Developing the catalytic asymmetric hydroarsination reaction

Tay, Wee Shan

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SINGAPORE

**DEVELOPING THE CATALYTIC ASYMMETRIC
HYDROARSINATION REACTION**

TAY WEE SHAN

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2020

DEVELOPING THE CATALYTIC ASYMMETRIC HYDROARSINATION REACTION

TAY WEE SHAN

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

A thesis submitted to the Nanyang Technological
University in partial fulfilment of the requirement for the
degree of Doctor of Philosophy

2020

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research done by me except where otherwise stated in this thesis. The thesis work has not been submitted for a degree or professional qualification to any other university or institution. I declare that this thesis is written by myself and is free of plagiarism and of sufficient grammatical clarity to be examined. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

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7 July 2020

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Date

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Leung Pak Hing

7 July 2020

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Date

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Sumod A. Pullarkat

Authorship Attribution Statement

This thesis contains material from seven paper(s) published in the following peer-reviewed journals where I was the first author.

Chapter 1 is published as Tay, W. S.; Pullarkat, S. A. C–As Bond Formation Reactions for the Preparation of Organoarsenic(III) Compounds. *Chem. Asian. J.* **2020**. DOI: 10.1002/asia.202000606.

The contributions of the co-authors are as follows:

- Dr Pullarkat, S. A. revised the manuscript draft,
- I identified the area for review and gathered the relevant literature, and
- I conducted the literature review and prepared the manuscript draft.

Chapter 2 is published as Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. Divergent Reactivity of Phosphapalladacycles toward E–H (E = N, P, As) Bonds. *Organometallics* **2020**, 39, 182. DOI: 10.1021/acs.organomet.9b00723.

The contributions of the co-authors are as follows:

- Dr Li, Y. collected and resolved the X-ray crystallographic data,
- Dr Pullarkat, S. A. revised the manuscript draft and assisted in idea generation,
- Prof Leung, P.-H. revised the manuscript draft and assisted in idea generation,
- I designed the study, performed the experiments and analyzed the results,
- I collected the Nuclear Magnetic Resonance (^1H , ^{13}C and $^{31}\text{P}\{^1\text{H}\}$), High Resolution Mass Spectroscopy and melting point characterization data, and
- I prepared the manuscript draft and Supporting Information.

Chapter 2 is also published as Tay, W. S.; Yang, X.-Y.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. Investigating Palladium Pincer Complexes in Catalytic Asymmetric Hydrophosphination and Hydroarsination. *Dalton Trans.* **2019**, 48, 4602. DOI: 10.1039/C9DT00221A.

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The contributions of the co-authors are as follows:

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- Dr Yang, X.-Y. provided the pincer complexes used in the study,
- Dr Li, Y. collected and resolved the X-ray crystallographic data,
- Dr Pullarkat, S. A. revised the manuscript draft and assisted in idea generation,
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- Dr Lu, Y. contributed the computational calculations,

- Dr Pullarkat, S. A. revised the manuscript draft and assisted in idea generation,
- Prof Leung, P.-H. revised the manuscript draft and assisted in idea generation,
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- I prepared the manuscript draft and Supporting Information.

7 July 2020

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Date

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Tay Wee Shan

Abstract

The asymmetric hydroarsination reaction is arguably the most atom-economical and efficient manner to produce chiral arsines with high enantiopurities. Although various catalysts have been developed for the analogous hydrophosphination reaction, none have been effective for the hydroarsination reaction thus far. Herein, the development of organometallic (Pd- and Ni-based) and organic (phosphine-based) catalytic systems for the hydroarsination reaction is discussed. Mechanistic investigations reveal that arsines were not direct substitutes of phosphines in this instance. Consequently, arsines were applied in several novel applications such as in deuteration, decomplexation and as a directing group. The relevance of these developments to general synthetic chemistry is also outlined.

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Nomenclature

The nomenclature used throughout the thesis conforms to the format adopted by Chemical Abstracts (Chemical Abstracts, 13th Collective Index, Index Guide, 1992-1996).

X-ray Structural Data

The single crystal X-ray analyses were kindly performed by Dr. Li. Yongxin at the Nanyang Technological University (Division of Chemistry and Biological Chemistry). Full structural data (listings of crystal and refinement data, bond distances/angles, and thermal parameters) are available from Prof. Leung Pak-Hing upon request.

Abbreviations and Symbols

a.u.	arbitrary unit(s)
AIBN	azobisisobutyronitrile
Ar	aryl group
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
bp	boiling point
br	broad
calcd.	calculated
CDCl ₃	chloroform-d ₁
CHCl ₃	chloroform
CD ₃ CN	acetonitrile-d ₃

conc.	concentrated
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
dec.	decomposed
<i>de</i>	diastereomeric excess
DEE	diethylether
DIPEA	diisopropylethylether
dm	decimeter
d	doublet (NMR)
dd	doublet of doublets (NMR)
DMF	<i>N,N</i> -dimethylformamide
EA	ethyl acetate
<i>ee</i>	enantiomeric excess
equiv.	equivalence
ESI-MS	electrospray ionization mass spectrometry
Et	ethyl
g	gram(s)
h	hour(s)
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
Hz	hertz
LMCT	ligand-to-metal charge transfer
m	multiplet (NMR)
Me	methyl
min	minute(s)

mL	milliliter
mmol	millimole(s)
mp	melting point
NMR	Nuclear Magnetic Resonance
Ph	phenyl
ppm	parts per million
Pr	propyl
<i>R</i>	rectus (Latin right absolute configuration)
RT	room temperature
<i>S</i>	sinister (Latin left absolute configuration)
s	singlet (NMR)
t	triplet (NMR)
T	temperature
THF	tetrahydrofuran
TMS	tetramethylsilane
δ	NMR chemical shift in ppm
°	degree of angles
Å	angstrom(s)
°C	degree Celsius
$[\alpha]_D^T$	specific rotation measured at sodium D line (589 nm), at temperature T
μL	microlitre

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Summary

This thesis is a compilation of research conducted over a period of three and a half years targeting the development of the catalytic asymmetric hydroarsination reaction.

In Chapter 1, the central themes of toxicity and speciation in arsenic chemistry are raised to frame the importance of the chosen research topic. Following which, a thorough literature review of various As–C bond formation methods *via* substitution, addition, metal-mediated, and radical reactions is presented. The catalytic asymmetric hydroarsination reaction is identified as a promising alternative for greener As–C bond formation. Subsequently, relevant research by our group involving the stoichiometric asymmetric hydroarsination reactions and catalytic asymmetric hydrophosphination reactions are summarized. The aims and objectives of the project are rationalized based on recent developments in these areas.

In Chapter 2, strategies involving the direct application of Pd-catalyzed asymmetric hydrophosphination conditions for hydroarsination are explored. In the first section, bidentate palladacycles are explored as potential hydroarsination catalysts. The fates of these bidentate complexes are investigated with deuterium labelling to propose key interactions between the palladacycle and secondary arsine reagent. In the second section, tridentate palladacycle catalysts are employed for the hydroarsination of α,β -unsaturated enones. A mechanism is proposed based on a series of controlled experiments observed by NMR spectroscopy. Notable differences in the workup and handling of phosphines and arsines are identified.

In Chapter 3, tridentate nickel-based pincer complexes are explored as a cheaper alternative to palladium. Mechanistic investigation involving computational calculations are conducted to rationalize the observed differences in reactivities. X-ray crystallographic data is presented as evidence of the dissimilarity between phosphines and arsines with respect to

structure and bonding. A variety of functionalized nitrostyrenes are screened to demonstrate the synthetic potential of the methodology.

In Chapter 4, non-transition metal-based strategies are explored for the catalytic asymmetric hydroarsination reaction. In the first section, tertiary phosphines are investigated for their potential as organocatalysts in the hydroarsination of nitrostyrenes. A mechanism is proposed based on a significant side reaction observed. In the second section, a substrate-controlled diastereoselective As–C bond formation strategy is explored. An unexpected side reaction leading to structurally interesting products is identified. A mechanism is proposed and 2D Nuclear Overhauser Effect Spectroscopy experiments are conducted to elucidate the solution-state structure of the cyclic products.

In Chapter 5, synthetic applications of the hydroarsination reaction is explored. Based on various limitations identified thus far, the hydroarsination reaction is employed to prepare highly-functionalized β -oxovinylarsines as an improved air-stable arsine precursor. The preparation of both *E*- and *Z*-isomers are outlined. Controlled experiments are conducted to rationalize the catalyst-free formation of the thermodynamically less-favoured *Z*-isomer. The reactivity of β -oxovinylarsines is evaluated with model nucleophilic, electrophilic and transition metal-based reagents.

In Chapter 6, developments presented in Chapters 2 to 5 are assessed. The three catalytic systems are first evaluated against the 12 Principles of Green Chemistry. The results attained from their respective optimized conditions are summarized and the formation of key active catalytic intermediates are reiterated. Secondly, new reactivities observed of secondary arsines are compiled to highlight their contributions to the field. Lastly, future work for the synthesis and application of chiral arsines are outlined.

Chapter 1

Introduction

1.1 Central themes in arsenic chemistry

A few recurring themes have appeared over the course of arsenic's history. These themes have posed challenges to both previous and current research and remains to be satisfactorily addressed even today. It is imperative that future work is directed at minimizing or even resolving the innate challenges of the field. A brief overview regarding the underlying themes of toxicity and speciation of arsenic has been provided to offer a better perspective on why these are central in guiding the development of new synthetic methods for organoarsine compounds.

1.1.1 Toxicity

Arsenic-containing compounds are almost ubiquitously associated with toxicity. Chronic exposure to arsenic and its derivatives has been identified as the largest environmental health hazard in the world with up to 100 million people at risk of arsenic-related diseases.¹ For its frequency, toxicity and potential for human exposure, arsenic has been ranked first in the latest United States Agency for Toxic Substances and Disease Registry's Substance Priority List, coming ahead of lead (2nd place), mercury (3rd place) and cyanide (35th place).² The adverse health effects associated with acute and chronic exposure to sources of arsenic have been well-documented. Other than immediate symptoms of vomiting, abdominal pain and diarrhoea,³ exposure to arsenic has also caused cancers of the bladder, lungs and skin,⁴ diabetes,⁵ and cardiovascular disease.⁶ Comparatively much less is known regarding arsenic's role in human pathology and toxicology- not just collectively but as each individual elemental, organic and inorganic derivative. This is also complicated by facile interconversion of one

arsenic species to another, thus making it difficult to correlate an identified mode of action to a single arsenic species (see Section 1.1.2 regarding arsenic speciation). Nevertheless, several interactions of arsenic-containing compounds with the human body have been highlighted on account of the extensive research that has been conducted in their respective areas.

The structural similarity of arsenate to phosphate has been documented to affect many biochemical reactions involving phosphate-containing receptors, enzymes or transport channels.⁷ For example, this is observed in the biosynthesis of glucose-6-arsenate and 6-arsenogluconate which competitively inhibits dehydrogenase enzymes of glucose-6-phosphate and 6-phosphogluconate respectively.⁸ Phosphate ions in sodium pumps and anion exchange transport systems were documented to be prone to replacement by arsenate.⁹ When chemically incorporated into biomolecules such as ATP,¹⁰ hydrolysis leading to release of arsenate was proposed to be a result of the weaker As–O bond strength.⁷ Consequently, ATP could not be generated *via* substrate phosphorylation when arsenate was present instead of phosphate.¹¹ With the phosphate ion being a key component of many metabolic processes and biomolecules of the human body such as ATP, DNA, RNA, the effect of arsenate is both multifarious and extensive. Significant controversy was generated when a bacterium GFAJ-1 was claimed to use arsenate in place of phosphate in its DNA.¹² The study has since been disproven,¹³ which reinforced the hazardous consequences of replacing phosphate with arsenate in biomolecules and metabolic pathways.

The toxicity of trivalent arsenic species is widely believed to arise from their ability to chemically bind to sulfhydryl groups in peptides and proteins.¹⁴ The chemical warfare agent Lewisite decomposed the pyruvate dehydrogenase multienzyme complex by ring formation between two distal thiol groups.¹⁵ Three-dimensional structural modification caused by arsenic binding lead to a loss of function by altering the protein's interaction with other biomolecules.¹⁴

Up to 200 enzymes have been proposed to be affected by trivalent arsenic compounds, explaining its multifaceted effects on the human body.¹⁶

The carcinogenic properties of arsenic-containing compounds have been proposed to be a result of several different pathways. Defining a mechanism for arsenic carcinogenicity has been challenged by 1) the lack of evidence for arsenic being a point mutagen, 2) the cascade effect of arsenic on cell signaling, 3) negative results for carcinogenic effects in a standard animal bioassay, and 4) interference by other toxic metabolites of the original arsenic source.¹⁷ The complexity of arsenic-induced cancers was evident from an overview of the various proposed mechanisms. Genotoxicity has been identified for trivalent methylated arsenicals upon observing their ability to nick supercoiled DNA and damage human lymphocyte DNA.¹⁸ Chromosomal aberrations induced by DNA cross-linking agents in lymphocytes¹⁹ and fibroblasts²⁰ were potentiated by sodium arsenite. Oncogene amplification in animal and human tumors suggested that arsenic-induced gene amplification was a possible mechanism.²¹ Arsenicals may also inhibit DNA repair²² or decrease the activity of DNA ligase,²³ thus causing cancer by altering gene-repair pathways. DNA methylation, which has been identified to play a prominent role in cancer development,²⁴ has been observed to be both up- and down-regulated by arsenite in the DNA of human lung cells.²⁵ Arsenic may also directly cause oxidative stress or inhibit reductases thereby decreasing the ability of cells to protect themselves against oxidation.²⁶

Lastly, the toxicity of arsenic has been exploited in its use as chemical warfare agents. Severe symptoms rapidly developed upon exposure to arsenic warfare agents.²⁷ These agents were classified under categories depending on their mode of action. For instance, blistering agent Lewisite caused painful blisters upon contact with the skin and irritated the lungs by causing swelling, inflammation and destruction of the airway lining.²⁸ Vomiting agents Clark I, Clark II and Adamsite caused nausea, vomiting, diarrhea, abdominal cramps, headaches and

mental status changes for several hours after exposure through inhalation, ingestion or skin contact.²⁹ Similarly, Dick and Methyldick were highly toxic and potentially fatal if inhaled, ingested or absorbed through skin.³⁰ While these agents typically possessed As–Cl bonds (Figure 1), their mode of action goes beyond the effects of HCl released upon As–Cl bond

Figure 1. Chemical structures of arsenic warfare agents.

hydrolysis.³¹ For example, exposure to Lewisite may cause the development of refractory hypotension, hypovolemia and kidney damage as well.³²

Many other arsenic-containing compounds exist beyond the listed examples, making it almost impossible to characterize every single compound. This is particularly relevant in the development of Safety Data Sheets for specially-designed chemicals in academic research. In place of a full toxicology profile, lethal dose, 50% (LD₅₀) values may serve as a convenient indicator. This is advantageous in benchmarking the lethality of arsenic compounds against other poisons such as cyanide, cadmium oxide, mercury chloride and strychnine.³³

Despite the documented tendency of arsenic to be unfavourable for human health and the environment, the toxicity of arsenic-containing compounds has been constructively employed on occasion. Arsenic trioxide was used to control rat populations to curb the spread of the European bubonic plague.³⁴ Lead arsenate was used as a pesticide against underground worms and as a herbicide against common weeds such as crab grass and dandelions.³⁵ Copper acetoarsenite (otherwise known as Paris Green) was once widely used in North America as a pesticide and fungicide in the late 1800s.³⁶ Monosodium methanearsonate was employed in hopes of eradicating a mountain pine beetle infestation of British Columbia's pine forests.³⁷

While such remedies have enjoyed some success, they were often discouraged for the arsenic introduced into the environment. As wryly put by Konkola during the years of the Black Death: “it just might be that the beginning of industrial-scale toxic pollution brought about a vast improvement in the health conditions of Europe”.³⁴

In addition, arsenic-containing pharmaceuticals have also been developed and the intriguing observation of therapeutic effects deserves some mention. Arsenic trioxide (As_2O_3) has been used to treat patients suffering from acute promyelocytic leukemia. While the binding of arsenic to sulfhydryl groups of proteins was identified as hazardous,¹⁴ arsenic trioxide was proposed to achieve therapeutic effect from the same arsenic binding in zinc fingers of the aberrant promyelocytic leukemia-retinoic acid receptor (PML-RAR) fusion protein expressed in patients.³⁸ Other arsenic-containing drugs such as Atoxyl, Melarsoprol, Salvarsan and Tryparsamide have also been investigated.³⁹ The observed clinical activity undoubtedly provides compelling reason to explore the design and synthesis of arsenic compounds such that well-controlled reactivity may be achieved for functional utility.

1.1.2 Speciation

The toxicity associated with certain compounds of arsenic is irrefutable. Perpetuated by sweeping statements of toxicity, arsenicals have been stigmatized without regard to widely differing individual properties. Even within the scientific community, *total elemental arsenic* levels are often used to conveniently characterize a given sample,⁴⁰ despite its inability to acknowledge that toxicities differ between individual arsenicals.⁴¹ This is in part limited by the inability of quantitative analytical methods (eg. colourimetric techniques or spectroscopic methods involving inductively coupled plasma) in determining the identity of compounds present in the sample.⁴² Efforts have been made to develop specialized techniques for the speciation of arsenic-containing compounds in a given sample.⁴³ High performance liquid chromatography with inductively coupled mass spectroscopy (HPLC-ICP-MS) is the most

commonly employed method although two limitations have been identified: 1) an extraction step (usually from a solid sample) is required for sample preparation which, upon incomplete extraction or chemical alteration, might not be representative of the actual arsenic species originally present, and 2) it provides no structural information because identification is made based on matching sample peaks to a standard.⁴⁴ Consequently, several speciation methods have been developed for samples collected from specific areas of concern (eg. groundwater, paddy rice, landfill leachate, aquatic environment systems and seafood). The challenges and consequences of accurate arsenic speciation have been highlighted accordingly.

In West Bengal, groundwater supply wells provide fresh water for families with no access to a municipal water supply.⁴⁵ For such wells drawn from alluvial aquifers, *total elemental arsenic* levels can exceed up to 100 times the recommended value ($10\mu\text{g L}^{-1}$), threatening the health of up to 70 million people.⁴⁶ Since As(III) sources are more toxic than sources of As(V),^{17,47} proper speciation was required to quantify As(III) and As(V) species separately. From evaluating contradictory information regarding appropriate sample preservation/preparation and analytical techniques, Korte and Fernando concluded that reported occurrences of As(V) might have been predominantly As(III) instead.⁴⁸ With variables such as composition of the sample, concentration, pH or even exposure to sunlight, the absence of a universal sample preparation method meant results differed greatly across different studies.⁴⁸ Nevertheless, sample preparation was necessary because the detection limits of available analytical techniques were above the concentrations of most forms of arsenic present.⁴⁹ In addition, separation and analysis processes were highly diverse as well because analytical techniques had to account for interferences from confounding variables.⁵⁰ As such, different separation methods (eg. electrophoresis, gas chromatography, high pressure liquid chromatography, ion exchange column chromatography) introduced variables which limited cross-study comparisons. Recently, multivariate statistical techniques have been employed to

identify correlations between arsenic levels obtained from different sampling sites.⁵¹ Nevertheless, inaccuracies introduced during the sample collection, treatment and analysis process still remain a challenge for quantitative speciation of arsenic compounds in groundwater today.

Speciation techniques developed for a certain sample source (eg. groundwater, landfill leachate, rice) were not transferrable to one another. For example, groundwater samples often have lower-than-detectable levels of arsenic and face contamination by other non-native sources of arsenic (eg. trialkylarsines, trialkylarsine oxides, arsenobetaine). As such, groundwater sample preparation methods involve concentration and separation techniques. On the other hand, landfill samples contain colloids, solutions and particulate matter which required specialized attention in extraction and physical fractionation methods, making groundwater sample preparation methods inapplicable.⁵² Since no standardized procedure was available and free arsenic ions made up less than 10-30% of total arsenic concentration, quantified arsenic levels were prone to significant error.⁵² Even amongst key studies on metal speciation in landfill leachate,⁵³ significant variations exist with regard to data sets, sample preparation and data analysis. These variations include 1) classifying the heavy metals into groups or none at all, 2) the extent to which computer speciation models are used, 3) the extent to which a sample is spiked to increase concentrations to detection limits, and 4) extent of sample dilution by groundwater.⁵² The difficulty this imposes on comparing the conclusions of key studies highlight how speciation hinders an accumulation of scientific knowledge required to assess long-term environmental effects that landfills exert on neighboring terrestrial environments and water bodies.

Speciation utilized to evaluate the risk posed by an accumulation of arsenic in farmed crop was similarly challenged by a unique set of problems. Firstly, individual varieties of crop (eg. rice, vegetables, pulses, spices) accumulated and metabolized arsenic differently.

Speciation was necessary to distinguish between the more-toxic As(III) species from As(V) before and after plant metabolic processes.⁵⁴ Secondly, crops could be grown from aquifers that were or were not contaminated by arsenic, with different irrigation practices, during different (dry or wet) seasons. Finally, such agricultural produce were often cooked prior to consumption which affected arsenic speciation.⁵⁵ Smaller-scale studies were conducted to accurately estimate the human exposure of inorganic arsenic which consequently led to many repetitive, laborious and time-consuming studies before an overall picture could be provided.⁵⁶

In aquatic environments, sources of arsenic include treated or untreated human waste, agricultural chemicals and natural geological sources which introduced an exceptionally wide spectrum of arsenic-containing species.⁵⁷ At least fifteen unique arsenic-containing compounds have been identified to be of appreciable concentrations thus necessitating speciation prior to evaluating the risk in such environments.⁵⁷ Water parameters and amounts of organic matter, adsorbents, phosphates and sulfides all influenced the speciation of arsenic samples in a dynamic and interwoven manner.⁴⁹ Resultant strategies for arsenic remediation and removal (eg. using adsorbants,⁵⁸ chemical oxidation,⁵⁹ phytoremediation,⁶⁰ photocatalytic oxidation techniques)⁶¹ depended heavily on accurate speciation of arsenic.

Lastly, seafood has been an intriguing category for arsenic speciation. Arsenobetaine, a non-toxic arsenic analogue of betaine,⁶² is commonly encountered in marine life. *Total arsenic levels* determined for seafood often wrongly indicate the imminent threat posed by apparent high concentrations of total arsenic.⁶³ Speciation was complicated by the additional influence of culinary treatment which introduced variations in pH or organic matter present in the sample.⁶⁴ Quantitative measurements also needed to account for arsenic-extraction processes during cooking (by oil, water, butter)⁶⁵ or mass changes (by water loss, protein coagulation, or absorption of oil during frying)⁶⁶ in the cooking process before a reliable recommendation could be issued regarding the acceptable “safe” levels of seafood to ingest.

The importance of accurate speciation is evident to avoid mistaken conclusions regarding permissible safe levels and potential adverse effects on human health and the environment. An understanding of the challenges faced in arsenic speciation offered some perspectives on synthetic organoarsenic chemistry. Firstly, the blanket claim regarding the toxicity of arsenic compounds should be moderated by the knowledge that some (albeit few) arsenicals are characteristically non-toxic.⁶⁷ Unless explicitly demonstrated, synthetic methodologies should not be negatively evaluated based on apparent “toxicity”. Developments in arsenic chemistry should not also be shunned, especially in favour of phosphorus analogues instead. Arsenic-based chemical warfare agents are often cited as a representative example for the hazards of arsenic-containing compounds,⁶⁸ yet phosphorus compounds (eg. sarin, VX and Novichok nerve agents) are rarely discussed.⁶⁹ Speciation is rarely a problem in organoarsenic synthetic chemistry because of the many complementary characterization techniques available (eg. NMR spectroscopy, mass spectroscopy, elemental analysis, X-ray crystallography) and thus, organoarsenic compounds should not be treated in an *all-in-one* manner. Lastly, developments in synthetic arsenic chemistry should focus on reducing arsenic-containing waste. Even with proper containment and disposal, challenges in arsenic speciation mean that new species arising out of processed waste may go unnoticed, eventually leaching out of landfills and into the environment.⁷⁰ Needless to say, atom-economical and high-yielding protocols are exceptionally relevant in organoarsenic chemistry to minimize byproducts of such reactions.

1.2 Syntheses of organoarsine compounds

With an electronegativity of 2.18,⁷¹ arsenic is less electronegative than nitrogen, oxygen, halogens and even carbon. Three oxidation states, As(I), As(III) and As(V), typically manifest in organoarsenic compounds. For clarity, several representative examples of organo-As(I), As(III) and As(V) compounds have been highlighted in Figures 2-4.

Organoarsenic compounds of As(I) typically feature 3 bonds, two of which are single As–As bonds while the other is necessarily an As–C bond (Figure 2). This characteristic

Figure 2. Representative examples of organoarsenic(I) compounds.

bonding mode is clearly observable in the oligomeric structures of Salvarsan which was first introduced in the early 1910s as a treatment for syphilis.³⁹ Originally proposed to be a dimeric structure consisting of As=As bonds, this has since been disproven after a detailed investigation was conducted on its structure by mass spectrometric methods.⁷² Consistent with the classical “double bond rule”,⁷³ Salvarsan was eventually acknowledged to consist of a mixture of the cyclic trimer and pentamer.

Organic compounds of As(III) are by far the most common oxidation state of organoarsenic compounds in synthetic chemistry (Figure 3). With a minimum of one As–C

Figure 3. Representative examples of organoarsenic(III) compounds.

bond, the other two arsenic-containing bonds can involve other elements which are more electronegative than arsenic, making bonds of As–C, As–O, As–N and As–halogen common amongst organoarsine compounds. Triphenylarsine is a straightforward example of an organoarsenic(III) compound with three As–C bonds. A structural analogue of triphenylphosphine, triphenylarsine is a common ligand for transition metal catalysis and has even been demonstrated to occasionally outperform its phosphine counterpart.⁷⁴ Arsenicin A,

a 3-dimensional caged structure consisting of As–C and As–O bonds,⁷⁵ is a natural product isolated from marine sponge *Echinochalina bargibanti*.⁷⁶ As a chiral molecule with no internal plane of symmetry, its structural complexity is an outstanding example of an asymmetric naturally-occurring organoarsenic compound. The stereoselective synthesis of Arsenicin A was eventually accomplished by Wild in 2010.⁷⁷ Subsequently, this methodology gained recognition when Arsenicin A demonstrated chemotherapeutic activity against promyelocytic leukemia cells at lower concentrations than Trisenox (As₂O₃).⁷⁷ Aromatic compounds of As(III) such as arsole are also known. A metallole isoelectronic to pyrrole, arsole only features 40% the aromaticity of pyrrole.⁷⁸ Due to poor aromatic stabilization, derivatives of arsole have been used as a diene in Diels Alder reactions to incorporate As atoms into bridged structures.⁷⁹ Lastly, BINAs is an example of a bidentate chelating ligand of As(III) analogous to the widely-popular axially-chiral ligand BINAP, synthesized from BINOL as a starting precursor.⁸⁰ This highlights the importance of accessible As–C bond formation methodologies such that desired scaffolds can be intentionally designed and synthesized.

As(V) is the highest oxidation state attainable for organoarsenic compounds. Compounds of As(V) containing only bonds to carbon are rare (Figure 4). Instead, most are

Figure 4. Representative examples of organoarsenic(V) compounds.

hydroxyarsenic acids of the type R₂As(O)OH or RAs(O)(OH)₂. For example, Roxarsone first surfaced as an additive in poultry feed but was recently banned due to controversy regarding the accumulation of inorganic arsenic in livestock meant for human consumption.⁸¹ The water-soluble phenylarsonic acid motif is also observable in the Thorin scaffold. As an arsenical, Thorin is classified accordingly under hazard class 6.1 in the MSDS and use of Thorin as an indicator in spectrophotometry is cautioned against.⁸² Lastly, arsenobetaine is an example of a

naturally-occurring organoarsenic compound of As(V) predominant in marine life.⁸³ Being the arsenic analogue of betaine, is biosynthesized in a similar manner.⁸⁴ In the zwitterionic form, arsenobetaine can be classified as an arsonium compound- identified and characterized by the quaternary positively charged arsenic atom. Its apparent lack of observed toxicity has been the subject of interest for many years even up till today.^{1,85}

The following subsections focus on the synthesis of organoarsenic(III) compounds from various arsenic precursors. These arsenic precursors may be of +1, +3 or +5 oxidation states and changes in oxidation state were occasionally encountered. However, the focus remains on As–C bond formation and thus, redox transformations without explicit As–C bond formation has been excluded.

1.2.1 Substitution reactions

Both nucleophilic and electrophilic substitutions have been reported to occur at the As(III) center. Arsenic functionalized with a halide leaving group R_nAsX_{3-n} ($X = Cl, Br, I$) were compatible with carbanion nucleophiles for As–C bond formation. In the presence of $tBuLi$, a double substitution of As–Br bonds of dibromophenylarsine **2** was achieved with a carbanionic derivative of binaphthyl **1**, affording cyclic arsine **3** in 52% yield under mild conditions (Scheme 1).⁸⁶ Although straightforward in terms of the choice of nucleophile,

Scheme 1. Nucleophilic substitution of $PhAsBr_2$ with a strong carbanion.

As–C bond construction involving arsenic halides have since fallen out of favour due to the high toxicities associated with arsenic halides.⁶⁸ Instead, cyclooligoarsine precursors **4** have been developed by Naka and coworkers to generate reactive arsenic iodide species in situ, thus eliminating the need to weigh and handle arsenic halide reagents directly.⁸⁷ In the presence of

iodine, cyclooligoarsine **4** generated phenylarsenic iodide **4'** which demonstrated similar reactivity to typical arsenic halides (Scheme 2). Reacting iodide **4'** with a carbanion afforded

Scheme 2. In-situ iodination of cyclooligoarsines.

cyclic arsine **6** in good yields of 89%.^{87a} In this aspect, cyclooligoarsines **4** are remarkably successful in emulating characteristics of arsenic halide reactions such as short reaction times and well-controlled reactivity under mild conditions. Notable benefits of this synthetic methodology include the convenience of handling bench-stable and non-volatile solids of cyclooligoarsines as opposed to hazardous and moisture-sensitive arsenic halide reagents. On the other hand, progress has yet to be made regarding the commercial unavailability of cyclooligoarsines. Their preparation from arsonic acids limit cyclooligoarsines to only phenyl derivatives because of the lack of other functionalized arsonic acids.

Alternatively, arylarsine oxides may be considered as synthetic equivalents of arsenic halides. Although anhydrous arylarsine oxides are often depicted as containing a π -bond, spectroscopic experiments have shown that arylarsine oxides exists as well-defined oligomers $(\text{ArAsO})_x$ in both solid and solution states (Figure 5).⁸⁸ Sequential cleavage of polarized

Figure 5. Oligomeric structure of arylarsine oxides.

As–O σ -bonds by carbanion reagents can yield the desired As–C bond. Substitution of As–O bonds was first demonstrated by Blicke with the use of Grignard reagents.⁸⁹ Under a large excess of phenylmagnesium bromide, a single As–O bond cleavage of arylarsine oxide **7** afforded diarsine oxide **8** in moderate yield of 44% (Scheme 3). The second As–O bond was

Scheme 3. Single As–O bond cleavage.

more resistant to bond cleavage and triphenylarsine **9** was only obtained under reflux (Scheme 4). Although such methodologies afforded the organoarsine products in moderate to excellent

Scheme 4. Double As–O bond cleavage.

yields, only symmetrical substitution at the As(III) center was possible which made such methods poorly adapted for asymmetric synthesis. To address the challenging second As–O bond cleavage, Keller and coworkers explored the use of di-Grignard reagents in an intramolecular di-substitution reaction at the As atom.⁹⁰ Cyclic organoarsines **11** were successfully isolated without reflux conditions, albeit in poor yields of 9–43% (Scheme 5).

Scheme 5. Addition of di-Grignard reagents to arylarsine oxide.

