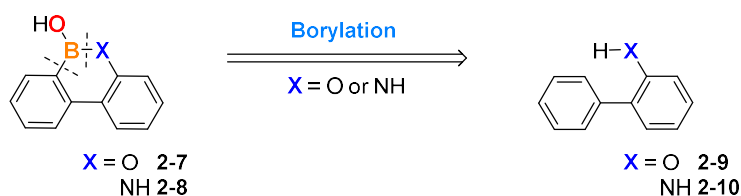


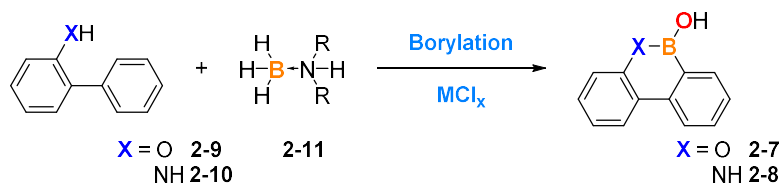
Figure 14: 1,3-*N,O*-chelating ligands with carbon or boron as central atoms; Equation I: examples of 1,3-*N,O*-chelating metal complexes and their ligand equivalents; Equation II: potential alkoxyaminoborane metal complex and the potential ligand equivalent.

In the first part the synthesis and development of boronic acid derivatives like boroxaro- and borazaro-phenanthrenes will be described (Scheme 20). This route features the creation of one carbon-boron bond. Then these products can be applied in the synthesis of potential 1,3-*N,O*-chelating ligands. In the second part the synthesis of related potential 1,3-*N,N*-chelating ligands using a borinic acid synthetic route will be introduced. This class of potential ligands will be accessed by the creation of two carbon-boron bonds. As showed in Scheme 20 the retrosynthesis demands breaking the carbon-boron and the donor (X, oxygen or nitrogen)-boron bonds. This would facilitate the synthesis and the stability of the resulting product toward air and moisture. Indeed, aminoborane derivatives are generally unstable and tend to hydrolyse into their boronic derivative equivalents *via* an oxidation reaction. For this reason, 2-biphenyl derivatives **2-9** and **2-10** were envisioned as potential substrates. It was anticipated that the carbon backbone would stabilize the resulting product toward hydrolysis after borylation. For an electrophilic borylation, the 2-(amino- or hydroxy)-biphenyl was selected as the most promising substrate to form the alkoxyaminoborane derivatives **2-7** and **2-8** (Scheme 20).



Scheme 20: Retrosynthesis pathway considered in this project.

To create boron-carbon bonds, several pathways can be used including nucleophilic addition, electrophilic aromatic substitution, hydroboration or cross-coupling reactions. Based on the work developed by Dewar²¹⁰ and Zhou,²¹¹ to synthesize boroxaro- and borazaro-phenanthrenes derivatives **2-7** and **2-8** using Friedel-Craft reactions with boron trichloride, we decided to develop a new synthetic approach to prepare the desired phenanthrene derivatives based on avoiding boron trichloride as the boron source, since its low boiling point of 12.6 °C makes it challenging to use. Toxicity and the formation of chloride salts are also two major drawbacks of boron trichloride usage. It is also highly sensitive to air and moisture which complicates its utilization in organic synthesis. On the contrary, the use of amineborane complexes **2-11** (Scheme 21) is more interesting because they are air and moisture stable, they are also handled more readily.²¹² Amineborane adducts do not form chloride salt by-products which further motivates their utilization. However, amineborane adducts are not sufficiently electrophilic to be used in electrophilic borylation. Hence, addition of a chloride source like aluminium trichloride would form the electrophile *in situ* and avoid the use of air and moisture sensitive boron halides. The designed synthesis would involve the addition of an amineborane adduct and a chloride source to the desired alcohol or amine substituted phenanthrene (**2-8** and **2-10**) starting material as showed below (Scheme 21).



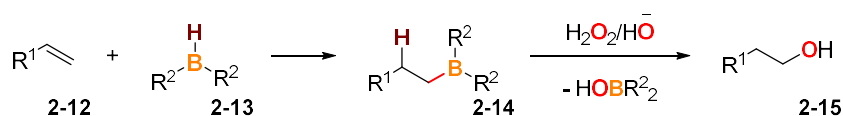
Scheme 21: Boroxaro- and borazaro-phenanthrenes synthesis with amineborane complexes.

Boronic acids have been used in the literature for their biologic properties²¹³, material applications²¹⁴ and they have been widely employed as cross-coupling partner for the Suzuki-Miyaura cross-coupling reaction.²¹⁵ Syntheses of boroxaro- and borazaro-phenanthrenes are similar to those used for boronic acid derivatives: the new carbon-boron bond is created *via* a Friedel-Crafts reaction in the presence of a Lewis acid.²¹⁶ However, before the formation of the carbon-boron bond, the amino or alkoxy donor group reacts with the boron atom and forms the donor-boron bond. Literature on boroxaro- and borazaro-phenanthrenes syntheses is described in this section followed by the preparation of these compounds. The developed methodology was then extended to the 2-aminobiphenyl synthesis.

2.1.2 Synthetic methodology of carbon-boron bond formation

2.1.2.1 Hydroboration of unsaturated carbon-carbon bonds

The hydroboration reaction of unsaturated carbon-carbon bonds such as alkenes **2-12** and alkynes is one method to form carbon-boron bonds. This transformation has been largely used to further functionalize the organic molecule after an oxidation step that transforms the organoborane **2-14** into an alcohol **2-15**.²¹⁷ This transformation was reported in 1956 by Brown who reported the hydroboration of olefins and their oxidation to synthesize alcohols (Scheme 22).²¹⁸



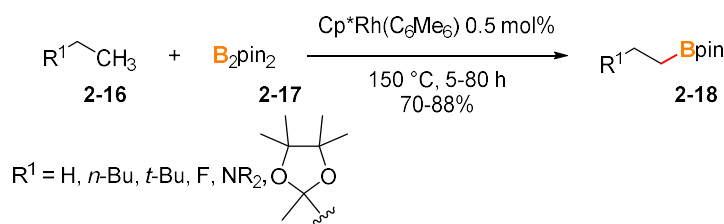
Scheme 22: Brown hydroboration reaction of alkenes followed by oxidation.²¹⁸

Regioselectivity and chemoselectivity can be tuned by changing the nature and property of the substituents (steric hindrance, inductive effect) either on the unsaturated substrate or on the organoborane.²¹⁷ Based on this, the development of asymmetric hydroboration has been developed to synthesize chiral alcohols after oxidation of the organoborane.²¹⁹ The mechanism of hydroboration invokes a four-centred transition state with an asynchronous addition process. The formation of the carbon-boron bond happens first, followed by the carbon-hydrogen bond formation.²²⁰ The *syn* addition toward the unsaturated carbon-carbon bond with the addition of the boron onto the less substituted carbon centre impacts the stereospecificity of the transformation.²²⁰ In the early 2000s, a variant of the Brown hydroboration has been published using transition metal complexes, for instance, by using a catalytic quantity of rhodium metal complex they observed hydroboration of olefins with a reverse of the regioselectivity.²²¹ The creation of carbon-boron bonds is by hydroboration limited by the fact that only unsaturated carbon-carbon bonds are reactive toward this transformation.^{217, 220, 222}

2.1.2.2 Borylation of carbon-hydrogen bonds

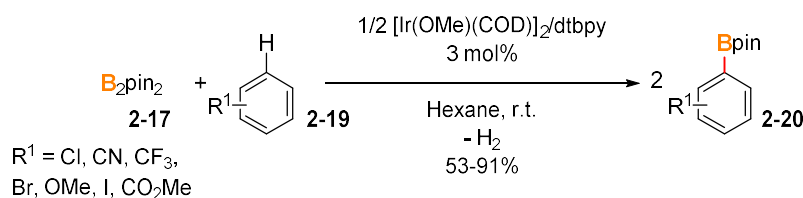
Hartwig and co-workers observed functionalization of carbon-hydrogen bonds by using main group elements to give organoborane substrates.²²³ Although the original method was not catalytic, they developed a catalytic process using late transition metals and more particularly rhodium.²²⁴ The carbon-hydrogen functionalization process exclusively targets the less hindered primary carbon-hydrogen bond in the molecule **2-16**. Different substituents

like alkoxides, fluoride, tertiary amines and acetal are tolerant to this carbon-hydrogen bond functionalization catalyzed by either rhodium or ruthenium metal as reported by Hartwig and co-workers (Scheme 23).²²⁵⁻²²⁶



Scheme 23: Aliphatic carbon-hydrogen functionalization reaction.²²⁵

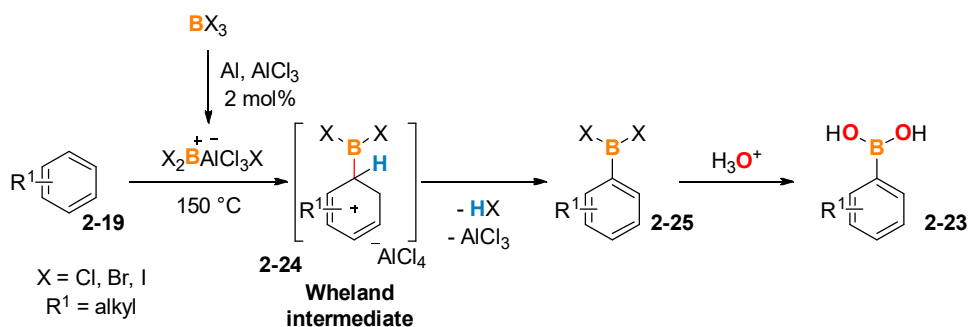
In contrast with functionalization of aliphatic carbon-hydrogen bonds, aromatic carbon-hydrogen bonds demand the use of iridium catalyst instead of rhodium or ruthenium metal complexes.²²⁷ However, the iridium system remains unreactive with alkanes in contrast to the rhodium and ruthenium systems. Different examples with deactivated arenes **2-19** (Cl, CN, CF₃, Br, I) were developed, and some examples containing electron donating groups such as methoxy or ester groups have been reported (Scheme 24).²²⁸ However, these direct borylation methods are limited to the terminal methyl position for aliphatic carbon-hydrogen bond functionalization and to deactivated arenes for aromatic carbon-hydrogen bond functionalization.²²⁵⁻²²⁷



Scheme 24: Aromatic carbon-hydrogen functionalization reaction for the synthesis of organoboranes.²²⁸

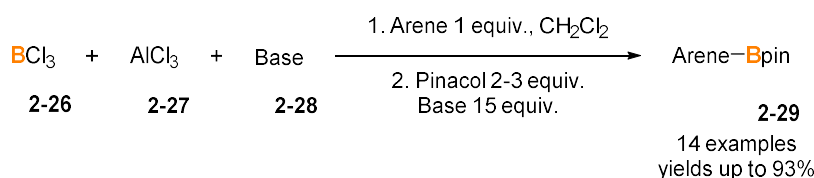
2.1.2.3 Nucleophilic addition for the creation of carbon-boron bonds

Organometallic compounds such as organolithium and organomagnesium reagents are versatile reagents for carbon-boron bond formation. In 1926, Gilman and Vernon published the addition of phenylmagnesium bromide to trimethylborate to give phenyl boronic acid after acidic hydrolytic work-up (Scheme 25).²²⁹ In 1983, Brown reacted organolithium reagents **2-21** with various trialkoxyborates at -78 °C in diethyl ether, and several boronates were isolated by distillation **2-22**.²³⁰ These two methods are the first reported examples of a creation of carbon-boron bond by nucleophilic addition of organometallic compounds.²²⁹⁻²³⁰



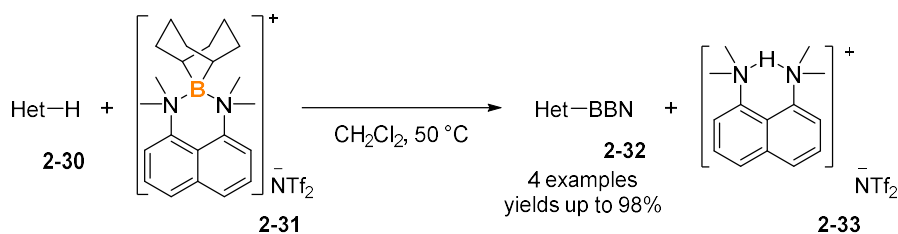
Scheme 26: General boronic acids synthesis pathway described by Muetterties.²³⁶⁻²³⁷

Ingleson and co-workers developed another approach for electrophilic borylation by adding amine, such as 2,6-lutidine or 4-dimethylaminotoluene, *in situ* as base (Scheme 27).²³⁸ Subsequent addition of pinacol with a large excess of triethylamine afforded desired products **2-29** in 60% to 93% yields.



Scheme 27: Electrophilic Friedel-Crafts reaction using amine bases.

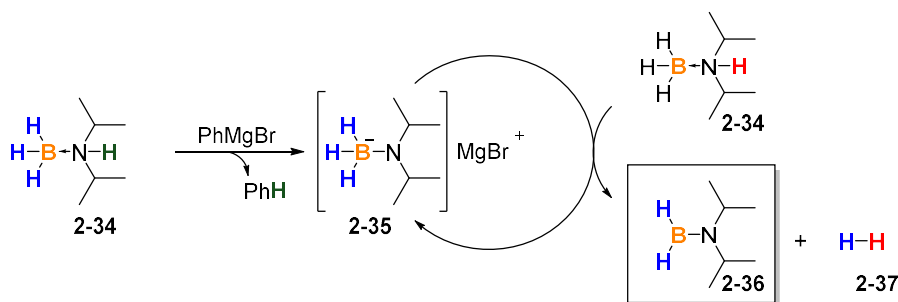
Vedejs and co-workers published boron-carbon bond formation using another electrophilic intermediate (Scheme 28).²³⁹ They disclosed the synthesis of a new boronium ion using 1,8-bis(dimethylamino)naphthalene and 9-borabicyclo[3.3.1]nonane. Through an electrophilic borylation reaction, they obtained the formation of the desired boron derivative **2-32**. Four different examples giving yields up to 98% were reported. However, there is a limitation to this synthetic pathway since it has only been described for pyrrole derivatives and may not be applicable to a large variety of substrates.



Scheme 28: Electrophilic borylation using borenium ion.

2.1.2.5 Magnesium promoted C-B bond formation using aryl halide and amineborane complexes

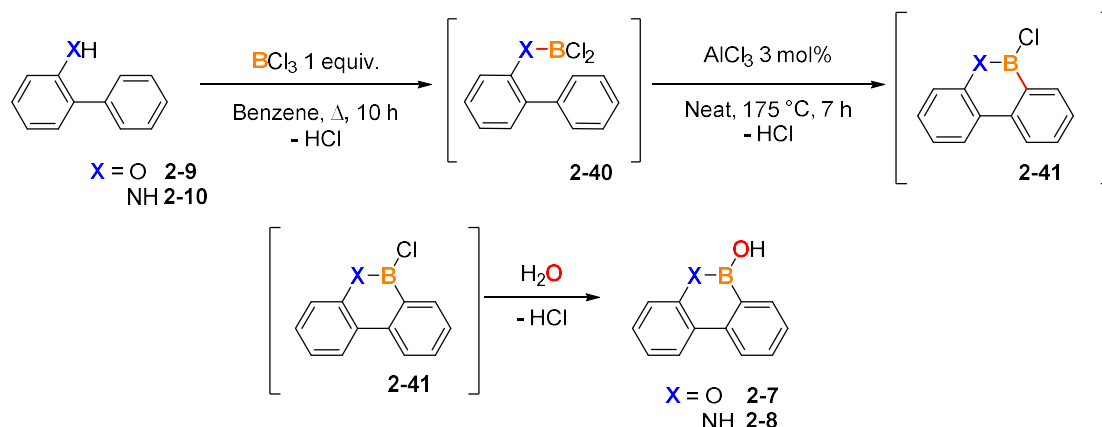
Amineborane complexes have been widely used in hydrogen storage applications and in dehydrocoupling reactions.²⁴⁰⁻²⁴¹ Various preparation methods of amineborane complexes are already described in the literature involving the replacement of a weak ligand (THF, SMe_2) with a stronger ligand (RNH_2 , R_2NH , etc.).²⁴⁰⁻²⁴¹ Using amineborane adducts, the Pucheault group developed a reliable autocatalytic dehydrogenation method to synthesize *in situ* aminoboranes.²⁴² It involves deprotonation of the amineborane complex (here diisopropylamineborane) **2-34** by phenylmagnesium bromide to form the aminoborohydride intermediate **2-35** (Scheme 29).²⁴² This intermediate can then release dihydrogen **2-37** by reacting with another equivalent of the amineborane complex **2-34** (Scheme 29). Aminoborane **2-36** is then formed and the intermediate **2-35** is regenerated.²⁴² This process occurs until full consumption of the amineborane complex **2-34**. The formation of the diisopropylaminoborane **2-34** takes place in a few minutes (10 to 15 minutes) (Scheme 29).²⁴²



Scheme 29: Proposed catalytic cycle of aminoborane formation.²⁴²

Using amineborane complexes **2-34** and this advantageous aminoborane synthetic method, the Pucheault group developed a new approach for the formation of carbon-boron bond and the synthesis of boronic acids **2-39** (Scheme 30).²⁴³ Due to the air- and water-stability of amineborane complexes compared to boron halides or boronate esters, this method can be easily used for the synthesis of various boronic acids.²⁴³ Furthermore, the use of amineborane complexes does not require cryogenic conditions as required with previous organoboranes, and can be easily scaled up to access boronic acids on gram-scale. In 2018 the Pucheault group reported the easy synthesis of various boronic acids **2-39** in 49% to 95% yields (Scheme 30).²⁴³

the formation of the carbon-boron bond and quenching with water gave the desired products **2-7** and **2-8** (Scheme 32).²¹⁰⁻²¹¹

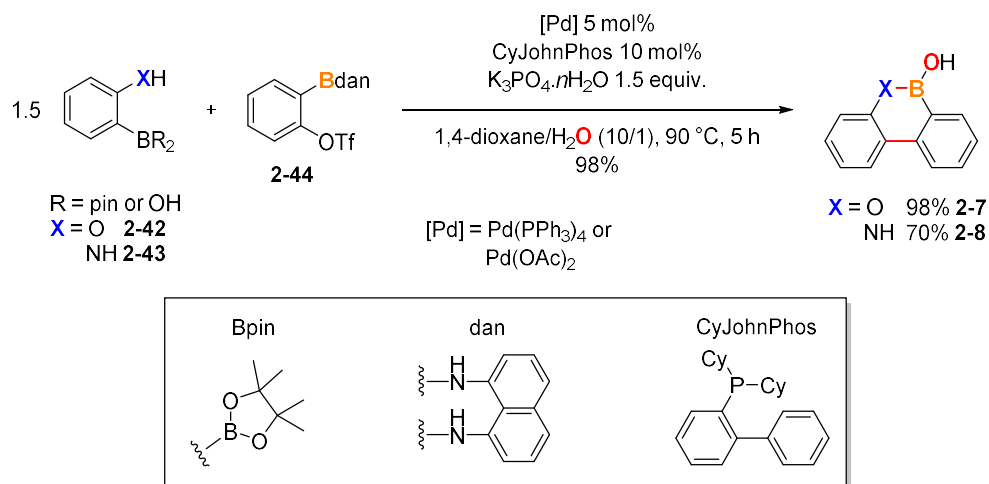


Scheme 32: Electrophilic borazaro- or boroxaro-phenanthrene synthesis.²¹⁰⁻²¹¹

In 2004, Zhou and co-workers optimized the reaction conditions and accessed the boroxarophenanthrene **2-7** with only 1.5 equivalents of the borylating agent and a catalytic amount of aluminium was added in a stepwise manner.²¹¹ The reaction was completed in six hours and afforded the boroxarophenanthrene **2-7** in 99% yield,²¹¹ whereas two to three equivalents of boron trichloride reagent were needed for the synthesis of the borazarophenanthrene **2-8**. Using this approach, they obtained 50% yield after the borazarophenanthrene recrystallization in aqueous acetic acid.²¹¹

2.1.3.1.2 Suzuki-Miyaura cross-coupling reaction to synthesize potential boron-containing ligands

The Suzuki-Miyaura cross-coupling reaction has been largely reported for the creation of carbon-carbon bonds.²⁴⁴ Hosoya and co-workers also prepared with success the **2-7** boroxaro- and **2-8** borazaro-phenanthrenes using Suzuki-Miyaura cross-coupling which avoids the use of boron halides but requires preparation steps (Scheme 33).^{211, 245}



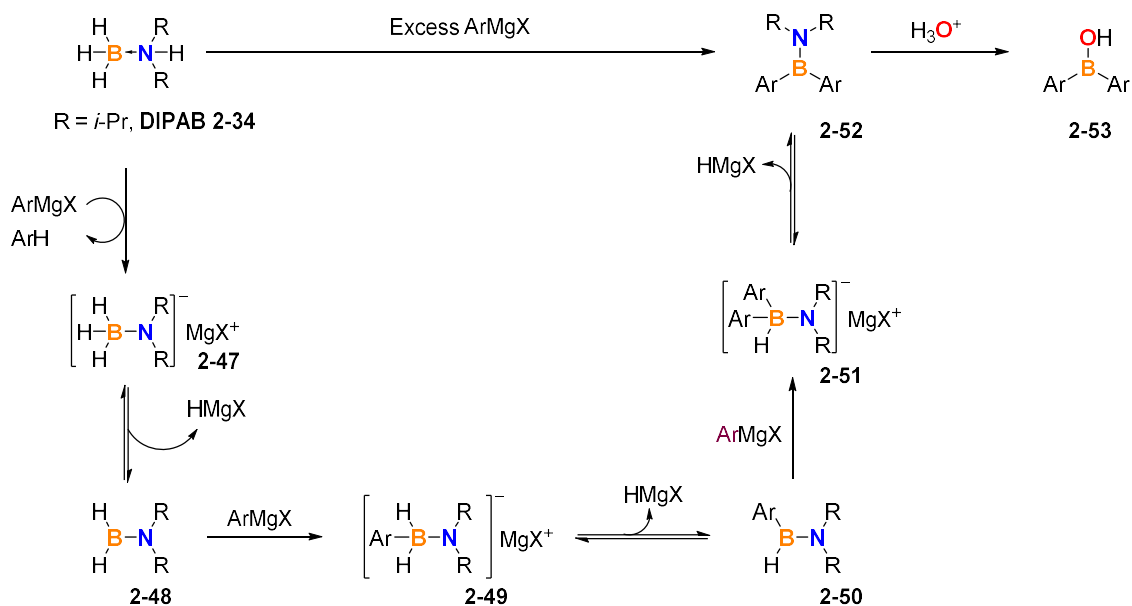
Scheme 33: Boroxaro- and borazaro-phenanthrene synthesis involving Suzuki-Miyaura cross-coupling developed by Hosoya.²⁴⁵

2.1.3.2 Preparation of potential ligand by formation of two carbon-boron bonds obtained via borinic acid synthesis

Several methods have been reported for the synthesis of borinic acid derivatives via the formation of two carbon-boron bonds within the synthesis.²⁴⁶⁻²⁴⁸ Borinic acids derivatives are versatile organic compounds that can be used either in biology as inhibitors of acyl protein thioesterases 1 and 2,²⁴⁹ in OLEDs,²⁵⁰ or as cross-coupling partners in Suzuki-Miyaura cross-coupling reactions.²⁵¹ Their enhanced Lewis acidities make them great catalyst for the formation of amide bonds.²⁴⁷

2.1.3.2.1 Nucleophilic addition toward borate derivatives for formation of two carbon-boron bonds

The formation of two carbon-boron bonds, leading to the synthesis of borinic acid **2-46**, involves the addition of organolithium or organomagnesium reagents **2-21** in excess to trimethylborate or triisopropylborate reagents (Scheme 34). This approach is directly related to that described previously for boronic acid synthesis.²⁴⁸ Although an acidic workup generally affords the borinic acid product **2-46**, reversible binding of the alkoxide groups to the boron centre leads to mixtures of boronic acid, borinic acid and borate products.²⁴⁸ This phenomenon affords low yields and highly complicates the purification step (Scheme 34).²⁴⁸



Scheme 36: Proposed borinic acid synthesis mechanism involving aminoborane intermediates.²⁴²

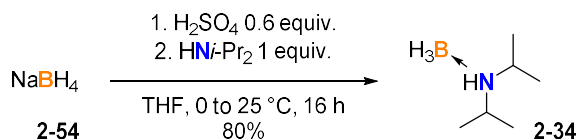
2.2 Development of a new approach for the synthesis of boroxaro- and borazaro-phenanthrenes

2.2.1 General method for amineborane complex synthesis

Amineborane complexes are useful in organic synthesis as new boron sources. Compared to classical boron sources like boron halides (BCl_3 or BBr_3) or borate derivatives (B(OMe)_3 or B(Oi-Pr)_3), amineborane complexes are more attractive reagents because they are easy to handle due to their high stability to air and moisture. The Pucheault group has developed amineborane complexes like DIPAB (diisopropylamineborane complex) and DICAB (dicyclohexylamineborane complex) as polyvalent reagents for the formation of new carbon-boron bonds.^{212, 242, 246} This new electrophilic borylation method using amineborane adducts for the synthesis of boroxarophenanthrene and borazarophenanthrene would be ground-breaking as it could further be developed for the synthesis of various organoboranes without using boron halides. One major advantage of this transformation would be the formation of the chloride electrophile species *in situ*.

Amineborane complexes **2-34** can be synthesized using inexpensive and commercially available reagents. The general method to synthesize amineborane complexes is described below (Scheme 37). Prior to the addition of 0.6 equivalents of sulphuric acid, sodium borohydride **2-54** is dissolved in tetrahydrofuran. After stirring two hours at room temperature, the secondary amine (diisopropylamine or dicyclohexylamine) is slowly added

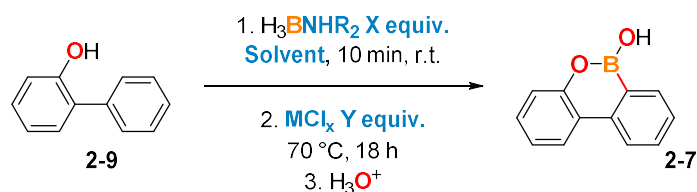
to the reaction mixture. After stirring 16 hours at room temperature, the desired adduct **2-34** is isolated in high yield after workup with water and dichloromethane (Scheme 37).



Scheme 37: Example of amineborane complex synthesis: diisopropylamineborane complex synthesis.²⁴²

2.2.2 Investigation of key parameters for the electrophilic borylation with amineborane complexes

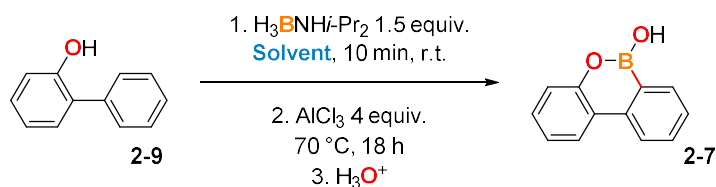
The aforementioned amineborane complexes were prepared *in situ* and then used for the borylation reaction of the 2-hydroxybiphenyl **2-9**. As presented in the following sections, key parameters and reaction conditions were determined by screening various, amineborane complexes, chloride sources, solvents, and amounts of reagents (Scheme 38).



Scheme 38: Study of the reaction parameters.

2.2.2.1 Influence of solvents

The choice of solvents was studied for the development of the desired electrophilic borylation reaction using amineborane complexes (Table 1). Zhou disclosed the reaction in hexane, which is an apolar and aprotic solvent.²¹¹ For this reason, we chose cyclohexane as the first solvent to study, since it has similar properties to hexane but it is less toxic.



Entry	Solvent	Conversion [%] ^a
1	Cyclohexane	66 (30%) ^b
2	Toluene	15
3	Mesitylene	15
4	<i>p</i> -xylene	10
5	Diglyme	0
6	Chloroform	0

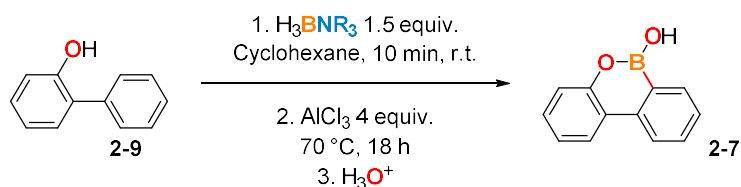
Table 1: Screening of reaction solvents.

a. Conversion determined by ¹H NMR spectroscopy between the integration differences of the aromatic protons of the starting material **2-9** vs. the aromatic protons of the product **2-7**. b. Isolated yield after recrystallization.

In cyclohexane 66% conversion into the boroxarophenanthrene **2-7** was observed by ¹H NMR spectroscopy (entry 1, Table 1). Other organic solvents were also tested: non-polar aromatic solvents (toluene, *p*-xylene, and mesitylene) and more polar aprotic solvents such as diglyme and chloroform. Toluene and mesitylene afforded low conversions (15%) while *para*-xylene was even lower (10%) (entries 2-4, Table 1). These results may be due to side reactions, like a Friedel-Crafts reaction with the aromatic rings, which would lead to low product formation observed by ¹H NMR spectroscopy, but was not isolated. In diglyme and chloroform (entries 5-6, Table 1) no conversions were observed. An apolar and aprotic aliphatic solvent like cyclohexane is necessary for this transformation as the use of other solvents led to the formation of by-products or to no observable reaction. Only 30% yield was isolated as the boroxarophenanthrene **2-7** formed borazine by-product upon heating through the recrystallization. Thus, cyclohexane was the solvent used moving forward.

2.2.2.2 Influence of amineborane complexes

Different types of amineborane adducts were screened to determine the most efficient complex for the transformation of the 2-hydroxybiphenyl **2-9** into the boroxarophenanthrene **2-7**. A stirring solution of slight excess of the selected boron derivatives (1.5 equivalents), with four equivalents of aluminium trichloride in cyclohexane at 70 °C for 18 hours, afforded the desired product **2-7**. Conversions of **2-9** into the boroxarophenanthrene **2-7** were determined by ¹H NMR spectroscopy and are shown in the Table 2.



Entry	Amineborane complex	Conversion [%] ^a
1	Diisopropylamineborane (DIPAB)	66
2	Dicyclohexylamineborane (DICAB)	65
3	Dimethylamineborane	64
4	Pyridineborane	66
5	Triethylamineborane	20
6	Morpholineborane	0
7	DABCO borane	0
8	Triphenylphosphineborane	0

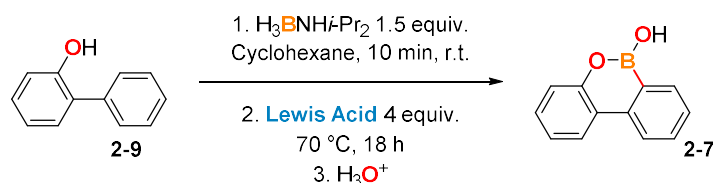
Table 2: Screening of the amineborane complexes.

a. Determined by ^1H NMR spectroscopy.

Amineborane complexes of entries one to six are commercially available adducts, while complexes of entries 7 and 8 have been synthesized *in situ* using the previously described pathway. DIPAB (entry 1, Table 2) has been used as the control for this transformation. DICAB, synthesized on a 10-gram scale in our laboratory, disclosed 65% conversions into the product (monitored by ^1H NMR spectroscopy) after 18 hours of reaction (entries 1-2, Table 2). Dimethylamineborane and pyridineborane complexes, led to 64% and 66% conversion (entries 3-4, Table 2). Triethylamineborane complex only showed a limited conversion of 20% into the product **2-7** (entry 5, Table 2). Increasing the steric bulk at either the boron or the nitrogen centre generally decreases the complex stability as it has been reported in the literature.²⁴⁰ Hence, DIPAB, DICAB and dimethylamineborane complex are most probably more stable than triethylamineborane in solution and reacted more favourably toward the formation of product **2-7**. No conversion was observed for morpholineborane, DABCO borane and triphenylphosphineborane complexes (entries 6-8, Table 2). DABCO borane and morpholineamineborane were completely ineffective for this transformation. Indeed, such amineborane complexes can lead to borane dimerization in solution, which results into low conversion of the desired product. Amineborane adducts like DIPAB or DICAB, pyridineborane and dimethylamineborane complex are necessary for electrophilic borylation reaction. DIPAB was selected as the amineborane complex to use for the following study due to its gram scale synthesis in our laboratory.

2.2.2.3 Influence of chloride reagents

The chloride reagent is important to achieve the desired transformation because it increases the electrophilicity of the amineborane adduct. Different chloride reagents were next screened, in the presence of DIPAB in cyclohexane. Aluminium trichloride has been used as the control Lewis acid and three other Lewis acids were tested: zinc chloride, titanium(IV) chloride and iron(III) trichloride. All reactions were monitored by ^1H NMR spectroscopy.



Entry	Amineborane complex	Lewis acid	Conversion [%] ^a
1	DIPAB	ZnCl ₂	0
2		TiCl ₄	0
3		FeCl ₃	0
4		AlCl ₃	66
5	DIMAB	ZnCl ₂	0
6		TiCl ₄	0
7		FeCl ₃	0
8		AlCl ₃	65

Table 3: Screening of chloride reagents.

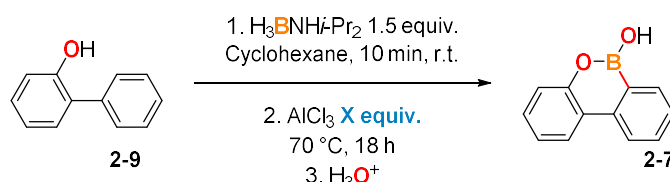
a. Conversion determined by ^1H NMR spectroscopy.

Zinc chloride (entry 1, Table 3) was first studied by using the procedure described in the previous part 2.2.2. of this chapter. After workup in diethyl ether and water, no conversion into the desired product **2-7** was observed (entry 1, Table 3). This result was confirmed by ^{11}B NMR spectroscopy as there was an absence of the distinctive broad singlet at 28 ppm. The same negative results were obtained with titanium tetrachloride and iron trichloride (entries 2-3, Table 3). These results contrast with the experiment in the presence of aluminium trichloride which offers 66% conversion (entry 4, Table 3). Observation of the different conversions was clear and only aluminium trichloride worked for this reaction. To confirm that this result did not depend on the amineborane complex used (DIPAB), the same trials were performed with DIMAB as the boron electrophile source (entries 5-8, Table 3). The results corroborated those obtained with DIPAB; only aluminium trichloride worked, and is the necessary chloride source for electrophilic borylation. To rationalize the result obtained

in Table 3, the Gutmann-Beckett method theory can be used. Hence, according to the literature, AlCl_3 has the highest acceptor number value (85) while TiCl_4 is only at 70 and ZnCl_2 is at 66 (FeCl_3 could not be found in the literature).²⁵²⁻²⁵⁴ Aluminium trichloride having the highest acceptor number value allow explaining why only this Lewis Acid worked, the others were not enough Lewis acidic for the transformation.

2.2.2.4 Screening of the equivalents of aluminium trichloride

Aluminium trichloride is the best Lewis acid to carry out the desired reaction however four equivalents were used in this preliminary protocol. Thus screening has been performed to determine the preferred number of equivalents required for the reaction. The reaction was performed using DIPAB in cyclohexane with stepwise addition of increasing equivalents of aluminium trichloride to determine in one reaction the number of equivalents needed. Each hour, an aliquot was taken and diluted in deuterated benzene to monitor the reaction by ^{11}B NMR spectroscopy, followed by the addition of one equivalent of aluminium trichloride to the reaction mixture, and this procedure was performed until the desired amount of Lewis acid was added. Two sets of experiments were done, the first one was performed to identify the range of optimal amount of AlCl_3 with an increment of one equivalent each hour, and then the experiment was performed again with an increase of 0.5 equivalents each hour around the optimal quantity of Lewis acid. This first experiment determined that the optimal amount of Lewis acid was two to three equivalents, thus the reaction was started a second time with increments of half equivalent starting from one equivalent to three equivalents.



Entry	Equivalents	^{11}B NMR	Conversion [%] ^a
1	1	-20 ppm (q)	0
2	1.5	-20 ppm (q); 28 ppm (bs)	- ^b
3	2	-20 ppm (q); 28 ppm (bs)	- ^b
4	2.5	28 ppm (bs)	66
5	3	28 ppm (bs)	66

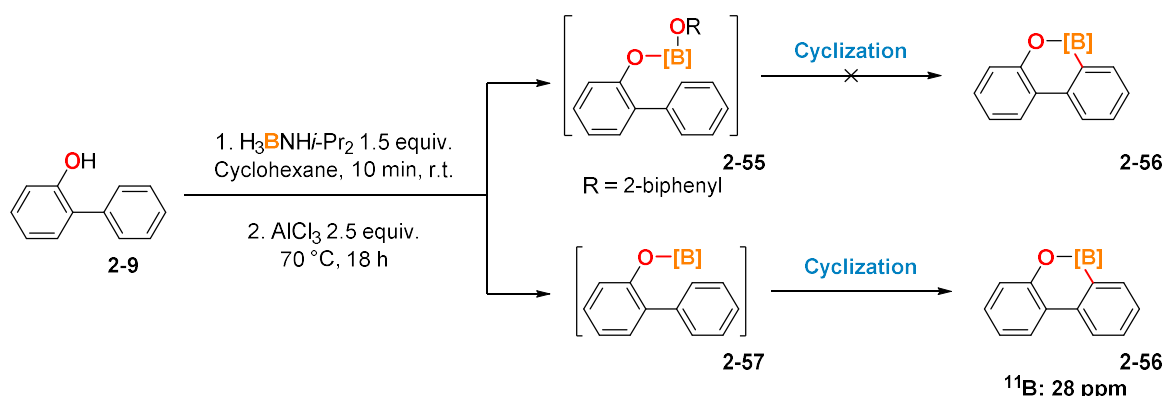
Table 4: Addition of one to three equivalents of aluminium trichloride.

a. Conversion determined by ^1H NMR spectroscopy. b. Conversion impossible to determine by ^{11}B NMR spectroscopy.

No conversion into the desired product **2-7** was observed with only one equivalent of aluminium trichloride (entry 1, Table 4). According to the presence of a quartet around -20 ppm on the ^{11}B NMR spectroscopy there was only DIPAB in the reaction mixture. When 1.5 or two equivalents of aluminium trichloride were added to the reaction mixture, conversion into the boroxarophenanthrene **2-7** was observed with the broad singlet at 28 ppm on the ^{11}B NMR spectrum (entries 2-3, Table 4). No exact conversion could be obtained through those experiments because the ^{11}B NMR spectroscopy procedure used was not quantitative. However, full conversion of DIPAB was obtained with at least 2.5 equivalents of Lewis acid (entries 4-5, Table 4). To obtain entire conversion of both amineborane complex and the 2-hydroxybiphenyl into the desired product **2-7**, at least 2.5 equivalents of aluminium trichloride are required. These observations would suggest that all hydrides of the amineborane adduct need to react with aluminium trichloride to form the active species, which can then react with the 2-hydroxybiphenyl **2-9**.

2.2.2.5 Determination of others parameters

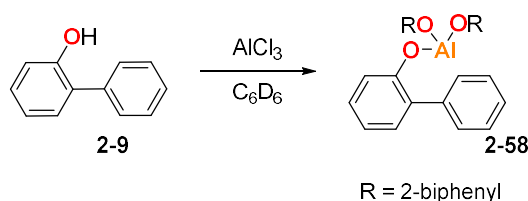
Attempts to optimize electrophilic borylation by changing the amineborane adduct, the Lewis acid and solvent did not improve the conversion into the desired product **2-7**. Despite best efforts the conversion remained at 66%. This conversion limit could be explained by competitive addition side reactions of the alcohol with the boron active species. According to the literature, the disubstituted intermediate **2-55** would not be sensitive to electrophilic cyclization to form the desired product **2-56**, as it would not be sufficiently electrophilic (Scheme 39).²¹³



Scheme 39: Formation of dimer compounds with the boron active specie.

A side-reaction of aluminium trichloride with 2-hydroxybiphenyl **2-9** might occur during the electrophilic borylation reaction to generate an aluminium aryloxy complex **2-58** (Scheme 40). This could explain the limited conversion observed. The ^1H NMR spectrum

confirmed this hypothesis as a reaction could be observed between the alcohol **2-9** and aluminium trichloride in deuterated benzene. Comparison of ^1H NMR spectra of starting material **2-9** and of reaction mixture revealed that there is a shift of aromatic protons of **2-9**, which corresponds to the consumption of starting material **2-9** and to the formation of product **2-58**. Disappearance of the singlet of the hydroxy group at 4.77 ppm on the ^1H spectrum of compound **2-9** in the ^1H NMR spectrum of the reaction mixture confirmed full consumption of **2-9** and is in favour of the formation of **2-58**.



Scheme 40: Reaction between the 2-biphenylalcohol and aluminium trichloride.

The reactivity between DIPAB **2-34** and aluminium trichloride has also been studied by ^1H and ^{11}B NMR spectroscopy in deuterated benzene (Figure 15). ^{11}B NMR spectroscopy was recorded few minutes after the addition of **2-34** and AlCl_3 , and the spectrum revealed the presence of a doublet of triplets on the ^{11}B NMR spectrum corresponding to the proposed formation of compound **2-59**, with full consumption of DIPAB based by ^{11}B NMR spectroscopy (disappearance of the quartet, -20 ppm) (Figure 15). Based on the correlation, the doublet of triplets on the ^{11}B NMR spectrum would correspond to two bridged hydrides H^2 ($J_{\text{H}^2-\text{B}} = 31.7$ Hz) and the terminal hydride H^1 ($J_{\text{H}^1-\text{B}} = 125.8$ ppm) on the boron atom. This hypothesis was confirmed thanks to the literature, the coupling range of terminal hydrogen and boron occurs in the region of 120-190 Hz whereas coupling to bridged hydrogen and boron occur in the region of 30 to 60 Hz.²⁵⁵ The impossibility to isolate the complex **2-59** made difficult to confirm the nature of the substituents R, which most probably could be diisopropylamide substituents according to ^1H NMR spectroscopy. This molecule **2-59** could be the active species that reacts with 2-hydroxybiphenyl **2-9** during the reaction. To try this hypothesis, one equivalent of 2-hydroxybiphenyl was added to the resulting adduct **2-59** and heated up to 70 °C, but after overnight reaction no more boron signal was detected on the ^{11}B NMR spectrum, the reaction failed.

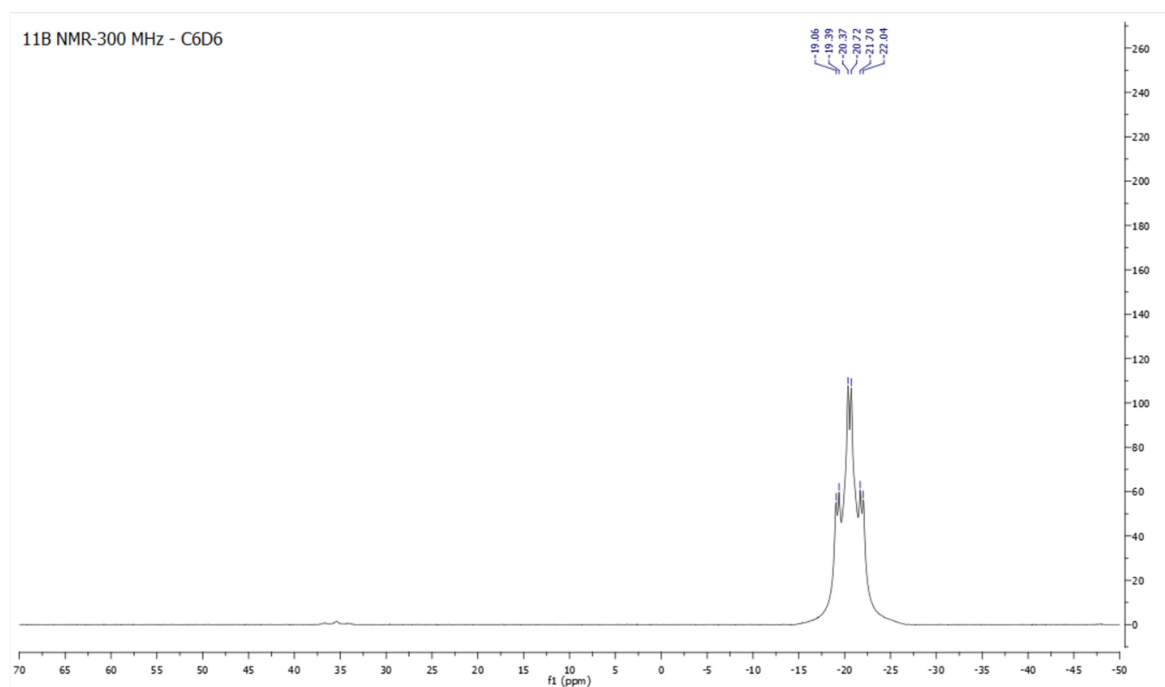
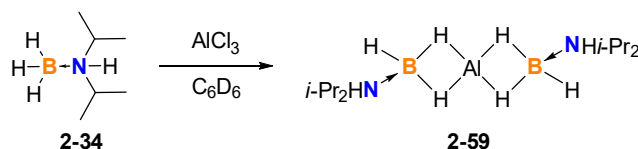
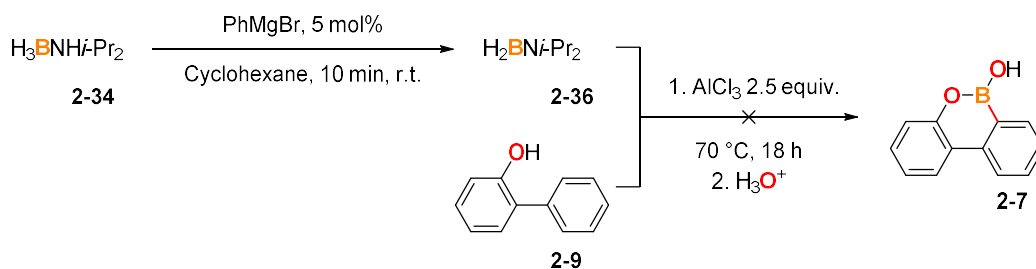


Figure 15: Reaction between DIPAB and aluminium trichloride and ^{11}B NMR spectrum of the reaction.

2.2.3 Synthetic optimization of electrophilic borylation

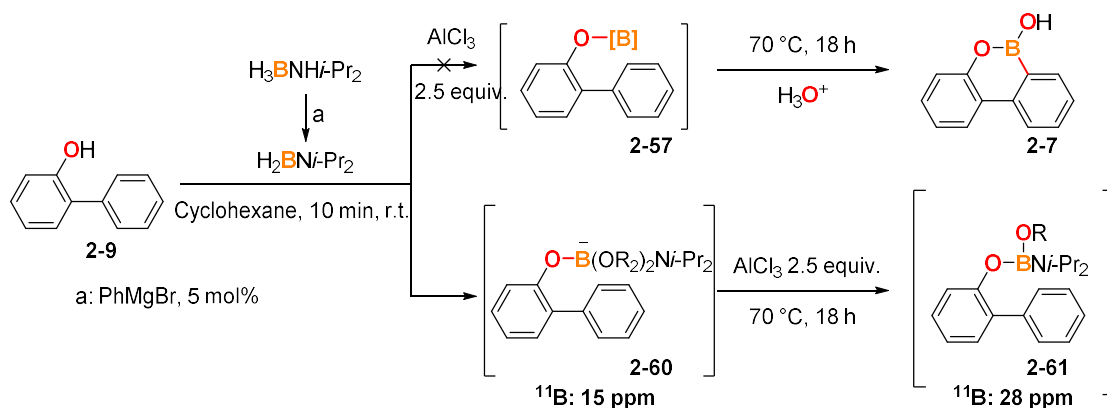
2.2.3.1 Reaction optimization using aminoborane reagent

In this synthetic reaction, amineborane complex were used as the borylation reagent. Using another synthetic approach, the amineborane complex **2-34** was transformed into aminoborane **2-36**, furthermore it could hypothetically react with the 2-hydroxybiphenyl **2-9** before the addition of aluminium trichloride. Thus, a stepwise reaction was performed using an aminoborane derivative instead of the amineborane complex previously described (Scheme 41). Reacting one equivalent of amineborane adduct, here DIPAB, with 5 mol% of Grignard reagents, for example phenylmagnesium bromide, can form the diisopropylaminoborane **2-36** *in situ*.²⁴³ When reacted with aluminium trichloride and the 2-hydroxybiphenyl **2-9**, the boron derivative is expected to form the desired product **2-7** after cyclisation and aqueous workup (Scheme 41).



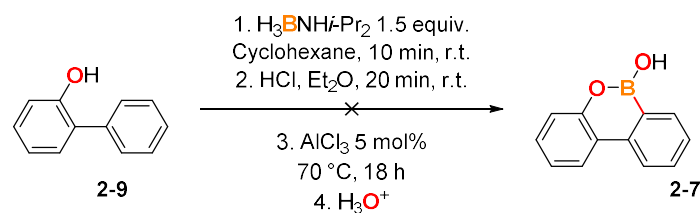
Scheme 41: Stepwise reaction using aminoborane as boron electrophile.

The reaction was run and followed by ^{11}B NMR spectroscopy. An intermediate was detected as a singlet with a chemical shift at 15 ppm before the addition of aluminium trichloride but could not be identified. After this addition, the previous peak shifted and a broad singlet at 28 ppm was obtained by ^{11}B NMR spectroscopy. But, the desired product **2-7** was not isolated after the typical workup with ice and diethyl ether. Stepwise addition of the aminoborane **2-36** formed beforehand and added to a solution of the phenol derivative **2-9** did not drive the reaction to the formation of the desired boroxarophenanthrene **2-7** (Scheme 42). It is hypothesised that an unknown intermediate corresponding to the multiple addition of the alcohol **2-9** on the diisopropylaminoborane **2-36** is formed. Like explained previously, this intermediate is less prone to electrophilic borylation and after hydrolysis it is more likely that it regenerates the 2-hydroxybiphenyl **2-9** starting material.



Scheme 42: Proposed reaction mechanism with 2-hydroxybiphenyl and diisopropylaminoborane.

To elucidate the mechanism of the reaction and confirm the formation of the intermediate species **2-59**, dry hydrochloric acid in diethyl ether solution was used for the reaction. A catalytic amount of aluminium trichloride was then added to the reaction mixture to get the expected boroxarophenanthrene **2-7**. However, no conversion of **2-9** into the product was observed after heating for 18 hours at 70 °C (Table 5).



Entry	HCl (equiv.)	Conversion [%] ^a
1	1	0
2	2	0
3	3	0
4	4	0

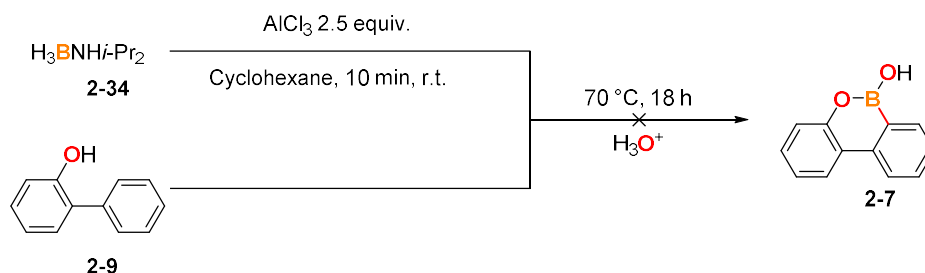
Table 5: Stepwise reaction using dry hydrochloric acid for the formation of aminochloroborane.

a. Conversion determined by ^1H NMR spectroscopy.

Changing the order of addition between aluminium trichloride and the 2-hydroxybiphenyl **2-9** did not impact the reaction results. Addition of supplementary equivalents of dry hydrochloric acid did not change the reaction and there were no formation of the desired product **2-7** (Table 5). It is highly possible that the Wheland intermediate did not form, and this could account for the reaction ineffectiveness.

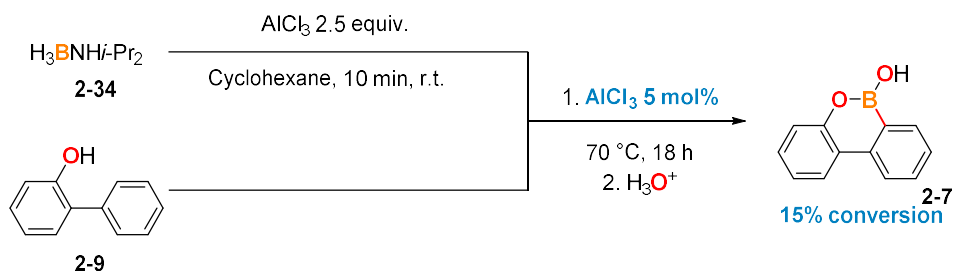
2.2.3.2 Reverse addition of aluminium trichloride

The procedure developed was based on the addition of DIPAB on a solution of 2-hydroxybiphenyl **2-9** followed by the addition of aluminium trichloride, in this study the addition was reversed to study if the addition order had any effect on the reaction. Aluminium trichloride was added to a solution of DIPAB **2-34** in cyclohexane. After ten minutes, the 2-hydroxybiphenyl **2-9** was added to the resulting mixture and heated at 70 °C for 18 hours. After the usual workup, there was no product formation and no peak on the ^{11}B NMR spectrum was obtained; one hypothesis could be the full consumption of aluminium trichloride by starting materials like previously explained. Without available aluminium trichloride, there is no Friedel-Craft cyclization possible and thus no formation of the desired cyclic product (Scheme 43).



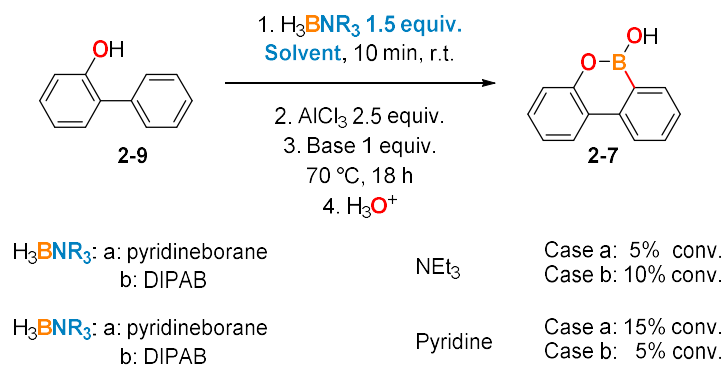
Scheme 43: Formation of aminochloroborane with aluminium trichloride reagent.

Inspired by classic Friedel-Crafts reaction condition, one solution could be adding a catalytic amount of aluminium trichloride to overcome that phenomenon. The same reaction was then carried out with first aluminium trichloride added to a mixture of DIPAB **2-34** in cyclohexane followed by the subsequent addition of the 2-hydroxybiphenyl **2-9**. Then 5 mol% of aluminium trichloride were added again and left 18 hours at $70\text{ }^\circ\text{C}$. Even if a small conversion (15%) of **2-9** was observed, it was still lower than the pathway described before (Scheme 44).



Scheme 44: Subsequent addition of catalytic amount of aluminium trichloride after the addition of DIPAB, aluminium trichloride and the 2-hydroxybiphenyl.

Another idea for increasing the conversion was to trap the molecule of hydrochloric acid formed *in situ* during the reaction. Since Vedejs and Ingleson reported the use of amine bases in electrophilic Friedel-Crafts reaction, bases like pyridine or triethylamine were added to the system.²³⁸⁻²³⁹ Two different amineborane complexes were studied: DIPAB and pyridineborane complex. Addition of triethylamine afforded 5% to 10% conversions of **2-9**, whereas addition of pyridine gave 5% to 15% conversions. Hence, addition of base did not affect the system as expected and the conversion of **2-9** remained low compared to the previous results (Scheme 45). Addition of base prior to the addition of aluminium trichloride (change in the order of addition) in the last step did not give any conversion of **2-9** into the desired boroxarophenanthrene product **2-7**. Results obtained on bases addition and amineborane complexes are too low and close to be relevant and conclusive.



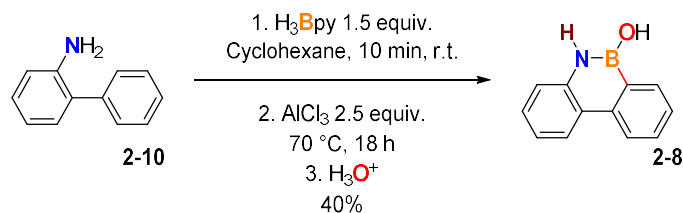
Scheme 45: Addition of base prior to the addition of aluminium trichloride.

Despite the various experiments ran and studied, we were unable to determine an exact mechanism for the reaction studied. On one hand, no reactivity was detected between the 2-hydroxybiphenyl and amineborane complexes. On the other hand, aluminium trichloride reacted with the 2-hydroxybiphenyl but addition of amineborane complexes showed no conversion into the boroxarophenanthrene. The reverse addition *i.e.* first the amineborane complex and aluminium trichloride followed by the addition of the 2-hydroxybiphenyl also showed no conversion of the alcohol starting material into the boroxarophenanthrene. Hence, we were unable to determine exactly the first step of the mechanism of this transformation.

2.2.4 Synthesis of an *O,B,N* potential ligand using the borazarophenanthrene

2.2.4.1 Borazarophenanthrene synthesis following the method developed for the boroxarophenanthrene

The synthesis developed for the 2-hydroxybiphenyl was then applied for the 2-aminobiphenyl **2-10** synthesis through the use of pyridineborane as this reagent works well like DIPAB or DICAB (Scheme 46). The reaction was limited to 66% conversion like for the 2-hydroxybiphenyl, and after recrystallization, 40% yield of the desired product was isolated. The reaction was also studied using DIPAB and DICAB as for the 2-hydroxybiphenyl and led to the same results as with pyridineborane with respectively 65% and 66% conversions.



Scheme 46: Borazarophenanthrene synthesis with the method developed.

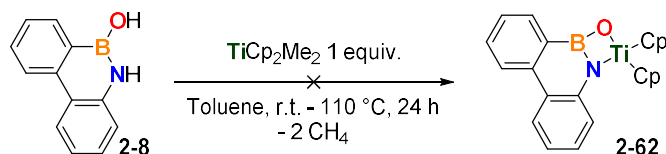
The yield obtained is relatively similar to the one reported by Zhou and co-workers in 2004.²¹¹ Indeed, they isolated only 50% of the desired borazarophenanthrene **2-8** despite a full conversion of the starting material **2-10**.²¹¹ They explained this yield by the dimerization of the borazarophenanthrene and the same phenomenon could have occurred with our system. Even if the conversion and the system was not optimal, the borazarophenanthrene **2-8** was isolated and studied as new potential 1,3-*N,O*-chelating ligand.

2.2.4.2 Towards the synthesis of potential 1,3-*N,O*-chelating titanium complexes

With the desired borazarophenanthrene in hand, the synthesis of potential metal complexes using titanium compounds was investigated. Developing new potential metal complexes with early transition metals is one of the main research projects studied in the Schafer group. Indeed, early transition metals are less toxic and less expensive than late transition metals like palladium or platinum.^{11, 35, 74} Borazarophenanthrene **2-8** was first investigated as a potential X_2 type ligand suitable for ligating titanium in a bidentate fashion. A standard protocol for installing 1,3-*N,O*-chelating ligands is a protonolysis reaction which avoids to use of an exogenous base that could interact with the electrophilic boron centre. Titanium cyclopentadiene derivatives were selected as suitable candidates to probe this reaction.

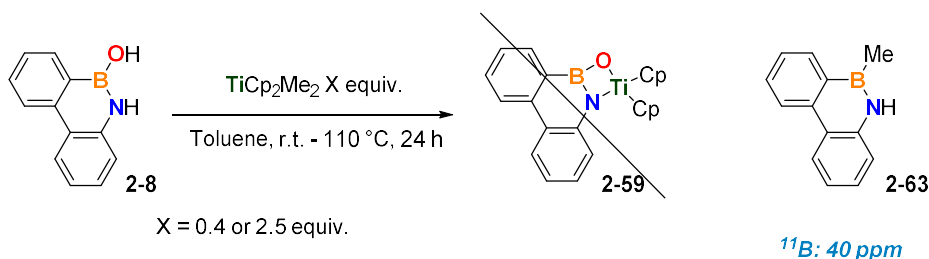
Thus a protonolysis reaction was performed with one equivalent of dimethyltitanocene added to a mixture of borazarophenanthrene **2-8** in toluene and monitored by NMR spectroscopy at room temperature for eight hours. However no reactivity and no gas evolution were observed, thus we tried to push the reaction by heating up the following mixture at 110°C for 16 hours (Scheme 47). The reaction was monitored by ^1H and ^{11}B NMR spectroscopy, in which a disappearance of the broad singlet at 28 ppm was observed. This change in the NMR spectrum corresponds to the consumption of borazarophenanthrene **2-8**. Moreover, the boron resonance shifted from 28 to 40 ppm indicating the formation of a new product. Purification by recrystallization was performed but no crystals were obtained and the boron resonance reverted back to 28 ppm: the borazarophenanthrene **2-8** was obtained

again and TiCp_2Me_2 formed titanium oxide. Thus the reaction was reiterated with 2.5 equivalents of the boron derivative.



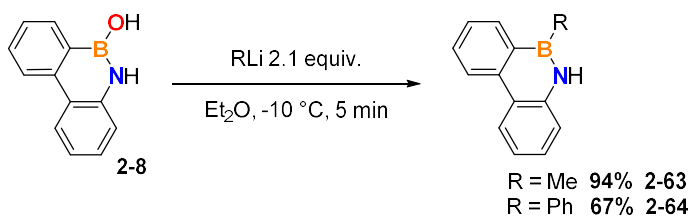
Scheme 47: Borazarophenanthrene reaction with one equivalent of dimethyl titanocene.