Increasing the temperature did not improve yields further because of suspected polymerization of the arsine oxide reagent. Although this was not explored by Keller, unsymmetrically substituted di-Grignard reagents may present a possible avenue for the synthesis of chiral cyclic arsines bearing central chirality on As. In the same report, Keller also evaluated the performance of arylarsine oxides **7** versus traditional arsenic halides (Scheme 6). Using the same di-Grignard reagent **10**, arylarsine oxides afforded products in slightly lower yields. No mention was made regarding the possible (polymeric) side products arising from arylarsine oxide **7**. Nevertheless, Keller maintained that the safety benefits of using air-stable arylarsine

Scheme 6. Comparing arsenic halides and arsenic oxides.

oxides far outweighed their lower reactivity especially in larger-scale preparations.⁹¹

Arsenic nucleophiles have also been developed for As–C bond formation by substitution reactions. For example, a reactive lithium arsenide species **12'** was generated in situ from the deprotonation of secondary arsine **12** by nBuLi (Scheme 7).⁹² Subsequent

Scheme 7. Synthesis of macrocyclic organoarsine via lithium arsenide intermediate.

nucleophilic substitution at a C–Br bond of substrate **13** furnished the eleven-membered macrocyclic arsenic product **14** in 20% yield. Tertiary arsines were also suitable precursors for nucleophilic arsenide species. Unlike from the deprotonation of secondary arsines, potassium diphenylarsenide intermediate **15** was obtained with a single As–C bond cleavage of triphenylarsine **9** by potassium metal under refluxing dioxane. This arsenide intermediate then reacted with aziridine in a ring-opening reaction to afford aminoarsine **17** in 32% yield (Scheme 8).⁹³ Other alkali metals (eg. Li, Na) (occasionally in combination with liquid

Scheme 8. Potassium arsenide intermediate generated from triphenylarsine.

ammonia) have also been used to generate metal arsenides from tertiary arsines.⁹⁴ On a separate note, such As–C bond cleavage of tertiary arsines by alkali metals have also been adapted to synthesize secondary arsines by quenching the intermediate arsenide with H₂O.⁹⁵ Reactions proceeding by arsenide intermediates generated from coordinated secondary arsines have also been reported such as with Fe-As complex **18** (Scheme 9).⁹⁶ Intramolecular cyclization was

Scheme 9. Template-directed cyclization of 4-membered ring.

achieved in 85% yield *via* arsenide substitution of the C–Cl bond. Understandably, such intramolecular reactions impose restrictions in the choice of base. Nucleophilic bases and alkali metals were avoided to prevent unwanted bond cleavage at the C–Cl bond.

Lastly, cyclooligoarsines **4** were demonstrated to generate a lithium arsenide intermediate **4''** by As–As bond cleavage. As a testament to the versatility of these reagents, Naka demonstrated that phenyllithium could afford nucleophilic intermediates that were complementary to electrophilic arsenic iodides.⁹⁷ Upon nucleophilic substitution of benzyl chloride by intermediate **4''**, tertiary arsine **20** was isolated in 83% yield (Scheme 10). Once

Scheme 10. In-situ generation of lithium arsenide nucleophile.

again, a major drawback was noted in the synthesis of functionalized cyclooligoarsines **4**. If addressed, cyclooligoarsines hold great potential as a one-stop As(III) precursor for a wide range of substitution reactions.

To summarize, substitution reactions leading to As–C bond formation comprise of strategies involving both nucleophilic and electrophilic As(III) reagents. Traditional arsenic

halides have become less favourable since the inception of cyclooligoarsines or arylarsine oxides. On the other hand, methods involving nucleophilic arsine reagents tend to require strong bases to generate the reactive arsenide species from secondary/tertiary arsines which may find less synthetic utility for complex molecules. These substitution reactions are reasonably straightforward and easily controlled, making them reliable options for As–C bond formation.

1.2.2 Addition reactions

Addition reactions are 100% atom-economical by design and thus highly relevant in reducing arsenic-containing waste. Many addition reactions employ catalysts or stoichiometric metal complexes to assist with reactivity. While this may suggest that such reactions are more challenging, additional control was observed for reactivity and even stereoselectivity. The simplest addition methodologies involve the addition of secondary arsines to unsaturated C,C bonds. Also termed as hydroarsination reactions, this involved the formation of C–H and C–As bonds in a single reaction. Zr-based complex **23** has been utilized as catalyst by Waterman and coworkers.⁹⁸ From the hydroarsination of phenylacetylene **21**, vinylarsine **24** was isolated in 76% yield as a mixture of geometrical isomers (Scheme 11). In the absence of a catalyst

Scheme 11. Zr-catalyzed hydroarsination of phenylacetylene.

(and light), no conversion was obtained even after heating at reflux for 24 h. Waterman subsequently extended this Zr-catalyzed hydroarsination protocol to primary arsines in the photoinduced addition of tolylarsine **26** to styrene **25** (Scheme 12).⁹⁹ This was proposed to

Scheme 12. Zr-catalyzed hydroarsination with primary arsines.

proceed by an analogous photoexcitation and LMCT event after observing that changes to the light source varied the yields from 44-54%.¹⁰⁰ The unsymmetrical secondary arsine product may be highly relevant in the construction of tertiary arsines bearing central chirality at the As atom *via* further hydroarsination reactions. Unfortunately, the use of primary arsines limited widespread applications of such protocols because of hazards associated with handling the volatile primary arsine precursor. Base-catalyzed hydroarsination reactions have been reported by Nelson and coworkers with a Mo-coordinated phosphinoalkyne **29** (Scheme 13).¹⁰¹

Scheme 13. Base-catalyzed addition of HAsPh_2 .

Complexed phosphinoarsine **30** was isolated in moderate yields of 46% in an elegant example of how such As–C bond formation strategies may lead to the synthesis of specifically-designed arsenic-containing ligands.

[4+2] cycloaddition reactions (Diels-Alder reactions) have been employed in the niche synthesis of bridged organoarsine compounds by addition reactions. For example, the [4+2] cycloaddition involving phenylarsole **31** and tetracyanoalkene **32** rapidly led to the formation of compound **33** containing a bridgehead As atom in 86% yield under mild conditions (Scheme 14).^{79a} Together with chiral palladium templates, Diels-Alder reactions involving arsoles have been developed to synthesize chiral bridged organoarsine compounds for use as ligands in organometallic complexes.¹⁰² In Diels-Alder reactions involving arsenic-

Scheme 14. Diels-Alder reaction with arsoles.

bearing dienes and dienophiles, concurrent multiple As–C bond formation have led to the synthesis of diarsine compounds. For example, reaction between Pd-coordinated arsole (*S*)-**34** and diphenylvinylarsine led to the formation of enantiopure diarsine **35** in 75% yield (Scheme 15). The diarsine ligand was subsequently liberated from palladium with aqueous KCN.^{79b}

Scheme 15. Bridged diarsine synthesis by the Diels-Alder reaction.

Similar scaffolds bearing mixed As,P donors have been achieved by the inclusion of a phosphole/vinylphosphine reactant instead.¹⁰³

Lastly, addition-elimination reactions proceeding *via* arsonium intermediates have received limited attention and only a few works have been directed towards controlled As–C bond formation by such methodologies.¹⁰⁴ Mann and Baker reported the addition of dibromoethane **37** to tertiary arsine **36** at 130°C to yield arsonium salt **38** (Scheme 16).^{104a}

Scheme 16. Addition-elimination of tertiary arsine **36** *via* arsonium intermediate **38**.

Heating arsonium salt **38** subsequently resulted in thermal decomposition from the elimination of methyl bromide and bromine to yield products **39** and **40**. No yields were reported, reflecting the complicated product mixture derived with scrambling and elimination of the intermediate arsonium species.

The lack of literature examples available for addition methodologies leading to As–C bond formation suggest that such protocols are less straightforward than substitution methodologies. Metal complexes are generally employed either as catalysts or stoichiometric reagents to assist with lower reactivities. This may signal a rich avenue for re-developing addition protocols in light of current advancements in transition metal catalysis.

1.2.3 Metal-mediated reactions

The rise of palladium-catalyzed cross coupling reactions have led to several strategies being adapted for As–C bond formation. Three such methods have been reported which displayed reactivity at the metal center beyond classical Lewis acid/base activity.

Firstly, Stille coupling conditions have been adapted for As–C bond formation with the use of trialkyltin-based arsenic reagents.¹⁰⁵ Aryl iodides (even sterically hindered 1,2-substituted aryl iodides **41**) were cross-coupled with arsino-tributyltin reagent **42** to yield functionalized triarylarsines in 43-88% yield (Scheme 17).^{105a} The reaction was selective for

Scheme 17. Pd-catalyzed arsination with trialkyltin reagents.

C–I bonds even in the presence of chloride and bromide substituents, which hinted at some unreactivity of these alternative aryl halides. While aryl iodides are undeniably expensive, this tolerance to chloride/bromide substituents may however be used intentionally as a handle for further functionalizing triarylarsines **43**.

Secondly, the creative exploitation of aryl-aryl scrambling faced in Pd-catalyzed cross coupling reactions by Chan and co-workers deserves some mention. A series of aryl-diphenylarsines **45** were synthesized in 31-51% yield from scrambling at the Pd center (Scheme 18).¹⁰⁶ Undesirable aryl-aryl exchanges between the palladium-bound Ar ring and the

Scheme 18. Pd-catalyzed arsination via Pd-Ar scrambling

reactions (Scheme 19).¹⁰⁷ Such scrambling typically lead to the formation of unwanted side

Scheme 19. Scrambling of Pd-Ar and As-Ph groups.

products but have been used favourably in this instance for the synthesis of substituted triarylarsines **45**. More notably, this protocol holds great potential in addressing the current lack of commercially-available functionalized triarylarsines. Mono-, di- and tri-substituted products were expected from the product distribution, although the authors did not comment on their respective yields.

Lastly, a Ni-catalyzed synthesis of BINAs **49** in 34% yield was reported by Shibasaki to proceed between binol triflate **48** and diphenylarsine **22** (Scheme 20).⁸⁰ This demonstrated

Scheme 20. Ni-catalyzed synthesis of BINAs.

the possibility of As–C bond formation by reductive elimination without specialized transmetalating reagents (such as arsino-tributyltin **42**). This reduced the number of steps involved in handling arsenic-containing compounds, making such methodologies more attractive than those requiring specially-prepared transmetalating reagents.

Soft organoarsine compounds generally have good affinities to transition metals and can act as catalyst poisons by coordination, particularly under catalytic loadings of the

transition metal. For stoichiometric metal-mediated protocols, particular attention should also be paid to liberating the organoarsine products from the metal without significant loss in yield.

1.2.4 Radical reactions

Radical methods have been known to cleave As–As and As–H bonds to initiate radical As–C bond formation reactions.¹⁰⁸ In the presence of AIBN, cyclooligoarsine **50** was reported to undergo homolytic As–As bond cleavage to generate arsenic radicals (Scheme 21). These

Scheme 21. Radical-mediated synthesis of cyclic diarsines.

methylarsenic radicals were trapped by acetylenes to afford cyclic diarsine **51** in 34% yield. This was found to be useful for the synthesis of arsenic-containing polymers (poly(vinylenearsines)) by ring collapsed radical alternating copolymerization (RCRAC) of cyclooligoarsines and acetylene derivatives (Scheme 22). Homolytic As–H bond cleavage in

Scheme 22. Radical-initiated synthesis of poly(vinylenearsine).

primary arsines was also achieved with AIBN as a radical initiator. In a similar manner, acetylene **54** was used to trap the arsenic radical species to afford cyclic arsine **55** in 33% yield (Scheme 23).¹⁰⁹ The authors did not comment on the *cis/trans* distribution of the product even

Scheme 23. Radical-mediated double hydroarsination with H₂AsPh.

though it might have caused the low yield of arsa-borane **55**.

Arsenic radicals were also successfully generated by photostimulating potassium arsenide **15** (Scheme 24).¹¹⁰ Irradiation with Pyrex-filtered UV light for 1 h in the presence of

Scheme 24. Photostimulated $S_{RN}1$ reaction with diphenylarsenide anion.

p-tolyl chloride **56** led to a discharge of the characteristic dark red colour of potassium arsenide **15** and the concurrent formation of a mixture of products. No reaction was observed in the absence of light even after 24 h. The formation of triarylsarsines **9**, **58** and **59** suggested that As–C_{aryl} bonds were also prone to homolytic bond cleavage, although this feature has not been synthetically applied thus far.

Radical reactions remain the least developed for controlled As–C bond formation. Nevertheless, the rapid reaction rates are desirable for symmetrical or polymeric products. Photostimulation may be useful for initiating reactions involving particularly inert reagents. For example, light was used in conjunction with Zr-catalysts to achieve the addition of primary arsines to styrene as reported by Waterman (discussed above in Section 1.2.2).⁹⁹

1.2.5 Miscellaneous

Methodologies discussed in the above sections revolved around functionalizing known (or developed) organoarsine compounds. These precursors (eg. arsenic halides/oxides, cyclooligoarsines, primary/secondary/tertiary arsines or arsoles) were generally derived from commercially-available organoarsines such as triphenylarsine, sodium cacodylate and arsonic acids. Inorganic arsenic compounds (eg. elemental arsenic, arsenic trioxide) were rarely used as precursors for As–C bond formation reactions. Nevertheless, such examples are valuable for their industrial applicability since inorganic arsenic compounds can be directly mined from naturally-occurring arsenic-containing ores.

A mixture of diarsine oxide **8** and triphenylarsine **9** was derived from arsenic trioxide **60** with the addition of phenylmagnesium bromide with a series of As–O and As–C bond cleavages and formations respectively (Scheme 25).^{89a} Also, elemental arsenic **61** was shown

Scheme 25. Organoarsine synthesis from As₂O₃.

to afford mono- and di-haloarsines **62** and **63** by flow chemistry upon addition across a C–X (X = Cl, Br) bond (Scheme 26). Methyl halides, ethyl chloride, halobenzene and vinyl halides

Scheme 26. Synthesis of arsenic halides from elemental arsenic.

were all reactive with elemental arsenic in the presence of metallic copper, silver or zinc catalysts.¹¹¹ Despite the proof of concept as shown, arsenic halides such as compounds **62** and **63** are rarely derived from elemental arsenic because they can be easily derived from arsenic trihalides without the use of any catalyst.

Industrial preparation of commercial arsenic precursors also typically involve inorganic arsenic trioxide. Being the primary source of arsenic derived from arsenic-containing ores (or as a byproduct from processing other ores), many methods have been developed to functionalize the As–O bond. An overview of the industrial preparation of organoarsenic(III) precursors may be found in Ullmann’s Encyclopedia of Industrial Chemistry: Arsenic and Arsenic Compounds.¹¹²

1.3 Previous work done by our group

Our group has focused on the synthesis of chiral ligands containing phosphorus and arsenic donor atoms. Both stoichiometric and catalytic methods have been developed which often involved cyclometalated palladium complexes. Two segments are particularly relevant:

1) *stoichiometric* asymmetric hydroarsination reactions (Section 1.3.1), and 2) *catalytic* asymmetric hydrophosphination reactions (Section 1.3.2). These methods focus on the optical resolution and isolation of enantiopure compounds of As and P. This differs from the abovementioned As–C bond formation strategies in their control, identification, separation and isolation of new chiral centers.

1.3.1 Stoichiometric asymmetric hydroarsination reactions

The first documented instance of a stoichiometric asymmetric hydroarsination reaction by our group was achieved with coordination complex (*S*)-**64** bearing a vinylphosphine substrate (Scheme 27).¹¹³ Addition of diphenylarsine afforded diastereomeric

Scheme 27. Stoichiometric template-assisted asymmetric hydroarsination reaction.

complexes **65** with the hydroarsination product trapped in a Pd,As,C,C,P-chelate ring. Major isomer (*S,R*)-**65** was physically separated from the 8:1 diastereomeric mixture (as determined by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy) by a series of column chromatography and fractional recrystallization techniques, finally affording complex (*S,R*)-**65** in 34% isolated yield. The product was finally liberated from Pd with aqueous KCN to yield enantiopure arsinophosphine (*R*)-**66** in 31% overall yield. Being the first successful example from our group, several aspects required fine-tuning. Firstly, the 8:1 diastereomeric ratio consequently resulted in low product yield after successive fractional recrystallization. Secondly, necessary product liberation from Pd was an additional step leading to loss of yield. Lastly, the use of KCN for the liberation step

was unfavourable in terms of safety. Proper quenching and disposal of the cyanide waste was required which contributed to the drawbacks of this protocol.

Nevertheless, this example was useful in determining key reaction steps of the Pd-mediated hydroarsination reaction (Scheme 28).¹¹³ The reaction was proposed to proceed by

Scheme 28. Proposed mechanism for stoichiometric asymmetric hydroarsination of complex **64**.

an initial displacement of the weakly-coordinated perchlorate anion in complex **64** by diphenylarsine to afford intermediate **A**. Coordination to Pd polarized the As–H bond and resultant deprotonation generated a highly reactive arsenido species **B**. Alcoholic solvents were required to stabilize arsenido intermediate **B**; no reaction was observed in non-polar or even polar aprotic solvents. Subsequently, intramolecular addition of diphenylarsine to the C=C bond of intermediate **B** proceeded in a stepwise manner with sequential As–C and solvent-assisted C–H bond formation to generate the coordinated hydroarsination product **65**. Intramolecular addition allowed for complete regioselective control arising from the formation of a favourable 5-membered Pd,As,C,C,P-chelate ring. Geometric isomers of complexes **65** were not observed and the phosphine donor remained *trans* to the N atom of the naphthylamine ligand.

The use of the naphthylamine Pd-template in complex (*R*)-**67** similarly yielded the hydroarsinated product bound in a 5-membered chelate ring (Scheme 29).¹¹⁴ As expected, no geometric isomers of complexes **68** were observed although diastereomers were obtained in a 2.6 : 1 ratio. The major complex (*R,R*)-**68** was isolated in low yield of 25%, partly due to an

Scheme 29. Template-mediated hydroarsination adduct and elimination product.

unexpected elimination (dehydration) which afforded achiral complex (*R*)-**69**. X-ray crystallographic analysis of complex (*R*)-**67** revealed that the hydroxy O and Pd atoms in close proximity. This Pd–O interaction activated the O–C bond which led to elimination of water from complex **68** thus forming an unsaturated C=C bond in complex (*R*)-**69**.¹¹⁵

Subsequently, hydroarsination protocols progressed to a one-pot addition of Pd-template, substrate and diphenylarsine without isolating the template-coordinated substrate complex. Naphthylamine palladium complex (*R*)-**70** was stirred with 2-pyridyl enone **71** in the presence of diphenylarsine to afford diastereomeric product complexes **72** (Scheme 30).¹¹⁶

Scheme 30. Metal-templated synthesis of pyridyl arsines.

With DCM instead of methanol as solvent, the reaction took much longer and required up to 12 days for complete conversion. Under such one-pot conditions, product complexes **72** were still obtained exclusively with As coordinated *trans* to the N atom of the naphthylamine ligand. In the absence of a phosphorus-containing compound, ³¹P{¹H} NMR spectroscopy could not be used to determine the diastereomeric ratio. Diastereomers of **72** were inseparable by column chromatography, instead requiring fractional recrystallization to isolate major product (*R,R*)-**72** in 30% yield.

Generally, physical separation of the intermediate diastereomeric complexes led to a significant loss of yield for stoichiometric methodologies involving chiral complex (*R*)-**70**.

This was particularly unfavourable in terms of cost and safety because of the palladium metal and arsenic-containing compounds involved respectively. In addition, the presence of multiple coordination sites complicated metal-templated hydroarsination reactions. While the hydroarsination of 2-pyridyl enone **71** proceeded smoothly with 1,4-regioselectivity as expected of an arsa-Michael reaction (Scheme 30), this regioselectivity was not observed with propenoate **73**. Instead, 1,3-adduct in the form of coordination complex (*R,R*)-**74** was the only product observed (Scheme 31).¹¹⁶ This was likely to have arisen out of a transient interaction

Scheme 31. 1,3-hydroarsination adduct isolated from reaction with propenoate **73**.

between Pd and the ester O atom which aligned the coordinated arsenido species and the 1,3-position in a favourable 5-membered ring. Notably, no 1,2-adducts were formed despite electronic activation by the ketone which alluded to the considerable influence of favourable coordination chemistry on the overall reaction.

With an additional element of chirality, strategies for As–C bond formation now included considerations such as 1) optical purity of the desired product, 2) physical separation of intermediate diastereomeric complexes and 3) retention of yield throughout the optical resolution process. Several shortcomings identified from these stoichiometric process inspired the subsequent development of catalytic protocols. Firstly, a catalytic use of Pd would allow direct access to the free arsine product and thus would not require separation of diastereomeric intermediates. This would also negate the use of aqueous KCN as a liberating agent, thus reducing the hazards associated with such reactions. With good stereoselective control, the direct generation of enantiopure arsine products would also improve yields by reducing loss from the optical resolution process. Lastly, catalytic quantities of Pd would greatly improve costs associated with stoichiometric quantities of reagents. Many features of these

stoichiometric hydroarsination reactions were observed over the course of developing the Pd-catalyzed hydroarsination reaction (Chapter 2). The mechanism proposed for the Pd-mediated stoichiometric hydroarsination reaction was also referenced to when elucidating the mechanism for the catalytic version.

1.3.2 Catalytic asymmetric hydrophosphination reactions

Catalytic asymmetric hydrophosphination reactions were successfully accomplished by our group with both bidentate and tridentate complexes of Pd. Enantiopure chiral phosphines were synthesized in a single step without any optical resolution. No protection-deprotection steps were required from this one-pot addition protocol, leading to excellent isolated yields of the free phosphine. Such reactions were also convenient in terms of handling air-sensitive phosphines. Based on the close group relationship between phosphorous and arsenic, this reaction was viewed as an analogue to the hydroarsination reaction. Notable milestones in developing the catalytic asymmetric hydrophosphination reaction are highlighted to guide developments in the corresponding hydroarsination reaction.

Pd-catalyzed asymmetric hydrophosphination was first achieved with the use of CN-palladacycle (*R*)-**70** (Scheme 32).¹¹⁷ From a series of functionalized enones **75**, free phosphines

Scheme 32. Asymmetric hydrophosphination of enone **75** catalysed by CN-Pd complex (*R*)-**70**.

76 were isolated with 40-70% yield in 85-99% *ee*. Air-sensitive free phosphines **76** oxidized under column chromatography conditions and thus faced some loss in yield from purification by recrystallization. Complete conversion of diphenylphosphine to tertiary phosphine **76** was otherwise observed on $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy. To improve the stereoselectivity of P–C bond formation, the reaction was conducted at -80°C . While complex (*R*)-**70** was still catalytically active, 7 days were required before complete conversion was observed.

It was subsequently observed that CP-palladacycle (*R*)-**78** was a better catalyst in terms of turnover rates. When the same reaction was conducted at -80°C, complete conversions were obtained within 14-40 h instead, a fraction of the 7 days required for CN-palladacycle (*R*)-**70** (Scheme 33).¹¹⁸ This was attributed to the *trans* effect contributed by the CP ligand of

Scheme 33. Asymmetric hydrophosphination of enone **75** catalysed by CP-Pd complex (*R*)-**78**.

complex (*R*)-**78**. By labilizing the P–Pd bond of the Pd-coordinated phosphine intermediate, rapid product liberation resulted in faster reaction times. Quantitative yields were observed with ³¹P{¹H} NMR spectroscopy and free phosphines **77** were derived in 85-99% *ee*. A single recrystallization from the crude afforded enantiopure free phosphines **77** without requiring lengthy optical resolution/protection-deprotection processes. From the same protocol, tertiary phosphines bearing central chirality on the phosphorus atom were also synthesized from a racemic mixture of secondary phosphines. Excellent stereochemical control was achieved for the simultaneous construction of C*- and P*-chiral centres by CP-palladacycle (*R*)-**78** which afforded enantiopure C*- and P*-chiral tertiary phosphines upon a single recrystallization.

The hydrophosphination of enones **75** catalysed by CP-palladacycle **78** was proposed to proceed with four main steps (Scheme 34).¹¹⁸ First, active catalyst **A** was generated in situ from complex **78** by ligand exchange under a large excess of secondary phosphine. Between the two reactive phosphido sites in intermediate **A**, the phosphine *trans* to the naphthyl ring was concluded to dissociate more readily due to a strong *trans* effect.¹¹⁷ Phosphine displacement and subsequent coordination of enone **75** at the carbonyl O afforded intermediate **B**. This preferential coordination of the carbonyl O instead of the C=C bond was also observed in other similar complexes in which the coordination site on Pd *trans* to a naphthalene donor preferentially coordinated to hard O-donors such as amide-, carbonyl-, perchlorate- and

Scheme 34. Proposed mechanism for the hydrophosphination of enone **75** catalysed by CP-palladacycle **78**.

sulfoxide-O atoms.¹¹⁹ With the P–H bond in intermediate **B** acidified by coordination to Pd, sequential deprotonation by an external base and intramolecular P–C bond formation afforded intermediate **C** bearing a 6-membered chelate ring. Protonation afforded intermediate **D** and dissociation of tertiary phosphine **77** regenerated active catalyst **A**. This proposed mechanism closely resembled the mechanism proposed for stoichiometric Pd-mediated hydroarsination reactions, with the exception of unsuccessful product dissociation in the latter.

Regioselective P–C bond formation was investigated with the use of $\alpha,\beta,\gamma,\delta$ -malonate ester **79** in which the 1,4- and 1,6-positions were electronically activated and available for P–C bond formation (Scheme 35).¹²⁰ CP-catalyst (*S*)-**78** afforded 1,4-adduct **80** cleanly in >99% yield (determined by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy). Excellent enantioselectivity was observed and oxidation by H_2O_2 did not affect optical purity. However, 1,6-regioisomer **81** was obtained as the major product when PCP Pd-pincer complex (*R,R*)-**82a** was employed as catalyst. Clearly, the electronic and steric ligand profiles of CP-palladacycle (*S*)-**78** and PCP-Pd pincer

Scheme 35. 1,4- and 1,6-addition hydrophosphination products of $\alpha,\beta,\gamma,\delta$ -malonate ester **79**.

complex (R,R) -**82a** contributed to different regioselectivities favoured for P–C bond formation. It was determined that 1,6-regioisomer **81** was formed preferentially upon minimizing steric interactions between substrate **79** and catalyst (R,R) -**82a**. On the other hand, the CP-catalyst (S) -**78** favoured addition at the 1,4-position because of greater electronic activation by the malonate moiety of substrate **79**.

A mechanism was proposed for the hydrophosphination reaction catalyzed by PCP-Pd pincer complex **82a** (Scheme 36).¹²⁰ This was achieved with a series of stoichiometric

Scheme 36. Proposed mechanism for the hydrophosphination of malonate ester **79** catalysed by PCP-Pd pincer complex **82a**.

experiments involving all species of the hydrophosphination reaction. Firstly, a 1:1 molar ratio of complex **82a** and malonate ester **79** did not result in any noticeable changes to the ^1H NMR signal of the pincer AcO^- counteranion nor the $^{31}\text{P}\{^1\text{H}\}$ NMR signal of complex **82a**. ^1H NMR signals of malonate ester **79** were also identified from the mixture, suggesting the absence of interaction between complex **82a** and substrate. On the other hand, a stoichiometric mixture of complex **82a** and HPPH_2 resulted in new peaks on the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum which was attributed to intermediate **B**. Intermediate **A** was not observed because the acidified P–H bond of HPPH_2 was rapidly deprotonated by the acetate anion. Subsequently, intramolecular nucleophilic attack was proposed to proceed between the coordinated phosphide species **B** and malonate ester **79** to afford intermediate **C**. Protonation then generated intermediate **D**, and release of tertiary phosphine adduct **81'** was facilitated by displacement with excess HPPH_2 . Under catalytic conditions, it was undetermined if the release of tertiary phosphine **81'** was accompanied by regenerating acetate complex **82a** or phosphine-Pd complex **A** as the active catalyst. Nevertheless, these complexes were rapidly interconvertible by an equilibrium exchange of the auxiliary ligand and were not of significant consequence.

The different coordination modes of CP-palladacycle **78** and PCP-Pd pincer complex **87a** conferred notable differences in terms of reactivity, regioselectivity and stereoselectivity. Bidentate CP complex **78** was prone to catalyst poisoning by chelate ring formation with the functionalized phosphine product.¹²¹ For example, the hydrophosphination of 2-pyridyl enone **83** catalyzed by CP complex (*S*)-**78** afforded the desired phosphine (derivatized as the air-stable oxide **84**) in only 16% yield (Scheme 37). The low yield was attributed to the formation of a stable 5-membered Pd,P,C,C,N-chelate ring such as in intermediates **84'** and **84''** which inhibited the regeneration of the active catalytic species (Figure 6). However, with the oxidation of enone **83** to N-oxide analogue **85**, CP-complex (*S*)-**78** catalyzed the reaction smoothly to afford product **86** quantitatively (Scheme 37). Alternatively, pyridyl phosphine oxide **84** was

Scheme 37. Catalyst poisoning of complex **(S)-78** by chelate effect.

Figure 6. 5-membered Pd,P,C,C,N -chelate ring formation involving CP-complex **(S)-78**.

isolated in excellent yields of 92% in the presence of tridentate PCP-Pd pincer catalyst **(R,R)-87a** because no chelate ring formation was possible at the remaining free coordination site (Scheme 38). While PCP-Pd complex **87a** may seem more robust in terms of reactivity,

Scheme 38. Hydrophosphination of N-functionalized enones **83** and **85** catalysed by PCP-Pd complex **(R,R)-87a**.

screening should still be conducted for stereoselectivity. Unexpectedly, racemic mixtures of products **84** and **86** were obtained under optimized conditions as opposed to the excellent stereoselectivity observed with CP-complex **(S)-78** (Scheme 37, **86**: 90% *ee*).

The Pd-catalyzed hydrophosphination reaction was applied to a series of different electron-deficient olefin substrates (Scheme 39).¹²² While the catalysis was notably limited to only electron-withdrawing keto, ketoester and imine groups, several of these activating groups

Scheme 39. Substrate scope of hydrophosphination reactions by CP-catalyst **78** and PCP-catalyst **87a**.

were masked functionalities which could be derived directly from the tertiary phosphine product. For example, ester- and carboxylic acid-functionalized phosphines were previously inaccessible with the hydrophosphination protocol because ester groups were poorly activating while the acidic carboxylic acid group ionized under basic conditions of the hydrophosphination reaction. However, these functionalized phosphines were derived from *N*-enoylbenzotriazole-phosphine adduct **88** upon hydrolysis of the benzotriazole moiety.^{122a} The *N*-acylphthalimide moiety present in phosphines **90** served as masked amides which were unsuitable as an activating group because it was also poorly electron-withdrawing.^{122b} Nevertheless, enantioenriched amide-functionalized phosphines were still accessible with the Pd-catalyzed hydrophosphination methodology by deprotecting phosphine **90** under mild conditions. Stabilization by aromatization was also exploited as a driving force for the reaction and phosphinite **91** was isolated from the hydrophosphination of benzoquinone.^{122d} CP-palladacycle **78** could catalyze double hydrophosphination reactions, affording phosphine **94** from the formation of two P–C bonds at a primary phosphine.^{122g} Alternatively, two phosphine moieties could be installed on a single substrate to afford diphosphine **95** by a series of

consecutive P–C bond formations.^{122h} Lastly, tridentate PCP Pd-complexes were capable of generating both 1,4- and 1,6-hydrophosphination adducts in a regioselective manner. It was previously discussed that keto-functionalized pincer complex **82a** afforded the 1,6-adduct **81** of $\alpha,\beta,\gamma,\delta$ -malonate ester **79** in 88% *dr* (Scheme 35). Comparatively, ester-functionalized pincer complex **87a** afforded the 1,4-adduct **96** of $\alpha,\beta,\gamma,\delta$ -unsaturated ketones in 78-92% yield.¹²²ⁱ

These Pd-catalyzed hydrophosphination reactions were applied in the synthesis of chiral phosphine ligands. Generally, this involved designing a substrate such that the desired ligand scaffold was generated upon addition of a phosphine moiety. These enantiopure phosphine preligands were then directly cyclometalated to afford the desired chiral phosphine-containing metal complexes. For example, malonate **88** was designed to bear a naphthyl motif such that the resulting hydrophosphination adduct would resemble the ligand of CP-palladacycle **78** (Scheme 40).¹²³ Free phosphine (*S*)-**89** was generated quantitatively with 91% *ee*

Scheme 40. Synthesis of CP complex (*S*)-**92** by catalytic hydrophosphination.

ee and directly coordinated to palladacycle **90** to afford complex (*S*)-**91** without prior purification, resolution or protection of free phosphine **89**. Complex (*S*)-**91** was subsequently heated at reflux with a strong acid to protonolyze the amine followed by the addition of NaOAc to furnish dimeric complex (*S*)-**92** by base-assisted cyclometallation. Enantiopure complex (*S*)-

92 was finally isolated by recrystallization as an air-stable solid. As compared to the optical resolution to isolate enantiopure forms of CP-palladacycle (*R*)-**78**, complex (*S*)-**92** was synthesized in a comparatively streamlined manner in excellent overall yields of 91%.

Wide-bite angle phosphine preligands (*R,R*)-**93'** were generated in situ by a double hydrophosphination of substrate **93** and palladated in a one-pot methodology to afford PCP-Pd pincer complexes (*R,R*)-**82b** in excellent yields with up to >99% *de* and *ee* (Scheme 41).¹²⁴

Scheme 41. Synthesis of PCP pincer complexes by catalytic hydrophosphination.