To promote complete conversion to the desired product **2-62**, the reaction was started using an excess of the borazarophenanthrene **2-8** in one hand and an excess of dimethyltitanocene on the other hand (Scheme 48). After leaving the reaction eight hours at room temperature and then heating the mixture overnight at 110 °C in toluene, the same results were obtained in both cases. Purification on silica gel column chromatography was performed to determine the product formed. The formation of the product **2-63** was showed as the main product with a typical shift at 40 ppm in the ^{11}B NMR spectrum and the corresponding shift on the ^1H NMR spectrum.²¹⁶



Scheme 48: Reactions of the borazarophenanthrene with dimethyltitanocene.

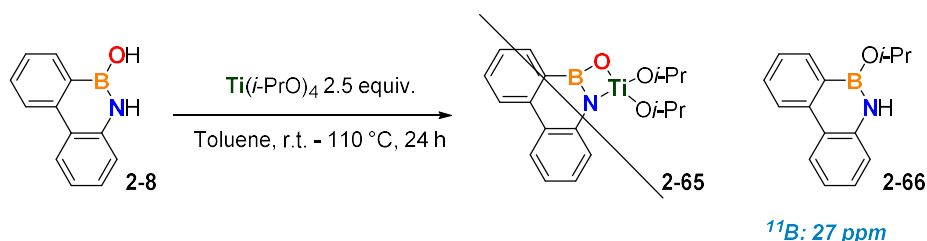
This methylated product **2-63** was unstable to air and moisture so no yield could be reported even if a 100% conversion was confirmed by ^{11}B NMR spectroscopy, with a complete shift of the broad singlet at 28 ppm to another broad singlet at 40 ppm. Degradation of product **2-63** occurred through oxidation after few hours to form again the borazarophenanthrene **2-8**, and accounted for the result obtained when one equivalent of each starting material were used. This methylated product **2-63** was first published in the literature in 1961 by Dewar (Scheme 49).²¹⁶ As presented on the scheme below, they reported this synthesis using more than two equivalents of organolithium reagents in diethyl ether at low temperature, the alkylated/arylated compounds **2-63** and **2-64** were obtained in high yields (Scheme 49).²¹⁶



Scheme 49: Borazarophenanthrene alkylation/arylation reaction.²¹⁶

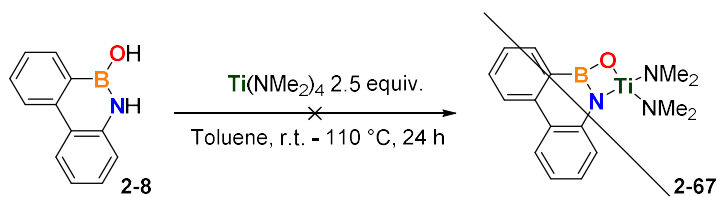
Thus, dimethyltitanocene acted analogously as an organolithium reagent by transferring one methyl group from the metal centre to the boron centre. The driving force of this reaction could be the formation of titanium oxide after reaction between dimethyltitanocene and the borazarophenanthrene.

The reaction of the borazarophenanthrene with titanium(IV) isopropoxide under the same reaction conditions (toluene, r.t. - 110 °C for 24 hours) led to a similar result (Scheme 50). Formation of product **2-66** was observed with a signal in the ¹¹B NMR spectrum at 27 ppm instead of 28 ppm, and the ¹H NMR spectrum confirmed the formation of the product **2-66**. The product could not be isolated due to its high reactivity toward moisture and form the borazarophenanthrene starting material.



Scheme 50: Borazarophenanthrene reaction with titanium(IV) isopropoxide.

Consequently, a protonolysis reaction was performed using another titanium source. Tetrakis(dimethylamido)titanium(IV) was slowly added to a solution of the borazarophenanthrene **2-8** in toluene and was monitored by ¹¹B NMR spectroscopy at room temperature for eight hours. Due to no reactivity, the resulting mixture was heated to 110 °C for 16 hours (Scheme 51). Concentration *in vacuo* followed by ¹¹B NMR spectroscopy was performed, there was no complexation and only the boron starting material **2-8** was recovered with a broad singlet at 28 ppm.

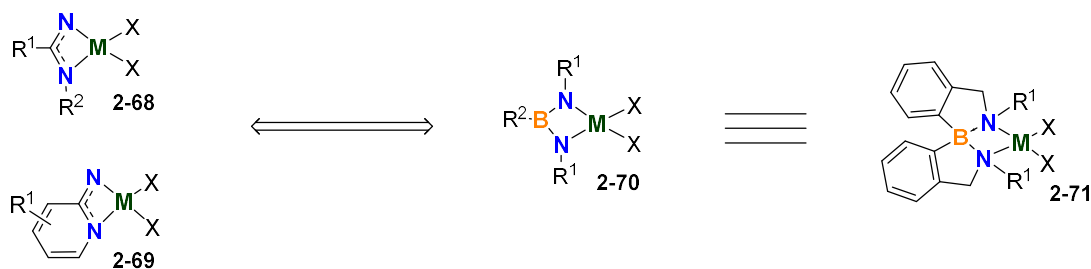


Scheme 51: Borazarophenanthrene reaction with tetrakis(dimethylamido)titanium(IV).

To conclude, varying the amineborane complex, Lewis acid, solvent and order of addition did not improve the conversion above 66%. The main hypothesis regarding the modest yields is the multiple additions onto the boron centre of the alcohol which prevents reactivity toward electrophilic cyclization. Complexation reactions with the borazarophenanthrene **2-8** and different titanium(IV) sources were unsuccessful. It was found instead that a substitution of the borazarophenanthrene hydroxyl group by the methyl or isopropoxyl group initially linked to the metal occurred, even if the resulting product was very moisture sensitive. Furthermore, the absence of reactivity of the borazarophenanthrene **2-8** with tetrakis(dimethylamido)titanium(IV) was seen in the previous reaction (Scheme 51), and could be due to the difference in reactivity between the boron-oxygen and the boron-nitrogen bonds.²⁵⁶ Despite all our efforts and research to prepare 1,3-*N,O*-chelating ligands with boron moieties, we decided to investigate borinic acid functionalized ligands to develop the related potential 1,3-*N,N*-chelating ligands.

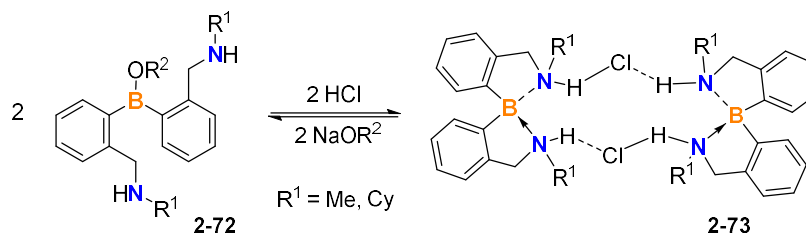
2.3 Development of potential 1,3-*N,N*-chelating ligands with the use of borinic acid synthetic derivatives

Synthesizing new potential 1,3-*N,O*-chelating agents containing a boron atom at the centre using the borazarophenanthrene was successful, but complexation to obtain new potential ligands were not as effective as we expected. A lots of examples of 1,3-*N,N*-chelating ligands have been reported in the literature, so we decided to switch our investigation from 1,3-*N,O*-chelating ligands to the development of such potential 1,3-*N,N*-chelating ligands.¹⁰ To obtain 1,3-*N,N*-chelating equivalents **2-68** and **2-69**, the *N,B,N* motif **2-70** was considered. Replacing the oxygen atom by one nitrogen should stabilize the entire framework. This *N,B,N* motif **2-70** considered would be accessible from the framework of compound **2-71**, which synthesis has been reported in the literature (Scheme 52).



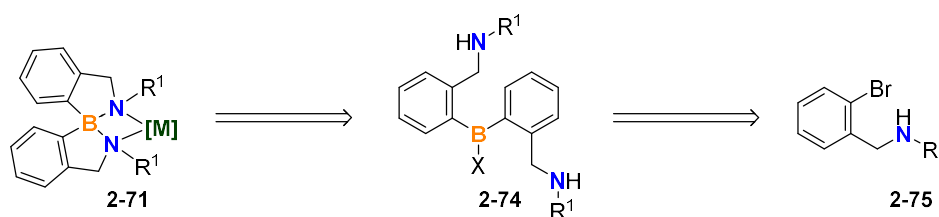
Scheme 52: Chemical frameworks of 1,3-*N,N*-chelating ligands amidinate and pyridinate (2-68-and 2-69) and boraamidinate 2-70 with the target compound 2-71.

In 2009, Saito and co-workers observed the existence of monomeric **2-72** and dimeric **2-73** aminoorganoboron complexes.²⁵⁷⁻²⁵⁸ They reported catalytic activities for selective alcoholysis using such systems due to the equilibrium between the open **2-72** and the closed **2-73** conformations (Scheme 53).²⁵⁷⁻²⁵⁸



Scheme 53: Acid/base equilibrium between the two forms.²⁵⁷⁻²⁵⁸

Inspired by this work, application of this system for the development of new potential 1,3-*N,N*-chelating agents was investigated. The open conformation would be an interesting molecular target to form the desired potential 1,3-*N,N*-ligand **2-71**, and a retrosynthetic approach was considered (Scheme 54). The *N,B,N* motif **2-71** could be obtained from a borinic acid intermediate **2-74** synthesized from the corresponding aryl bromide **2-75** by classic boron chemistry and the formation of the two carbon-boron bonds. *N*-substituted aryl bromide starting materials like *N*-substitued-2-bromobenzylamines **2-75** were considered. Their syntheses have been well documented in the literature.²⁵⁸ they are usually obtained by bimolecular nucleophilic substitution involving 2-bromobenzylbromide reagent or, by reductive amination using 2-bromobenzaldehyde.²⁵⁸

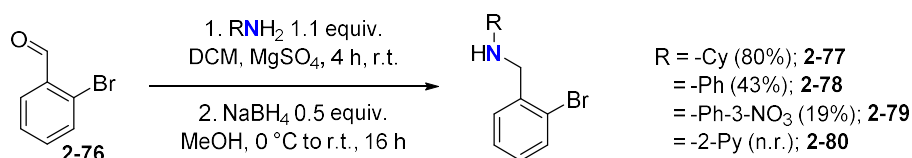


Scheme 54: Retrosynthesis for the formation of the desired potential complex.

2.3.1 Synthesis of *ortho*-substituted aryl bromides

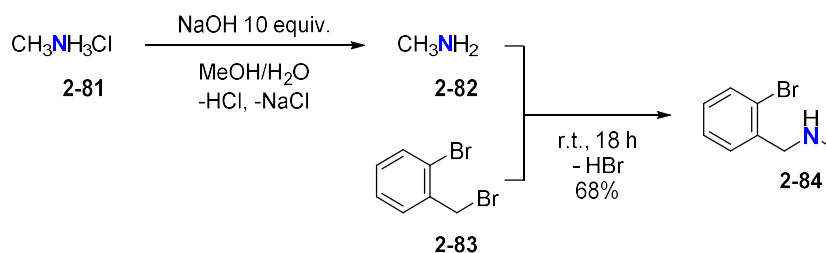
2.3.1.1 Preparation of *ortho*-substituted aryl bromides containing amine substituents

Ortho-substituted aryl bromides were synthesized following literature precedent.²⁵⁸ Reductive amination of the 2-bromobenzaldehyde **2-76** with the desired primary amine was performed in dichloromethane with an excess of magnesium sulfate (Scheme 55). Sodium borohydride reduction gave the desired product **2-77** in 80% yield, which is consistent with the literature. This procedure was also applied to aryl amines such as, aniline **2-78**, 3-nitroaniline **2-79**, and 2-aminopyridine **2-80**. Aniline **2-78** and 3-nitroaniline **2-79** were obtained in 43% and 19% yields respectively, while no reactivity was observed with 2-aminopyridine **2-80** (Scheme 55). This reaction shows different reactivity which is probably due to the difference of pKa and basicity between alkyl and aryl amines leading to lower yields in aryl amines cases.²³³ After comparing with the literature, **2-78** and **2-79** were already synthesized throughout another synthetic procedure.²⁵⁹ The authors left the reaction mixture 12 hours at room temperature under MgSO₄ and then added one equivalent of sodium borohydride to afford **2-78** in 95% yield and **2-79** in 90% yield.²⁵⁹ Aniline substituents needed longer reaction time than alkyl substituents probably because of the electronic effects impacting their reactivity.



Scheme 55: *Ortho*-substituted aryl bromides synthesis.²⁵⁸

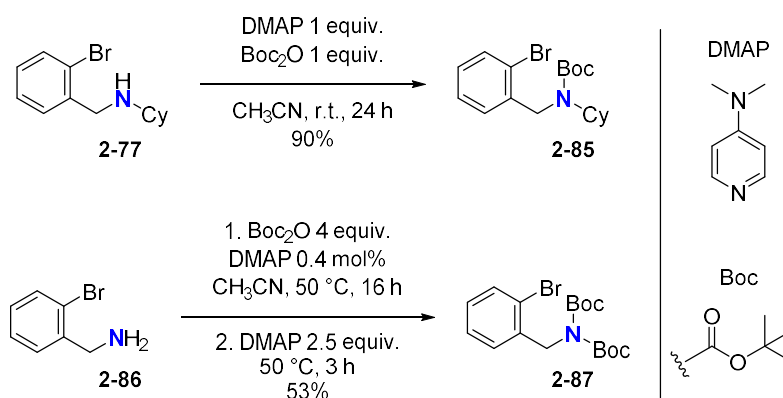
2-bromo-*N*-methylbenzylamine **2-84** was synthesized using a described procedure,²⁶⁰ from 2-bromobenzylbromide **2-83** which was diluted in a mixture of water and methanol. Methylamine **2-82**, beforehand deprotonated with sodium hydroxide in methanol and water, was added to the solution of **2-83** and left under stirring for 18 hours at room temperature. The desired product **2-84** was isolated without further purification in 68% yield (Scheme 56), which is consistent with the literature procedure.



Scheme 56: Synthesis of *N*-methyl-2-bromobenzylamine over binuclear nucleophilic substitution.²⁶⁰

2.3.1.2 Preparation of *ortho*-substituted aryl bromides containing protected amine substituents

Protected primary and secondary amines have been also synthesized using literature procedures with Boc substituent as protective group (Scheme 57).²⁶¹⁻²⁶² Compound **2-77** previously synthesized (Scheme 55), was solubilized in acetonitrile with DMAP and Boc₂O. After 24 hours at room temperature the desired product **2-85** was obtained in 90% yield. 2-bromobenzylamine **2-86** was protected using another procedure, four equivalents of Boc₂O were added into the solution of aryl bromide **2-86** in acetonitrile and DMAP was added.³¹ After several hours at 50 °C, the desired product **2-87** was isolated in 53% yield without further purification (Scheme 57). The yields obtained for both compounds are similar to the one described in the literature.

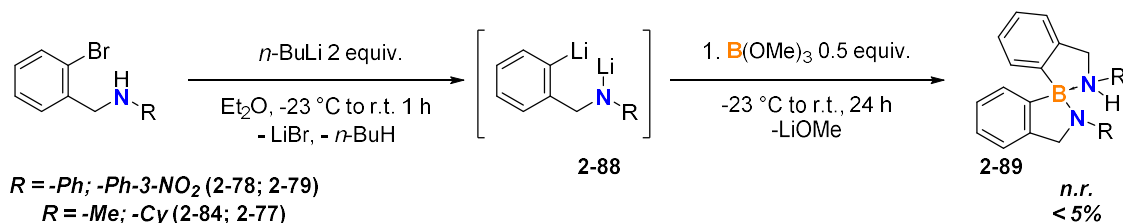


Scheme 57: Boc protected amines synthesis.²⁶¹⁻²⁶²

2.3.2 Synthesis of potential 1,3-*N,N*-chelating ligands

Having in hand a small library of various *ortho*-bromobenzylamine, we turned our attention towards the synthesis of *N,B,N* derivatives from borinic acids using two synthetic pathways: one described by Saito in 2009, and the other one developed in the Pucheault group.²⁵⁷⁻²⁵⁸ The synthesis described by Saito was first studied to obtain the desired compound **2-89** (Scheme 58). The *ortho*-bromo-*N*-alkylbenzylamine was diluted in diethyl

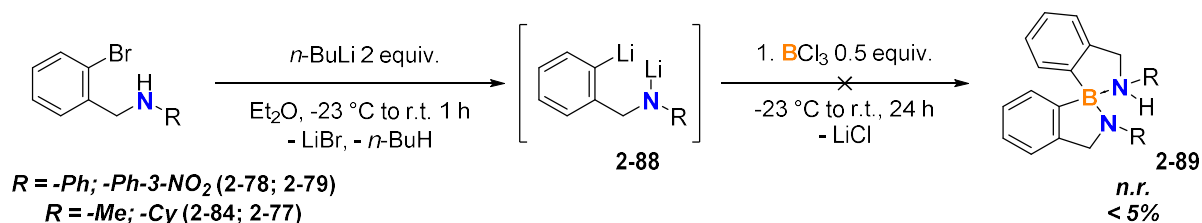
ether and *n*-BuLi was added to form the organolithium intermediate **2-88**. Then, half equivalents of trimethylborate reagent were added to the reaction mixture at -23 °C and left 24 hours at room temperature. Four reactions were performed with four different ortho-bromo-*N*-alkylbenzylamines as starting materials.



Scheme 58: Bis(borinate) compounds synthesis with trimethyl borate.

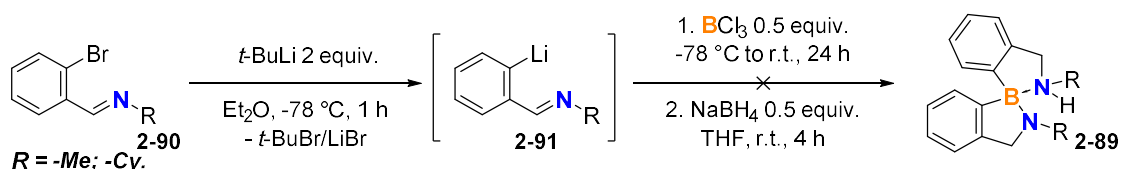
Ortho aryl bromides substituted by aryl amine **2-78** and **2-79** did not show any product formation after 24 hours of reaction. ^1H and ^{11}B NMR spectroscopy were performed to monitor both reactions with **2-78** and **2-79** and spectra of both reaction mixtures did reveal that full consumption of starting materials occurred. Signals on ^1H NMR spectra of the products formed were not consistent with corresponding compounds **2-79**, and no signals were observed on ^{11}B NMR spectra. Isolation of the unknown compounds was not efficient and full characterization of such products was not possible. This was an unexpected reactivity which was then attributed to the donor inductive effect of the amine substituents and benzyl groups that affected the formation of the intermediate **2-88** and probably its addition toward the boron centre. The reaction was performed with aliphatic substituents **2-77** and **2-84** and after a quick workup corresponding compounds **2-89** were obtained as crude products in less than 5% yield. The yields of crude products obtained were too low to consider purification by recrystallization, so the reaction was reiterated to improve the yield, but it remained lower than the one described in the literature. One major drawback of this reaction is the elimination of lithium methoxide in the second reaction step which is not known as the most efficient leaving group. One explanation for the yield difference between the one obtained and the one described by Saito would be the lack of details in the experimental procedure published.²⁵⁷⁻²⁵⁸ Indeed, they reported the formation of **2-89** with hydrochloric acid in their scheme while the use of this reagent and its quantity were not detailed in their experimental procedures.²⁵⁷⁻²⁵⁸ Hence, to improve the yield, the reaction was done with an alternative boron source, *i.e.* boron trichloride (Scheme 59). This latter is known to react following the same mechanism as borate derivatives but is more electrophilic. The same procedure was applied and ^1H and ^{11}B NMR spectroscopy were used to monitor the reaction, but no product formation was observed with any of the aryl bromide derivatives we

tried to react with (Scheme 59). At the opposite of borate derivatives, boron chloride forms lithium chloride salts **2-88** which can interact and affect the reaction outcome.



Scheme 59: Bis(borinate) compounds synthesis with boron trichloride.

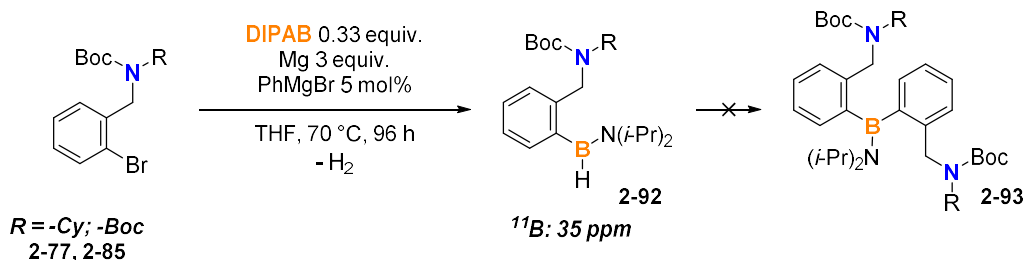
To overcome this synthetic problem, lithium/halide exchange was attempted on imine **2-90** (prepared using the previous procedure without the reduction step) by reacting it with two equivalents of *t*-BuLi (Scheme 60). Lithium/halide exchange is known in the literature to be fast and irreversible.²⁶³ Half equivalents of boron trichloride were then slowly added to the reaction mixture of **2-91** and left under stirring overnight. After reduction with sodium borohydride, the desired product **2-89** was not formed as observed by ¹H and ¹¹B NMR spectroscopy. There were no signals on the ¹¹B NMR spectrum, and the signals observed on ¹H NMR spectrum of the reaction mixture did reveal the presence of multiple signals hard to assign. Decomposition of the imine intermediate **2-91** is most likely to occur by forming different by-products, however it is also possible that boron trichloride over-reacted to form different chloride salts preventing the desired reaction to occur.



Scheme 60: Lithium/halide exchange followed by reduction reaction.

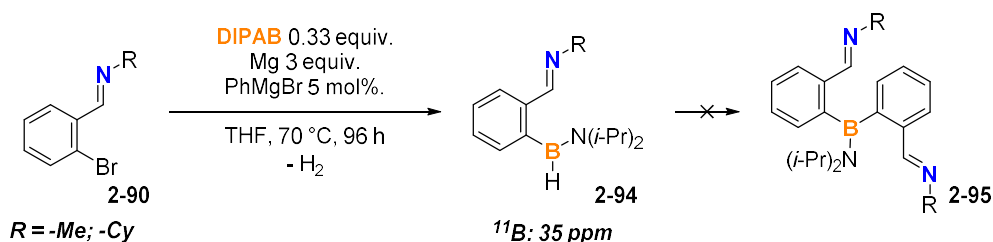
Synthesis of *N,B,N* product **2-89** was not successful with the method developed by Saito, so we tried to synthesize it using the methodology developed in the Pucheault laboratory for the synthesis of borinic acids with amineborane adducts as boron source.^{242, 246} Diisopropylaminoborane was synthesized *in situ* with one equivalent of DIPAB diluted in tetrahydrofuran and 5 mol% of organomagnesium reagent. Then aryl bromide **2-77** or **2-85** was added to the reaction mixture and heated at 70 °C for three days (Scheme 61). The reaction was monitored by ¹¹B NMR spectroscopy, and showed the first addition occurred by the formation of intermediate **2-92** as indicated by a doublet at 35 ppm on the ¹¹B NMR spectrum. Extending the reaction time did not afford the final product **2-93** and many reasons for the failure of the reaction can be hypothesized. The degradation of the intermediate **2-92**

can be one, and the steric hindrance of the *ortho* substituent could prevent the second addition onto the boron centre and constitutes a second hypothesis for the failure of the reaction. Another hypothesis could be the decreasing electrophilic character of the boron centre. Indeed, the first addition has formed intermediate **2-92** which is probably not electrophilic enough to react a second time and form the desired product **2-93**. The solvent was changed, and diglyme was also tried to heat at higher temperature, but there were no improvement of reactivity and was not successful (Scheme 61).



Scheme 61: Electrophilic borylation of *ortho*-substituted aryl bromides.

Electrophilic borylation process through lithium/halide exchange has also been performed with imine product **2-90** but instead of using boron trichloride, DIPAB has been used as the borylating agent (Scheme 62). Although product **2-94** from the mono-addition was observed by ^{11}B NMR spectroscopy the desired di-substituted product **2-95** did not form. It seems that the formation of carbon-carbon bond is the most critical step during this borylation reaction and after the first addition of the nucleophile toward the boron centre, boron intermediate is less electrophile and the second addition is less favoured than the first one. Hence, only one carbon-boron bond can be formed.

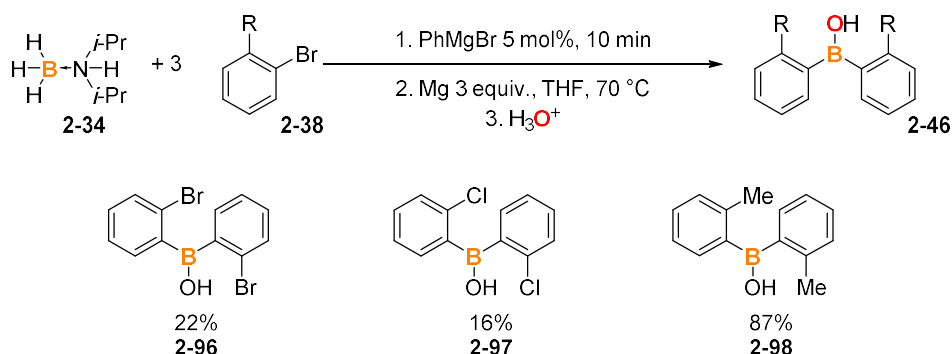


Scheme 62: Electrophilic borylation through lithium/halide exchange reaction.

2.3.2.1 Development of simple *ortho*-substituted borinic acids

The procedure developed in the Pucheault group was not efficient to synthesize borinic acid from corresponding *ortho-N*-substituted benzylamine as described in section 3.2. However, this procedure was tried and performed with available *ortho*-aryl bromides **2-38** as *ortho*-toluaniline, 2-chlorobromobenzene or 1,2-dibromobenzene. Electron withdrawing

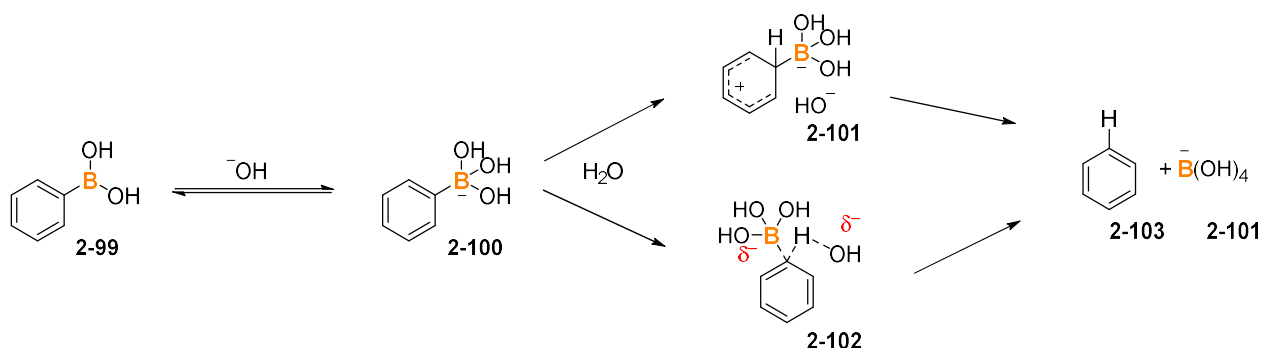
substituents such as bromide **2-96** and chloride **2-97** afforded poor yields (respectively 22% and 16%), whereas electron donating groups like methyl substituents gave high yield (87%, **2-98**) (Scheme 63).



Scheme 63: Examples of *ortho*-substituted borinic acids.

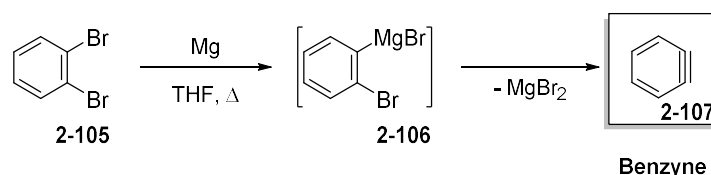
From literature precedent; two different hypotheses can be advanced to rationalize limitation with electron deficient aryl compounds in the case of compounds **2-96** and **2-97**. The first one is the protodeboronation of borinic acids which is made easier in the case of electron deficient substrate and the second implies benzyne formation.

Protodeboronation mechanism of boronic acids **2-99** has been described in the literature, and it involves the addition of hydroxide anion toward the boron centre forming the anionic intermediate **2-100**.²⁶⁴ This intermediate can then undergo through two different pathways. Either, through a dissociative process or through a cooperative pathway, leading to the formation of the protodeboronated product **2-103** and B(OH)₄ **2-104** (Scheme 64).²⁶⁴ Based on literature precedent, we suggest that borinic acids compounds can go through the same process leading to the degradation of desired product **2-96** and **2-97** and decrease the yield of the reaction.



Scheme 64: Protodeboronation mechanism.

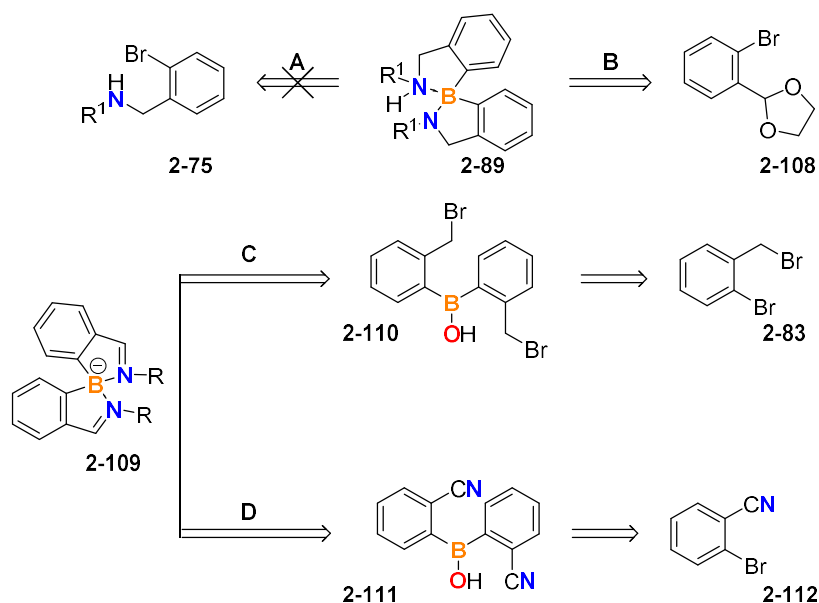
As mentioned before, benzyne formation could lead to low yields (Scheme 65). Literature precedent mentioned that addition of magnesium to a solution of 1,2-dibromobenzene **2-105** (or 1,2-dichlorobenzene) forms the Grignard intermediate **2-106**, which eliminate MgBr_2 and forms benzyne **2-107** (Scheme 65).²⁶⁵ Hence, we suppose that the low yield obtained with 1,2-dihalobenzene **2-96** and **2-97** (Scheme 63) is due to this intramolecular process which can be faster than the intermolecular reaction expected with the diisopropylaminoborane complex.



Scheme 65: Side reaction of the 1,2-dibromobenzene reactant.

2.3.2.2 Development of new synthetic approach for the formation of *N,B,N* motif

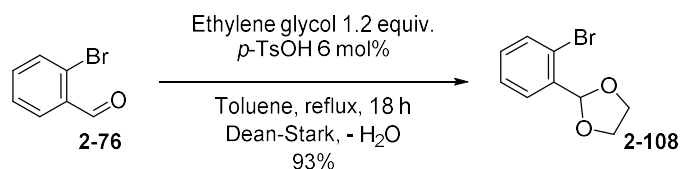
The approach developed by Saito was not efficient to obtain the desired *N,B,N* motif. Inspired by the work performed on simple borinic acid, we knew that the synthesis of *ortho* borinic acid was possible as presented in section 3.2.1. So, we decided to investigate new approaches and three different retrosynthetic strategies have been developed (Scheme 66). The first one uses protected 2-bromobenzaldehyde through a borylation route to obtain the desired product **2-89**. In the second strategy, 2-bromobenzylbromide **2-83** is thought to be an appropriate precursor for the formation of the desired *N,B,N* molecule **2-109** via borinic acid **2-110**. The last approach considered involves a borylation reaction of 2-bromobenzonitrile **2-112** with DIPAB via the procedure reported in the Pucheault laboratory (Scheme 66).



Scheme 66: New retrosynthetic pathways considered: A: retrosynthetic pathway developed before; B: reverse retrosynthetic of A; C and D: two retrosynthetic pathway involving the same molecular target.

2.3.2.2.1 Borylation reaction of protected 2-bromobenzaldehyde

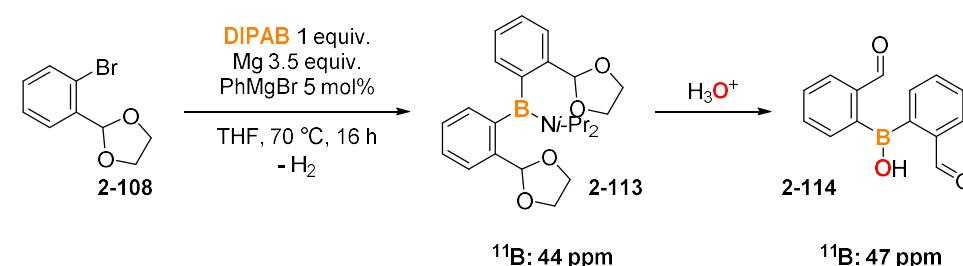
This strategy was developed starting with protected 2-bromobenzaldehyde **2-76** to obtain the borinic acid equivalent after borylation. Then, deprotection and reductive amination would form the desired *N,B,N* compound. The first step was protection of the 2-bromobenzaldehyde **2-76** using a known procedure in the literature with ethylene glycol to protect the aldehyde into acetal.²⁶⁶ For this, the acetal product **2-108** was synthesized by refluxing 1.2 equivalents of ethylene glycol and 2-bromobenzaldehyde **2-76** in toluene with a catalytic amount of *p*-TsOH (6 mol%).²⁶⁶ A dean stark apparatus was used to trap water generated *in situ* and the reaction was refluxed 18 hours. The desired product **2-108** was obtained in 96% yield without further purification, this yield is consistent with literature precedent (Scheme 67).²⁶⁶



Scheme 67: Protection reaction of the 2-bromobenzaldehyde.

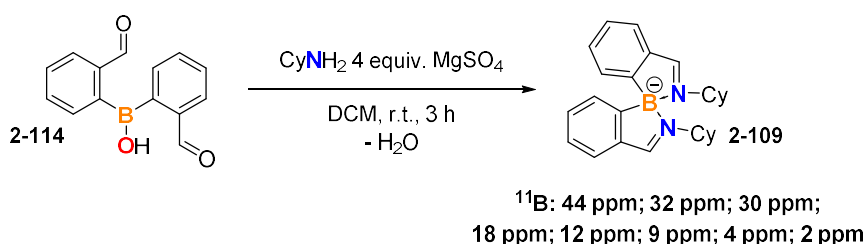
The procedure reported previously for the synthesis of borinic acid was applied to the resulting product **2-108**. One equivalent of DIPAB, a catalytic quantity of phenylmagnesium bromide (5 mol%) and 3.5 equivalents of magnesium were dissolved in tetrahydrofuran. The reaction mixture was heated at 70 °C for 16 hours and followed by ¹¹B NMR spectroscopy.

The diarylamino borane intermediate **2-113** was detected in the specific region of aryl aminoborane (resonance shift at 44 ppm on the ^{11}B NMR spectrum) with the presence of the arylaminoborane by-product at 39 ppm on the ^{11}B NMR spectrum. The conversion into the diarylamino borane was not complete. After acidic workup, product **2-114** was observed by ^{11}B NMR spectroscopy with a specific shift at 47 ppm and the boronic acid by-product at 33 ppm and an unidentified product at 3 ppm were also present on the ^{11}B NMR spectrum. Different workup and purifications on silica gel column chromatography were tried to purify this reaction mixture, but the compound **2-113** could not be properly isolated due to its sensitivity toward moisture. Indeed, borinic acid compounds are known in the literature to be hard to purify.^{242, 247} The reaction was performed with different source of boron, and the result obtained revealed that it worked well either with DIPAB or DICAB as boron sources (Scheme 68).



Scheme 68: Laboratory developed procedure for amineborane complex borylation process.

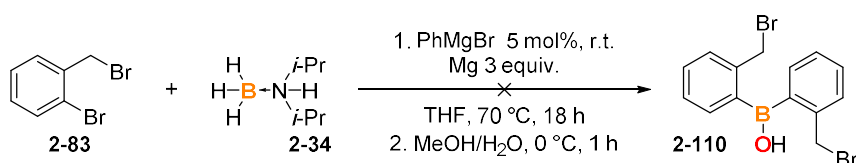
The next step which is the formation of the diamine was tried. Four equivalents of cyclohexylamine were slowly added to the mixture of borinic and boronic acid and magnesium sulfate in dichloromethane. After three hours at room temperature, the mixture was filtered and analysed by ^{11}B NMR spectroscopy. The ^{11}B NMR spectrum shows eight peaks that respectively correspond to eight potential boron compounds; ^1H NMR spectroscopy was also run but was not helpful to identify all of the compounds. There were too many signals overlapped to assign properly. Purification by recrystallization failed to afford pure product **2-109** (Scheme 69). Thus, it was not possible to conclude on the formation of the desired product through this synthesis route.



Scheme 69: Reductive amination reaction of boronic acid **2-114** to synthesize **2-109**. Chemical shifts observed on the ^{11}B NMR spectrum of the reaction mixture are indicated.

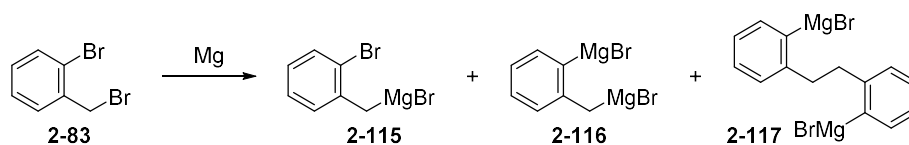
2.3.2.2.2 Nucleophilic substitution to form the desired *N,B,N* motif

The second approach was to form the desired *N,B,N* motif using nucleophilic substitution on the borinic acid intermediate (Scheme 70). This borinic acid compound would be obtained after the borylation of the 2-bromobenzylbromide **2-83** using the laboratory procedure. The first step consisted in the borylation reaction of the commercially available 2-bromobenzylbromide **2-83**. Likewise, the borylation developed in our laboratory was applied to the 2-bromobenzaldehyde. After quenching and workup of the reaction mixture, the desired product **2-110** was not obtained (Scheme 70).



Scheme 70: 2-bromobenzylbromide borylation reaction.

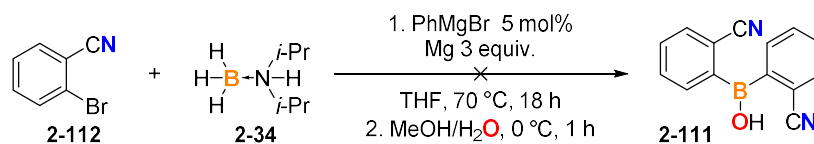
The impossibility to form **2-110** could be due to the lack of regioselectivity between the two bromide moieties. This led to the formation of three different Grignard intermediates: the benzylic Grignard **2-115**, the benzylic and aryl Grignard **2-116** and the one obtained after the Wurtz coupling **2-117** (Scheme 71). All those Grignard intermediates may be formed by-products instead of the desired borinic acid **2-110**.²⁶⁷



Scheme 71: Reaction between magnesium and 2-bromobenzylbromide.

2.3.2.2.3 Borylation reaction of the 2-bromobenzonitrile

For the last approach it was necessary to prepare first the borinic acid **2-111** from 2-bromobenzonitrile **2-112** (Scheme 72). The synthesis was applied with the classical conditions developed in our laboratory (Scheme 72).^{242, 246} 2-bromobenzonitrile **2-113** and one equivalent of DIPAB were diluted in tetrahydrofuran with three equivalents of magnesium. Catalytic amount of phenylmagnesium bromide was added at room temperature and the reaction was left at 70 °C. However after workup with methanol and water, no boron shift was detected on the ¹¹B NMR spectrum. Once again, there was no formation of *ortho* substituted borinic acid **2-111** with this approach. This could be due to the presence of the nitrile substituent on the aryl which could react in presence of Grignard reagent.



Scheme 72: 2-bromobenzonitrile borinic acid synthesis.

2.4 Conclusion

Development of new borylation pathways from the 2-hydroxybiphenyl and the 2-aminobiphenyl using amineborane complexes to replace toxic, air and moisture sensitive boron halide was studied. Different amineborane adducts, Lewis acids and solvents have been used to achieve the desired transformation. The maximum conversion obtained with our system has been 66% of conversion of starting material. It is possible that the conversion cannot be up to 66% due to side reactions of multiple addition of the alcohol on the boron centre, which leads to unreactive intermediate toward electrophilic borylation.

Coordination chemistry has been studied with dimethyltitanocene but no complexes were obtained with early transition metals. Indeed, dimethyltitanocene was not undergoing protonolysis reaction with the borazaphenanthrene as it was expected to. It was reacting instead like organomagnesium or organolithium reagent to form the alkylated product. To overcome this problem, different sources of titanium(IV), as titanium(IV) isopropoxide or tetrakis(dimethylamido)titanium(IV) has been employed without any success.

Synthetic development of the boroxaro- and the borazaro-phenanthrene synthesis showed narrow successes. Borylation of *ortho* substituted aryl bromide has been successfully showed with disparate yields. Hence, this advantageous transformation was applied to different *ortho* aryl bromides. *N*-substituted alkyl amines have been synthesized using known procedures from the literature and used through borylation process. Limited success has been obtained with the impossibility to obtain the desired *N,B,N* motif targeted molecule. Purification failed to isolate the desired product and in some cases only one carbon-boron bond had formed but the second carbon-boron bond did not form because of less reactive intermediates. Protection or tuning the aryl bromide starting material has been performed but resulted in the absence of formation of the desired compound.

The majority of this work has been developed at the University of Bordeaux, during the first part of my *Ph.D.*, and could not be further optimized at the University of British Columbia where I have done the second part of my *Ph.D.* However, the synthesis of different potential 1,3-*N,N*-chelating ligands have still been studied in UBC. Indeed, the presence of glovebox

material was useful to study another family of boron derivative: boraamidinates; which are highly air and moisture sensitive and will be presented in the next chapter.

3 CHAPTER III: DEVELOPMENT OF A NEW APPROACH FOR POTENTIAL BORON BASED LIGANDS: FORMATION OF 1,3-*N,N*-CHELATING LIGANDS

3.1 Potential Cyclic boraamidine ligands: synthetic development

3.1.1 Introduction

1,3-*N,O*-ligands have been widely used in organometallic chemistry for catalytic reactions.³⁵⁻⁷ They have notably been used in hydroamination¹⁰¹ and hydroaminoalkylation¹⁶² reactions, and more recently for monomer synthesis in polymerization chemistry.²⁶⁸ In 2013 Schafer and co-workers reported a phosphoramidate complex that can achieve the hydroaminoalkylation reaction at room temperature.²⁰² This improvement was due to the effect of the phosphorus centre which increased dramatically the electropositivity of the metal complex, and increased its reactivity for hydrofunctionalization. Based on this work, development of new potential 1,3-chelating ligands with an electrophilic heteroelement like boron seemed promising. Boraamidine was thought to be an appealing target for such transformations, since this type of potential ligand has not been applied to this chemistry. Due to the electrophilicity of boron atom, the resulting potential boraamidinate complex should be more reactive for hydrofunctionalization reactions as it is known that more electrophilic metal centres favour faster reactivity (Figure 16).^{13, 133}

In chapter two borinic acid synthesis was used to develop potential 1,3-chelating ligands containing the boron atom, but the synthetic pathway selected suffered from significant limitations. In this chapter another approach has been attempted featuring either acyclic or cyclic boraamidine derivatives. In the first part of this chapter, a literature study of cyclic boraamidines and their syntheses will be presented as well as a new retrosynthetic approach that we considered to obtain the desired boraamidine. The complexation chemistry of prepared boraamidine with early transition metals will then be discussed, followed by the synthesis of other acyclic boraamidines through another synthetic approach. The reactivity of the resultant potential ligands with early transition metals will also be presented at the end of this chapter, along with the catalytic activities of *in situ* prepared catalyst systems applied to the hydroamination and hydroaminoalkylation hydrofunctionalization reactions.

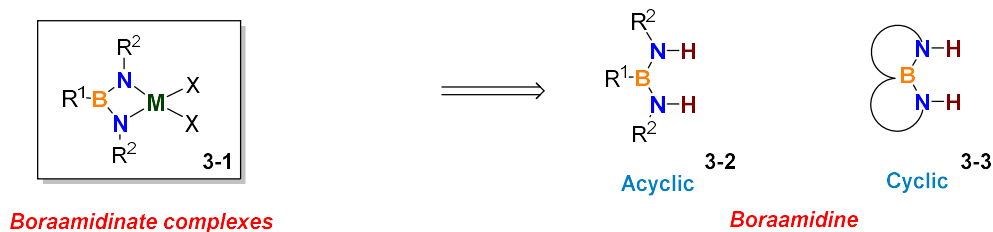
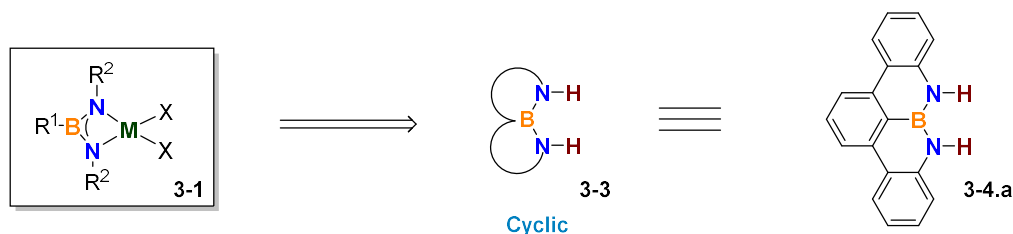


Figure 16: Introduction of the new 1,3-*N,N*-chelating target containing boron atom.

Cyclic and acyclic boraamidine derivatives were both considered for the synthesis of potential boraamidinate complexes. Acyclic boraamidine frameworks have a strong tendency to hydrolyse when they are in contact with air and moisture. Cyclic boraamidines, on the contrary, are less prone to hydrolysis and oxidation: their aromatic backbones promote enhanced stability of the boron-nitrogen bond. As cyclic boraamidines are more stable than acyclic variants, they were the first class of potential ligands to be studied and discussed in this section. Thus the main target considered was a pentacyclic compound in which the carbon-boron and nitrogen-boron bonds are part of the cyclic motif which should stabilize the resulting framework. This target was considered to develop new potential 1,3-*N,N*-chelating derivatives containing boron as a central element, thus forming a nitrogen-boron-nitrogen (*N,B,N*) type ligand (Scheme 73).

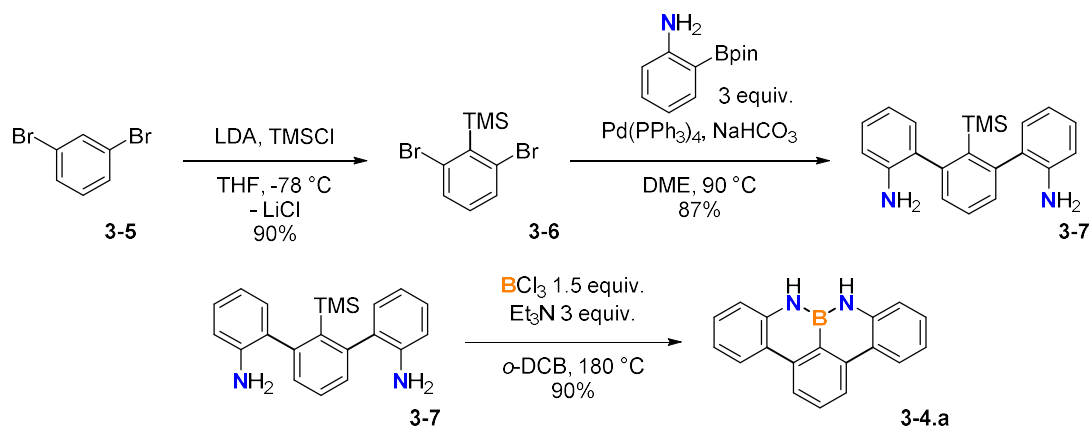


Scheme 73: Cyclic boraamidine targeted.

3.1.2 Precedent in the literature

The synthesis of such *N,B,N*-type polycyclic compounds namely, 1,9-diaza-9a-boraphenylene, was reported by Feng and co-workers in 2016.²⁶⁹ The reaction involved a first step of silylation using TMSCl to form the 1,2,3-trisubstituted benzene. A Suzuki-Miyaura cross-coupling reaction with more than two equivalents of boronate ester formed the desired tri(aryl) product. Addition of base and boron trichloride gave the final *N,B,N* polycyclic product in 90% yield through a transmetalation reaction (Scheme 74). By modifying the substituents on the aryl rings of the final product the authors reported new electrochemical and photochemical properties of these compounds.²⁶⁹⁻²⁷⁰ This synthesis requires pinacol boronate ester, which can be either bought or prepared in advance from 2-bromoaniline *via* a

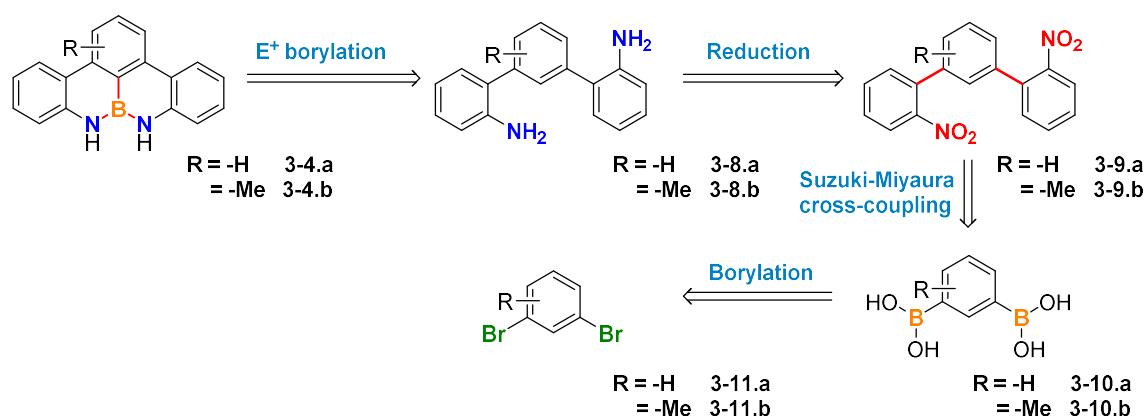
borylation reaction. The use of this pinacol boronate ester is the main disadvantage of this synthetic strategy for the generation of such *N,B,N*-type polycyclic compounds; the cost of 94.90 USD per gram is expensive. A significant amount of base is also generally required, which generates chemical waste. Another retrosynthetic approach is then required to afford the desired *N,B,N*-type polycyclic compound.



Scheme 74: Synthesis of the 1,9-diaza-9a-boraphenalene reported by Feng and co-workers.²⁶⁹

3.1.3 Method and strategy

The retrosynthetic analysis considered here contains four different steps to obtain the desired *N,B,N* polycyclic molecule **3-4** (**3-4.a** if R = -H, or **3-4.b** if R = -Me) (Scheme 75). The molecule could be obtained after an electrophilic borylation process of the precursor **3-8**. This same precursor could be obtained after reduction of the nitro-groups of molecule **3-9**. And **3-9** could be prepared using a Suzuki-Miyaura cross-coupling reaction. Finally the di(boronic) acid compound **3-10** could be synthesized using the 1,3-dibromobenzene derivative **3-11** through a Miyaura borylation using diisopropylaminoborane.²⁷¹



Scheme 75: Retrosynthesis for the synthesis of **3-4.a** and **3-4.b**.

The Suzuki-Miyaura cross-coupling reaction and the reduction of nitro groups have already been well documented in the literature and will be applied in the synthesis envisioned.²⁷²⁻²⁷³ The first borylation reaction, takes advantage of a pathway developed in our laboratory to synthesized boronic acid derivatives using amineborane complexes.²⁷¹ Finally, an electrophilic Friedel-Crafts borylation reaction was envisioned to complete the synthesis.

As shown in Figure 17 three different available positions on molecule **3-8.a** can go through a Friedel-Crafts reaction. Thus to avoid the formation of different products during the electrophilic Friedel-Crafts reaction, the molecule **3-8.b** having two methyl groups was chosen has the ideal substrate.

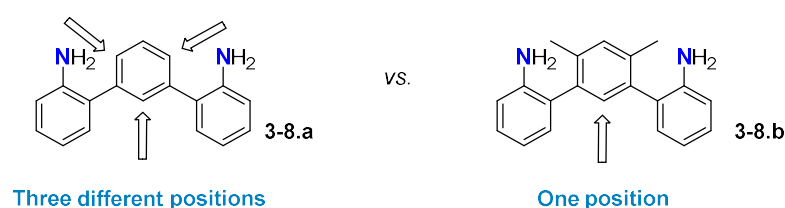
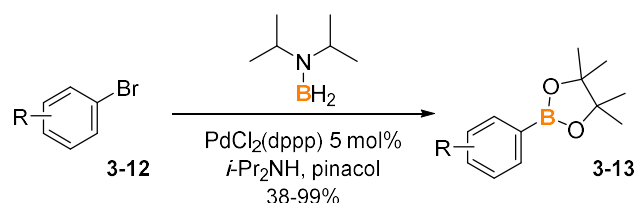


Figure 17: Potential reactive positions for electrophilic aromatic substitution on compound **3-8.a** and **3-8.b**.

3.1.4 Results of the synthesis

3.1.4.1 Miyaura borylation step

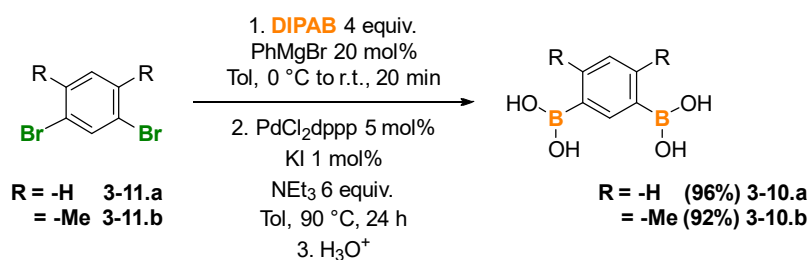
Inspired by the Miyaura borylation step, the Pucheault group has developed techniques to synthesize boronic acid derivatives in high yields.²⁷⁴ This pathway involves aminoborane as the boron source, using palladium(II) as catalyst and diisopropylamine as base. These conditions offer a Miyaura borylation to form the desired boronate ester upon quenching with dry pinacol (Scheme 76).²⁷⁴



Scheme 76: Palladium-catalyzed Miyaura borylation involving aminoborane developed by Pucheault.²⁷⁴

This reaction starts with the generation of the diisopropylaminoborane adduct *in situ*. This adduct is obtained by reacting diisopropylamineborane complex with a catalytic amount of phenylmagnesium bromide, as described in chapter two. This reaction leads to the release

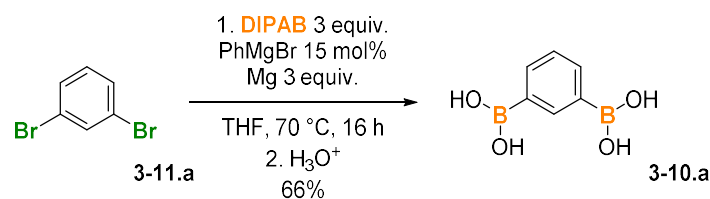
of dihydrogen. In toluene, after twenty minutes there was no more gas released, which indicated a complete conversion of diisopropylamineborane complex to diisopropylaminoborane. This result was confirmed by ^{11}B NMR spectroscopy with the shift of a quadruplet at -20 ppm of the amineborane adduct to a triplet at 36 ppm corresponding to the diisopropylaminoborane. Addition of the desired *meta*-dibromobenzene, 5 mol% of palladium catalyst, 1 mol% of potassium iodide, and an excess of base (triethylamine) to the reaction mixture promoted the formation of the desired di(boronic) acid derivatives. Di(boronic) acids were purified by precipitation with Ca^{2+275} and were obtained in high yields of 92% and 96% after a 24 hour reaction (Scheme 77).



Scheme 77: Synthesis of di(boronic) acids 3.10.a and 3.10.b.

The reaction has been easily scaled up to synthesize sub-gram scale (~5 g) of the product. When the reaction was carried out on 50 mmol scale, a reduced yield of 65% was obtained which is common for scaled up reactions considering the limitations of glassware for large scale synthesis and reaction headspace. This reaction is highly effective and tolerates substituted aryl bromides. Indeed, there are many examples in the literature comprising such reactions with other substituted aryl boronic acids containing either electron withdrawing or electron donating substituents.²⁷⁴

However, this procedure is not the only method possible to prepare di(boronic) acid. As described in the previous chapter, the Pucheault laboratory has developed another procedure to synthesize boronic acid compounds without catalysts. This pathway includes addition of 1,3-dibromobenzene to a mixture of DIPAB, phenylmagnesium bromide and magnesium. Heating the reaction at 70 °C for 16 hours also afforded the desired 1,3-diboronic acid in 66% yield (Scheme 78).²⁴³ This procedure results in a lower yield than the reaction incorporating the use of a catalyst.



Scheme 78: Synthesis of di(boronic) acid 3-10.a using Grignard reaction.

After isolating bis(boronic) acids **3-10.a** and **3-10.b**, the Suzuki-Miyaura cross-coupling reaction step was studied using 2-nitrobromobenzene and different palladium catalysts and different solvent systems. Optimization using a model substrate was first studied, followed then by the study of the desired transformation.

3.1.4.2 Suzuki-Miyaura cross-coupling reaction

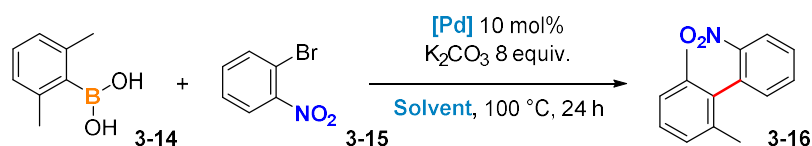
The Suzuki-Miyaura cross-coupling was first reported in 1981.²⁷⁶ This palladium-catalyzed cross-coupling reaction forms C-C bonds between organoborons and alkyl or aryl halides.²⁷⁶ The reaction was first observed using 1-alkenylboranes obtained through hydroboration, but is now largely applied to different organoborane derivatives like boronate esters or boronic acids.²⁷⁶⁻²⁷⁷

3.1.4.2.1 Optimization using a model substrate

The experimental conditions of the Suzuki-Miyaura cross-coupling reaction as applied to the synthesis of *N,B,N*-polycyclic molecules have been studied and executed using a model substrate: the 2,6-dimethylphenylboronic acid, which is a sterically hindered boronic acid like di(boronic) acids, but less expensive. Two different catalysts were used, *i.e.* palladium(II) acetate or tetrakis(triphenylphosphine)palladium(0) reagents. Potassium carbonate was chosen as base for the reaction with 2-nitrobromobenzene based on recent literature.²⁷⁸ The reaction was carried out in four different solvents (Table 6), PEG-400, ethanol, DMF and diglyme due to their high solubilizing properties. A mixture of the chosen solvent:water was used in a 5:1 ration (v:v) to ensure solubility of the potassium carbonate.²⁷⁹

With palladium(II) acetate catalyst, no product formation was observed by ¹H NMR spectroscopy. However, GC/MS analysis showed consumption of the 2-nitrobromobenzene **3-15** and formation of nitrobenzene which implies oxidative addition toward the palladium catalyst but the absence of product signify the impossibility to the reaction to continue (entries 1-4, Table 6). In contrast, tetrakis(triphenylphosphine)palladium(0) was found to be active. PEG-400:H₂O or EtOH:H₂O afforded 29% and 25% yields respectively (entries 5-6, Table 6). However, DMF:H₂O resulted in higher yield (33%) (entry 7, Table 6) and the best system was with diglyme and water which afforded the desired product in 43% yield (entry 8,

Table 6). The systems using PEG-400 and ethanol (both with water) did not solubilize the organic compounds, (*i.e.* 2-nitrobromobenzene and tetrakis(triphenylphosphine)palladium(0)) which resulted in the formation of inhomogeneous mixtures, thereby lowering the yields. However, DMF:water and diglyme:water systems were more efficient for the dissolution of all organic and inorganic compounds, leading to higher yields.



Entry	Catalyst	Solvents (5:1)	Yield [%] ^a
1		PEG-400:H ₂ O	n.r. ^b
2	Pd(OAc) ₂	EtOH:H ₂ O	n.r. ^b
3		DMF:H ₂ O	n.r. ^b
4		Diglyme:H ₂ O	n.r. ^b
5		PEG-400:H ₂ O	29%
6	Pd(PPh ₃) ₄	EtOH:H ₂ O	25%
7		DMF:H ₂ O	33%
8		Diglyme:H ₂ O	43%

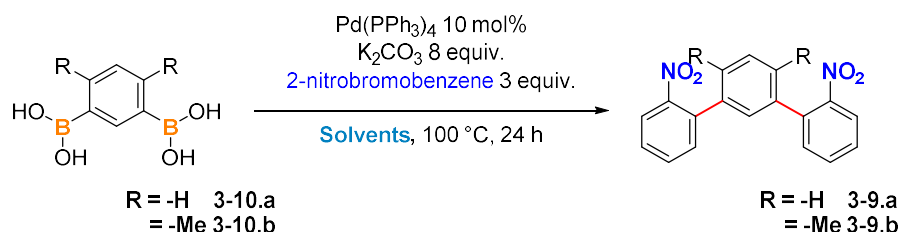
Table 6: Catalysts and solvents scope of the Suzuki-Miyaura reaction involving 2,6-dimethylphenylboronic acid and 2-nitrobromobenzene.

a. Isolated yield as determined after silica gel column chromatography (eluent: hexane:ethyl acetate). b. Determined by ¹H NMR spectroscopy and GC/MS analysis.

3.1.4.2.2 Application to the desired transformation

The developed reaction conditions were next applied to the synthesis of **3-9.a** and **3-9.b**. For R = -H (entry 4, Table 7), 44% yield of **3-9.a** was obtained in the optimized solvent system diglyme:water. Therefore, for **3-9.b** the designed procedure was not efficient, the reaction carried out in diglyme:H₂O – 5:1 resulted in only 5% yield with R = -Me (entry 1, Table 7) due to the low solubility in the diglyme/water system. Hence, two alternative solvents systems have been developed: mixture of DMF:water, and mixture of toluene:ethanol:water.²⁸⁰ A catalytic amount of tetrakis(triphenylphosphine)palladium(0) was still used with eight equivalents of base and three equivalents of the 2-nitrobromobenzene compound. With these solvent systems, low yields were obtained: 4% in DMF/water and, 15% in the ternary system (entries 2-3, Table 7). Despite a number of attempts to increase the reactivity, the yield never exceeded 15%. These results can be due to the low solubility of the di(boronic) acid starting material in organic solvents and in water. For R = -H, PEG-400:water and the system toluene, ethanol, water afforded 24% to 26% yield (entries 5-6,

Table 7). The best solvent system remained diglyme:H₂O. For both di(boronic) acid derivatives, each attempt failed to increase the yield higher than 44%. The decrease in reactivity of the 2-nitrobromobenzene toward cross-coupling reaction can be due of the low solubility of starting materials.²⁸¹

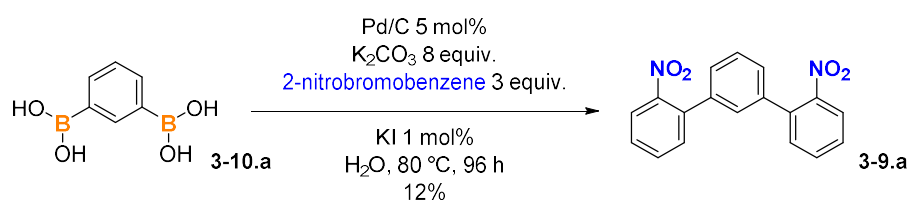


Entry	Substituents	Solvents (v:v)	Yield [%] ^a
1		Diglyme:H ₂ O (5:1)	5
2	R = -Me	DMF:H ₂ O (5:1)	4
3		Toluene:EtOH:H ₂ O (70:14:16)	15
4		Diglyme:H ₂ O (5:1)	44
5	R = -H	PEG400:H ₂ O (5:1)	24
6		Toluene:EtOH:H ₂ O (70:14:16)	26

Table 7: Solvents scope of the Suzuki-Miyaura cross-coupling reaction of di(boronic) acid derivatives and 2-nitrobromobenzene.

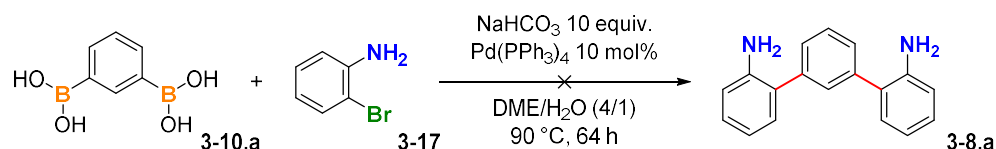
a. Isolated yield as determined after silica gel column chromatography.

To improve the catalytic system and to make the reaction greener and cheaper, palladium on activated charcoal was investigated as a replacement for tetrakis(triphenylphosphine)palladium(0). Palladium on activated charcoal has been reported as an efficient catalyst for the Suzuki-Miyaura reaction.²⁸² Thus, this catalyst was used for the desired transformation using the procedure reported: water as solvent at 80 °C during 96 hours of reaction. After silica gel column chromatography, the desired aryl product was isolated in only 12% yield showing no improvement (Scheme 79). The reason could be due to the low solubility of the boronic acid and the 2-nitrobromobenzene in water. Indeed, this particular procedure was reported with alcohol functions on boronic acids and aryl bromides, thereby increasing their solubility in water solvent.²⁸²



Scheme 79: Suzuki-Miyaura cross-coupling reaction using palladium activated on charcoal as catalyst.²⁸²

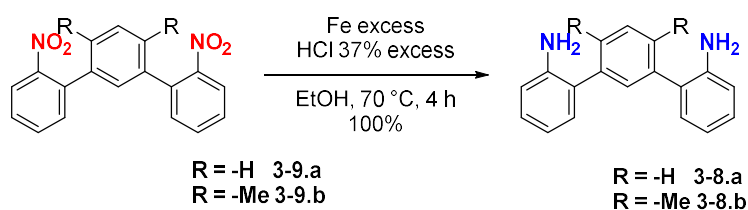
These experiments outline the entire retrosynthetic route using 2-nitrobromobenzene and a Suzuki-Miyaura cross-coupling reaction. This pathway was considered to avoid the amine containing substrate that could behave as a base and not as a cross-coupling partner. This alternative role in the reaction would not result in the formation of the desired product. Nevertheless to verify that this was the case, the reaction with 1,3-diboronic acid **3-10.a** and 2-bromoaniline **3-17** was attempted following a reported procedure.²⁶⁹ Ten equivalents of sodium bicarbonate were diluted in a mixture of DME and water.²⁶⁹ Then, both starting materials were added to the resulting solution along with tetrakis(triphenylphosphine)palladium(0).²⁶⁹ The reaction was monitored by TLC for 64 hours and only the mono-substituted product from the Suzuki-Miyaura cross-coupling reaction was observed and confirmed by GC/MS analysis. Extending the reaction time did not result in the desired product **3-8.a** (Scheme 80).²⁸³ However, another procedure to synthesize **3-8.a** was reported and developed in 2015.²⁸⁴ The authors mentioned the synthesis of **3-8.a** using potassium carbonate, Pd(dppf)Cl₂, in THF/H₂O at 70 °C for 18 hours and they isolated the product in 88% yield.²⁸⁴



Scheme 80: Suzuki-Miyaura cross-coupling reaction with *meta*-diboronic acid **3-10.a** and 2-bromoaniline **3-17**.

3.1.4.3 Reduction step

The next step was the reduction of the nitro moieties on compounds **3-9.a** and **3-9.b**. The reduction step of **3-9.a** and **3-9.b** was studied using a known procedure, selected because it involved readily available cheap reagents such as iron and hydrochloric acid.²⁷³ An excess of iron and hydrochloric acid were added to a solution of **3-9.a** or **3-9.b** in ethanol. After heating at 70 °C for four hours, substrates **3-9.a** and **3-9.b** were quantitatively reduced into the amine compounds **3-8.a** and **3-8.b** (followed by TLC and GC/MS analysis) (Scheme 81). Products **3-8.a** and **3-8.b** were isolated after work-up as pure yellow oil without the need of purification.

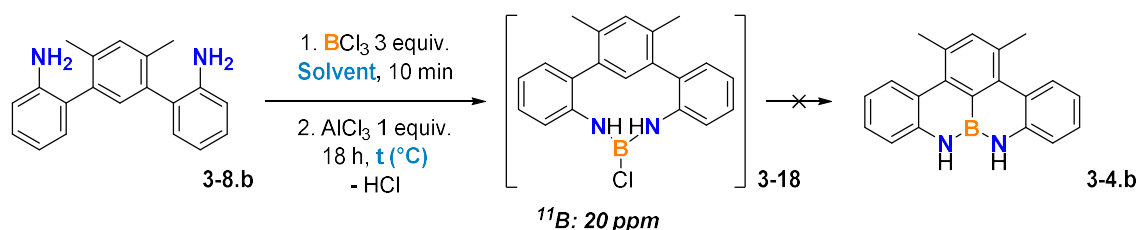


Scheme 81: Reduction of the nitro moieties of compounds **3-9.a** and **3-9.b**.

3.1.4.4 Electrophilic borylation step

3.1.4.4.1 Boron trichloride procedure

The fourth step of the strategy developed was the electrophilic borylation of resulting compounds **3-8.a** and **3-8.b**. For this transformation the conditions developed in the chapter two for the synthesis of the borazarophenanthrene were applied. An excess of boron trichloride was added to the mixture of starting material in cyclohexane with one equivalent of aluminium trichloride at 70 °C overnight (entry 1, Table 8). Unfortunately, the desired product **3-4.b** was not obtained and after workup the starting material was recovered. Monitoring the reaction by ^{11}B NMR spectroscopy showed the formation of the diaminochloride intermediate **3-18** as indicated by the observation of a typical chemical shift at 20 ppm in the ^{11}B NMR spectrum. In order to heat at higher temperature and to favour the electrophilic reaction, cyclohexane was replaced by *p*-xylene (bp = 133 °C), mesitylene (bp = 167 °C) and decaline (bp = 190 °C). Heating at the solvent reflux temperature did not overcome the problem: electrophilic cyclization did not occur (entries 2-4, Table 8).



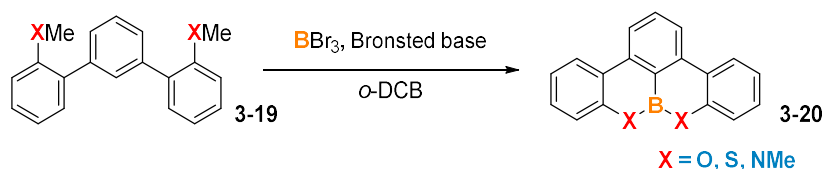
Entry	Solvents	Temperature [°C]	Yield [%] ^a
1	Cyclohexane	70	n.r.
2	<i>p</i> -xylene	133	n.r.
3	Mesitylene	164	n.r.
4	Decaline	190	n.r.

Table 8: Solvents scope for the electrophilic borylation reaction using boron trichloride.

a. Determined by ^{11}B NMR spectroscopy.

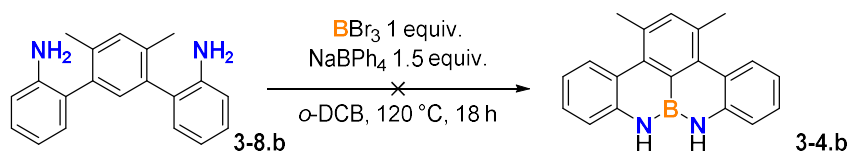
3.1.4.4.2 Boron tribromide procedure: demethylation/borylation

In 2016, Hatakeyama and co-workers published the borylation reaction of compound **3-19** using boron tribromide as a reagent in the presence of a Bronsted base in *ortho*-dichlorobenzene solvent.²⁸⁵ This process involved a demethylation mechanism process to form the desired product **3-20** (Scheme 82).²⁸⁵



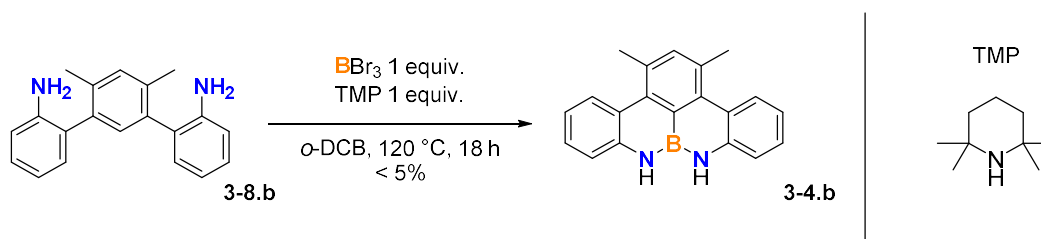
Scheme 82: Formation of **3-20** through demethylation reaction involving boron tribromide.²⁸⁵

This procedure was applied in the case of compound **3-14**, using one equivalent of boron tribromide and 1.5 equivalents of NaBPh_4 as base. After heating the reaction mixture at 120 °C for 18 hours in *ortho*-dichlorobenzene, the reaction was monitored by ^{11}B NMR spectroscopy. No conversion of **3-8.b** into the desired product **3-4.b** was observed without no observation of boron signal between 20 to 30 ppm on the ^{11}B NMR spectra (Scheme 83). Hence, **3-8.b** was recovered after the reaction workup.



Scheme 83: Borylation reaction of **3-14** using boron tribromide and NaBPh_4 .

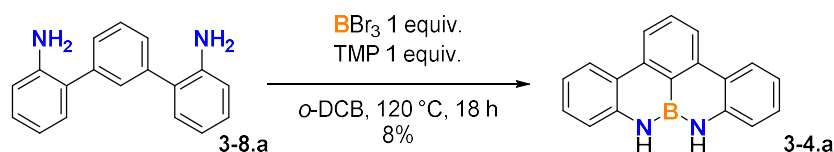
The reaction was performed again by changing NaBPh_4 with another Bronsted base. After heating for 18 hours at 120 °C, traces of the desired product were obtained which was confirmed by a small peak at 28 ppm on the ^{11}B NMR spectrum (Scheme 84). Due to the small amount of product formation, purification of **3-4.b** could not be performed. Increasing the scale of the reaction to obtain a decent amount of product **3-4.b** always resulted in low yield making impossible any purification.



Scheme 84: Borylation using boron tribromide and TMP.

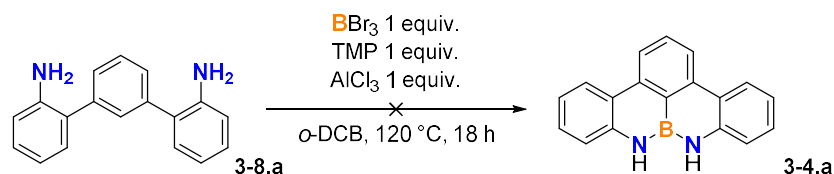
The borylation reaction was applied to **3-8.a**, using the same reaction condition as described with **3-4.a**. Herein, the desired product was isolated after silica column chromatography in low yield (8%) (Scheme 85). 1D and 2D NMR analyses confirmed the isolation of the desired product **3-4.a** and analyses were also confirmed with literature

precedent. The protection of the two *ortho* positions using methyl groups was not a necessary condition to achieve this transformation.



Scheme 85: Borylation of 3-8.a using boron tribromide and TMP.

Attempts to improve the reaction were done by adding one equivalent of aluminium trichloride. The reaction was heated at 120°C for 18 hours and was monitored by ^{11}B NMR spectroscopy. Unfortunately, the desired product was not formed under this reaction condition (Scheme 86). Aluminium trichloride was not working as a usual catalyst for the formation of the desired product through an electrophilic borylation process. Instead, it probably formed aluminium salt leading to the absence of reactivity toward electrophilic cyclization.



Scheme 86: Borylation of 3-8.a using boron tribromide and aluminium trichloride.

3.1.5 Towards potential early transition metal complexes

While the synthesis of the desired compound could not be optimized to obtain the desired product in high yields, a reliable synthetic protocol was developed. With compound 3-4.a in hand the reactivity with early transition metals was studied. Compound 3-4.a was diluted either in deuterated tetrahydrofuran or deuterated toluene and one equivalent of tetrakis(dimethylamido)titanium(IV) was slowly added to the resulting mixture (Figure 18) then the reaction was monitored by ^1H and ^{11}B NMR spectroscopy. The first NMR analysis recorded after the addition showed no reaction as well as after 18 hours at room temperature under stirring. Hence the reaction was heated at 80°C for an extended period of time (until 72 hours), but it only resulted into product degradation due to heating (Figure 18).

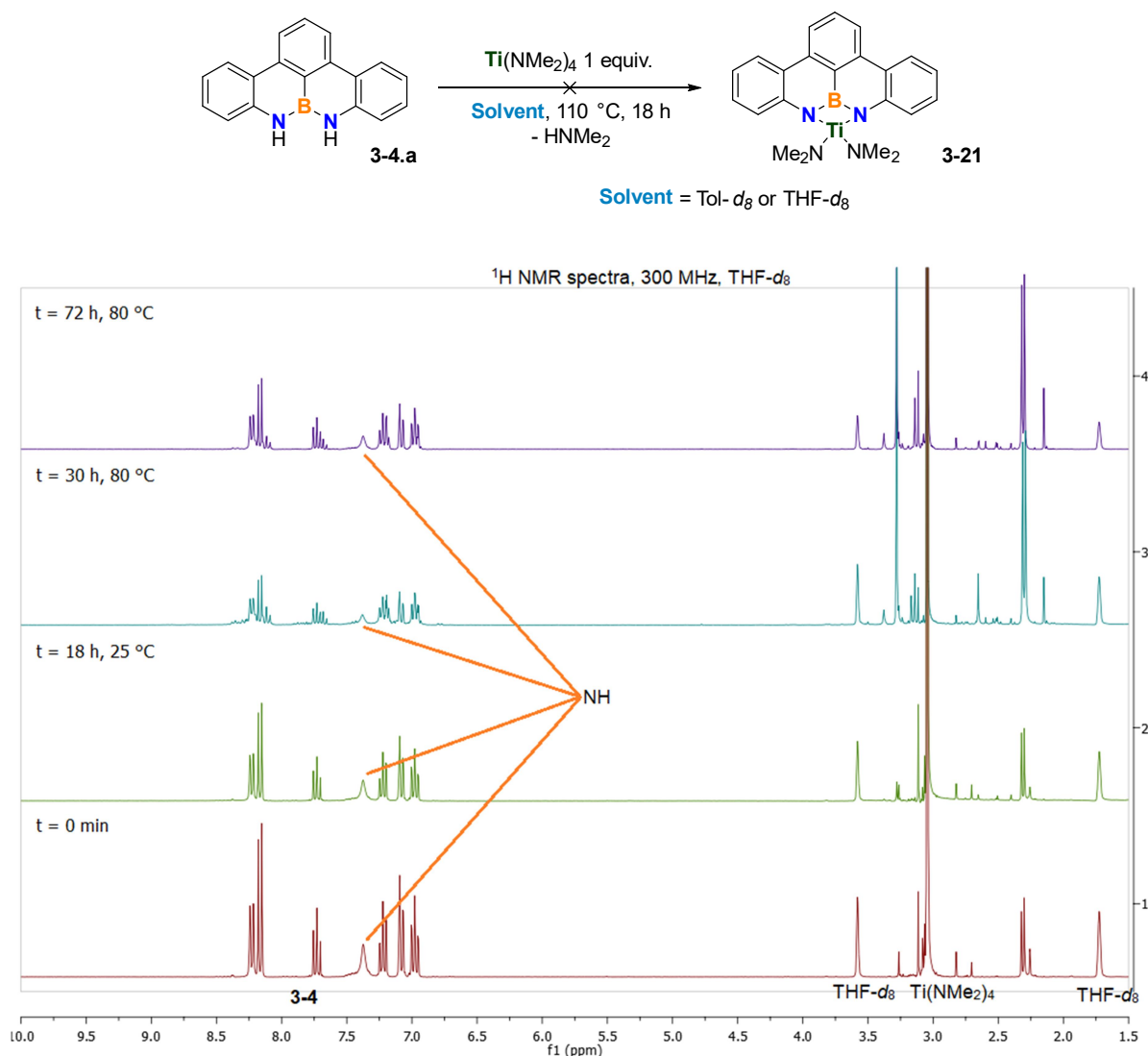
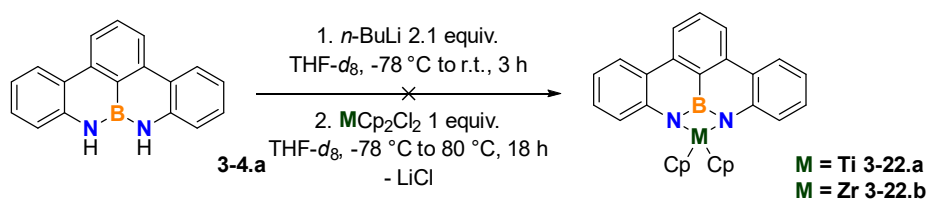


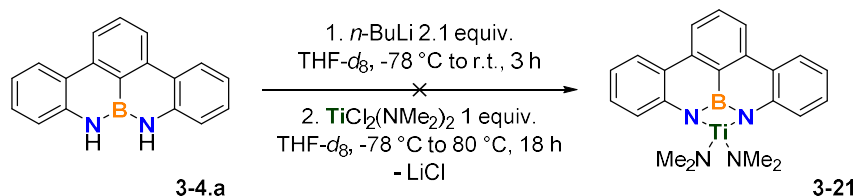
Figure 18: a) Protonolysis reaction between **3-4.a** and tetrakis(dimethylamido)titanium(IV). b) ^1H NMR spectra of the protonolysis reaction.

Instead of using the previous protonolysis type reaction, a salt metathesis reaction was proposed. A slight excess of organolithium reagent was first added to a solution of **3-4.a** in deuterated THF at low temperature. Next, one equivalent of either dichlorobis(cyclopentadienyl)-titanium(IV) or zirconium(IV) was added at -78 °C and the reaction was left six hours. Monitoring the reaction by ^{11}B and ^1H NMR spectroscopy did not show any formation of the desired product **3-22.a** or **3-22.b** (Scheme 87).



Scheme 87: Salt metathesis reaction between **3-4.a** and bis(cyclopentadienyl)-titanium(IV) or zirconium(IV).

The reaction was attempted another time through the same procedure as employed previously, but a more reactive titanium complex *i.e.* dichloro(dimethylamido)titanium(IV) was used instead. However, in this scenario, no more boron signal was detected after 18 hours at 80 °C, and the ¹H NMR spectrum showed degradation of the reaction mixture (Scheme 88).



Scheme 88: Salt metathesis reaction between 3-4.a and dichloro(dimethylamido)titanium(IV).

In all these cases, recrystallization in apolar solvent such as hexane did not form any crystal, and NMR spectroscopy (¹H and ¹¹B) was not efficient to characterize products formed after each reaction. All attempts of having such complexes failed. Hence, the synthesis of cyclic boraamidine was successful but the formation of potential 1,3-*N,N*-chelating metal complexes failed. For this reason another approach was studied throughout the use of acyclic boraamidine. For the synthesis of such compounds, syntheses of aminochloroborane intermediates were required because dichlorophenylborane was the main starting material used.

3.2 Potential acyclic boraamidine ligands: synthetic development

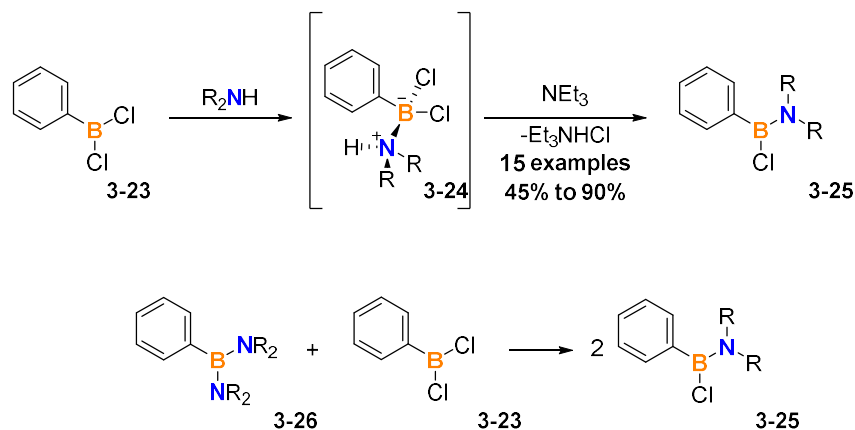
3.2.1 Introduction

3.2.1.1 Synthesis of aminochloroboranes

Acyclic boraamidine derivatives have been reported for several years in the literature, and can be synthesized using nucleophilic addition onto boron halide derivatives.²⁸⁶ In 1982, Miller and Cragg developed a series of aminoborane derivatives by using dichlorophenylborane and primary or secondary amines as starting materials.²⁸⁶ Two methods were developed: 1) either starting with dichlorophenylborane followed by use of appropriate secondary amine, or 2) by mixing dichlorophenylborane and the desired boraamidine derivative (Scheme 89).²⁸⁶

The first route involved the addition of a solution of secondary amine to dichlorophenylborane **3-23** in benzene. The adduct **3-24** was then obtained and triethylamine was added to the resulting solution to afford the aminochloroborane **3-25** and ammonium salt

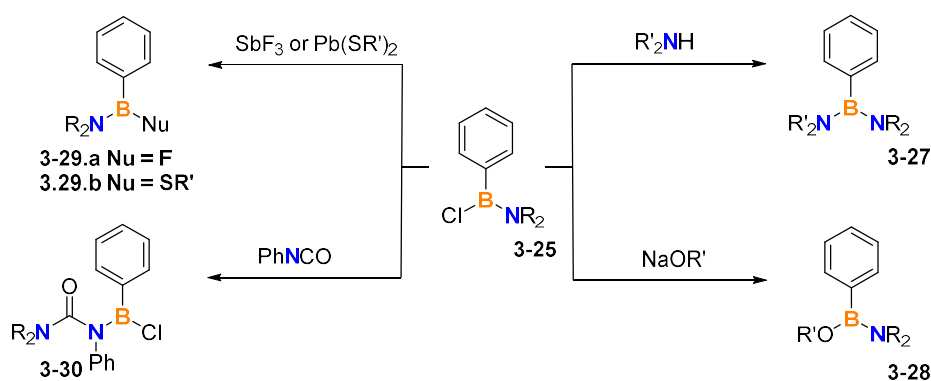
(Scheme 89).²⁸⁶ The second method was a redistribution reaction between a dichlorophenylborane **3-23** and a bis(dialkylamino)phenylborane **3-26** giving two equivalents of aminochloroborane **3-25** (Scheme 89).²⁸³ This second method requires the synthesis of the boraamidine beforehand.²⁸⁶



Scheme 89: General routes for aminochloroboranes syntheses.²⁸³

3.2.1.2 Aminochloroborane reactivity

Chlorodialkylaminophenylboranes **3-23** have a versatile reactivity for the synthesis of different organoboranes.²⁸⁶ Reaction with primary or secondary amines leads to the formation of bis(alkyl)aminophenylborane compounds **3-27**. Reactions with antimony trifluoride, lead thiolate, or sodium hydroxide (or alkoxide) have resulted in the formation of compounds **3-28** or **3-29**. When reacted with phenylisocyanate aminochloroborane **3-23** undergoes insertion to form the product **3-30** (Scheme 90).²⁸³



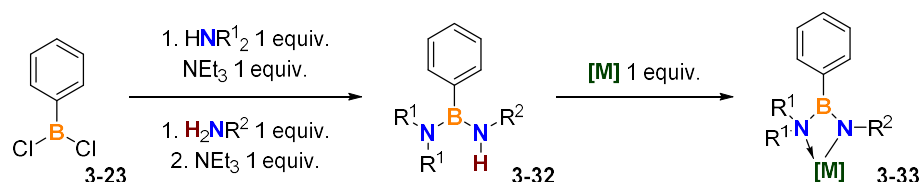
Scheme 90: Reactivity of chlorodialkylaminophenylboranes **3-25**.²⁸³

Aminochlorophenylboranes and bis(amino)phenylboranes have several mesomeric forms. Indeed, the lone pair located on the nitrogen can be delocalized over the boron-nitrogen bond which complicates ¹H and ¹³C NMR spectroscopic characterization.²⁸⁶ The

NMR assignments are even more complicated when unsymmetric bis(amino)phenylborane derivatives are synthesized.²⁸⁶

3.2.1.3 Unsymmetric boraamidine synthesis

The idea to develop such 1,3-chelating ligands was based on the results obtained by Doye in 2017, using a formamidine titanium complex for hydroaminoalkylation as presented in chapter one.⁵⁹ Based on those promising results for hydroaminoalkylation, and on the precedent for the formation of the 1,3-*N,N*-chelating ligands, development of new potential 1,3-*N,N*-ligands containing a boron atom centre with a similar backbone skeleton have been designed. Unsymmetric boraamidines could be synthesized using the same synthetic route as symmetric boraamidines.²⁸⁶ Then the resulting potential protic ligands could undergo a protonolysis reaction using metal complexes of titanium or tantalum (Scheme 91).

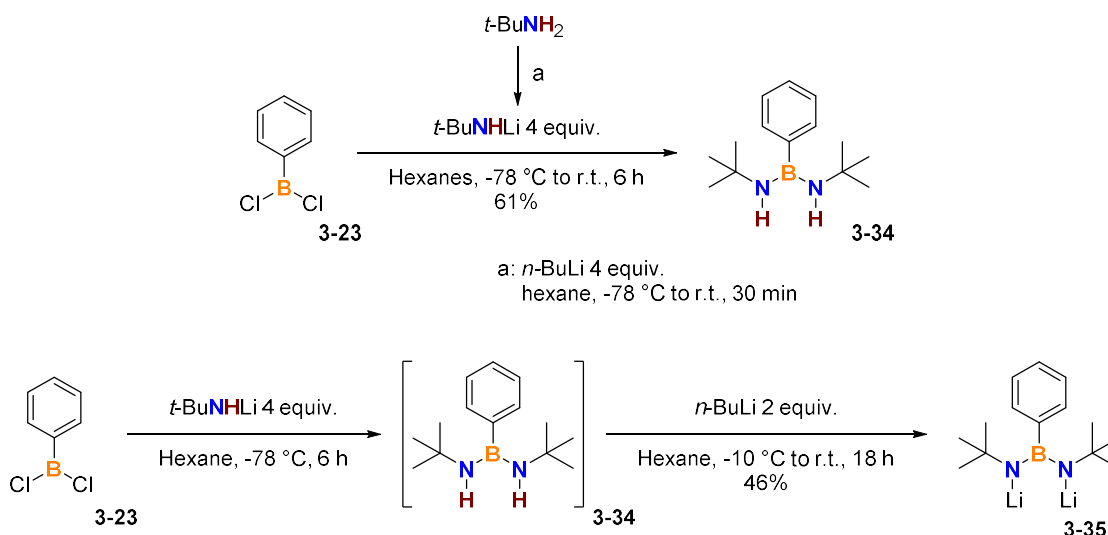


Scheme 91: Synthetic approach for potential unsymmetric boraamidinate metal complexes.

3.2.2 Potential acyclic boraamidine ligand synthesis

3.2.2.1 Synthesis of symmetric boraamidine potential ligands

Symmetric boraamidine compounds were successfully synthesized following the literature procedure described by Brask and co-workers in 2002.²⁸⁷⁻²⁸⁸ Slow addition of four equivalents of deprotonated *tert*-butylamine at -78 °C to a solution of dichlorophenylborane in hexane resulted in the formation of **3-34**. The product was isolated in 61% yield after filtration to eliminate all salts (Scheme 92). For this reason, the reaction was performed again without isolation of compound **3-34**. Instead, two equivalents of organolithium reagent were slowly added to the resulting mixture. The desired lithium salt **3-35** was isolated after filtration, and concentration *in vacuo* of all volatiles, and was isolated as a white solid (Scheme 92). ^1H and ^{13}C NMR analyses of the solid were corresponding to the one from the literature as well as the ^{11}B signal at 36 ppm as a broad singlet.²⁸⁷⁻²⁸⁸

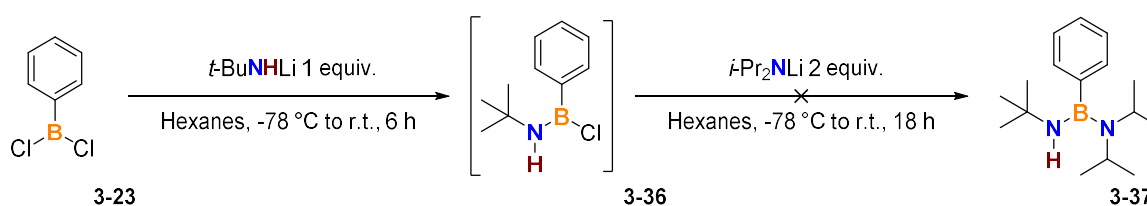


Scheme 92: Synthesis of boraamidine 3-34 and boraamidinate 3-35.

3.2.2.2 Synthesis of unsymmetric boraamidine potential ligands

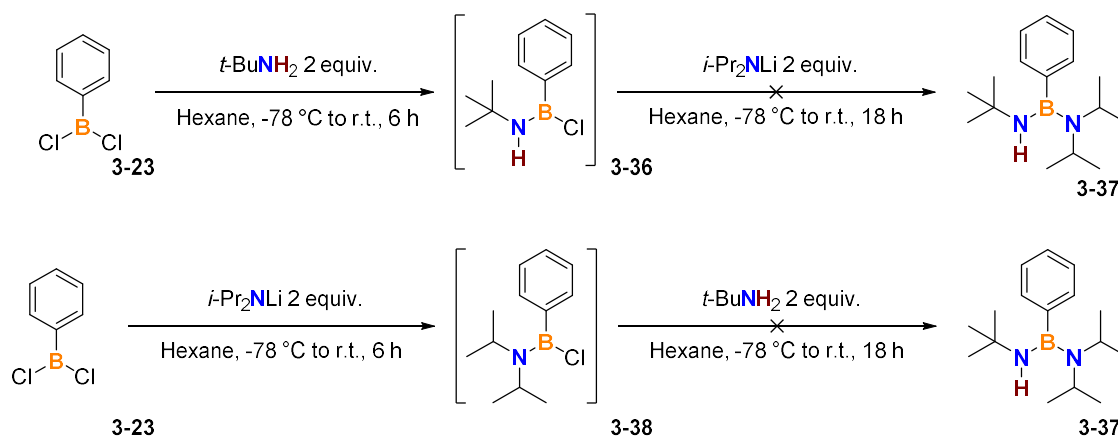
3.2.2.2.1 Synthesis using a one pot reaction

Synthesis of unsymmetric boraamidinate has been studied to obtain potential mono-anionic *N,B,N* ligands. The reaction was performed using the same procedure as reported previously but with one equivalent of lithiated *tert*-butylamine. Intermediate **3-38** was not isolated and two equivalents of lithiated diisopropylamine were added to the mixture. The reaction was monitored by ^{11}B NMR spectroscopy, and multiple products were formed. Due to the high sensitivity of those products to air and moisture, purification failed to isolate the desired product (Scheme 93).



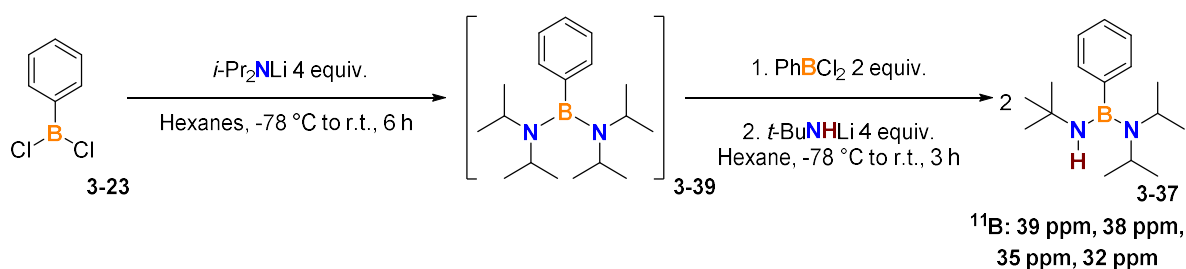
Scheme 93: Synthesis of unsymmetric boraamidinate 3-37.

Modifying the nucleophile by using *tert*-butylamine instead of the lithiated *tert*-butylamine did not solve the problem and neither did changing the order of addition of the amines (Scheme 94). Both syntheses resulted in complicated mixtures as analysed by ^{11}B NMR spectroscopy analysis, without the possibility of isolating the desired product.



Scheme 94: Change of nucleophile and addition's order for the synthesis of unsymmetric boraamidinate **3-37**.

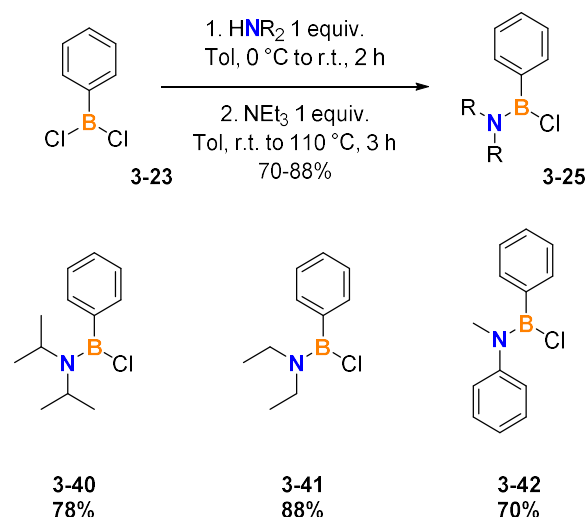
Unsymmetric boraamidinate **3-37** can be obtained by amine exchange with chloroborane derivatives as presented in the introduction of this part.²⁸³ Formation of the symmetric boraamidinate **3-39** was done *in situ* prior to the addition of two equivalents of dichlorophenylborane to the reaction mixture as reported in the literature.²⁸³ The resulting reaction led to a complicated mixture with several different ¹¹B shifts (39, 38, 35, and 32 ppm) which were hard to separate (Scheme 95).



Scheme 95: Synthesis of unsymmetric boraamidinate **3-37** using symmetric boraamidinate **3-39**.²⁸³

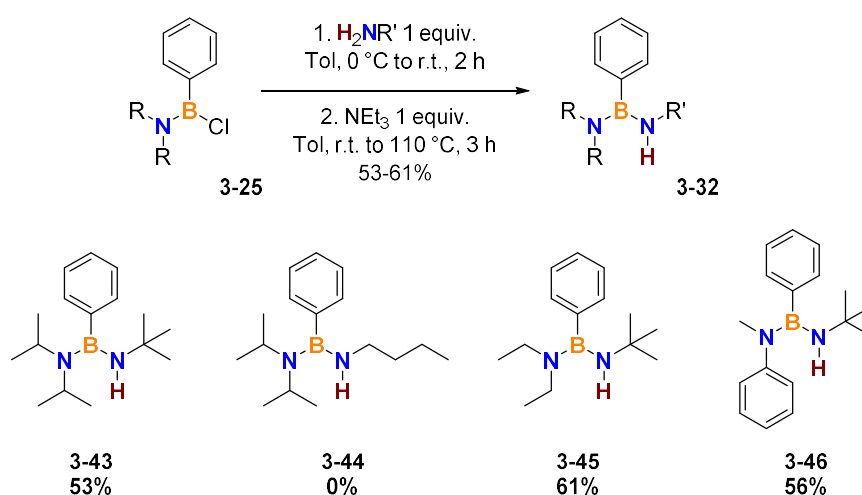
3.2.2.2.2 Synthesis using a two steps reaction pathway

The synthesis of **3-37** was modified and one equivalent of secondary amine was added to a solution of dichlorophenylborane **3-23** in toluene. After two hours at room temperature, one equivalent of triethylamine was added and the reaction was heated under reflux. After filtration, desired aminochloroborane products were obtained in high yield depending on the secondary amine used (Scheme 96). Different aminochloroborane derivatives were synthesized and were isolated after distillation. Diisopropylamine or diethylamine generated compound **3-40** and **3-41**, in 78% and 88% yields respectively and methylaniline gave compound **3-42** in 70% yield (Scheme 96).²⁸⁹ Compounds **3-40**, **3-41**, and **3-42** were analysed by NMR spectroscopy and ESI-MS and were in agreement with the literature.²⁸⁹



Scheme 96: Aminochloroborane synthesis and examples.

The desired unsymmetric aminoboranes were synthesized using the same procedure with one equivalent of primary amine added to a solution of aminochloroborane and one equivalent of triethylamine to trap hydrochloric acid (Scheme 97). Using *tert*-butylamine, compounds **3-43**, and **3-45** were obtained in moderate yields (53% and 61%). Aliphatic primary amine like *n*-butylamine gave a complicated mixture probably due to the less sterically hindered substituent. The resulting mixture was hard to purify, and the desired compound has not been isolated. Finally, aminochloroborane, in the presence of *tert*-butylamine formed compounds **3-46**, in 56% (Scheme 97). Compounds **3-43** and **3-45** were already reported in the literature and MS (ESI) and NMR analyses were in good agreement with the literature; while **3-46** was newly reported using the established procedure.²⁸⁹



Scheme 97: Unsymmetric boraamidine synthesis and examples.

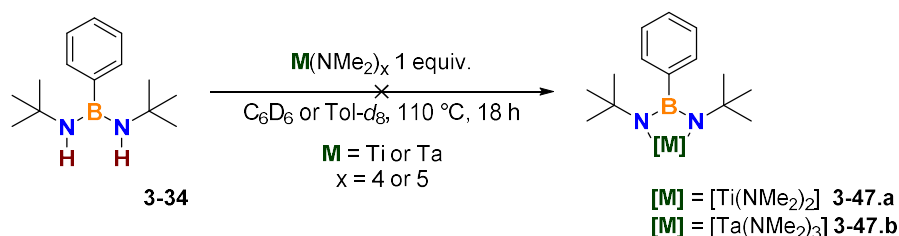
The synthesis of unsymmetric boraamidine throughout a two steps synthesis was successful while using only one step resulted to formation of complicated mixtures. This was likely due to amines exchange and formation of several different amineboranes and aminochloroboranes through a one-step synthesis. This formation of complicated mixture was more challenging for the isolation and purification of the desired product, whereas isolating the aminochloroborane and then the boraamidine avoided any amine redistribution and resulted into the formation of the desired product.

3.2.3 Toward potential early transition metal complexes containing boron atom

3.2.3.1 Protonolysis reactions

3.2.3.1.1 Reaction with early transition metal amido complexes

With the desired symmetric boraamidine in hand, the next step was the study of reaction complexation with early transition metals. Boraamidine **3-34** was diluted in deuterated benzene or toluene and one equivalent of tetrakis(dimethylamido)titanium(IV) diluted in deuterated solvent (toluene or benzene) was added to the resulting solution in a glovebox under inert atmosphere (Scheme 98). The reaction was then monitored by ^{11}B and ^1H NMR spectroscopy after the addition: protonolysis reaction did not occur. Hence, the mixture was heated for 18 hours at 110 °C, one new boron peak at 33 ppm was obtained on the ^{11}B NMR spectrum but the reaction was not complete as the starting material was still detected on ^1H and ^{11}B NMR spectroscopy. The reaction was left 18 hours more under heating, but the same results was obtained The ^1H NMR spectrum showed only one singlet for the NMe_2 which correspond to the tetrakis(dimethylamido)titanium(IV) starting material. Recrystallization in hexane of the mixture failed to afford crystals and the same results were obtained with pentakis(dimethylamido)tantalum(V).



Scheme 98: Boraamidine **3-34** reaction with tetrakis(dimethylamido)titanium(IV) or pentakis(dimethylamido)tantalum(V).

Using the same reaction conditions, unsymmetric boraamidines derivatives were also studied with the same early transition metal starting materials (*i.e.* titanium and tantalum amido). One equivalent of compounds **3-43**; **3-45**; **3-46**, were diluted in deuterated toluene and one equivalent of tetrakis(dimethylamido)titanium(IV) or pentakis(dimethylamido)tantalum(V) solubilized in deuterated toluene was added to the mixture in glovebox under dinitrogen and then heated at 110 °C. The reactions were monitored by ^{11}B and ^1H NMR spectroscopy, no formations of the desired products were observed with titanium or tantalum homoleptic complexes (Figure 19). However, monitoring the reaction by ^{11}B NMR spectroscopy disclosed two main boron peaks at 31 ppm and 33 ppm, both as broad overlapping singlets (Figure 19). 31 ppm peak corresponded to the unsymmetric boraamidine starting materials **3-43**, **3-45** or **3-46**, depending of the reaction. However the signal at 33 ppm on the ^{11}B NMR spectrum corresponded to an unknown species and could neither be isolated through recrystallization nor be clearly identified through NMR and ESI-MS analyses.

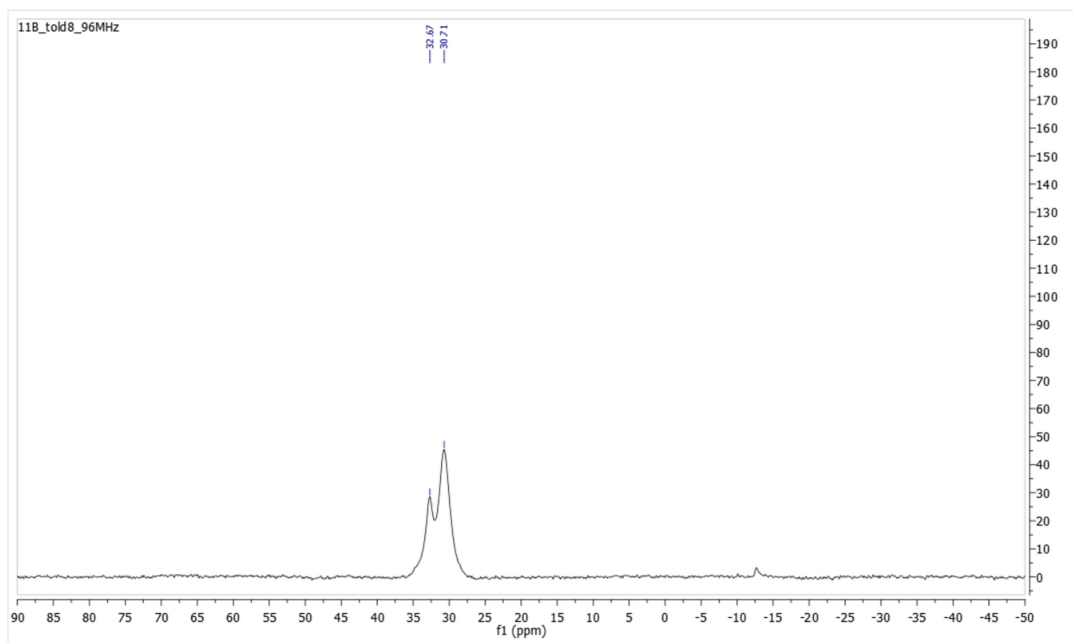
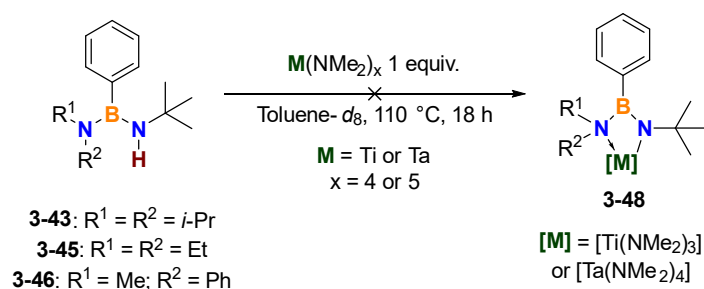
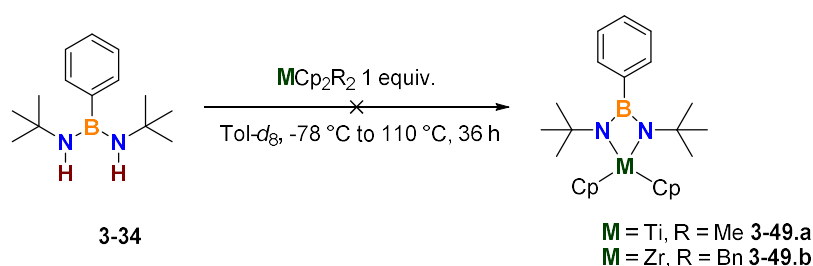


Figure 19: a) Unsymmetric boraamidines reactions with tetrakis(dimethylamido)titanium(IV) or pentakis(dimethylamido)tantalum(V). b) ^{11}B NMR spectrum of reaction mixture of **3-43** and $\text{Ti}(\text{NMe}_2)_4$ in deuterated toluene after 18 hours at 110 °C.

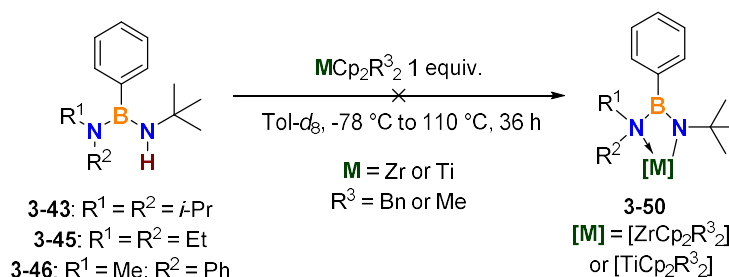
3.2.3.1.2 Reaction with early transition metal alkyl complexes

To overcome this problem of reactivity, alkyl metal complexes were synthesized using the literature procedure.²⁹⁰ First, dibenzyltitanocene was added at low temperature to a solution of boraamidine **3-34** in deuterated toluene. Then, the reaction was heated to room temperature and the reaction was monitored by ¹¹B and ¹H NMR spectroscopy. After 18 hours, no reactivity was observed; indeed there was no formation of toluene which was confirmed through ¹H NMR spectroscopy and the ¹¹B NMR signal was still at 30 ppm. Changing the metal source to dimethyltitanocene,²⁹¹ led to the same result without any product formation after 18 hours of reaction, and no methane formation with the possibility to see the same ¹¹B NMR signal at 30 ppm. Extending the reaction time and increasing the temperature to 110 °C in both cases did not change the outcome of the reactions (Scheme 99).²⁹²



Scheme 99: Boraamidine reactions with alkyl metal complexes.

The reaction was also studied with unsymmetric boraamidines (**3-43**, **3-45**, **3-46**) and the same alkyl metal complexes: dibenzylzirconocene or dimethyltitanocene. Dibenzylzirconocene was added to the resulting solution of unsymmetric boraamidine (**3-43**, **3-45**, **3-46**) in deuterated toluene at low temperature and the reaction was monitored by ¹¹B and ¹H NMR spectroscopy. But no reactivity between both starting materials was observed after 18 hours at room temperature, and the same result was observed with dimethyltitanocene (Scheme 100). Again, this absence of reactivity was observed by no gas evolution (methane) or formation of toluene *in situ*. To push the reaction forward, the reaction mixture was heated at 110 °C for 18 hours and monitored by NMR spectroscopy. The main boron peak at 30 ppm on ¹¹B NMR spectroscopy was closely related to starting materials, and decomposition of the alkyl metal was observed through ¹H NMR spectroscopy suggesting a possible reaction. Changing the amido homoleptic metal complex to alkyl metal complex led in both cases to the same conclusion, formation of the desired potential chelate metal complex was not successful and degradation or unidentified product was observed.

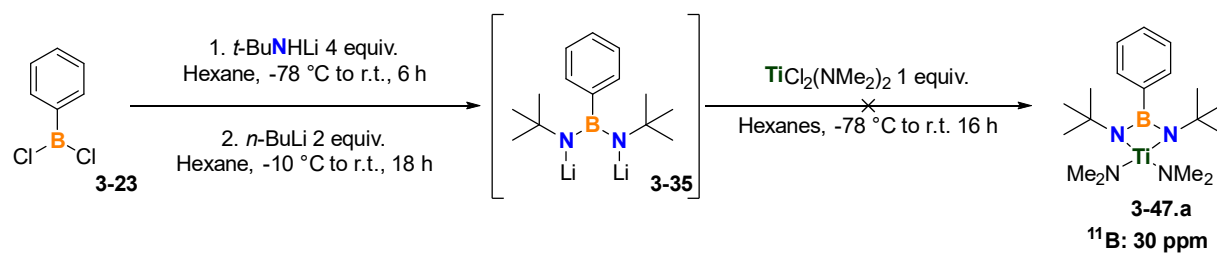
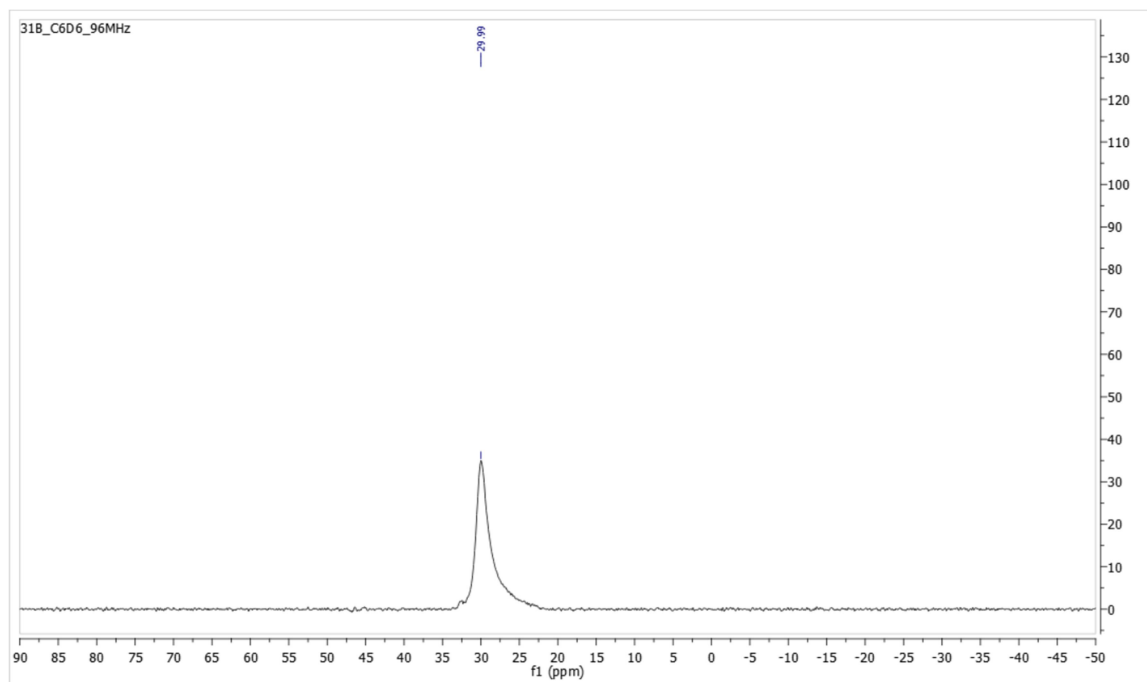


Scheme 100: Unsymmetric boraamidines reactions with alkyl metal complexes.

All trials to obtain either symmetric boraamidinate or unsymmetric boraamidinate metal complexes failed. The hemilability of amine moieties and their tendency to rearrange themselves could be the reason for the absence of product formation when amido metal complexes were used. Moreover, alkyl metal complexes showed no reactivity and degradation of the potential metal complex appeared when the reaction mixture was heated. Thus to overcome this problem, a salt metathesis reaction was then studied and is depicted in the next section.

3.2.3.2 Salt metathesis reactions

Salt metathesis reactions were performed with the boraamidinate lithium salt **3-35**. Using four equivalents of lithiated *tert*-butylamine with dichlorophenylborane **3-23** as starting material afforded the boraamidine compound. With two equivalents of lithium reagent, the bis(boraamidinate) lithium salt **3-35** was formed *in situ*. One equivalent of dichlorodimethylamidotitanium(IV) complex was added to the resulting mixture at $-78\text{ }^\circ\text{C}$ and the reaction was left overnight at room temperature (Scheme 101). ^{11}B NMR spectroscopy showed only one major peak at 30 ppm in the region of boraamidine derivatives (Figure 20) which is different from the boraamidinate **3-35** peak at 36 ppm. Crystals were obtained using hexane as a crystallization solvent and X-ray diffraction led to the following crystal structure *vide infra* (Figure 21). The structure shows a bis titanium complex bridged with two *tert*-butylamine moieties with a bond length of 1.9182(10) Å (Ti1-N1) and a bond length of 1.9196(10) Å between Ti1-N2 and the complex symmetry was C_2 as previously reported in the literature.²⁹³

Scheme 101: Lithiated boraamidinate salt **3-47.a** salt metathesis reaction.Figure 20: ^{11}B NMR spectrum of the reaction mixture above after the addition of dichlorodimethylamidotitanium(IV).

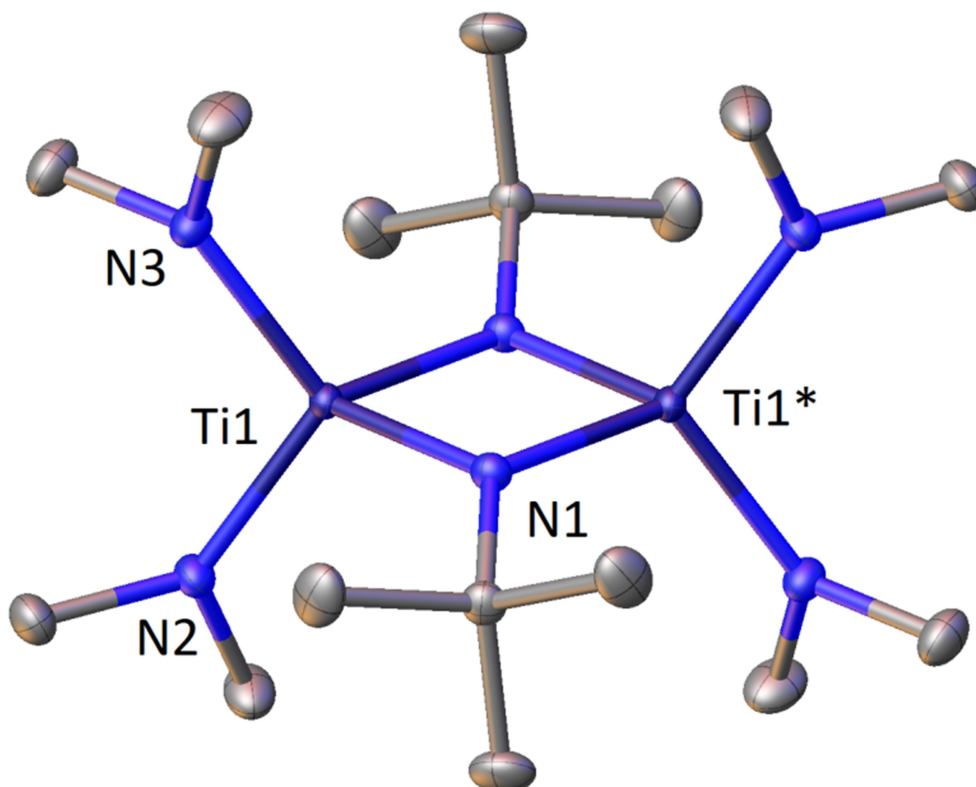
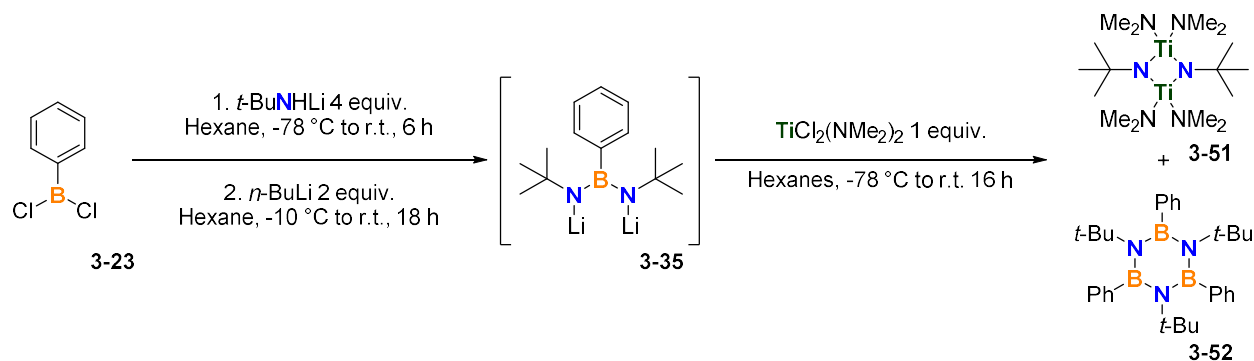


Figure 21: ORTEP representation of the solid-state molecular structure of **3-51** in crystals. Ellipsoids drawn at 50% probability. All hydrogen atoms have been omitted for clarity. Selected bond lengths (Å): (Ti1-N1) 1.9182(10), Ti1-N2 1.9196(10).

The resulting boron compound with a shift at 30 ppm on the ^{11}B NMR spectra was probably the borazine derivative **3-52** and not the desired product **3-54.a** (Scheme 102).²⁹⁴ Indeed, based on the literature, ^{11}B chemical shifts of borazine derivatives are centred around 30-34 ppm.²⁹⁴ The ^1H NMR spectrum also confirmed the possibility of borazine formation with five protons in the aromatic region and one singlet integrating for 18 protons in the aliphatic region. Which is the same as intermediate **3-35** but the shift were different of 0.10 to 0.20 ppm.

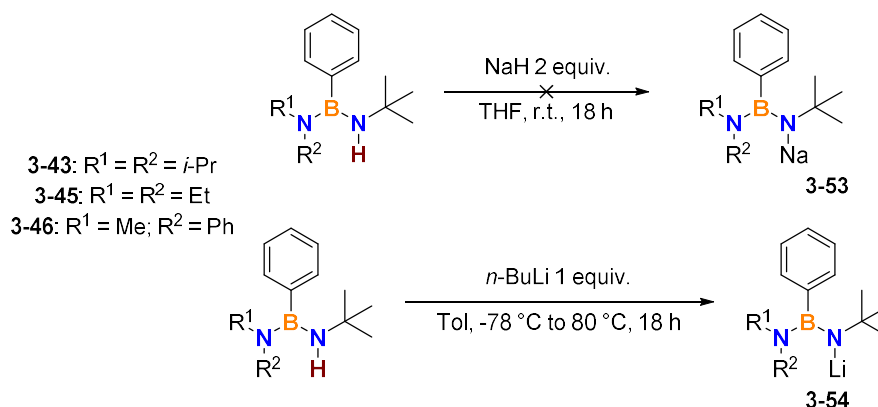
Manke and Nocera reported the synthesis of compound **3-47-a** in 45% yield, and the corresponding vanadium complex in 59% yield by using the same procedure.¹⁵ In the reaction reproduced five times, it resulted in the formation of **3-51** and not **3-47-a** as expected and reported.¹⁵ This difference could be explained by the formation of a more stable product **3-47.a** instead of **3-51** due to amine redistribution. Furthermore, another explanation may also be the temperature of the reactor during the reaction. In the procedure's paper, the reaction was run in frozen toluene but no precision was given for purification and isolation of product **3-47.a** and the corresponding vanadium complex.¹⁵ Hence, reproducing the desired result was challenging and resulted in the formation of **3-51**.