Excellent diastereoselectivity of the transformation catalyzed by CP-palladacycle (*S*)-**78** simplified the purification of complexes **82**. Other than Pd-based pincer complexes, diphosphine **93'** was also metalated with other platinum group metals to afford PCP-pincer complexes of Pt and Ni (complexes **94** and **95** respectively). Cyclometallation did not affect chirality installed during P–C bond formation and complexes **94** and **95** were obtained in excellent yields and stereoselectivities. This phosphination-metalation protocol could synthesize a library of pincer complexes with different ligand backbones. Ester-functionalized pincer complexes **87b**, **96** and **97a**,¹²⁴ complexes bearing a *para*-N pyridinyl backbone **98** and **99** and complexes of a *para*-N-oxide pyridinyl backbone **100** and **101** were all furnished with slight modifications to this methodology.¹²⁵

Lastly, protected (oxidized or sulfurized) phosphines arising from the hydrophosphination protocol could also be applied as air-stable ligands themselves. NCE (E = O, S)-Pd pincer complexes (*R,R*)-**104** were derived from the phosphine oxide/sulfide product (*S*)-**103** of the hydrophosphination of enone **102** (Scheme 42).¹²⁶ NCE-Pd complex **104**

Scheme 42. Synthesis of mono- and bi-metallic NCE (E = O, S) Pd pincer complexes.

generated some interest for the chiral centre constructed upon C(*sp*³)-H bond activation during the cyclometallation of preligand **103**. Diastereoselective C-H bond activation was proposed to be controlled by the adjacent chirality at P-C* which led to the isolation of complexes **104** in absolute diastereoselectivity. Larger bimetallic complexes **105**, **106** and **107** could also be synthesized with excellent control of up to 4 chiral centres.¹²⁷ These NCE complexes were efficient catalysts for the hydrophosphination reaction themselves. Complex **104** was even successfully applied to a “self-breeding” methodology in which complex **104** catalyzed the enantiopure synthesis of preligand **103** itself (Scheme 43).^{126a}

Scheme 43. “Self-breeding” of NCE pincer complexes (R,R) -**104**.

To summarize, asymmetric hydrophosphination reactions have been demonstrated to proceed with both bidentate CP-palladacycles and PCP-Pd pincer complexes as catalysts. With different ligand scaffolds, these catalysts behaved differently in terms of activity, regioselectivity and stereoselectivity. CP-palladacycles were generally more reactive and reactions proceeded smoothly even at -80°C . However, such complexes were prone to catalyst poisoning by chelate formation when multiple donor atoms were present on the substrate/product. CP-palladacycles were also observed to favour 1,4-addition for substrates containing multiple activated C=C bonds. On the other hand, PCP pincer complexes can furnish both 1,4- and 1,6-adducts depending on the steric bulk of the ligand and the substrate. While hydrophosphination reactions developed by our group are still currently limited to electron-deficient olefins, efforts have been made to design activating groups which can be unmasked after P–C bond formation. Lastly, protocols have also been developed for the one-pot synthesis of platinum group metal complexes bearing chiral phosphine ligands.

1.4 Aims and objectives

Following developments in our group, this thesis describes the progress made in advancing *catalytic* asymmetric hydroarsination reactions. Hydrofunctionalization reactions have already been established as an exceptionally efficient C-heteroatom bond formation methodology,¹²⁸ conferring absolute atom-economy by reaction design. However, such reactions have only been sparingly utilized for As–C bond formation despite being well-primed to circumvent innate challenges of synthesizing organoarsenic compounds. For instance, the

potential to afford enantiopure arsines in a single step greatly reduces the exposure to arsenic by eliminating the need for additional decomplexation and optical resolution procedures. While this convenience is similarly enjoyed for other catalytic hydrofunctionalization (eg. hydrophosphination,¹²⁹ hydroamination)¹³⁰ reactions, hydroarsination reactions confers an additional aspect of safety by reducing the degree of exposure to potentially toxic compounds of arsenic. Improving reactivity, lowering the cost of catalysts used, achieving better catalytic control over stereoselectivity and isolating well-defined (chiral) organoarsine compounds are all central to achieving synthetic utility for the asymmetric hydroarsination reaction.

The 12 Design Principles of Green Chemistry have been used to guide the development of methodologies presented in this thesis where possible.¹³¹ With the knowledge of environmental hazards (and challenges in speciation) posed by arsenic-containing compounds, greener chemicals, processes and products are essential to minimize the burden incurred. In essence, this involves the following:

- 1) Preventing waste instead of cleaning up after it has been generated,
- 2) Designing reactions towards 100% atom-economy,
- 3) To use and generate the least toxic substances possible,
- 4) Re-designing chemicals to retain function while reducing toxicity,
- 5) Minimizing the use of solvents and auxiliaries,
- 6) Minimizing energy requirements in terms of heat and pressure,
- 7) Using renewable feedstocks,
- 8) Reducing derivatives such as protecting/blocking groups,
- 9) Using catalytic amounts of reagents,
- 10) Designing chemical products for degradation,
- 11) Allowing real-time, in-process monitoring and control of products, and
- 12) Choosing safer substance/conditions/processes for accident prevention.

Several points such as 7 and 11 were less relevant in context of the synthetic nature of the work. On the other hand, principles 2, 5, 8 and 9 were already intrinsic features of the catalytic asymmetric hydroarsination reaction that validated further improvements to existing hydroarsination protocols. These metrics are reiterated where relevant in the subsequent chapters.

To improve efficiency, the catalytic asymmetric hydrophosphination reaction was used as a model to develop the corresponding hydroarsination reaction. Throughout the course of this work, it was noted that arsines were not direct analogues of phosphines despite their close group relationship. Often, a direct replacement of the secondary phosphine reagent with secondary arsines led to unsuccessful reactions even when the same catalyst was used. Systematic investigations were conducted to establish reasons for the observed differences in reactivity.

References

- [1] Bhattacharya, P.; Welch, A. H.; Stollenwerk, K. G.; McLaughlin, M. J.; Bundschuh, J.; Panaullah, G. *Sci. Total Environ.* **2007**, *379*, 109.
- [2] Agency for Toxic Substances and Disease Registry. 2017 Substance Priority List. <https://www.atsdr.cdc.gov/SPL/index.html> (accessed Sep 3, 2019).
- [3] National Research Council (US) Subcommittee on Arsenic in Drinking Water. Arsenic in Drinking Water. Washington (DC): National Academies Press (US); 1999. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK230893/> doi: 10.17226/6444.
- [4] (a) Cantor, K. P.; Lubin, J. H. *Toxicol. Appl. Pharmacol.* **2007**, *222*, 252, (b) Heck, J. E.; Andrew, A. S.; Onega, T.; Rigas, J. R.; Jackson, B. P.; Karagas, M. R.; Duell, E. J. *Environ. Health Perspect.* **2009**, *117*, 1718.
- [5] Chen, C.-J.; Wang, S.-L.; Chiou, J.-M.; Tseng, C.-H.; Chiou, H.-Y.; Hsueh, Y.-M.; Chen, S.-Y.; Wu, M.-M.; Lai, M.-S. *Toxicol. Appl. Pharmacol.* **2007**, *222*, 298.
- [6] Chen, Y.; Graziano, J. H.; Parvez, F.; Liu, M.; Slavkovich, V.; Kalra, T.; Argos, M.; Islam, T.; Ahmed, A.; Rakibuz-Zaman, M.; Hasan, R.; Sarwar, G.; Levy, D.; van Geen, A.; Ahsan, H. *BMJ* **2011**, *342*, 2431.
- [7] Dixon, H. B. F. *Adv. Inorg. Chem.* **1996**, *44*, 191.
- [8] Lagunas, R. *Arch. Biochem. Biophys.* **1980**, *205*, 67.
- [9] Kenney, L. J.; Kaplan, J. H. *J. Biomol. Chem.* **1988**, *263*, 7954.
- [10] Gresser, M. J. *J. Biomol. Chem.* **1981**, *256*, 5981.
- [11] Aposhian, H. V. Biochemical Toxicology of Arsenic. In *Reviews in Biochemical Toxicology*; Hodgson, E.; Bend, J. R.; Philpot, R. M., Ed.s; Elsevier: New York, 1989.
- [12] Wolfe-Simon, F.; Blum, J. S.; Kulp, T. R.; Gordon, G. W.; Hoeft, S. E.; Pett-Ridge, J.; Stoltz, J. F.; Webb, S. M.; Weber, P. K.; Davies, P. C.; Anbar, A. D.; Oremland, R. S. *Science* **2011**, *332*, 1163.

- [13] (a) Cressey, D. *Nature* **2012**, DOI: 10.1038/nature.2012.11520, (b) Hayden, E. C. *Nature* **2012**, DOI: 10.1038/nature.2012.9861.
- [14] Shen, S.; Li, X.-F.; Cullen, W. R.; Weinfeld, M.; Le, X. C. *Chem. Rev.* **2013**, *113*, 7769.
- [15] Stevenson, K. J.; Hale, G.; Perham, R. N. *Biochemistry* **1978**, *17*, 2189.
- [16] Webb, J. L. *Enzyme and Metabolic Inhibitors*; Academic Press: New York, 1966.
- [17] Hughes, M. F. *Toxicol. Lett.* **2002**, *133*, 1.
- [18] Mass, M. J.; Tennant, A.; Roop, B. C.; Cullen, W. R.; Styblo, M.; Thomas, D. J.; Kligerman, A. D. *Chem. Res. Toxicol.* **2001**, *14*, 355.
- [19] Wiencke, J. K.; Yager, J. W. *Environ. Mol. Mutagen.* **1992**, *19*, 195.
- [20] Jha, A. N.; Noditi, M.; Nilsson, R.; Natarajan, A. T. *Mutat. Res.-Fund. Mol. M.* **1992**, *284*, 215.
- [21] Lee, T.-C.; Tanaka, N.; Lamb, P. W.; Gilmer, T. M.; Barrett, J. C. *Science* **1988**, *241*, 79.
- [22] Okui, T.; Fujiwara, Y. *Mutat. Res.-Gen. Tox.* **1986**, *172*, 69.
- [23] (a) Li, J.-H.; Rossman, T. G. *Mol. Toxicol.* **1989**, *2*, 1, (b) Li, J.-H.; Rossman, T. G. *Biol. Metals* **1991**, *4*, 197.
- [24] Counts, J. L.; Goodman, J. I. *Cell* **1995**, *83*, 13.
- [25] Zhong, C. X.; Mass, M. J. *Toxicol. Lett.* **2001**, *122*, 223.
- [26] (a) Razo, L. M. D.; Styblo, M.; Cullen, W. R.; Thomas, D. J. *Toxicol. Appl. Pharmacol.* **2001**, *174*, 282, (b) Styblo, M.; Serves, S. V.; Cullen, W. R.; Thomas, D. J. *Chem. Res. Toxicol.* **1997**, *10*, 27, (c) Lin, S.; Cullen, W. R.; Thomas, D. J. *Chem. Res. Toxicol.* **1999**, *12*, 924.)
- [27] Radke, B.; Jewell, L.; Piketh, S.; Namieśnik, J. *Crit. Rev. Env. Sci. Tec.* **2014**, *44*, 1525.
- [28] Vilensky, J. A. *Dew of Death. The Story of Lewisite, America's World War I Weapon of Mass Destruction*; Butler, R., Ed.; Indiana University Press, 2005.
- [29] Medscape Reference, Drugs, Diseases and Procedures. CBRNE - Vomiting Agents - Dm, Da, Dc. <https://emedicine.medscape.com/article/833391-overview> (accessed Sep 4, 2019).

- [30] Jacobs, M. B. *War Gases: Their Identification and Decontamination*; Interscience Publishers, Inc.: New York, 1942.
- [31] Centers for Disease Control and Prevention. The National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/ershdb/emergencyresponsecard_29750006.html (accessed Sep 4, 2019).
- [32] Chauhan, S.; Chauhan, S.; D'Cruz, R.; Faruqi, S.; Singh, K. K.; Varma, S.; Singh, M.; Karthik, V. *Environ. Toxicol. Pharmacol.* **2008**, *26*, 113.
- [33] Cullen, W.; Reimer, K. *Arsenic is Everywhere: Cause for Concern?*; The Royal Society of Chemistry, Cambridge, UK, 2017, p 89 and 115.
- [34] Konkola, K. *J. Hist. Med. Allied Sci.* **1992**, *47*, 186.
- [35] Hood, E. *Environ. Health Perspect.* **2006**, *114*, A471.
- [36] Hughes, M. F.; Beck, B. D.; Chen, Y.; Lewis, A. S.; Thomas, D. J. *Toxicol. Sci.* **2011**, *123*, 305.
- [37] Morrissey, C. A.; Dods, P. L.; Elliott, J. E. *Ecol. Appl.* **2008**, *18*, 172.
- [38] (a) Zhang, X.-W.; Yan, X.-J.; Zhou, Z.-R.; Yang, F.-F.; Wu, Z.-Y.; Sun, H.-B.; Liang, W.-X.; Song, A.-X.; Lallemand-Breitenbach, V.; Jeanne, M.; Zhang, Q.-Y.; Yang, H.-Y.; Huang, Q.-H.; Zhou, G.-B.; Tong, J.-H.; Zhang, Y.; Yu, J.-H.; Hu, H.-Y.; de Thé, H.; Chen, S.-J.; Chen, Z. *Science* **2010**, *328*, 240, (b) Jeanne, M.; Lallemand-Beitenbach, V.; Ferhi, O.; Koken, M.; Bras, M. L.; Duffort, S.; Peres, L.; Berthier, C.; Soilihi, H.; Raught, B.; de Thé, H. *Cancer Cell* **2010**, *18*, 88.
- [39] Gibaud, S.; Jaouen, G. *Top. Organomet. Chem.* **2010**, *32*, 1.
- [40] Ng, J. C.; Wang, J.; Shraim, A. *Chemosphere* **2003**, *52*, 1353-1359.
- [41] World Health Organization. *Guidelines for drinking-water quality*, 4th ed.; World Health Organization, 2017.

- [42] Cullen, W. R.; Reimer, K. J. *Chem. Rev.* **1989**, *89*, 713.
- [43] For an overview of speciation methods, see Francesconi, K. A.; Kuehnelt, D. *Analyst* **2004**, *129*, 373.
- [44] Nearing, M. M.; Koch, I.; Reimer, K. J. *Spectrochim. Acta B.* **2014**, *99*, 150.
- [45] Bhowmick, S.; Pramanik, S.; Singh, P.; Mondal, P.; Chatterjee, D.; Nriagu, J. *Sci. Total Environ.* **2018**, *612*, 148.
- [46] Burgess, W. G.; Hoque, M. A.; Michael, H. A.; Voss, C. I.; Breit, G. N.; Ahmed, K. M. *Nature Geoscience* **2010**, *3*, 83.
- [47] (a) Domingo, J. L. *Reprod. Toxicol.* **1995**, *9*, 105, (b) Singh, A. P.; Goel, R. K.; Kaur, T. *Toxicol. Int.* **2011**, *18*, 87.
- [48] Korte, N. E.; Fernando, Q. *Crit. Rev. Env. Contr.* **1991**, *21*, 1.
- [49] Terlecka, E. *Environ. Monit. Assess.* **2005**, *107*, 259.
- [50] Sturgeon, R. E.; Siu, K. W. M.; Willie, S. N.; Berman, S. S. *Analyst* **1989**, *114*, 1393.
- [51] Baig, J. A.; Kazi, T. G.; Shah, A. Q.; Kandhro, G. A.; Afridi, H. I.; Arain, M. B.; Jamali, M. K.; Jalbani, N. *Ecotox. Environ. Safe.* **2010**, *73*, 914.
- [52] Baun, D. L.; Christensen, T. H. *Waste Manage. Res.* **2004**, *22*, 3.
- [53] (a) Jensen, D. L.; Christensen, T. H. *Water Res.* **1999**, *33*, 2139, (b) Gounaris, V.; Anderson, P. R.; Holsen, T. M. *Environ. Sci. Technol.* **1993**, *27*, 1381, (c) Klein, T.; Niessner, R. *Microchim. Acta* **1998**, *129*, 47, (d) Jensen, D. L.; Ledin, A.; Christensen, T. H. *Water Res.* **1999**, *33*, 2642, (e) Lun, X. Z.; Christensen, T. H. *Water Res.* **1989**, *23*, 81, (f) Holm, P. E.; Andersen, S.; Christensen, T. H. *Water Res.* **1995**, *29*, 803, (g) Papini, P.; Majone, M.; Rolle, E. *Water Sci. Technol.* **2001**, *44*, 343.
- [54] (a) Williams, P. N.; Islam, M. R.; Adomako, E. E.; Raab, A.; Hossain, S. A.; Zhu, Y. G.; Feldmann, J.; Megarg, A. A. *Environ. Sci. Toxicol.* **2006**, *40*, 4903, (b) Roychowdhury, T.;

- Tokunaga, H.; Ando, M. *Sci. Total Environ.* **2003**, *308*, 15, (c) Alam, M. G. M.; Snow, E. T.; Tanaka, A. *Sci. Total Environ.* **2003**, *308*, 83.
- [55] Williams, P. N.; Price, A. H.; Raab, A.; Hossain, S. A.; Feldmann, J.; Meharg, A. A. *Environ. Sci. Toxicol.* **2005**, *39*, 5531.
- [56] (a) Duxbury, J. M.; Mayer, A. B.; Lauren, J. G.; Hassan, N. *J. Environ. Sci. Heal. A.* **2003**, *38*, 61, (b) Meharg, A. A.; Rahman, M. M. *Environ. Sci. Technol.* **2003**, *37*, 229.
- [57] Sharma, V. K.; Sohn, M. *Environ. Int.* **2009**, *35*, 743.
- [58] For selected examples, see (a) Mohan, D.; Pittman, C. U. *J. Hazard. Mater.* **2007**, *142*, 1, (b) Gu, Z.; Fang, J.; Deng, B. *Environ. Sci. Technol.* **2005**, *39*, 3833, (c) Chuang, C. L.; Fan, M.; Xu, M.; Brown, R. C.; Sung, S.; Saha, B.; Huang, C. P. *Chemosphere* **2005**, *61*, 478.
- [59] For selected examples, see (a) Lin, T.-F.; Wu, J.-K. *Water Res.* **2001**, *35*, 2049, (b) Bissen, M.; Frimmel, F. H. *Acta Hydroch. Hydrob.* **2003**, *31*, 97, (c) Ghurye, G.; Clifford, D.; Tripp, A. *J. Am. Water Works Ass.* **2004**, *96*, 143, (d) Leupin, O. X.; Hug, S. J. *Water Res.* **2005**, *39*, 1729.
- [60] For an overview, see (a) Cherian, S.; Oliveira, M. M. *Environ. Sci. Technol.* **2005**, *39*, 9377, (b) Lasat, M. M. *J. Environ. Qual.* **2002**, *31*, 109.
- [61] For selected examples, see (a) Bissen, M.; Vieillard-Baron, M.-M.; Schindelin, A. J.; Frimmel, F. H. *Chemosphere* **2001**, *44*, 751, (b) Bang, S.; Patel, M.; Lippincott, L.; Meng, X. *Chemosphere* **2005**, *60*, 389, (c) Dutta, P. K.; Pehkonen, S. O.; Sharma, V. K.; Ray, A. K. *Environ. Sci. Technol.* **2005**, *39*, 1827.
- [62] Francesconi, K. A. *Pure Appl. Chem.* **2010**, *82*, 373.
- [63] (a) Zmozinski, A. V.; Llorente-Mirandes, T.; Damin, I. C. F.; López-Sánchez, J. F.; Vale, M. G. R.; Welz, B.; Silva, M. M. *Talanta* **2015**, *134*, 224, (b) Petursdottir, A. H.; Gunnlaudsdottir, H.; Jorundsdottir, H.; Raab, A.; Krupp, E. M.; Feldmann, J. *Pure Appl. Chem.*

- 2012**, 84, 191, (c) Duarte, F. A.; Pereira, J. S. F.; Barin, J. S.; Mesko, M. F.; Dressler, V. L.; Flores, E. M. M.; Knapp, G. *J. Anal. At. Spectrom.* **2009**, 24, 224.
- [64] Devesa, V.; Macho, M. L.; Jalón, M.; Urieta, I.; Muñoz, O.; Súnier, M. A.; López, F.; Vélez, D.; Montoro, R. *J. Agric. Food Chem.* **2001**, 49, 4132.
- [65] Schmidt, L.; Landero, J. A.; Santos, R. F.; Mesko, M. F.; Mello, P. A.; Flores, E. M. M.; Caruso, J. A. *J. Anal. At. Spectrom.* **2017**, 32, 1490.
- [66] Schmidt, L.; Bizzi, C. A.; Duarte, F. A.; Muller, E. I.; Krupp, E.; Feldmann, J.; Flores, E. M. M. *Food Control* **2015**, 47, 413.
- [67] (a) Popowich, A.; Zhang, Q.; Le, X. C. *Natl. Sci. Rev.* **2016**, 3, 451, (b) Caumette, G.; Koch, I.; Reimer, K. J. *J. Environ. Monit.* **2012**, 14, 2841.
- [68] (a) *Handbook of Toxicology of Chemical Warfare Agents*; Gupta, R. C., Ed.; Academic Press, 2009 (b) Dill, K.; O'Connor, R. J.; McGown, E. L. *Inorg. Chim. Acta.* **1990**, 168, 11, (c) Stocken, L. A.; Thompson, R. H. S. *Physiol. Rev.* **1949**, 29, 168.
- [69] (a) Barthold, C. L.; Schier, J. G. *Crit. Care Clin.* **2005**, 21, 673, (b) Yang, Y.-C. *Acc. Chem. Res.* **1999**, 32, 109.
- [70] (a) Clancy, T. M.; Hayes, K. F.; Raskin, L. *Environ. Sci. Technol.* **2013**, 47, 10799, (b) Mandal, P.; Debbarma, S. R.; Saha, A.; Ruj, B. *Procedia Environ. Sci.* **2016**, 35, 943.
- [71] Allred, A. L.; Hensley Jr, A. L. *J. Inorg. Nucl. Chem.* **1961**, 17, 43.
- [72] Lloyd, N. C.; Morgan, H. W.; Nicholson, B. K.; Ronimus, R. S. *Angew. Chem. Int. Ed.* **2005**, 44, 941.
- [73] (a) Pitzer, K. S. *J. Am. Chem. Soc.* **1948**, 70, 2140, (b) Mulliken, R. S. *J. Am. Chem. Soc.* **1950**, 72, 4493, (c) Jutzi, P. *Angew. Chem. Int. Ed.* **1975**, 14, 232.
- [74] (a) Kojima, A.; Honzawa, S.; Boden, C. D. J.; Shibasaki, M. *Tetrahedron Lett.* **1997**, 38, 3455, (b) Denmark, S. E.; Ober, M. H. *Adv. Synth. Catal.* **2004**, 346, 1703, (c) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, 113, 9585, (d) Rossi, R.; Bellina, F.; Carpita, A.;

- Mazzarella, F. *Tetrahedron* **1996**, *52*, 4095, (e) Baber, R. A.; Collard, S.; Hooper, M.; Orpen, A. G.; Pringle, P. G.; Wilkinson, M. J.; Wingad, R. L. *Dalton Trans.* **2005**, 1491, (f) Trost, B. M.; Edstrom, E. D.; Carter-Petillo, M. B. *J. Org. Chem.* **1989**, *54*, 4489, (g) Ceccarelli, S.; Piarulli, U.; Gennari, C. *J. Org. Chem.* **2000**, *65*, 6254.
- [75] Tähtinen, P.; Saielli, G.; Guella, G.; Mancini, I.; Bagno, A. *Chem. Cur. J.* **2008**, *14*, 10445.
- [76] Mancini, I.; Guella, G.; Frostin, M.; Hnawia, E.; Laurent, D.; Debitus, C.; Pietra, F. *Chem. Eur. J.* **2006**, *12*, 8989.
- [77] (a) Lu, D.; Rae, D.; Salem, G.; Weir, M. L.; Willis, A. C.; Wild, S. B. *Organometallics* **2010**, *29*, 32, (b) Lu, D.; Coote, M. L.; Ho, J.; Kilah, N. L.; Lin, C.-Y.; Salem, G.; Weir, M. L.; Willis, A. C.; Wild, S. B.; Dilda, P. J. *Organometallics* **2012**, *31*, 1808.
- [78] Johansson, M. P.; Juselius, J. *Lett. Org. Chem.* **2005**, *2*, 469.
- [79] (a) Sennyey, G.; Mathey, F. *Tetrahedron Lett.* **1981**, *22*, 4713, (b) Yao, W.; Ma, M.; Wang, W.; Cheng, J.; Xu, L.; Pullarkat, S. A.; Leung, P.-H. *Tetrahedron:Asymmetry* **2014**, *25*, 1100.
- [80] (a) Cho, S. Y.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 1773, (b) Kojima, A.; Boden, C. D. J.; Shibasaki, M. *Tetrahedron Lett.* **1997**, *38*, 3459.
- [81] (a) Nachman, K. E.; Baron, P. A.; Raber, G.; Francesconi, K. A.; Navas-Acien, A.; Love, D. C. *Environ. Health Perspect.* **2013**, *121*, 828, (b) Konkel, L. *Environ. Health Perspect.* **2016**, *124*, 124.
- [82] Haartz, J. C.; Eller, P. M.; Hornung, R. W. *Anal. Chem.* **1979**, *51*, 2293.
- [83] Edmonds, J. S.; Francesconi, K. A.; Cannon, J. R.; Raston, C. L.; Skelton, B. W.; White, A. H. *Tetrahedron Lett.* **1977**, *18*, 1543.
- [84] Adair, B. M.; Waters, S. B.; Devesa, V.; Drobna, Z.; Styblo, M.; Thomas, D. J. *Environ. Chem.* **2005**, *2*, 161.
- [85] (a) Ng, J. C. *Environ. Chem.* **2005**, *2*, 146, (b) Francesconi, K. A. *Environ. Chem.* **2005**, *2*, 141.

- [86] Dai, W.-M.; Wu, A.; Wu, H. *Tetrahedron:Asymmetry* **2002**, *13*, 2187.
- [87] (a) Kato, T.; Tanaka, S.; Naka, K. *Chem. Lett.* **2015**, *44*, 1476, (b) Ishidoshiro, M.; Matsumura, Y.; Imoto, H.; Irie, Y.; Kato, T.; Watase, S.; Matsukawa, K.; Inagi, S.; Tomita, I.; Naka, K. *Org. Lett.* **2015**, *17*, 4854.
- [88] (a) Blicke, F. F.; Smith, F. D. *J. Am. Chem. Soc.* **1930**, *52*, 2946, (b) Sollott, G. P.; Peterson Jr., W. R. *J. Org. Chem.* **1965**, *30*, 389, (c) Merijanian, A.; Zingaro, R. A. *Inorg. Chem.* **1966**, *5*, 187, (d) Ioannou, P. V. *Appl. Organometal. Chem.* **2000**, *14*, 261.
- [89] (a) Blicke, F. F.; Smith, F. D. *J. Am. Chem. Soc.* **1929**, *51*, 1558, (b) Blicke, F. F.; Smith, F. D. *J. Am. Chem. Soc.* **1929**, *51*, 3479, (c) Blicke, F. F.; Cataline, E. L. *J. Am. Chem. Soc.* **1938**, *60*, 419.
- [90] Gregson, A. M.; Wales, S. M.; Bailey, S. J.; Keller, P. A. *J. Organomet. Chem.* **2015**, 785, 77.
- [91] For examples of synthesizing cyclic arsines with arsenic halides, see (a) Lambert, J. B.; Sun, H.-N. *J. Org. Chem.* **1977**, *42*, 1315, (b) Gruttner, G.; Wiernik, M.; *Ber. Dtsch. Chem. Ges.* **1915**, *48*, 1473, (c) Garje, S. G.; Jain, V. K.; Varghese, B. *Appl. Organometal. Chem.* **1999**, *13*, 47, (d) Monagle, J. J. *J. Org. Chem.* **1962**, *27*, 3851.
- [92] Kyba, E. P.; Chou, S.-S. P. *J. Am. Chem. Soc.* **1980**, *102*, 7012.
- [93] DuBois, T. D.; Smith, F. T. *Inorg. Chem.* **1973**, *12*, 735.
- [94] (a) Wittenberg, D.; Gilman, H. *J. Org. Chem.* **1958**, *23*, 1063, (b) Morris, T. L.; Taylor, R. C. *J. Chem. Soc., Dalton Trans.* **1973**, 175, (c) Mann, F. G.; Pragnell, M. J. *J. Chem. Soc.* **1965**, 4210, (d) Ellerman, J.; Schössner, H.; Haag, A.; Schödel, H. *J. Organomet. Chem.* **1974**, *65*, 33.
- [95] Ng, J. K.-P.; Tan, G.-K.; Vittal, J. J.; Leung, P.-H. *Inorg. Chem.* **2003**, *42*, 7674.
- [96] Bader, A.; Kang, Y. B.; Pabel, M.; Pathak, D. D.; Willis, A. C.; Wild, S. B. *Organometallics* **1995**, *14*, 1434.

- [97] Tanaka, S.; Imoto, H.; Kato, T.; Naka, K. *Dalton Trans.* **2016**, 45, 7937.
- [98] Roering, A. J.; Davidson, J. J.; MacMillan, S. N.; Tanski, J. M.; Waterman, R. *Dalton Trans.* **2008**, 4488.
- [99] Bange, C. A.; Waterman, R. *Polyhedron* **2018**, 156, 31.
- [100] The mechanism of the LMCT event is proposed to be analogous to the light-driven catalytic hydrophosphination reaction. Bange, C. A.; Conger, M. A.; Novas, B. T.; Young, E. R.; Liptak, M. D.; Waterman, R. *ACS Catal.* **2018**, 8, 6230.
- [101] Maitra, K.; Catalano, V. J.; Clark III, J.; Nelson, J. H. *Inorg. Chem.* **1998**, 37, 1105.
- [102] (a) Ma, M.; Lu, R.; Pullarkat, S. A.; Deng, W.; Leung, P.-H. *Dalton Trans.* **2010**, 39, 5453, (b) Ma, M.; Pullarkat, S. A.; Yuan, M.; Zhang, N.; Li, Y.; Leung, P.-H. *Organometallics* **2009**, 28, 4886, (c) Ma, M.; Yu, Z.; Zhu, L.; Pullarkat, S. A.; Leung, P.-H. *J. Organomet. Chem.* **2014**, 756, 34.
- [103] (a) Ma, M.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. *J. Organomet. Chem.* **2008**, 693, 3289, (b) Ma, M.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. *Inorg. Chem.* **2007**, 46, 9488, (c) Tan, K.-W.; Liu, F.; Li, Y.; Tan G.-K.; Leung, P.-H. *J. Organomet. Chem.* **2006**, 691, 4753.
- [104] (a) Mann, F. G.; Baker, F. C. *J. Chem. Soc.* **1952**, 4142, (b) Jones, E. R. H.; Mann, F. G. *J. Chem. Soc.* **1955**, 411.
- [105] (a) Uberman, P. M.; Lanteri, M. N.; Martín, S. E. *Organometallics* **2009**, 28, 6927, (b) Quinteros, G. J.; Uberman, P. M.; Martín, S. E. *Eur. J. Org. Chem.* **2015**, 2698, (c) Bonaterra, M.; Martín, S. E.; Rossi, R. A. *Org. Lett.* **2003**, 5, 2731, (d) Martín, S. E.; Bonaterra, M.; Rossi, R. A. *J. Organomet. Chem.* **2002**, 664, 223, (e) Uberman, P. M.; Caira, M. R.; Martín, S. E. *Organometallics* **2013**, 32, 3220, (f) Uberman, P. M.; Lanteri, M. N.; Puenzo, S. C. P.; Martín, S. E. *Dalton Trans.* **2011**, 40, 9229.

- [106] (a) Kwong, F. Y.; Lai, C. W.; Yu, M.; Tan, D.-M.; Lam, F. L.; Chan, A. S. C.; Chan, K. S. *Organometallics* **2005**, *24*, 4170, (b) Kwong, F. Y.; Lai, C. W.; Chan, K. S. *J. Am. Chem. Soc.* **2001**, *123*, 8864.
- [107] For selected examples, see (a) O’Keefe, D. F.; Dannock, M. C.; Marcuccio, S. M. *Tetrahedron Lett.* **1992**, *33*, 6679, (b) Segelstein, B. E.; Butler, T. W.; Chenard, B. L. *J. Org. Chem.* **1995**, *60*, 12, (c) Hunt, A. R.; Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1993**, *34*, 3599, (d) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918, (e) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694, (f) Ghosh, A.; Sieser, J. E.; Riou, M.; Cai, W.; Rivera-Ruiz, L. *Org. Lett.* **2003**, *5*, 2207, (g) Barañano, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 2937.
- [108] (a) Nakahashi, A.; Naka, K.; Chujo, Y. *Organometallics* **2007**, *26*, 1827, (b) Arita, M.; Naka, K.; Morisaki, Y.; Nakahashi, A.; Chujo, Y. *Organometallics* **2009**, *28*, 6109.
- [109] Berger, H.-O.; Nöth, H. *J. Organomet. Chem.* **1983**, *250*, 33.
- [110] (a) Rossi, R. A.; Alonso, R. A.; Palacios, S. M. *J. Org. Chem.* **1981**, *46*, 2498, (b) Pierini, A. B.; Rossi, R. A. *J. Org. Chem.* **1979**, *44*, 4667.
- [111] Maier, L.; Rochow, E. G.; Fernelius, W. C. *J. Inorg. Nucl. Chem.* **1961**, *16*, 213.
- [112] Grund, S. C.; Hanusch, K.; Wolf, H. U. *Arsenic and Arsenic Compounds*, 2008. DOI: 10.1002/14356007.a03_113.pub2
- [113] Bungabong, M. L.; Tan, K. W.; Li, Y.; Selvaratnam, S. V.; Dongol, K. G.; Leung, P.-H. *Inorg. Chem.* **2007**, *46*, 4733.
- [114] Cheow, Y. L.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. *J. Organomet. Chem.* **2012**, *696*, 4215.
- [115] In the absence of this Pd–O interaction, C–O bond cleavage (via an S_N⁺ pathway, for instance) was not observed. Pullarkat, S. A.; Yi, S.; Li, Y.; Tan, G.-K.; Leung, P.-H. *Inorg. Chem.* **2006**, *45*, 7455.

- [116] Liu, F.; Pullarkat, S. A.; Li, Y.; Chen, S.; Leung, P.-H. *Eur. J. Inorg. Chem.* **2009**, 4134.
- [117] Huang, Y.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. *Chem. Commun.* **2010**, 46, 6950.
- [118] Huang, Y.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. *Inorg. Chem.* **2012**, 51, 2533.
- [119] (a) Leung, P.-H.; Siah, S. Y.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Dalton Trans.* **1998**, 27, 893, (b) Leung, P.-H.; Loh, S. K.; Mok, K. F.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1996**, 42, 591, (c) Leung, P.-H.; He, G.; Lang, H.; Liu, A.; Loh, S. K.; Selvaratnam, S.; Mok, K. F.; White, A. J. P.; Williams, D. J. *Tetrahedron* **2000**, 56, 7, (d) Leung, P.-H.; Loh, S. K.; Vittal, J. J.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1997**, 43, 1987, (e) Leung, P.-H.; Lang, H. F.; White, A. J. P.; Williams, D. J. *Tetrahedron: Asymmetry* **1998**, 9, 2961, (f) Loh, S. K.; Mok, K. F.; Leung, P.-H.; White, A. J. P.; Williams, D. J. *Tetrahedron: Asymmetry* **1996**, 7, 45.
- [120] Yang, X.-Y.; Gan, J. H.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Dalton Trans.* **2015**, 44, 1258.
- [121] Yang, X.-Y.; Jia, Y.-X.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Dalton Trans.* **2016**, 45, 13449.
- [122] (a) Chew, R. J.; Sepp, K.; Li, B.-B.; Li, Y.; Zhu, P.-C.; Tan, N. S.; Leung, P.-H. *Adv. Synth. Catal.* **2015**, 357, 3297, (b) Chew, R. J.; Lu, Y.; Jia, Y.-X.; Li, B.-B.; Wong, E. H. Y.; Goh, R.; Li, Y.; Huang, Y.; Pullarkat, S. A.; Leung, P.-H. *Chem. Eur. J.* **2014**, 20, 14514, (c) Chew, R. J.; Li, X.-R.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Chem. Eur. J.* **2015**, 21, 4800, (d) Huang, Y.; Li, Y.; Leung, P.-H.; Hayashi, T. *J. Am. Chem. Soc.* **2014**, 136, 4865, (e) Chew, R. J.; Teo, K. Y.; Huang, Y.; Li, B.-B.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Chem. Commun.* **2014**, 50, 8768, (f) Huang, Y.; Chew, R. J.; Pullarkat, S. A.; Leung, P.-H. *J. Org. Chem.* **2012**, 77, 6849, (g) Huang, Y.; Pullarkat, S. A.; Teong, S.; Chew, R. J.; Li, Y.; Leung, P.-H. *Organometallics* **2012**, 31, 4871, (h) Huang, Y.; Chew, R. J.; Li, Y.; Pullarkat, S. A.; Leung,

- P.-H. *Org. Lett.* **2011**, *13*, 5862, (i) Yang, X.-Y.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Organometallics* **2015**, *34*, 5196.
- [123] (a) Li, X.-R.; Yang, X.-Y.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Dalton Trans.* **2017**, *46*, 1311, (b) Li, X.-R.; Chen, Y.; Pang, B. P.; Tan, J.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Eur. J. Inorg. Chem.* **2018**, *2018*, 4385.
- [124] Yang, X.-Y.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Organometallics* **2015**, *34*, 1582.
- [125] Wong, E. H. Y.; Jia, Y.-X.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *J. Organomet. Chem.* **2018**, *862*, 22.
- [126] (a) Yang, X.-Y.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Chem. Commun.* **2016**, *52*, 4211, (b) Balázs, L. B.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Organometallics* **2018**, *37*, 2272.
- [127] Tay, W. S.; Yang, X.-Y.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *RSC Adv.* **2016**, *6*, 75951.
- [128] Ananikov, V. P.; Tanaka, M. *Top. Organomet. Chem.* **2013**, *43*, 1.
- [129] (a) Glueck, D. S. *Top. Organomet. Chem.* **2010**, *31*, 65, (b) Sadow, A. D.; Togni, A. *J. Am. Chem. Soc.* **2005**, *127*, 17012, (c) Chew, R. J.; Leung, P.-H. *Chem. Rec.* **2016**, *16*, 141, (d) Pullarkat, S. A. *Synthesis* **2016**, *48*, 493, (e) Sadow, A. D.; Haller, I.; Fadini, L.; Togni, A. *J. Am. Chem. Soc.* **2004**, *126*, 14704.
- [130] (a) Roesky, P. W.; Müller, T. E. *Angew. Chem. Int. Ed.* **2003**, *42*, 2708, (b) Hultsch, K. *C. Adv. Synth. Catal.* **2005**, *347*, 367, (c) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. *J. Chem. Rev.* **2015**, *115*, 2596.
- [131] Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998; p 30.

Chapter 2

Pd-catalyzed asymmetric hydroarsination reactions

2.1 Introduction

Based on the close group relationship between As and P, it was envisioned that the most efficient way to develop the catalytic asymmetric hydroarsination reaction was to systematically adapt conditions used for the catalytic asymmetric hydrophosphination reaction. Arsines are generally regarded as less nucleophilic than the corresponding phosphines,¹ which suggest that hydroarsination reactions proceeding by nucleophilic addition are challenged by poorer reactivity. Activation of the H–E (E = As, P) bond is also of significant relevance in such addition reactions (Scheme 44). Conversely, the lower pK_a of arsines (pK_a of HPPPh₂ =

Scheme 44. Representation of the addition of secondary arsines/phosphines to a C=C bond.

21.7, pK_a of HAsPh₂ = 20.3)² predicted that milder or less activating conditions were required for hydroarsination reactions to achieve similar reactivities. However, factors such as ionization potentials, bond energies and energies of solvation operate in tandem and therefore, accurately predicting the reactivity of phosphine or arsine nucleophiles under experimental conditions can be complex.³ In addition, the introduction of a transition metal catalyst to fine-tune reactivity, regio- and stereo-selectivities introduces additional electronic, steric and rate variables that reduce the predictability of experimental outcomes. With the precedence that established catalytic systems for the asymmetric hydrophosphination reaction hold some (albeit indeterminate) potential to promote the corresponding hydroarsination reaction, it was both valid and crucial that experimental investigations were conducted to evaluate this potential.

Different catalytic systems (eg. complexes based on platinum group metals, cinchona alkaloids, amino acid organocatalysts)⁴ have been applied to the asymmetric hydrophosphination reaction with differing degrees of success. With palladium-based complexes being the most established catalysts for the asymmetric hydrophosphination reaction thus far, the asymmetric hydroarsination reaction was first investigated with bidentate and tridentate complexes of palladium.

2.1.1 Bidentate palladacycle catalysts

Enantiopure bidentate palladacycles currently employed in hydrophosphination reactions are notably challenging to synthesize. Unlike the plentiful options for bisphosphines bearing central (eg. DuPhos, DIPAMP), axial (eg. BINAP, SegPhos) and planar (eg. JosiPhos) chirality elements, chiral palladacycles are typically synthesized from commercially-available (1-naphthyl)ethylamine **108** (Figure 7) and therefore lack variety in their structural scaffold.

Figure 7. Structure of (1-naphthyl)ethylamine **108**.

CN-palladacycles derived from amine **108** were rather inefficient in the hydrophosphination reaction, requiring up to 1 week for complete conversion (Scheme 45).⁵ Alternatively,

Scheme 45. Hydrophosphination reaction catalysed by CN-palladacycle **70**.

enantiopure phosphapalladacycles could be directly synthesized from commercially-available MOP ligands and such complexes have been employed in the hydrophosphination of achiral heterobicyclic alkenes (Scheme 46).⁶

Scheme 46. Hydrophosphination reaction catalysed by CP-palladacycle **111**.

In order to tune the electronic or steric profile of such complexes, secondary modifications have been made by auxiliary ligand substitution. Strongly-coordinating N-heterocyclic carbene ligands have been used to increase the steric bulk around Pd although complexes **112** were catalytically less active than the parent CN-palladacycle **70** (Scheme 47).⁷

Scheme 47. Hydrophosphination reaction catalysed by CN-palladacycle **112**.

The desired pre-ligand could alternatively be synthesized from scratch, although such racemic syntheses understandably required an often-lengthy and tedious subsequent optical resolution

Scheme 48. From-scratch synthesis of CP-palladacycle **78**.

process. In the synthesis of CP-palladacycle **78** by our group, chiral transcyclometalating agents (such as CN-palladacycle **115** itself) were employed to resolve the racemic pre-ligand, followed by C–H bond activation and auxiliary halide cleavage to generate the desired palladacycle in overall yield of 42% (Scheme 48).⁸ Fortunately, CP-palladacycle **78**, as previously discussed in Chapter 1, turned out to exhibit much better activity for the catalytic asymmetric hydrophosphination reaction than CN-palladacycle **70** (Scheme 49).⁹

Scheme 49. Hydrophosphination reaction catalysed by CP-palladacycle **78**.

While there are only a handful of bidentate palladacycles acting as hydrophosphination catalysts, their reactivity as catalyst for other transformations have been well-established.¹⁰ Catalyst decomposition was a limiting factor for such bidentate palladacycles when subjected to high temperatures, long reaction times or highly-reactive/coordinating reagents. Decomposition either resulted in the release of palladium black or highly reactive colloidal palladium nanoparticles.¹¹ Clearly, subsequent catalysis by such $\text{Pd}(0)$ species would result in racemic transformations due to the loss of the chiral ligand.

2.1.2 Tridentate palladacycle catalysts

Tridentate palladacycles belong to a subgroup of cyclopalladated complexes termed as “pincer complexes”. These complexes are identified by their characteristic bonding mode involving a tridentate organic ligand chelating to a metal core in a meridional fashion, giving rise to two fused bicyclic chelate rings.¹² Generally, such complexes are referred to by their coordinating atoms- an EYE-M pincer complex would denote a monoanionic ligand bearing two neutral donor atoms (E) and one anionic donor atom (Y) coordinated to a metal centre (M). This tridentate framework allows for a significant degree of fine-tuning of electronic and steric

factors by varying the nature of and substituents on the E, Y and X (auxiliary ion) directly bonded to the metal (Figure 8). In comparison to bidentate cyclopalladated complexes, pincer

Figure 8. Representative diagram of a typical pincer scaffold.

complexes exhibit heightened stabilities to heat, air and moisture, thus allowing easy handling, storage and improved durability in catalytic cycles.¹² For square planar, four-coordinate systems such as Pd(II) complexes, tridentate pincer ligands also reduces the number of free coordination sites available for catalysis to one, thereby limiting the formation of undesirable side products from the ligand exchange process. Reduction to Pd(0) often causes an irreversible cleavage of the Pd–Y (usually Pd–C) bond, leading to catalyst decomposition.¹¹ Resultantly, Pd(II)-pincer catalyst tend to operate as Lewis acids instead of through a Pd(0)/Pd(II) redox cycle.

PCP-Pd pincer complexes **82**¹³ and **87**¹⁴ have been established as efficient catalysts for the asymmetric hydrophosphination reaction by our group (Figure 9). The activity, substrate

Figure 9. PCP-Pd pincer complexes **82** and **87** developed by Leung.

scope and mechanism of these complexes were previously summarized in section 1.3.2. Notably, ester-functionalized complex **87** was remarkably more stereoselective than the keto-functionalized complex **82**. This was attributed to the *ring lock* phenomenon in complex **87**

(and corresponding absence in complex **82** as determined by a 2-dimensional ^1H - ^1H Nuclear Overhauser Effect spectroscopy (NOESY) experiment), which prevented a δ -to- λ interconversion of the chelate ring in solution.^{14a} In addition, the nature of the auxiliary ligand X (in particular with respect to basicity) was demonstrated to significantly influence the outcome of the catalytic hydrophosphination reaction (Scheme 50).¹³

Scheme 50. Hydrophosphination reaction catalysed by PCP-PdX (X = OAc, Cl) complexes **82**.

Another PCP-Pd pincer complex **120** developed by Duan also catalyzed the asymmetric hydrophosphination reaction effectively (Figure 10).¹⁵ As expected from the

Figure 10. PCP-Pd pincer complex (S,S)-**120** developed by Duan.

highly similar PCP ligand, both PCP-Pd pincer complexes **87** and **120** displayed similar reactivities across several examples. For example, complex **120** could also catalyze the hydrophosphination of 2-pyridyl enone **83** without catalyst poisoning (Scheme 51).¹⁶ Also,

Scheme 51. Hydrophosphination of 2-pyridyl enone **83** catalyzed by complex (S,S)-**120**.

regiodivergence was observed with substrates of different steric bulks. Although the 1,4-position was more electronically activated, complex **120** similarly favoured the formation of the 1,6-adduct for bulkier substrates (Scheme 52).¹⁷ This may seem unintuitive because the

Scheme 52. Regiodivergent hydrophosphination of various substrates catalysed by complex **120**.

methyl pendant arms of complex **120** are arguably less bulky than the malonate moieties of complex **87**. However, the steric profile of a pincer complex is more commonly assessed by their characteristic twist angle and percent buried volume (%V_{bur}).¹⁸ A more compact conformation indicated by a lower %V_{bur} restricts the access of a reagent to the metal center at the position directly trans to the central Y donor atom,¹⁹ and therefore serves as a gauge to predict the behavior of a pincer complex when faced with reactants of different steric bulks. Most importantly, an independent investigation by Duan regarding the mechanism of complex **120**-catalyzed hydrophosphination reactions closely agreed with that derived for complex **87a**.²⁰ This involved a four-step intermolecular mechanism, namely, 1) auxiliary ligand exchange with the secondary phosphine, 2) deprotonation of the coordinated secondary phosphine to generate a phosphido intermediate, 3) P–C bond formation *via* intermolecular phospho-Michael addition, and 4) release of the phosphine product with concurrent regeneration of the active catalytic species.

On occasion, PCP-Pd pincer complexes bearing chirality on the phosphine donor atoms have also been used as catalysts.^{20,21} This includes complex *(R,R)*-**125** bearing point chirality on the phosphorus donor atom of the ligand backbone and complex *(S,S)*-**126** bearing axially-chiral substituents on the phosphorus donor atom (Figure 11). Similar to the

Figure 11. PCP-Pd pincer complexes **125** and **126** developed by Zhang and Duan respectively.

privileged ligand DIPAMP, it was believed that such P-chiral phosphine ligands imparted better stereo-control by bringing chirality elements directly adjacent to the reaction site.²² It must be clear, however, that such ligand designs do not guarantee superior (or even good) stereoselectivity. For example, complex *(R,R)*-**125** furnished nitro-functionalized phosphine oxide **128a** in lower *ee*'s than complex *(S,S)*-**126** under their respective optimized conditions (Scheme 53).^{21,23} In addition, complex *(S,S)*-**125** was determined to afford racemic products in

Scheme 53. Hydrophosphination of nitrostyrene **127a** catalysed by complexes **125** and **126**.

a preliminary catalyst screening for the hydrophosphination of enone substrates and subsequent optimization was thus discontinued.²⁰

As an alternative to PCP-Pd pincer complexes, unsymmetrical PCN-Pd and C₂-symmetric NCN-Pd pincer complexes have been reported to catalyze hydrophosphination reactions (Figure 12).²⁴ These complexes are generally more electron-rich at palladium as

Figure 12. PCN-Pd complex **129** and NCN-Pd complex **130** developed by Gong and Song.

compared to their PCP-Pd counterparts because of the σ -donating and non- π -withdrawing properties of the amine donor atom.²⁵ Nevertheless, their reactivities remained comparable to PCP-Pd complexes **87a** and **120** and hydrophosphinated enones were also obtained in excellent *ee*'s (up to 98% *ee*'s) within 12 h.^{24a,c} No mechanism was proposed and it was undetermined if PCN complexes **129** and **130** proceeded by a similar Lewis-acid activation of the secondary phosphine reagent. It may be interesting to note that PCN-Pd complex **129** was the first example of an unsymmetrical pincer complex used as a catalyst for the asymmetric hydrophosphination reaction (as opposed to the C_2 -symmetric pincer complexes of **87a**, **120**, and **130**). Although C_2 -symmetry is often a favourable attribute in pincer complexes due to its ability to reduce the number of ways a substrate can approach the catalytic center,²⁶ unsymmetrical complexes can be specifically designed to introduce additional kinetic stability to the resulting complexes. PCN-Pd complexes have been documented to possess shorter (and by inference, stronger) P–Pd bonds as compared to their symmetrical PCP-Pd counterparts.²⁷ It remains to be clearly demonstrated how mixed-type PCN-Pd complexes can offer an edge over symmetrical PCP- and NCN-Pd pincer complexes in a catalytic scenario.

Hemilability may also manifest in tridentate pincer complexes of weaker-coordinating donor atoms such as complex **131** (Figure 13).^{14b,28} For pincer complexes which demonstrate

Figure 13. NCE-Pd (E = O, S) pincer complexes **104** and **131** developed by Leung.

transient coordination of one or both of the side arms, multiple possible reaction pathways may proceed as a result of variable number of coordination sites, steric and electronic factors upon dissociation. When not well-controlled, this may cause poor regio- and stereo-selectivity of the transformation such as that observed in Scheme 54.²⁸

Scheme 54. Regiodivergent hydrophosphination of $\alpha,\beta,\gamma,\delta$ -unsaturated malonate **79** catalyzed by NCE-Pd complexes **131**.

2.2 Results and discussion

Research questions

- 1) Moving forward from the hydrophosphination reaction, were hydroarsination reactions encumbered by incompatible catalysts, reagents or substrates?
- 2) Were hydroarsination reactions previously thought to be unsuccessful because of accidental product degradation upon workup, and not because of unreactivity?

2.2.1 Adapting hydrophosphination methodologies

2.2.1.1 With bidentate palladacycle catalysts

Overview

Bidentate palladacycle catalysts rapidly decomposed when exposed to secondary arsine reagents under hydroarsination conditions. Instead of As–H bond acidification, migratory insertion led to *ortho*-protonation of the C,P-ligand. A mechanism for the migratory insertion of As–H into the Pd–C bond was proposed. The intramolecular proton transfer mechanism explained why bidentate palladacycles were suitable for stoichiometric

hydroarsination reactions but decomposed under catalytic conditions. Nevertheless, this fundamental palladacycle reactivity was synthetically-useful in catalytic deuteration by directed *ortho*-metalation (DoM) and decomplexation strategies. In the former, HAsPh₂ was a convenient deuterium shuttle which facilitated the *ortho*-deuteration of DoM-palladacycle intermediates under neutral conditions. In the latter, HAsPh₂ afforded the preligands of monomeric, dimeric, bidentate and tridentate complexes of Pd in excellent yields of 95-98% within 30 mins at RT.

Investigating phosphapalladacycle activity towards As–H bonds

Palladacycle-activated P–H bonds have been relevant in catalytic hydrophosphination reactions while As–H bonds have never been investigated in this context.^{9,13,20,29} A key catalytic step involved coordination of the secondary phosphine to Pd which acidified the P–H bond for deprotonation. In the absence of a base, such bonds were inert and no further reactivity was observed from the phosphine-palladacycle adducts (Scheme 55).^{9,30} Notably, the Pd–C

Scheme 55. Stepwise coordination and deprotonation of P–H bonds.

bond remained inert with retention of the P,C,C,C,Pd chelate ring.

Polarizing and acidifying effects to the As–H bond were also expected upon coordination of secondary arsines to Pd. However, rapid decomposition of palladacycle **78** was observed upon addition of HAsPh₂. The decomposition was closely followed on ³¹P{¹H} NMR spectroscopy to reveal a mixture of P-containing compounds (Scheme 56, Figure 14).

Scheme 56. Decomposition of complex **78** to preligand **132**.

Unlike the well-defined signals observed from stirring palladacycle **78** with secondary phosphines,⁹ the complicated distribution prompted a consideration of non-specific decomposition pathways. Surprisingly, subsequent sulfurization of the crude solution cleanly yielded sulfurized C,P preligand **132** as the only P-containing product in 77% yield (Figure 15).

Table 1. Solvent screening for the protonolysis of complex **78**.^a

Entry	Solvent	Condition	Yield ^b (%)
1	MeOH	Regular	77(79)
2	MeOH	Anhydrous	69(75)
3	DCM	Regular	98(>99)
4	DCM	Anhydrous	56(59)
5	THF	Regular	55(60)
6	THF	Anhydrous	85(84)
7	Toluene	Regular	50(53)
8	Toluene	Anhydrous	66(68)
9	DEE	Regular	32(33)
10	DEE	Anhydrous	37(39)
11	MeCN	Regular	52(52)
12	MeCN	Anhydrous	62(66)
13 ^c	DCM	Regular	0

^aReaction conditions: complex **78** (19.50 mg, 0.03 mmol, 1.0 equiv.), HAsPh₂ (36.0 mg, 0.15 mmol, 5.0 equiv.), solvent (2.4 mL). S₈ (4.80 mg, 0.15 mmol, 5.0 equiv.) added after 30 mins. ^bIsolated yield. Yield determined by ¹H NMR with an internal standard indicated in parentheses. ^cReaction was conducted with HAsPh₂ (2.4 mg, 0.01 mmol, 1.0 equiv.) instead.

The *ortho*-protonation was consistently observed across a range of solvents (Table 1) with protonolysis occurring in good to excellent yields of up to 98% (DCM, Entry 3). In all solvents, only a single signal corresponding to phosphine sulfide **132** was observed on ³¹P{¹H}NMR spectroscopy. The reaction also proceeded smoothly under dry conditions with generally higher yields. When conducted under anhydrous aprotic conditions (DCM, THF, toluene, DEE), appreciable yields of phosphine sulfide **132** indicated that HAsPh₂ was the likely proton source (Entries 4, 6, 8, 10). Preligand **132** was not observed with a stoichiometric amount of HAsPh₂ (Entry 13), plausibly due to the absence of HAsPh₂-labilized phosphine intermediates for sequestration by S₈.

Other phosphapalladacycles were screened and quantitative yields indicated the consistence of this observation (Scheme 57). Comparable yields were obtained for the dimeric parent chloride complex **117**. Palladacycles **134-137** did not exhibit any reactivity differences between the dimeric and monomeric forms either. Increasing the steric bulk at the aryl

substituent and benzylic position did not hinder protonolysis and their respective preligands **138** and **139** were obtained in excellent yields. Non-cyclometalated complex **133** was specially-designed to probe the decomplexation pathway further. Stirring complex **133** in sulfur failed to liberate preligand **132** and HAsPh₂ was required before preligand **132** was furnished in 81% yield. Overall, the *ortho*-protonation resulting in complex decomposition made bidentate palladacycles **70** and **78** unsuitable catalysts for the hydroarsination reaction (Table 2).

Table 2. Bidentate palladacycle-catalyzed hydroarsination reaction.^a

Entry	Catalyst	Yield ^b (%)	ee ^c (%)
1	70	0	-
2	78	0	-

^aReaction conditions: nitrostyrene **127a** (14.9 mg, 0.10 mmol, 1.0 eq.), HAsPh₂ (27.6 mg, 0.12 mmol, 1.2 eq.), cat. (5.00 μmol, 5 mol %), MeOH (2 mL), RT, 24h. ^bDetermined by ¹H NMR spectroscopy. ^cDetermined by chiral HPLC of the crude reaction mixture.

Proposed mechanism

Interestingly, C,N complex **70** was effective in stoichiometric asymmetric hydroarsination reactions previously conducted by our group.³¹ Mechanistic investigations

were conducted to shed light on the reactivity differences of bidentate palladacycles under catalytic and stoichiometric conditions. HAsPh_2 is neither strongly acidic, basic, nucleophilic nor electrophilic, and mild conditions rapidly afford the protonated ligand quantitatively within 30 mins. An extensive literature search suggested that stable C,P-type palladacycles were rarely prone to protonolysis. Documented instances of Pd–C bond cleavage have required treatment with reducing agents (eg. NaBH_4)³² or strong acids (eg. 1M HCl).³³ Weaker acids such as HOAc had a negligible impact on the Pd–C bond.³⁴ Control reactions determined that complex **78** was inert to sulfurization and direct protonolysis (by acid) as expected.

The *ortho*-protonation reaction was proposed to proceed *via* a direct insertion of the As–H bond into the Pd–C_{aryl} bond with simultaneous As–H bond cleavage and C–H bond formation (Scheme 58). Coordination of HAsPh_2 *trans* to the phosphine donor (intermediate

Scheme 58. Proposed intramolecular *ortho*-protonation and decomplexation.

A) was critical in facilitating a *cis* relationship between the naphthyl acceptor and arsine proton donor. Insertion leading to protonolysis of the C,P ligand generated monodentate phosphine complex **B**. Kinetic labilization consequently allowed trapping of the tertiary phosphine by S_8 , thus furnishing sulfurized preligand **132** quantitatively.³⁵ Rapid ligand redistribution under dynamic equilibrium was expected at the last free coordination site. Several signals indicative of a monodentate Pd-coordinated phosphine (intermediate **B**) were observed on $^{31}\text{P}\{^1\text{H}\}$ NMR

spectroscopy (Figure 14). However, single crystals of intermediate **B** suitable for X-ray crystallographic analysis could not be obtained due to the reactive Pd-arsenido motif.³⁶

The regioselectivity required in intermediate **A** may be worth some mention. Without a *cis* spatial proximity between the involved C, As and H atoms, *ortho*-protonation by insertion was unlikely to occur. For stoichiometric hydroarsination reactions conducted with bidentate palladacycles **64** and **67** previously reported by our group,^{31a,b} substrate coordination occurred exclusively at the position *cis* to the naphthyl moiety (Figure 16). Consequently, *ortho*-

Figure 16. Pd-mediated stoichiometric hydroarsination reactions.

protonation by HAsPh₂ did not occur and addition to the olefin was favoured instead. This As–H migratory insertion phenomenon may, however, have manifested in the one-pot reaction involving complex **70**, pyridyl enone **71** and HAsPh₂, thus contributing to the loss in yield (Scheme 59).^{31c} Complete decomposition of complex **70** might have been prevented by the

Scheme 59. Metal-templated synthesis of pyridyl arsines.

basic pyridyl group facilitating deprotonation of HAsPh₂ before migratory insertion into the Pd–C bond occurred. It should be highlighted that the presence of other confounding variables in complexes **64**, **67** and **70** suggest that correlations drawn between regioselectivity and As–H migratory insertion are not conclusive in nature. The naphthylamine ligand of C,N-palladacycles **64**, **67** and **70** could have contributed to a different electronic/steric character of the palladacycle as opposed to the naphthylphosphine ligand of C,P-palladacycle **78**. In

addition, the presence of the vinylphosphine substrates in complexes **64** and **67** may have an overall effect on the acidity of the As–H bond as well.

Deuterium labelling experiments were conducted to establish the intramolecular nature of the protonation. Protonolysis was first conducted in aprotic deuterated solvents (THF, toluene and MeCN) with HAsPh₂ (Table 3). Preligand **132** was obtained with >99% hydrogen

Table 3. Effect of deuterated solvents on hydrogen incorporation.^a

Entry	Solvent ^b	Yield ^c (%)	H : D
1	THF-d ₈	51	>99 : 0
2	Toluene-d ₈	72	>99 : 0
3	MeCN-d ₃	68	>99 : 0
4	MeOD-d ₄	72	0 : >99
5 ^d	Toluene-d ₈	69	0 : >99
6	MeOH:MeOD = 1:1	68	87 : 13

^aReaction conditions: complex **78** (19.50 mg, 0.03 mmol, 1.0 equiv.), HAsPh₂ (36.0 mg, 0.15 mmol, 5.0 equiv.), solvent (2.4 mL). S₈ (4.80 mg, 0.15 mmol, 5.0 equiv.) added after 30 mins. ^bHAsPh₂ was first stirred in the stated solvent for 2 h at RT. ^cIsolated yield. ^dHAsPh₂ was first stirred in MeOD for 2 h at RT before the reaction was conducted in the stated solvent.

incorporation at the *ortho* position (Entries 1-3). No isotope exchange was observed when phosphine sulfide **132** was stirred in a range of deuterated solvents overnight. However, a straightforward H/D isotope exchange was identified to occur for H–AsPh₂ under neutral conditions in protic solvents. Consequently, >99% *ortho*-deuterated phosphine **132'** was isolated when HAsPh₂ was pre-stirred in MeOD (Entry 4). Similarly, >99% *ortho*-deuterated phosphine **132'** was also obtained when DAsPh₂ (derived from pre-stirring HAsPh₂ in MeOD) was reacted with complex **78** in toluene (Entry 5). A significant kinetic isotope effect was observed when a 1:1 mixture of MeOH:MeOD resulted in only 13% deuterium incorporation (Entry 6). These results were able to confirm the proposed mechanism in terms of intramolecular migratory insertion although the requirements for *cis* addition remains unproven thus far.

Applications of the *ortho*-protonation reaction

This insertion reaction immediately rationalized the inability of C,P-palladacycles to catalyze the addition of HAsPh_2 to activated olefins. On the other hand, the proposed mechanism suggested exceptional potential for application in other synthetically-valuable reactions. For instance, palladacycles have been identified as the key catalytic intermediate for directed *ortho*-metalation (DoM) strategies.³⁷ Ironically, their stability has hindered the development of catalytic deuteration (by cyclopalladation) protocols and only two weakly-coordinating palladacycles have been viable catalytic intermediates thus far.³⁸ Strongly acidic conditions were required to protonolyze the stable C,E-chelate ring thus limiting substrate scope. The convenience of employing secondary arsines as a deuterium shuttle under neutral conditions minimized the use of specialized pre-formed deuterating agents. In addition, the significant kinetic effects observed over the course of deuterium labelling may be functional when employing deuterium as a “protecting group” to facilitate cyclopalladation at an alternative less-favourable site.³⁹

Secondary arsines also demonstrated potential as a powerful palladacycle decomplexation agent. Even strongly-chelating C,P complexes were receptive to the tandem decomplexation effects of HAsPh_2 (first in protonolysis and second in kinetic labilization). Unlike other ligand-displacing agents (eg. KCN, phosphines or EDTA), the facile single-proton transfer step may be advantageous for bulky or poorly kinetically-labile complexes. For instance, rotameric and conformational fluxionality were deemed absent in NCE-pincer type complexes **131** by complimentary solid-state and 2-D ^1H - ^1H NOESY experiments.^{14b} These structurally-rigid chelate complexes were resistant to decomplexation by phosphines even under catalytic conditions.²⁸ However, HAsPh_2 rapidly afforded preligands **140** after 30 mins at RT (Scheme 60). No undesirable/uncontrolled fragmentation to the ligand backbone

Scheme 60. Decomplexation of tridentate NCE-Pd pincer complexes.

was observed for this quantitative transformation. Several features made secondary arsines favourable as a decomplexation agent. Firstly, the significant kinetic *trans* effect originating from the arsenido moiety was crucial in achieving quantitative decomplexation of strongly-chelating complexes under mild conditions. Secondly, mild chemical reactivities of secondary arsines mitigated secondary transformations to the decomplexed ligand. Lastly, excess HAsPh₂ rapidly oxidized to the highly-polar arsinic acid derivative (HOAs(O)Ph₂) under ambient conditions which remained strongly adsorbed to silica upon workup. Alternatively, HAsPh₂ could be easily washed away with hexane if ligand workup required oxygen-free environments instead.