Other reactions involving early transition metal complexes were tried, such as $[\text{TaCl}_2(\text{NMe}_2)_3]_2$ and $\text{TaCl}_2(\text{CH}_2\text{SiMe}_3)_3$ starting materials. With tantalum metal complexes each reaction led to decomposition without any more boron peak detected on the ^{11}B NMR spectrum, which was not the case with $\text{TiCl}_2(\text{NMe}_2)_2$.



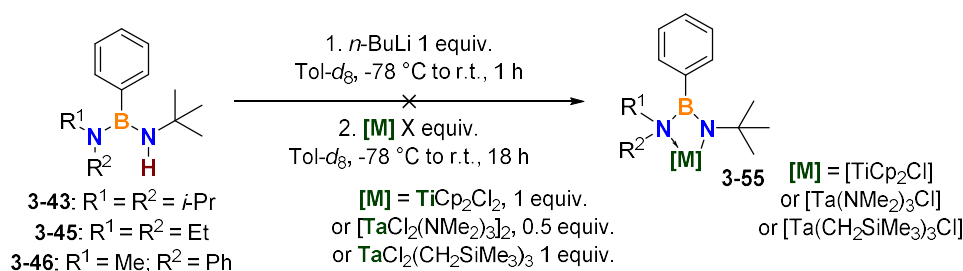
Scheme 102: Resulting products, including the proposed borazine from the reaction of bis(boraamidinate) and dichloro(dimethylamido)titanium(IV).

To obtain the desired potential unsymmetric boraamidinate metal complexes metathesis reaction was performed. Formation of boraamidinate salt was needed first to perform the desired salt metathesis reaction; sodium hydride was then used as a base to synthesize the chosen boraamidinate salt. After stirring overnight and filtration, ^{11}B and ^1H NMR spectroscopy disclosed the absence of the desired product and only the starting material was recovered (Scheme 103). Sodium hydride was not basic enough to deprotonate the unsymmetric boraamidinate and form the desired boraamidinate salt. Then an organolithium reagent was used to achieve the transformation and form the boraamidinate salt. Hence, one equivalent of *n*-butyllithium was added to a solution of boraamidinate in toluene at -78 °C. The mixture was then heated at 80 °C for 18 hours. After concentration *in vacuo*, NMR spectroscopy was performed. In all cases, complicated NMR spectra were obtained in which assignments were hard, and purification process based on recrystallization failed to isolate the resulting product (Scheme 103).



Scheme 103: Unsymmetric boraamidines deprotonation reactions with sodium hydride or organolithium reagent.

Due to the problem of purification of the deprotonated boraamidine derivatives, isolation was not performed and direct complexation using early transition metal chloride starting materials was tried. First, one equivalent of *n*-butyllithium onto the boraamidine was added and then one equivalent (or 0.5 equivalents for [TaCl₂(NMe₂)₃]₂) of titanium or tantalum derivative was added to the resulting mixture. NMR spectroscopy was performed on the reaction mixture after 18 hours of reaction. Again, the desired potential boraamidinate complexes could not be obtained. ¹H NMR analysis was complicated to analyse and the resonance at 30 ppm of the boraamidine disappeared without new boron peak in the ¹¹B NMR spectrum, this led to the conclusion of degradation of the starting material (Scheme 104). This could be due to the high reactivity of such dichloro tantalum and titanium derivatives.

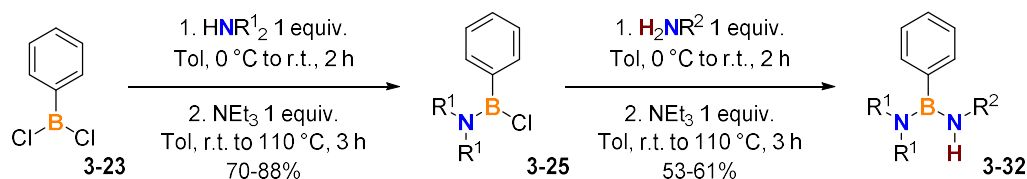


Scheme 104: Unsymmetric boraamidinate reactions with group 4 and 5 transition metals.

3.2.4 Conclusion

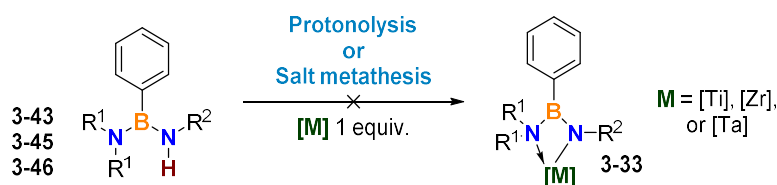
Based on the literature, the synthesis of symmetric boraamidine compounds was achieved by Miller and Craig.²⁸⁶ This pathway was then extended to the development of unsymmetric boraamidine derivatives. By isolation of the desired aminochloroborane intermediate, and the addition of the primary amine, desired compounds were isolated through distillation steps (Scheme 105). The identity of these products was established by

Miller and Craig. Ultimately three different potential proligands were assembled and characterized using this approach, one was new compounds and two were already reported.



Scheme 105: General pathway for unsymmetrical boraamidines synthesis.

With the desired potential proligands in hand, complexation chemistry through either protonolysis or salt metathesis reactions was attempted. Group 4 and 5 metals were used due to their low toxicity and their low cost compared to late transition metals like palladium or platinum. Unfortunately, no potential unsymmetric boraamidinate complexes could be isolated after recrystallization, and instead the formation of six-membered borazine rings was observed (Scheme 106).



Scheme 106: Protonolysis or salt metathesis reactions for the formation of potential unsymmetric boraamidinate metal complexes.

Despite, the fact that it proved impossible to isolate or characterize the targeted complexes, hydrofunctionalization reactions were attempted by using complexes that may be accessible through *in situ* preparation. By using the desired potential proligand *in situ* with the appropriate group 4 or 5 metal complexes, the hydroaminoalkylation reaction has been investigated. These *in situ* hydroaminoalkylation catalysis studies were realised at the same time as the protonolysis and salt metathesis reactions presented earlier.

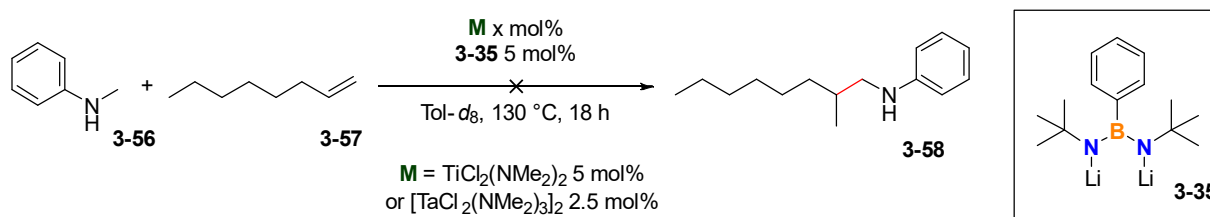
3.3 Application to the hydroaminoalkylation reaction using early transition metal complexes

3.3.1 Hydroaminoalkylation using titanium and tantalum amido complexes

Complexation reactions between boraamidine and early transition metal were tried in the previous part, but difficulties to isolate the potential resulting boraamidinate metal complex

happened. Hence, hydrofunctionalization catalysis was studied using *in situ* preparation of the catalyst with the potential boraamidine ligand and the metal complex. Titanium was used first to achieve the desired transformation, and this was then extended to tantalum complexes.

N-methylaniline and 1-octene are readily available reagents in chemistry, and they have been largely reported for the hydroaminoalkylation and the resulting product is generally obtained in high yields (88 to 96%).^{112, 295} Hence, *N*-methylaniline and 1-octene were the starting materials used for the desired transformation. Prior to their addition, dichloro(dimethylamido)titanium(IV) or bis(dichloro-bis(dimethylamido)tantalum(V)) was solubilized in deuterated toluene, and added onto a solution of boraamidinate **3-35**. Then, the olefin and the secondary amine were added to the resulting reaction mixture and heated at 130 °C for 18 hours. However, no conversion of *N*-methylaniline was detected by ¹H NMR spectroscopy by looking for new chemical shift in the aromatic region (6.50 to 6.30 ppm), or by GC/MS analysis using dichloro(dimethylamido)titanium(IV) and with or without the potential ligand **3-35** (entries 1-2, Table 9). The control reference with only the tantalum(V) complex and no potential ligand **3-35** showed 100% conversion of **3-56**, by ¹H NMR spectroscopy. Using boraamidinate salt **3-44** did not show any conversion of **3-56** (entry 3, Table 9) compared to the control (entry 4, Table 9). The potential metal complex that may result from the reaction with **3-35** did not show any reactivity for hydroaminoalkylation and probably interact only with the tantalum complex to inhibit the catalysis. With the two metal complexes used for *in situ* hydroaminoalkylation with potential ligand **3-35**, no catalytic activity was recorded with such systems.



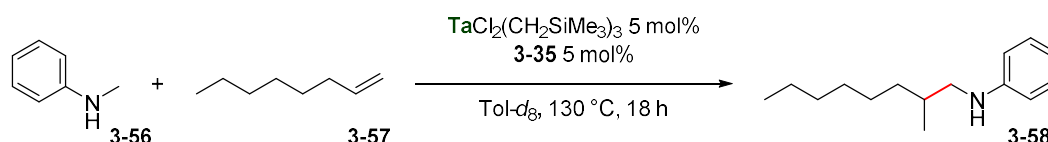
Entry	Amine (equiv.)	Alkene (equiv.)	Ligand	[M]	Conversion of 3-56 [%] ^a
1	1	1.5	3-35 5 mol%	[Ti] 5 mol%	n.r.
2	1	1.5	0 mol%	[Ti] 5 mol%	n.r.
3	1	1.5	3-35 5 mol%	[Ta] 2.5 mol%	n.r.
4	1	1.5	0 mol%	[Ta] 2.5 mol%	100

Table 9: Hydroaminoalkylation reaction with titanium or tantalum complexes and boraamidinate **3-35**.

- a. Conversion of **3-56** determined by ^1H NMR spectroscopy by integration the doublet-doublet at 6.35 ppm of **3-56** vs. the doublet-doublet of **3-58** at 6.45 ppm, each integrate for two protons.

3.3.2 Hydroaminoalkylation with $\text{TaCl}_2(\text{CH}_2\text{SiMe}_3)_3$

Pentakis(dimethylamido)tantalum(V) and bis(dichloro-bis(dimethylamido)tantalum(V)) complexes pre-catalyst have not showed any catalysis reactivity when they were used with boraamidinate **3-35**. The dichlorotris(trimethylsilylethyl)tantalum(V) was recently reported by Schafer and co-workers for the hydroaminoalkylation reaction.¹³³ This starting material was also tested for the *in situ* system.¹³³ This complex alone with no ligand offered the formation of the branched product with 50% conversion after 18 hours at 130 °C (entry 2, Table 10). On the contrary, introducing the potential ligand in the reaction mixture improved the conversion to 80% after 18 hours and by using the same reaction conditions (entry 1, Table 10). As presented in section 3.2.3.2 isolation of the potential tantalum complex was tried after reacting $\text{TaCl}_2(\text{CH}_2\text{SiMe}_3)_3$ with **3-35** but it only resulted into the formation of degradation products.



Entry	Amine (equiv.)	Alkene (equiv.)	[Ta] (mol%)	3-35 (mol%)	Conversion of 3-56 [%] ^a
1	1	1	5	No	50
2	1	1	5	5	80

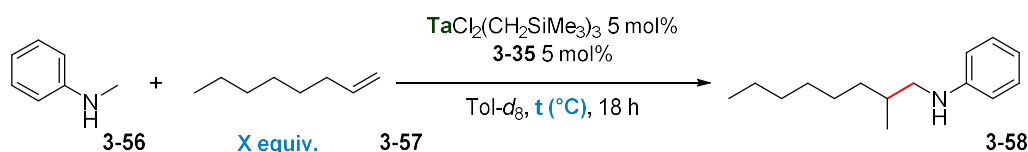
Table 10: Hydroaminoalkylation reaction with $\text{TaCl}_2(\text{CH}_2\text{SiMe}_3)_3$ and boraamidinate **3-35**.

- a. Conversion of **3-56** determined by ^1H NMR spectroscopy by integration the doublet-doublet at 6.35 ppm of **3-56** vs. the doublet-doublet of **3-58** at 6.45 ppm, each integrate for two protons.

The reaction was performed in deuterated toluene using one equivalent of $\text{TaCl}_2(\text{CH}_2\text{SiMe}_3)_3$ mixed beforehand with one equivalent of the boraamidinate salt **3-35**. Then one equivalent of *N*-methylaniline **3-56** and 1.5 or one equivalent of alkene **3-57** were added to the reaction mixture (Table 11). After one hour, only 10% conversion was obtained in both cases (entries 1 and 4, Table 11), but 60% conversion was obtained after two hours when 1.5 equivalents were added (entry 2, Table 11) while only 20% conversion was attained with one equivalent (entry 5, Table 11). After 18 hours, full conversion of *N*-methylaniline was obtained with 1.5 equivalents of alkene (entry 3, Table 11), while only 80% conversion was observed with one equivalent of alkene (entry 6, Table 11).

Control of the temperature is an important aspect when carrying out hydroaminoalkylation, this reaction usually requires high temperature (130 °C to 150 °C).¹⁶² When reducing the temperature to 110 °C only 20% conversion of **3-56** was obtained after one hour of reaction (entries 7 and 9, Table 11). When 1.5 equivalent of 1-octene were used, only 90% conversion of *N*-methylaniline into the branched product was observed (entry 8, Table 11) after heating at 110 °C for 18 hours. However, with one equivalent, only 30% of the conversion of the aniline into the branched product was achieved (entry 10, Table 11) in the same reaction conditions.

Higher conversion was obtained with 1.5 equivalents of alkenes after 18 hours at 130 °C. Furthermore reducing the temperature from 130 °C to 110 °C decreased the conversion obtained when one equivalent of 1-octene was used, while using 1.5 equivalents of olefin increased the conversion up to 90% after 18 hours of reaction. Compared to the results reported by the Schafer group in 2018, they reported the hydroaminoalkylation using this tantalum pre-catalyst with higher reactivity. They showed the possibility to isolate the hydroamination product in high yields: between 75 to 85% in less than six hours at 110 °C or 130 °C.



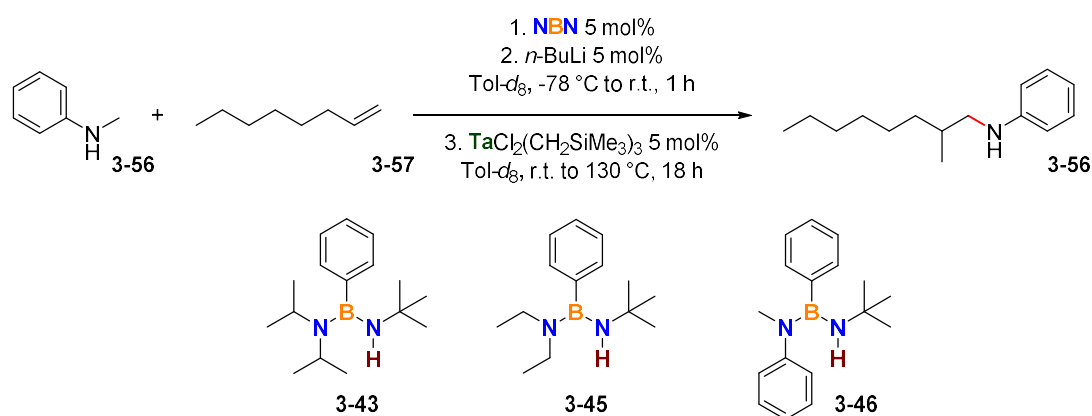
Entry	t [h]	Alkene (equiv.)	T [°C]	Conversion of 3-56 [%] ^b
1	1	1.5	130	10
2	2	1.5	130	60
3	18	1.5	130	100
4	1	1	130	10
5	2	1	130	20
6	18	1	130	80
7	2	1.5	110	20
8	18	1.5	110	90
9	2	1	110	20
10	18	1	110	30

Table 11: Hydroaminoalkylation reaction using different equivalents of 1-octene and different reaction temperatures.

a. Conversion of **3-56** determined by ¹H NMR spectroscopy by integration the doublet-doublet at 6.35 ppm of **3-56** vs. the doublet-doublet of **3-58** at 6.45 ppm, each integrate for two protons.

3.3.3 Hydroaminoalkylation using unsymmetric boraamidines

Unsymmetric boraamidine derivatives were then studied for this hydrofunctionalization reaction. Due to the problem of purifying the lithium salts, the deprotonation reaction was done *in situ*. Then one equivalent of tantalum chloride complex diluted in solution was then carefully added to the resulting mixture of the boraamidinate solution (also one equivalent). Finally, *N*-methylaniline and 1-octene were added to the resulting mixture and heated at 130 °C for 18 hours. Compared to the symmetric boraamidinate salt variant, limited conversions into the product **3-58** were observed. Indeed, with potential ligands **3-43** and **3-45**, only 5% and 10% conversions of *N*-methylaniline were obtained (entry 1-2, Table 12), while potential ligand **3-46**, showed 30% conversion into the branched product of hydroaminoalkylation (entries 3, Table 12). These conversion were lower than the one reported with the system described earlier and the one from the literature, hence monoanionic boraamidine derivatives **3-43**, **3-45** or **3-46** are not suitable potential ligands for hydrofunctionalization.¹³³



Entry	t [h]	Ligand	Conversion of 3-56 [%] ^b
1	18	3-43	5
2	18	3-45	10
3	18	3-46	30

Table 12: Hydroaminoalkylation reactions using different unsymmetric boraamidine derivatives.

a. Conversion of **3-56** determined by ¹H NMR spectroscopy by integration the doublet-doublet at 6.35 ppm of **3-56** vs. the doublet-doublet of **3-58** at 6.45 ppm, each integrate for two protons.

3.4 Conclusion

Cyclic boraamidine **3-4.a** was synthesized with a new synthetic method developed during this project. However, the last electrophilic cyclization to form the carbon-boron bond led to low yield under all conditions tested. However, ~100 mg of potential ligand could be

isolated for further experimentation. Coordination chemistry was then studied using titanium complexes. Unfortunately no boraamidinate complexes have been isolated despite all attempts to form the desired product.

Different aminochloroborane derivatives were then isolated using a known procedure²⁸⁶ which involved the reaction of a desired secondary amine with dichlorophenylborane as starting material. After isolation of chloro bis(alkyl)aminophenylboranes, addition of primary amines to a solution of the boron derivative was performed and unsymmetric boraamidine were successfully isolated.

Complexation reactions were tried using group 4 and 5 transition metals. Titanium complexes were first attempted without success, so tantalum derivatives were also used to try to form the desired products. Because the protonolysis reaction encountered little success to form the desired product, salt metathesis was tried. A first deprotonation step was realized *in situ* followed by the addition of the desired metal complex to the resulting mixture. Unfortunately, no 1,3-chelated complex could be isolated through salt metathesis reaction. On the contrary, recrystallization showed the formation of a known bis(titanium) bridged complex with two *tert*-butylamine groups. This result led to the conclusion that the formation of the desired 1,3-chelating metal complex is probably occurring, but could go onto further reactions to form a bridged titanium dimer characterized through X-ray spectroscopy. It is possible that the second by-product found during this reaction corresponds to a six-membered borazine compound.

Hydroaminoalkylation catalysis was developed using the potential ligand *in situ* with the desired metal complex. Titanium and tantalum amido showed no reactivity for the desired reaction. However, $\text{TaCl}_2(\text{CH}_2\text{SiMe}_3)_3$ revealed high reactivity for hydroaminoalkylation with full conversion at 130 °C for 18 hours. Despite the progress made to perform the hydroaminoalkylation reaction with this system, the Schafer group recently disclosed another catalytic system using ureate ligands with $\text{TaCl}_2(\text{CH}_2\text{SiMe}_3)_3$ to achieve hydroaminoalkylation reaction with full conversion in less than one hour.¹³³

As conclusion, various aminochloroborane and boraamidine have been successfully synthesized, isolated and characterized. However, formation of new potential 1,3-chelating metal complexes containing boron showed narrow success due to various problems. Either no reactivity between the potential ligand and the early transition metal complex was observed by protonolysis reactions, or side reactions occurred with degradation of the potential ligand and the metal complex through salt metathesis reactions. For all these explanation above, we extended our scope of synthesizing new heteroelement based ligand throughout a new synthetic approach targeting aminophosphine derivatives.

4 CHAPTER IV: SYNTHESIS AND DEVELOPMENT OF β -AMINOPHOSPHINE LIGANDS: A NEW SYNTHETIC APPROACH

4.1 Literature Review

4.1.1 Introduction

The work dedicated to the synthesis of potential 1,3-chelating ligands with boron atoms contributed to broaden the understanding of chelating ligands containing heteroelements. The results obtained were limited to the study of such 1,3-chelating ligands without a carbon centre. However, another heteroelement that is commonly incorporated into ligand sets is phosphorous. Many examples of *P*-containing chelating ligands have been reported. The synthesis and application of *P,N*-ligands, particularly β -aminophosphines have been widely described in the literature.²⁹⁶⁻³⁰⁰ Those *P,N*-ligands generally bear stereogenic centres or axial chirality, which explain their extensive use in asymmetric catalysis for hydrogenation or hydrosilylation reactions. More recently, β -aminophosphine metal complexes were applied in cross-coupling reactions to form new carbon-carbon bonds. The design of such ancillary *P,N*-ligands rose from their ability to have different hapticities and hemilabilities, as has been featured on other aspects of this thesis. The nitrogen and phosphorus moieties allow for the formation of monodentate or bidentate coordination modes toward the metal centre. These variable coordination modes have been extended to *N,P,N*-ligands. These ligands, when complexed to transition metals, have been reported to mediate new catalytic possibilities in organic synthesis due to their bonding mode as a tridentate ligand.³⁰¹⁻³⁰³ *N,P,N*-ligand metal complexes of early transition metals have been applied in catalysis for the polymerization of ethylene,³⁰³ and for the activation of small gas molecules.^{296, 304} Typically the syntheses of such *N,P,N*-ligands are tedious, produce stoichiometric waste, and are not flexible in the substituents that can be accommodated, which limits the development of new ligands.^{296, 303,}
305

Based on the 100% atom-economic hydroamination reaction, which is achieved using a Ti-*N,O*-chelated complex, we developed an alternative synthetic approach to synthesize *N,P,N*-ligands by hydroamination. Different substitution patterns were explored and the limitations of this approach were delineated. With isolated proligands, the coordination of such *N,P,N*-ligands with early transition metals has also been studied. In this chapter, a

review of several N,P,N -ligands is presented and their synthesis is detailed and their use in catalysis has been explored. Most importantly, the synthetic strategy developed here features regioselective hydroamination and is reported for the first time.

4.1.2 Major classes of β -aminophosphines

4.1.2.1 β -aminophosphine ligands in the literature

β -aminophosphine ligands complexed to transition metals have been largely used for asymmetric catalysis such as hydrogenation or hydrosilylation, due to their tunable steric and electronic properties and variable coordination modes (Figure 22, **4-1**). Indeed, the phosphorus can serve as a π -acceptor, allowing for stabilization of electron rich metal centres, whereas the σ -donation of the nitrogen makes the metal even more electron rich, which may result in a more reactive metal centre.²⁹⁹ This combination can offer complementary electronic features that can stabilize a changing metal complex over the course of the catalytic cycle. Moreover, the phosphorus and nitrogen atoms can be easily tuned either electronically or sterically.²⁹⁹

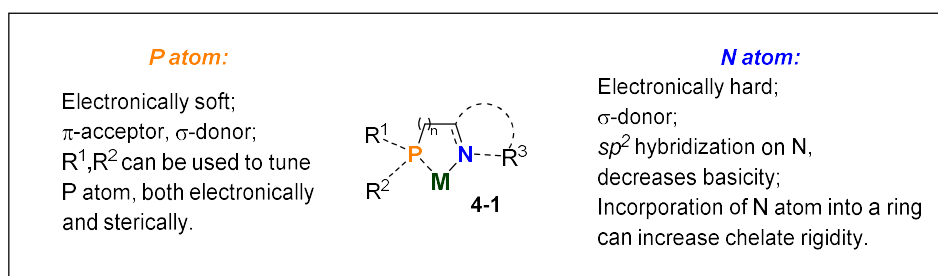


Figure 22: General features of β -aminophosphine ligands.²⁹⁹

Different classes of P,N -ligands containing a tether between the nitrogen and the phosphorus have been reported in the literature (Figure 23). The first example reported contained ferrocene derivatives **4-2** first published by Kumada in 1974. They were applied as chiral ligands for asymmetric transformations.³⁰⁶ However this P,N -ligand is not an example of a β -aminophosphine. Other research groups published different varieties of ligands containing phosphorus and nitrogen donors for catalytic purposes such as cyclic P,N -ligand, P,N,P -ligands, but will not be discussed as these ligands are not β -aminophosphines.^{298, 307-}

315

With respect to β -aminophosphines the P,N -oxazoline ligands **4-3** complexed to transition metals are another major group of P,N -ligands used for asymmetric hydrogenation

or hydrosilylation.³¹⁶⁻³²³ Derivatives of amino acids **4-4**, containing a chiral aliphatic backbone, have also been widely applied for asymmetric catalysis. Milstein disclosed the first unsymmetric *N,N,P*-ligand **4-5** on ruthenium and rhodium metal.³²⁴ β -aminophosphines generally require two to five steps for their syntheses, excluding the last coordination step to the metal centre.³⁰⁰ These syntheses can be long and also produce a significant amount of waste. In comparison, our proposal is based on the synthesis of β -aminophosphine ligands **4-6** through a 100% atom-economic process by using the hydroamination reaction of alkyne such as **4-7** with primary amines **4-8**.

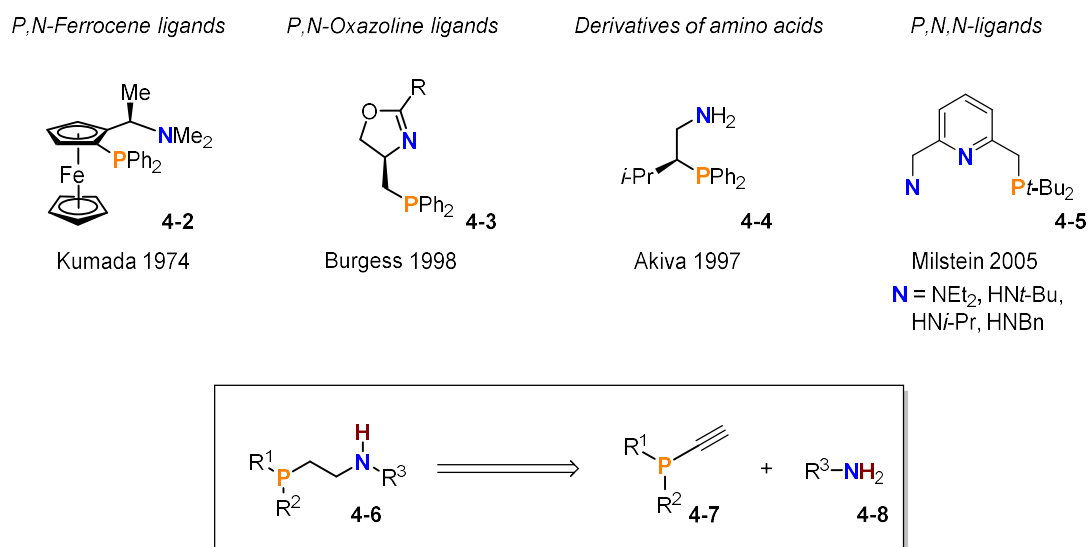


Figure 23: a) Examples of the different groups of β -aminophosphine ligands reported in the literature. b) General strategy considered.³⁰⁶⁻³²⁵

4.1.2.2 Bis(β -aminophosphine) ligands in the literature

Compared to their β -aminophosphine ligands equivalents, bis(β -aminophosphine) pincer ligands have been less commonly reported in the literature. These preparative routes involve three to four different steps involving the use of organolithium derivatives and chlorophosphines reagents.^{296, 303} Moreover, these ligands have not been reported as chiral ligands as it has been the case with β -aminophosphine equivalents, thus they have not been used in enantioselective transformations. However, over the last decade, different research groups have made a lot of progress using the unique features of these tridentate ligands, such that their application as ligands for metal complexes for small molecules activation or in oligomerization of olefins have been explored.^{296, 303}

Different *N,P,N*-ligands were developed by different research groups and using transition metals for transamination chemistry can lead to the formation of the appropriate metal amido complex through a protonolysis reaction.²⁹⁶ *N,P,N*-ligands containing a silicon

backbone **4-9** have been reported, and the silicon tether facilitates its synthesis (Figure 24). The two other related N,P,N -ligands **4-10** and **4-11** have an aryl backbone which make them accessible by using lithium/halide exchange.²⁹⁶ Having an aryl backbone stabilizes the resulting ligand due to ring constraints when compared to aliphatic carbon-carbon bonds. These N,P,N -ligands containing an aryl backbone have been reported as metal complexes on rhodium and the ligand hemilability has been discussed.³²⁶ Their application as a catalyst in cross-coupling reactions such as Suzuki-Miyaura cross-coupling have also been reported.³⁰² Another family of N,P,N -ligands in the literature are bis(picoly)phosphines **4-12**. They were first synthesized in 1983 by Lindner.³²⁷⁻³²⁸ They showed catalytic activity for the homologation of methanol to ethanol when complexed with group 6 metals,³²⁷⁻³²⁸ and in the oligomerization of ethylene when complexed to nickel or cobalt.^{303, 329} They can also be coordinated to other transition metals such as Pd, Ir, Cr and Ti.³³⁰⁻³³¹ A derivative of bis(picoly)phosphine led to the generation of phosphino-oxazoline ligands **4-13** which, as metal complex, exhibited catalytic activity for the oligomerization of olefins.³⁰³ The synthesis of N,P,N -ligands generally involves several synthetic steps to form the desired ligand using different phosphorus sources. These syntheses are highlighted in the next section.

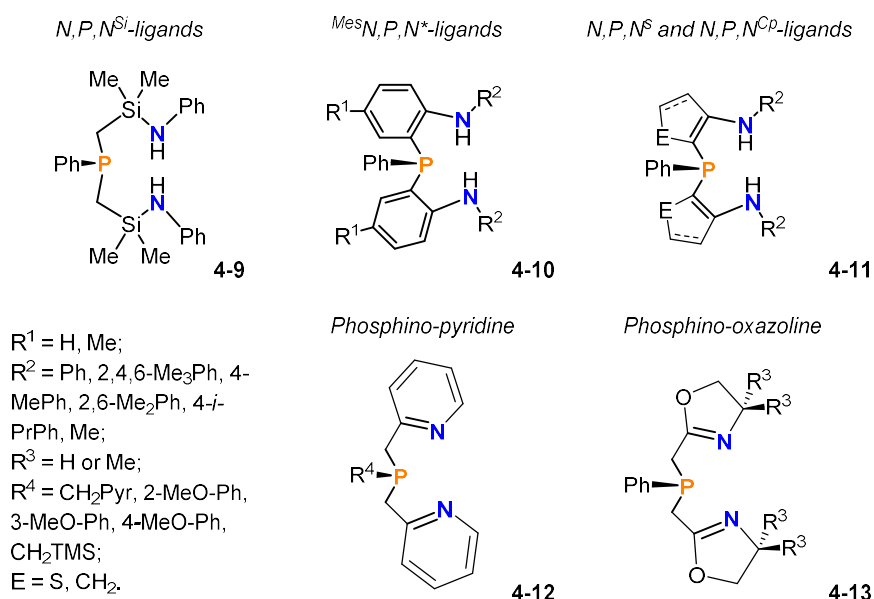


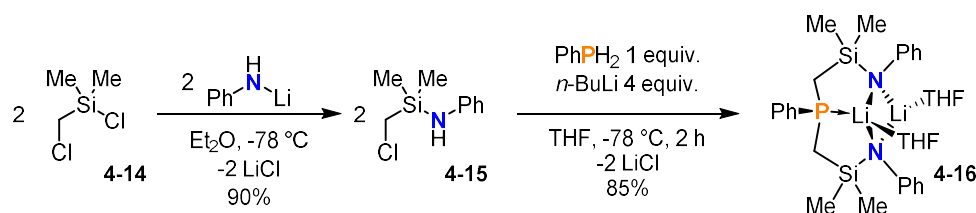
Figure 24: Examples of different bis(β -aminophosphine) ligands reported in the literature.^{302, 326-330}

4.1.3 Synthesis of bis(β -aminophosphine) ligands: design and strategy

N,P,N -ligands are an important class of pincer ligands and when complexed to early transition metals they have been used for the activation of small molecules such as dinitrogen, and for polymerization.^{303-305, 332} Three main molecular targets have been

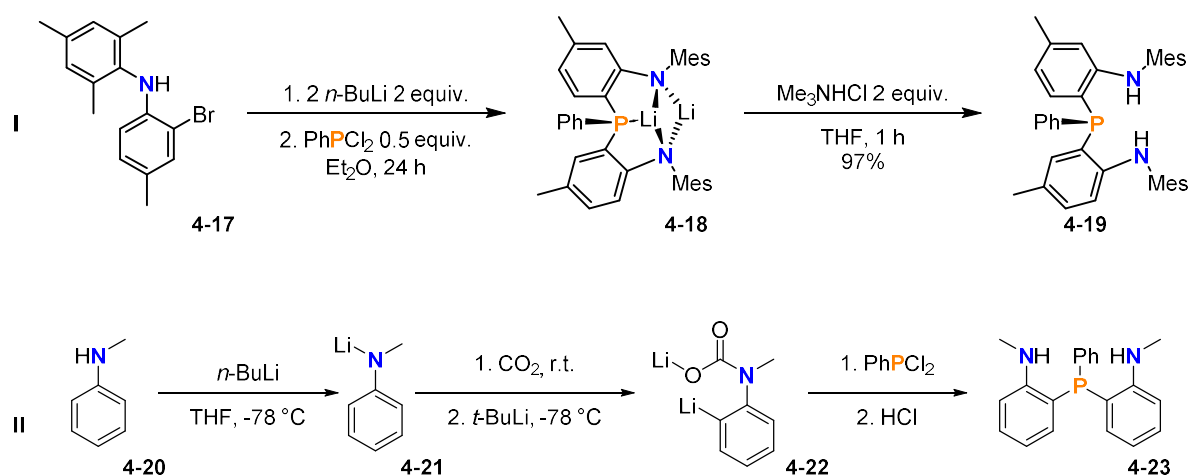
published in the literature. The first target: N,P,N^{Si} -ligand, involves the synthesis of an aliphatic silicon-carbon tether (Scheme 107), the second one: N,P,N^* -ligands features unsaturated carbon-carbon bonds in the tether (Scheme 108), and the third molecular target: phosphine-pyridine invoke the use of substituted pyridine (Scheme 109).

The synthesis of N,P,N^{Si} -ligand was described by Fryzuk and co-workers who published its synthesis using $\text{ClSiMe}_2\text{CH}_2\text{Cl}$ **4-14** by adding lithiated aniline to form the requisite intermediate **4-15**.³³³ The subsequent addition of organolithium reagent (*n*-BuLi) and phenylphosphine forms the dilithio diamidophosphine N,P,N -ligand by nucleophilic addition (Scheme 107, **4-16**).³³³⁻³³⁴



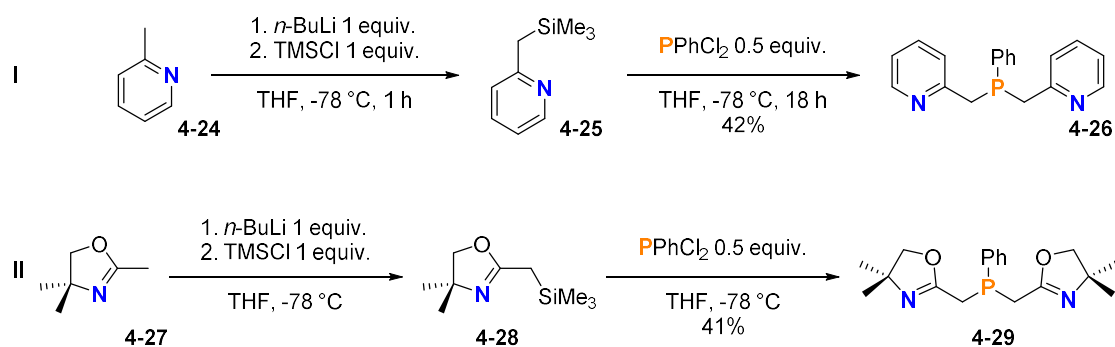
Scheme 107: Synthetic pathway for synthesizing N,P,N^{Si} -ligand.³³³⁻³³⁴

N,P,N^* -ligands were published in the literature using another synthetic route and presents another motif which has unsaturated carbon-carbon bonds in the tether (Scheme 108). Lithium/halide exchange (Scheme 108.I) or *ortho*-lithiation (Scheme 108.II) followed by addition onto the phosphorus reagent to form the carbon-phosphorus bond. These approaches afford the N,P,N^* -ligands.³³⁵ In Scheme 108.I the *ortho*-aryl amine **4-17** can react with organolithium and dichlorophenylphosphine to form the lithium salt product **4-18**.³³⁵ Quenching with the hydrochloric amine salt formed the desired N,P,N^* -ligands **4-19** which can then be used in coordination chemistry.³³⁵ Here, the amine and the phosphine donors are linked through an *ortho*-phenyl unit; the authors suggest that the proligand basicity does not change based on pKa values of Ph_2NH (24.95) and $(\text{Me}_3\text{Si})_2\text{NH}$ (25.8) respectively.³³⁶ As illustrated in Scheme 108.II *ortho*-functionalization of secondary *N*-substituted aniline **4-20** is another approach to access these ligands; however formation of side-products is generally observed. Hence a first protection step using *n*-BuLi and carbon dioxide to form **4-21** is required. Then addition of *t*-BuLi for the formation of the *ortho*-lithiated intermediate **4-22** can be done, followed by the *ortho*-functionalization using dichlorophenylphosphine to obtain **4-23** after hydrolysis.³³⁷ The major drawback of this route is the absolute exclusion of air and moisture due to the sensitivity of the intermediates **4-21** and **4-22**.³²⁶



Scheme 108: I Synthetic pathway involving lithium/halide exchange for the formation of N,P,N^* -ligands. II Synthetic pathway involving *ortho*-lithiation for the formation of N,P,N -ligands.³³⁶⁻³³⁷

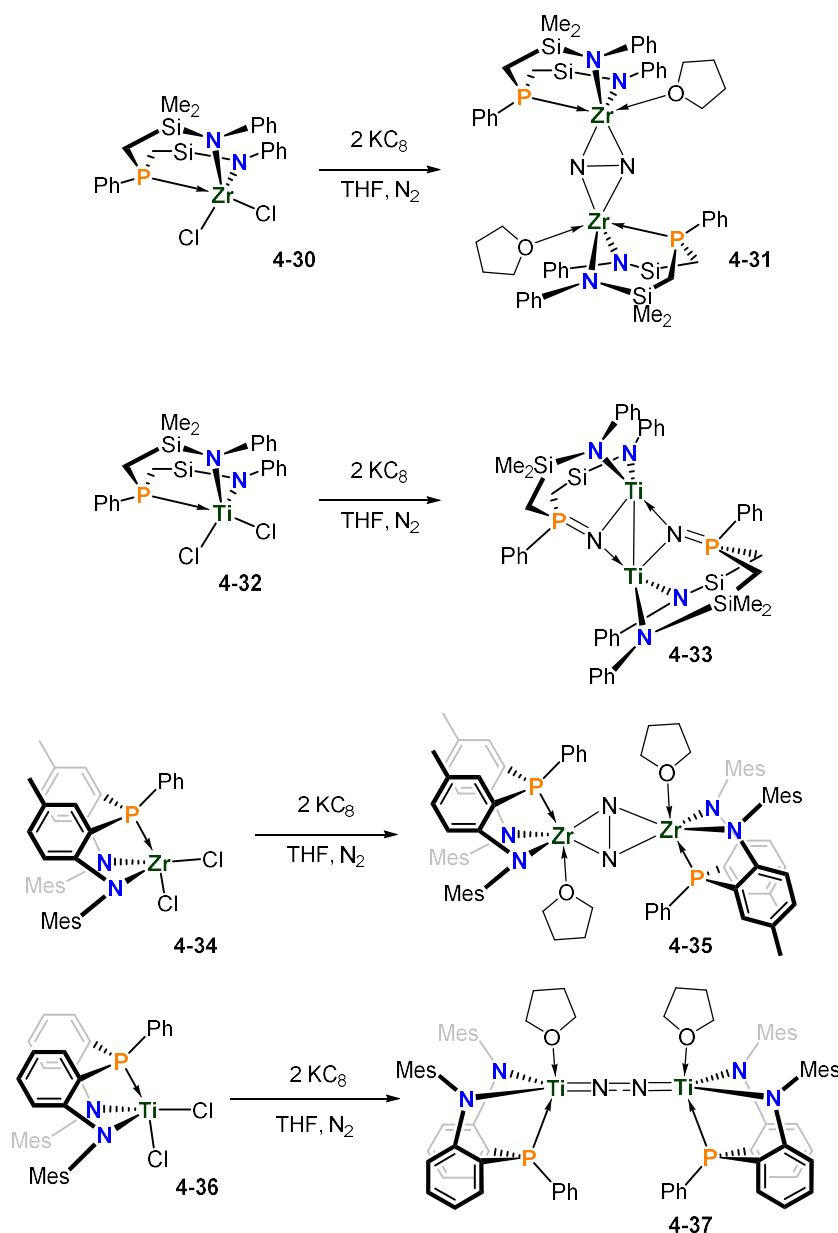
The last synthetic strategy to form N,P,N -ligands involves the use of dichlorophenylphosphine and pyridine derivatives (Scheme 109). This method requires the deprotonation of *o*-methylpyridine **4-24** using *n*-BuLi, followed by the addition of TMSCl, to afford the intermediate **4-25**.^{303, 338} Addition of dichlorophenylphosphine forms the desired phosphino-pyridine derivative **4-26**.^{303, 338} Phosphino-oxazoline ligands are obtained through the same process; *n*-BuLi deprotonated the oxazoline **4-27** which reacts with TMSCl to form **4-28** then, addition of dichlorophenylphosphine forms the desired ligand **4-29**.^{305, 339} Different examples containing either silicon-carbon or saturated double bonds have been reported in the literature, but N,P,N -ligands with an sp^3 - sp^3 carbon-carbon backbone is still unknown due to synthetic challenges.



Scheme 109: Synthetic route for the formation of phosphino-pyridine and phosphino-oxazoline ligands.³³⁸⁻³³⁹

4.1.4 Application of bis(β -aminophosphine) ligands in chemistry

The main examples of applications reported for N,P,N -ligands complexed to transition metals are polymerization of olefins with group 4 metals and Suzuki-Miyaura cross-coupling reaction when complexed to palladium.³⁰¹⁻³⁰³ However activation of small molecules such as dinitrogen, hydrogen or alkene activation have been reported in the literature.²⁹⁶ The first metal complex reported for the activation of dinitrogen was $[\text{Ru}(\text{NH}_3)_5\text{N}_2]^{2+}$,³⁴⁰ but nowadays other metal complexes can achieve this activation such as N,P,N -ligand complexes with the use of KC_8 as reductant. Indeed, activation of dinitrogen is difficult due to the unreactivity of such an apolar and inert substrate.³⁴¹⁻³⁴³ However, Fryzuk and co-workers have shown that N,P,N^{Si} -ligand complexed to an early transition metal **4-30** exhibits nitrogen activation by reduction using KC_8 to give a dinitrogen that bridges two zirconium(IV) centres (Scheme 110, **4-31**).³⁰⁴ The analogous precursor $[\text{NPN}^{\text{Si}}]\text{TiCl}_2$ **4-32** obtained as titanium complex can also be reduced following the same procedure but formed another product **4-33**. The resulting compound was obtained by the formation of a phosphinimide derivative and not the bridged dinitrogen complex. Hence both titanium centres were reduced to titanium(III) and each phosphine was oxidized to phosphinimide. The success of N,P,N^{Si} -ligands for dinitrogen activation inspired the Fryzuk research group to broaden the scope of N,P,N -ligand for activation of small molecule. Therefore they developed the $^{\text{Mes}}N,P,N$ -ligands to increase the stability of the N,P,N backbone. Analogous to the silicon ligand, $^{\text{Mes}}N,P,N^*$ -ligands were also found to exhibit gas activation with group 4 metals. After protonolysis with tetrakis(dimethylamido)-zirconium(IV) or titanium(IV) $^{\text{Mes}}N,P,N^*$ -complexes activate dinitrogen after reduction with KC_8 (Scheme 110).³³² $[\text{Mes}N,P,N^*]\text{ZrCl}_2$ **4-34** forms a dimer complex **4-35** bridged with two nitrogens, whereas the titanium complex equivalent **4-36** forms an end-on bridging dinitrogen unit **4-37**.³⁴⁴ $^{\text{Mes}}N,P,N^*$ -complexes were also reported with tantalum for activation of dinitrogen or dihydrogen through the formation of a bridged complex.^{296, 345}

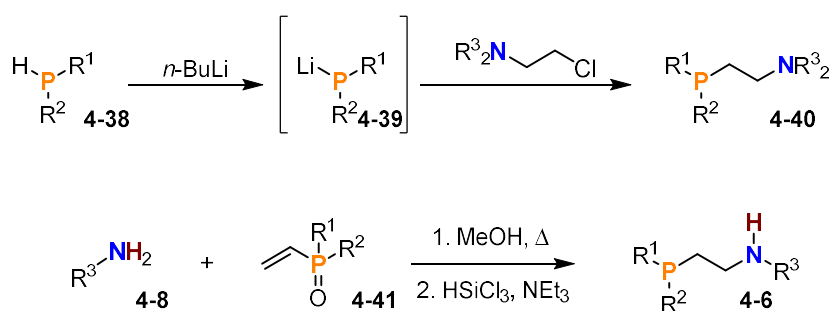


Scheme 110: Dinitrogen activation using N,P,N^{Si} - and $\text{MesN,P,N}^{\text{Si}}$ -ligands complexed to titanium and zirconium transition metals.¹

4.1.5 Method and strategy

Two main approaches can be used for the synthesis of β -aminophosphines containing an aliphatic tether; either *via* the formation of a carbon-phosphorus bond or the creation of a carbon-nitrogen bond. The synthesis of the carbon-phosphorus bond requires the use of a phosphide intermediate and consists of the addition of a basic organolithium reagent such as *n*-BuLi to a solution of pyrophoric disubstituted phosphine **4-38** to form the phosphide intermediate **4-39** (Scheme 111).^{310, 346} This compound can then be added to 1-amino-2-chloro derivatives to form β -aminophosphines **4-40** upon chloride substitution. The strategy featuring formation of the carbon-phosphorus bond only allows for tertiary amines

because the presence of the lithium intermediate is not compatible with primary or secondary amines. However, the formation of a carbon-nitrogen bond is an alternative of the carbon-phosphorus bond strategy to synthesize β -aminophosphines. Primary and secondary amines are tolerated in the 1,4-conjugate addition onto a vinyl phosphine oxide **4-41** as showed in Scheme 111. This addition forms an oxidized β -aminophosphine product which is reduced with trichlorosilane to afford the desired β -aminophosphine derivatives **4-6**.³⁴⁷ Vinyl phosphine oxide compounds are not commercially available and generally need to be synthesized over three to four steps using oxidation, and protection/deprotection routes.³⁴⁷ This leads to the formation of several by-products and is therefore a low atom-economy reaction and gives an overall poor yield of the desired vinyl phosphine oxide.

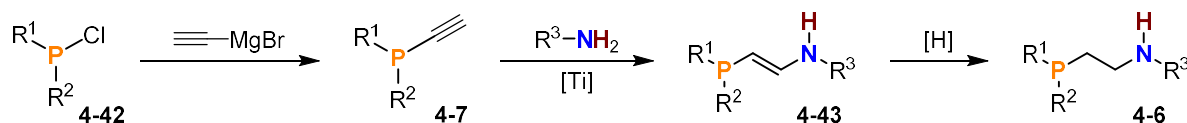


Scheme 111: Synthesis of β -aminophosphine ligands using disubstituted phosphine derivatives.^{310, 346-347}

The synthesis of β -aminophosphines present several drawbacks and new synthetic approaches are investigated in this chapter. For this, an α -ethynylphosphine derivative was targeted as an appealing target since it would already contain the phosphorus centre. Then, through the hydroamination reaction, it would result into the formation of the nitrogen centre linked with a carbon tether to the phosphorus centre. Ethynylphosphine was synthesized through addition of ethynyl Grignard onto the desired chlorophosphine. The synthesis of β -aminophosphine could then be performed through subsequent hydroamination and reduction reactions.

The hydroamination reaction of unsaturated bonds has been reported by the Schafer group. The hydroamination reaction considered involves primary amines, phosphine alkynes and the Schafer's amidate catalyst (Scheme 112).⁹⁵ Amines are commercially available and phosphine alkynes **4-7** were synthesized in a one-pot reaction from commercially available reagent **4-42**. The main advantage of using phosphine alkynes is the absence of a multi-step synthesis required to prepare β -aminophosphines and the large possibility of products through the use of primary amines. The regioselective hydroamination reaction of amines and phosphine alkyne **4-7** would form the enamine/imine intermediate **4-43** which upon

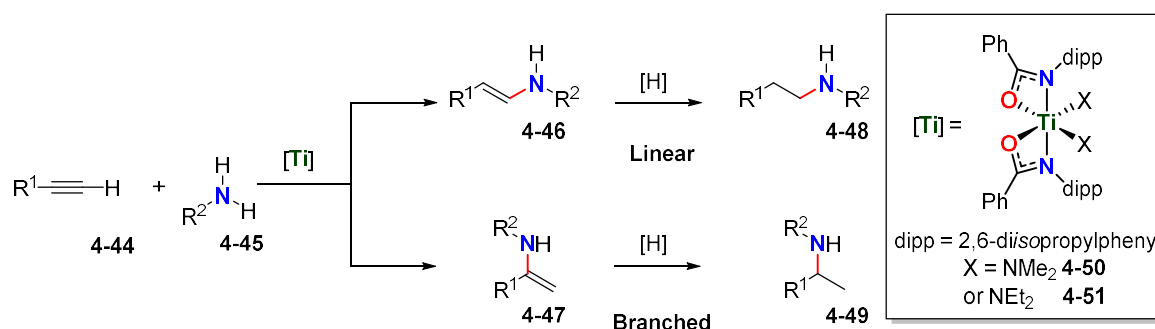
reduction with sodium borohydride result into the formation of β -aminophosphine **4-6** (Scheme 112).



Scheme 112: New synthetic approach for the formation of the desired β -aminophosphine ligands.

4.1.6 Alkyne hydroamination

The hydroamination reaction was introduced in the first chapter as an application of 1,3-*N,O*-chelating complexes in catalysis. Since 1992, when Bergman highlighted the mechanism of this reaction, this transformation has been widely applied for the synthesis of amines moieties.³⁴⁸⁻³⁵⁵ Alkynes and allenes, in combination with the desired amines, are the required starting materials to achieve this transformation. Hydroamination can produce either branched **4-47** or linear **4-46** products and modification of the catalyst can target one product or the other. Late transition metals such as gold and platinum, offer the branched product preferentially.¹⁰⁷ Titanium metal complexes have the capacity to form both linear and branched products depending on the ligand properties. In 2003, the Schafer group published a bulky bis(amido)bis(amidate)titanium(IV) **4-50** and **4-51** complexes to achieve the desired transformation with terminal alkynes **4-44** and a variety of primary amines **4-45**. Moreover, this precatalyst showed excellent regioselectivity as only the linear product was obtained due to the steric bulk provided by the ligand around the metal centre (Scheme 113).^{95, 100-101}

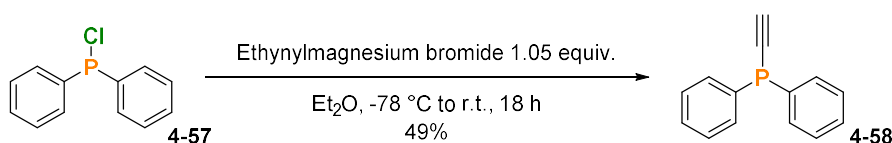


Scheme 113: Hydroamination using bis(amido)bis(amidate)titanium(IV) precatalyst, followed by reduction.¹⁰⁷

The reaction mechanism using early-transition metals like titanium was described in chapter one. However, the hydroamination of a phosphine alkyne had never been reported and it was unknown if the inclusion of a phosphine would affect reactivity and/or regioselectivity. The only attempt to form carbon-nitrogen bond with a phosphorus

4.2.1.1 Synthesis using dichlorophenylphosphine

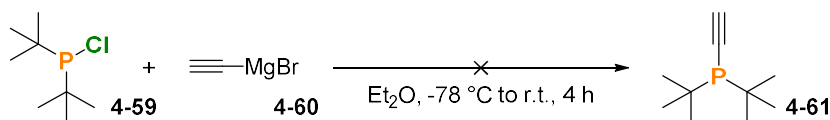
Chlorodiphenylphosphine **4-57** was used first to obtain the phosphine alkyne derivative. A reported procedure features a standard nucleophilic addition by the addition of ethynylmagnesium bromide to a solution of chlorodiphenylphosphine **4-57** (Scheme 116).³⁵⁸ The disclosed procedure has been reproduced here and the desired product **4-58** was isolated in 49% yield after filtration. The isolated yield was lower than the one reported in the literature (91%) probably due to the scale-up of the reaction, but ^1H and ^{31}P NMR spectroscopy and GC/MS analysis were consistent with the literature.



Scheme 116: Diphenylethynylphosphine synthesis.³⁵⁸

4.2.1.2 Synthesis using di-tert-butylchlorophosphine

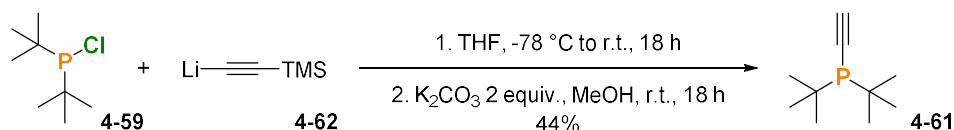
It was proposed that dialkyl ethynyl phosphine can also be synthesized using a Grignard reagent with the appropriate chlorophosphine, as in Scheme 116. Thus, a solution of ethynylmagnesium bromide **4-60** in THF was mixed with a solution of di-tert-butylchlorophosphine **4-59** in diethyl ether at low temperature, until it reached room temperature over four hours (Scheme 117). At the end of the reaction, the mixture was filtered and concentrated under vacuum. By ^{31}P NMR spectroscopy, no signal for the desired sp^3 phosphorus alkyl region (60 to -60 ppm) was observed and the chlorophosphine starting material had degraded.³⁵⁹ This reaction was performed twice and the same result was obtained each time, furthermore the purity of each starting materials were checked before the reaction and cannot account for the failure of the reaction.



Scheme 117: Salt metathesis reaction involving ethynylmagnesium bromide and di-tert-butylchlorophosphine.

To overcome this problem, we prepared **4-61** with lithium(trimethylsilyl)acetylide. The lithiation reaction of (trimethylsilyl)acetyl was performed using a literature procedure by adding *n*-BuLi to a solution of ethynyltrimethylsilane in diethyl ether at $-78\text{ }^\circ\text{C}$ for one hour.³⁶⁰ This solution was prepared and added to a solution of di-tert-butylchlorophosphine **4-59** and left to stir overnight while warming to room temperature. After concentration under vacuum

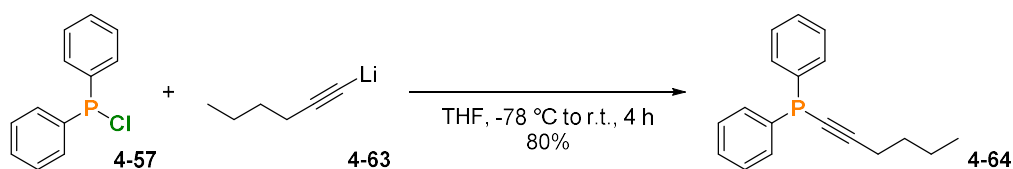
and dilution in methanol, potassium carbonate was added to the reaction for the deprotection of the silyl group. The phosphine alkyne **4-61** was isolated after filtration and concentration under reduced pressure followed by purification through a column of neutral alumina.³⁶⁰ 44% yield was isolated, which was likely similar to the reported yield of 56% after purification (Scheme 118).³⁶⁰ The ^1H NMR spectroscopy was consistent with the literature as well as the ^{31}P NMR spectra with a typical shift at 12 ppm without any trace of by-product, furthermore GC/MS analysis confirmed product **4-61**.³⁶⁰



Scheme 118: Ditert-butylethynylphosphine synthesis using lithium (trimethylsilyl)acetylide and ditert-butylchlorophosphine.³⁶⁰

4.2.1.3 Synthesis of an internal phosphine alkyne

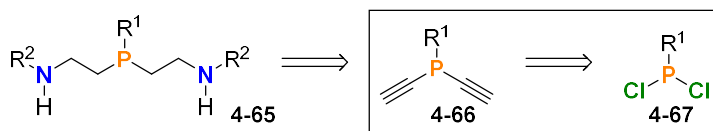
Synthesis of phosphine substituted internal alkynes has been reported in the literature and has been successfully reproduced in this project.³⁶¹ Chlorodiphenylphosphine **4-57** was diluted in THF and the lithiated alkyne **4-63** was slowly added to the resulting mixture at low temperature. After stirring for four hours while warming to room temperature, the desired phosphine alkyne **4-64** was isolated without further purification in 80% yield after filtration and concentrated under vacuum (Scheme 119). The yield obtained is consistent with the one reported in literature precedent and NMR and GC/MS analyses confirmed product **4-64**.³⁶¹



Scheme 119: Synthetic pathway for diphenylhexynephosphine.³⁶¹

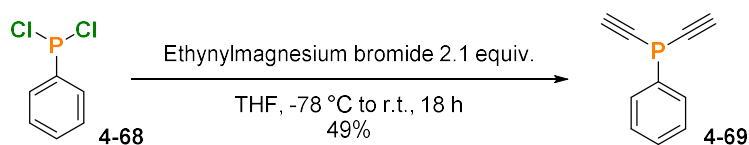
4.2.2 Synthesis of phosphine derivatives containing two to three alkynes

Synthesis of diethynylphosphine and triethynylphosphine was envisioned as an alternative route to access multidentate ligands as well as to broaden the scope for the hydroamination reaction. The retrosynthetic approach considered is very similar to the one designed for mono-ethynylphosphines (Scheme 120). The reaction was attempted first with ethynylmagnesium bromide, which is readily available and do not require further deprotection step, and dichlorophenylphosphine or phosphorus trichloride.



Scheme 120: Retrosynthetic approach to obtain the desired diethynylphosphine or triethynylphosphine derivatives.

We first attempted to synthesize diethynylphosphine **4-69** with this synthetic strategy (Scheme 121). More than two equivalents of ethynylmagnesium bromide reagent were added to a solution of dichlorophenylphosphine **4-68** in THF at $-78\text{ }^\circ\text{C}$. The reaction was left to stir overnight while warming to room temperature. The desired phosphine alkyne **4-69** was isolated after filtration of the magnesium salt and without further purification. A yield of 49% was obtained; ^1H and ^{13}C NMR spectroscopy confirmed **4-69** as well as ^{31}P NMR spectroscopy with a signal at -62.6 ppm. GC/MS analysis also confirmed product **4-69**.

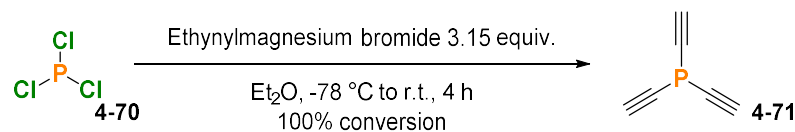


Scheme 121: Synthesis of diethynylphenylphosphine using dichlorophenylphosphine and ethynylmagnesium bromide.

As diethynylphenylphosphine **4-69** was successfully synthesized and isolated, attempts to prepare triethynylphosphine **4-71** was performed, this compound has never been reported in the literature (Scheme 122). The same preparation was used, a slight excess of ethynylmagnesium bromide solution in THF was slowly added to a solution of phosphorus trichloride **4-70** in THF at $-78\text{ }^\circ\text{C}$. Then, the resulting mixture was left to warm slowly to room temperature and finally it was concentrated *in vacuo*. ^{31}P and $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy confirmed full conversion of phosphorus trichloride ($\delta_{\text{P}} = +220$ ppm) and formation of a sharp singlet at -90.4 ppm in the phosphorus alkyl region which would correspond to the desired product **4-71**.³⁵⁹ GC/MS analysis confirmed the purity of triethynylphosphine **4-71**. Even if the reaction was successful and the conversion was total, no yield was obtained. Indeed, isolation of compound **4-71** was challenging. The solid obtained after concentration *in vacuo* was washed several times with toluene, and since the boiling point of triethynylphosphine ($129.8\text{ }^\circ\text{C}$) is very close to the one of toluene ($110.6\text{ }^\circ\text{C}$), further drying *in vacuo* was not possible and the desired product was kept as a stock solution in toluene after repeating the reaction.

The strategy of nucleophilic addition for the preparation of di- and tri-ethynylphosphines worked very well. With all the requisite phosphine alkynes in hand, the next step of testing

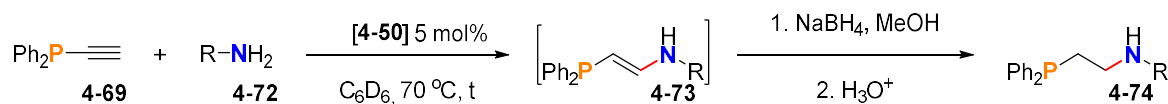
the hydroamination reaction with a titanium catalyst was performed using the method developed in the Schafer lab.¹⁰¹



Scheme 122: Synthesis of triethynylphosphine derivative using phosphorus trichloride and ethynylmagnesium bromide.