In conclusion, both C,P- and C,N-palladacycles **70** and **78** were ineffective catalysts for the hydroarsination reaction. Instead of As–H bond acidification, a proton insertion pathway was observed for palladacycle-activated As–H bonds. Migratory insertion into the Pd–C bond led to ligand protonolysis and complex decomposition. This was markedly different from the reactivity of palladacycles with secondary phosphines under hydrophosphination conditions. Catalyst screening was continued with strongly-coordinating P,C,P-palladacycles instead to determine if the tridentate ligand could circumvent *ortho*-deprotonation by occupying both positions on palladium *cis* to the Pd–C bond.

2.2.1.2 With tridentate palladacycle catalysts

Overview

Based on its excellent track record as a hydrophosphination catalyst, PCP-Pd complex **87** was selected for initial screening in the hydroarsination reaction. Simple α,β -unsaturated

ketones were selected as the model substrate because 1) such enones have never been employed as substrates for the PCP-Pd complex **87**-catalyzed hydrofunctionalization reaction, 2) enones are only mildly electron-deficient which allowed for a clearer rate distinction based on the intrinsic P and As nucleophilicities, and 3) no regioisomers or diastereomers were expected out of the product mixture. Separate optimization processes were conducted for the hydrophosphination and hydroarsination reactions. Directly comparing catalyst behavior under their respective optimization conditions revealed that secondary arsine reagents were not direct phosphine substitutes. Reagent loading, base addition, ancillary ligand and temperature were optimized to increase both the yield and *ee* of the hydroarsination reaction. Notable differences between the two reactions were highlighted to guide further developments in the field. Lastly, respective mechanisms were proposed and contrasted for the activation of HEPH₂ (E = P, As).

Establishing catalyst activity in hydrophosphination

The catalytic activity and stereoselectivity of PCP Pd(II)-pincer complex **87** in hydrophosphination was first established with α,β -unsaturated ketone **75a** (Table 4). Acetone

Table 4. Pd-catalyzed asymmetric hydrophosphination reaction.^a

Entry	Cat.	Solvent	T (°C)	t (h)	Yield ^b (%)	<i>ee</i> ^c (%)
1	87b	Acetone	RT	24	4	ND
2	87a	Acetone	RT	8	90	81
3	87a	Acetone	-25	18	95	86
4	87a	Acetone	-40	30	96	90 (>99)(<i>S</i>) ^d
5	87a	MeOH	RT	15	88	11

^aReaction conditions: Enone **75a** (12.1 mg, 0.05 mmol, 1.0 eq.), HPPH₂ (13.96 mg, 0.08 mmol, 1.5 eq.), cat. (R,R)-**87** (2.50 μ mol, 5 mol %), solvent (2 mL). ^bIsolated yield. ^cDetermined by chiral HPLC of pure phosphine sulfide **141**. *ee* in parentheses obtained after a single recrystallization. ND = not determined. ^dAbsolute stereochemical configuration determined by X-ray crystallographic analysis.

was selected as the solvent based on previous optimization studies.^{14a} Good stereoselectivity was expected and observed for PdOAc-complex **87a** which generated phosphine sulfide **141** in 81% *ee* at RT (Entry 2). At -40 °C, phosphine sulfide **141** was isolated in 96% yield with 90% *ee* (Entry 4). A single recrystallization afforded enantiopure phosphine sulfide (*S*)-**141** (Figure 17). Notably, the poor catalytic activity of PdCl-complex **87b** in the hydrophosphination of enone **75a** suggested a stark influence of ancillary ligands on catalytic activity (Entry 1).

Figure 17. Molecular structure of chiral phosphine sulfide (*S*)-**141**.

Catalyst activity in hydroarsination

From the promising results obtained in Table 4, PdOAc-complex **87a** was further investigated for its efficiency in the corresponding hydroarsination reaction (Table 5). No arsine adduct **142a** was obtained from the hydroarsination of enone **75a** conducted in acetone (Entry 1). Further solvent screening similarly led to poor yields of arsine **142a** (Entries 2-11). With 10% *v/v* MeOH/H₂O (Entry 12) being the best-performing solvent thus far, three strategies to improve yields and stereoselectivities were attempted. Firstly, reducing the reaction temperature to 0 °C increased *ee* to 49% albeit with lower yield of 28% (Entry 13). Evidently, lower temperatures could not singlehandedly improve catalytic performance as no catalytic activity was observed below -40 °C (Entry 14). Secondly, conducting the reaction at

Table 5. Optimization of hydroarsination conditions.^a

Entry	Solvent	T (°C)	Yield ^b (%)	ee ^c (%)
1	Acetone	25	0	-
2	MeOH	25	24	13
3	EtOH	25	9	46
4	DEE	25	11	16
5	MeCN	25	0	-
6	DMSO	25	0	-
7	MeNO ₂	25	0	-
8	DCM	25	0	-
9	Toluene	25	0	-
10	THF	25	0	-
11	hexane	25	0	-
12	MeOH/H ₂ O(10%)	25	33	42
13	MeOH/H ₂ O(10%)	0	28	49
14	MeOH/H ₂ O(10%)	-40	0	-
15	MeOH/H ₂ O(10%)	35	16	40
16 ^d	MeOH/H ₂ O(10%)	25	23	41

^aReaction conditions: Enone **75a** (12.1 mg, 0.05 mmol, 1.0 eq.), HAsPh₂ (17.26 mg, 0.08 mmol, 1.5 eq.), cat. (5 mol %), solvent (2 mL). ^b¹H NMR yield with respect to enone **75a**. ^cDetermined by chiral HPLC of the crude reaction mixture. ^dCat. (R,R)-**87a** (6.74 mg, 7.50 μmol, 15 mol %) was used instead.

35 °C resulted in a diminished yield of 16% (Entry 15) even though higher temperatures typically improve reactivities. Lastly, increasing the catalyst loading to 15 mol % decreased yield to 23% (Entry 16).

During the PdOAc-complex **87a**-catalyzed hydroarsination reaction, a homocoupling of diphenylarsine to form tetraphenyldiarsine **143** was observed and confirmed by X-ray crystallography (Figure 18). Formally an As(II) species, various synthetic methods have been described for the formation of tetraphenyldiarsine **143** from diphenylarsine in the presence of iodine, chloramines, haloarsines, tetraphenylarsyloxide ((Ph₂As)₂O) and triphenylmethane.⁴⁰ Additional screening revealed that diarsine **143** could also be isolated from diphenylarsine with 1) heating at 50°C in MeOH/H₂O (10% v/v), 2) PdOAc-complex **87a** (5 mol %) or 3) DIPEA

Figure 18. Molecular structure of diarsine **143**.

Scheme 61. Formation of diarsine **143** from HAsPh₂.

(1.1 equivalents) (Scheme 61), plausibly from the formation of diphenylhydroxyarsine Ph₂AsOH⁻⁴¹ an unstable intermediate known to spontaneously decompose into tetraphenylarsyloxide ((Ph₂As)₂O).^{40b} These conditions correlated well with the lower yields observed when enone **75a** was hydroarsinated at higher temperatures (Entry 15) or with increased catalyst loading (Entry 16). It is worth mentioning that no arsine product **142a** was formed when diarsine **143** was used as an alternative arsine precursor in the presence of catalyst **87a**.

Effect of base on hydroarsination

Subsequently, the use of water as an additive, high temperatures and PdOAc-complex **87a** were avoided. Since DIPEA was able to generate diarsine **143**, bases were screened to improve their compatibility with HAsPh₂. PdCl-complex **87b** bearing a non-basic counteranion was optimized for activity and stereoselectivity (Table 6). To fully observe the influence of

Table 6. Optimization of conditions for PCP Pd-Cl catalyst **87b**.^a

Entry	Base	T (°C)	Yield ^b (%)	ee ^c (%)
1	-	RT	0	-
2	K ₂ CO ₃	RT	55	62
3	DIPEA	RT	36	11
4	Pyridine	RT	16	31
5	NaSO ₃	RT	49	71
6	K ₃ PO ₄	RT	60	19
7	Na ₂ CO ₃	RT	5	44
8	NaHCO ₃	RT	28	1
9	KF ^d	RT	24	66
10	CsCl ^d	RT	36	61
11	KCl ^d	RT	0	-
12	CsF	RT	18	56
13	CsF (2 equiv.)	RT	40	71
14	CsF (5 equiv.)	RT	54	74
15	CsF (10 equiv.)	RT	72	85
16	CsF (20 equiv.)	RT	73	81
17	CsF (10 equiv.)	0	54	80
18	CsF (10 equiv.)	-20	23	65
19	CsF (10 equiv.)	35	63	70
20 ^e	CsF (10 equiv.)	RT	55	81
21 ^f	CsF (10 equiv.)	RT	91	85

^aReaction conditions: Enone **75a** (12.1 mg, 0.05 mmol, 1.0 eq.), HAsPh₂ (17.26 mg, 0.08 mmol, 1.5 eq.), cat. (*R,R*)-**87b** (2.12 mg, 2.50 μmol, 5 mol %), base (0.05 mmol, 1.0 eq.), solvent (2 mL). ^b¹H NMR yield. ^cDetermined by chiral HPLC of the crude reaction mixture. ^dBase (0.50 mmol, 10 equiv.) was used instead. ^eReaction was stirred for 50 h instead.

^fHAsPh₂ (36.82 mg, 0.16 mmol, 3 equiv.) was used instead.

bases on the reaction, EtOH was selected to suppress any background reaction in the absence of a base (Entry 1). Overall, 10 equivalents of CsF afforded arsine **142a** in the highest yield (72%) and *ee* (85%) (Entry 15). Cross examination clearly demonstrated the non-negligible effect of both cation (Cs⁺) and anion (F⁻) on stereoselectivity and yield (Entries 9-12). A potential combination of factors such as 1) an increase of the solvent's dielectric constant leading to the stabilization of catalytic intermediates,⁴² 2) minimizing the competing achiral

base-catalyzed reaction, and 3) substrate activation by hydrogen bonding, were likely operative in the observed improvement of reactivities and stereoselectivities. Due to the large excess of CsF under optimized conditions (200 mol % of catalyst **87b**), the possible formation of species bearing a Pd–F bond cannot be conclusively dismissed, although this remains unlikely given the mild reaction conditions.⁴⁴ It should be noted that the complexity of a catalytic system makes it difficult to detangle such effects without in depth investigations and other catalytic systems were pursued in favour of a demanding mechanistic study in this instance (see Chapter 3).⁴⁵ Several loadings of CsF were screened (Entries 12-16) which revealed a positive relationship between CsF concentration, yields and stereoselectivities (Figure 19).⁴⁶ No

Figure 19. Relationship between [CsF], yield and *ee*.

complication arose from the plausible formation of diarsine **143** even with a large excess of CsF. As expected, low and high temperatures were less favourable for yields (23-63%) and *ee*'s (65-80%) (Entries 17-19). Longer reaction times of up to 50 h was unsuccessful in raising reaction yields (Entry 20). Instead, yield could be increased to 91% without compromising stereoselectivities (85% *ee*) by using 3 equivalents of diphenylarsine (Entry 21).

Substrate scope

Under optimized conditions, PdCl-catalyst **87b** was screened for substrate tolerance (Table 7). The hydroarsination reaction proceeded smoothly for less-sterically hindered substrates with substituents at the *para* position. Generally, stereoselectivities were relatively

Table 7. Substrate scope of Pd-Cl cat. **87b**.^a

Entry	75	Ar	Yield ^b (%)	<i>ee</i> ^c (%)
1	75a	4-ClC ₆ H ₄	72	85
2	75b	C ₆ H ₅	45	78
3	75c	4-OCH ₃ C ₆ H ₄	34	72
4	75d	4-CH ₃ C ₆ H ₄	36	81
5	75e	4-CF ₃ C ₆ H ₄	73	84

^aReaction conditions: Enone **75** (0.05 mmol, 1.0 eq.), HAsPh₂ (17.26 mg, 0.08 mmol, 1.5 eq.), cat. (*R,R*)-**87b** (2.19 mg, 2.50 μmol, 5 mol %), CsF (76.0 mg, 0.50 mmol, 10.0 eq.), solvent (2 mL). ^b¹H NMR yield. ^cDetermined by chiral HPLC of the crude reaction mixture.

consistent at 72-85% *ee* (Entries 1-5). Yields of arsine adduct **142** were lower (34-45%) for electron-rich enones **142b-d** (Entries 2-4). Conversely, comparable yields were observed for enones with 4-chloro (**142a**, 72% yield) and 4-trifluoromethyl (**142e**, 73% yield) substituents (Entries 1 and 5). Enones bearing substituents at the 2'- and 3'-positions of the aryl ring were incompatible with catalyst **87b** and poor overall reactivity was observed. With electronic and stereochemical limitations imposed by PdCl-catalyst **87b**, an existing repository of other pincer complexes bearing structurally dissimilar ligands may be advantageous.

Comparing the hydrophosphination and hydroarsination reactions

Differences in handling phosphine and arsine derivatives of enone **75** were highlighted as a reference for future adaptive work (Table 8). Typically, free hydrophosphination adducts were protected prior to work-up for ease of handling. Reagents chemically reacted with (H₂O₂,^{20,21,24a,c,28} S₈^{14b,47} etc.) or coordinated to (BH₃,²³ transition metals^{5,8b,13} the free tertiary phosphines which converted them to bench-stable compounds tolerant of common purification processes (eg. extraction, column chromatography). However, such reagents were incompatible

Table 8. Summary of differences.

	E = As	E = P
Stability of E(III) state	Higher	Lower
Common workup procedure	No protection	Protection of lone pair (eg. with H ₂ O ₂ , S ₈ , BH ₃)
Byproduct formation	Ph ₂ As–AsPh ₂	Ph ₂ P–PPh ₂ (slow)
Stereoselectivity of hydrofunctionalization ^a	Lower	Higher
Scope of chiral ligands	Limited (eg. PCP)	More (eg. PCP, NCN, PCN, NCS, CP, CN)

^aWith respect to PCP Pd catalyst **87** used.

(H₂O₂, transition metals) or unreactive (S₈, BH₃) with arsines **142** and degraded products such as enone **75** were observed. In fact, free arsines **142** were stable in solid and solution states and resisted oxidation under ambient conditions for a prolonged period of time. Other reactivity differences were also observed for secondary phosphines and arsines. No formation of tetraphenyldiphosphine was observed under conditions that rapidly form tetraphenyldiarsine **143** (Scheme 61). Consequently, higher loadings of arsine were required for comparable yields. The hydrophosphination of enone **75** was slightly more stereoselective than the corresponding hydroarsination under respective optimized conditions (P: 90% *ee*, As: 85% *ee*). Lastly, coordinatively robust tridentate pincer complexes may have an advantage over other common catalyst classes such as bidentate cyclometalated complexes or even other pincer complexes (mono- or bi-metallic) with weaker donor atoms (Figure 20).

Figure 20. Alternative bidentate and tridentate palladacycles.

Proposed mechanism

PdOAc-complex **87a** was an efficient catalyst for the hydrophosphination reaction but underperformed for the hydroarsination of enones **75**. Instead, it was observed that the catalysis could be optimized by employing PdCl-complex **87b** in tandem with external bases such as CsF. While the mechanism for Pd-catalyzed hydrophosphinations is generally well-understood,^{13,20} there is a lack of evidence to suggest that these mechanisms are immediately applicable to the hydroarsination reaction. Herein, a series of $^{31}\text{P}\{^1\text{H}\}$ NMR studies were conducted in deuterated methanol to determine if the same catalytic intermediate **A** could be obtained from PdOAc-complex **87a** and PdCl-complex **87b** under different conditions (Scheme 62).

Scheme 62. Proposed formation of intermediate **A**.

Based on the mechanistic investigations conducted by Leung and Duan,^{13,20} the formation of intermediate **A** was expected upon addition of HAsPh_2 to PdOAc-complex **87a** (pathway a). With the acetate anion functioning as an internal base,¹³ subsequent addition of DIPEA did not result in any observable changes to the signal at 53.3 ppm (Figure 21). To further affirm that deprotonation had indeed occurred, PdBF₄ complex **87c** was specially prepared in an attempt to observe intermediate **B** (pathway d). Duan had previously identified the phosphine analogue of intermediate **B** upon ligand substitution of BF_4^- with HPPH_2 under neutral conditions.²⁰ The addition of HAsPh_2 to PdBF₄ complex **87c** in this instance resulted in

the formation of a new signal (assigned as intermediate **B**) which was converted to 53.3 ppm (intermediate **A**) with the addition of DIPEA (Figure 22).

Figure 21. $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of PdOAc complex **87a** with reagents.

Figure 22. $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of PdBF₄ complex **87c** with reagents.

Since experimental evidence was in good agreement with existing literature thus far, it was of interest to determine if PdCl-complex **87b** could yield the same catalytic intermediate **A**. When PdCl-complex **87b** was stirred with HAsPh₂, the original signal at 48.3 ppm remained unchanged and a minor signal at 53.3 ppm corresponding to intermediate **A** was observed (pathway b, Figure 23). Subsequent addition of DIPEA resulted in a clean conversion to

Figure 23. ³¹P{¹H} NMR spectra of PdCl complex **87b** with reagents.

intermediate **A**. Notably, no signal corresponding to intermediate **B** was observed on the NMR timescale (pathway c). Three explanations for the unexpected formation of intermediate **A** in the absence of DIPEA can be considered:

- 1) HAsPh₂ displaced the chloride anion to generate intermediate **B** which immediately underwent deprotonation to generate intermediate **A** and HCl. Addition of DIPEA removed HCl from the system, further driving the equilibrium formation of intermediate **A** forward;

- 2) An equilibrium dissociation of HAsPh_2 occurred in MeOD to generate $^-\text{AsPh}_2$, which displaced the chloride anion to generate intermediate **A**.⁴⁸ Addition of DIPEA assisted the deprotonation of HAsPh_2 , thereby increasing the formation of intermediate **A**;
- 3) In the absence of an equilibrium dissociation of HAsPh_2 to yield $^-\text{AsPh}_2$ anions (see above), transient axial interactions of the catalyst with HAsPh_2 acidified the H–As bond to generate $^-\text{AsPh}_2$.^{8a,31b,49}

A supporting $^{31}\text{P}\{^1\text{H}\}$ NMR study was designed with HPPh_2 as a convenient NMR-active handle to monitor the H/D exchange equilibrium in MeOD (point 2). Since HPPh_2 was less acidic than HAsPh_2 ,² it should be even harder to deprotonate HPPh_2 . An ongoing H/D-isotope exchange was observed which generated a characteristic 1:1:1 triplet corresponding to D-PPh_2 . This triplet was observed only in the presence of DIPEA, requiring up to 30 mins before complete conversion was achieved (Figure 24). While rate of the base-assisted H/D exchange

Figure 24. $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of HPPh_2 with DIPEA in MeOD.

of HPPH₂ in MeOD is relatively slow, it was likely that the H/D exchange for HAsPh₂ would proceed at a faster rate due to the higher acidity of HAsPh₂.

Although we were unable to conclusively explain the trace formation of intermediate **A** under neutral conditions in Figure 23, it was evident that both PdOAc-complex **87a** and PdCl-complex **87b** afforded the same catalytic intermediate **A** under their respective conditions. The formation of hydroarsination adducts **142** was proposed to resemble the hydrophosphination pathway given the similar stereo- and regio-selectivities observed in Pd-complex **87**-catalyzed hydrophosphination and hydroarsination reactions (Scheme 63). An

Scheme 63. Proposed catalytic cycle for the hydroarsination of enone **75**.

intermolecular nucleophilic attack of intermediate **A** on enone **75** would generate intermediate **C**. Under highly protic reaction conditions, several proton sources may be involved in the protonation of intermediate **C** to furnish the coordinated hydroarsination adduct **D**. From the ³¹P{¹H} NMR investigations conducted above (Figures 21-23), two pathways to regenerate intermediate **A** were plausible. Product **142** could either be liberated by trace amounts of ⁻AsPh₂ anions in solution to afford intermediate **A**, or could proceed by the stepwise formation and deprotonation of intermediate **B** triggered by ligand substitution with HAsPh₂. In the absence

of C–As or C–H bond formation, mechanistic variety in the regeneration of the active catalytic species **A** from intermediate **D** remains inconsequential to the best of our knowledge.

2.3 Conclusion

Remarkable differences were observed in the reactivity of bidentate and tridentate palladacycles towards secondary arsine reagents. HAsPh₂ resulted in the rapid decomposition of phospho-palladacycle catalysts by an insertion reaction, resulting in ligand decomplexation upon formation of a C–H bond. On the other hand, tridentate pincer complexes were excellent catalysts for the hydroarsination of functionalized enones. Up to 91% yield and 85% *ee* was obtained under optimized conditions. Several differences in the reactivity, workup and catalytic mechanism of hydro-arsination and -phosphination reactions were summarized. Strikingly, it was determined that product degradation could have occurred if the same workup procedures for hydrophosphination reactions were applied to hydroarsination.

A brief evaluation of the developments in Pd-catalyzed asymmetric hydroarsination reactions with the *12 Design Principles of Green Chemistry* quickly justified further work in the field. Preliminary triumphs of this methodology were acknowledged in terms of atom economy and solvent/energy requirements (EtOH, RT). However, it was pertinent to address the formation of arsine-containing byproducts such as tetraphenyldiarsine. In addition, the reaction could be further streamlined by reducing the amount of arsine (3.0 equiv. of HAsPh₂) and base (10.0 equiv. of CsF) currently required, while still maintaining comparable yields and stereoselectivities.

2.4 Experimental section

General information. All reactions were carried out under a positive pressure of nitrogen using standard Schlenk techniques. Solvents were purchased from their respective companies (ACN, MeOH, DCM: VWR Chemicals, DEE: Merck, toluene, n-hexane: Avantor, Acetone: Sigma-Aldrich, THF: Tedia) and distilled under an atmosphere of nitrogen prior to use. A Low Temp Pairstirrer PSL-1400 was used for controlling low temperature reactions. Column chromatography was done on Silica gel 60 (Merck). Melting points were measured using SRS Optimelt Automated Point System SRS MPA100. NMR spectra were recorded on Bruker AV 300, AV 400 and AV 500 spectrometers. Chemical shifts were reported in ppm and referenced to an internal SiMe₄ standard (0 ppm) for ¹H NMR, chloroform-d (77.23 ppm) for ¹³C NMR, and an external 85% H₃PO₄ for ³¹P{¹H} NMR.

The compounds **75c**,⁵⁰ **75d**,⁵⁰ **75e**,⁵⁰ **87a**,^{14a} **87b**,²⁷ **117**,^{8a} **131**,²⁸ **133**,^{8a} **135**⁵¹ and **137**⁵¹ and were prepared according to literature methods. All other reactants and reagents were used as supplied.

Caution! All the complexes described as perchlorate salts should be handled as potentially explosive compounds.

Synthesis of metal perchlorate complexes 78, 134 and 136. Dimeric chloro complexes **117**, **135** and **137** (1.56 mmol) was dissolved in DCM (80 mL) and MeCN (5 mL) at RT. Following the addition of a solution of AgClO₄ (0.48 g, 2.34 mmol, 1.5 equiv.) in H₂O (2 mL), the solution was stirred vigorously in the dark for 1 h. The crude was passed through short plug of silica, washed with H₂O (15 mL X 3), dried over MgSO₄ and recrystallized from DCM/DEE to give pure yellow crystals of complexes **78**, **134** and **136**. Spectroscopic data obtained was consistent with literature.^{5,8b}

General procedure for sample preparation involving complex 78 for NMR investigation (Figure 14). Palladacycle **78** (6.50 mg, 0.01 mmol, 1.0 equiv.) and HAsPh₂ (12.0 mg, 0.05

mmol, 5.0 equiv.) were stirred in MeOD (0.8 mL) at RT. After monitoring for 24 h, S₈ (1.60 mg, 0.05 mmol, 5.0 equiv.) was added and the reaction was stirred for another 30 mins.

General procedure for protonolysis of C,P-palladacycles 78, 117, 134-137 (Table 1 and Scheme 57). HAsPh₂ (36.0 mg, 0.15 mmol, 5.0 equiv. to Pd) was added to a solution of palladacycle (0.03 mmol, 1.0 equiv.) in the stated solvent (2.4 mL) and stirred for 30 mins at RT. S₈ (4.80 mg, 0.15 mmol, 5.0 equiv.) was subsequently added. After stirring for another 30 mins, volatiles were removed and the crude was purified by column chromatography (1 DCM : 1 hexane) to afford the pure sulfurized ligands **132**, **138** and **139** as white solids. Colourless crystals of sulfurized ligand **132** could be recrystallized from DCM/hexane at -15°C.

132 White solid. Mp: 72.8- 73.6°C. ¹H NMR (CDCl₃, 500 MHz): δ 8.22-8.18 (m, 2H, Ar), 8.13-8.12 (m, 1H, Ar), 7.75-7.71 (m, 2H, Ar), 7.67-7.66 (m, 1H, Ar), 7.61-7.58 (m, 3H, Ar), 7.50-7.47 (m, 1H, Ar), 7.33-7.30 (m, 1H, Ar), 7.23-7.18 (m, 3H, Ar), 7.06-7.03 (m, 1H, Ar), 6.90-6.87 (m, 2H, Ar), 4.91 (m, 1H, PCH), 1.70 (dd, 3H, ³J_{PH} = 19.0 Hz, ³J_{HH} = 7.0 Hz, CH₃); ¹³C NMR (CDCl₃, 126 MHz): δ 133.7-122.0 (22C, Ar), 34.5 (d, 1C, ¹J_{PC} = 51.7 Hz, H₃CC), 17.1 (s, 1C, H₃C); ³¹P{¹H} NMR (CDCl₃, 162 MHz): δ 52.6 (1P). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₂₄H₂₂PS, 373.1180; found, 373.1183.

138 White deliquescent solid. ¹H NMR (CDCl₃, 400 MHz): δ 8.15-8.09 (m, 2H, Ar), 7.63-7.56 (m, 4H, Ar), 7.32-7.28 (m, 1H, Ar), 7.21-7.11 (m, 4H, Ar), 6.95-6.94 (m, 1H, Ar), 6.82-6.80 (m, 1H, Ar), 4.17 (m, 1H, PCH), 2.35 (s, 3H, C_{meta}H), 1.75 (s, 3H, C_{ortho}H), 1.52 (dd, 1H, ³J_{PH} = 19.2 Hz, ³J_{HH} = 7.2 Hz, CH₃); ¹³C NMR (CDCl₃, 75 MHz): δ 135.7-127.9 (18C, Ar), 36.3 (d, 1C, ¹J_{PC} = 49.5 Hz, H₃CC), 21.4 (s, 1C, C_{meta}CH₃), 19.2 (s, 1C, C_{ortho}CH₃), 16.6 (s, 1C, PCCH₃); ³¹P{¹H} NMR (CDCl₃, 162 MHz): δ 51.8 (1P). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₂₂H₂₄PS, 351.1336; found, 351.1341.

139 White solid. Mp: 273.8- 274.3°C. ¹H NMR (CDCl₃, 400 MHz): δ 7.78-7.73 (m, 4H, Ar), 7.47-7.45 (m, 4H, Ar), 7.43-7.43 (m, 2H, Ar), 7.41-7.39 (m, 4H, Ar), 7.19-7.15 (m, 6H, Ar),

5.21 (d, 1H, $^2J_{\text{PH}} = 11.6$ Hz, *PCH*); ^{13}C NMR (CDCl_3 , 126 MHz): δ 136.9-101.6 (24C, Ar), 53.7 (d, 1C, $^1J_{\text{PC}} = 49.1$ Hz, H_3CC); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 162 MHz): δ 47.3 (1P). HRMS (+ESI) m/z : ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{25}\text{H}_{22}\text{PS}$, 385.1180; found, 385.1185.

General procedure for hydroarsination of nitrostyrene 127a catalyzed by complexes 70 and 78 (Table 2). A stock solution of the catalyst in MeOH (1.00 mM, 5 mL, 5 mol %) was added to a solution of HAsPh_2 (2.76 mg, 12.00 μmol , 1.2 equiv.) in MeOH (1 mL) and brought to the desired temperature. Nitrostyrene **127a** (1.49 mg, 10.0 μmol , 1.0 equiv.) was subsequently added and washed down with the stated solvent to make 2 mL. The reaction was stirred at RT and checked every 15 mins by TLC to monitor the consumption of nitrostyrene.

General procedure for the deuteration of C,P-palladacycle 78 (Table 3). HAsPh_2 (36.0 mg, 0.15 mmol, 5.0 equiv. to Pd) was pre-stirred in the stated solvent (2.4 mL) for 2 h at RT. Palladacycle **78** (19.50 mg, 0.03 mmol, 1.0 equiv.) was added, and the solution was stirred for 30 mins at RT. S_8 (4.80 mg, 0.15 mmol, 5.0 equiv.) was subsequently added. After stirring for another 30 mins, volatiles were removed and the crude was purified by column chromatography (1 DCM : 1 hexane) to afford the pure sulfurized ligand **132** as a white solid. **132'** (deuterated). White solid. Mp: 72.9- 73.9°C. ^1H NMR (CDCl_3 , 300 MHz): δ 8.24-8.16 (m, 2H, Ar), 7.75-7.71 (m, 2H, Ar), 7.69-7.67 (m, 1H, Ar), 7.62-7.54 (m, 3H, Ar), 7.50-7.47 (m, 1H, Ar), 7.34-7.29 (m, 1H, Ar), 7.24-7.18 (m, 3H, Ar), 7.07-7.02 (m, 1H, Ar), 6.91-6.86 (m, 2H, Ar), 4.91 (m, 1H, *PCH*), 1.70 (dd, 3H, $^3J_{\text{PH}} = 18.6$ Hz, $^3J_{\text{HH}} = 6.9$ Hz, CH_3); ^{13}C NMR (CDCl_3 , 75 MHz): δ 133.7-122.1 (20C, Ar), 34.5 (d, 1C, $^1J_{\text{PC}} = 51.0$ Hz, H_3CC), 17.1 (s, 1C, H_3C); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 162 MHz): δ 52.6 (1P). HRMS (+ESI) m/z : ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{24}\text{H}_{21}\text{DPS}$, 374.1243; found, 374.1246.

General procedure for protonolysis of E,C,N-palladacycles 131 (Scheme 60). HAsPh_2 (36.0 mg, 0.15 mmol, 5.0 equiv. to Pd) was added to a solution of palladacycle (0.03 mmol, 1.0 equiv.) in DCM (2.4 mL) and stirred for 30 mins at RT. Volatiles were removed and the

crude was purified by column chromatography (**140a** : EA; **140b** : 5 DCM : 1 hexane) to afford the pure ligands **140a** and **140b** as white solids. Spectroscopic data obtained was consistent with literature.²⁸

General procedure for the asymmetric hydrophosphination reaction of enone 75a catalyzed by complex 87 (Table 4). HPPH₂ (13.96 mg, 0.08 mmol, 1.5 equiv.) was charged to a pre-weighed Schlenk vessel under N₂. Catalyst **87** (2.50 μmol, 5 mol %) was added, washed down with the stated solvent (2 mL) and brought to the desired temperature. Enone **75a** (12.1 mg, 0.05 mmol, 1.0 equiv.) was subsequently added and the reaction was stirred at the stated temperature. Reaction progress was monitored with ³¹P{¹H} NMR spectroscopy and upon complete conversion, S₈ (3.21 mg, 0.10 mmol, 2.0 equiv.) was added and the solution was allowed to RT. After stirring for 30 mins at RT, volatiles were removed and the crude product was purified *via* silica gel chromatography (5 Hexane: 1 EA).

141 White solid. The *ee* was determined on a Daicel Chiralpak IC column with *n*-hexane/2-propanol = 97/3, flow = 0.8 mL/min, wavelength = 220 nm. Retention times: 9.5 min (major, *S* isomer), 12.1 min (minor, *R* isomer). [α]_D²⁵ = -226.0 (*c* 1.00, DCM). Mp: 117.1-118.2°C. ¹H NMR (CDCl₃, 400 MHz): δ 8.18-8.12 (m, 2H, Ar), 7.86-7.84 (m, 2H, Ar), 7.55-7.50 (m, 6H, Ar), 7.42-7.40 (m, 3H, Ar), 7.28-7.25 (m, 4H, Ar), 7.08-7.06 (m, 2H, Ar), 4.83 (ddd, 1H, ³J_{PH} = 10.2 Hz, ³J_{HH} = 10.2 Hz, ³J_{HH} = 2.4 Hz, PCCH), 4.06 (ddd, 1H, ²J_{PH} = 18.3 Hz, ³J_{HH} = 10.5 Hz, ²J_{HH} = 5.24 Hz, PCH), 3.30 (ddd, 1H, ²J_{PH} = 18.0 Hz, ³J_{HH} = 11.6 Hz, ²J_{HH} = 2.4 Hz, PCH); ¹³C NMR (CDCl₃, 100 MHz): δ 196.8 (s, 1C, C=O), 133.8-128.3 (12C, Ar), 40.8 (s, 1C, C(O)CH), 39.8 (d, 1C, ¹J_{PC} = 3.9 Hz, PC); ³¹P{¹H} NMR (CDCl₃, 162 MHz): δ 51.0. HRMS (+ESI) *m/z*: (M + H)⁺ calcd for C₂₇H₂₃ClOPS, 461.0896; found, 461.0892.

General procedure for the asymmetric hydroarsination reaction of enone 75 catalyzed by complex 87 (Tables 5-7). HAsPh₂ (17.26 mg, 0.08 mmol, 1.5 equiv.) was charged to a pre-weighed Schlenk vessel under N₂. Catalyst (2.50 μmol, 5 mol %) and base (0.50 mmol, 10.0

equiv.) was added, washed down with the stated solvent (2 mL) and brought to the desired temperature. Enone **75** (0.05 mmol, 1.0 equiv) was subsequently added and the reaction was stirred at the stated temperature. After 24 h, volatiles were removed and two drops of the crude reaction mixture was withdrawn from the flask and diluted with IPA (1 mL) to prepare the HPLC sample. Arsine adduct **142a** could be crystallized from DEE to afford the pure product **142a** as white crystalline needles.

142a White solid. 72% yield. The *ee* was determined on a Daicel Chiralpak IF column with *n*-hexane/2-propanol = 98/2, flow = 1.0 mL/min, wavelength = 230 nm. Retention times: 10.2 min (major), 11.2 min (minor). $[\alpha]_{\text{D}}^{25} = -171.8$ (*c* 4.70, DEE) (measured for Table 7 Entry 1). Mp: 137.2-138.2°C. ¹H NMR (CDCl₃, 400 MHz): δ 7.76-7.73 (m, 2H, Ar), 7.63-7.61 (m, 2H, Ar), 7.52-7.48 (m, 1H, Ar), 7.42-7.35 (m, 5H, Ar), 7.23-7.15 (m, 3H, Ar), 7.11-7.08 (m, 4H, Ar), 7.06-7.02 (m, 2H, Ar), 4.19 (dd, 1H, ³*J*_{HH} = 11.2 Hz, ²*J*_{HH} = 3.2 Hz, AsCCH), 3.67 (dd, 1H, ³*J*_{HH} = 17.2 Hz, ³*J*_{HH} = 11.2 Hz, AsCH), 3.22 (dd, 1H, ³*J*_{HH} = 17.2 Hz, ²*J*_{HH} = 3.2 Hz, AsCCH); ¹³C NMR (CDCl₃, 100 MHz): δ 198.2 (s, 1C, C=O), 134.1-128.2 (12C, Ar), 42.2 (s, 1C, AsC), 40.2 (s, 1C, C(O)CH). HRMS (+ESI) *m/z*: (M + H)⁺ calcd for C₂₇H₂₃AsClO, 473.0653; found, 473.0648.

142b White solid. The *ee* was determined on a Daicel Chiralpak IF column with *n*-hexane/2-propanol = 99/1, flow = 0.8 mL/min, wavelength = 230 nm. Retention times: 18.5 min (major), 20.1 min (minor). $[\alpha]_{\text{D}}^{25} = -38.6$ (*c* 4.90, DEE) (measured for Table 7 Entry 2). Mp: 126.3-127.2°C. ¹H NMR (CDCl₃, 400 MHz): δ 7.75-7.73 (m, 2H, Ar), 7.65-7.63 (m, 2H, Ar), 7.50-7.46 (m, 1H, Ar), 7.41-7.34 (m, 5H, Ar), 7.22-7.18 (m, 1H, Ar), 7.15-7.12 (m, 6H, Ar), 7.08-7.05 (m, 3H, Ar), 4.23 (dd, 1H, ³*J*_{HH} = 11.2 Hz, ²*J*_{HH} = 3.2 Hz, AsCCH), 3.73 (dd, 1H, ³*J*_{HH} = 17.2 Hz, ³*J*_{HH} = 11.2 Hz, AsCH), 3.21 (dd, 1H, ³*J*_{HH} = 16.8 Hz, ²*J*_{HH} = 3.2 Hz, AsCCH); ¹³C NMR (CDCl₃, 100 MHz): δ 198.5 (s, 1C, C=O), 135.3-126.3 (12C, Ar), 42.4 (s, 1C, AsC),

40.9 (s, 1C, C(O)CH). HRMS (+ESI) m/z : (M + H)⁺ calcd for C₂₇H₂₄AsO, 439.1043; found, 439.1043.

142c White solid. The *ee* was determined on a Daicel Chiralpak IF column with *n*-hexane/2-propanol = 97/3, flow = 1.0 mL/min, wavelength = 254 nm. Retention times: 15.5 min (major), 17.8 min (minor). $[\alpha]_D^{25} = -23.7$ (*c* 3.80, DEE) (measured for Table 7 Entry 3). ¹H NMR (CDCl₃, 400 MHz): δ 7.74-7.72 (m, 2H, Ar), 7.64-7.62 (m, 2H, Ar), 7.50-7.46 (m, 1H, Ar), 7.42-7.33 (m, 5H, Ar), 7.20-7.13 (m, 3H, Ar), 7.09-7.04 (m, 4H, Ar), 6.70-6.68 (m, 2H, Ar), 4.18 (dd, 1H, ³*J*_{HH} = 11.1 Hz, ²*J*_{HH} = 3.0 Hz, AsCCH), 3.67 (dd, 1H, ³*J*_{HH} = 16.9 Hz, ³*J*_{HH} = 11.3 Hz, AsCH), 3.17 (dd, 1H, ³*J*_{HH} = 17.0 Hz, ²*J*_{HH} = 3.1 Hz, AsCCH). HRMS (+ESI) m/z : (M + H)⁺ calcd for C₂₈H₂₆AsO₂, 469.1149; found, 469.1148.

142d White solid. The *ee* was determined on a Daicel Chiralpak IF column with *n*-hexane/2-propanol = 98/2, flow = 1.0 mL/min, wavelength = 254 nm. Retention times: 11.9 min (major), 13.4 min (minor). $[\alpha]_D^{25} = -48.8$ (*c* 3.70, DEE) (measured for Table 7 Entry 4). ¹H NMR (CDCl₃, 400 MHz): δ 7.80-7.78 (m, 2H, Ar), 7.66-7.63 (m, 3H, Ar), 7.49-7.38 (m, 6H, Ar), 7.16-7.12 (m, 6H, Ar), 7.07-7.05 (m, 2H, Ar), 4.22 (dd, 1H, ³*J*_{HH} = 11.1 Hz, ²*J*_{HH} = 3.2 Hz, AsCCH), 3.70 (dd, 1H, ³*J*_{HH} = 17.0 Hz, ³*J*_{HH} = 11.1 Hz, AsCH), 3.18 (dd, 1H, ³*J*_{HH} = 16.9 Hz, ²*J*_{HH} = 3.2 Hz, AsCCH), 2.35 (s, 3H, CH₃). HRMS (+ESI) m/z : (M + H)⁺ calcd for C₂₈H₂₆AsO, 453.1200; found, 453.1198.

142e White solid. The *ee* was determined on a Daicel Chiralpak IF column with *n*-hexane/2-propanol = 99/1, flow = 0.8 mL/min, wavelength = 260 nm. Retention times: 14.8 min (major), 16.2 min (minor). $[\alpha]_D^{25} = -56.6$ (*c* 6.80, DEE) (measured for Table 7 Entry 5). ¹H NMR (CDCl₃, 400 MHz): δ 7.80-7.76 (m, 3H, Ar), 7.64-7.62 (m, 2H, Ar), 7.58-7.47 (m, 4H, Ar), 7.42-7.36 (m, 6H, Ar), 7.21-7.14 (m, 3H, Ar), 7.01-7.05 (m, 1H, Ar), 4.28 (dd, 1H, ³*J*_{HH} = 11.2 Hz, ²*J*_{HH} = 3.2 Hz, AsCCH), 3.75 (dd, 1H, ³*J*_{HH} = 17.4 Hz, ³*J*_{HH} = 11.2 Hz, AsCH), 3.29 (dd, 1H, ³*J*_{HH}

= 17.5 Hz, $^2J_{\text{HH}} = 3.3$ Hz, AsCCH); ^{19}F NMR (CDCl_3 , 377 MHz): δ -62.4 (s). HRMS (+ESI) m/z : $(\text{M} + \text{H})^+$ calcd for $\text{C}_{28}\text{H}_{23}\text{AsF}_3\text{O}$, 507.0917; found, 507.0911.

General procedure for sample preparation involving complexes **87 for NMR investigation (Figures 21-23).** HAsPh₂ (11.51 mg, 0.05 mmol, 1.0 equiv.) and Pd complex **87** (5.00 μmol , 10 mol %) were stirred in CD_3OD (1.2 mL) for 5 mins at RT. Subsequently, DIPEA (9.58 μL , 0.06 mmol, 1.1 equiv.) was added and the solution was stirred for another 5 mins at RT.

Investigating deprotonation of HPPh₂ in MeOH by weak bases (Figure 24). HPPh₂ (9.30 mg, 0.05 mmol, 1.0 equiv.) was stirred in CD_3OD (1.2 mL) for 5 mins at RT. Subsequently, DIPEA (9.58 μL , 0.06 mmol, 1.1 equiv.) was added and the solution was stirred for the stated time at RT.

References

- [1] (a) Davies, W. C.; Lewis, W. P. G. *J. Chem. Soc.* **1934**, 1599, (b) *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; John Wiley and Sons: West Sussex England, 1990; Vol. 1.
- [2] (a) Issleib, K.; Kümmel, R. *J. Organomet. Chem.* **1965**, 3, 84, (b) Li, J.-N.; Liu, L.; Fu, Y.; Guo, Q.-X. *Tetrahedron* **2006**, 62, 4453, (c) Birchall, T.; Jolly, W. L. *Inorg. Chem.* **1966**, 5, 2177, (d) Wyatt, R. H.; Holtz, D.; McMahon, T. B.; Beauchamp, J. L. *Inorg. Chem.* **1974**, 13, 1511.
- [3] (a) Pearson, R. G.; Sobel, H. R.; Songstad, J. *J. Am. Chem. Soc.* **1968**, 90, 319, (b) Fernández, I.; Frenking, G.; Uggerud, E. *J. Org. Chem.* **2010**, 75, 2971.
- [4] For an overview of the different chiral catalysts applied to hydrophosphination reactions, see Koshti, V.; Gaikwad, S.; Chikkali, S. H. *Coord. Chem. Rev.* **2014**, 265, 52.
- [5] Huang, Y.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. *Chem. Commun.* **2010**, 46, 6950.
- [6] Sadeer, A.; Ong, Y. J.; Kojima, T.; Foo, C. Q.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Chem. Asian. J.* **2018**, 13, 2829.
- [7] Sabater, S.; Mata, J. A.; Peris, E. *Organometallics* **2013**, 32, 1112.
- [8] (a) Ng, K.-P. J.; Tan, G.-K.; Vittal, J. J.; Leung, P.-H. *Inorg. Chem.* **2003**, 42, 7674, (b) Huang, Y.; Chew, R. J.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Org. Lett.* **2011**, 13, 5862.
- [9] Huang, Y.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. *Inorg. Chem.* **2012**, 51, 2533.
- [10] Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, 105, 2527.
- [11] Selander, N.; Szabó, K. J. *Chem. Rev.* **2011**, 111, 2048.
- [12] For an overview on pincer complexes, see (a) Dupont, J.; Consorti, C. S.; Spencer, J. Organometallic pincer-type complexes: recent applications in synthesis and catalysis. In *The Chemistry of Pincer Compounds*; Morales-Morales, D.; Jensen, C., Ed.s; Elsevier B. V., 2007,

- (b) Szabó, K. J. *Top. Organomet. Chem.* **2013**, *40*, 203, (c) Albretch, M.; van Koten, G. *Angew. Chem. Int. Ed.* **2001**, *40*, 3750.
- [13] Yang, X.-Y.; Gan, J. H.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Dalton Trans.* **2015**, *44*, 1258.
- [14] (a) Yang, X.-Y.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Organometallics* **2015**, *34*, 5196, (b) Yang, X.-Y.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Chem. Commun.* **2016**, *52*, 4211
- [15] (a) Du, D.; Lin, Z.-Q.; Lu, J.-Z.; Li, C.; Duan, W.-L. *Asian J. Org. Chem.* **2013**, *2*, 392, (b) Huang, J.; Zhao, M.-X.; Duan, W.-L. *Tetrahedron Lett.* **2014**, *55*, 629, (c) Lu, J.; Ye, J.; Duan, W.-L. *Org. Lett.* **2013**, *15*, 5016, (d) Chen, Y.-R.; Duan, W.-L. *Org. Lett.* **2011**, *13*, 5824, (e) Du, D.; Duan, W.-L. *Chem. Comm.* **2011**, *47*, 11101.
- [16] Song, Y.-C.; Dai, G.-F.; Xiao, F.; Duan, W.-L. *Tetrahedron Lett.* **2016**, *57*, 2990.
- [17] Lu, J.; Ye, J.; Duan, W.-L. *Chem. Commun.* **2014**, *50*, 698.
- [18] Roddick, D. A. *Top. Organomet. Chem.* **2013**, *40*, 49.
- [19] (a) Clavier, H.; Nolan, S. P. *Chem. Commun.* **2010**, *46*, 841, (b) Poater, A.; Cosenza, B.; Correa, A.; Guidice, S.; Ragone, F.; Scarano, V.; Cavallo, L. *Eur. J. Inorg. Chem.* **2009**, *2009*, 1759.
- [20] Feng, J.-J.; Chen, X.-F.; Shi, M.; Duan, W.-L. *J. Am. Chem. Soc.* **2010**, *132*, 5562.
- [21] Ding, B.; Zhang, Z.; Xu, Y.; Liu, Y.; Sugiya, M.; Imamoto, T. Zhang, W. *Org. Lett.* **2013**, *15*, 5476.
- [22] Knowles, W. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1998.
- [23] Feng, J.-J.; Huang, M.; Li, Z.-Q.; Duan, W.-L. *Adv. Synth. Catal.* **2012**, *354*, 3122.
- [24] (a) Hao, X.-Q.; Huang, J.-J.; Wang, T.; Lv, J.; Gong, J.-F.; Song, M.-P. *J. Org. Chem.* **2014**, *79*, 9512, (b) Yang, M.-J.; Liu, Y.-J.; Gong, J.-F.; Song, M.-P. *Organometallics* **2011**, *30*, 3793, (c) Hao, X.-Q.; Zhao, Y.-W.; Yang, J.-J.; Niu, J.-L.; Gong, J.-F.; Song, M.-P.

- Organometallics* **2014**, *33*, 1801, (d) Yang, M.-J.; Liu, Y.-J.; Gong, J.-F.; Song, M.-P. *Organometallics* **2011**, *30*, 3793.
- [25] (a) Rahman, M. M.; Liu, H. Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1, (b) Ansell, J.; Wills, M. *Chem. Soc. Rev.* **2002**, *31*, 259.
- [26] Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.
- [27] Yang, X.-Y.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Organometallics* **2015**, *34*, 1582.
- [28] Tay, W. S.; Yang, X.-Y.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *RSC Adv.* **2016**, *6*, 75951.
- [29] (a) Li, X.-R.; Yang, X.-Y.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Dalton Trans.* **2017**, *46*, 1311, (b) Li, X.-R.; Chen, Y.; Pang, B. P.; Tan, J.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Eur. J. Inorg. Chem.* **2018**, *2018*, 4385.
- [30] Kukowski, J. E.; Stepanova, V. A.; Smoliakova, I. P. *J. Organomet. Chem.* **2017**, *830*, 155.
- [31] (a) Bungabong, M. L.; Tan, K. W.; Li, Y.; Selvaratnam, S. V.; Dongol, K. G.; Leung, P.-H. *Inorg. Chem.* **2007**, *46*, 4733, (b) Cheow, Y. L.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. *J. Organomet. Chem.* **2012**, *696*, 4215, (c) Liu, F.; Pullarkat, S. A.; Li, Y.; Chen, S.; Leung, P.-H. *Eur. J. Inorg. Chem.* **2009**, 4134.
- [32] Clark, H. C.; Goel, A. B.; Goel, S. *Inorg. Chem.* **1979**, *18*, 2803.
- [33] Spencer, J.; Maassarani, F.; Pfeffer, M.; DeCian, A.; Fischer, J. *Tetrahedron:Asymmetry* **1994**, *5*, 321.
- [34] Spencer, J.; Pfeffer, M. *Tetrahedron:Asymmetry* **1995**, *6*, 419.
- [35] Sulfurization of the tertiary monodentate phosphine ligand was possible even in the absence of NMR-observable quantities of the free tertiary phosphine ligand. Leung, P. H.; Martin, J. W. L.; Wild, S. B. *Inorg. Chem.* **1986**, *25*, 3396.

- [36] While Pd-arsenido complexes have been reported as intermediates, these complexes are rarely isolated due to their instability and high reactivity at the arsenide and Pd centres. Cecconi, F.; Ghilardi, C. A.; Midollini, S.; Moneti, S.; Orlandini, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1583.
- [37] For an overview on Pd-catalyzed C-H activation reactions, see (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094, (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507, (c) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740.
- [38] (a) Ma, S.; Villa, G.; Thuy-Boun, P. S.; Homs, A.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2014**, *53*, 734, (b) Xu, H.; Liu, M.; Li, L.-J.; Cao, Y.-F.; Yu, J.-Q.; Dai, H.-X. *Org. Lett.* **2019**, *21*, 4887.
- [39] Deuteration has been used to suppress an undesired synthetic pathway by the kinetic isotope effect: Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. *Science* **2004**, *305*, 495.
- [40] (a) Blicke, F. F.; Powers, L. D. *J. Am. Chem. Soc.* **1932**, *54*, 3353, (b) Blicke, F. F.; Powers, L. D. *J. Am. Chem. Soc.* **1933**, *55*, 1161, (c) Blicke, F. F.; Oneto, J. F. *J. Am. Chem. Soc.* **1935**, *57*, 749, (d) Busse, P. J.; Irgolic, K. J.; Dominguez, R. J. G. *J. Organomet. Chem.* **1974**, *81*, 45, (e) Krannich, L. K.; Sisler, H. H. *Inorg. Chem.* **1969**, *8*, 1032, (f) Busse, P. J.; Hrung, C.-P.; Irgolic, K. J.; O'Brien, D. H.; Kolar, F. L.; El Seoud, O. A. *J. Organomet. Chem.* **1980**, *185*, 1.
- [41] A plausible explanation for the formation of diphenylhydroarsine Ph₂AsOH could be the hydrolysis of diphenylarsine in a similar manner to that of the hydrolysis of chlorodiphenylarsine. Smedts, B. R.; Baeyens, W.; De Bisschop, H. C. *Anal. Chim. Acta.* **2003**, *495*, 239.
- [42] (a) Wyman, J. *J. Am. Chem. Soc.* **1931**, *53*, 3292, (b) Albright, P. S.; Gosting, L. J. *J. Am. Chem. Soc.* **1946**, *68*, 1061.

- [43] Lee, J.-W.; Oliveira, M. T.; Jang, H. B.; Lee, S.; Chi, D. Y.; Kim, D. W.; Song, C. E. *Chem. Soc. Rev.* **2016**, *45*, 4638.
- [44] (a) Grushin, V. V. *Chem. Eur. J.* **2002**, *8*, 1006, (b) Pagenkopf, B. L.; Carreira, E. M. *Chem. Eur. J.* **1999**, *5*, 3437.
- [45] Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 1570.
- [46] For examples of fluoride effects on activity and stereoselectivity, see (a) Fagnou, K.; Lauten, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 26, (b) Dorta, R.; Egli, P.; Zürcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857, (c) Pagenkopf, B. L.; Carreira, E. M. *Chem. Eur. J.* **1999**, *5*, 3437 and references therein.
- [47] Huang, M.; Li, C.; Huang, J.; Duan, W.-L.; Xu, S. *Chem. Commun.* **2012**, *48*, 11148.
- [48] The extent of ionization of secondary arsines was investigated in (a) Gupta, V. K.; Krannich, L. K.; Watkins, C. L. *Inorg. Chim. Acta.* **1987**, *134*, 197, (b) Cullen, W. R.; Leeder, W. R. *Can. J. Chem.* **1970**, *48*, 3757.
- [49] (a) Maresca, L.; Natile, G. *Comments Inorg. Chem.* **1993**, *14*, 349, (b) Leung, P.-H.; McLaughlin, G. M.; Martin, J. W. L.; Wild, S. B. *Inorg. Chem.* **1986**, *25*, 3392, (c) Salem, G.; Wild, S. B. *Inorg. Chem.* **1992**, *31*, 581.
- [50] Duan, M.; Liu, Y.; Ao, J.; Xue, L.; Luo, S.; Tan, Y.; Qin, W.; Song, C. E.; Yan, H. *Org. Lett.* **2017**, *19*, 2298.
- [51] Ng, J. K.-P.; Chen, S.; Tan, G.-K.; Leung, P.-H. *Eur. J. Inorg. Chem.* **2007**, *2007*, 3124.

Chapter 3

Ni-catalyzed asymmetric hydroarsination reactions

3.1 Introduction

We were interested in whether differences in the intrinsic reactivity of nickel could offer solutions to drawbacks encountered for Pd-catalyzed hydroarsination reactions. Nickel-based catalysts were observed to be vastly less popular hydrophosphination catalysts. Only two mechanistic investigations have been conducted to date.¹

Togni and coworkers utilized a series of preparative experiments, kinetic studies and DFT calculations to probe the Ni(II)-catalyzed hydrophosphination of vinyl nitriles.^{1a,b} The “olefin-activation” mechanism proposed was not previously observed for Pd-catalyzed hydrophosphination reactions (Scheme 64). Coordination of substrate **145** to precatalyst **144**

Scheme 64. Mechanism for the Ni-catalyzed hydrophosphination of olefin **145** proposed by Togni.

via interaction with the nitrile moiety generated active catalyst **A**, which subsequently underwent intermolecular nucleophilic attack by the secondary phosphine to afford phosphonium intermediate **B**. An intramolecular, and consequently stereochemically-controlled, proton transfer resulted in the formation of the desired product **146** which was released upon displacement by another unit of the vinyl nitrile **145**. Stereoselective intramolecular proton transfer was established with deuterium labelling in which 90% deuterium incorporation was observed in the phosphine product. However, the authors identified a H/D-isotope exchange occurring at the secondary phosphine reagent even in the presence of weak proton sources such as other phosphines or from oven-dried glassware and thus could not conduct rigorous crossover labelling experiments. In addition, DFT studies were conducted to support the proposed mechanism in which several simplifications were made to reduce the complexity. For instance, the PigiPhos ligand was simplified to trisphosphine ($\text{H}_2\text{PCH}=\text{CHCH}_2$)₂PH and solvent effects were not considered. The overall reaction was found to be approximately thermoneutral, which was used to partially explain the lack of catalytic systems for the hydrophosphination reaction. Deuterium labelling studies featured a large primary isotope effect which suggested that the rate determining step involved bond cleavage/formation with H/D instead of the stereochemically-important C–P bond formation step. Finally, the use of a tridentate P,P,P ligand was deemed to be important in maintaining structural integrity of the catalyst in the presence of large excesses of secondary phosphine reagent.

In a purely computational study involving POCOP Ni pincer complexes **147**, Downey proposed that addition of secondary phosphines to unactivated alkenes proceeded by initial phosphine activation instead (Scheme 65).^{1c} This differed from the mechanism proposed by Togni, although direct comparisons were ill-disposed based on differences in the substrate and ligand frameworks of complexes **144** and **147**. Basis sets were first benchmarked against

Scheme 65. Mechanism for Ni-catalyzed hydrophosphination of unactivated olefin **148** proposed by Downey.

experimentally-determined molecular geometries based on X-ray diffraction. Overall results suggested that an initial reduction of the phosphine to generate phosphido intermediate **A** was possible based on significant electron density surrounding the metal center calculated in the HOMO of complex **147**. Subsequently, 1,2-insertion and product displacement by another unit of secondary phosphine regenerated the active intermediate **A**. Computational calculations predicted an indifference of the catalysis to solvent and auxiliary ligand ($X = \text{H}, \text{Me}$) effects based on negligible disturbance to electron distributions and molecular orbital energies. In addition, semiempirical, Hartree-Fock and DFT models were utilized for this assessment which concluded that DFT was the best-suited model while the semiempirical approach had only qualitative use and the Hartree-Fock method was completely ineffective.

To supplement the lack of examples in Ni-catalyzed hydrophosphination reactions, a review of general nickel catalysis was conducted to provide relevant perspectives on catalytic reactivity. Several aspects of nickel chemistry were highlighted in a Viewpoint by Ananikov and applicable points have been summarized as follows.² Firstly, the contribution of 1-electron processes was established to be the most probable for nickel amongst the Group 10 metals, thus allowing nickel vastly more accessible oxidation states ($\text{Ni}(0)$, $\text{Ni}(\text{I})$, $\text{Ni}(\text{II})$, $\text{Ni}(\text{III})$, $\text{Ni}(\text{IV})$) and thereby more flexibility in catalytic pathways. Secondly, the binding of alkenes and

alkynes to nickel is exceptionally stronger than to palladium or platinum, making this substrate activation mode plausible for hydroarsination reactions involving C,C double or triple bonds.

Several of these aforementioned findings were useful in jump-starting the Ni-catalyzed hydroarsination reaction. For instance, the use of tridentate pincer complexes were rational in light of the conclusions drawn by Togni. Substrate choice was also narrowed down to olefins bearing non-basic but coordinating atoms. Computational calculations were to be investigated first with DFT instead of semiempirical or Hartree-Fock models. A detailed mechanistic investigation for the Ni-catalyzed hydroarsination reaction was crucial in light of the few examples in the field.

3.2 Results and discussion

Research questions

- 1) *Are the proposed mechanism for Ni-catalyzed hydrophosphination reactions relevant to the hydroarsination reaction?*
- 2) *Could differences in mechanism, if any, remediate limitations of the Pd-catalyzed hydroarsination reaction?*

Overview

The feasibility of Ni-based pincer complexes as catalysts were first benchmarked against activity of the Pd- and Pt-analogues. With the initial success observed, an extensive optimization process was used to probe plausible mechanisms. Computational calculations were used to evaluate three possible catalytic intermediates. The resultant proposed mechanism was found to be distinct from those previously-reported for hydrophosphination reactions. Subsequently, the methodology was further developed to furnish a library of enantioenriched

nitro-functionalized arsines in high yields. From this, structural investigations were carried out with a series of bond lengths and angles derived from X-ray crystallography.

Evaluating choice of metal

Based on the previous success in Pd-catalyzed hydroarsination of enones, solvent screening was first conducted with complex **87a** on the hydroarsination of nitrostyrene **127a** (Table 9). Unfortunately, *ee*'s remained consistently low (1-29%) across the solvents screened

Table 9. Screening of conditions for catalytic asymmetric hydroarsination reaction.^a

Entry	Solvent	T (°C)	<i>t</i> ^b (mins)	Yield ^c (%)	<i>ee</i> ^d (%)
1	DCM	RT	120	86	26
2	DEE	RT	60	94	26
3	ACN	RT	180	93	4
4	Toluene	RT	90	91	29
5	Acetone	RT	60	89	1
6	THF	RT	60	95	2
7	Hexane	RT	45	96	12
8	MeOH	RT	60	80	22
9	DCM	0	150	90	24
10	DEE	0	90	95	25
11	Toluene	0	120	86	21

^aReaction conditions: nitrostyrene **127a** (14.9 mg, 0.10 mmol, 1.0 eq.), HAsPh_2 (27.6 mg, 0.12 mmol, 1.2 eq.), cat. (R,R) -**87a** (4.1 mg, 5.00 μmol , 5 mol %), solvent (2 mL). ^bComplete conversion of nitrostyrene **127a** was observed *via* TLC, correct to the nearest 15 min interval. ^cDetermined by HPLC at 260 nm. ^dDetermined by chiral HPLC of the crude reaction mixture.

(Entries 1-8). Lowering the reaction temperature to 0°C did not improve stereoselectivities (Entries 9-11) which prompted modifications in catalyst design. The reaction was therefore re-examined with related pincer complexes of (R,R) -**87a**, namely the platinum, nickel and their chloride derivatives.

Platinum and nickel pincer complexes **96** and **97** were also catalytically active (Table 10). When compared to Pd-OAc complex **87a**, both chloride and acetate Pt-complexes **96a** and

Table 10. Catalyst screening for catalytic asymmetric hydroarsination reaction.^a

Entry	Cat.	Solvent	T (°C)	t ^b (mins)	Yield ^c (%)	ee ^d (%)
1	96b	MeOH	RT	150	97	15
2	97b	MeOH	RT	180	97	50
3	87a	MeOH/H ₂ O ^e	RT	<5	90	27
4	96b	MeOH/H ₂ O ^e	RT	<5	97	61
5	97b	MeOH/H ₂ O ^e	RT	<5	89	59
6	87b	MeOH/H ₂ O ^e	RT	10	98	18
7	86a	MeOH/H ₂ O ^e	RT	45	88	31
8	97a	MeOH/H ₂ O ^e	RT	15	84	75
9	97a	MeOH/H ₂ O ^e	-20	15	76	80
10 ^f	97a	MeOH/H ₂ O ^e	-20	75	73	77
11 ^g	97a	MeOH/H ₂ O ^e	-20	75	77	78

^aReaction conditions: nitrostyrene **127a** (14.9 mg, 0.10 mmol, 1.0 eq.), HAsPh₂ (27.6 mg, 0.12 mmol, 1.2 eq.), cat. (5.00 μmol, 5 mol %), MeOH (2 mL). ^bComplete conversion of nitrostyrene **127a** was observed *via* TLC. ^cDetermined by HPLC at 260 nm. ^dDetermined by chiral HPLC of the crude reaction mixture. ^eH₂O (200 μL, 10 % v/v of solvent) was added. ^fCat. (0.8 mg, 1.00 μmol, 1 mol %) was used instead. ^gReaction conditions: nitrostyrene **127a** (149.0 mg, 1.00 mmol, 1.0 eq.), HAsPh₂ (276.0 mg, 1.20 mmol, 1.2 eq.), cat. (8.3 mg, 10.00 μmol, 1 mol %), MeOH (10 mL).

96b were not significantly more stereoselective for C–As bond formation (31% and 15% respectively, Entries 7 and 1). Surprisingly, Ni-OAc complex **97b** afforded arsine **150a** with respectable *ee* of 50% (Entry 2). Further attempts were made to increase the stereoselectivity. Firstly, controlled addition of water (10% v/v) increased the *ee* to 59% (Entry 5) with an evident acceleration of the reaction rate (<5 mins). This phenomenon was also observed for Pd- and Pt-OAc complexes **87a** and **96b** (Entries 3 and 4). Secondly, the presence of the non-basic chloride ion on Ni-Cl **97a** boosted *ee* to 75% (Entry 8). Lastly, lowering the temperature to -20°C furnished the desired product **150a** in 80% *ee* within 15 mins (Entry 9). Further decreasing the temperature did not result in any appreciable increase in stereoselectivity. The excellent reactivity of complex **97a** was demonstrated by comparable results attained with a five-fold

decrease in catalyst loadings to 1% (Entry 10). In addition, the scale of the reaction could be increased to 1 mmol at 1% catalyst loading (Entry 11) to afford adduct **150a** in 78% *ee*. These cursory observations clearly indicate the superior catalytic activity of Ni-Cl complex **97a** in comparison to the previously-developed Pd-OAc complex **87a**.

Optimization of conditions

Two aspects of the Ni-catalyzed hydroarsination reaction were probed empirically, (1) solvent effect on H–AsPh₂ bond cleavage, and (2) catalyst participation in C–H bond formation. Results of these investigations are sequentially discussed as follows.