4.3 Hydroamination reaction of alkynylphosphine derivatives

The study of the hydroamination reaction of phosphine alkyne was first applied to ethynyldiphenylphosphine **4-69** by another group member in the Schafer group, Han Hao (Table 13). He disclosed the use of different primary amines **4-72** containing alkyl substituents such as *sec*-Bu, *t*-Bu, CH₂Ph, or (S)-CH(Me)Ph showing high reactivity with full conversion of ethynyldiphenylphosphine after 30 to 120 minutes, but moderate yields were obtained (entries 1-4, Table 13). Aromatic primary amines were also good substrates and only 10 to 20 minute long reactions afforded full conversion of ethynyldiphenylphosphine with *para*-methylaniline and *para*-methoxyaniline (entries 5-6, Table 13), whereas 30 to 120 minutes were necessary when electron withdrawing substituents were incorporated (entries 7-8, Table 13). 24 hours were required to achieve full conversion of the alkyne starting material when the bulkier primary amine 2,6-dimethylaniline was used. Here 96% yield was obtained after purification (entry 9, Table 13). Gratifyingly, in all these cases Han Hao demonstrated the formation of only the linear product **4-74**.

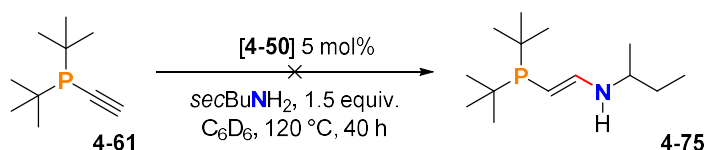


Entry	Compound	R	t/min	Yield [%]
1	4-74a	<i>sec</i> -Bu	30	61
2	4-74b	<i>t</i> -Bu	30	56
3	4-74c	PhCH ₂	120	51
4	4-74d	(S)-CH(Me)Ph	30	61
5	4-74e	4-Me-Ph	20	65
6	4-74f	4-OMe-Ph	10	50
7	4-74g	4-CF ₃ -Ph	120	56
8	4-74h	4-Br-Ph	30	30
9	4-74i	2,6-Me-Ph	1 d	96

Table 13: Amines scope of the hydroamination of ethynyl diphenylphosphine.

4.3.1 Hydroamination of *ditert*-butylethynylphosphine

In the following part, I investigated the hydroamination reaction with a bulkier aliphatic phosphine such as *ditert*-butylethynylphosphine **4-61**. The alkyne was solubilized in deuterated benzene, and the aliphatic *sec*-butylamine was added to the mixture followed by the titanium precatalyst. The reaction was monitored by ¹H and ³¹P NMR spectroscopy, and no reactivity was observed. Increasing the reaction time to 40 hours at 120 °C instead of 70 °C, did not result in the formation of the enamine product **4-75** (Scheme 123).

Scheme 123: Hydroamination of *ditert*-butylethynylphosphine with *sec*-butylamine and titanium(IV) precatalyst.

As no reactivity for the hydroamination reaction was observed using aliphatic primary amine, the reaction was then attempted with aromatic amines such as *p*-toluaniline **4-76**, which are generally more reactive than aliphatic amines towards hydroamination as reported in the literature.³⁵⁴ This characteristic is likely induced through electronic effects of aromatic amines vs. aliphatic amines.³⁵⁴ In this reaction, full consumption of the starting material **4-61** was observed after 40 hours at 120 °C and the formation of three new phosphorus peaks

appearing in the ^{31}P NMR spectra. These three peaks in the ^{31}P NMR spectrum correspond to the *trans*-enamine **4-77**, the corresponding imine **4-78** and the *cis*-enamine **4-79** (Figure 25). Formation of *cis*-enamine was also observed by Han Hao in the reaction of ethynyldiphenylphosphine **4-69**. He showed by 1D (^1H , ^{31}P , $^{31}\text{P}\{^1\text{H}\}$, and $^1\text{H}\{^{31}\text{P}\}$) and 2D (^1H - ^1H COSY and HMBC(^1H , ^{31}P)) NMR that the *cis*-enamine was obtained after the isomerization of the carbon-nitrogen bond. Such isomerizations of unsaturated carbon-carbon bonds, such as enamines, are well documented in the literature.³⁶²⁻³⁶⁵

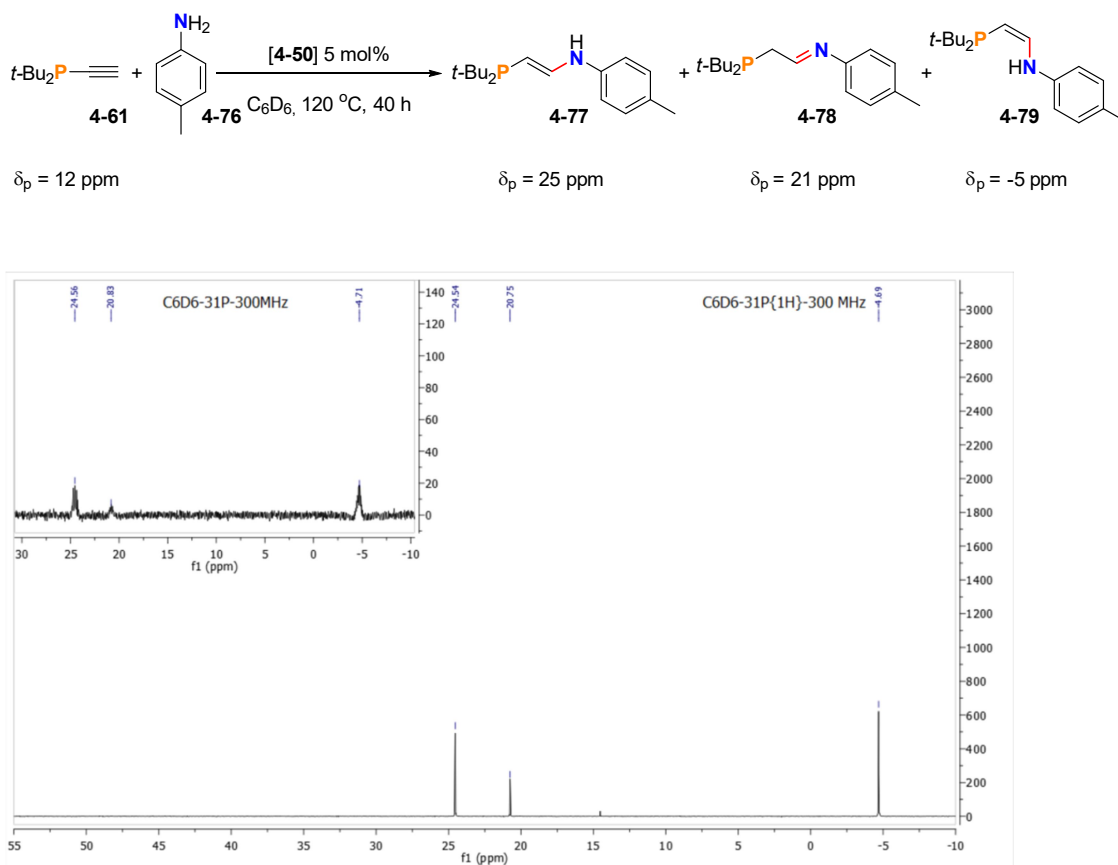
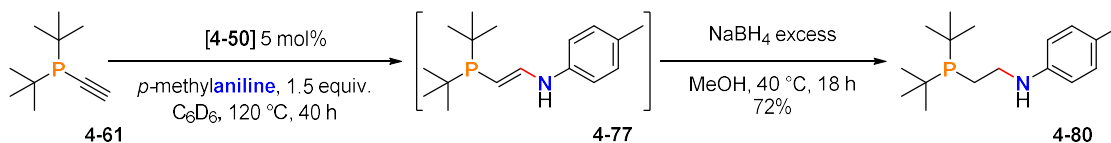


Figure 25: a) The $^{31}\text{P}\{^1\text{H}\}$ chemical shift of the starting material and the three potential tautomer products of the reaction between *para*-methylaniline and di-*tert*-butylethyne. b) ^{31}P and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of the reaction between di-*tert*-butylethyne and *para*-methylaniline after 40 hours at 120 °C.

The mixture of intermediates **4-77**, **4-78** and **4-79**, was treated with sodium borohydride in methanol at 40 °C for 18 hours to undergo reduction (Scheme 124). Compound **4-80** was the only product formed and its structure was confirmed by ^{31}P NMR spectroscopy where a shift of 21 ppm was observed. After silica gel column chromatography, the desired β -aminophosphine product was isolated as a yellow oil in 72%, and HRMS (ESI) confirmed product **4-80**. To avoid further degradation after the purification this compound was dried and kept in glovebox under dinitrogen atmosphere. Thus the preparation of β -aminophosphine ligands by the hydroamination reaction was successful with aromatic amine

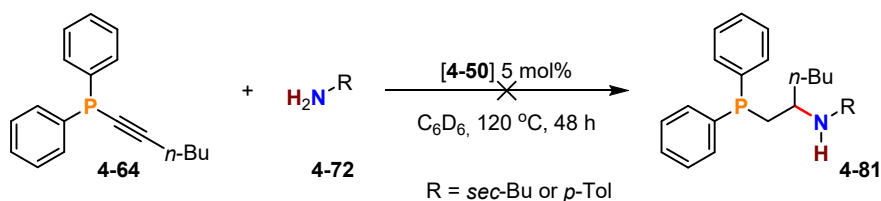
and terminal alkyl substituted phosphine alkyne giving product **4-80** never reported in the literature.



Scheme 124: Hydroamination reaction of ditert-butylethynylphosphine with *p*-toluaniline with subsequent reduction using sodium borohydride.

4.3.2 Hydroamination of an internal alkyne

Internal phosphine alkynes are more challenging substrates for reaction, due to the increased steric hinderance.³⁵⁴ The electronic features of the molecule can be tuned by changing the substituents on the alkyne. Nevertheless, we tried to perform the hydroamination reaction with a phosphine substituted internal alkyne with the more reactive aromatic amine substrates. Phosphine alkyne **4-64** was diluted in deuterated benzene followed by the addition of *sec*-butylamine and the titanium pre-catalyst (Scheme 125). However, no reaction was observed by ^{31}P NMR spectroscopy, thus the reaction was also studied using *p*-toluaniline. No reaction was also observed in this case either, as determined by 1H and ^{31}P NMR spectroscopy. The failure of the reaction might be due to steric hindrance, indeed Han Hao disclosed the hydroamination reaction using a phenyl substituent in place of the *n*-butyl group and *p*-toluaniline and he obtained 67% yield.



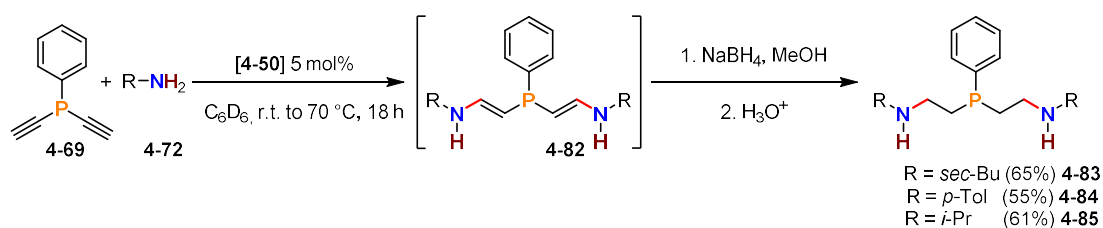
Scheme 125: Hydroamination of internal phosphine alkyne with *para*-toluaniline or *sec*-butylamine.

4.3.3 Hydroamination of diethynylphenylphosphine

The hydroamination of diethynylphenylphosphine was then considered as such aminophosphine would generate bis(β -aminophosphine) (Scheme 126). Monitoring the reaction by ^{31}P NMR spectroscopy showed full consumption of the phosphine alkyne starting material after 18 hours at 70 °C. Indeed, the ^{31}P NMR spectrum showed the shift of the starting material peak at -62.6 ppm to the formation of three new deshielded peaks at -23.7, -24.0, and -32.1 ppm. 1H NMR spectroscopy confirmed the exclusive formation of the linear

product. Indeed the coupling constant of 15.0 Hz found for the *trans* protons confirmed the formation of the *trans* enamine which is in equilibrium with the imine form and no *cis* product could be distinguished on the ^1H NMR spectra. Then, reduction using sodium borohydride afforded the diaminophosphine. NMR spectroscopy confirmed the formation of only the bis(β -aminophosphine) **4-83** as the sole product with one peak on the ^{31}P NMR spectrum at -33.0 ppm. To eliminate the trace remaining catalyst, the product was purified by silica gel column chromatography and isolated as a yellow oil in 65% yield (Scheme 126).

The use of racemic *sec*-butylamine led to the possibility of compound **4-83** to be formed as a mixture of various diastereomers. Determination of the different isomers was tried to be clarified through NMR spectroscopy, but ^1H and $^1\text{H}\{^{31}\text{P}\}$ was not conclusive as only one product was clearly identified and no trace of diastereoisomers. Furthermore only one peak was distinguished on the ^{31}P and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra. GC/MS analysis also showed one major peak without the possibility to conclude on the formation of one product or different products. Chiral HPLC was also tried, and only one peak was observed but the retention time ($t_r = \sim 2$ min) was too short to be conclusive. Another method was tried to answer this stereochemistry question: coordination of the enamine/imine intermediate **4-82** to a metal to form a *N,P,N*-metal complex. ^{31}P and $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy should show the formation of various peaks corresponding to different *N,P,N*-metal complexes if several diastereoisomers are obtained during the hydroamination reaction. The coordination of the enamine product is not presented in this section but is developed in section four of this chapter (*vide infra*).



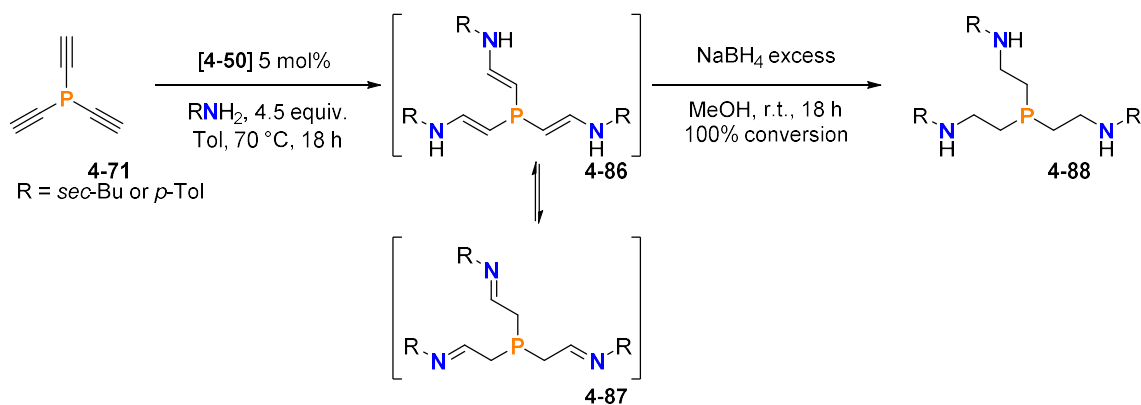
Scheme 126: Hydroamination of diethynylphosphine using *sec*-butylamine or *para*-methylaniline, followed by the subsequent reduction.

The scope of the hydroamination reaction to form *N,P,N*-ligands was also examined with an aromatic primary amine such as *p*-toluaniline (Scheme 126). This amine exhibited good reactivity and required a shorter reaction time (8 hours) at 70 °C (and 18 hours at room temperature) than aliphatic amine. Signals corresponding to the ligand formation were observed by ^{31}P NMR spectroscopy, and after column chromatography the *N,P,N*-product **4-84** has been isolated as a yellow oil in 55% yield and the same chemical shift was observed at -33 ppm. Using *isopropylamine* also worked and resulted into 61% yield after isolation

under silica gel chromatography. The yields obtained for compounds **4-83**, **4-84** and **4-85** are moderate after purification even if full conversion of ethynylphosphine starting materials was observed by ^{31}P NMR spectroscopy. The purification step is the main limitation of this synthetic procedure. Indeed silica gel chromatography is generally Lewis acidic and it has been reported that silica may bind with the Lewis basic amine, leading to smaller quantities of isolated product.³⁶⁶ These compounds were never reported in the literature until the use of this synthetic approach for the formation of β -aminophosphines.

4.3.4 Hydroamination of triethynylphosphine

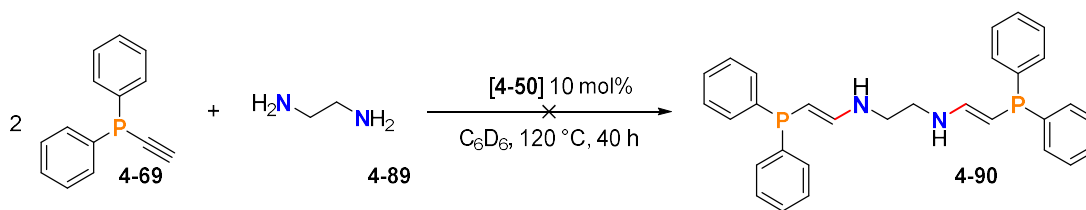
Inspired by the results obtained, we were then interested in trying the hydroamination of the triethynylphosphine **4-71** prepared in section two. To do so, we chose to use similar reaction conditions as mentioned for the hydroamination of diethynylphenylphosphine with *sec*-butylamine or *para*-toluaniline as amine sources, followed by a reduction step with sodium borohydride (Scheme 127). Since triethynylphosphine **4-71** was prepared and stored as a solution in toluene, the solvent used for hydroamination was also toluene. The reaction was monitored by ^{31}P NMR spectroscopy, and the enamine/imine intermediates **4-86** and **4-87** have been observed by ^{31}P NMR spectroscopy after 18 hours at 70 °C with the observation of two shielded signals at -70.1 and -73.8 ppm. The disappearance of the ^{31}P NMR signal at -90.4 ppm confirmed the full consumption of phosphine starting material. Neither ^1H NMR spectroscopy nor GC/MS could be used to further confirm the formation of the desired product. As in the general method to obtain β -aminophosphines with hydroamination, subsequent reduction was performed with sodium borohydride, using the reaction mixture that showed complete consumption of the starting material in the hydroamination reaction. Isolation of the desired product **4-88** was not possible due to purification problems. This tri-substituted amine derivative sticks more likely with silica gel. Further efforts toward purification of ligands obtained from the hydroamination reactions of diethynylphenylphosphine and triethynylphosphine are required to optimize these reactions.



Scheme 127: Hydroamination of triethynylphosphine.

4.3.5 Extension to the formation of P,N,N,P -ligands

As presented in the introduction, different P,N -ligand groups have been described in the literature.³⁰⁰ Since the method we developed successfully for P,N - and N,P,N -ligands with primary amine and phosphine alkyne worked well through the hydroamination reaction, we then considered P,N,N,P -ligands as an appealing target. Indeed the chemistry we have developed could be extended to a reaction with phosphine alkyne and a diamine. The formation of N,P,P,N could also be considered, but would require the synthesis of diphosphine compounds, which are more challenging to acquire than diethyl diamine for P,N,N,P -ligands. Since this approach seems easier as an attempt to extend our chemical system, we first investigated the formation of P,N,N,P -ligands by hydroamination. To achieve the desired transformation, the same method described for hydroamination reaction of mono-, di- and tri-ethynylphosphine was used (Scheme 126). Two equivalents of ethynyl-diphenylphosphine **4-69** were diluted in deuterated benzene with 10 mol% of bis(amido)bis(amidate)titanium(IV) catalyst and the primary diamine **4-89** were stirred and heated (Scheme 128). The reaction was monitored by ^1H and ^{31}P NMR spectroscopy for 40 hours, at 70 °C for 18 hours and then at 120 °C. However, no conversion of **4-69** was observed after 18 and 40 hours. No modification of the chemical shift at -33.3 ppm of the phosphine starting material happened. This reaction did not work because of the coordination of the diamine with the titanium pre-catalyst probably forming an unreactive species toward hydroamination reaction, as has been suggested in the literature by Clark and co-workers.³⁶⁷

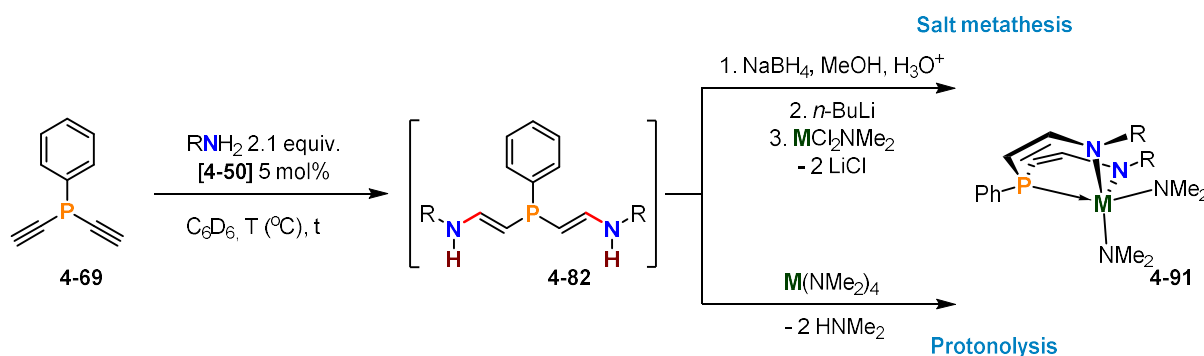


Scheme 128: Hydroamination using ethynylphenylphosphine and ethylenediamine.

4.4 Synthesis of new early transition metal N,P,N -complexes

4.4.1 Introduction

Hydroamination of diethynylphenylphosphine led first to the formation of enamine/imine intermediates and then to β -aminophosphines after reduction with sodium borohydride. These products were then used as proligands to obtain N,P,N -metal complexes. The synthesis of N,P,N -metal complexes can be achieved using the same approach as 1,3-chelating metal complexes by protonolysis or salt metathesis (Scheme 129).⁷⁴ However, in the former, the starting material can be in equilibrium with the product, whereas elimination of salt through salt metathesis displaces the equilibrium toward formation of the desired metal complex. Other research groups have done this reaction with N,P,N -ligands to obtain the desired complexes through salt metathesis.²⁹⁶ However, it only resulted in mixture of products that were difficult to purify.²⁹⁶ For this reason, protonolysis was the first reaction studied.

Scheme 129: Two different approaches for the formation of the desired N,P,N -metal complexes using either salt metathesis or protonolysis reactions.

4.4.2 N,P,N -ligand metal complexes

Herein, different homoleptic metal complexes have been used to study the formation of the desired N,P,N -metal complexes via protonolysis. First,

tetrakis(dimethylamido)zirconium(IV) was used followed by tetrakis(dimethylamido)titanium(IV) and dichlorobis(dimethylamido)zirconium(IV).

4.4.2.1 Reaction using tetrakis(dimethylamido)zirconium(IV)

Diethynylphenylphosphine **4-69** was diluted in deuterated benzene with diisopropylamine **4-92** and bis(amido)bis(amidate)titanium(IV) catalyst **4-50**, and after 18 hours at 70 °C, the enamine/imine intermediate was observed by ^1H and ^{31}P NMR spectroscopy with the same chemical shift as presented previously. The *trans,trans*-isomer **4-93** was still in equilibrium with the *cis,cis*-isomer **4-94** as explained previously, due to the isomerization of the carbon-nitrogen bond. Hence, after addition of the homoleptic zirconium metal, the desired penta-coordinated zirconium complex **4-95** was obtained (Figure 26.a). $^{31}\text{P}\{^1\text{H}\}$ confirmed the formation of only one product containing a phosphorus moiety with a sharp singlet at -21.1 pm (Figure 26.b). ^{31}P NMR spectrum showed a triplet of triplets corresponding to the phosphorus coupled to eight protons in 2J and 3J (Figure 26.b).

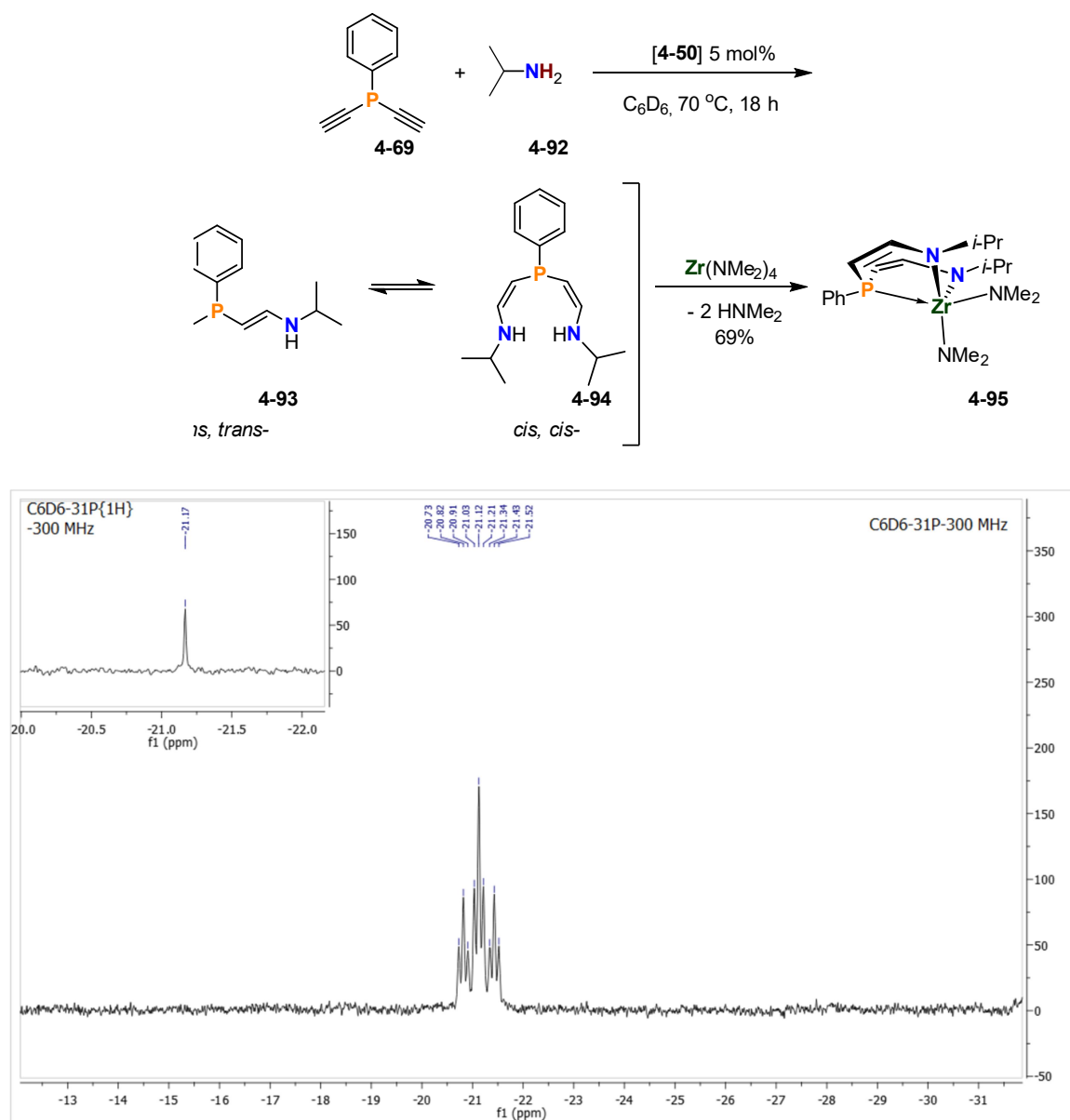


Figure 26: a) Formation of 5-membered zirconium complex containing *N,P,N*-ligand after protonolysis between the enamine and tetrakis(dimethylamido)zirconium(IV). b) ³¹P and ³¹P{¹H} NMR spectra of the protonolysis reaction with tetrakis(dimethylamido)zirconium(IV).

Recrystallization in HMDSO resulted in crystals suitable for X-ray crystallography which showed a distorted trigonal bipyramidal geometry (Figure 27). Electron delocalization over the C-C-N moieties was confirmed by bond lengths measured by X-ray crystallography (C1-C2 (1.362(7) Å) and C10-C9 (1.358(7) Å)). Similar zirconium metal complexes have been reported by Fryzuk and co-workers and most bond lengths and angles are in agreements with previously reported structures.³⁰⁴ However, the angle of N1-Zr1-N2, 130.17(15)° is larger than that reported by Fryzuk (123.52(4)°), presumably due to the absence of substituents on the carbons C1, C2, C9 and C10. Angles N3-Zr1-P1 of 107.88(12)° and of N4-Zr1-P1 150.68(13)° are also different compared to the structure

reported in the literature, because of the substituents on the nitrogen: indeed diisopropyl groups are less bulky than the 2,6-dimethylphenyl groups previously reported (angles $(89.90(3)^\circ$ for N3Zr1P1 and $164.75(3)^\circ$ for N4Zr1P1, respectively).³⁰⁴

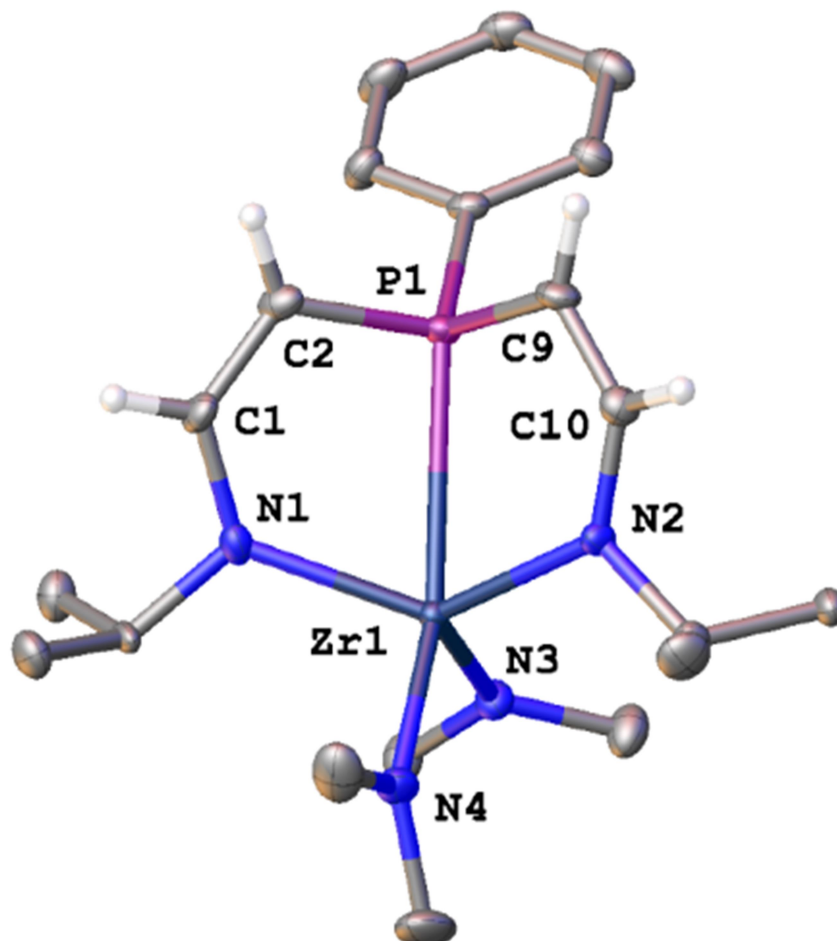


Figure 27: ORTEP representation of the solid-state molecular structure of 4-95 in crystals. Ellipsoids drawn at 50% probability. All hydrogen atoms besides the hydrogens on C1, C2, C9 and C10 have been omitted for clarity. Selected bond lengths (Å): Zr1-P1: 2.8170(12), Zr1-N1: 2.152(4), Zr1-N2: 2.140(4), Zr1-N3: 2.016(4), Zr1-N4: 2.068(4), C1-C2: 1.362(7), C9-C10: 1.358(7), and selected bond angles ($^\circ$): N1-Zr1-P1: 72.56(11), N4-Zr1-N3: 101.43(17), N2-Zr1-P1: 71.58(10), N2-Zr1-N1: 130.17(15), N3-Zr1-N1: 113.51(16), N3-Zr1-P1: 107.88(12), N4-Zr1-P1: 150.69(13), N4-Zr1-N1: 96.23(16), N4-Zr1-N2: 98.44(15), N3-Zr1-N2: 109.72(15), C2-C1-N1: 124.7(4), C9-C10-N2: 124.9(4), C11-N1-Zr1: 121.5(3), C14-N2-Zr1: 117.6(3).

The ready formation of such a complex directly from the crude product of hydroamination allow for the use of tetrakis(dimethylamido)zirconium(IV) for analysing if diastereoisomers of compound **4-83** have been obtained from racemic *sec*-butylamine and diethynylphenylphosphine. In our system, the hydroamination reaction is not expected to be diastereoselective, although by NMR spectroscopy, GC/MS and chiral HPLC of compound **4-83** it was not clear if more than one product was being formed during hydroamination. Therefore we tried to make complex of ligand **4-83** with tetrakis(dimethylamido)zirconium(IV).

Complexation was performed with the same protocol used to form N,P,N -Zr complex **4-95**. Once the enamine/imine intermediates were formed, the homoleptic amido zirconium complex was added and the ^{31}P NMR spectrum showed the formation of a multiplet at -19.6 ppm and not a triplet of triplets as expected (Figure 28). Further analysis by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy revealed the presence of three different peaks (Figure 28). These three different peaks most probably correspond to three potential diastereoisomers resulting from the use of racemic *sec*-butylamine. Hence, this observation is in agreement with the formation of three different N,P,N -Zr complexes. These results confirmed that the hydroamination reaction is not diastereoselective and the two stereogenic centres were too far away from each other to interact. For this reason only one product could be observed by NMR spectroscopy and chiral HPLC after the reduction step.

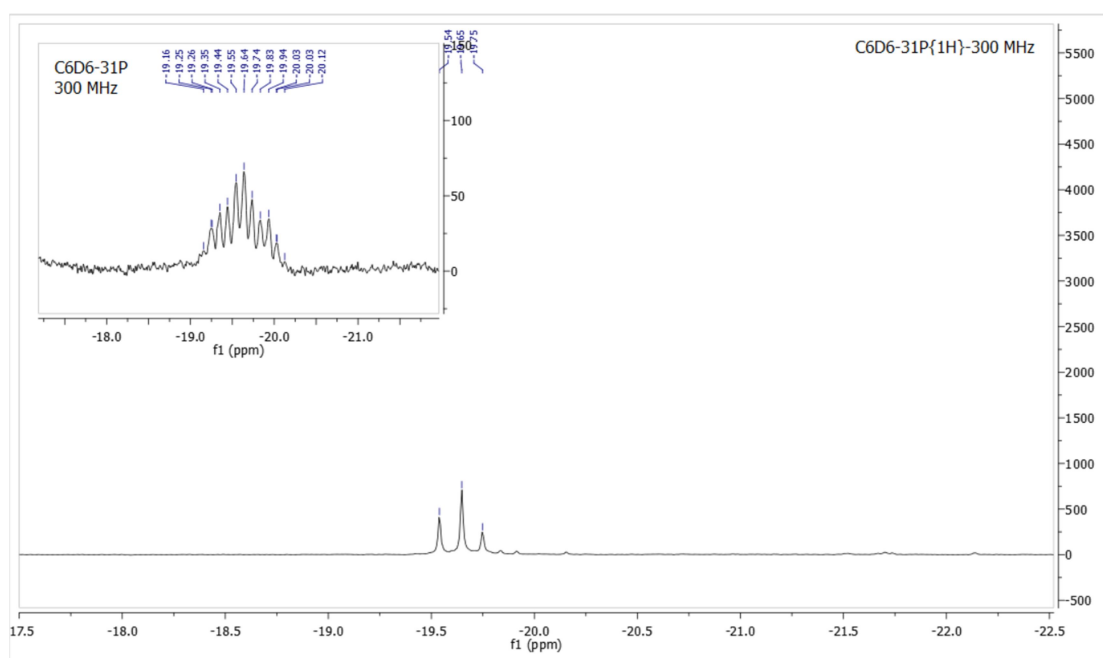


Figure 28: ^{31}P and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of the protonolysis reaction with tetrakis(dimethylamido)zirconium(IV) on the resulting enamine/imine intermediates of the hydroamination between diethynylphenylphosphine and *sec*-butylamine.

4.4.2.2 Reaction using dichlorodimethylamidozirconium(IV)

Based on the work with tetrakis(dimethylamido)zirconium(IV), the protonolysis reaction has also been applied to dichlorodimethylamidozirconium(IV).³⁶⁸ The enamine/imine intermediate **4-96** was obtained by hydroamination using diisopropylamine and diethynylphenylphosphine **4-69** after 18 hours at 70 °C. Then the zirconium metal precursor was added to the resulting mixture and the reaction was monitored by NMR spectroscopy (Figure 29.a).

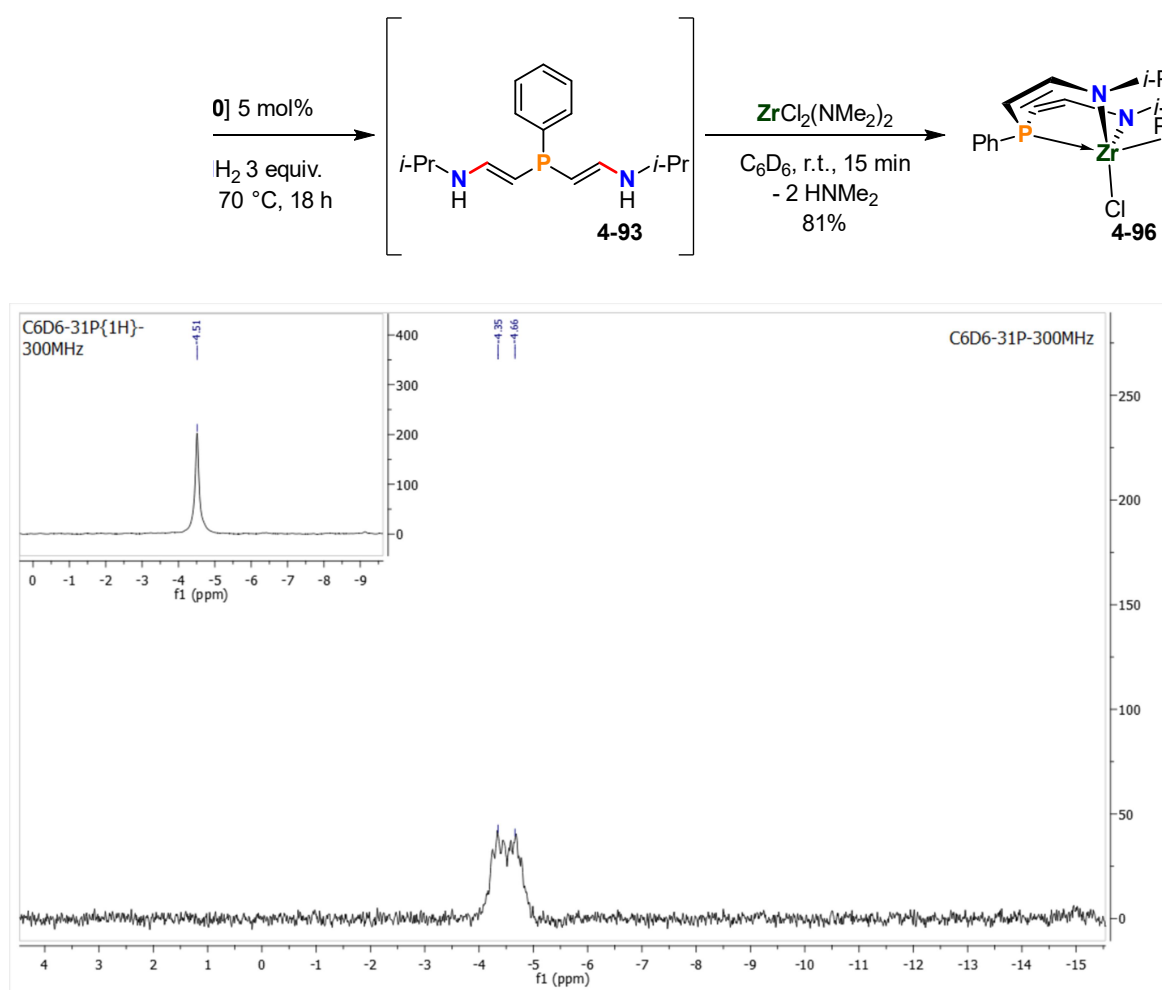


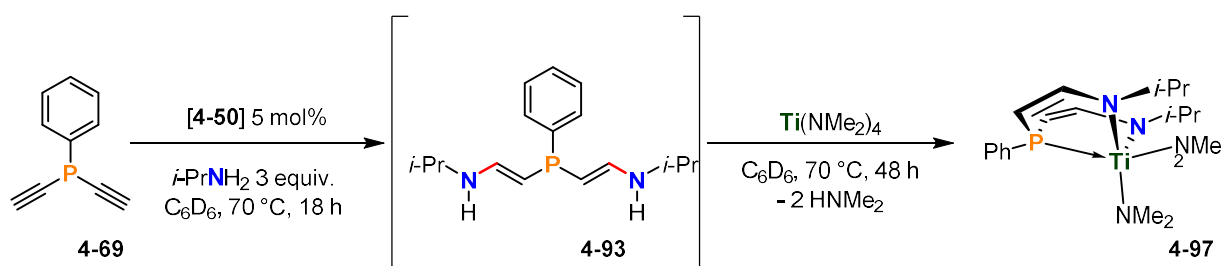
Figure 29: a) Reaction with *N,P,N*-proligand and $\text{ZrCl}_2(\text{NMe}_2)_2$. b) ^{31}P and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of the reaction with $\text{ZrCl}_2(\text{NMe}_2)_2$.

Crystals of the previous complex **4-95** had been obtained using HMDSO as solvent; however no crystal could be obtained for complex **4-96**. The complex was characterized by NMR spectroscopy. One broad multiplet has been observed by ^{31}P NMR spectroscopy corresponding to the phosphorus coupled to proton atoms in 2J and 3J at -4.5 ppm, looking like a multiplet. The signal on the ^{31}P was broad, thus $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy was performed to confirm the formation of a single product with one sharp singlet at -4.5 ppm (Figure 29.b). Lastly, ^1H and 2D NMR spectroscopy were in good agreement compared to the complex obtained above and confirmed the formation of the *N,P,N*-zirconium based complex **4-96**.

4.4.2.3 Reaction using tetrakis(dimethylamido)titanium(IV)

The reaction worked well using zirconium(IV) complexes and for this reason the reaction was studied with another group 4 metal, titanium(IV). Using the same general procedure as previously described for the synthesis of the enamine/imine intermediate **4-93**,

tetrakis(dimethylamido)titanium(IV) was added to the resulting mixture of intermediates **4-93** and heated at 70 °C for 48 hours to reach full conversion of compound **4-93** to the desired *N,P,N*-metal complex **4-97** (Scheme 130).



Scheme 130: Reaction with *N,P,N*-proligand and Ti(NMe₂)₄.

Hexane as well as HMDSO did not afford formation of any crystals, but, ³¹P and ³¹P{¹H} NMR spectroscopy were similar to the results obtained with tetrakis(dimethylamido)zirconium(IV). One sharp singlet at -8.7 ppm in the ³¹P{¹H} spectrum confirmed the formation of only one product, and the ³¹P NMR spectrum showed one triplet of triplets at -8.8 ppm. These results are in agreement with those obtained with Zr(NMe₂)₄ (Figure 30). The difference between the zirconium and the titanium complexes was the chemical shift. For the *N,P,N*-titanium complex, -8.8 ppm has been observed while -21.1 ppm has been shown on the NMR spectrum using the *N,P,N*-zirconium complex. This change is likely due to the difference between the two metals: zirconium has a larger atomic radius than titanium which could result in a deshielded signal for the titanium complex compared to the zirconium complex.³⁶⁹

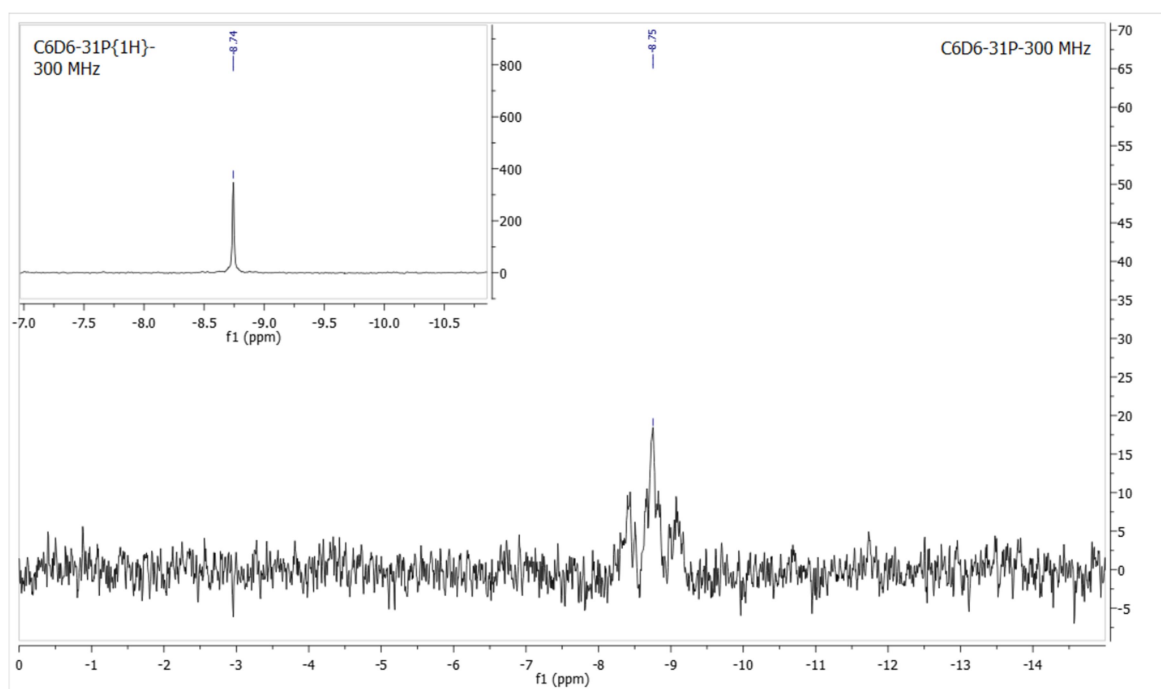


Figure 30: ^{31}P and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of the reaction with $\text{Ti}(\text{NMe}_2)_4$.

4.5 Conclusion

A novel approach has been developed to synthesize β -aminophosphines and bis(β -aminophosphines) using hydroamination with a bis(amido)bis(amidate)titanium(IV) precatalyst developed in the Schafer laboratory. Attempts to prepare phosphine alkyne derivatives with one, two, and three alkynes were performed prior to the hydroamination. Nucleophilic addition was successfully used to generate these phosphines. These syntheses are the very first examples of phosphine containing more than one alkyne groups on the phosphorus centre. Derivatives with one alkyne on the phosphine were generated using lithium (trimethylsilyl)acetylide as described in the literature. Synthesis of internal phosphine alkyne was also performed successfully from literature precedent. Prior to hydroamination, phosphine alkyne derivatives were synthesized using a nucleophilic addition reaction.

Han Hao, another *Ph.D.* student in the Schafer group developed the hydroamination reaction as a novel approach for the synthesis of β -aminophosphines. He demonstrated the flexibility of this process by using various different primary amines and the same phosphine alkyne: ethynyldiphenylphosphine. I extended the alkyne scope using sterically hindered *di**tert*-butylethynylphosphine to obtain *P,N*-ligands. This chemistry was extended to other phosphine starting materials containing two alkynes. Hence, symmetric *N,P,N*-ligands have been obtained using the desired primary amine and pre-synthesized diethynylphenylphosphine.

Finally, the coordination chemistry of those *N,P,N*-ligands have been studied with early transition metals such as zirconium and titanium based on the work developed in the literature by Fryzuk and co-workers.^{296, 304, 332, 345} Crystallization using HMDSO afforded the formation of crystals suitable for X-ray spectroscopy, confirming the formation of a distorted trigonal bipyramidal metal complex. Extension to utilization of tetrakis(dimethylamido)titanium(IV) and dichlorobis(dimethylamido)zirconium(IV) formed the desired metal complexes as confirmed by NMR spectroscopy (^1H , ^{31}P , $^{31}\text{P}\{^1\text{H}\}$, ^{13}C and 2D) in the absence of X-ray structures.

Reactivity towards the activation of dinitrogen has been tried without any success due to decomposition of the complex after concentration *in vacuo*. Future work on this project could be based on the reactivity toward those complexes to activate small molecules as dinitrogen or dihydrogen. Formation of asymmetric *N,P,N*-ligands could also be another idea to then extend the synthesis to chiral ligands, which have not been reported for such *N,P,N*-ligands.

5 CHAPTER V: CONCLUSION

5.1 Summary

This thesis focuses on the development of new hemilabile ligands for catalysis. The key design question focused on the potential application of new ligands for early transition metals featuring heteroelement moieties like boron and phosphorus. The first chapter reviewed the synthesis and application in organic chemistry of 1,3-chelating ligands such as 1,3-*N,O*- and 1,3-*N,N*-ligands.

Chapter two focused on the development of potential new 1,3-*N,O*-chelating ligands using an alkoxyaminoborane motif. A new synthetic pathway involving the use of aminochloroboranes as key intermediates, which avoided the use of boron halides as reagents, was presented. Although the desired potential chelating metal complex was not obtained, an unexpected reactivity was observed: the dimethyltitanocene was reacting as a Grignard reagent. Methyl addition onto the boron atom of the borazarophenanthrene occurred, and this methyl-borazarophenanthrene was characterized by ^1H , ^{11}B and ^{13}C NMR spectroscopy. This unexpected side reaction occurred in each attempts to install *O,B,N*-ligands onto the metal centre.

The third chapter showed the synthesis of boraamidine proligands as new molecular targets for the development of potential hemilabile 1,3-*N,N*-chelating ligands. In the Pucheault laboratory at the University of Bordeaux cyclic boraamidine was synthesized in four steps including electrophilic Friedel-Crafts cyclization, Suzuki-Miyaura cross-coupling and Miyaura borylation steps. The last step reaction yielded less than 10% of the desired *N,B,N* products. Nevertheless, one *N,B,N*-ligand was synthesized successfully and used in coordination chemistry with titanium as transition metal. No chelated metal complex was obtained due to amine rearrangement. At the University of British Columbia (UBC), another procedure was investigated for the synthesis of air and moisture sensitive acyclic boraamidines. One symmetric and four asymmetric boraamidine proligands were successfully synthesized, four were in good agreement with the literature and the last one was never reported. Primary and secondary amines having different steric and electronic properties were used to synthesize the five boraamidine derivatives. Then reactivity toward group 4 and 5 metals was studied. Formation of a bis(titanium) imido bridged complex was obtained through the reaction of symmetric boraamidinate and dichlorobis(dimethylamido)titanium(IV), but the desired potential 1,3-*N,N*-chelating metal complexes could not be obtained from the five boraamidines. Hydrofunctionalization catalysis was then carried out by using alkene, *N*-methylaniline, tantalum metal complex prepared *in*

situ using the targeted boraamidines as proligands. Activity for hydroaminoalkylation of alkenes with *N*-methylaniline was observed and full conversion of the amine was achieved but longer reaction times were required to witness full conversion compared to the method reported in the Schafer group with ureate ligands on tantalum.

While the development of 1,3-chelating ligands with boron in the backbone was not successful, a novel synthetic route for accessing 1,4-chelating *P,N*-ligands was developed that would feature a state-of-the-art hydroamination catalyst from the Schafer group at UBC. Chapter four discloses the advances made in accessing this new class of ligands. The work presented in this chapter was completed in collaboration with Han Hao (*Ph.D.* candidate at UBC) who first showed that the hydroamination of phosphorus substituted alkynes was feasible. I developed the synthesis of *N,P,N*-ligands using the same procedure, and I further isolated five reduced β -aminophosphines or bis(β -aminophosphines). Moderate yields were obtained despite full consumption of substrates due to challenging purifications.

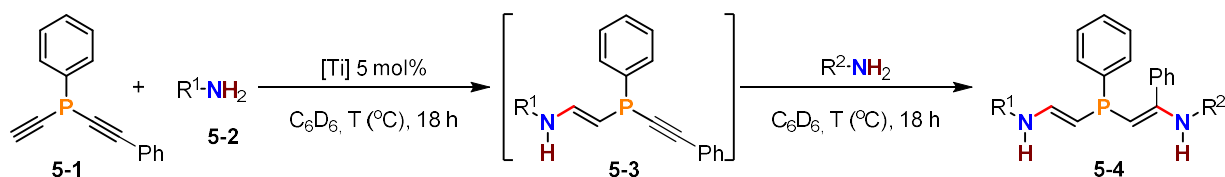
Coordination chemistry was carried out with *N,P,N*-ligands using early transition metals like zirconium and titanium. One X-ray structure was obtained as a distorted trigonal bipyramidal zirconium complex and the crystalline structure shows a five-membered zirconium complex presenting a phosphorus-zirconium bond. This X-ray structure is similar to the ones reported in the literature for related complexes, but some variations of angles were observed. This *N,P,N*-zirconium complex was also characterized by mass spectrometry and 1D and 2D NMR spectroscopy. Analytical data from this *N,P,N*-zirconium complex allow the possibility to corroborate the structures of two other metal complexes: a *N,P,N*-zirconium complex, and a *N,P,N*-titanium complex. Although no crystallographic structures were obtained for both of them, but the presence of similar coupling patterns in NMR spectroscopy in comparison with the first *N,P,N*-zirconium complex solved by X-ray structure, confirmed the formation of the two new complexes. Detailed analyses of the bonding modes in these complexes are to be found when crystalline structures will be obtained.

5.2 Future work

5.2.1 ***Extension of the phosphine alkyne hydroamination scope***

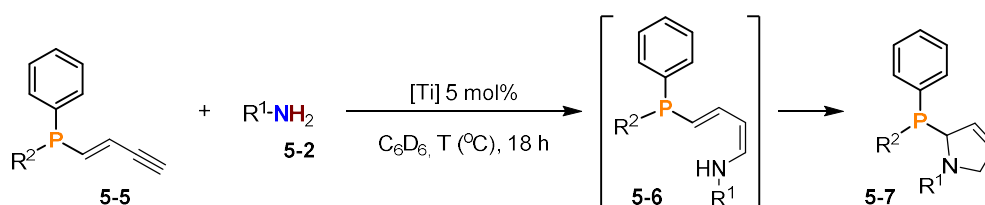
The discovery of a new synthetic approach using a hydroamination reaction to synthesize *N,P,N*-ligands offers access to new tunable ligand possibilities. This advancement could help to either electronically or sterically tune the *N,P,N* backbone by changing the substituents on either the phosphine or the amine. There are many reported examples in the literature of various aliphatic *P,N*-ligands for asymmetric catalysis.^{300, 311, 320, 370} To synthesize

a chiral *P,N*-ligand by hydroamination, an unsymmetric internal phosphine alkyne **5-1** could be used. As showed in this thesis, aliphatic and aromatic primary amines required distinct reaction conditions: heating was necessary with aliphatic amine substrate, whereas, aromatic amine can be used for hydroamination at room temperature. Internal and terminal alkynes also demonstrated different reactivity: higher temperatures and longer reaction times are generally required for internal alkynes while 70 °C or room temperature for 18 hours is necessary for terminal alkynes. Thus, by choosing the select amine **5-2** and the right alkyne **5-1**, *N,P,N*-ligands **5-4** could be synthesized (Scheme 131). The chiral metal complex that would result with the *N,P,N*-ligands could be obtained using the same protonolysis with the method described in the fourth chapter.



Scheme 131: Hypothetical hydroamination of asymmetric phosphine alkynes.

Applying hydroamination to enynes **5-5** could lead to the development of cyclic *P,N*-ligand **5-7** which is another well-known group of *P,N*-ligands. The alkyne hydroamination would then form the 1,3-diene intermediate **5-6** which could react again through an intramolecular hydroamination step to form the desired 5-membered ring *P,N*-ligand (Scheme 132).³⁷¹

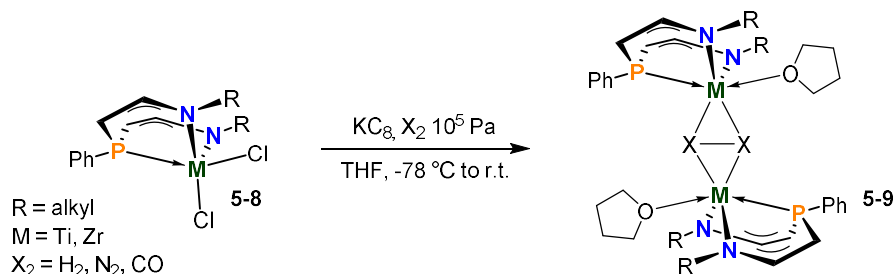


Scheme 132: Theoretical hydroamination of β -phenyl-enyne.

5.2.2 Synthetic applications of the enamine/imine intermediate

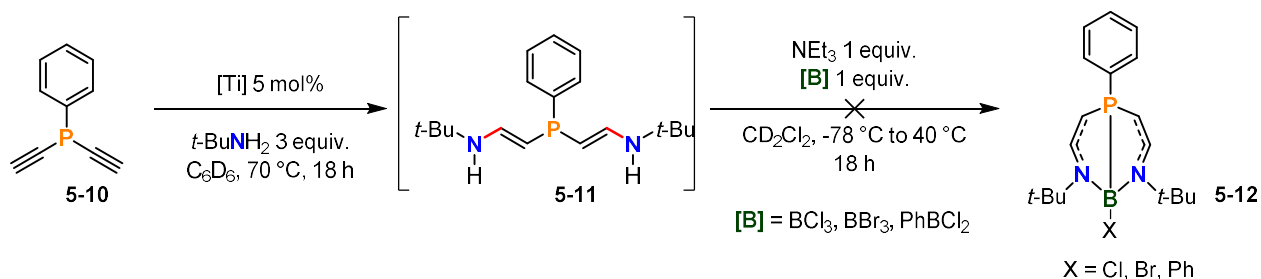
While *P,N*- and *N,P,N*-ligands have been widely used for asymmetric hydrogenation, as shown in chapter four, their properties as ligands that support complexes capable of activating small molecules is of interest. Fryzuk and co-workers published impressive results on the activation of dinitrogen, dihydrogen or alkene using *N,P,N*-metal complexes of early transition metals (tantalum, zirconium, and titanium).^{296, 304, 332, 345} Hence, preliminary work was performed for activation of dinitrogen using first a reduction step with

potassium graphite as reductant, but resulted in degradation. It could be interesting to try the reaction again and monitor the reaction by IR spectroscopy to confirm the activation of dinitrogen. Other gases could be considered, like dihydrogen or carbon monoxide, with the use of the *N,P,N*-metal complex **5-8** (Scheme 133).



Scheme 133: Gas activation using *N,P,N*-metal complex.

The enamine/imine intermediates **5-11** formed through hydroamination could be used to form new Frustrated Lewis Pairs (FLP) using boron chemistry. Frustrated Lewis Pairs is well documented in the literature and generally involve carbon-boron, nitrogen-boron or phosphorus-boron bonds.³⁷²⁻³⁷⁴ The resulting combination of sterically encumbered Lewis acids and bases have been used for dihydrogen activation and applied for metal free catalytic hydrogenation.³⁷⁴ Thus, preliminary experiments were performed using boron halides, such as boron trichloride, or tribromide, or dichlorophenylborane. The enamine/imine ligand **5-11** was formed using the hydroamination reaction. One equivalent of base (e.g. triethylamine) and the appropriate boron halide (boron trichloride or tribromide) were added at -78 °C. Because no reactivity was observed at room temperature for 18 hours, the resulting mixture was then heated at 40 °C. Monitoring the reaction with ³¹P{¹H}, ¹H, and ¹¹B NMR spectroscopy showed the degradation of the enamine/imine intermediate. The absence of formation of the desired product **5-12** was inferred because there were no more peaks in the ³¹P{¹H} spectra. However, only one peak on the ¹¹B NMR spectrum was observed at 10 ppm, which corresponds to the triethylamine chloroborane adduct (Scheme 134).



Scheme 134: Preliminary result for the formation of new Frustrated Lewis Pairs.

5.3 Concluding remarks

This thesis has provided evidence for the development of new hemilabile heteroelement ligands. While boron atoms could not be incorporated into robust 1,3-chelating ligands, phosphorus containing ligands showed promising results. The *P,N*- and *N,P,N*-ligands developed through a new pathway using a hydroamination reaction, were fully isolated and characterized either as reduced amine or as metal complexed ligands. This work has shown a flexible approach for the formation of β -aminophosphine with a tethered carbon-carbon framework. For *N,P,N*-ligands such tethered carbon-carbon bonds were unknown in the literature previous to this work. This thesis shows that by using the hydroamination reaction a large variety of *N,P,N*-ligands can be accessed by a 100% atom economic process.

Development of new synthetic strategies accessing a variety of ligands and metal complexes with early transition metals constitute preliminary works as a fundamental study for hemilabile ligands containing one of the following motifs *1,3-N,N*-, *1,3-N,O*-, *P,N*-, *N,P,N*-moieties. One crystal structure of an *N,P,N*-metal complex containing a zirconium centre has been characterized and showed a similar bonding mode to those described in the literature. Having more X-ray structures of ligated early transition metal complexes and their related reactivity studies are necessary for the field to design new ligands frameworks and new reactive complexes. All the work of this thesis will allow others to optimize the conception of ligands and therefore their complexes, which could be then used as catalyst in organic synthesis. All this *Ph.D.* work contributed to the state-of-the-art in chelating ligands that incorporate heteroelements such as boron and phosphorous atoms.

6 EXPERIMENTAL SECTION

6.1 General considerations and materials

All chemicals were purchased from commercial sources and used without further purification, and those which were not already dried and stored under inert atmosphere were dried and degassed *via* the freeze-pump-thaw method before use. All air and moisture sensitive compounds were manipulated under inert N₂ atmosphere using an MBraun LABmaster glovebox or standard Schlenk techniques. Glassware was allowed to dry in a 160 °C oven prior to transferring to the glovebox or Schlenk manifold. All amine substrates were either distilled from calcium hydride and degassed or sublimed under vacuum. Toluene and hexanes were passed through an activated alumina column under N₂ gas, collected in a Teflon sealed Straus flask, and sparged with N₂ for 30 minutes prior to use. Deuterated benzene and toluene were purchased from Sigma-Aldrich and were dried over activated 4 Å molecular sieves. Deuterated chloroform was purchased from Sigma-Aldrich and used directly.

Thin layer chromatography (TLC) was performed on silica gel 60 F254 (Merck) with detection by UV light and charring with 1% w/w ninhydrin in water/butanol (5/5) followed by heating. Flash column chromatography was carried out on silica gel (40-63 µm, Merck).

¹H, ¹¹B, ¹³C and ³¹P NMR spectra were recorded on Bruker 300 MHz and 400 MHz Avance spectrometers at 298 K unless otherwise noted. Chemical shifts are reported in parts per million (ppm, δ) relative to the residual signal of the deuterated solvent used. ¹H NMR splitting patterns with observed first-order coupling are designated as singlet (s), broad singlet (bs), doublet (d), triplet (t), or quartet (q). Not defined ¹H NMR splitting patterns are designated as multiplet (m). Assignments were made on the basis of chemical shift, coupling constants, 2D correlation and comparison with spectra of related compounds. Coupling constants (*J*) are reported in Hertz (Hz). NMR spectra are shown using MestReNova 6.0.2 NMR processing software.

Gas chromatography-mass spectrometry (GC/MS) analyses were conducted at the University of Bordeaux on a Agilent 7890A equipped with a J&W Scientific DB-1701 capillary column, a Agilent 5975C triple axis detector (EI), using the following method: 70 °C for 2 min then 20 °C.min⁻¹ until 230 °C, at a flow rate of 2 mL.min⁻¹ and a pressure of 18.54 psi. GC/MS analyses performed at University of British Columbia were conducted on an Agilent 7890B GC with an Agilent 5977 inert CI mass detector (ESI), utilizing methane as the ionization gas. Fragment signals are given in mass per charge number (*m/z*).

High-resolution mass spectra were measured by the mass spectrometry and microanalysis service at the Department of Chemistry, University of British Columbia. Mass spectra were recorded on a Kratos MS-50 spectrometer using an electron impact (70 eV) source or a Bruker Esquire LC spectrometer using electrospray ionization source. Fragment signals are given in mass per charge number (m/z).

For X-ray diffractions studies of metal complexes, collections were performed at the X-ray crystallography lab at the Department of Chemistry, University of British Columbia by Dr. Damon Gilmour and Dr. Pargol Danesh. Data were collected on a Bruker APEX DUO diffractometer using graphite-monochromated Mo K α radiation ($\lambda = 0.71073 \text{ \AA}$). The crystals were mounted on cryo-loops after quick soaking on Paratone-N oil from Hampton research and flash-frozen. Diffractometer has partial chi geometry goniometer allowing omegascan data collections. Unless otherwise noted, data were processed with the Bruker SAINT(v.8.38A)³⁷⁵ and absorption correction was performed using Bruker SADABS (2016/2).¹ All crystal structures were solved using intrinsic phasing SHELXT³⁷⁶ and were refined using SHELXL (2018/1)³⁷⁷ using the OLEX2³⁷⁸ interface. Fullmatrix least-squares refinements were performed on F^2 for all unique reflections, with anisotropic displacement parameters for non-hydrogen atoms. Hydrogen atoms were positioned in idealized positions and refined with a riding model, with Uiso constrained to 1.2 Ueq value of the parent atom (1.5 Ueq when CH₃). The positions and isotropic displacement parameters of the remaining hydrogen atoms were refined freely. SIMU and DELU commands were used to restrain some side chains as rigid groups and restrain their displacement parameters.

6.2 Experimental data of chapter 2

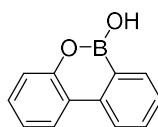
Following starting materials diisopropylamineborane complex **2-38**²⁴², *N*-alkylbromobenzylamines²⁵⁸ **2-78**, **2-79**, **2-80**,²⁵⁹ *N*-methyl-bromobenzylamine **2-85**,²⁶⁰ *N,N*-bromobenzylamine **2-86**²⁶² and **2-88**²⁶¹ and *ortho*-substituted bromobenzene **2-109**³⁷⁹ were prepared according to literature procedures.

6.2.1 *Synthesis of boroxaro- and borazaro-phenanthrenes 2-7 & 2-8*

Boroxarophenanthrene **2-7** was prepared using a previously described procedure.²¹¹ To a solution of boron trichloride in hexane (1.5 equiv., 150 mL, 150 mmol) were added dropwise a solution of 2-hydroxybiphenyl (1 equiv., 17.0 g, 100 mmol) in cyclohexane (1 mmol.mL⁻¹), the mixture was stirred at room temperature for 20 min. Aluminium trichloride (4 mol%) was then added to the resulting solution and stirred at 75 °C for 16 hours. The reaction mixture was then cooled down, and 5 mL of ice and 5 mL of diethyl ether were

added to the mixture which was stirred at room temperature for 30 minutes. The aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by recrystallization in cyclohexane to give the desired product which was obtained as a pale brown solid in 98% yield (19.2 g).

6H-dibenzo[c,e][1,2]oxaborinin-6-ol 2-7 CAS: [14205-96-0]²¹¹



Chemical Formula: C₁₂H₉BO₂
Molecular Weight: 196,01

¹H NMR (CDCl₃, 300 MHz) δ (ppm): 8.19 (1H, d, *J* = 6.0 Hz), 8.16 (1H, dd, *J* = 9.0 Hz, 3.1 Hz), 8.10 (1H, dd, *J* = 6.0 Hz, 3.0 Hz), 7.73 (1H, td, *J* = 9.2 Hz, 3.0 Hz), 7.50 (1H, td, *J* = 9.1 Hz, 1.5 Hz), 7.40 (1H, m), 7.27 (2H, m), 4.78 (1H, s).

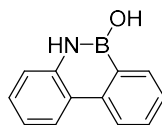
¹¹B NMR (CDCl₃, 96 MHz) δ (ppm): 28 (bs).

¹³C NMR (CDCl₃, 75 MHz) δ (ppm): 151.1, 140.3, 133.3, 132.6, 129.0, 127.2, 123.6, 123.0, 122.7, 121.6, 119.6.

Melting point: 114 °C.

Borazarophenanthrene **2-8** was prepared using a previously described procedure.²¹¹ To a solution of boron trichloride in hexane (3 equiv., 30 mL, 30 mmol) were added dropwise a solution of 2-aminobiphenyl (1 equiv., 1.7 g, 10 mmol) in cyclohexane (1 mmol.mL⁻¹), the mixture was stirred at room temperature for 20 min. Aluminium trichloride (4 mol%) was then added to the resulting solution and stirred at 75 °C for 16 hours. The reaction mixture was then cooled down, and 5 mL of ice and 5 mL of diethyl ether were added to the mixture which was stirred at room temperature for 30 minutes. The aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by recrystallization in cyclohexane to give the desired product which was obtained as a white solid in 45% yield (880 mg).

Dibenzo[c,e][1,2]azaborinin-6(5H)-ol 2-8 CAS: [17012-25-8]²¹¹



Chemical Formula: C₁₂H₁₀BNO
Molecular Weight: 195,03

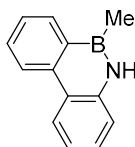
¹H NMR (CDCl₃, 300 MHz) δ (ppm): 8.39 (1H, d, *J* = 6.0 Hz), 8.30 (1H, d, *J* = 6.0 Hz), 7.97 (1H, d, *J* = 6.0 Hz), 7.73 (1H, dt, *J* = 6.0 Hz, *J* = 3.0 Hz), 7.51 (1H, t, *J* = 9.0 Hz), 7.37 (1H, m), 7.16 (1H, m), 7.09 (1H, m).

¹¹B NMR (CDCl₃, 96 MHz) δ (ppm): 29 (bs).

¹³C NMR (CDCl₃, 75 MHz) δ (ppm): 131.1, 130.7, 128.3, 126.0, 123.0, 122.6, 120.3, 118.6.

Melting point: 187 °C.

2-methylborazaronaphtalene 2-64 CAS: [15813-13-5]²¹⁶



Chemical Formula: C₁₃H₁₂BN
Molecular Weight: 193,06

In a reactor was added the borazaronaphthalene **2-8** (1 equiv., 1 mmol, 193 mg) to bis(cyclopentadienyl)bis(dimethyl)titanium(IV) (1 equiv., 1 mmol, 204 mg) in dry toluene (1 mmol.mL⁻¹) and the reaction mixture was heated to 110 °C for 18 hours under stirring. The mixture was then concentrated under reduced pressure and purified by silica gel column chromatography (hexane/ethyl acetate 9/1) to isolate 2-methylborazaronaphtalene. No yield could be reported due to the air and moisture sensitivity of the compound. The analytical data were consistent with literature.²¹⁶

¹H NMR (CDCl₃, 300 MHz) δ (ppm): 8.45 (1H, d, *J* = 9.0 Hz), 8.41 (1H, dd, *J* = 6.0 Hz, *J* = 3.0 Hz), 8.18 (1H, dd, *J* = 6.0 Hz, *J* = 3.0 Hz), 7.75 (1H, t, *J* = 6.0 Hz), 7.54 (1H, t, *J* = 6.0 Hz), 7.42 (1H, t, *J* = 6.0 Hz), 7.22 (2H, m), 1.03 (3H, s).

¹¹B NMR (CDCl₃, 96 MHz) δ (ppm): 39 (bs).

¹³C NMR (CDCl₃, 75 MHz) δ (ppm): 139.0, 138.0, 134.6, 130.8, 128.3, 127.8, 126.0, 123.9, 122.1, 121.1, 118.7, 29.7.

R_f = 0.46 (hexane/EtOAc, 95/5).

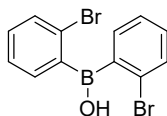
6.2.2 Synthesis of borinic acids

6.2.2.1 General procedure A for borinic acid synthesis

Borinic acids were prepared using a previously described procedure.²⁴² To a solution of aryl bromide (3 equiv.), magnesium (3 equiv.), and DIPAB (1 equiv.) in dry tetrahydrofuran (1 mL.mmol⁻¹) was added at room temperature a solution of phenylmagnesium bromide in THF (2 M, 5 mol%). After ten minutes (or at the end of gas evolution), the mixture was heated to 70 °C until no aryl bromide remained in the mixture after 8 to 16 hours. The reaction mixture was then cooled down at 0 °C and dry methanol (1 mL.mmol⁻¹) was added (*caution*, exothermic reaction). After one hour stirring at room temperature, the mixture was concentrated under reduced pressure, and diluted in a mixture of 1 M HCl/MeOH (7/3, 10 mL.mmol⁻¹) and allowed to stir for one hour at room temperature. The product was extracted with diethyl ether (3 x 10 mL.mmol⁻¹), the combined organic phases were washed with 1M hydrochloric acid (10 mL.mmol⁻¹) and brine (3 x 10 mL.mmol⁻¹), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification using silica gel chromatography (eluent: ethyl acetate/hexane) afforded the desired borinic acid.

6.2.2.2 Results of synthesis

B,B-Bis(2-bromophenyl)borinic acid 2-97 CAS: [1809269-31-5]²⁴⁷



Chemical Formula: C₁₂H₉BBr₂O
Molecular Weight: 339,82

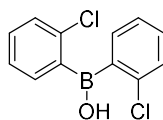
B,B-Bis(2-bromophenyl)borinic acid was synthesized on a 40 mmol scale of 1,2-dibromobenzene (4.8 mL) following the previous general procedure. The product was isolated as a yellow oil in 22% yield (748 mg). Analytical data were consistent with literature.²⁴⁷

¹H NMR (CDCl₃, 300 MHz) δ (ppm): 8.00 (3H, m), 7.63 (5H, m).

¹¹B NMR (CDCl₃, 96 MHz) δ (ppm): 46 (bs).

¹³C NMR (CDCl₃, 75 MHz) δ (ppm): 171.9; 146.0; 142.9; 135.8; 135.0; 131.1; 129.1; 128.7; 128.0; 127.8.

R_f = 0.24 (pentane/EtOAc, 90/10).

B,B-Bis(2-chlorophenyl)borinic acid 2-98 CAS: [1809269-30-4]²⁴⁷Chemical Formula: C₁₂H₉BCl₂O

Molecular Weight: 250.91

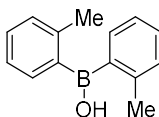
B,B-Bis(2-chlorophenyl)borinic acid was synthesized on a 40 mmol scale of 1-bromo-2-chlorobenzene (4.8 mL) following the general procedure. The product was isolated as a yellow oil in 16% yield (412 mg). Analytical data were consistent with literature.

¹H NMR (CDCl₃, 400 MHz) δ (ppm): 8.10 (3H, m), 7.66 (5H, m).

¹¹B NMR (CDCl₃, 128 MHz) δ (ppm): 46 (bs).

¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 136.1; 135.0; 131.6; 131.3; 128.2.

R_f = 0.28 (pentane/EtOAc, 90/10).

B,B-Bis(2-methylphenyl)borinic acid 2-99 CAS: [73774-44-4]²⁴⁷Chemical Formula: C₁₄H₁₅BO

Molecular Weight: 210.08

B,B-Bis(2-methylphenyl)borinic acid was synthesized on a 15 mmol scale of 2-bromotoluene (1.8 mL) following the general procedure. The product was isolated in 87% yield (1.3 g). Analytical data were consistent with literature.

¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.34 (2H, dd, *J* = 3.0 Hz), 7.07 (6H, m), 2.41 (6H, s).

¹¹B NMR (CDCl₃, 96 MHz) δ (ppm): 44 (bs).

¹³C NMR (CDCl₃, 75 MHz) δ (ppm): 141.0, 133.8, 129.2, 124.0, 21.9.

6.2.3 Preparation of compound 2-90

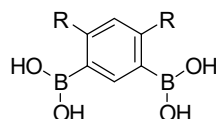
Compound **2-90** was prepared from a method described in the literature by Oishi and co-workers.²⁵⁸ To an anhydrous diethyl ether (160 mL) solution of the starting material (50 mmol) was added a 1.6 M hexane solution of *n*-BuLi (100 mmol) at -44 °C (acetonitrile-dry ice) under argon and the mixture was stirred at -44 °C for one hour. To the mixture was added B(OMe)₃ or BCl₃ (25 mmol) at the same temperature. The mixture was allowed to

warm to room temperature and stirred for 24 hours. The reaction mixture was quenched with a small portion of water, and the organic phase was removed in vacuo. The residue was dissolved into dichloromethane and washed with water. The organic layer was dried over sodium sulfate and filtrated. The evaporation of the filtrate gave a yellow oil, which was dissolved again into chloroform. ^1H and ^{11}B NMR analyses of crude products were consistent to the literature precedent, however NMR data also revealed the presence of many impurities, and since the yields obtained were lower than 5%, purifications were not performed.

6.3 Experimental procedure of Chapter 3

6.3.1 Synthesis of boronic acids

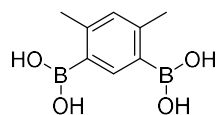
6.3.1.1 General procedure B



The catalytic method to synthesize boronic acids has been described in the literature.²⁷¹ In a 25 mL round bottom flask, DIPAB (4 equiv.) were added in dry toluene (1 mL.mmol⁻¹) followed by the addition of phenyl magnesium bromide in THF (2M, 20 mol%) and the reaction mixture was left stirring for 15 minutes under argon. Then, aryl bromide (1 equiv., 5 mmol), 5 mol% of PdCl₂dppp, 1 mol% of potassium iodide, and triethylamine (6 equiv.) were added to the resulting mixture with toluene. The mixture was stirred at 90 °C for 24 hours before being quenched with dry methanol (1 mL.mmol⁻¹) at 0 °C and left to stir for a further one hour followed by concentration under reduced pressure. The resulting solid was diluted in methanol and 1N hydrochloric acid was added at 0 °C and left for one hour under stirring. Then the product was dissolved in ethyl acetate (10 mL) and washed with water (3 x 10 mL). The organic fraction was dried over sodium sulfate and concentrated under reduce pressure. Purification was performed *via* precipitation with Ca²⁺ according to a literature procedure.²⁷⁵

6.3.1.2 Results of synthesis

2,4-dimethylbenzene-1,5-diboronic acid 3-10.b



Chemical Formula: $C_8H_{12}B_2O_4$
Molecular Weight: 193,80

3-10.b was prepared according to general procedure **B** on a 10 mmol scale from 1,5-dibromo-2,4-dimethylbenzene (2.6 g). After purification, **3-10.b** was isolated in 92% yield as a white powder (1.8 g).

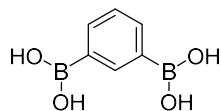
$^1\text{H NMR}$ (DMSO- d_6 , 300 MHz) δ (ppm): 7.80 (4H, bs), 7.61 (1H, s), 6.85 (1H, s), 2.33 (6H, s).

$^{13}\text{C NMR}$ (DMSO- d_6 , 75 MHz) δ (ppm): 142.3, 139.8, 130.9, 22.5.

$^{11}\text{B NMR}$ (DMSO- d_6 , 96 MHz) δ (ppm): 30 (bs).

GC/MS (EI): t_r = 6.00 min: m/z 195.0 [M+H] $^+$.

Phenyl-1,3-diboronic acid 3-10.a CAS: [4612-28-6]³⁸⁰



Chemical Formula: $C_6H_8B_2O_4$
Molecular Weight: 165,75

3-10.a was prepared according to general procedure **B** on a 10 mmol scale from 1,3-dibromobenzene (1.2 mL). After purification, **3-10.a** was isolated in 96% yield as a white powder (1.6 g).

$^1\text{H NMR}$ (DMSO- d_6 , 300 MHz) δ (ppm): 8.21 (1H, s), 7.95 (4H, bs), 7.81 (2H, dd, J = 6.0 Hz, J = 3.0 Hz), 7.29 (1H, m).

$^{13}\text{C NMR}$ (DMSO- d_6 , 75 MHz) δ (ppm): 140.8, 136.2, 126.8.

$^{11}\text{B NMR}$ (DMSO- d_6 , 96 MHz) δ (ppm): 29 (bs).

GC/MS (EI): m/z 167.0 [M+H] $^+$.

6.3.2 Suzuki-Miyaura cross-coupling reaction

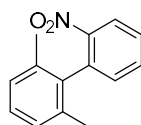
6.3.2.1 General procedure C

In a 25 mL flask were added boronic acid (1 equiv.), potassium carbonate (8 equiv.), 10 mol% of tetrakis(triphenylphosphine)palladium(0) and 2-nitrobromobenzene (1 to 3

equiv.). The mixture was diluted in a solvent/water system (5/1) (1 mL.mmol⁻¹) and heated at 100 °C for 24 hours under stirring. Water (10 mL) was added and the organic layer was extracted three times with ethyl acetate (10 mL), dried over sodium sulfate and concentrated under reduced pressure. Purification through silica gel column chromatography (hexane/ethyl acetate, 9/1) afforded pure nitrobenzene derivative product.

6.3.2.2 Results of synthesis

1,3-dimethyl-2-(2-nitrophenyl)benzene 3-16



Chemical Formula: C₁₄H₁₃NO₂
Molecular Weight: 227,26

1,3-dimethyl-2-(2-nitrophenyl)benzene **3-16** was prepared according to procedure **C** on a 0.5 mmol scale from 2,6-dimethylphenylboronic acid (76 mg), 2-nitrobromobenzene (1 equiv., 0.5 mmol, 101 mg). Solvent involved in the solvent/water system were: PEG-400, ethanol, diglyme, and DMF. Yields of pure 1,3-dimethyl-2-(2-nitrophenyl)benzene **3-16** ranged from 25 to 43%, and the best yield of 43% (49 mg) was obtained in the diglyme/water solvent system (5/1). The analytical data of **3-16** were consistent with literature.

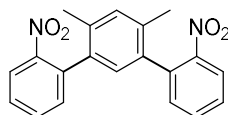
¹H NMR (CDCl₃, 300 MHz) δ (ppm): 8.07 (1H, dd, *J* = 9.0 Hz, *J* = 3.0 Hz), 7.71 (1H, m), 7.57 (1H, m), 7.30 (1H, m), 7.24 (1H, m), 7.14 (2H, m), 2.02 (6H, s).

¹³C NMR (CDCl₃, 75 MHz) δ (ppm): 149.1, 137.1, 135.8, 135.5, 133.9, 133.6, 133.1, 131.8, 128.3, 127.9, 127.4, 124.2, 20.5.

GC/MS (EI): t_r = 7.48 min: m/z 228.0 [M+H]⁺.

R_f = 0.31 (hexane/EtOAc, 95/5).

1,5-dimethyl-2,4-bis(2-nitrophenyl)benzene 3-9.b



Chemical Formula: C₂₀H₁₆N₂O₄
Molecular Weight: 348,36

1,5-dimethyl-2,4-bis(2-nitrophenyl)benzene **3-9.b** was prepared according to procedure **C** on a 1 mmol scale from 1,5-(2,4-dimethyl)diboronic acid **3-10.b** (195 mg), 2-

nitrobromobenzene (3 equiv., 3 mmol, 616 mg). Solvent involved in the solvent/water system were: diglyme, DMF and toluene/ethanol. Yields of pure 1,5-dimethyl-2,4-bis(2-nitrophenyl)benzene **3-9.b** ranged from 5 to 15%, and the best yield 15% (113 mg) was obtained in the toluene/ethanol/water solvent system (70/14/16).

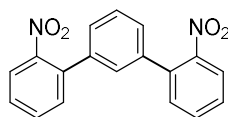
$^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ (ppm): 7.97 (2H, d, $J = 9.0$ Hz), 7.62 (2H, m), 7.49 (2H, m), 7.37 (2H, m), 7.17 ppm (1H, m), 6.87 (1H, m), 2.12 ppm (6H, s).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ (ppm): 135.9, 135.5, 134.9, 132.7, 132.6, 132.3, 131.8, 128.3, 124.2, 124.0, 19.6.

GC/MS (EI): $t_r = 16.20$ min: m/z 349.1 $[\text{M}+\text{H}]^+$.

Rf = 0.22 (hexane/EtOAc, 95/5).

1-nitro-2-[3-(2-nitrophenyl)phenyl]benzene 3-9.a CAS: [60392-09-8]³⁸¹



Chemical Formula: $\text{C}_{18}\text{H}_{12}\text{N}_2\text{O}_4$
Molecular Weight: 320,30

1-nitro-2-[3-(2-nitrophenyl)phenyl]benzene **3-9.a** was prepared according to procedure **C** on a 10 mmol scale from 1,3-diboronic acid **3-10.a** (1.7 g) and 2-nitrobromobenzene (3 equiv., 30 mmol, 6.1 g). Solvent involved in the solvent/water system were: diglyme, PEG-400 and toluene/ethanol. Yields of pure 1-nitro-2-[3-(2-nitrophenyl)phenyl]benzene **3-9.a** ranged from 24 to 44%, and the best yield of 44% (1.4 g) was obtained in the diglyme/water solvent system (5/1).

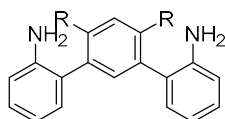
$^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ (ppm): 7.89 (2H, m), 7.64 (3H, m), 7.49 (5H, m), 7.33 (3H, m).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ (ppm): 136.9, 135.5, 134.7, 132.4, 132.3, 132.0, 131.1, 128.3, 125.2, 124.1.

GC/MS (EI): $t_r = 16.04$ min: m/z 321.1 $[\text{M}+\text{H}]^+$.

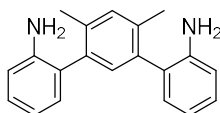
Rf = 0.24 (hexane/EtOAc, 95/5).

6.3.3 Reduction reaction



The reduction of nitro moieties were performed according to literature procedure.²⁷³ In a 25 mL round bottom flask, **3-8.a** or **3-8.b** (1 equiv.) was diluted in ethanol (10 mL). Excess of iron and HCl 37% were added and the reaction mixture was stirred and heated at 70 °C for four hours. The mixture was then directly worked up in ethyl acetate and water, dried over sodium sulfate and concentrated under reduced pressure.

2-[5-(2-aminophenyl)-2,4-dimethyl-phenyl]aniline 3-8.b



Chemical Formula: C₂₀H₂₀N₂
Molecular Weight: 288,39

Reaction was performed on a 0.31 mmol scale of starting material **3-9.b** (108 mg). 2-[5-(2-aminophenyl)-2,4-dimethyl-phenyl]aniline **3-8.b** was obtained as pure product without purification in 99% yield (89 mg).

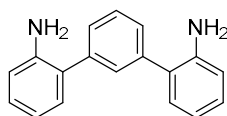
¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.16 (6H, m), 6.81 (4H, m), 3.84 (4H, bs), 2.23 (6H, s).

¹³C NMR (CDCl₃ 75 MHz) δ (ppm): 143.8, 132.3, 132.3, 131.7, 131.6, 130.3, 128.3, 118.3, 118.2, 115.1, 115.1, 19.4.

GC/MS (EI): t_r = 12.32 min: m/z 289.8 [M+H]⁺.

R_f = 0.36 (hexane/EtOAc, 95/5).

2-[3-(2-aminophenyl)phenyl]aniline 3-8.a CAS: [959119-19-0]³⁸²



Chemical Formula: C₁₈H₁₆N₂
Molecular Weight: 260,34

Reaction was performed on a 0.21 mmol scale of starting material **3-9.a** (82 mg). 2-[3-(2-aminophenyl)phenyl]aniline **3-8.a** was obtained as pure product without purification in 100% yield (54 mg). The analytical data were consistent with literature.³⁸²

¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.50 (4H, m), 7.24 (4H, m), 6.82 (4H, m), 3.93 (4H, bs).

¹³C NMR (CDCl₃ 75 MHz) δ (ppm): 143.8, 140.5, 130.8, 130.0, 129.6, 129.0, 128.1, 127.6, 119.1, 116.1.

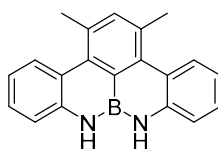
GC/MS (EI): t_r = 12.87 min: m/z 261.1 [M+H]⁺.

R_f = 0.29 (hexane/EtOAc, 95/5).

6.3.4 Electrophilic borylation step

In a tube reactor, tetramethylpiperidine (1.5 equiv.) was added to **3-4.a** or **3-4.b** starting material (1 equiv.) diluted in *ortho*-dichlorobenzene (1 mL.mmol⁻¹). Boron tribromide (1 equiv.) was added in the reaction mixture which was then heated at 120 °C. After 18 hours, water was added (10 mL); the organic layer was extracted and washed three times with ethyl acetate (10 mL), dried over sodium sulfate and concentrated under reduced pressure. Purification on silica gel column chromatography (pentane 100%, then pentane/ethyl acetate 5/5) afforded pure product.

17,19-dimethyl-8H,9H-8,9-diaza-8a-borabenzof[fg]tetracene 3-4.b



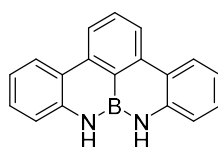
Chemical Formula: C₂₀H₁₇BN₂
Molecular Weight: 296,18

Reaction was performed on a 0.1 mmol scale of starting material **3-8.b** (29 mg). Trace of 17,19-dimethyl-8H,9H-8,9-diaza-8a-borabenzof[fg]tetracene **3-4.b** was isolated. There was not enough quantity of final product to perform full characterization by mass spectrometry and ¹³C NMR spectroscopy. A NMR spectrum acquisition with more than 6000 scans was performed, but the signals obtained were too close to the NMR noise signal to be relevant for analysis.

¹H NMR (CDCl₃, 300 MHz) δ (ppm): 8.18 (2H, m), 7.53 (2H, m), 7.01 (5H, m), 2.20 (6H, s).

¹¹B NMR (CDCl₃, 96 MHz) δ (ppm): 28 (bs).

8H,9H-8,9-diaza-8a-borabenzof[fg]tetracene 3-4.a²⁶⁹



Chemical Formula: C₁₈H₁₃BN₂
Molecular Weight: 268,13

Reaction was performed on a 3.8 mmol scale of starting material **3-8.a** (980 mg). 8H,9H-8,9-diaza-8a-borabenzof[fg]tetracene **3-4.a** was isolated in 8% yield (80 mg). The analytical data were consistent with literature.²⁶⁹

$^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ (ppm): 8.25 (2H, dd, $J = 9.0$ Hz, $J = 3.0$ Hz), 8.17 (2H, d, $J = 9.0$ Hz), 7.80 (1H, m), 7.32 (2H, t, $J = 9.0$ Hz), 7.10 (2H, m), 7.03 (2H, dd, $J = 9.0$ Hz, $J = 3.0$ Hz), 6.27 (2H, bs).

$^{11}\text{B NMR}$ (CDCl_3 , 96 MHz) δ (ppm): 27 (bs).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ (ppm): 128.4, 124.4, 120.0, 119.0, 118.2.

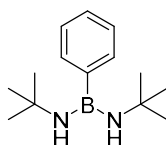
GC/MS (EI): $t_r = 10.88$ min: m/z 269.0 $[\text{M}+\text{H}]^+$.

$R_f = 0.25$ (pentane/EtOAc, 95/5).

6.3.5 Synthesis of boraamidine and boraamidinate

6.3.5.1 Preparation of ditert-butylaminophenylborane

Ditert-butylaminophenylborane 3-34 CAS: [10375-18-5]²⁸⁶



Chemical Formula: $\text{C}_{14}\text{H}_{25}\text{BN}_2$
Molecular Weight: 232.18

Ditert-butylaminophenylborane was prepared following a reported procedure.²⁸⁶ A solution of dichlorophenylborane (1 equiv., 1.3 mL, 10 mmol) in *n*-hexane (20 mL) was added to a slurry solution of $\text{Li}[\text{N}(\text{H})\text{-}t\text{-Bu}]$ (4 equiv., 5 mL, 40 mmol) in *n*-hexane (30 mL) at -78 °C. The reaction mixture was stirred for four hours at room temperature and then filtered off twice with glass-sintered frit. Volatile materials were removed under vacuum to give ditert-butylaminophenylborane as a golden yellow oil in 61% yield (1.4 g). The analytical data were consistent with literature.

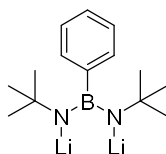
$^1\text{H NMR}$ (C_6D_6 , 300 MHz) δ (ppm): 7.58 (2H, dd, $J = 9.0$ Hz, $J = 3.0$ Hz), 7.24 (3H, m), 2.82 (2H, bs), 1.13 (18H, s).

$^{11}\text{B NMR}$ (C_6D_6 , 96 MHz) δ (ppm): 30 (bs).

$^{13}\text{C NMR}$ (C_6D_6 , 75 MHz) δ (ppm): 133.7, 127.2, 127.0, 48.8, 33.2.

6.3.5.2 Synthesis of dilithium ditert-butylamidophenylboraamidinate

Dilithium ditert-butylamidophenylboraamidinate 3-35 CAS: [878047-18-8]³⁸³



Chemical Formula: $C_{14}H_{23}BLi_2N_2$
Molecular Weight: 244,04

Synthesis of dilithium di-*tert*-butylamidophenylboramidinate was performed using a described procedure. A solution of dichlorophenylborane (1 equiv., 1.3 mL, 10 mmol) in *n*-hexane (20 mL) was added to a slurry solution of Li[N(H)-*t*-Bu] (4 equiv., 5 mL, 40 mmol) in *n*-hexane (30 mL) at $-78\text{ }^{\circ}\text{C}$. The reaction mixture was stirred for four hours at room temperature and then filtered off twice with glass-sintered frit. Volatile materials were removed under vacuum to give di-*tert*-butylaminophenylborane which was directly used as such and dissolved in *n*-hexane (20 mL). Resulting reaction mixture was cooled down to $-78\text{ }^{\circ}\text{C}$, followed by addition of *n*-BuLi in hexane (1.7 equiv., 10.6 mL, 17 mmol), and the reaction mixture was heated at reflux for 17 hours. A white precipitate was formed and was allowed to settle for several hours, a yellow solution was then removed with a cannula. The product recovered was washed twice with *n*-hexane (5 mL) at $0\text{ }^{\circ}\text{C}$, and obtained in 46% yield (1.1 g). The analytical data were consistent with literature.

$^1\text{H NMR}$ (C_6D_6 , 300 MHz) δ (ppm): 7.31 (5H, m), 1.10 (18H, s).

$^{11}\text{B NMR}$ (C_6D_6 , 96 MHz) δ (ppm): 36 (bs).

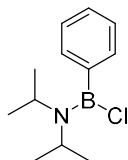
$^{13}\text{C NMR}$ (C_6D_6 , 75 MHz) δ (ppm): 133.7, 126.4, 124.9, 51.1, 35.2.

6.3.6 Synthesis of asymmetric boraamidines

6.3.6.1 Preparation of chloroaminoborane

Chloroaminoboranes were prepared according to literature procedure.²⁸⁶ To a solution of dichlorophenylborane (1 equiv.) dissolved in toluene (30 ml) and cooled to $0\text{ }^{\circ}\text{C}$, was added dropwise a solution of amine (1 equiv.) in toluene (10 ml). Resulting mixture was allowed to reach room temperature, and triethylamine (1 equiv.) dissolved in toluene (10 ml), was added dropwise to this mixture. The resultant slurry was refluxed for three hours and then filtered to yield triethylammonium chloride. Removal of solvent from the filtrate gave a clear mobile liquid which afforded the desired chloro(amino)phenylborane without further purification.

Chloro(diisopropylamine)phenylborane 3-40 CAS: [33441-68-8]²⁸⁶



Chemical Formula: $C_{12}H_{19}BClN$
Molecular Weight: 223,55

Chloro(diisopropylamino)phenylborane was synthesized on a 20 mmol scale of dichlorophenylborane (2.6 mL) and diisopropylamine (2.8 mL). Chloro(diisopropylamino)phenylborane was obtained in 65% yield (2.9 g). The analytical data were consistent with literature.

1H NMR (C_6D_6 , 300 MHz) δ (ppm): 7.45 (2H, m), 7.16 (3H, m), 3.86 (1H, m), 3.26 (1H, m), 1.42 (6H, d, $J = 6.0$ Hz), 0.79 (6H, d, $J = 9.0$ Hz).

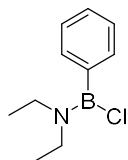
^{13}C NMR (C_6D_6 , 75 MHz) δ (ppm): 131.3, 128.2, 127.6, 51.3, 46.1, 23.0, 21.4.

^{11}B NMR (C_6D_6 , 96 MHz) δ (ppm): 37 (bs).

ESI-MS: m/z 224.11 $[M+H]^+$.

Boiling point: 65 °C (1 mmHg).

Chloro(diethylamino)phenylborane 3-41 CAS: [33441-65-5]²⁸⁶



Chemical Formula: $C_{10}H_{15}BClN$
Molecular Weight: 195,50

Chloro(diethylamino)phenylborane was synthesized on a 25 mmol scale of dichlorophenylborane (3.2 mL) and diethylamine (2.6 mL). Chloro(diethylamino)phenylborane was obtained in 70% yield (3.4 g). The analytical data were consistent with literature.

1H NMR (C_6D_6 , 300 MHz) δ (ppm): 7.51 (2H, m), 7.16 (3H, m), 3.19 (2H, q, $J = 9.0$ Hz), 2.89 (2H, q, $J = 9.0$ Hz), 0.99 (3H, t, $J = 9.0$ Hz), 0.75 (6H, t, $J = 9.0$ Hz).

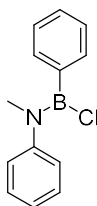
^{13}C NMR (C_6D_6 , 75 MHz) δ (ppm): 132.1, 128.7, 127.6, 43.3, 42.6, 15.1, 14.6.

^{11}B NMR (C_6D_6 , 96 MHz) δ (ppm): 36 (bs).

ESI-MS: m/z 196.59 $[M+H]^+$.

Boiling point: 50 °C (1 mmHg).

Chloro(*N,N*-methyl-phenylamino)phenylborane 3-42



Chemical Formula: C₁₃H₁₃BClN
Molecular Weight: 229,51

Chloro(*N,N*-methyl-phenylamino)phenylborane was synthesized on a 5 mmol scale of dichlorophenylborane (649 μL) and *N*-methylaniline (535 μL). Chloro(*N,N*-methyl-phenylamino)phenylborane was obtained in 88% yield (1.0 g).

¹H NMR (C₆D₆, 300 MHz) δ (ppm): 7.39 (2H, m), 6.94 (8H, m), 3.15 (3H, s).

¹¹B NMR (C₆D₆, 96 MHz) δ (ppm): 37 (bs).

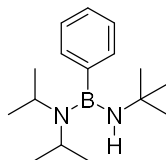
ESI-MS: m/z 230.55 [M+H]⁺.

Boiling point: 110 °C (1 mmHg).

6.3.6.2 Preparation of boraamidines

Diaminoboranes were prepared according to literature procedure.²⁸⁶ Chloro(amino)phenylborane (1 equiv.) was dissolved in toluene (1 mL.mmol⁻¹) at room temperature and the desired primary amine (1 equiv.) was added slowly while stirring. Triethylamine (1 equiv.) was added and the resultant mixture refluxed for three hours under stirring. Side-product triethylammonium chloride is removed after filtration, and removal of all volatiles afforded the desired product.

Tert-butylamino(diisopropylamine)phenylborane 3-43 CAS: [79867-07-5]²⁸⁶



Chemical Formula: C₁₆H₂₉BN₂
Molecular Weight: 260,23

Tert-butylamino(diisopropylamine)phenylborane was synthesized on a 2 mmol scale of chlorodiisopropylaminophenylborane (447 mg) and *tert*-butylamine (210 μL). *Tert*-

butylamino(diisopropylamine)phenylborane was obtained in 53% yield (273 mg). The analytical data were consistent with literature.²⁸⁶

¹H NMR (C₆D₆, 300 MHz) δ (ppm): 7.31 ppm (5H, m), 3.27 (2H, m), 1.13 (21H, m).

¹³C NMR (Tol-*d*₈, 75 MHz) δ (ppm): 137.1, 132.1, 126.5, 33.6, 32.1, 22.9.

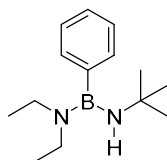
¹¹B NMR (C₆D₆, 96 MHz) δ (ppm): 31 (bs).

GC/MS: 260.2 (M+H⁺).

ESI-MS: m/z 261.21 [M+H]⁺.

Boiling point: 100 °C (1 mmHg).

Tert-butylamino(diethylamino)phenylborane 3-45 CAS: [79867-06-4]²⁸⁶



Chemical Formula: C₁₄H₂₅BN₂
Molecular Weight: 232,18

Tert-butylamino(diethylamino)phenylborane was synthesized on a 5 mmol scale of chlorodiethylaminophenylborane (979 mg) and *tert*-butylamine (525 μL). *Tert*-butylamino(diethylamino)phenylborane was obtained in 61% yield (708 mg). The analytical data were consistent with literature.²⁸⁶

¹H NMR (C₆D₆, 300 MHz) δ (ppm): 7.46 (2H, m), 7.20 (3H, m), 2.93 (1H, bs), 2.76 (4H, q, *J* = 9.0 Hz), 1.04 (9H, s), 0.93 (6H, t, *J* = 9.0 Hz).

¹³C NMR (Tol-*d*₈, 75MHz) δ (ppm): 132.4, 127.2, 126.6, 48.8, 33.5, 15.7.

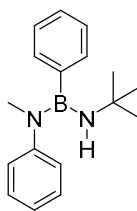
¹¹B NMR (C₆D₆, 96 MHz) δ (ppm): 31 (bs).

GC/MS: 233.2 (M+H⁺).

ESI-MS: m/z 233.19 [M+H]⁺.

Boiling point: 85 °C (1 mmHg).

Tert-butylamino(*N,N*-methyl,phenylmino)phenylborane 3-46



Chemical Formula: C₁₇H₂₃BN₂
Molecular Weight: 266,20

Tert-butylamino(*N,N*-methyl,phenylamino)phenylborane was synthesized on a 4 mmol scale of chloro(*N,N*-methyl,phenylamino)phenylborane (913 mg) and *tert*-butylamine (420 μ L). *Tert*-butylamino(*N,N*-methyl,phenylamino)phenylborane was obtained in 56% yield (595 mg).

¹H NMR (C₆D₆, 300 MHz) δ (ppm): 7.52 (2H, m), 7.19 (6H, m), 6.94 (2H, m), 3.28 (1H, bs), 2.76 (3H, s), 0.94 (9H, s).

¹³C NMR (Tol-*d*₈, 75 MHz) δ (ppm): 150.1, 150.0, 135.3, 134.9, 132.4, 129.0, 128.4, 127.5, 127.1, 126.2, 123.5, 123.0, 121.9, 49.0, 39.4, 38.7, 33.2.

¹¹B NMR (C₆D₆, 96 MHz) δ (ppm): 31 (bs).

GC/MS: 267.2 (M+H⁺).

ESI-MS: m/z 267.16 [M+H]⁺.

6.3.7 Applications to coordination and hydroaminoalkylation

6.3.7.1 Coordination method of *N,B,N*-ligand with early transition metals

Coordination reactions of *N,B,N*-ligands were performed according to usual salt metathesis or protonolysis procedure.¹³³ *N,B,N*-ligand was cooled down at -30 °C in deuterated toluene (1 mL.mmol⁻¹) in glove box filled of dinitrogen. A solution of metal complex was cooled down at -30 °C and added to the ligand solution. T₀ NMR spectra were collected, and the reaction was heated up at room temperature for 30 minutes and then 18 hours.

6.3.7.2 Catalytic application of *N,B,N*-ligands for hydroaminoalkylation

Hydroaminoalkylation reactions catalysed by *N,B,N*-ligands were performed using described procedure.¹³³ 1-octene (0.1 mmol), *N*-methylaniline (0.1 mmol) and desired group 4 or 5 catalyst (5 mol%) with appropriate ligand (5 mol%) were dissolved in deuterated toluene and transferred to a J-Young NMR tube in a glove box filled with dinitrogen. T_0 NMR spectra were collected and the reaction was heated up at the desired temperature (110 °C or 130 °C) for 30 minutes and then 18 hours. Conversions were determined by ^1H NMR spectroscopy according to literature procedure.¹³³

6.3.8 Solid State Molecular Structure and X-Ray Crystallographic Data

Crystallization was performed in standard solution crystallisation at -30 °C in hexane. Resolution of structure was performed by intrinsic phasic using SHELXT. Refinement and atomic model construction were performed with SHELXL package using OLEX2 software. Crystallographic parameters are reported in Table S1.

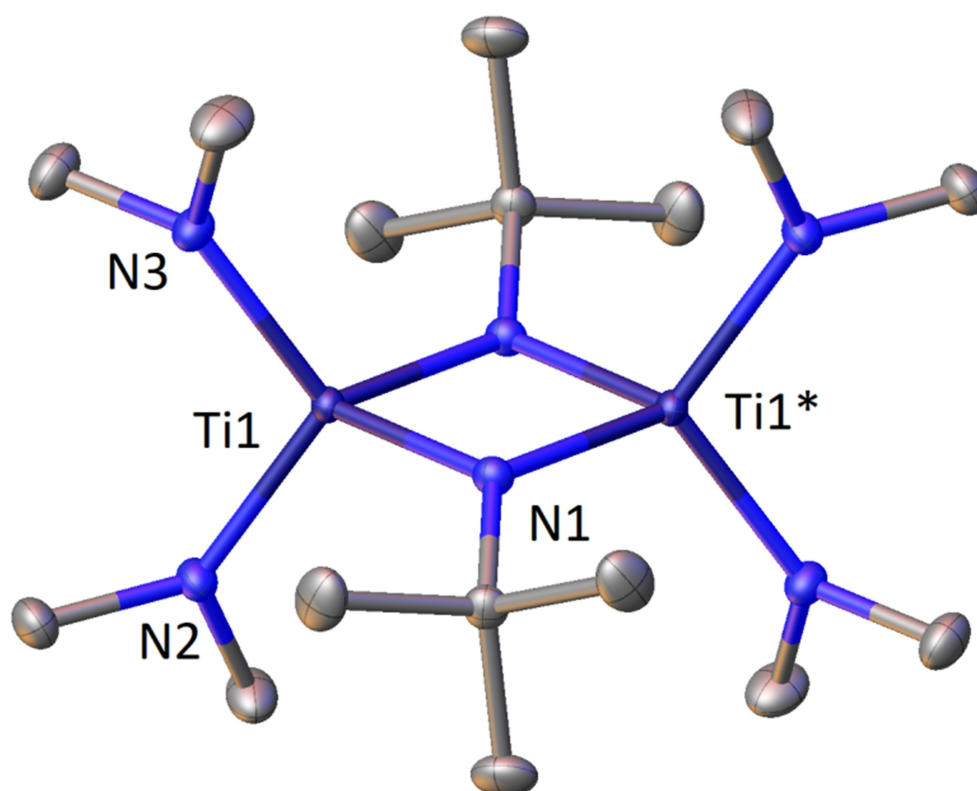


Figure S1: ORTEP representation of the solid-state molecular structure of 3-51 in crystals. Ellipsoids drawn at 50% probability. All hydrogen atoms have been omitted for clarity. Selected bond lengths (Å): (Ti1-N1) 1.9182(10), (Ti1-N2) 1.9196(10).

Compound	3-51
Empirical formula	$C_{16}H_{42}N_6Ti_2$
Formula weight	414.35
Temperature (K)	90 (2)
Color, habits	Red, prism
Crystal system	Monoclinic
Space group	P1 2 ₁ /n 1
a (Å)	8.669(5)
b (Å)	15.876(10)
c (Å)	9.308(6)
α (°)	90
β (°)	115.380(10)
γ (°)	90
Volume (Å ³)	1157.45(12)
Z	2
ρ_{calc} (g.cm ⁻³)	1.189
μ (mm ⁻¹)	0.699
F (000)	448
Crystal size (mm ³)	0.37x0.22x0.209
Radiation	Mo K α (λ = 0.71073)
2 θ range for data collection (°)	2.566 to 30.508
Index ranges	-12 \leq h \leq 12, -22 \leq k \leq 22, -13 \leq l \leq 13
Reflections collected	18377
Independent reflections	3538 (R_{int} = 0.0540, R_{sigma} = 0.0494)
Data/restraints/parameters	3538/0/116
Goodness-of-fit on F^2	1.063
R_1 (F^2 , all data)	0.0387
wR_2 (F^2 , all data)	0.0705
R_1 (F, [$I \geq 2 \sigma(I)$])	0.0275
wR_2 (F, [$I \geq 2 \sigma(I)$])	0.0662
Largest diff. peak/hole (e Å ⁻³)	0.411 / -0.200

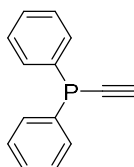
Table S14: Crystallographic parameters of bis titanium complex 3-51.

6.4 Chapter 4: Experimental procedure

6.4.1 Preparation of alkyne phosphines

6.4.1.1 Diphenyl(ethynyl)phosphine

Diphenyl(ethynyl)phosphine 4-58 CAS: [6104-47-8]³⁵⁸



Chemical Formula: C₁₄H₁₁P
Molecular Weight: 210.22

Ethynyl(diphenyl)phosphine was synthesized according to literature procedure.³⁵⁸ In a 100 mL Schlenk tube, chlorodiphenylphosphine (900 μ L, 5 mmol) was dissolved in 20 mL of diethyl ether and cooled to -78 °C under nitrogen atmosphere. Ethynylmagnesium bromide (0.5 M in THF, 11 mL, 5.5 mmol) was added dropwise. The reaction was slowly warmed to room temperature. The reaction was followed by ³¹P{¹H} NMR spectroscopy until completion. The volatiles were removed and the Schlenk tube was brought into the glovebox. In the glovebox, the solid was extracted with 3 x 20 mL of dry hexanes and the combined clear solution (filtration may be required) was concentrated to \sim 20 mL. The solution was cooled at -40 °C overnight, and a white precipitate was formed. The supernatant was transferred to another vial, and the solid was washed with 10 mL of cold hexanes. The combined solutions were concentrated to \sim 10 mL, cooled and the precipitate was collected. The solids were combined and dried under vacuum. Diphenyl(ethynyl)phosphine, was obtained in 49% yield (511 mg). The analytical data were consistent with literature.³⁵⁸

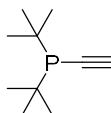
¹H NMR (C₆D₆, 300 MHz) δ (ppm): 7.63 (m, 4H), 7.01 (m, 6H), 2.70 (s, 1H).

¹³C NMR (C₆D₆, 75 MHz) δ (ppm): 135.8 (d, J_{C-P} = 4.5 Hz), 132.7 (d, J_{C-P} = 21.0 Hz), 129.0, 128.6 (d, J_{C-P} = 7.5 Hz), 96.3 (d, J_{C-P} = 2.2 Hz), 81.9 (d, J_{C-P} = 12.8 Hz).

³¹P NMR (C₆D₆, 121 MHz) δ (ppm): -33.3.

6.4.1.2 Di-tert-butyl(ethynyl)phosphine

Di-tert-butyl(ethynyl)phosphine 4-61 CAS: [15466-87-2]³⁶⁰



Chemical Formula: C₁₀H₁₉P
Molecular Weight: 170,24

Di-*tert*-butyl(ethynyl)phosphine was prepared following a literature procedure.³⁶⁰ (Trimethylsilyl)ethynyl lithium was added into a 100 mL Schlenk (0.8 M in THF, 10.5 mL, 13.1 mL) followed by the addition of di-*tert*-butylchlorophosphine (1.9 mL, 10 mmol) in THF (15 mL). The reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and left to stir for 30 minutes. The reaction was then warmed to room temperature and stirred overnight. The volatiles were removed under vacuum while the flask was kept in an ice bath. The residue was dissolved in pentane (15 mL) and filtered through Celite®. The solvent was removed under vacuum while the flask was placed in an ice bath. Potassium carbonate (2.8 g, 20 mmol) was added to the residue in methanol (17 mL) and stirred overnight, followed by filtration through Celite®. Pentane (10 mL) was then added to the filtrate and the two phases were separated under a nitrogen atmosphere. The methanol layer was extracted with pentane (2 x 10 mL). The pentane phases were combined and passed through a plug of neutral alumina to remove any methanol trace. The volatiles were evaporated while the flask was kept in an ice bath. The lightly colored liquid product was obtained in 44% yield (752 mg) and used in subsequent reactions without further purification. The compound was stored at $-30\text{ }^{\circ}\text{C}$ to avoid decomposition. The analytical data were consistent with literature.³⁶⁰

¹H NMR (C₆D₆, 300 MHz) δ (ppm): 2.56 (s, 1H), 1.21 (d, 18H, $J = 15.0$ Hz).

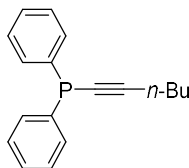
¹³C NMR (C₆D₆, 75 MHz) δ (ppm): 94.1 (d, $J_{\text{C-P}} = 4.5$ Hz), 83.6 (d, $J_{\text{C-P}} = 27.8$ Hz), 31.9 (d, $J_{\text{C-P}} = 17.2$ Hz), 29.3 (d, $J_{\text{C-P}} = 14.3$ Hz).

³¹P NMR (C₆D₆, 121 MHz) δ (ppm): 12.0.

GC/MS (EI): $t_r = 4.75$ min: m/z 170.2 [M+H]⁺.

6.4.1.3 1-Hexynyl(diphenyl)phosphine

1-Hexynyl(diphenyl)phosphine 4-64 CAS: [685527-56-4]³⁶¹



Chemical Formula: C₁₈H₁₉P
Molecular Weight: 266,32

1-Hexynyl(diphenyl)phosphine was synthesized according to literature procedure.³⁶¹

Under a nitrogen atmosphere, a solution of 1-hexyne (0.9 g, 11 mmol) in THF (15 mL) was placed in a 50 mL reaction flask. Butyllithium (1.6 M in hexane, 6.6 mL, 11 mmol) was added dropwise at $-78\text{ }^{\circ}\text{C}$ and the mixture was stirred for 30 min. Chlorodiphenylphosphine (2.2 g, 10 mmol) was added and the reaction mixture was stirred for one hour at room temperature, followed by the addition of water (20 mL). The mixture was extracted with a hexane and concentrated. Purification by silica gel chromatography under hexane:ethyl acetate (90:10) afforded the desired product in 80% yield (2.5 g) as a yellow oil. The analytical data were consistent with literature.³⁶¹

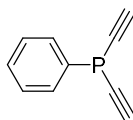
$^1\text{H NMR}$ (C_6D_6 , 300 MHz) δ (ppm): 7.75 (m, 4H), 7.10 (m, 6H), 1.27 (m, 6H), 0.72 (t, 3H, $J = 12.0$ Hz).

$^{13}\text{C NMR}$ (C_6D_6 , 75 MHz) δ (ppm): 135.3, 132.1, 128.7, 128.2, 110.8, 74.8, 30.2, 22.9, 20.3, 13.4.

$^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6 , 121 MHz) δ (ppm): -32.0.

6.4.1.4 Diethynyl(phenyl)phosphine

Diethynyl(phenyl)phosphine 4-69 CAS: [79698-33-2]³⁸⁴



Chemical Formula: $\text{C}_{10}\text{H}_7\text{P}$
Molecular Weight: 158,14

Diethynyl(phenyl)phosphine was synthesized following a modified literature procedure.³⁵⁸ In a 100 mL Schlenk tube, dichlorophenylphosphine (0.68 mL, 5 mmol) was dissolved in 25 mL of THF and cooled to $-78\text{ }^{\circ}\text{C}$ under a nitrogen atmosphere. Ethynylmagnesium bromide (0.5 M in THF, 21 mL, 10.5 mmol) was added dropwise under stirring and the reaction was slowly warmed to room temperature and concentrated. The resulting solid was extracted with dry hexanes, and the filtrate was passed through Celite®. After concentration under reduced pressure, the resulting oil was isolated in 49% yield (391 mg) and used without further purification.

$^1\text{H NMR}$ (d_8 -toluene, 300 MHz) δ (ppm): 7.72 (m, 2H), 7.01 (m, 3H), 2.48 (s, 2H).

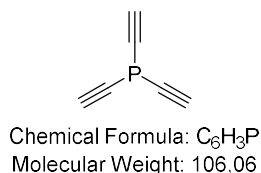
$^{13}\text{C NMR}$ (C_6D_6 , 75 MHz) δ (ppm): 132.5 (d, $J_{\text{C-P}} = 22.5$ Hz), 131.6 (d, $J_{\text{C-P}} = 3.75$ Hz), 129.7, 128.7 (d, $J_{\text{C-P}} = 8.3$ Hz), 95.1 (d, $J_{\text{C-P}} = 5.3$ Hz), 78.5 (d, $J_{\text{C-P}} = 9.8$ Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6 , 121 MHz) δ (ppm): -62.6.

GC/MS (EI): $t_r = 5.76$ min: m/z 158.1 $[M+H]^+$.

6.4.1.5 Triethynylphosphine

Triethynylphosphine 4-71 CAS: [687-80-9]



Triethynylphosphine was synthesized following a modified literature procedure.³⁵⁸ In a 100 mL Schlenk tube phosphorus trichloride (436 μ L, 5 mmol) was dissolved in 25 mL of THF and cooled to -78 °C under a nitrogen atmosphere. Ethynylmagnesium bromide (0.5 M in THF, 31.5 mL, 15.75 mmol) was added dropwise under stirring. The reaction was slowly warmed to room temperature and concentrated. The resulting solid was extracted with dry toluene and the filtrate was passed through Celite®. The resulting product was kept as a stock solution in toluene without further purification.

$^{31}P\{^1H\}$ NMR (C_6D_6 , 121 MHz) δ (ppm): -90.4.

GC/MS (EI): $t_r = 3.19$ min: m/z 107.1 $[M+H]^+$.

6.4.2 Synthesis of β -aminophosphines and bis(β -aminophosphines) through hydroamination reactions

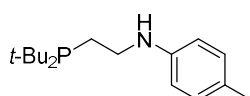
6.4.2.1 General method D for the hydroamination reaction

Hydroamination reactions were performed to synthesize β -aminophosphines and bis(β -aminophosphines) using a modified literature procedure.⁹⁵ Ethynylphosphine (1 equiv.), the corresponding amine and the titanium precatalyst (5 mol%) were dissolved in 0.7 mL of deuterated benzene and transferred to a J-Young NMR tube in the glove box. The reaction was heated at 70 °C in an oil bath for 18 hours until full consumption of the starting material was observed *via* ^{31}P NMR spectroscopy. The reaction mixture was poured into a vial charged with sodium borohydride (excess) and the J-Young NMR tube was rinsed with 3 x 1.5 mL of hexanes followed by 0.5 mL of methanol. After two hours at room temperature, the reaction mixture was extracted with 3 x 1.5 mL of a solution of sulfuric acid (2M in methanol). The alcohol layers were combined, concentrated to 1 mL, basified with sodium hydroxide (1M) and extracted with 3 x 1.5 mL of dichloromethane. The dichloromethane layers were

combined, washed with saturated ammonium chloride, sodium bicarbonate and brine, and dried over sodium sulfate. After purification by silica gel chromatography (DCM/Et₃N/hexanes = 1/1/12) a colorless oil was isolated. The titanium precatalyst (bis(amido)bis(amidate)titanium(IV)) was prepared from tetrakis(dimethylamido)titanium(IV) following a procedure adapted from literature.⁹⁵

6.4.2.2 Synthesis

N-(2-(di-*tert*-butylphosphanyl)ethyl)-4-methylaniline 4-80



Chemical Formula: C₁₇H₃₀NP
Molecular Weight: 279.41

Reaction was performed on a 0.10 mmol scale of di-*tert*-butyl(ethynyl)phosphine (17 mg) and *p*-methylaniline (1.5 equiv., 16 mg, 0.15 mmol). *N*-(2-(di-*tert*-butylphosphanyl)ethyl)-4-methylaniline was obtained in 72% yield (18 mg).

¹H NMR (C₆D₆, 300 MHz) δ (ppm): 7.01 (d, 2H, *J* = 9.0 Hz), 6.55 (d, 2H, *J* = 9.0 Hz), 3.23 (m, 2H), 2.19 (s, 3H), 1.48 (m, 2H), 1.05 (d, 18H).

¹³C NMR (C₆D₆, 75 MHz) δ (ppm): 146.1, 129.8, 125.9, 113.2, 44.4 (d, *J*_{C-P} = 32.3 Hz), 30.8 (d, *J*_{C-P} = 21.8 Hz), 29.4 (d, *J*_{C-P} = 14.3 Hz), 21.7 (d, *J*_{C-P} = 23.3 Hz), 20.3.

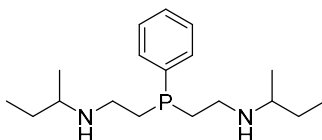
³¹P{¹H} NMR (C₆D₆, 121 MHz) δ (ppm): 20.4.

GC/MS: 280.2 (M+H⁺).

HRMS (ESI) *m/z* calculated for C₁₇H₃₁NP [M+H]⁺: 280.2194; found: 280.2197.

R_f = 0.31 (hexane/EtOAc/NEt₃, 90/5/5).

N,N'-((phenylphosphinediyl)bis(ethane-2,1-diyl))bis(butan-2-amine) 4-83



Chemical Formula: C₁₈H₃₃N₂P
Molecular Weight: 308.45

Reaction was performed on a 0.10 mmol scale of diethynyl(phenyl)phosphine (16 mg) and *sec*-butylamine (3 equiv., 22 mg, 0.30 mmol). *N,N'*-((phenylphosphinediyl)bis(ethane-2,1-diyl))bis(butan-2-amine) was obtained in 65% yield (20 mg).

^1H NMR (C_6D_6 , 300 MHz) δ (ppm): 7.59 (m, 2H), 7.13 (m, 3H), 2.72 (m, 4H), 2.40 (m, 2H), 1.90 (m, 4H), 1.25 (m, 4H), 0.91 (d, 6H, $J = 6.0$ Hz), 0.91 (m, 6H).

^{13}C NMR (C_6D_6 , 75 MHz) δ (ppm): 139.2 (d, $J_{\text{C-P}} = 15.8$ Hz), 132.5 (d, $J_{\text{C-P}} = 18.8$ Hz), 128.7, 128.3 (d, $J_{\text{C-P}} = 6.8$ Hz), 54.2, 44.2 (d, $J_{\text{C-P}} = 18.0$ Hz), 29.9 (d, $J_{\text{C-P}} = 12.0$ Hz), 29.4 (d, $J_{\text{C-P}} = 6.75$ Hz), 19.6 (d, $J_{\text{C-P}} = 3.8$ Hz), 20.2 (d, $J_{\text{C-P}} = 2.0$ Hz).

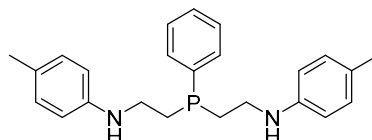
$^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6 , 121 MHz) δ (ppm): -32.9.

GC/MS: 309.2 ($\text{M}+\text{H}^+$).

HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{34}\text{N}_2\text{P}$ [$\text{M}+\text{H}$] $^+$: 309.2460; found: 309.2454.

Rf = 0.25 (hexane/EtOAc/ NEt_3 , 90/5/5).