(1) Solvent effect on H–AsPh₂ bond cleavage

A primary reaction step of the hydroarsination mechanism involves activating the H–As bond for subsequent bond breaking. Previous kinetic studies done by Cullen and Leeder have concluded that either an ionic or neutral mechanism may facilitate the proton transfer reaction of secondary arsines- the former involving reversible heterolytic H–As bond cleavage while the latter proceeding by a four-centered mechanism.³ In view of the potentially amphoteric character of HAsPh₂, catalytic screening was carried out to observe H–As bond dissociation during the hydroarsination reaction (Table 11). Preliminary results revealed a strong dependence on alcohols for good catalytic activity (Entries 5-7). Only alcoholic solvents allowed complete conversion of nitrostyrene **127a** within 2 h, albeit with moderate *ee*'s of 33-59% (Entries 5-7). Increasing the hydrophobicity of the alcohol resulted in increased reaction times and decreased stereoselectivities (Entries 5-7). Varying the water present in the reaction also affected the rate and stereoselectivity (Entries 9-11). Heterolytic cleavage of the H–As bond was supported by the absence of arsine **150a** when the reaction was conducted in protic but acidic conditions such as MeOH/AcOH (10% *v/v*) (Entry 12). The pK_a of HAsPh₂ (pK_a = 20.3 in THF)⁴ suggested that spontaneous dissociation of the proton was unlikely, thus

Table 11. Solvent effect on H–AsPh₂ bond cleavage.^a

Entry	Solvent	T (°C)	t ^b (min)	Yield ^c (%)	ee ^d (%)
1	CHCl ₃	RT	1440	NR	-
2	Acetone	RT	1440	NR	-
3	MeCN	RT	1440	NR	-
4	THF	RT	1440	NR	-
5	MeOH	RT	30	87	59
6	EtOH	RT	90	84	40
7	iPrOH	RT	120	97	33
8	AcOH	RT	1440	NR	-
9	MeOH/H ₂ O (5%) ^e	RT	<5	89	39
10	MeOH/H ₂ O (10%) ^f	RT	<5	99	75
11	MeOH/H ₂ O (15%) ^g	RT	<5	90	45
12	MeOH/AcOH (10%) ^h	RT	1440	NR	-
13 ⁱ	MeOH/H ₂ O (10%) ^f	-20	15	76	80
14	MeOH/H ₂ O (10%) ^f	-40	75	99	80

^aReaction conditions: nitrostyrene **127a** (7.46 mg, 0.05 mmol, 1.0 eq.), HAsPh₂ (13.80 mg, 0.06 mmol, 1.2 eq.), cat. (*R,R*)-**97a** (0.83 mg, 1.00 μmol, 2 mol %), solvent (2 mL). ^bComplete conversion was observed *via* TLC. ^cDetermined by HPLC at 254 nm. NR = no reaction. ^dDetermined by chiral HPLC of the crude reaction mixture. ^eH₂O (100 μL, 5 % v/v of solvent) was added. ^fH₂O (200 μL, 10 % v/v of solvent) was added. ^gH₂O (300 μL, 15 % v/v of solvent) was added. ^hAcOH (200 μL, 10 % v/v of solvent) was added. ⁱ5 mol % of cat. (2.08 mg, 2.50 μmol) was used instead.

explaining the lack of reactivity observed in THF (Entry 4). No data was available for the pK_a of HAsPh₂ in MeOH to the best of our knowledge.

To supplement pK_a values, an NMR study was designed to reflect the nature of the H–As bond in various solvents (Figures 25-27). It was expected that solvents which favoured the hydroarsination reaction should result a H/D exchange in (H/D)-AsPh₂. To combat the unreliability of ¹H NMR due to broad signals of the secondary arsine proton, an alternative experiment involving H–PPh₂ was adopted instead. With HPPPh₂ having a higher pK_a value,⁴ the extent of H–As bond lability should be well reflected by HPPPh₂. ³¹P{¹H} NMR spectroscopy was used as a convenient tool to monitor the H/D exchange of HPPPh₂. A characteristic ¹J_{D-P} coupling was easily observed upon H/D exchange (HPPPh₂: sharp singlet,

DPPh₂: 1:1:1 triplet). Results obtained were in close agreement with the solvent screening conducted and it was determined that the fastest H/D exchange occurred in MeOD/D₂O (10% v/v) (Figure 26). It was inferred that the addition of D₂O may encourage H/D exchange in certain solvents (eg. MeCN, MeOD), although it may be insufficient to promote H/D exchange in others (eg. acetone, THF). Consequently, H–As bond cleavage may indeed occur in the absence of catalyst, particularly in highly polar protic environments such as MeOH/H₂O (10% v/v).

Figure 25. $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of HPPh₂ in various deuterated solvents at 2.5 h.

Figure 26. $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of HPPH₂ in various deuterated solvents with D₂O (10% v/v) at 2.5 h.

Figure 27. $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of HPPH₂ in MeOD/D₂O (10% v/v).

(2) Catalyst participation in C–H bond formation

In catalytic asymmetric hydrofunctionalization reactions, up to two chiral carbon centers may be formed during C*–H and C*–E bond formations. Excellent control over stereoselectivity relies on close interactions with the chiral catalyst during bond formation steps. The stereoselective formation of C*–H bonds were notably challenging in the presence of highly protic environments such as aqueous or semi-aqueous/alcoholic conditions. α -nitrostyrenes **151a** were specially designed to evaluate the effectiveness of catalyst **97a** in controlling C*–H bond formations under highly protic conditions. C*–H bond formation would install a newly-generated chiral center from which the transfer (or absence) of chiral information from catalyst **97a** can be clearly observed. The tertiary carbon chiral center was intentionally designed to bear a highly-acidified proton due to the adjacent nitro moiety. Potentially, facile deprotonation may occur thus resulting in 1) racemization of the adduct or 2) elimination of the adjacent As moiety. Solvent screening for α -nitrostyrene **151a** revealed reactivities and stereoselectivities comparable to nitrostyrene **127a** (Table 12). Under optimal

Table 12. Solvent screening for hydroarsination of α -nitrostyrene **151a** catalyzed by complex (R,R) -**97a**.^a

Entry	Solvent	T (°C)	<i>t</i> ^b (min)	Yield ^c (%)	<i>ee</i> ^d (%)
1	MeOH	RT	15	91	71
2	EtOH	RT	30	98	48
3	iPrOH	RT	30	85	25
4	Dry MeOH	RT	30	92	61
5	MeOH/H ₂ O (5%) ^e	RT	15	86	50
6	MeOH/H ₂ O (10%) ^f	RT	15	91	40
7	MeOH/H ₂ O (15%) ^g	RT	15	83	53
8	MeOH	0	15	68	79
9	MeOH	-20	1440	NR	-

^aReaction conditions: nitroolefin **151a** (0.05 mmol, 1.0 eq.), HAsPh₂ (13.80 mg, 0.06 mmol, 1.2 eq.), cat. (R,R) -**97a** (0.83 mg, 1.00 μ mol, 2 mol %), solvent (2 mL). ^bComplete conversion was observed *via* TLC. ^cDetermined by HPLC at 254 nm. ^dDetermined by chiral HPLC of the crude reaction mixture. ^eH₂O (100 μ L, 5 % v/v of solvent) was added. ^fH₂O (200 μ L, 10 % v/v of solvent) was added. ^gH₂O (300 μ L, 15 % v/v of solvent) was added.

conditions, arsine **152a** was isolated in 91% yield with 71% *ee* at RT (Entry 1). Clearly, C*–H bond formation was efficiently controlled by chiral catalyst **97a**, even in the presence of a highly protic environment.

Mechanistic considerations

The structural integrity of the Ni-PCP ligand framework in complex **97a** was maintained during the course of the catalysis. No free diphosphine species was observed even from the attempted decomplexation of Ni-Cl **97a** with excess aq. KCN. Prior to mechanistic evaluations, a simple NMR investigation was conducted to identify if interactions were present between catalyst **97a** and nitrostyrene **127a**, HAsPh₂, or both. No visible interactions between Ni-Cl complex **97a** and nitrostyrene **127a** were observed (at least on the NMR timescale) (Figure 28 and 29). On the other hand, a series of variable temperature ³¹P{¹H} NMR experiments indicated the presence of possible interactions between complex **97a** (³¹P{¹H} = 46.5) and diphenylarsine due to the appearance of a new ³¹P{¹H} NMR signal (33.1 ppm) (Figures 30 and 31). However, these interactions existed in equilibrium and were thus not useful in revealing more structural information of the intermediate species.

Figure 28. VT ^1H NMR spectra of pure nitrostyrene **127a**. Signals corresponding to vinylic protons of nitrostyrene **127a** labeled with a black dot.

Figure 29. VT ^1H NMR spectra of sample nitrostyrene **127a** and complex **97a**.

Figure 30. VT $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of pure complex **97a**.

Figure 31. VT $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of HAsPh_2 and complex **97a**. Signals corresponding to catalyst **97a** labelled with a dot.

Due to the inability of NMR spectroscopy to shed light on structural information of the intermediates, we turned to DFT calculations to explore interactions between Ni(II)-catalyst **97a** and HAsPh₂ (Table 13). Optimized DFT calculations in the gas phase reflected a

Table 13. Summary of selected data from DFT calculations.^a

Charge	Anionic	Neutral
Free energy/ Hartree	-7570.6511	-7071.8305
$\Delta G(\text{formation})/\text{kcal mol}^{-1}$	-55.7	24244.4
Ni–X bond length/Å	2.415	-
As–X bond length/Å	2.289	-
As–C bond length/Å	1.945	

^aAll values were obtained in the gas phase at 298.15K.

Ni–Cl–As interaction between Ni(II)-catalyst **97a** and HAsPh₂ at 298.15 K. 4-coordinate intermediate **A1** was spontaneously formed over intermediate **A2**, and no 5-coordinate intermediates were derived. DFT calculations of the known Ni(II) complex **97a** were first benchmarked against bond lengths and angles determined by X-ray crystallography. The reliability of gas-phase DFT calculations in this instance was reflected by the close agreement between theoretical and experimental bond lengths (eg. For the Ni–Cl bond length, calc.: 2.218 Å, experimental: 2.2075(8) Å).⁵ The theoretical Ni–Cl bond length of complex **97a** also highly resembled that of other similar square planar PCP-Ni(II) pincer complexes between 2.20-2.24 Å.⁶ Interaction with [−]AsPh₂ lengthened the Ni–Cl bond of catalyst **97a** to 2.415 Å in intermediate **A1**. A thorough literature search of other As–Cl bonds in trivalent organoarsine chlorides of the type R₂AsCl were determined to be 2.19-2.34 Å.⁷ Theoretical calculations for intermediate **A1** revealed an As–Cl bond length of 2.289 Å, closely resembling that of Ph₂AsCl (2.26 Å).⁷ In addition to the described Ni–Cl–As interaction, other interactions between the [−]AsPh₂ anion and the electropositive Ni(II) center were also considered. While no energetically

favorable axial interactions leading to the formation of 5 coordinate intermediates were derived by DFT calculations, transient axial interactions remain a possibility. However, these axial interactions should be minor considering the high percent buried volume (%V_{bur}) of Ni(II) complex **97a** in limited access of reagents to the metal center.⁵

Intermediate **A1** was then investigated empirically. It was hypothesized that Ni–Cl–As interactions would not be hindered by an excess of chloride ions. In contrast, excess chloride ions should significantly slow down the rate of reaction if formation of the active intermediate required chloride dissociation from Ni(II)-catalyst **97a**. The hydroarsination of nitrostyrene **127a** catalyzed by Ni–Cl complex **97a** was conducted in a large excess of LiCl to suppress any equilibrium dissociation of the Ni–Cl bond (Table 14). As expected, the reaction proceeded

Table 14. Effect of excess LiCl on Ni-catalyst **97a**.^a

Entry	Additive ^b	Yield ^c (%)	ee ^d (%)
1	-	82	75
2	LiCl	77	50
3	AgClO ₄	0	-

^aReaction conditions: nitrostyrene **127a** (7.46 mg, 0.05 mmol, 1.0 eq.), HAsPh₂ (13.80 mg, 0.06 mmol, 1.2 eq.), cat. (*R,R*)-**97a** (1.00 μmol, 2 mol %), MeOH (2 mL), H₂O (200 μL), RT, 30 mins. ^bLiCl (6.49 mg, 0.15 mmol, 300 mol %) was added.

^cDetermined by HPLC at 254 nm. ^dDetermined by chiral HPLC of the crude reaction mixture.

with no notable difference in rate and afforded arsine **150a** in comparable yield and *ee*, within 5% that of the control reaction (Entries 1 and 2). Unlike intermediate **A2**, the formation of Ni–Cl–As intermediate **A1** remained favorable even in the presence of excess Cl[–]. An attempt was made to replace Cl[–] with weakly coordinating anions (eg. BF₄[–], PF₆[–], ClO₄[–]) to encourage alternative Ni–As interactions. Unfortunately, the use of such Ag⁺ salts as halide scavengers resulted in catalyst degradation and no accurate comparison could be made.

In fact, this Ni–X–As type interaction was not unique to only chlorides. DFT calculations were also attempted for Ni–Br–As complex **A1'** and $\Delta G(\text{formation})$ values were similarly spontaneous at $-52.3 \text{ kcal mol}^{-1}$ (Table 15). Longer theoretical Ni–X and As–X bonds

Table 15. Summary of selected data from DFT calculations.^a

Charge	Anionic	Anionic
Free energy/ Hartree	-7570.6511	-9684.4982
$\Delta G(\text{formation})/\text{kcal mol}^{-1}$	-55.7	-52.3
Ni–X bond length/Å	2.415	2.514
As–X bond length/Å	2.289	2.419
As–C bond length/Å	1.945	1.949

^aAll values were obtained in the gas phase at 298.15K.

observed for X = Br were reasonable upon accounting for the larger bromide ionic radius. The bromide variant of Ni–Cl catalyst **97a** was also catalytically active in the hydroarsination reaction (Table 16). Both percentage yields and *ee*'s obtained were within 5% of that furnished

Table 16. Effect of counteranion on Ni(II)-catalyzed hydroarsination reaction.^a

Entry	Cat.	<i>t</i> (min)	Yield ^b (%)	<i>ee</i> ^c (%)
1	97a	15	82	75
2	97c	15	79	70

^aReaction conditions: nitrostyrene **127a** (7.46 mg, 0.05 mmol, 1.0 eq.), HAsPh₂ (13.80 mg, 0.06 mmol, 1.2 eq.), cat. (*R,R*)-**97** (1.00 μmol, 2 mol %), MeOH (2 mL), H₂O (200 μL), RT, 30 mins. ^bDetermined by HPLC at 254 nm. ^cDetermined by chiral HPLC of the crude reaction mixture.

by Ni–Cl catalyst **97a**. Excellent correlation was also observed between the longer Ni–Br and As–Br bonds and the stereoselectivities of the transformation. Arsine **150a** was obtained in a slightly lower *ee* (Cl: 75%, Br: 70%) understandably due to the further distance between the

chiral ligand and reaction site on intermediate **A1'**. The Ni-F variant of catalyst **97** could not be successfully prepared to further observe other Ni-X-As interactions.⁸

The spontaneous formation of intermediate **A1** was calculated based on an expected equilibrium presence of AsPh_2^- under reaction conditions. The generation of intermediate **A1** was strongly unfavourable ($293.4 \text{ kcal mol}^{-1}$) without prior deprotonation of HAsPh_2 . Unlike other hydrofunctionalization (hydrophosphination) reactions in which coordination of HEPh_2 to the transition metal catalyst acidified the H–E bond for subsequent deprotonation,⁹ theoretical calculations involving the current unprecedented Ni–Cl–As interaction suggest otherwise. Instead, the H–As bond was expected to exhibit a degree of lability even in the absence of catalyst **97a** to afford an equilibrium concentration of AsPh_2^- in MeOH (*vide supra*, determined by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy). This was easily observed with solvent screening (Table 11): (1) an acidic environment hindered the hydroarsination reaction, and (2) increasing the aqueous character of the solvent resulted in a remarkable decrease in reaction times. Concurrently, theoretical calculations were utilized to evaluate the feasibility of an equilibrium dissociation of H–AsPh_2 (Table 17). Calculations determined that dissociation of H–AsPh_2 in

Table 17. $\Delta_r G$ in gaseous and methanolic states.^a

Reaction	Condition	$\Delta_r G / \text{kcal mol}^{-1}$
$\text{H}-\text{AsPh}_2 \longrightarrow \text{H}^+ + \text{AsPh}_2^-$	Gaseous	349.1
	MeOH	62.7
	THF	217.5
$\text{C} \begin{array}{c} \text{P} \\ \downarrow \\ \text{Ni} \\ \uparrow \\ \text{P} \end{array} \text{Cl} + \text{AsPh}_2^- \longrightarrow \left[\text{C} \begin{array}{c} \text{P} \\ \downarrow \\ \text{Ni} \\ \uparrow \\ \text{P} \end{array} \text{Cl} \text{AsPh}_2 \right]^-$ <p style="text-align: center;">97a A1</p>	Gaseous	-55.7
	MeOH	-46.6

^aAll values were obtained at 298.15K.

both the gas phase and in MeOH were non-spontaneous, although solvent effects of MeOH considerably reduced the $\Delta_r G$ to 62.7 kcal mol⁻¹. This non-spontaneity was expected considering the high pKa of HAsPh₂.⁴ Proton transfer process proceeding by an extended proton network, although more likely, could not be modelled due to constraints imposed by the

extended solvent model. Nevertheless, these calculations of the direct proton transfer provided another perspective regarding dissociation of the H–As bond in different solvents. The effect of MeOH on the spontaneity of H–AsPh₂ bond cleavage is clearly observable with the following evidence. Firstly, other solvents did not result in a significant reduction of Δ_rG . Even with similar oxygen-containing solvents such as THF, Δ_rG calculated for the H–As bond dissociation was only 217.5 kcal mol⁻¹, suggesting that the reported pK_a of HAsPh₂ in THF can only be loosely taken as a reference for the ionization of H–AsPh₂ in MeOH. Secondly, significantly lower Δ_rG values in MeOH was only uniquely observed for the dissociation of H–AsPh₂. When the formation of intermediate **A1** was taken as a reference reaction, the solvent effect exhibited was several orders smaller and calculated Δ_rG values differed only by 9.2 kcal mol⁻¹ as opposed to 286.4 kcal mol⁻¹ for H–As dissociation. The catalysis proceeded smoothly in MeOH/H₂O (10% v/v) even at -40°C (Table 11 Entry 14), suggesting that H–As bond dissociation energy of 62.7 kcal mol⁻¹ could be further reduced with an increase in the solvent's aqueous character under actual experimental conditions.

Lastly, establishing the inertness of the Ni–Cl bond in catalyst **97a** under highly polar conditions was of paramount importance to affirm the structure of intermediate **A1**. Molar conductivity measurements were conducted to investigate the degree of Ni–Cl bond ionization of Ni catalyst **97a** (Table 18). It was concluded that Ni catalyst **97a** exhibited a weak ionization

Table 18. Conductivity measurements in MeOH/H₂O (10% v/v).^a

Entry	Sample	Concentration/mM	Conductivity / $\mu\text{S cm}^{-1b}$
1	10% H ₂ O/90% MeOH (solvent)	-	2
2	KCl	2	195
3	KCl	20	1022
4	Ni-Cl complex 97a	2	5

^aMeasurements were conducted at 23 °C. ^bValues were averaged over 3 runs and reported to the nearest whole number.

equilibrium at best, observed from a conductivity of 4.90 $\mu\text{S cm}^{-1}$ which closely resembled the blank solvent (Entries 1 and 4). This was significantly smaller than that of KCl (195 $\mu\text{S cm}^{-1}$)

under the same conditions (Entry 2). Further attempts to confirm the weak dissociation equilibrium by obtaining more molar conductivity values of Ni catalyst **97a** were unsuccessful. Experiments repeated at higher concentrations (>5 mM) were hindered by the limited solubility of the catalyst in MeOH/H₂O (10% v/v). Concentrations less than 2 mM were avoided to minimize error affecting the accuracy of measurements obtained. Despite these limitations, it was clear that the Ni–Cl bond of Ni catalyst **97a** does not dissociate appreciably and, together with the theoretical and experimental evidence collected, support the formation intermediate **A1**.

The insights derived above was succinctly summarized in a proposed catalytic cycle (Scheme 66). The overall mechanism was outlined in 4 main steps: (1) Ni–Cl–As association

Scheme 66. Proposed mechanism of the Ni(II)-mediated asymmetric hydroarsination reaction.

between catalyst **97a** and AsPh_2^- , (2) intermolecular attack on the activated olefin, (3) stereoselective protonation and (4) dissociation to release the product and regenerate the active catalyst. Interaction of AsPh_2^- to 4-coordinate Ni(II)-complex **97a** generated Ni–Cl–As intermediate **A1**. A 1,4-nucleophilic attack of intermediate **A1** on nitroolefin **127** furnished arsine-nitronate species **B** which was proposed to proceed *via* a Michael-type reaction. Sequential protonation of intermediate **B** occurring within the catalyst sphere generated

intermediate **C**. Arsine dissociation in intermediate **B** may be a competing pathway prior to subsequent non-stereoselective protonation. This was supported by variations in *ee*'s (40% to 61%) observed when different ratios of water were present (Table 12, Entries 4-7). Even so, high overall *ee*'s suggest that excellent control is exerted over the C*–H bond formation process, signaling the preference for the stereoselective proton transfer step. Intermediates **B** and **C** consequently resulted in good stereoselectivities observed at the C*–As and C*–H chiral centers (Tables 11 and 12). Subsequent product dissociation from intermediate **C** regenerated 4-coordinate Ni complex **97a** with release of the desired product. Other minor 4-membered species are possibly formed along with the proposed intermediates. Nevertheless, no paramagnetic species were observed spectroscopically, indicating the unlikely occurrence of 4-membered tetrahedral derivatives of Ni(II)-catalyst **97a**.

The highly polar solvent environment may assist concurrent proton transfer between several potential shuttles such as water, MeOH, diphenylarsine and/or the nitroolefin. As such, the identity of the proton donor could not be conclusively assigned. Attempts at deuterium labelling were unsuccessful. Conducting the hydroarsination of nitrostyrene **127a** with catalyst **97a** in deuterated methanol caused a significant kinetic isotope effect such that attempts to isolate an adduct to pinpoint deuterium incorporation were to no avail. By inference, a large primary isotope effect suggested that the rate determining step involved bond cleavage/formation with H/D instead of the stereochemically-important C–As bond formation step. The short reaction times (<5 mins for complete conversion) introduced significant error when rate measurements were conducted to determine the kinetics of this reaction. Nevertheless, thermodynamic energy changes associated with each step of the catalytic cycle were acquired from DFT calculations (Figure 32). The overall $\Delta_r G$ was determined to be -10.9 kcal mol⁻¹, in close agreement with other olefin hydrophosphinations and hydroamination reactions.^{1a,10} Notably, intermediate **A1** was found to reside in an energy trough which may

Figure 32. DFT calculations of the reaction profile for the Ni(II)-mediated hydroarsination reaction at 298.15 K in MeOH. suggest the possibility of observing intermediate **A1** spectroscopically. This would appear to be in agreement with the $^{31}\text{P}\{^1\text{H}\}$ NMR spectra collected from the sample of HAsPh_2 and complex **97a** in which a new unidentified signal was observed (Figure 31).

As previously discussed in the introduction, both Togni and Downey proposed direct participation of the Ni(II) center in the catalysis. Due to different σ -donating/ π -accepting natures of arsines as compared to phosphines,¹¹ mechanisms for the hydrophosphination reaction cannot be assumed to be immediately applicable to the hydroarsination reaction. Both the mechanisms proposed by Togni (“olefin-activation” mechanism) and Downey (“phosphine-activation” mechanism) were inapplicable in this instance. Interaction between Ni(II)-catalyst **97a** and the electron-deficient olefin substrate was deemed absent by a series of low temperature NMR studies. Also, conducting the catalysis under large excess of Cl^- ions suggested that the Ni–Cl bond of Ni(II)-catalyst **97a** remained inert under hydroarsination conditions.

Substrate scope

A series of functionalized nitroolefins were selected to explore the electronic and steric effects of substituents on the catalytic pathway (Table 19). Generally, Ni-catalyst **97a**

Table 19. Electronic and steric effects on the hydroarsination reaction.^a

Entry	Arsine	T (°C)	<i>t</i> ^b (min)	Yield ^c (%)	<i>ee</i> ^d (%)
1	150b	-20	<5	74	74
2	150c	-20	<5	91	71
3	150d	-20	<5	75	73
4	150e	-20	<5	78	75
5	150f	-20	30	95	73
6	150g	-20	30	70	70
7	150h	0	60	94	53
8	150i	0	210	79	70
9	150j	0	60	73	68
10	150k	RT	1440	57 ^e	34
11	150l	0	60	69	32
12	152b	0	15	94	72
13	152c	0	15	62	72

^aReaction conditions: nitroolefin (0.05 mmol, 1.0 eq.), HAsPh₂ (13.80 mg, 0.06 mmol, 1.2 eq.), cat. (*R,R*)-97a (0.83 mg, 1.00 μmol, 2 mol %), MeOH (2 mL), H₂O (200 μL). ^bComplete conversion was observed *via* TLC. ^cDetermined by HPLC at 254 nm. ^dDetermined by chiral HPLC of the crude reaction mixture. ^eIncomplete conversion after 24 h.

exhibited good tolerance for a range of functionalized nitroolefins. Olefins **127b-e** bearing electron-deficient aryl rings achieved complete conversion within 5 mins (Entries 1-4) while olefins bearing electron-rich tolyl rings required 30 mins (Entries 5 and 6). Olefins with electron-donating methoxy substituents **127h** and **127i** required higher temperature and achieved complete conversion at 0 °C after 60 and 210 mins respectively (Entries 7 and 8). Overall, stereoselectivities were not significantly affected by substituents and a range of functionalized arsines could be obtained in 70-75% *ee*'s (Entries 1-8) except 2-methoxy-functionalized arsine **150h** (Entry 7). Sterically-bulkier naphthyl moieties were also tolerated and afforded arsine **150j** with 68% *ee* at 0 °C (Entry 9). Notably challenging nitroolefins were

also generated with appreciable yields and *ee*'s. Alkyl-substituted arsine **150k** was generated in 57% yield with 34% *ee* even with the less-rigid alkyl substituent (Entry 10). 2-pyridyl arsine **150l** was obtained in a moderate yield of 69% with 32% *ee* despite bearing potential catalyst-poisoning heteroatoms (Entry 11). The low stereoselectivity could be due to the presence of a basic pyridyl group which encouraged the undesirable formation of Ni–AsPh₂/Ni-pyridyl species that led to alternative reaction pathways or side reactions. Lastly, the hydroarsination reaction of other challenging terminal nitroolefins also proceeded smoothly to afford arsines **152b** and **152c** in 94% and 62% yields respectively with 72% *ee* (Entries 12 and 13). Ni(II)-catalyst **97a** was concluded to be sensitive to the electron density of the olefin, favouring electron-deficient olefins as expected from the proposed arsa-Michael reaction mechanism. Electron-rich olefins either required longer reaction times or higher temperatures to achieve comparable yields.

Structural evaluation of related phosphines and arsines

Despite the best of our ability, even highly enantioenriched mixtures of adducts **150/152** yielded only racemic crystals which were not useful for absolute structural determination by X-ray crystallography. An enantioenriched sample of tertiary arsine **150a** (80% *ee*) was treated with dimethylsulfide gold(I) chloride before recrystallization was attempted again (Scheme 67). In this instance, derivatization by coordination was successful at affording

Scheme 67. Coordination of tertiary arsine **150a**.

crystals of the enantiopure gold(I)-arsine complex (*S*)-**153** in 48% yield after a single recrystallization from acetonitrile. Based on the yield of the *S*-isomer isolated, it was concluded that the predominant handform of arsine **150a** arising from the catalysis by complex (*R,R*)-**97a**

was of the *S* configuration. Other structural features of complex **153** was also reviewed to confirm the coordination chemistry of arsine **150a**. The single crystal X-ray diffraction analysis revealed a nearly linear configuration around the Au atom with the Cl–Au–As bond angle at 176.63(7)° (Figure 33). The Au–As and Au–Cl bond lengths (2.33(11) Å and 2.28(3) Å

Figure 33. Solid-state molecular structure of Au-complex (*S*)-**153**.

respectively) showed no significant deviation from other arsine-gold(I) chloride complexes previously reported in literature.¹²

In addition, we were also interested in the structural differences between analogous tertiary phosphine and arsine compounds. From the racemic syntheses of compounds **150a** and **154**, coordination to Au could also generate arsine-Au(I) complex **153** and phosphine-Au(I) complex **155** (Scheme 68). The solid-state molecular structures of arsine **150a**, phosphine **154**,

Scheme 68. Racemic synthesis of free- and coordinated- arsines and phosphines.

complexes **153** and **155** were obtained *via* X-ray crystallographic analyses and selected bond lengths and angles were compiled in Table 20. The molecular structure of 4-chloro substituted adduct **150c** was also obtained.

Table 20. Selected bond lengths(Å) and angles (°) of compounds **150a**, **150c**, **153**, **154** and **155**.

		150a	150c^a	154^a	153	155^a
<p>150a E = As, R = H, 150c E = As, R = Cl, 154 E = P, R = H</p>	E–C1	1.956(3)	1.954(2)	1.840(3)	1.923(9)	1.806(4)
	E–C2	1.960(3)	1.954(2)	1.825(3)	1.913(9)	1.809(4)
	E–C3	2.007(3)	2.015(1)	1.872(3)	1.979(9)	1.846(4)
	E–Au	-	-	-	2.331(1)	2.223(1)
	Au–Cl	-	-	-	2.279(3)	2.282(1)
	C–E–C (ave)	98.9(1)	99.1(1)	101.5(1)	105.1(4)	106.1(2)
<p>153 E = As, 155 E = P</p>	E–C3–H	108.9	108.6	109.6	108.4	107.9
	E–C3–C (ave)	108.9(2)	108.5(1)	108.4(2)	107.8(6)	109.1(3)
	C–E–Au	-	-	-	113.5(3)	112.7(1)
	(ave)	-	-	-	-	-
	E–Au–Cl	-	-	-	176.6(1)	176.8(1)

^aMolecular structures of compounds **150a**, **150c**, **153**, **154** and **155** can be found in Appendix I.

Several key observations were made. Firstly, 4-chloro substituted arsine **150c** possessed similar bond lengths and angles to arsine **150a** despite the significant influence of electron-withdrawing substituents on the reaction time. Secondly, both compounds possessed longer As–C3 bond lengths than As–C1/2 bond lengths. Thirdly, C–As bond lengths of arsine **150a** were longer than the corresponding C–P bond lengths of phosphine **154**, understandably due to inherent differences in atomic radii. Despite differences in C–E bond lengths, no significant distortions to the tetrahedral shape of the adjacent C3 atom was observed (average angles of 108.9° for arsine **150a** and 108.8° for phosphine **154**). Lastly, bond angles around the heteroatom E averaging 98.9° for arsine **150a** and 101.6° for phosphine **154** suggest a larger degree of *s*-character present in the lone pair of As. Coordination increased average bond angles around the As heteroatom from 98.9° in arsine **150a** to 105.1° in complex **153**. A smaller increase in bond angles around P observed from phosphine **154** to complex **155** (in spite of a shorter P–Au bond length) clearly supports the larger *s*-character of the free lone pair in arsine **150a**. The C–E–C and C–E–Au bond angles of arsine complex **153** and phosphine complex **155** agree well with a lower degree of hybridization for arsine variants when compared directly

to their phosphine analogues. Computational calculations performed reaffirmed the nature of the arsine **150a** and phosphine **154** lone pairs (Table 21).

Table 21. NBO analysis on lone pairs of arsine **150a** and phosphine **154**.

Compound	NBO number	Orbital Component
150a	92	(1.96089) LP (1) As 1
		<i>s</i> (58.48%)
		<i>p</i> 0.71(41.51%)
		<i>d</i> 0.00(0.01%)
154	88	(1.94594) LP (1) P 42
		<i>s</i> (46.66%)
		<i>p</i> 1.14(53.32%)
		<i>d</i> 0.00(0.01%)

Two analyses stand out that may account for the relative scarcity of hydroarsination reactions: 1) the greater *s*-character of organoarsine lone pairs may be related to the challenging nature of lone pair activation for arsine compounds, and 2) longer C–E bond lengths in tertiary arsines may provide a weaker driving force towards formation of hydroarsination adducts. The larger *s*-character of As may also explain the better air-stabilities of arsine adducts **150** and **152** which can be handled under atmospheric conditions without oxidation to As(V).

3.3 Conclusion

In conclusion, Ni-catalyzed asymmetric hydroarsination reactions proceeded differently from the Pd-catalyzed version. After a series of preparative experiments and condition optimization, a catalytic cycle involving the PCP Ni(II)-Cl pincer catalyst was proposed, highlighting a novel Ni–Cl–As interaction as a key catalytic intermediate. This was based on a series of experiments, DFT calculations, $^{31}\text{P}\{^1\text{H}\}$ NMR studies and conductivity measurements. Furthermore, experimental observations indicate that the Ni-catalyzed hydrophosphination mechanisms proposed by Togni and Downey were inapplicable in this

instance. It was clear the hydroarsination reaction should not be taken as a simple extension of the well-established hydrophosphination reaction.