N,N' -((phenylphosphinediyl)bis(ethane-2,1-diyl))bis(4-methylaniline) 4-84



Chemical Formula: $\text{C}_{24}\text{H}_{29}\text{N}_2\text{P}$
Molecular Weight: 376.48

Reaction was performed on a 0.10 mmol scale of diethynyl(phenyl)phosphine (16 mg) and *para*-methylaniline (3 equiv., 32 mg, 0.30 mmol). N,N' -((phenylphosphinediyl)bis(ethane-2,1-diyl))bis(4-methylaniline) was obtained in 55% yield (21 mg).

^1H NMR (C_6D_6 , 300 MHz) δ (ppm): 7.43 (m, 2H), 7.12 (m, 3H), 6.98 (d, 4H, $J = 9.0$ Hz), 6.38 (d, 4H, $J = 6$ Hz), 3.17 (bs, 2H), 3.02 (m, 4H), 2.19 (s, 6H), 1.68 (m, 4H).

^{13}C NMR (C_6D_6 , 75 MHz) δ (ppm): 145.8, 132.5 (d, $J_{\text{C-P}} = 19.5$ Hz), 131.0 (d, $J_{\text{C-P}} = 13.5$ Hz), 129.7, 129.0, 128.5 (d, $J_{\text{C-P}} = 6.8$ Hz), 126.1, 113.0, 41.1 (d, $J_{\text{C-P}} = 19.5$ Hz), 28.4 (d, $J_{\text{C-P}} = 13.5$ Hz), 20.2.

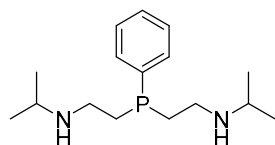
$^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6 , 121 MHz) δ (ppm): -34.6.

GC/MS: 377.2 ($\text{M}+\text{H}^+$).

HRMS (ESI) m/z calculated for $\text{C}_{24}\text{H}_{30}\text{N}_2\text{P}$ [$\text{M}+\text{H}$] $^+$: 377.2147; found: 377.2146.

Rf = 0.32 (hexane/EtOAc/ NEt_3 , 90/5/5).

N,N' -((phenylphosphanediy)bis(ethane-2,1-diyl))bis(propan-2-amine) 4-85



Chemical Formula: C₁₆H₂₉N₂P
Molecular Weight: 280,40

Reaction was performed on a 0.10 mmol scale of diethynyl(phenyl)phosphine (16 mg) and *iso*-propylamine (3 equiv., 18 mg, 0.30 mmol). *N,N'*-((phenylphosphanediyloxy)bis(ethane-2,1-diyl))bis(propan-2-amine) was obtained in 61% yield (17 mg).

¹H NMR (C₆D₆, 300 MHz) δ (ppm): 7.56 (m, 2H), 7.11 (m, 3H), 2.65 (m, 8H), 1.84 (m, 4H), 0.92 (d, 12H).

¹³C NMR (C₆D₆, 75 MHz) δ (ppm): 132.5 (d, *J*_{C-P} = 19.5 Hz), 128.6, 128.3 (d, *J*_{C-P} = 6.8 Hz), 48.4, 44.4 (d, *J*_{C-P} = 13.5 Hz), 30.1 (d, *J*_{C-P} = 12.8 Hz), 22.9, 17.8.

³¹P{¹H} NMR (C₆D₆, 121 MHz) δ (ppm): -33.0.

GC/MS: 281.3 (M+H⁺).

HRMS (ESI) *m/z* calculated for C₁₆H₃₀N₂P [M+H]⁺: 281.2147; found: 281.2145.

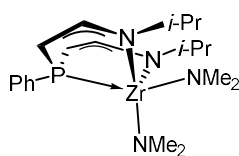
R_f = 0.27 (hexane/EtOAc/NEt₃, 90/5/5).

6.4.3 Synthesis of *N,P,N*-complexes with early transition metals

6.4.3.1 General method of complexation via protonolysis reaction

N,P,N-metal complexes were synthesized following a previously described hydroamination procedure (D). Diethynyl(phenyl)phosphine (1 equiv., 16 mg, 0.10 mmol), *iso*-propylamine (2.1 equiv., 12 mg, 0.21 mmol) and the titanium precatalyst (5 mol%) were dissolved in 0.7 mL of deuterated benzene and transferred to a J-Young NMR tube in the glove box. The reaction was heated at 70 °C in an oil bath for 18 hours until full consumption of the starting material was observed via ³¹P NMR spectroscopy. The solution of the corresponding group 4 metal complex (1 equiv.) in deuterated benzene was added to the reaction and the resulting mixture was analyzed by NMR spectroscopy.

6.4.3.2 Results of complexation via protonolysis reaction

[N,P,N]Zr(NMe₂)₂ 4-95

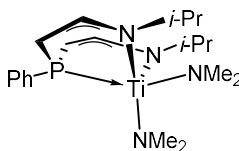
Chemical Formula: C₂₀H₃₅N₄PZr
Molecular Weight: 457,76

The reaction was performed in the presence of tetrakis(dimethylamido)zirconium(IV) (27 mg). Crystals of [N,P,N]Zr(NMe₂)₂ were isolated in HDMSO at -30 °C in 69% yield (31 mg). These crystals proved to be suitable for X-ray diffraction studies.

¹H NMR (C₆D₆, 300 MHz) δ (ppm): 7.64 (m, 3H), 7.38 (dd, 2H, *J* = 36.0 Hz, *J* = 6.0 Hz), 4.70 (dd, 2H, *J* = 9.0 Hz, *J* = 3.0 Hz), 3.94 (q, 2H, *J* = 6.0 Hz), 2.90 (d, 12H, *J* = 15.0 Hz), 1.24 (d, 6H, *J* = 6.0 Hz), 1.17 (d, 6H, *J* = 9.0 Hz).

¹³C NMR (C₆D₆, 75 MHz) δ (ppm): 156.8 (d, *J*_{C-P} = 27.8 Hz), 130.2 (d, *J*_{C-P} = 12.8 Hz), 128.1, 82.1 (d, *J*_{C-P} = 38.2 Hz), 51.7 (d, *J*_{C-P} = 2.2 Hz), 42.9, 40.3, 25.0, 23.8.

³¹P{¹H} NMR (C₆D₆, 121 MHz) δ (ppm): -21.1.

[N,P,N]Ti(NMe₂)₂ 4-97

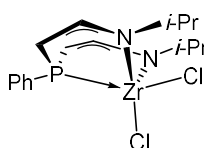
Chemical Formula: C₂₀H₃₅N₄PTi
Molecular Weight: 414,40

The reaction was performed in the presence of tetrakis(dimethylamido)titanium(IV) (22 mg) while heated at 70 °C for 48 hours and monitored by NMR spectroscopy. [N,P,N]Ti(NMe₂)₂ was observed *in situ* by ¹H and ³¹P NMR spectroscopy.

¹H NMR (C₆D₆, 300 MHz) δ (ppm): 7.58 (m, 2H), 7.42 (d, 1H, *J* = 6.0 Hz), 7.35 (m, 2H), 4.90 (dd, 2H, *J* = 9.0 Hz, *J* = 3.0 Hz), 4.20 (q, 2H, *J* = 6.0 Hz), 2.20 (d, 12H, *J* = 9.0 Hz), 1.26 (d, 6H, *J* = 6.0 Hz), 1.15 (d, 6H, *J* = 6.0 Hz).

³¹P{¹H} NMR (C₆D₆, 121 MHz) δ (ppm): -8.7.

³¹P NMR (C₆D₆, 121 MHz) δ (ppm): -8.7.

[N,P,N]ZrCl₂ 4-96Chemical Formula: C₁₆H₃₅Cl₂N₂PZr

Molecular Weight: 440,50

The reaction was performed in the presence of dichlorodimethylamidotitanium(IV) (30 mg). [N,P,N]ZrCl₂ was observed *in situ* by ¹H and ³¹P NMR spectroscopy.

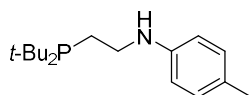
¹H NMR (C₆D₆, 300 MHz) δ (ppm): 7.67 (m, 2H), 7.33 (m, 2H), 7.08 (m, 1H), 4.73 (m, 1H), 4.51 (m, 1H), 4.17 (dd, 1H, *J* = 6.0 Hz, *J* = 3.0 Hz), 3.17 (s, 12H), 2.52 (m, 1H), 1.20 (d, 3H, *J* = 9.0 Hz), 1.13 (d, 6H, *J* = 6.0 Hz), 0.81 (d, 3H, *J* = 6.0 Hz).

³¹P{¹H} NMR (C₆D₆, 121 MHz) δ (ppm): -4.5.

³¹P NMR (C₆D₆, 121 MHz) δ (ppm): -4.4.

6.4.4 Selected NMR spectra

6.4.4.1 NMR spectra of β-aminophosphines and bis(β-aminophosphines)

Chemical Formula: C₁₇H₃₀NP

Molecular Weight: 279,41

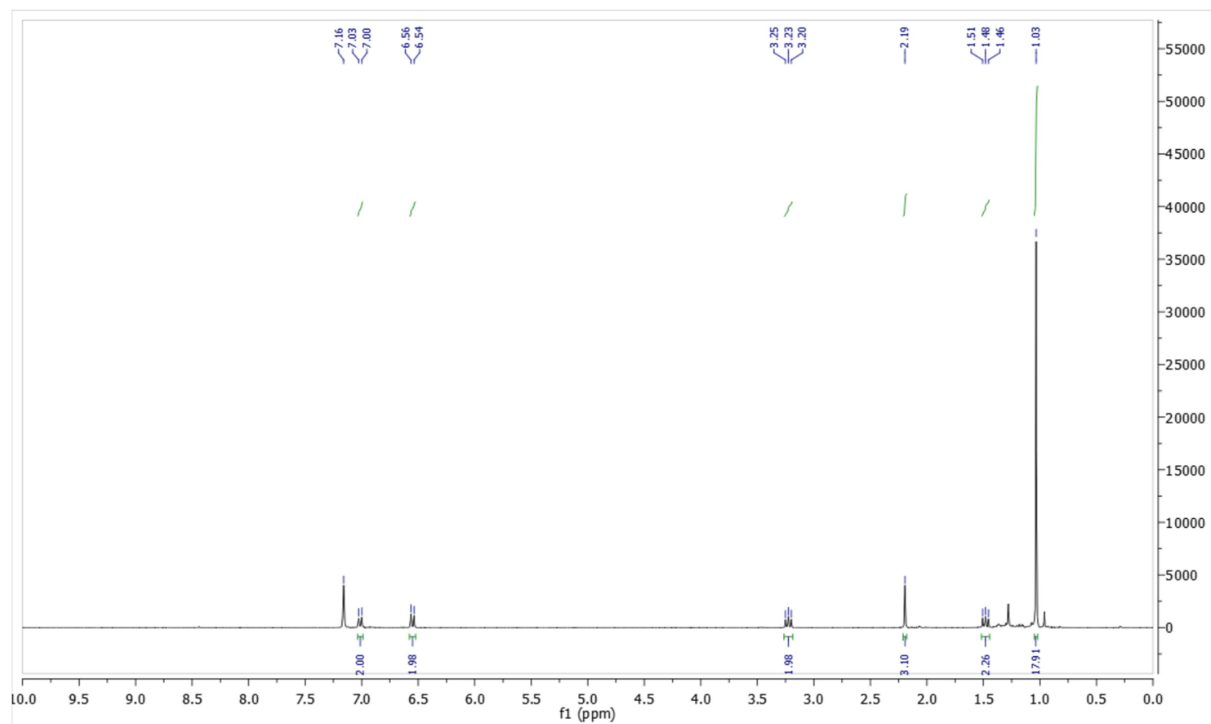


Figure S2: $^1\text{H}\{^{31}\text{P}\}$ NMR (C_6D_6 , 300 MHz) spectrum of β -aminophosphine 4-81.

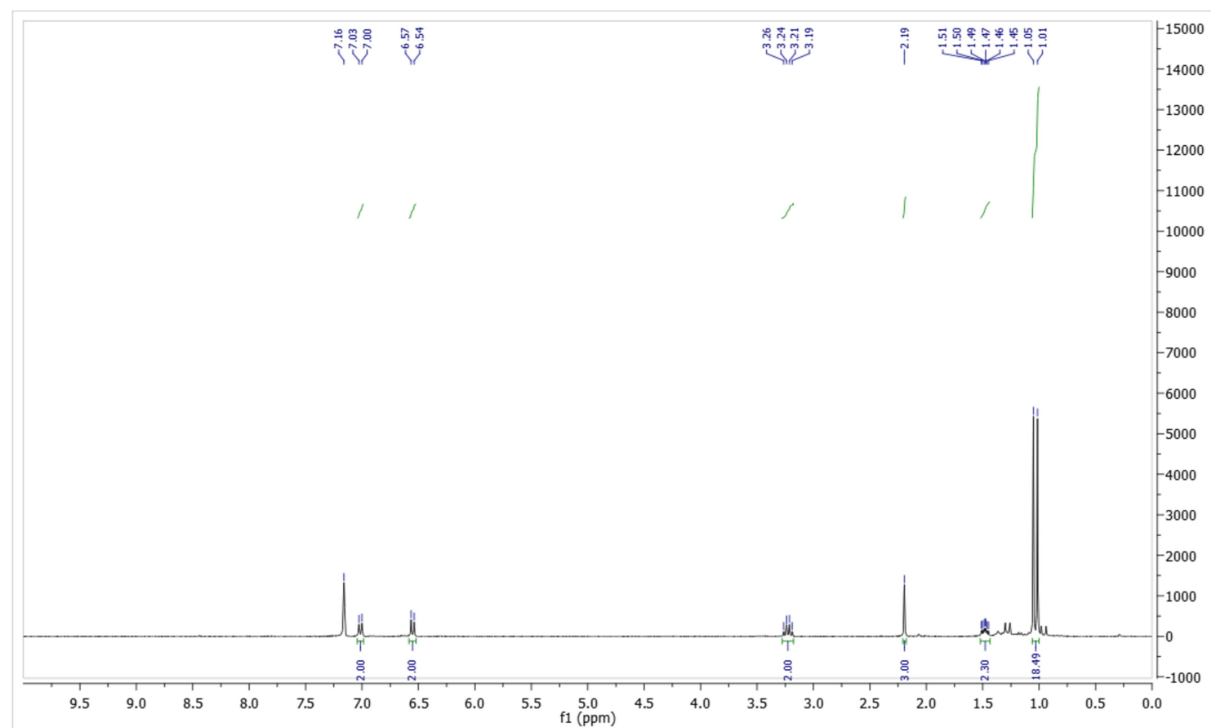


Figure S3: ^1H NMR (C_6D_6 , 300 MHz) spectrum of β -aminophosphine 4-81.

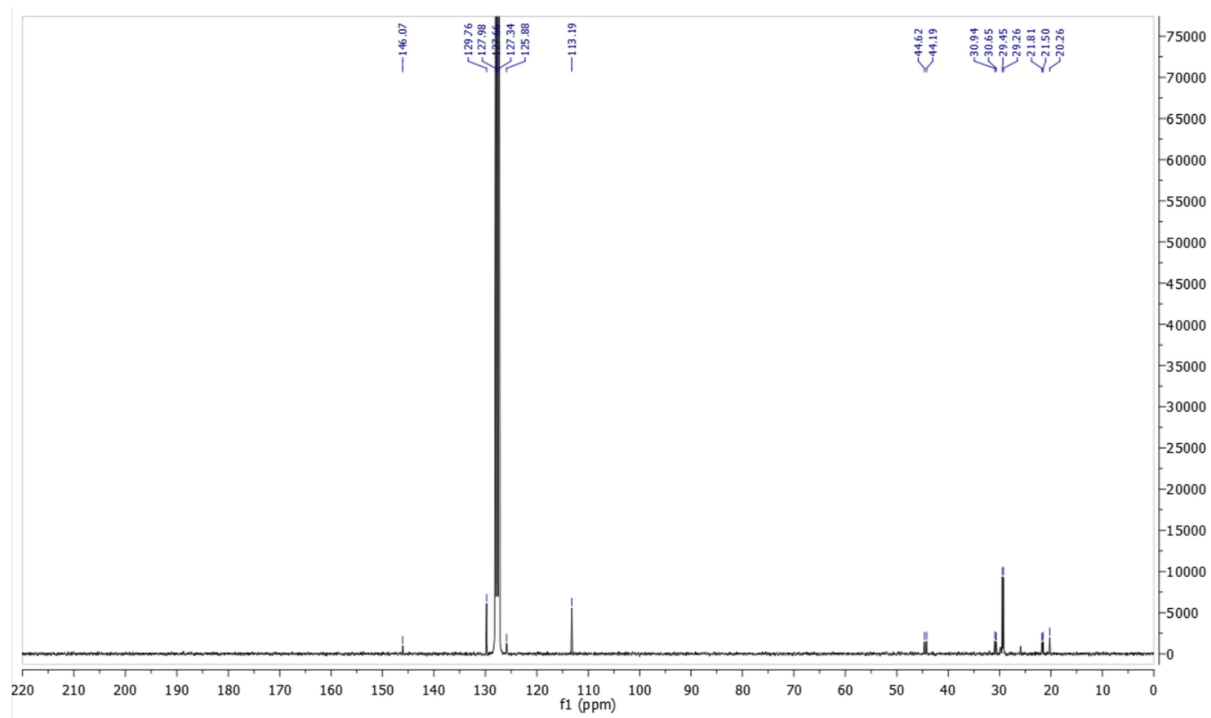


Figure S4: ^{13}C NMR (C_6D_6 , 75 MHz) spectrum of β -aminophosphine 4-81.

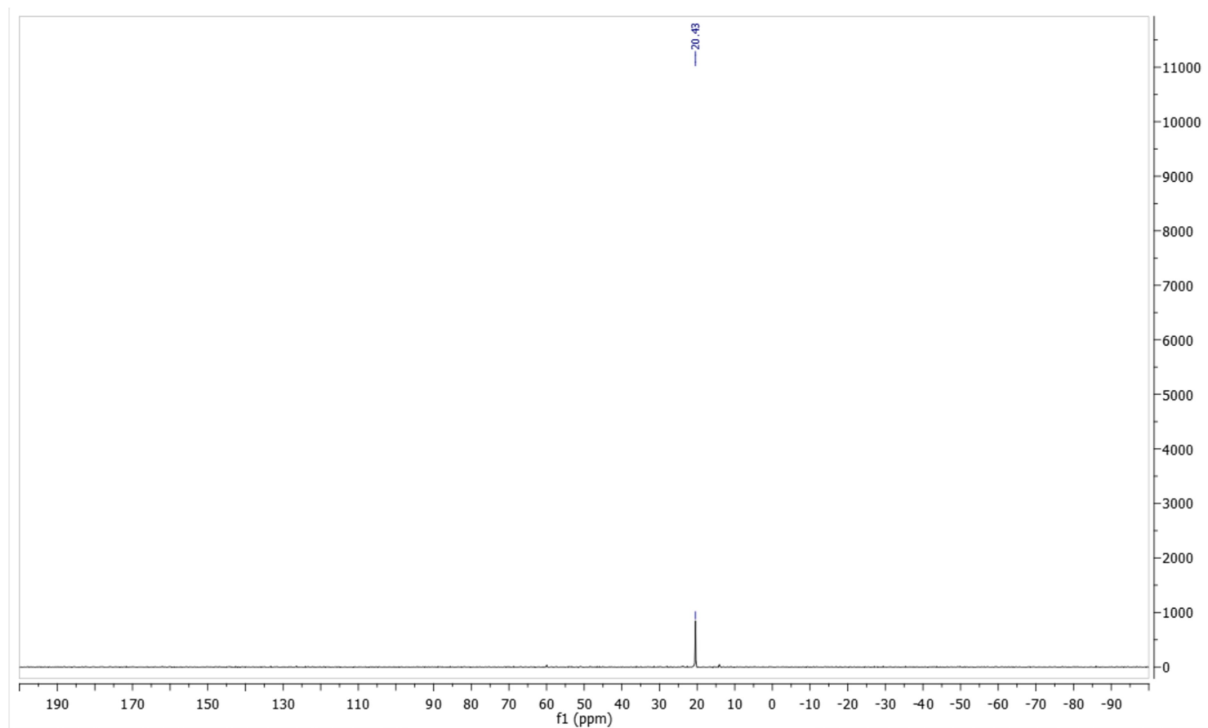


Figure S5: $^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6 , 121 MHz) spectrum of β -aminophosphine 4-81.

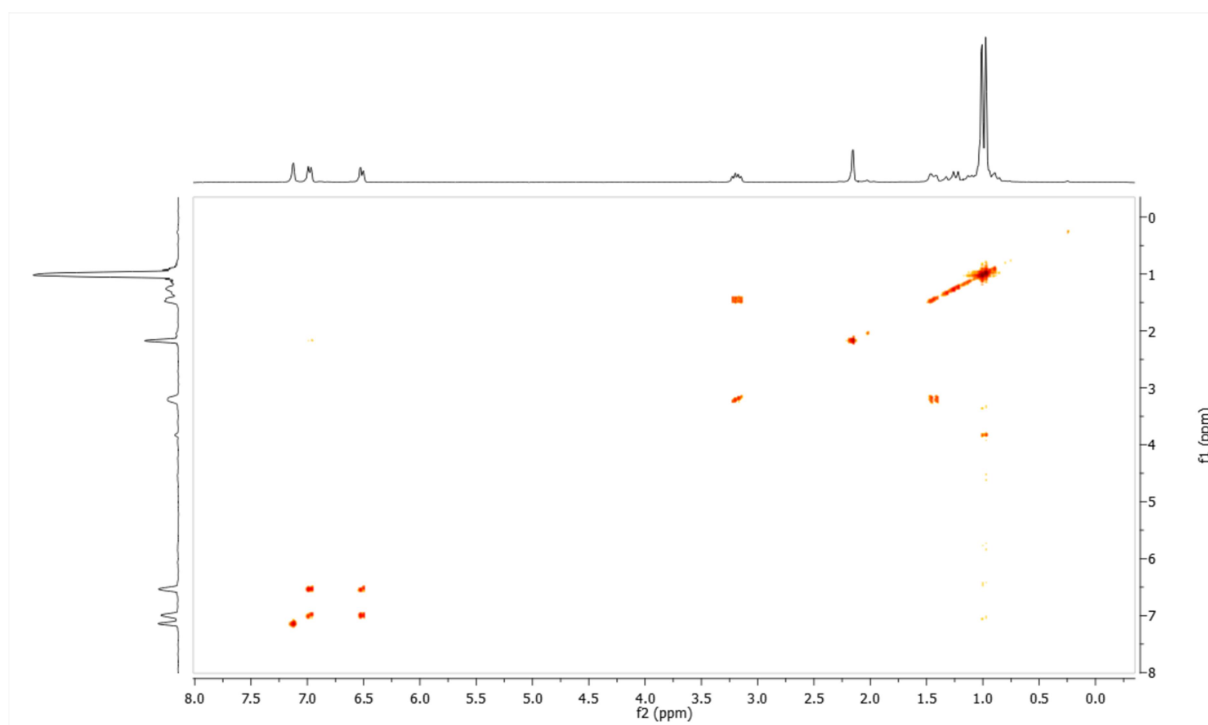


Figure S6: COSY{¹H,¹H} NMR (C₆D₆, 300 MHz) spectrum of β-aminophosphine 4-81.

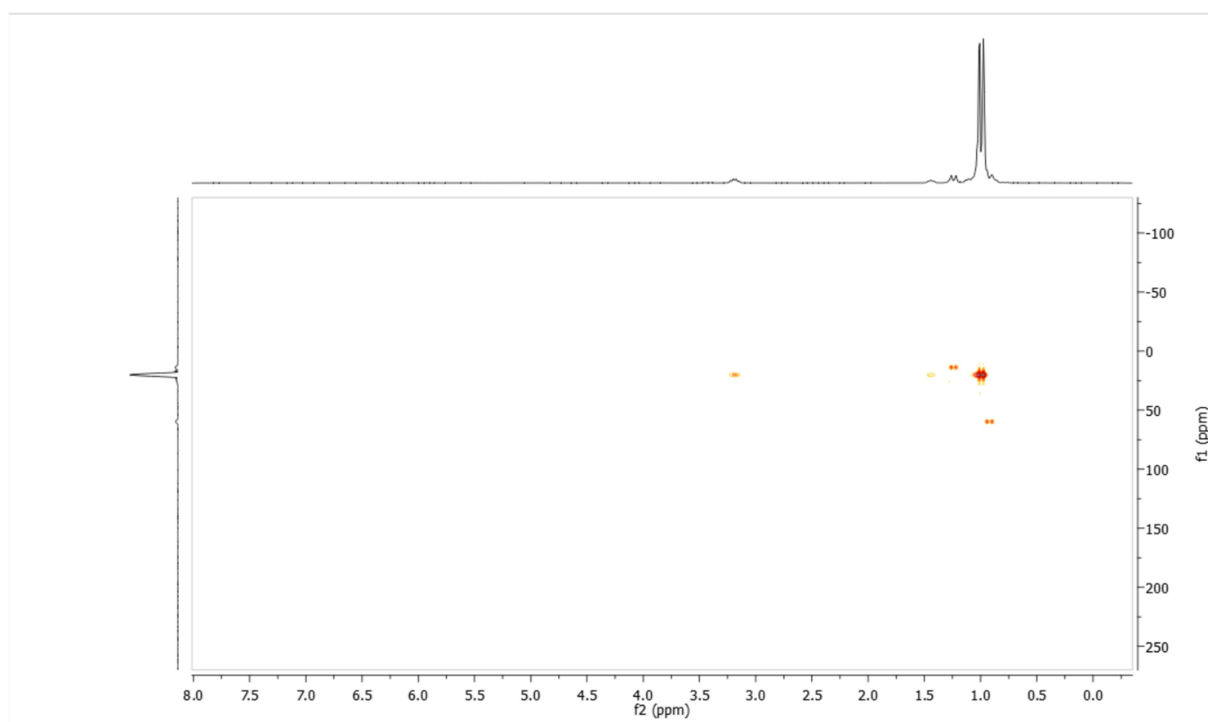
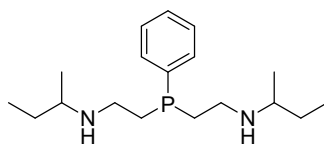


Figure S7: HMBC{¹H,³¹P} NMR (C₆D₆, 300 MHz) spectrum of β-aminophosphine 4-81.



Chemical Formula: $C_{18}H_{33}N_2P$
Molecular Weight: 308,45

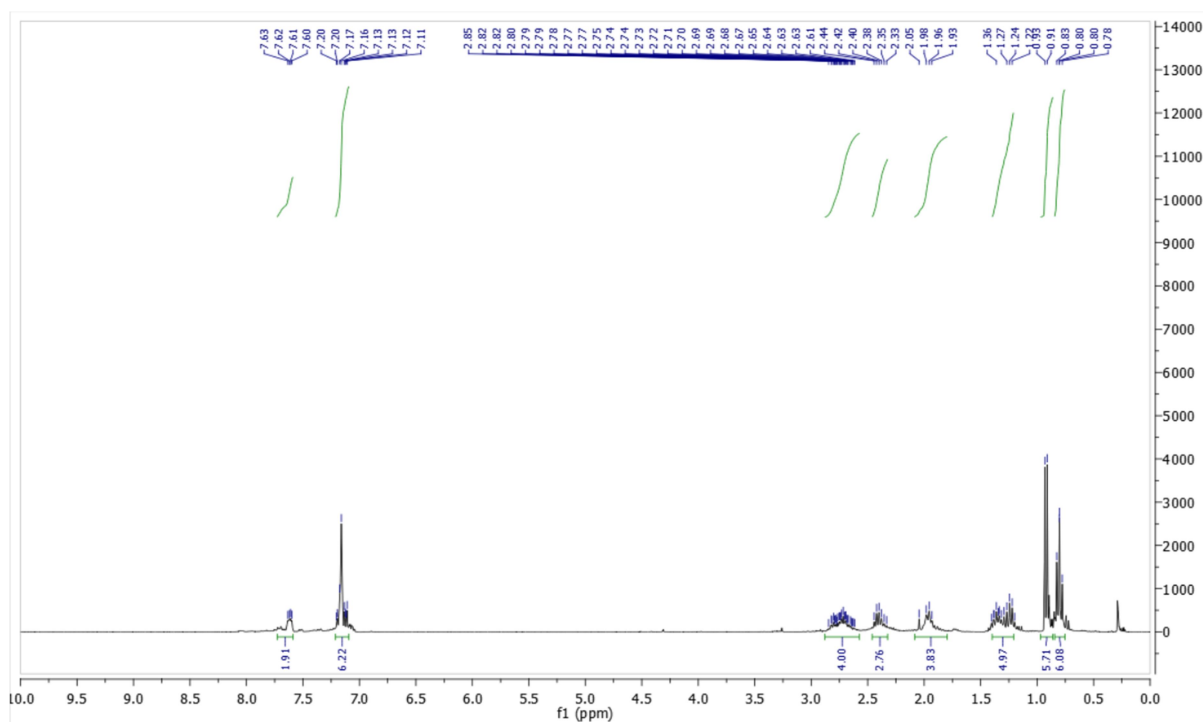


Figure S8: $^1H\{^{31}P\}$ NMR (C_6D_6 , 300 MHz) spectrum of bis(β -aminophosphine) 4-84.

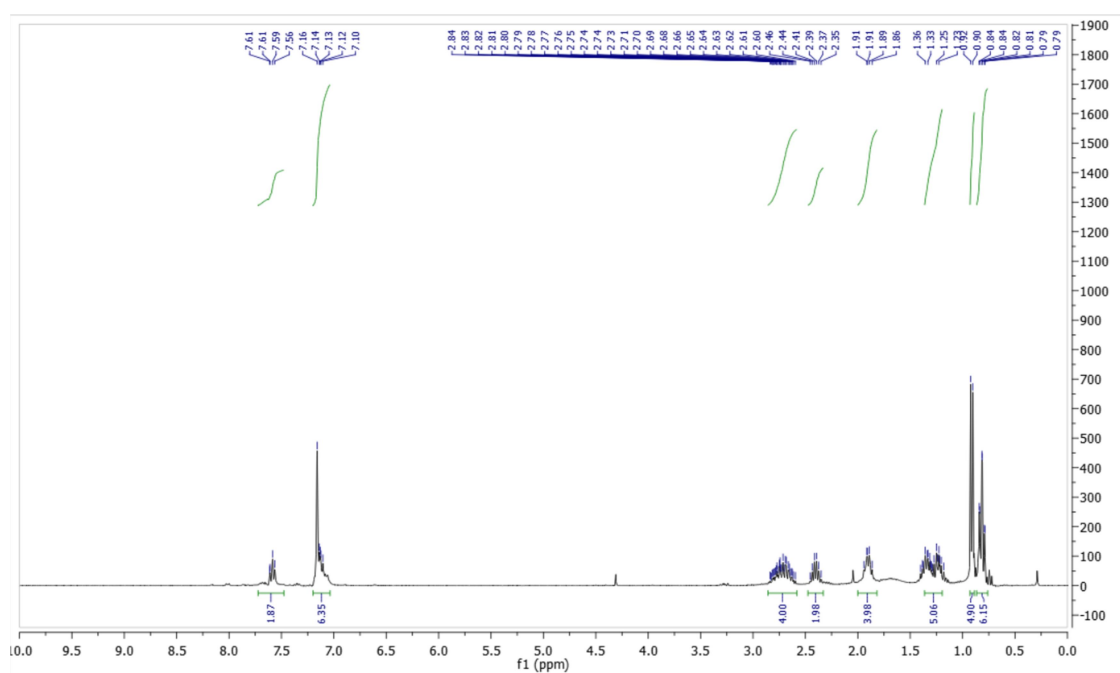


Figure S9: 1H NMR (C_6D_6 , 300 MHz) spectrum of bis(β -aminophosphine) 4-84.

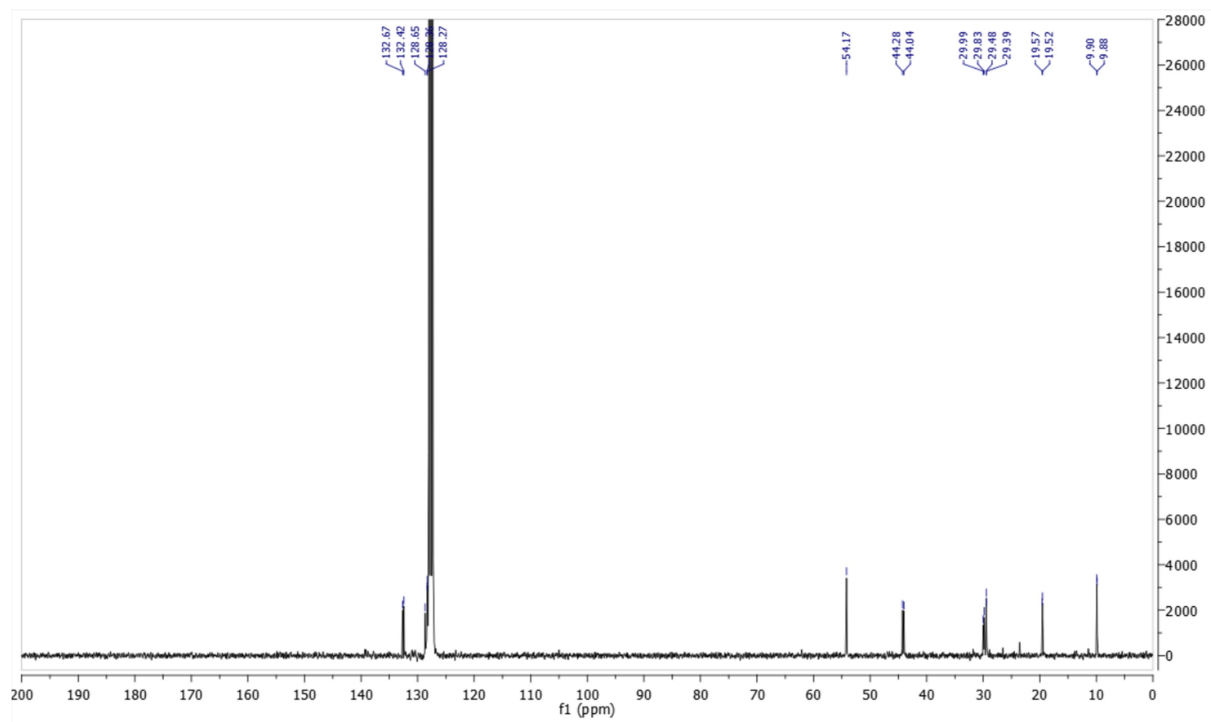


Figure S10: ^{13}C NMR (C_6D_6 , 75 MHz) spectrum of bis(β -aminophosphine) 4-84.

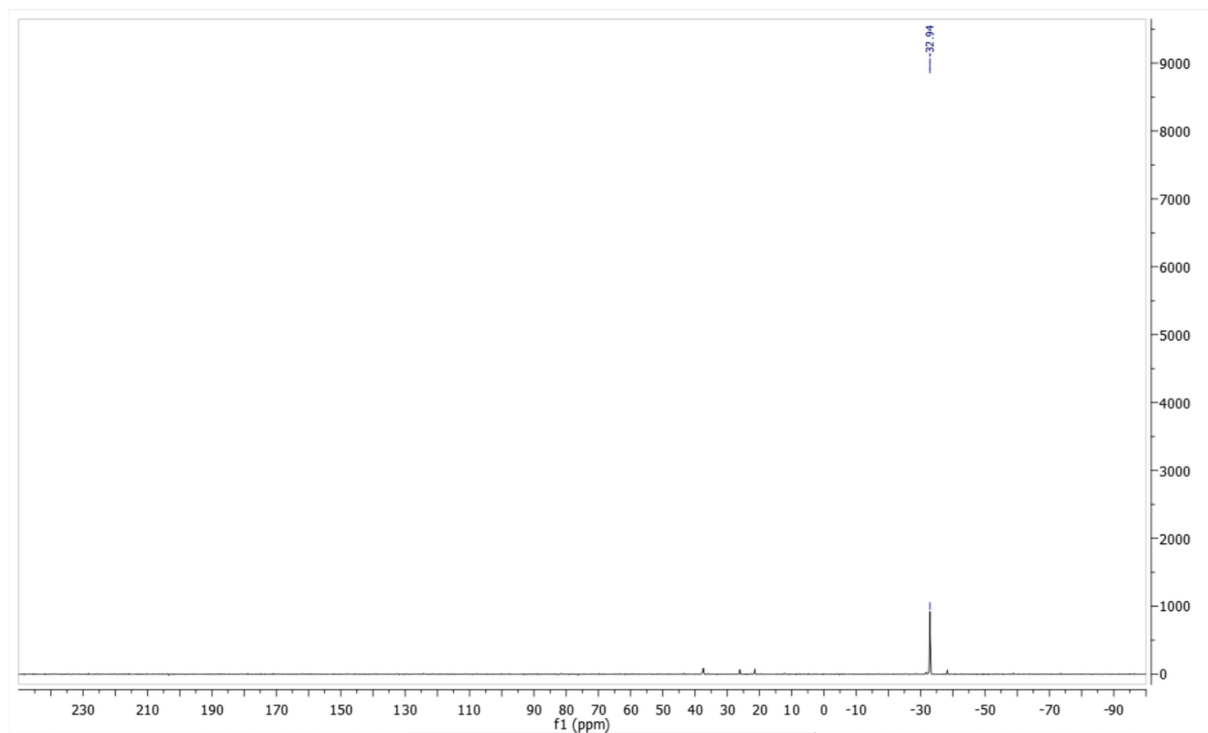


Figure S11: $^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6 , 121 MHz) spectrum of bis(β -aminophosphine) 4-84.

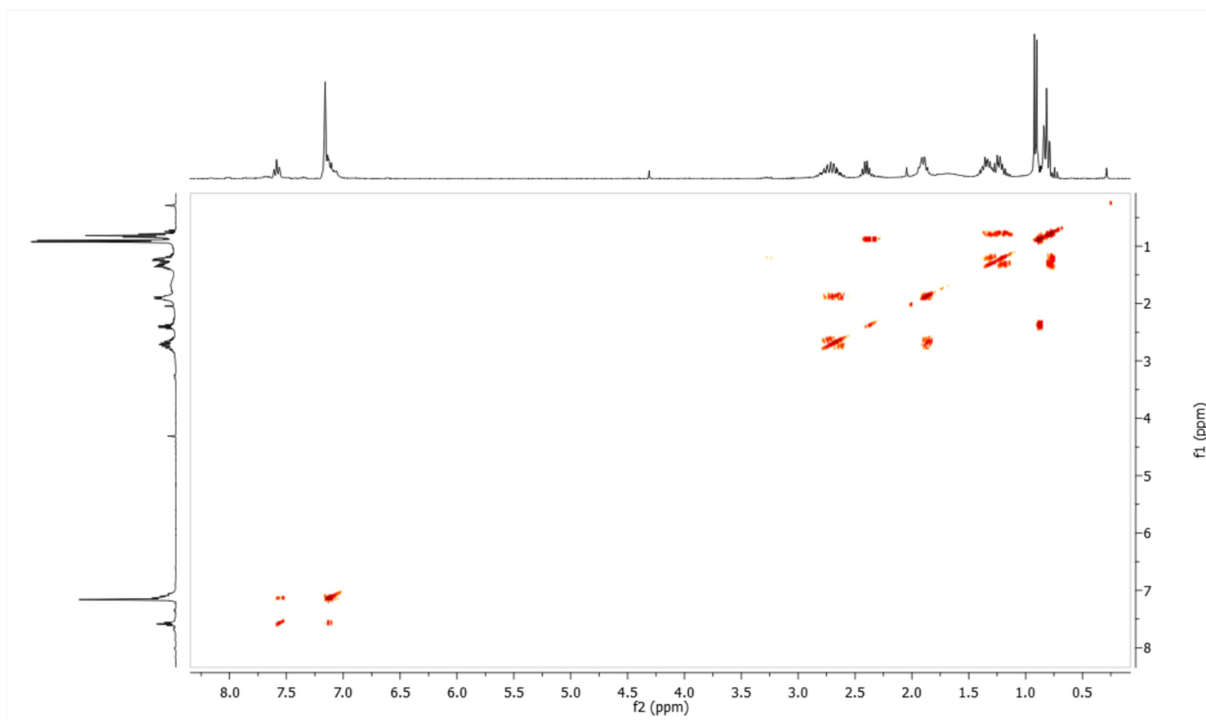


Figure S12: COSY{¹H,¹H} NMR (C₆D₆, 300 MHz) spectrum of bis(β-aminophosphine) 4-84.

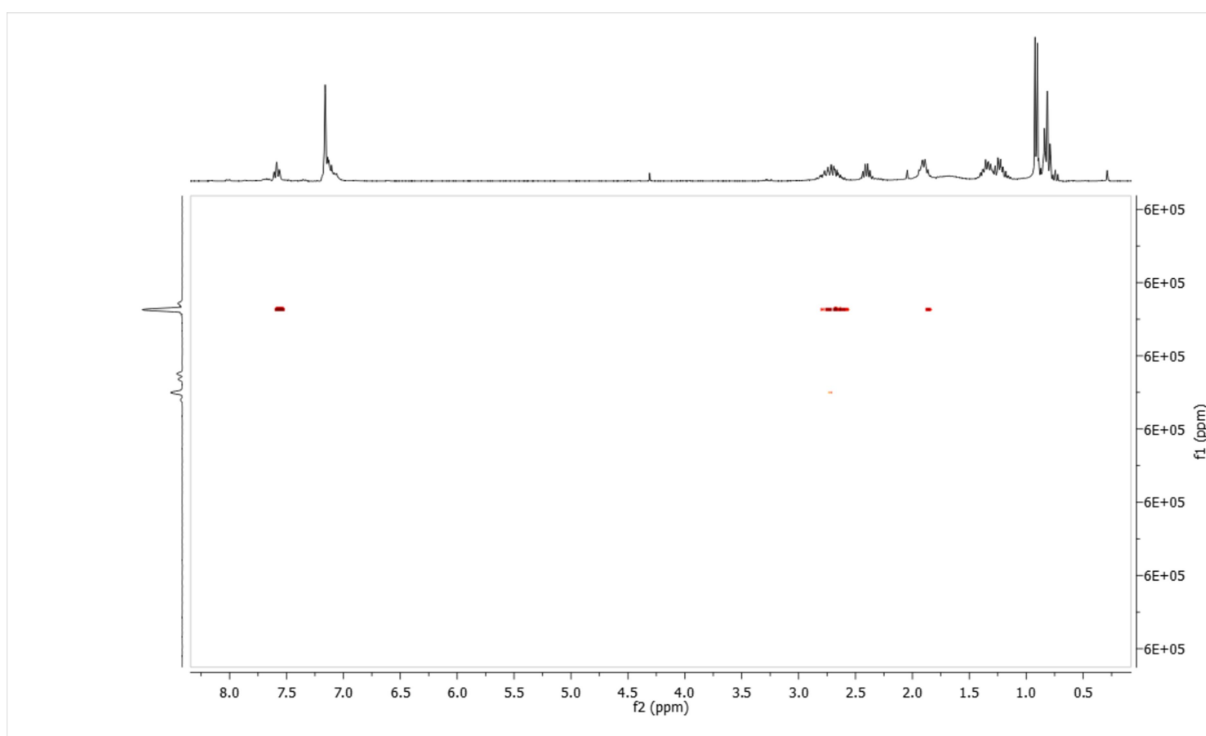
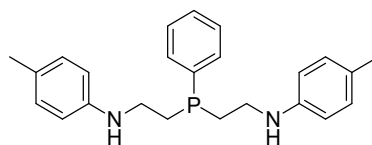


Figure S13: HMBC{¹H,³¹P} NMR (C₆D₆, 121 MHz) spectrum of bis(β-aminophosphine) 4-84.



Chemical Formula: $C_{24}H_{29}N_2P$
Molecular Weight: 376,48

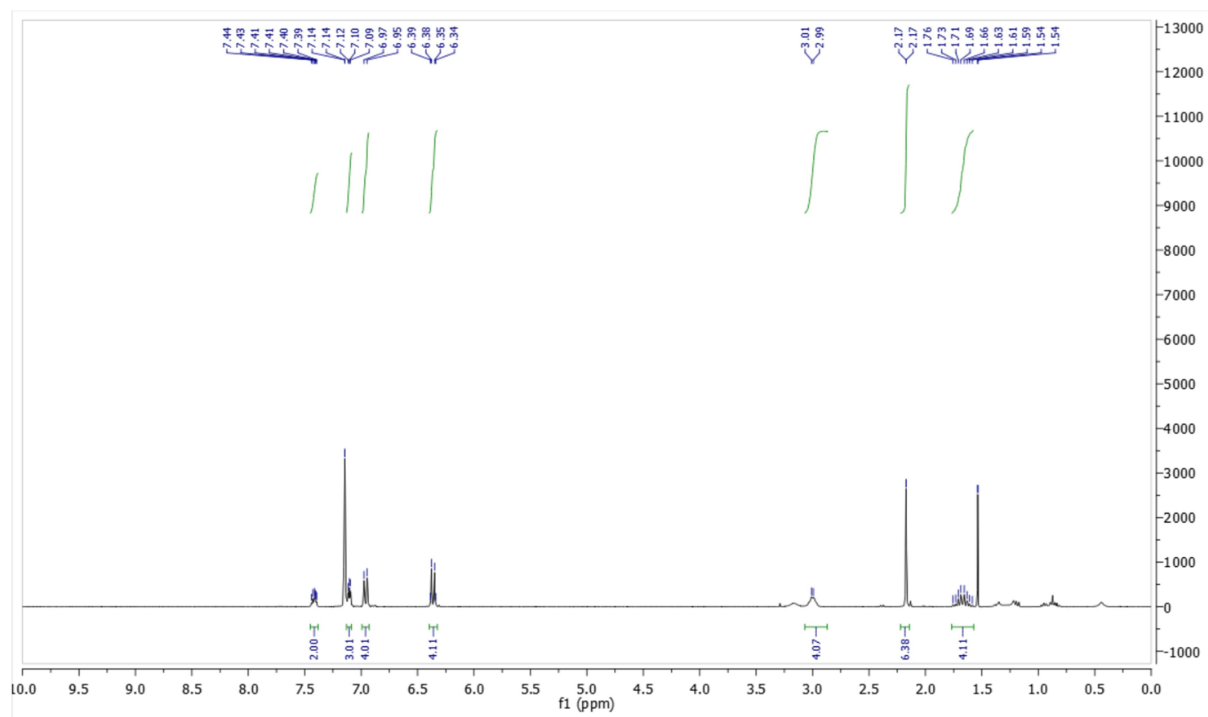


Figure S14: $^1H\{^{31}P\}$ NMR (C_6D_6 , 300 MHz) spectrum of bis(β -aminophosphine) 4-85.

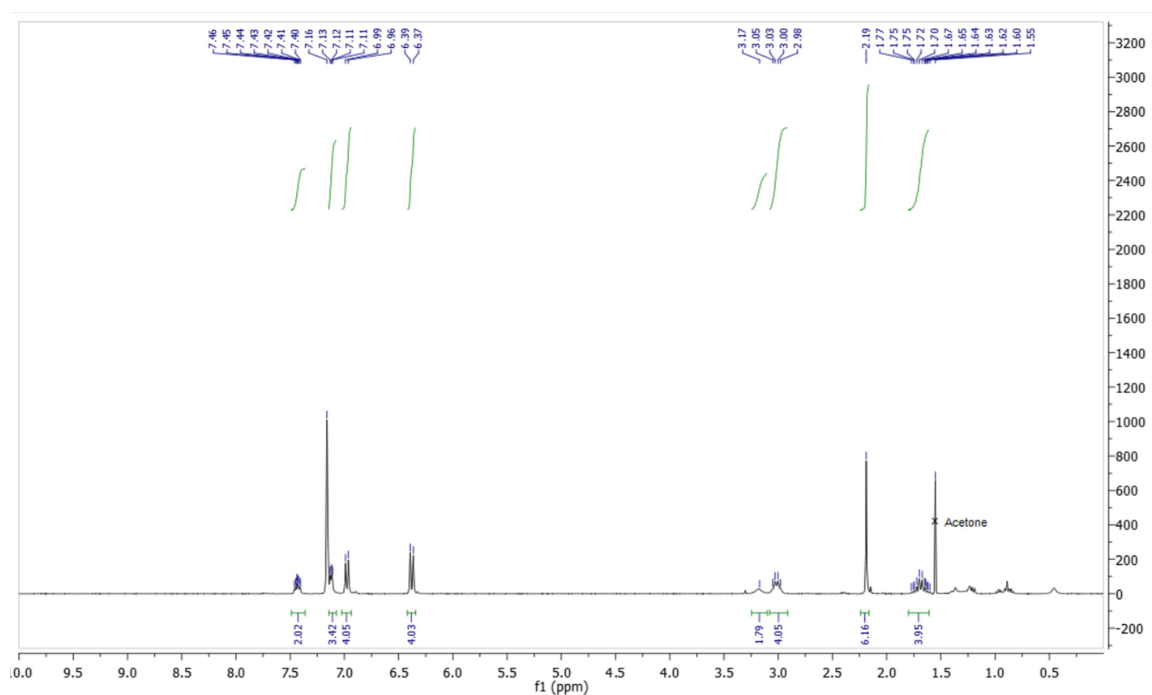


Figure S15: 1H NMR (C_6D_6 , 300 MHz) spectrum of bis(β -aminophosphine) 4-85.

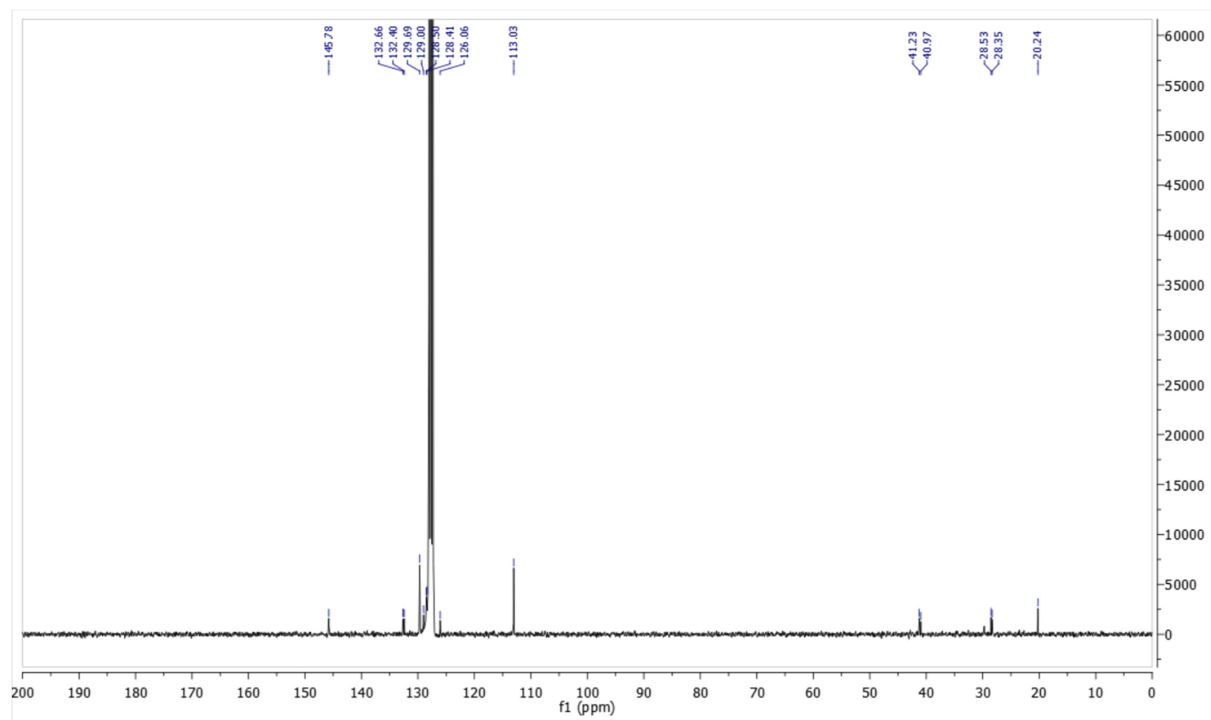


Figure S16: ^{13}C NMR (C_6D_6 , 75 MHz) spectrum of bis(β -aminophosphine) 4-85.

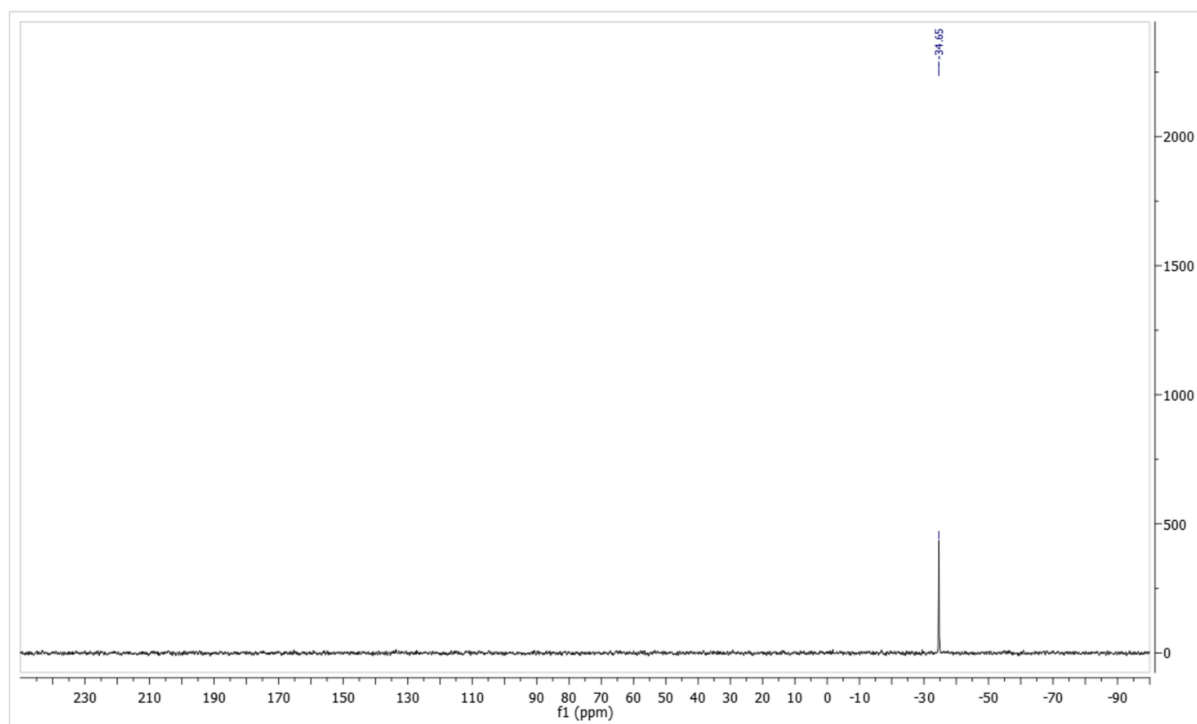


Figure S17: $^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6 , 121 MHz) spectrum of bis(β -aminophosphine) 4-85.

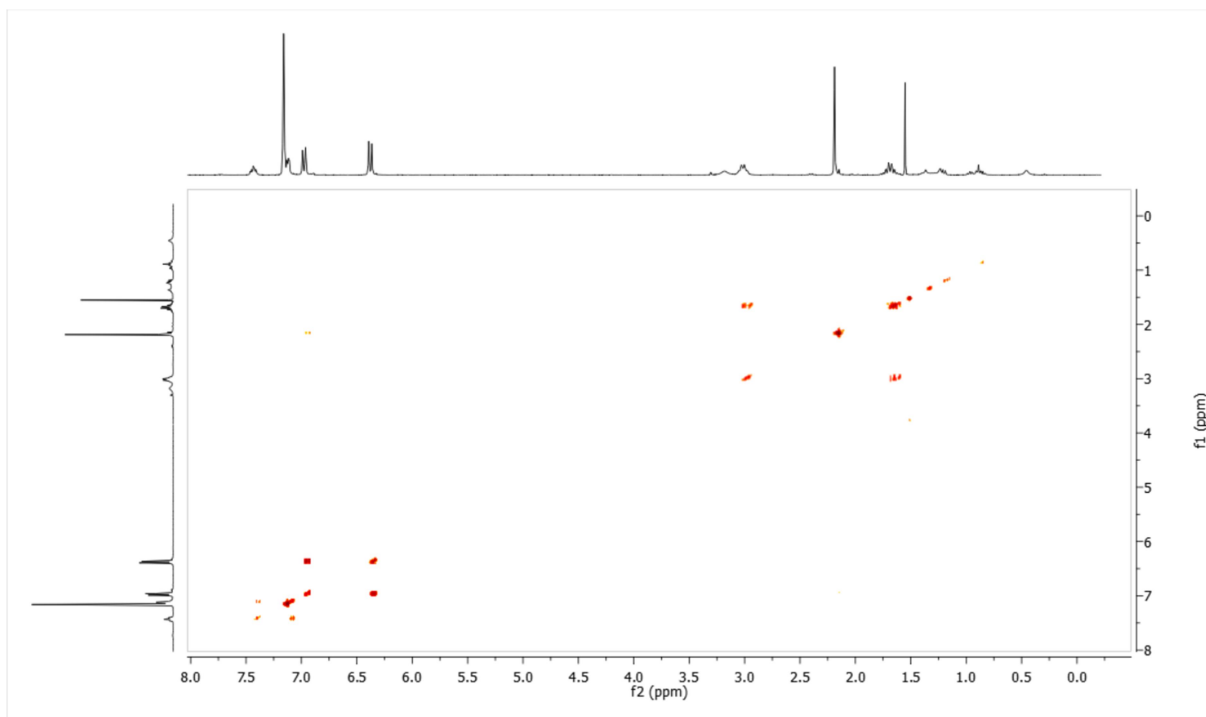


Figure S18: COSY{ $^1\text{H}, ^1\text{H}$ } NMR (C_6D_6 , 300 MHz) spectrum of bis(β -aminophosphine) 4-85.

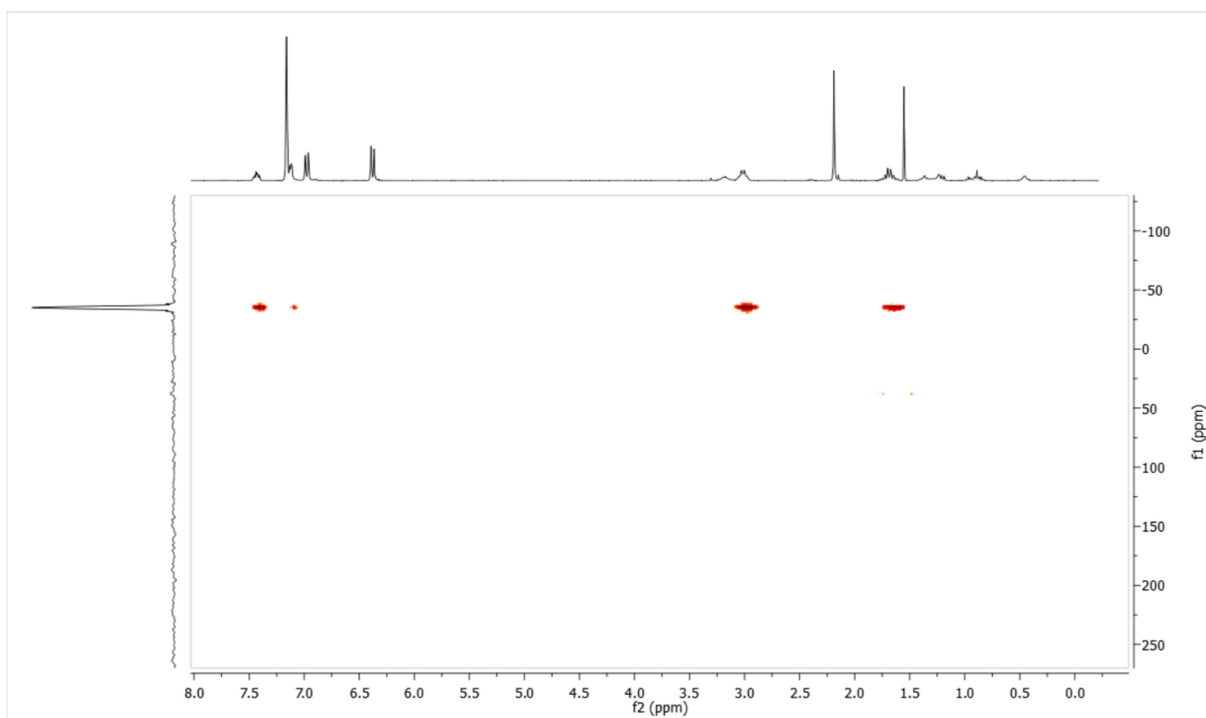


Figure S19: HMBC{ $^1\text{H}, ^{31}\text{P}$ } NMR (C_6D_6 , 121 MHz) spectrum of bis(β -aminophosphine) 4-85.

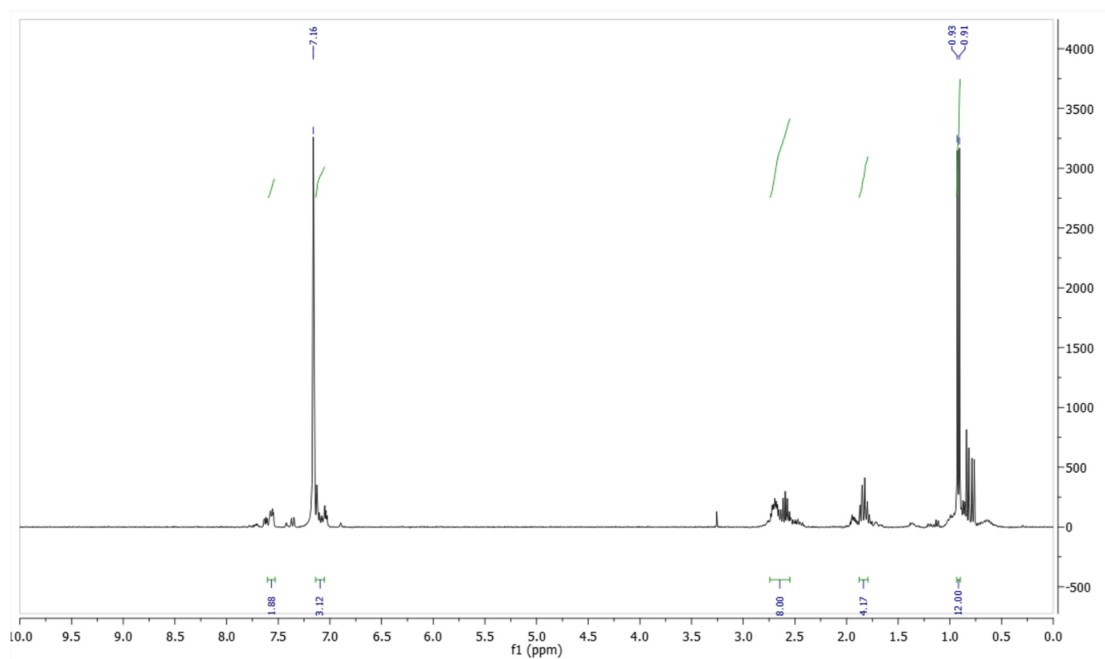
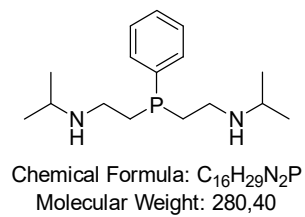


Figure S20: ^{31}P NMR (C_6D_6 , 300 MHz) spectrum of bis(β -aminophosphine) 4-86.

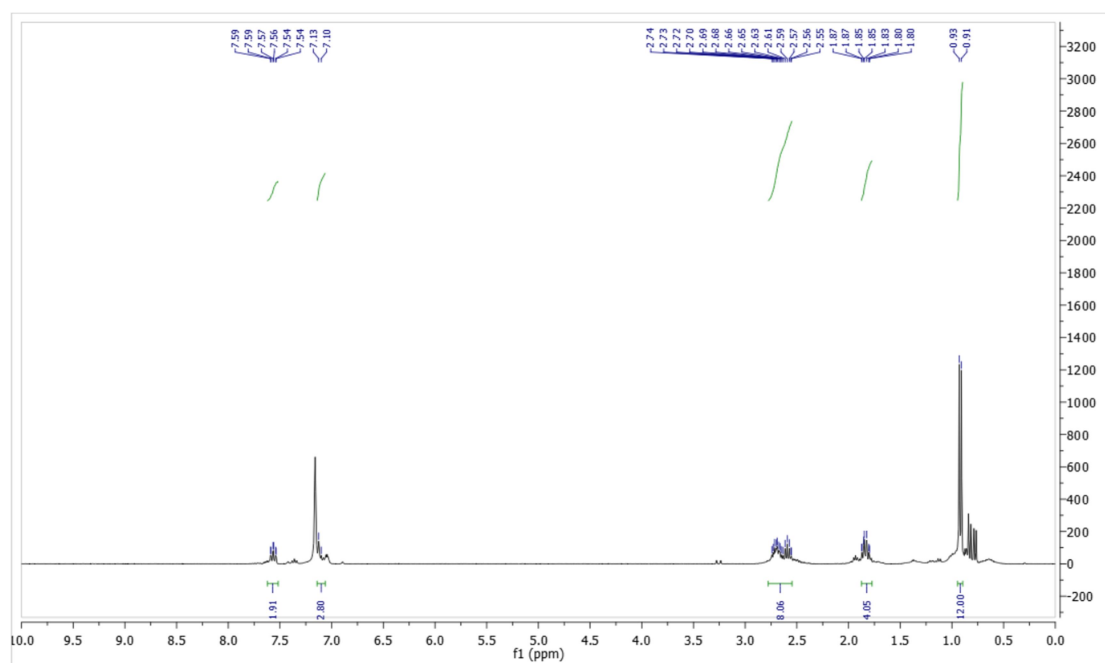


Figure S21: 1H NMR (C_6D_6 , 300 MHz) spectrum of bis(β -aminophosphine) 4-86.

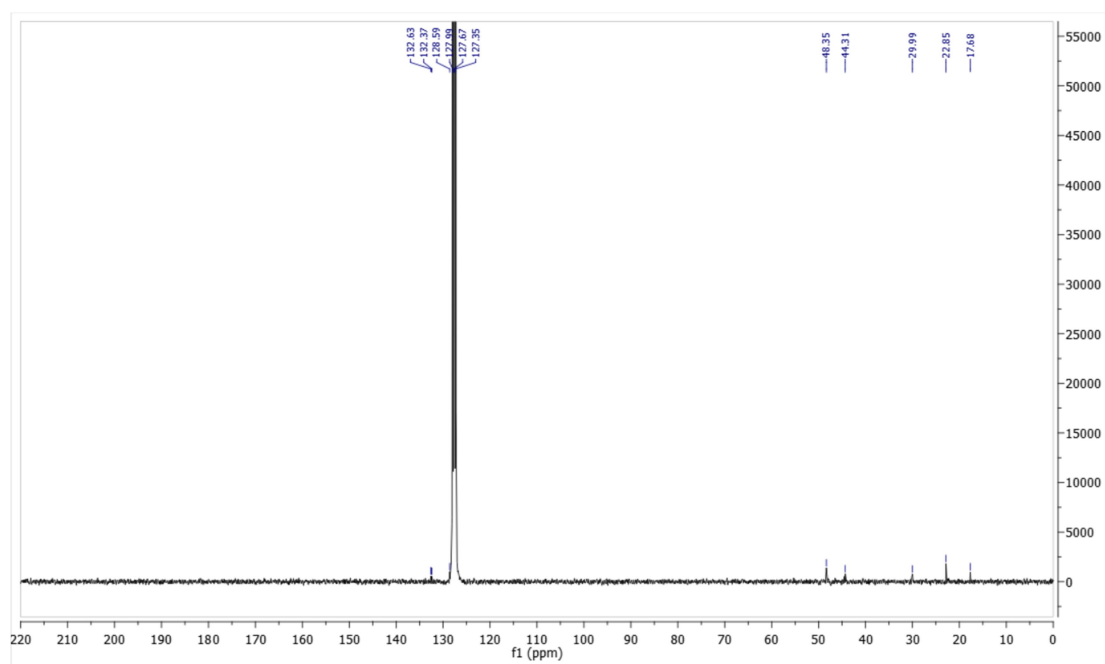


Figure S22: ^{13}C NMR (C_6D_6 , 75 MHz) spectrum of bis(β -aminophosphine) 4-86.

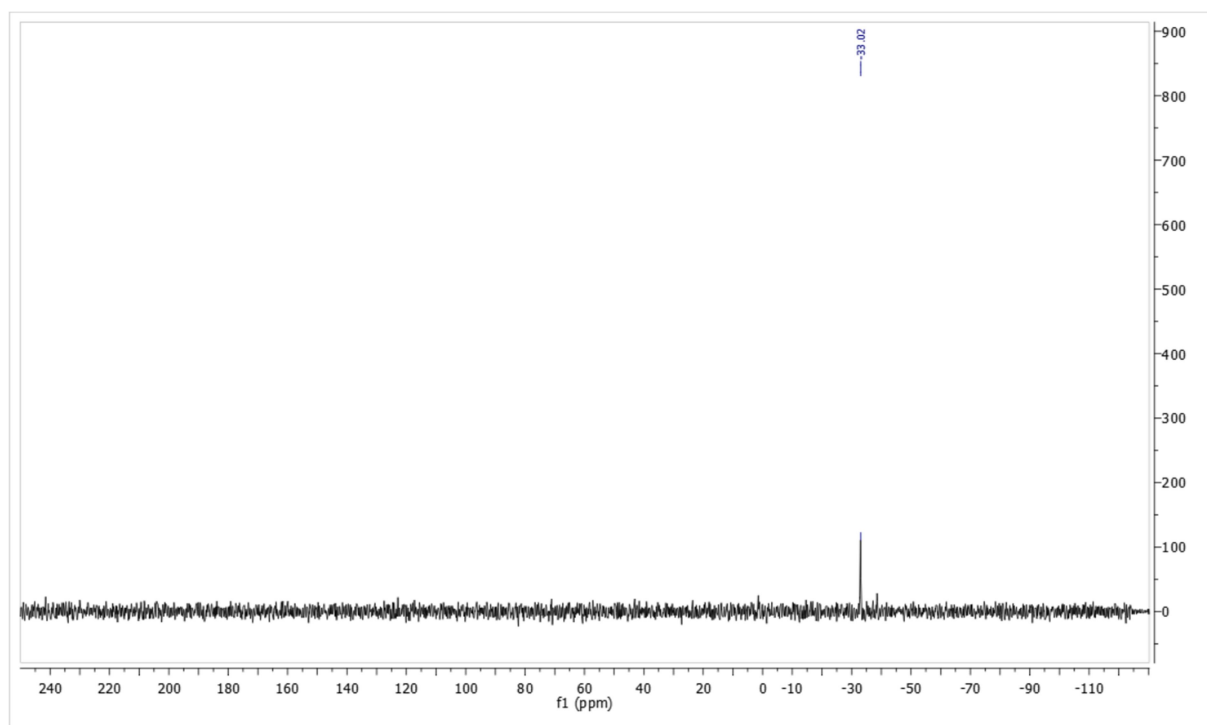


Figure S23: $^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6 , 121 MHz) spectrum of bis(β -aminophosphine) 4-86.

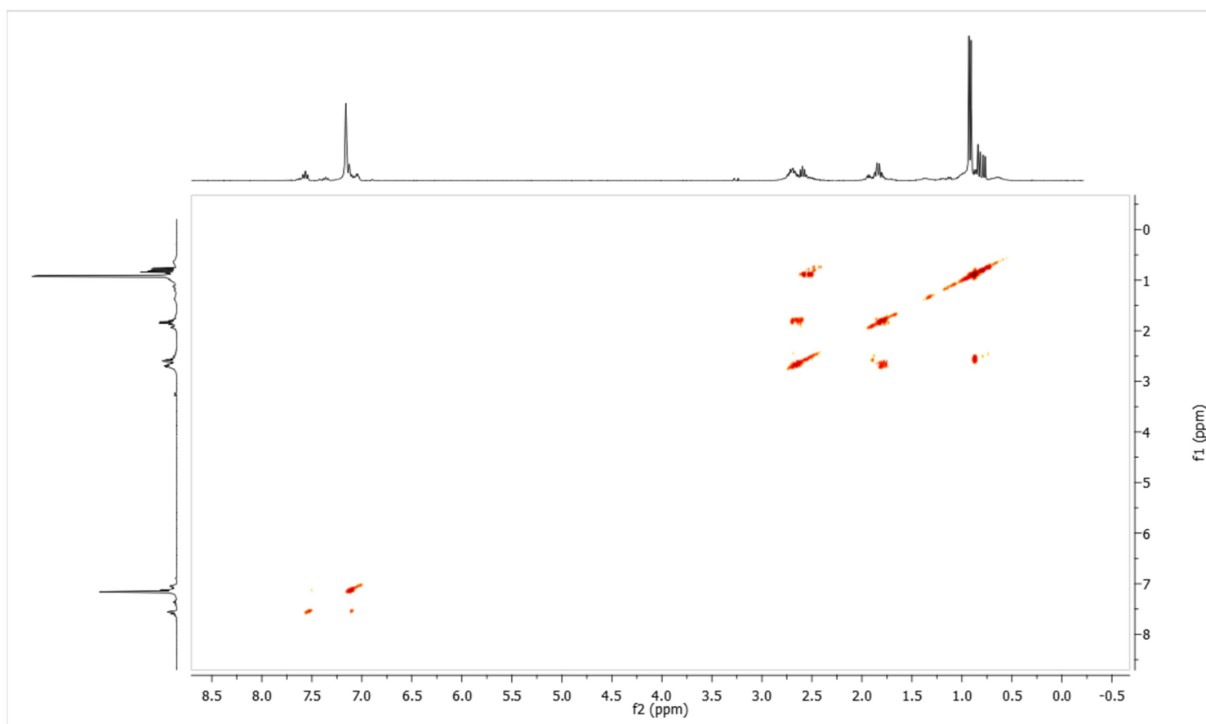


Figure S24: COSY{¹H,¹H} NMR (C₆D₆, 300 MHz) spectrum of bis(β-aminophosphine) 4-86.

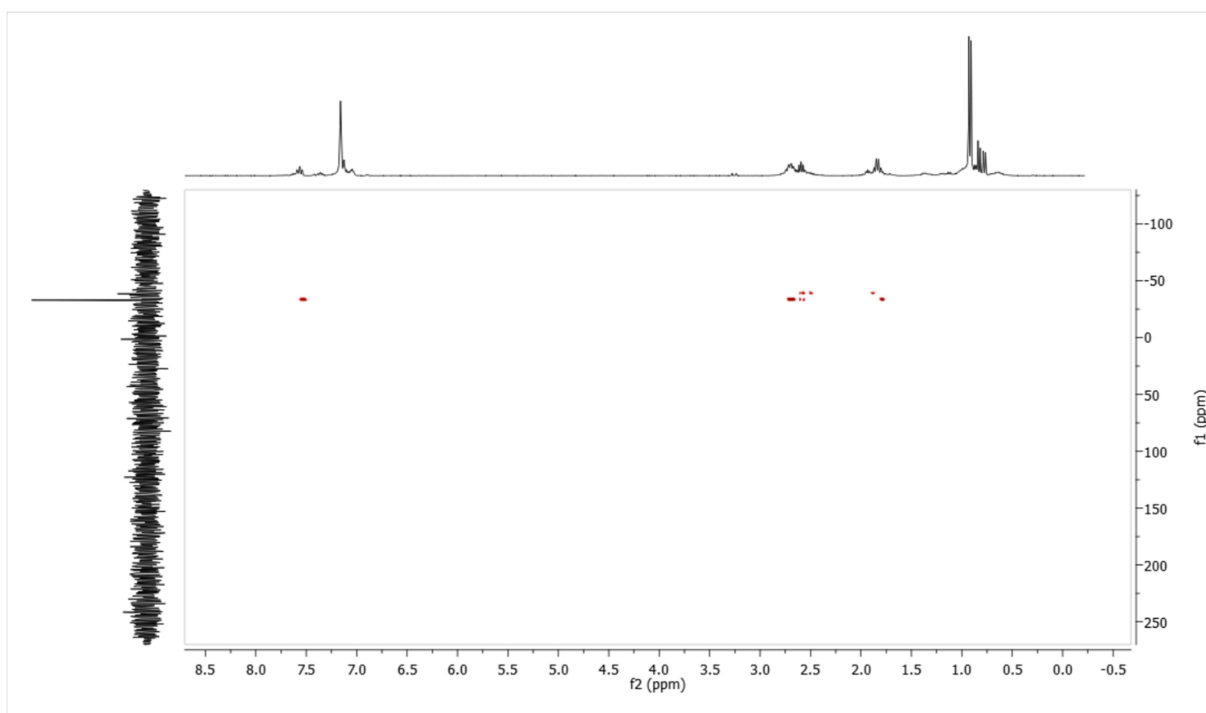
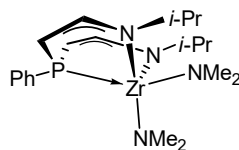


Figure S25: HMBC{¹H,³¹P} NMR (C₆D₆, 121 MHz) spectrum of bis(β-aminophosphine) 4-86.

6.4.4.2 NMR spectra of *N,P,N*-complexes with early transition metals

Chemical Formula: $C_{20}H_{39}N_4PZr$
Molecular Weight: 457,76

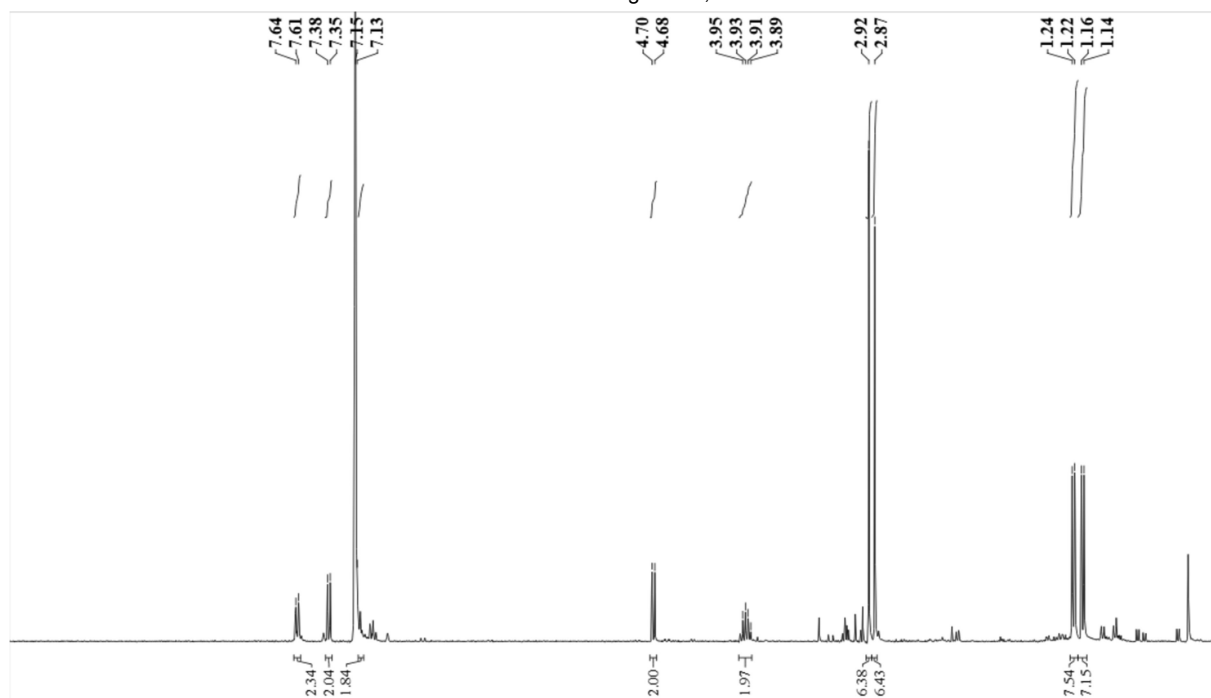


Figure S26: $^1H\{^{31}P\}$ NMR (C_6D_6 , 300 MHz) spectrum of *N,P,N*-complex 4-96.

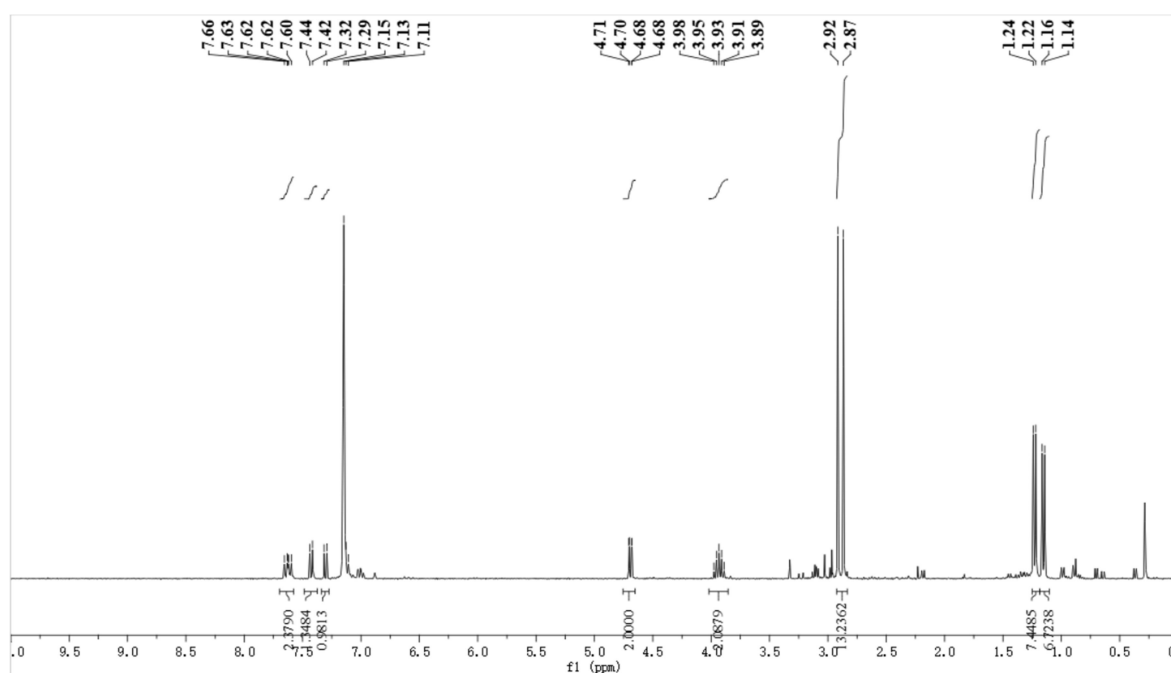


Figure S27: 1H NMR (C_6D_6 , 300 MHz) spectrum of *N,P,N*-complex 4-96.

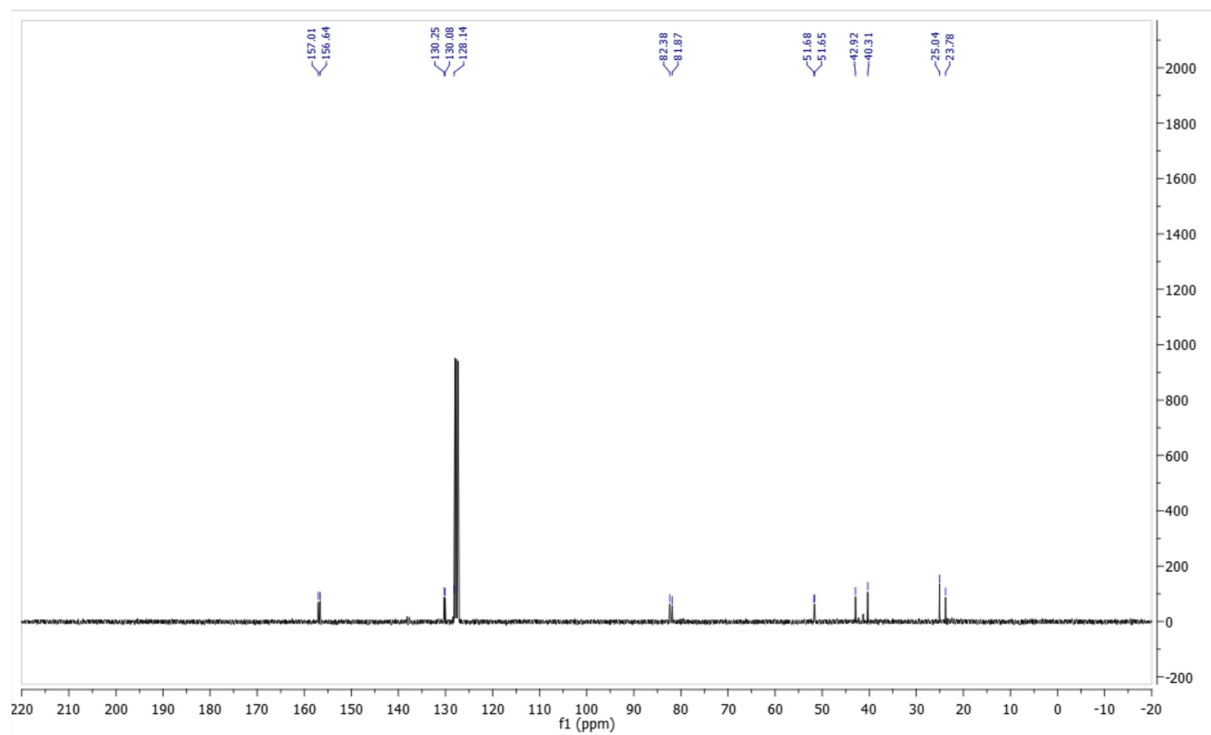


Figure S28: ^{13}C NMR (C_6D_6 , 75 MHz) spectrum of *N,P,N*-complex 4-96.

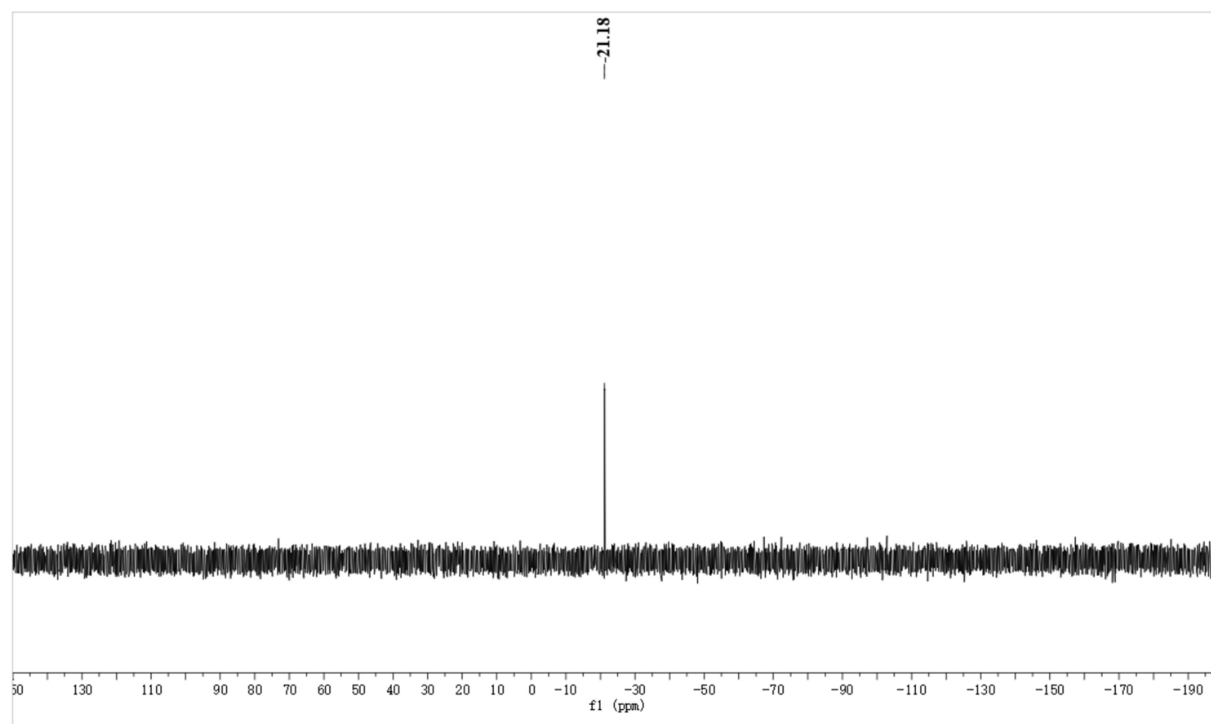


Figure S29: $^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6 , 121 MHz) spectrum of *N,P,N*-complex 4-96.

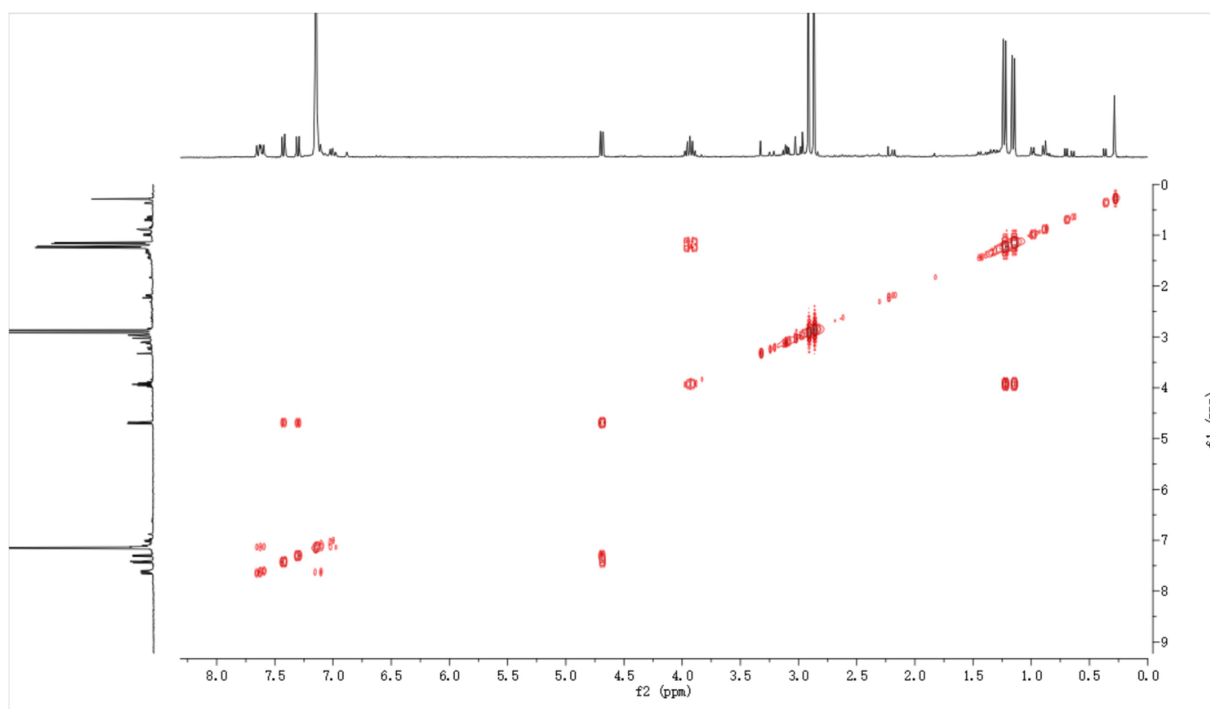


Figure S30: COSY{ ^1H , ^1H } NMR (C_6D_6 , 300 MHz) spectrum of *N,P,N*-complex 4-96.

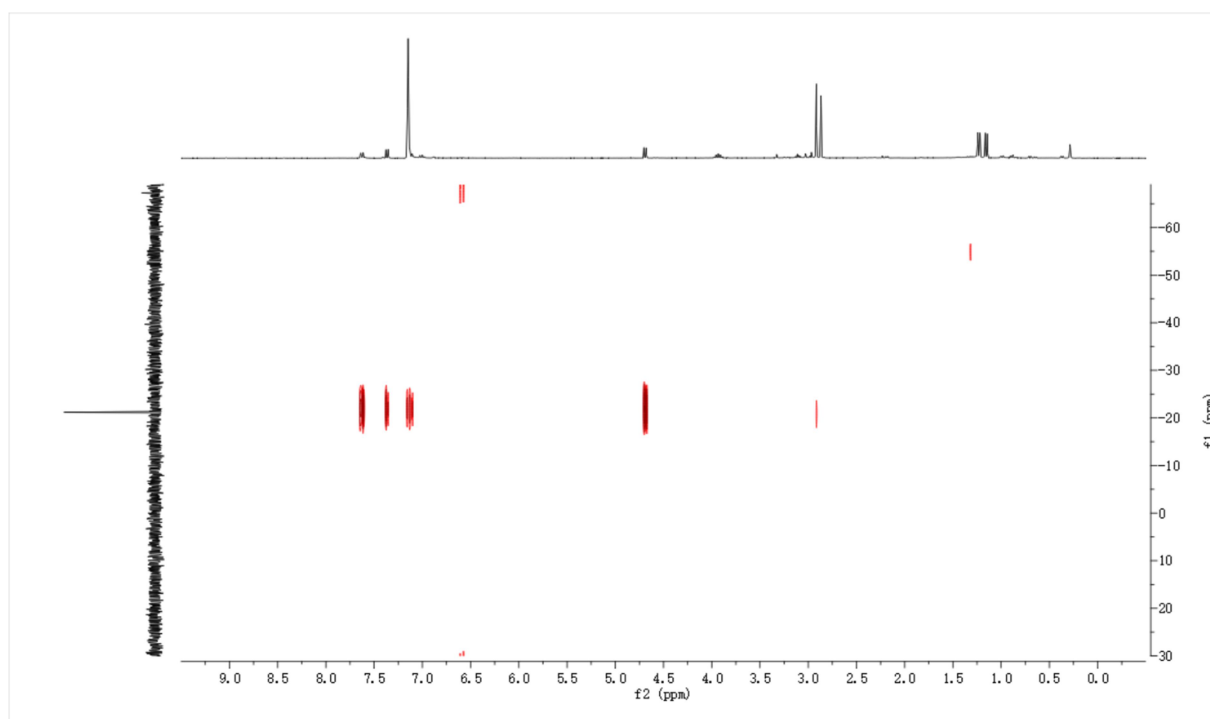
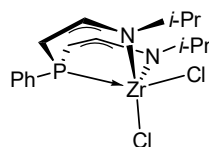


Figure S31: HMBC{ ^1H , ^{31}P } NMR (C_6D_6 , 121 MHz) spectrum of *N,P,N*-complex 4-96.



Chemical Formula: $C_{16}H_{27}Cl_2N_2PZr$
Molecular Weight: 440,50

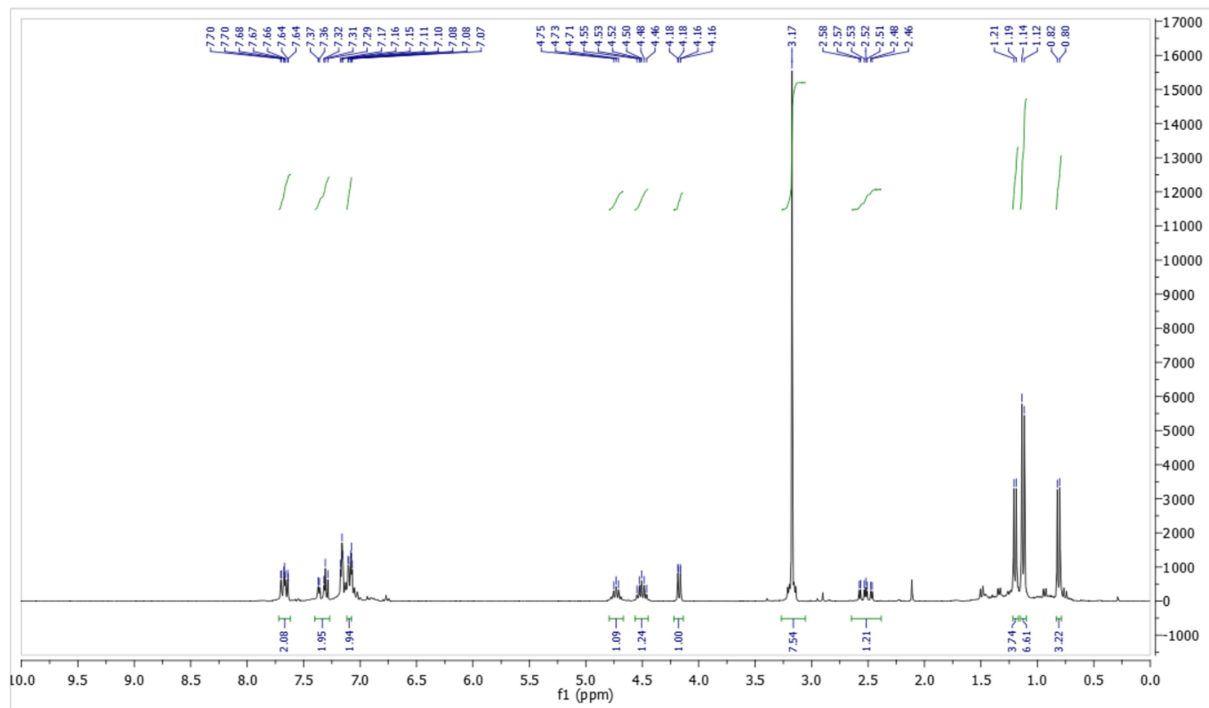


Figure S32: 1H NMR (C_6D_6 , 300 MHz) spectrum of *N,P,N*-complex 4-97.

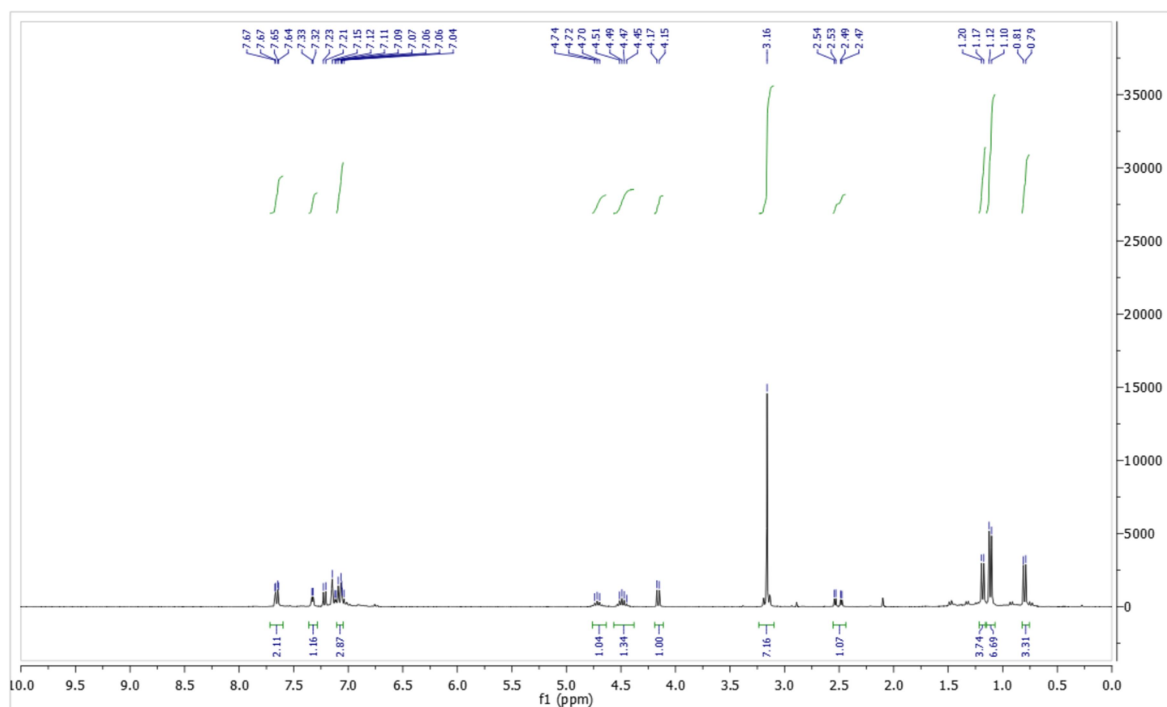


Figure S33: $^1H\{^{31}P\}$ NMR (C_6D_6 , 300 MHz) spectrum of *N,P,N*-complex 4-97.

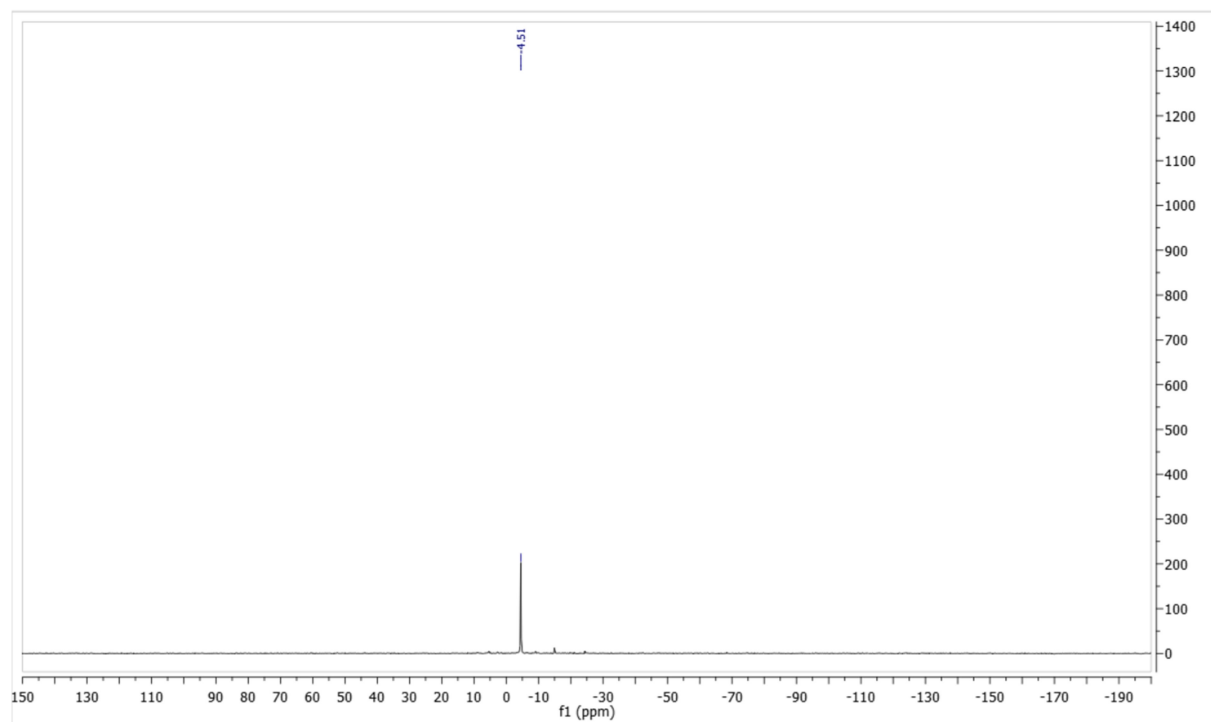


Figure S34: $^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6 , 121 MHz) spectrum of *N,P,N*-complex 4-97.

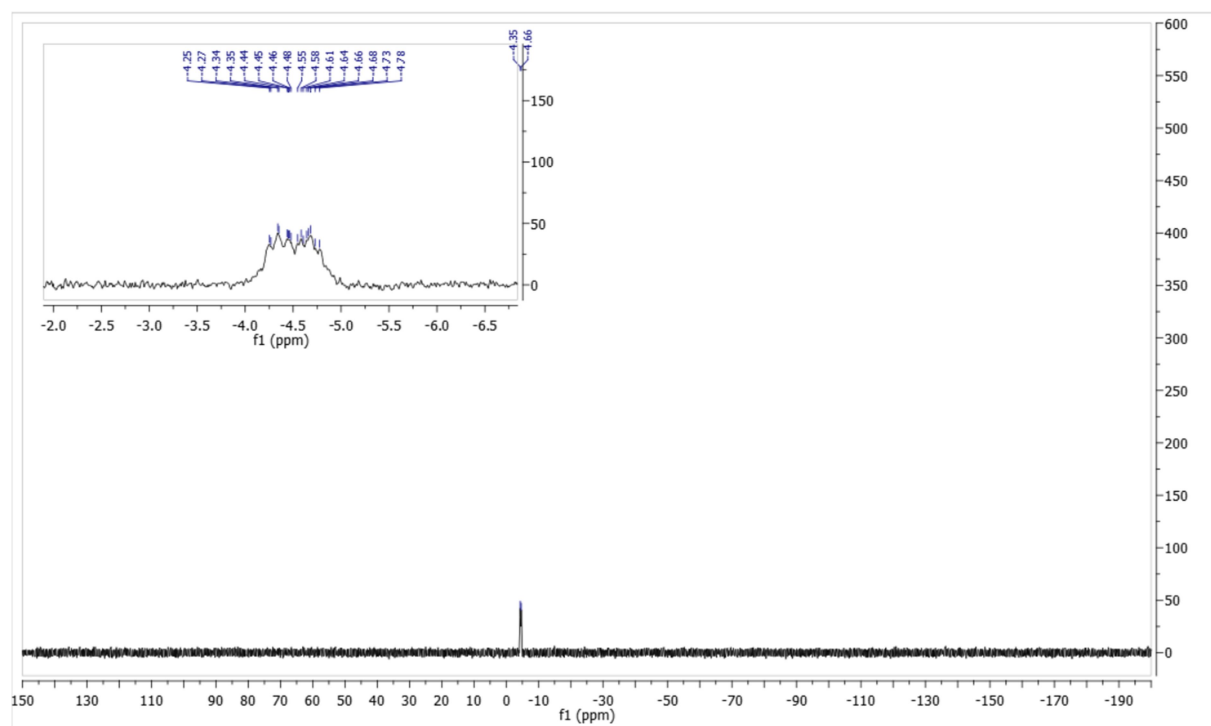
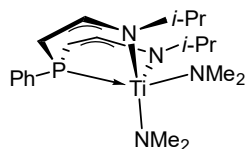


Figure S35: ^{31}P NMR (C_6D_6 , 121 MHz) spectrum of *N,P,N*-complex 4-97.



Chemical Formula: $C_{20}H_{39}N_4PTi$
Molecular Weight: 414,40

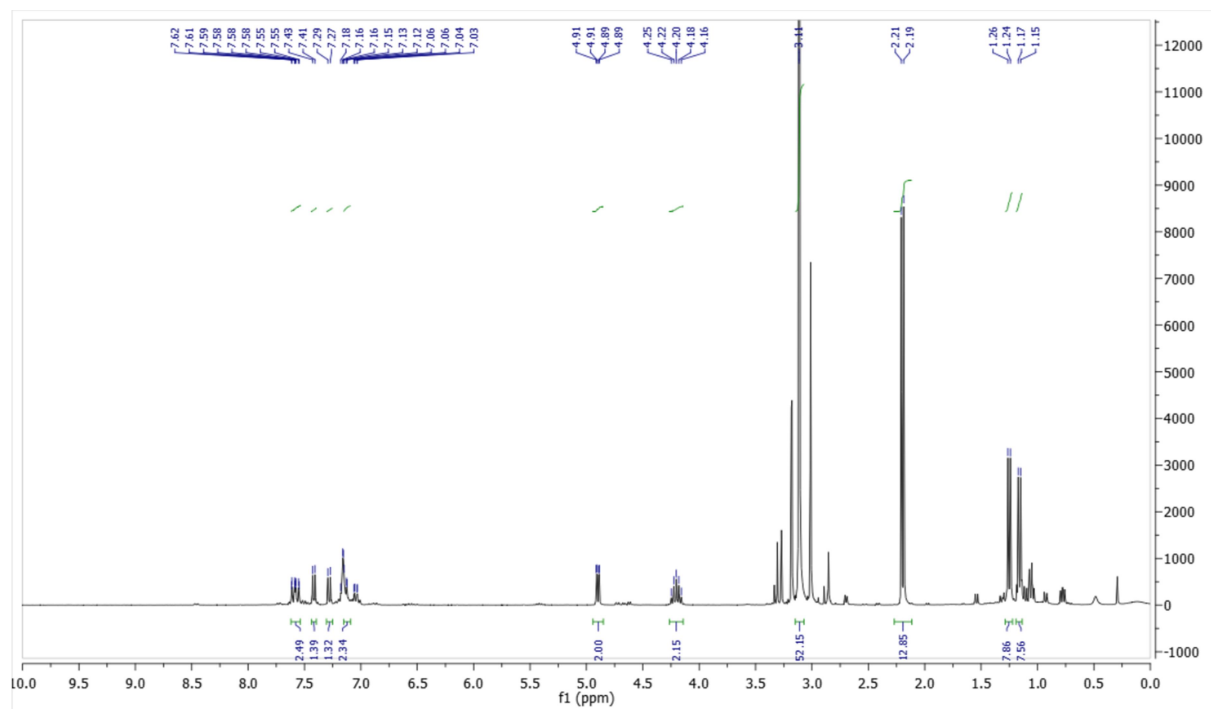


Figure S36: 1H NMR (C_6D_6 , 300 MHz) spectrum of *N,P,N*-complex 4-98.

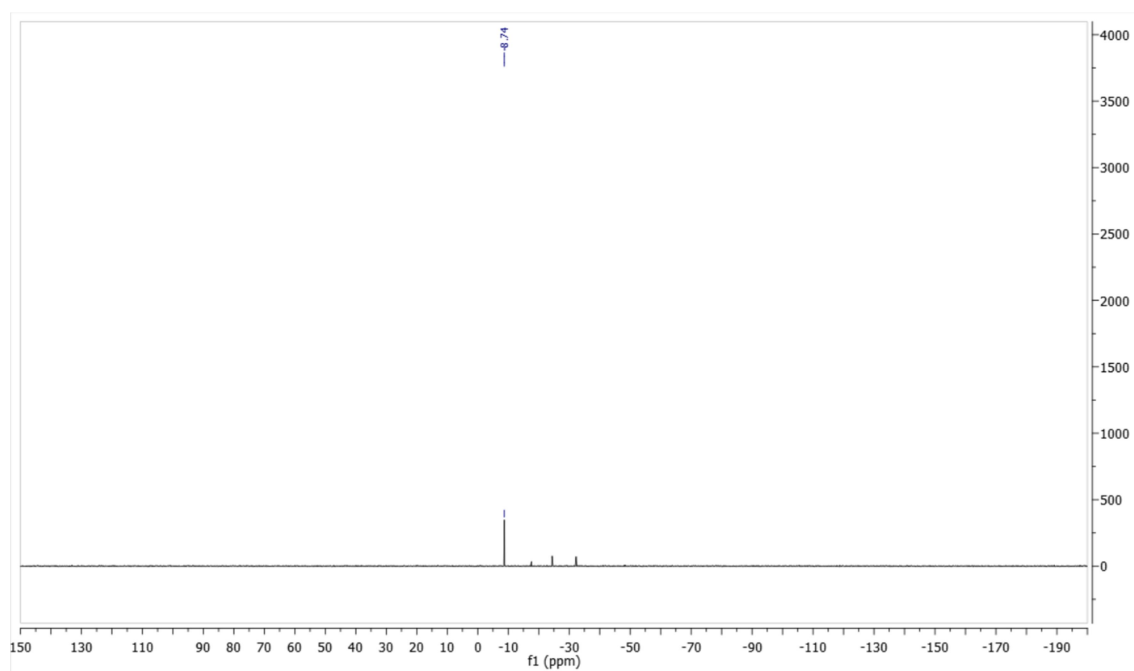


Figure S37: $^{31}P\{^1H\}$ NMR (C_6D_6 , 121 MHz) spectrum of *N,P,N*-complex 4-98.

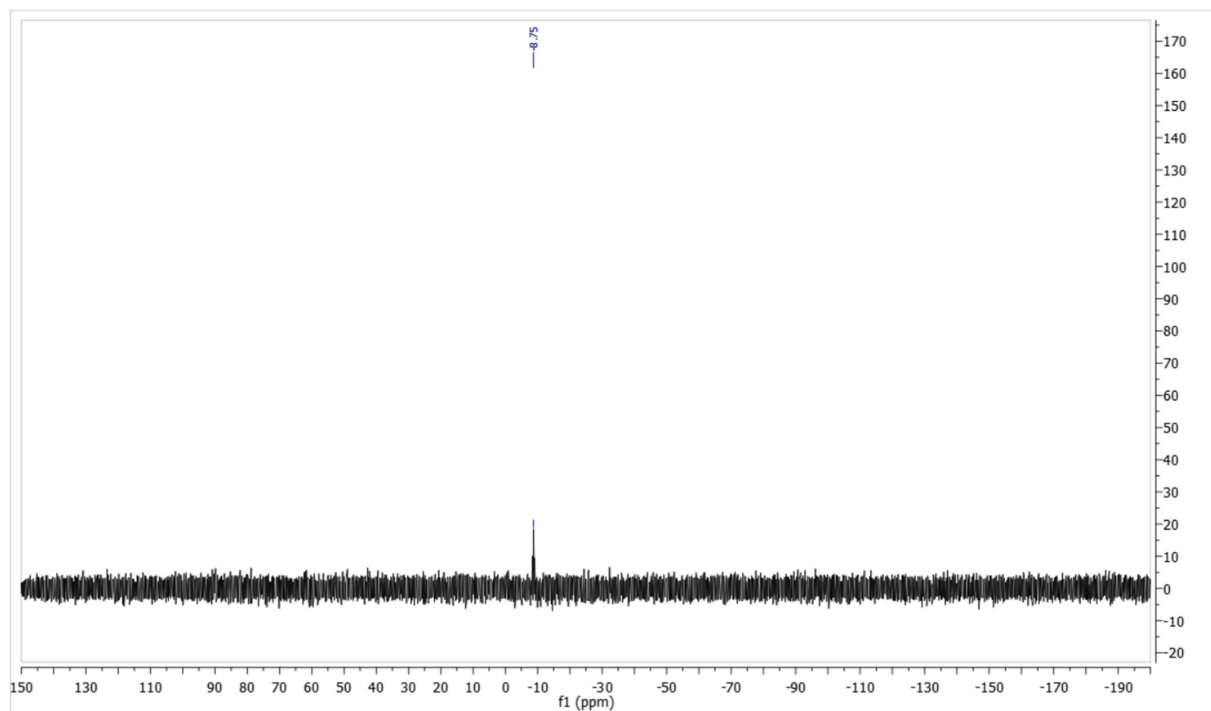


Figure S38: ^{31}P NMR (C_6D_6 , 121 MHz) spectrum of *N,P,N*-complex 4-98.

6.4.5 Solid State Molecular Structure and X-Ray Crystallographic Data of *N,P,N*-complex 4-96

Single crystals were obtained at $-30\text{ }^\circ\text{C}$ in HDMSO. Resolution of the structure was performed by intrinsic phasing using SHELXT. Refinement and atomic model construction were performed using OLEX.refine³⁸⁵ from OLEX2 software. Crystallographic parameters are reported in Table S2.

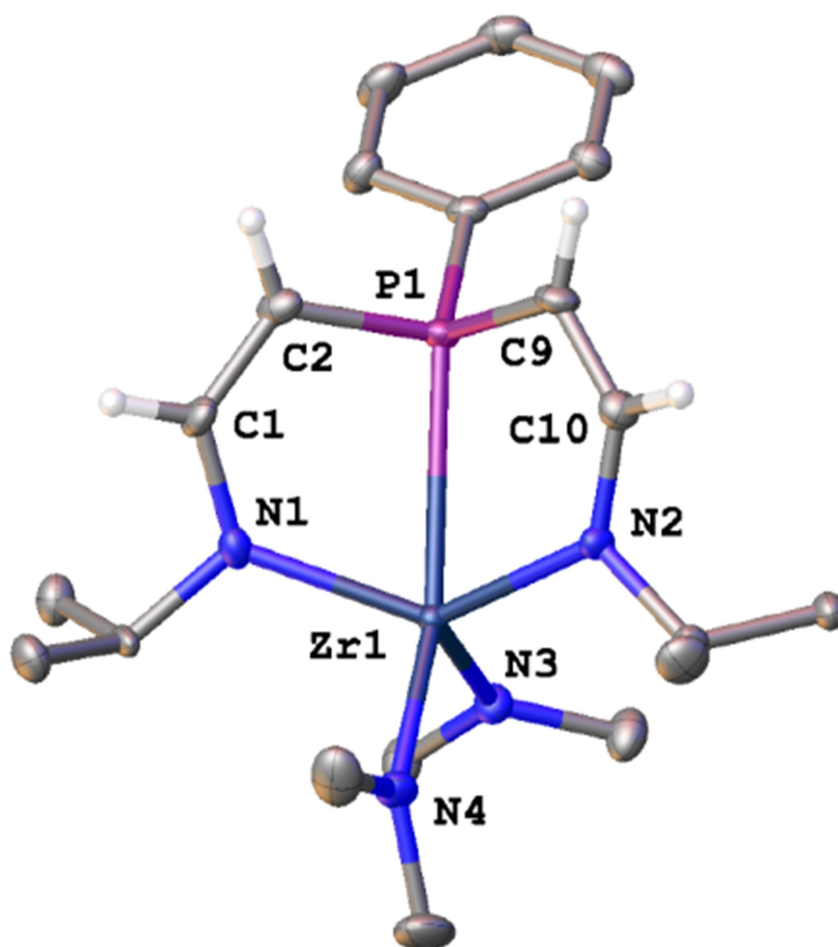


Figure S39: ORTEP representation of the solid-state molecular structure of 4-95 in crystals. Ellipsoids drawn at 50% probability. All hydrogen atoms besides the hydrogens on C1, C2, C9 and C10 have been omitted for clarity. Selected bond lengths (Å): Zr1-P1: 2.8170(12), Zr1-N1: 2.152(4), Zr1-N2: 2.140(4), Zr1-N3: 2.016(4), Zr1-N4: 2.068(4), C1-C2: 1.362(7), C9-C10: 1.358(7), and selected bond angles (°): N1-Zr1-P1: 72.56(11), N4-Zr1-N3: 101.43(17), N2-Zr1-P1: 71.58(10), N2-Zr1-N1: 130.17(15), N3-Zr1-N1: 113.51(16), N3-Zr1-P1: 107.88(12), N4-Zr1-P1: 150.69(13), N4-Zr1-N1: 96.23(16), N4-Zr1-N2: 98.44(15), N3-Zr1-N2: 109.72(15), C2-C1-N1: 124.7(4), C9-C10-N2: 124.9(4), C11-N1-Zr1: 121.5(3), C14-N2-Zr1: 117.6(3).

Compound	<i>N,P,N</i> -complex 4-95
Empirical formula	C ₂₀ H ₃₅ N ₄ PZr
Formula weight	453.73
Temperature (K)	273.15
Color, habits	Colorless, irregular
Crystal system	Triclinic
Space group	<i>P</i> (-1)
<i>a</i> (Å)	9.288(4)
<i>b</i> (Å)	9.316(4)
<i>c</i> (Å)	14.058(7)

α (°)	80.253(10)
β (°)	85.140(10)
γ (°)	78.967(10)
Volume (Å ³)	1175.00(9)
Z	2
ρ_{calc} (g.cm ⁻³)	1.282
μ (mm ⁻¹)	0.547
F (000)	470
Crystal size (mm ³)	0.08x0.08x0.08
Radiation	Mo K α (λ = 0.71073)
2 θ range for data collection (°)	1.47 to 30.03
Index ranges	-12 \leq h \leq 13, -12 \leq k \leq 13, 0 \leq l \leq 19
Reflections collected	24364
Independent reflections	6841 (R_{int} = 0.0614, R_{sigma} = 0.0546)
Data/restraints/parameters	6841/0/243
Goodness-of-fit on F^2	1.056
R_1 (F^2 , all data)	0.0942
wR_2 (F^2 , all data)	0.1698
R_1 (F, [$I \geq 2 \sigma(I)$])	0.0668
wR_2 (F, [$I \geq 2 \sigma(I)$])	0.1569
Largest diff. peak/hole (e Å ⁻³)	3.388 / -1.765

Table S15: Crystallographic parameters of *N,P,N*-zirconium complex 4-95.

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Etude Fondamentale et Application en Catalyse de Métaux de Transition Précoces Complexés à de Nouveaux Ligands Hénilabiles contenant des Hétéroéléments

De récents travaux ont mis en évidence l'augmentation de l'activité catalytique des catalyseurs contenant un centre métallique électrophile induit grâce aux ligands. L'insertion d'un atome de bore dans ces complexes métalliques représente une approche pertinente pour augmenter la nature électrophile de ces complexes grâce aux propriétés intrinsèques de l'atome de bore. Cependant, peu d'exemples de tels complexes métalliques sont décrits dans la littérature. Au cours de cette thèse, nous nous sommes intéressés à de nouveaux ligands hénilabiles pour la catalyse en hydrofonctionnalisation *via* l'emploi de la chimie des hétéroéléments. La préparation de 1,3-*N,O*-chélates a été investiguée en développant une méthodologie de synthèse de ces ligands borés basée sur la réaction de Friedel-Crafts. Leur réactivité a ensuite été étudiée pour la formation de complexes avec des métaux de transition précoces des groupes 4 (titanium, zirconium). Ces travaux ont été transposés au développement de ligand borés de type 1,3-*N,N*-chélates à partir de boraamidines cycliques ou acycliques. La réactivité de ces ligands avec des métaux de transitions précoces a été étudiée, puis appliquée à des réactions d'hydrofonctionnalisation telle que la réaction d'hydroaminoalkylation. Ces travaux ont conduit au développement d'une autre famille de catalyseurs contenant un atome de phosphore : les β -aminophosphines. La réaction d'hydroamination a permis d'accéder à une nouvelle voie de synthèse de ligands de type *N,P,N*, économe en atome à 100%. L'accès aux complexes métalliques *N,P,N* a été étudié et réalisé par une réaction de protonolyse en présence de titane et de zirconium comme métaux de transition précoces.

Mots clés : ligand, hénilabile, hétéroélément, métal de transition précoce, chélate, catalyse, hydroamination, hydroaminoalkylation.

Hemilabile Heteroelement Based Ligands for Transition Metal Complexes, Fundamental and Application for Catalysis

The development of new metal complexes for catalysis containing an electrophile moiety has been studied for many years. To develop new electrophilic metal complexes, the addition of a boron atom –highly electrophilic– would be an interesting approach to obtain new metal complexes. However, only limited examples of such complexes have been described in the literature. This thesis focused on the development of new hemilabile ligands based on the chemistry of heteroelements for catalytic applications such as hydrofunctionalization. First, the development of 1,3-*N,O*-chelates was studied with their reactivity in coordination chemistry using early transition metals like titanium or zirconium. A new method based on the electrophilic Friedel-Craft cyclization was developed using aminochloroboranes formed *in situ* through amineborane complexes. The study of such ligands was extended to the development of new 1,3-*N,N*-ligands, called boraamidines, containing either an acyclic or cyclic backbones. The reactivity toward coordination chemistry was then studied *in situ* for the hydroaminoalkylation catalysis. The last research axis of this thesis focused on the development of another family of catalysts with β -aminophosphines. The hydroamination was used to develop a new synthetic pathway 100% atom economic for their synthesis. Complexation of the *N,P,N*-ligands using early transition metals like zirconium and titanium was then studied to afford new *N,P,N*-complexes.

Keywords: ligand, hemilabile, heteroelement, early transition metal, chelate, catalysis, hydroamination, hydroaminoalkylation.

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