Several implications stand out regarding the proposed Ni–Cl–As interaction. Firstly, the transient nature of the Ni–Cl–As interaction could be related to the rapid generation of desired arsine products. Even without vigorous heating, reactions conducted under mild conditions (RT to -20°C) could afford arsine products almost quantitatively in <5 mins. Secondly, this is the first reported instance with catalysts bearing the same PCP chiral ligand that excellent stereoselectivity could still be obtained without direct interaction with the metal center. By extension, this may also reduce the risk of catalyst poisoning that is typically of concern with hydrofunctionalization reactions involving soft donor atoms such as P and As. Lastly, this mode of interaction was relatively robust and generated a library of nitro-functionalized arsines in up to 80% *ee*'s. This represents a remarkable progress in the arsenal of As–C bond forming methodologies, most of which rely on toxic reagents and/or harsh conditions thus resulting in a heavy burden on human health and the environment. As an extension, a series of analogous phosphine- and arsine-derivatives of nitrostyrene were also synthesized, coordinated to gold and analyzed by X-ray crystallography. By analyzing structural differences between these related compounds, the larger *s*-character of the As lone pair was evident which provided some basis for the reactivity differences observed from the hydrophosphination reaction.

Results of this investigation represented a satisfactory progress from Pd-catalyzed hydroarsination reactions. Comparable reaction times, yields and stereoselectivities were still observed. On the other hand, no noticeable arsenic-containing byproduct formation (such as tetraphenyldiarsine) was observed from the Ni-catalyzed reaction. In addition, the need for an external base was omitted and quantities of required reactants (secondary arsine, base and catalyst) were lowered. Less bulky terminal olefins were also suitable substrates for the Ni-

catalyzed asymmetric hydroarsination reaction, furnishing stable products with high enantioselectivities in the absence of a benzylic C–As bond. These improvements were likely a result of the Ni–Cl–As interaction which conferred new modes of reactivity and asymmetric induction. In the next step forward, enantioselective organocatalysis and diastereomeric C–As bond formation were examined as possible avenues to lower the cost associated with transition metal catalysts. These developments are detailed in Chapter 4.

3.4 Experimental section

General information. All reactions were carried out under a positive pressure of nitrogen using standard Schlenk techniques. Solvents were purchased from their respective companies (ACN, MeOH, DCM: VWR Chemicals, DEE: Merck, toluene, n-hexane: Avantor, Acetone: Sigma-Aldrich, THF: Tedia) and used as supplied. DCM and THF were dried and distilled. Where necessary, solvents were degassed prior to use. A Low Temp Pairstirrer PSL-1400 was used for controlling low temperature reactions. Column chromatography was done on Silica gel 60 (Merck). Melting points were measured using SRS Optimelt Automated Point System SRS MPA100. Optical rotations were measured with JASCO P-1030 Polarimeter in the specified solvent in a 0.1 dm cell at 22.0°C. NMR spectra were recorded on Bruker AV 300, AV 400 and AV 500 spectrometers. Chemical shifts were reported in ppm and referenced to an internal SiMe₄ standard (0 ppm) for ¹H NMR, chloroform-d (77.23 ppm) or acetonitrile-d (1.39 ppm) for ¹³C NMR, and an external 85% H₃PO₄ for ³¹P{¹H} NMR. Conductivity measurements were conducted with Radiometer Analytical IONcheck30 calibrated with Schott Instruments LF 2014 K.

The compounds **87b**,⁵ **96a**,⁵ **97a**,⁵ **127k**¹³ and **127l**¹⁴ were prepared according to literature methods. Conversion of M–Cl complexes **87b**, **96a** and **97a** to M–OAc complexes **87a**, **96b**

and **97b** were performed as described in literature.¹⁵ All other reactants and reagents were used as supplied.

Due to their instability in solution, arsine adducts **150** and **152** were characterized by ¹H NMR, HRMS, HPLC and optical rotation measurements except adducts **150a**, **150c**, **150g**, **150i** and **152c** which were characterized fully.

General procedure for the synthesis of *trans*-nitroolefins 127. Arylaldehyde (10 mmol, 1 equiv.) and NH₄OAc (0.19 g, 2.5 mmol, 0.25 equiv.) was heated at reflux in nitromethane (50 mL) with vigorous stirring for 5 h. Upon cooling, the crude reaction was extracted with DEE (3 X 30 mL). Combined organic layers were washed with brine (1 X 30 mL) and dried over MgSO₄, filtered and concentrated. The crude product was purified by silica gel chromatography (20 n-hexanes : 1 EA) to afford nitroolefins **127**.

127d Yellow solid. Yield: 1.61 g, 7.40 mmol, 74%. Mp: 99- 100°C. ¹H NMR (CDCl₃, 400 MHz): δ 8.43-9.39 (d, 1H, ²J_{HH}=13.68 Hz, NCH), 7.61-7.59 (m, 1H, Ar), 7.57-7.53 (m, 1H, ²J_{HH}=13.68 Hz, NCC_H), 7.50-7.48 (m, 1H, Ar), 7.31-7.26 (m, 1H, Ar); ¹³C NMR (CDCl₃, 100 MHz): δ 139.9 (s, 1C, Ar), 135.3-133.4 (4C, Ar), 131.0 (s, 1C, Ar), 128.0 (s, 1C, Ar), 126.8 (s, 1C, Ar). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₈H₆Cl₂NO₂, 217.9776; found, 217.9775.

127j Yellow solid. Yield: 1.71 g, 8.60 mmol, 86%. Mp: 88- 88°C. ¹H NMR (CDCl₃, 500 MHz): δ 8.76-8.72 (m, 1H, ²J_{HH}=13.40 Hz, NCH), 8.07-8.06 (m, 1H, Ar), 7.98-7.97 (m, 1H, Ar), 7.90-7.89 (m, 1H, Ar), 7.68-7.66 (m, 1H, Ar), 7.61-7.56 (d, 2H, Ar), 7.60-7.57 (m, 1H, ²J_{HH}=13.15 Hz, NCC_H), 7.50-7.46 (m, 1H, Ar); ¹³C NMR (CDCl₃, 126 MHz): δ 138.5 (s, 1C, Ar), 136.1 (s, 1C, Ar), 133.8 (s, 1C, Ar), 132.7 (s, 1C, Ar), 131.6 (s, 1C, Ar), 129.2 (s, 1C, Ar), 127.8 (s, 1C, Ar), 127.0 (s, 1C, Ar), 126.9 (s, 1C, Ar), 126.5 (s, 1C, Ar), 125.5 (s, 1C, Ar), 123.0 (s, 1C, Ar). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₁₂H₁₀NO₂, 200.0712; found, 200.0711.

General procedure for the synthesis of terminal nitroolefins 151. To a solution of NaNO₂ (1.32 g, 19.2 mmol, 4.0 equiv.) and ethylene glycol (0.80 mL, 14.4 mmol, 3 equiv.) in water

(2 mL) was added a solution of aryllolefin (4.8 mmol, 1.0 equiv.) in EA (15 mL). Iodine (1.83 g, 7.2 mmol, 1.5 equiv.) was added portionwise at 0°C and the mixture was gradually allowed to RT and stirred for 48 h under an inert atmosphere. The crude solution was extracted with EA (3 X 30 mL), organic layers were combined and washed with 10% aq. Na₂S₂O₃ (1 X 30 mL) and brine (1 X 30 mL), then dried over MgSO₄. Volatiles were removed and the crude product was purified by silica gel chromatography (3 n-hexanes : 1 EA) to afford compound **151**.

151a Yellow solid. Yield: 0.56 g, 3.74 mmol, 78%. Mp: 41- 42°C. ¹H NMR (CDCl₃, 500 MHz): δ 8.03-8.00 (d, 1H, ²J_{HH}=13.65 Hz, NCCH), 7.61-7.58 (d, 1H, ²J_{HH}=13.65 Hz, NCCH), 7.56-7.44 (m, 5H, Ar); ¹³C NMR (CDCl₃, 126 MHz): δ 139.3 (s, 1C, Ar), 137.3 (s, 1C, Ar), 132.3 (s, 1C, Ar), 130.2 (s, 1C, Ar), 129.5 (1C, Ar), 129.3 (s, 1C, Ar). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₈H₈NO₂, 150.0555; found, 150.0557.

151b Yellow solid. Yield: 0.42 g, 2.54 mmol, 53%. Mp: 111- 111°C. ¹H NMR (CDCl₃, 500 MHz): δ 7.98-7.95 (d, 1H, ²J_{HH}=13.65 Hz, NCCH), 7.58-7.55 (d, 1H, ²J_{HH}=13.65 Hz, NCCH), 7.50-7.43 (m, 4H, Ar). ¹³C NMR (CDCl₃, 126 MHz): δ 138.5 (s, 1C, NC), 137.9 (1C, Ar), 137.6 (s, 1C, Ar), 130.4 (s, 1C, Ar), 130.0 (s, 1C, Ar), 128.7 (s, 1C, NCC). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₈H₇ClNO₂, 184.0165; found, 184.0162.

151c Yellow solid. Yield: 0.33 g, 1.78 mmol, 37%. Mp: 102- 103°C. ¹H NMR (CDCl₃, 300 MHz): δ 8.01-7.97 (d, 1H, ²J_{HH}=13.65 Hz, NCCH), 7.59-7.54 (d, 1H, ²J_{HH}=13.60 Hz, NCCH), 7.46-7.43 (d, 2H, Ar), 7.27-7.25 (m, 2H, Ar); ¹³C NMR (CDCl₃, 126 MHz): δ 143.3 (s, 1C, NC), 139.3 (s, 1C, Ar), 136.5 (s, 1C, Ar), 130.3 (s, 1C, Ar), 129.3 (s, 1C, Ar), 127.4 (s, 1C, NCC). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₉H₁₀NO₂, 164.0712; found, 164.0716.

General procedure for the hydroarsination reaction of nitrostyrene 127a catalyzed by complexes 87, 96 and 97 (Table 11 and 12). A stock solution of the catalyst in MeOH (1.00 mM, 5 mL, 5 mol %) was added to a solution of HAsPh₂ (2.76 mg, 12.00 μmol, 1.2 equiv.) in

the stated solvent (1 mL) and brought to the desired temperature. Nitrostyrene **127a** (1.49 mg, 10.0 μ mol, 1.0 equiv.) was subsequently added and washed down with the stated solvent to make 2 mL. The reaction was stirred at the indicated temperature and checked every 15 mins by TLC to monitor the consumption of nitrostyrene. Upon completion of the reaction, two drops of the crude reaction mixture was withdrawn from the flask and diluted with hexane (1 mL) to prepare the HPLC sample. The arsine adduct could be crystallized from a mixture of DCM/MeOH to afford the pure product **150a** as white crystalline needles. The *ee* was determined on a Daicel Chiralpak ID column with n-hexane/2-propanol = 99/1, flow = 0.8 mL/min, wavelength = 254 nm. Retention times: 8.7 min (minor, R isomer), 9.5 min (major, *S* isomer). $[\alpha]_{\text{D}}^{25} = -45.2$ (c 2.75, MeOH) (measured for Table 12 Entry 9). Mp: 88-90°C. ^1H NMR (CD_3CN , 400 MHz): δ 7.68-7.65 (m, 2H, Ar), 7.48-7.47 (m, 2H, Ar), 7.29-7.27 (m, 3H, Ar), 7.25-7.21 (m, 6H, Ar), 7.19-7.16 (m, 1H, Ar), 4.99 (dd, 1H, $^3J_{\text{HH}} = 13.0$ Hz, $^3J_{\text{HH}} = 12.8$ Hz, AsCH), 4.60 (dd, 1H, $^3J_{\text{HH}} = 13.0$ Hz, $^2J_{\text{HH}} = 4.0$ Hz, NCH), (dd, 1H, $^3J_{\text{HH}} = 12.6$ Hz, $^2J_{\text{HH}} = 4.0$ Hz, NCH); ^{13}C NMR (CD_3CN , 100 MHz): δ 134.5-128.1 (15C, Ar), 79.7 (s, 1C, AsC), 43.8 (s, 1C, NC). HRMS (+ESI) *m/z*: (*M* + *H*)⁺ calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_2\text{As}$, 380.0632; found, 380.0625. Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{NO}_2\text{As}$: C, 63.33; H, 4.78; N, 3.69. Found: C, 63.34; H, 5.09; N, 3.95 %.

General procedure for the asymmetric hydroarsination of nitrostyrenes 127 and 151 catalyzed by complex 97 (Table 11, 12, 14, 16 and 19). Catalyst (*R,R*)-**97a** (1.00 μ mol, 2 mol %) was added to a solution of HAsPh_2 (13.80 mg, 0.06 mmol, 1.2 equiv.) in the stated solvent (1 mL) and brought to the desired temperature. Nitroolefin (0.05 mmol, 1.0 equiv.) was subsequently added and washed down with the stated solvent to make 2 mL. The reaction was stirred at the indicated temperature and checked every 15 mins by TLC to monitor the consumption of the substrate. The arsine adduct could be crystallized from a mixture of DCM/MeOH to afford the pure products **150a**, **150c**, **150g**, **150i** and **152c** as crystalline needles.

150a White solid. The *ee* was determined on a Daicel Chiralpak ID column with n-hexane/2-propanol = 99/1, flow = 0.8 mL/min, wavelength = 254 nm. Retention times: 8.7 min (minor), 9.5 min (major). $[\alpha]_{\text{D}}^{25} = -45.2$ (*c* 2.75, MeOH)(measured for Table 13 Entry 14). Mp: 88- 90°C. ^1H NMR (CD_3CN , 400 MHz): δ 7.68-7.65 (m, 2H, Ar), 7.48-7.47 (m, 2H, Ar), 7.29-7.27 (m, 3H, Ar), 7.25-7.21 (m, 6H, Ar), 7.19-7.16 (m, 1H, Ar), 4.99 (dd, 1H, $^3J_{\text{HH}} = 13.0$ Hz, $^3J_{\text{HH}} = 12.8$ Hz, AsCH), 4.60 (dd, 1H, $^3J_{\text{HH}} = 13.0$ Hz, $^2J_{\text{HH}} = 4.0$ Hz, NCH), 4.37 (dd, 1H, $^3J_{\text{HH}} = 12.6$ Hz, $^2J_{\text{HH}} = 4.0$ Hz, NCH); ^{13}C NMR (CD_3CN , 100 MHz): δ 134.5-128.1 (18C, Ar), 79.7 (s, 1C, AsC), 43.8 (s, 1C, NC). HRMS (+ESI) *m/z*: (*M* + *H*)⁺ calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_2\text{As}$, 380.0632; found, 380.0625.

150b White solid. The *ee* was determined on a Daicel Chiralpak ID column with n-hexane/2-propanol = 99/1, flow = 0.8 mL/min, wavelength = 250 nm. Retention times: 8.3 min (minor), 8.9 min (major). ^1H NMR (CD_3CN , 400 MHz): δ 7.66-7.14 (m, 14H, Ar), 5.02 (dd, 1H, $^3J_{\text{HH}} = 13.0$ Hz, $^3J_{\text{HH}} = 12.9$ Hz, AsCH), 4.63 (dd, 1H, $^3J_{\text{HH}} = 13.4$ Hz, $^2J_{\text{HH}} = 3.8$ Hz, NCH), 4.36 (dd, 1H, $^3J_{\text{HH}} = 12.6$ Hz, $^2J_{\text{HH}} = 3.5$ Hz, NCH). HRMS (+ESI) *m/z*: (*M* + *H*)⁺ calcd for $\text{C}_{20}\text{H}_{18}\text{ClNO}_2\text{As}$, 414.0242; found, 414.0231.

150c White solid. The *ee* was determined on a Daicel Chiralpak ID column with n-hexane/2-propanol = 99/1, flow = 0.8 mL/min, wavelength = 250 nm. Retention times: 8.2 min (minor), 8.9 min (major). $[\alpha]_{\text{D}}^{25} = -1.62$ (*c* 0.38, MeOH)(measured for Table 21 Entry 2). Mp: 96.5-97.2°C. ^1H NMR (CD_3CN , 400 MHz): δ 7.67-7.65 (m, 2H, Ar), 7.49-7.47 (m, 3H, Ar), 7.32-7.24 (m, 5H, Ar), 7.22-7.20 (m, 2H, Ar), 7.17-7.15 (m, 2H, Ar), 4.98 (dd, 1H, $^3J_{\text{HH}} = 13.4$ Hz, $^3J_{\text{HH}} = 12.8$ Hz, AsCH), 4.62 (dd, 1H, $^3J_{\text{HH}} = 13.4$ Hz, $^2J_{\text{HH}} = 4.0$ Hz, NCH), 4.37 (dd, 1H, $^3J_{\text{HH}} = 12.8$ Hz, $^2J_{\text{HH}} = 4.0$ Hz, NCH); ^{13}C NMR (CD_3CN , 100 MHz): δ 134.5-129.6 (18C, Ar), 79.4 (1C, AsC), 43.1 (s, 1C, NC). HRMS (+ESI) *m/z*: (*M* + *H*)⁺ calcd for $\text{C}_{20}\text{H}_{18}\text{AsClNO}_2$, 414.0242; found, 414.0228.

150d White solid. The *ee* was determined on a Daicel Chiralpak ID column with n-hexane/2-propanol = 99/1, flow = 0.8 mL/min, wavelength = 254 nm. Retention times: 7.8 min (minor), 8.5 min (major). ¹H NMR (CD₃CN, 400 MHz): δ 7.69-7.67 (m, 2H, Ar), 7.53-7.53 (m, 3H, Ar), 7.39-7.36 (m, 4H, Ar), 7.29-7.12 (m, 4H, Ar), 5.03-4.96 (m, 2H, AsCH and NCH), 4.71-4.69 (m, 1H, NCH). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₂₀H₁₇Cl₂NO₂As, 447.9852; found, 447.9847.

150e White solid. The *ee* was determined on a Daicel Chiralpak ID column with n-hexane/2-propanol = 99/1, flow = 0.6 mL/min, wavelength = 240 nm. Retention times: 10.3 min (minor), 11.0 min (major). ¹H NMR (CD₃CN, 400 MHz): δ 7.67-7.65 (m, 2H, Ar), 7.49-7.47 (m, 3H, Ar), 7.31-7.19 (m, 6H, Ar), 7.02-7.00 (m, 1H, Ar), 6.92-6.90 (m, 2H, Ar), 5.01 (dd, 1H, ³J_{HH} = 13.0 Hz, ³J_{HH} = 13.0 Hz, AsCH), 4.63 (dd, 1H, ³J_{HH} = 13.5 Hz, ²J_{HH} = 4.0 Hz, NCH), 4.39 (dd, 1H, ³J_{HH} = 12.7 Hz, ²J_{HH} = 3.8 Hz, NCH); ¹⁹F {¹H} NMR (CD₃CN, 377 MHz): δ -113.73 (s, 1F). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₂₀H₁₈FNO₂As, 398.0538; found, 398.0540.

150f White solid. The *ee* was determined on a Daicel Chiralpak IC column with n-hexane/2-propanol = 99.5/0.5, flow = 0.6 mL/min, wavelength = 210 nm. Retention times: 14.8 min (major), 16.3 min (minor). ¹H NMR (CD₃CN, 400 MHz): δ 7.65-7.64 (m, 2H, Ar), 7.46-7.46 (m, 3H, Ar), 7.28-7.22 (m, 5H, Ar), 7.13-7.09 (m, 1H, Ar), 7.01-6.98 (m, 3H, Ar), 4.98 (dd, 1H, ³J_{HH} = 13.0 Hz, ³J_{HH} = 12.9 Hz, AsCH), 4.59 (dd, 1H, ³J_{HH} = 13.2 Hz, ²J_{HH} = 3.8 Hz, NCH), 4.32 (dd, 1H, ³J_{HH} = 12.6 Hz, ²J_{HH} = 3.7 Hz, NCH). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₂₁H₂₁NO₂As, 394.0788; found, 394.0781.

150g White solid. The *ee* was determined on a Daicel Chiralpak ID column with n-hexane/2-propanol = 99/1, flow = 0.8 mL/min, wavelength = 280 nm. Retention times: 7.6 min (minor), 8.3 min (major). [α]_D²⁵ = +0.01 (*c* 0.98, MeOH)(measured for Table 6 Entry 6). Mp: 86.7-87.9°C. ¹H NMR (CD₃CN, 400 MHz): δ 7.66-7.64 (m, 2H, Ar), 7.47-7.45 (m, 3H, Ar), 7.33-7.24 (m, 5H, Ar), 7.12-7.10 (m, 2H, Ar), 7.05-7.03 (m, 2H, Ar), 4.94 (dd, 1H, ³J_{HH} = 12.8 Hz,

$^3J_{\text{HH}} = 12.8$ Hz, AsCH), 4.56 (dd, 1H, $^3J_{\text{HH}} = 12.8$ Hz, $^2J_{\text{HH}} = 4.0$ Hz, NCH), 4.34 (dd, 1H, $^3J_{\text{HH}} = 12.8$ Hz, $^2J_{\text{HH}} = 4.0$ Hz, NCH), 2.24 (s, 3H, CH₃); ^{13}C NMR (CD₃CN, 100 MHz): δ 134.6-129.3 (18C, Ar), 80.0 (1C, AsC), 43.5 (s, 1C, NC), 21.1 (s, 1C, CH₃). HRMS (+ESI) m/z : (M + H)⁺ calcd for C₂₁H₂₁NO₂As, 394.0788; found, 394.0786.

150h White solid. The *ee* was determined on a Daicel Chiralpak ID column with n-hexane/2-propanol = 99/1, flow = 0.8 mL/min, wavelength = 254 nm. Retention times: 9.3 min (minor), 10.1 min (major). ^1H NMR (CD₃CN, 400 MHz): δ 7.65-7.64 (m, 2H, Ar), 7.36-7.34 (m, 3H, Ar), 7.24-7.12 (m, 7H, Ar), 6.84-6.79 (m, 2H, Ar), 5.08 (dd, 1H, $^3J_{\text{HH}} = 12.4$ Hz, $^3J_{\text{HH}} = 12.4$ Hz, AsCH), 4.68 (dd, 1H, $^3J_{\text{HH}} = 11.96$ Hz, $^2J_{\text{HH}} = 3.9$ Hz, NCH), 4.60 (dd, 1H, $^3J_{\text{HH}} = 12.6$ Hz, $^2J_{\text{HH}} = 3.9$ Hz, NCH). HRMS (+ESI) m/z : (M + H)⁺ calcd for C₂₁H₂₁NO₃As, 410.0737; found, 410.0738.

150i White solid. The *ee* was determined on a Daicel Chiralpak ID column with n-hexane/2-propanol = 99/1, flow = 0.8 mL/min, wavelength = 254 nm. Retention times: 12.6 min (minor), 14.2 min (major). $[\alpha]_{\text{D}}^{25} = +4.18$ (*c* 0.12, MeOH)(measured for Table 21 Entry 8). Mp: 98.4-99.6°C. ^1H NMR (CD₃CN, 400 MHz): δ 7.66-7.64 (m, 2H, Ar), 7.47-7.46 (m, 3H, Ar), 7.30-7.24 (m, 5H, Ar), 7.14-7.12 (m, 2H, Ar), 6.79-6.76 (m, 2H, Ar), 4.93 (dd, 1H, $^3J_{\text{HH}} = 12.8$ Hz, $^3J_{\text{HH}} = 12.8$ Hz, AsCH), 4.56 (dd, 1H, $^3J_{\text{HH}} = 12.8$ Hz, $^2J_{\text{HH}} = 4.0$ Hz, NCH), 4.32 (dd, 1H, $^3J_{\text{HH}} = 12.8$ Hz, $^2J_{\text{HH}} = 4.0$ Hz, NCH), 3.71 (s, 3H, OCH₃); ^{13}C NMR (CD₃CN, 100 MHz): δ 134.6-129.6 (16C, Ar), 115.0 (s, 2C, Ar), 80.0 (1C, AsC), 56.0 (s, 1C, OCH₃), 43.2 (s, 1C, NC). HRMS (+ESI) m/z : (M + H)⁺ calcd for C₂₁H₂₁NO₃As, 410.0737; found, 410.0735.

150j White solid. The *ee* was determined on a Daicel Chiralpak ID column with n-hexane/2-propanol = 99/1, flow = 0.8 mL/min, wavelength = 280 nm. Retention times: 8.6 min (minor), 9.4 min (major). ^1H NMR (CD₃CN, 400 MHz): δ 8.16-8.16 (m, 1H, Ar), 7.84-7.82 (m, 1H, Ar), 7.75-7.71 (m, 3H, Ar), 7.56-7.51 (m, 4H, Ar), 7.46-7.46 (m, 3H, Ar), 7.17-7.13 (m, 2H, Ar), 7.11-7.09 (m, 1H, Ar), 7.05-7.01 (m, 2H, Ar), 5.28-5.28 (m, 1H, AsCH), 5.11-5.11 (m, 1H,

NCH), 4.81 (dd, 1H, $^3J_{\text{HH}} = 13.3$ Hz, $^2J_{\text{HH}} = 3.9$ Hz, *NCH*). HRMS (+ESI) *m/z*: (*M* + *H*)⁺ calcd for C₂₄H₂₁NO₂As, 430.0788; found, 430.0786.

150k White solid. The *ee* was determined on a Daicel Chiralpak ID column with n-hexane/2-propanol = 99.5/0.5, flow = 0.6 mL/min, wavelength = 230 nm. Retention times: 7.8 min (minor), 8.0 min (major). ¹H NMR (CDCl₃, 400 MHz): δ 7.53-7.53 (m, 2H, Ar), 7.41-7.38 (m, 4H, Ar), 7.34-7.33 (m, 4H, Ar), 4.32-4.21 (m, 2H, *NCH*), 3.16-3.11 (m, 1H, *AsCH*), 1.80-0.84 (m, 11H, cyclohexyl). HRMS (+ESI) *m/z*: (*M* + *H*)⁺ calcd for C₂₀H₂₅NO₂As, 386.1101; found, 386.1097.

150l White solid. The *ee* was determined on a Daicel Chiralpak ID column with n-hexane/2-propanol = 85/15, flow = 0.8 mL/min, wavelength = 210 nm. Retention times: 10.8 min (major), 11.3 min (minor). ¹H NMR (CD₃CN, 400 MHz): δ 7.64-7.25 (m, 12H, Ar), 7.10-7.07 (m, 1H, Ar), 6.95-6.93 (m, 1H, Ar), 5.32 (dd, 1H, $^3J_{\text{HH}} = 13.6$ Hz, $^3J_{\text{HH}} = 12.2$ Hz, *AsCH*), 4.64 (dd, 1H, $^3J_{\text{HH}} = 13.8$ Hz, $^2J_{\text{HH}} = 3.5$ Hz, *NCH*), 4.52 (dd, 1H, $^3J_{\text{HH}} = 12.0$ Hz, $^2J_{\text{HH}} = 3.5$ Hz, *NCH*). HRMS (+ESI) *m/z*: (*M* + *H*)⁺ calcd for C₁₉H₁₈N₂O₂As, 381.0584; found, 381.0581.

152a White solid. The *ee* was determined on a Daicel Chiralpak ID column with n-hexane/2-propanol = 99/1, flow = 0.8 mL/min, wavelength = 254 nm. Retention times: 8.4 min (minor), 9.4 min (major). ¹H NMR (CD₃CN, 400 MHz): δ 7.67-7.67 (m, 2H, Ar), 7.48-7.46 (m, 3H, Ar), 7.29-7.16 (m, 10H, Ar), 4.99 (dd, 1H, $^3J_{\text{HH}} = 12.8$ Hz, $^3J_{\text{HH}} = 12.8$ Hz, *AsCH*), 4.60 (dd, 1H, $^3J_{\text{HH}} = 13.2$ Hz, $^2J_{\text{HH}} = 4.0$ Hz, *NCH*), 4.37 (dd, 1H, $^3J_{\text{HH}} = 12.6$ Hz, $^2J_{\text{HH}} = 4.0$ Hz, *NCH*). HRMS (+ESI) *m/z*: (*M* + *H*)⁺ calcd for C₂₀H₁₉NO₂As, 380.0632; found, 380.0635.

152b White solid. The *ee* was determined on a Daicel Chiralpak ID column with n-hexane/2-propanol = 99/1, flow = 0.8 mL/min, wavelength = 254 nm. Retention times: 8.7 min (minor), 9.6 min (major). ¹H NMR (CD₃CN, 500 MHz): δ 7.75-7.15 (m, 15H, Ar), 4.98 (dd, 1H, $^3J_{\text{HH}} = 13.1$ Hz, $^3J_{\text{HH}} = 13.1$ Hz, *AsCH*), 4.62 (dd, 1H, $^3J_{\text{HH}} = 13.6$ Hz, $^2J_{\text{HH}} = 3.8$ Hz, *NCH*), 4.38 (dd,

1H, $^3J_{\text{HH}} = 12.6$ Hz, $^2J_{\text{HH}} = 3.8$ Hz, NCH). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₂₀H₁₈ClNO₂As, 414.0242; found, 414.0242.

152c White solid. The *ee* was determined on a Daicel Chiralpak ID column with n-hexane/2-propanol = 99/1, flow = 0.8 mL/min, wavelength = 254 nm. Retention times: 7.4 min (minor), 8.1 min (major). $[\alpha]_{\text{D}}^{25} = -1.48$ (*c* 0.54, MeOH)(measured for Table 21 Entry 13). Mp: 101.6-104.3°C. ¹H NMR (CD₃CN, 400 MHz): δ 7.66-7.64 (m, 2H, Ar), 7.47-7.45 (m, 3H, Ar), 7.33-7.24 (m, 5H, Ar), 7.12-7.10 (m, 2H, Ar), 7.05-7.03 (m, 2H, Ar), 4.94 (dd, 1H, $^3J_{\text{HH}} = 12.8$ Hz,

Investigating solvent effect of H/D exchange in HPPh₂ (Figures 25-27). HPPh₂ (9.30 mg, 0.05 mmol, 1.0 equiv) was stirred in the stated deuterated solvent (0.6 mL) at RT.

General procedure for sample preparation involving complexes 97a and nitrostyrene 127a for NMR investigation (Figures 28 and 29). Nitrostyrene **127a** (2.00 mg, 13.40 μmol , 1.0 equiv.) and complex **97a** (1.10 mg, 1.34 μmol , 0.1 equiv.) were stirred in MeOD (0.5 mL) for 10 mins at RT.

General procedure for sample preparation involving complexes 97a and HAsPh₂ for NMR investigation (Figures 30 and 31). HAsPh₂ (5.20 mg, 22.60 μmol , 1.0 equiv.) and complex **97a** (1.88 mg, 2.25 μmol , 0.1 equiv.) were stirred in MeOD (0.5 mL) for 10 mins at RT.

Computational methods (Tables 13, 15, 17 and Figure 32). All calculations were performed with Gaussian 09 (Rev. E.01) programs.¹⁶ Geometry optimization was conducted by the WB97D functional.¹⁷ The Def2-SVP set was employed for all atoms.¹⁸ Note: Calculations done with Def2-TZVP were within 1.0 kcal mol⁻¹ of the Def2-SVP set, but was not selected as the optimal basis set due to the longer computational time required. The vibrational analysis and thermodynamics energetic information at 298.15 K were calculated with the keyword Freq in Gaussian. The PCM solvent model has been used to calculate free energy change in the solution for proton transfer process: HAsPh₂ + MeOH $\rightarrow$ AsPh₂⁻ + MeOH₂⁺.¹⁹ The free energy values

and gas phase coordinates of compounds **97a**, **97c**, **127a** and **150a** and intermediates **A1**, **A1'**, **A2**, **B** and **C** may be found in literature.²⁰ For NBO analysis: NBO 3.0 analysis in the Gaussian 09 was applied to investigate chemical bond information on the optimized geometries, particularly on the orbital component analysis of lone electron pair on As and P atoms.

Synthesis of complex (S)-153 (Scheme 67). To a solution of arsine **150a** (10.10 mg, 29.00 μ mol, 1.0 equiv.) in DCM (3 mL) was added AuCl(SMe₂) (10.25 mg, 34.80 μ mol, 1.2 equiv.). The mixture was stirred in the dark overnight at RT and subsequently washed with H₂O (3 X 10 mL) and dried over MgSO₄. Crude complex **153** could be recrystallized from ACN to afford pure complex (S)-**153** as colourless crystals in 48% yield. $[\alpha]_D^{25} = -84.4$ (*c* 1.58, ACN). Mp: 130-131°C (*dec.*). ¹H NMR (CD₃CN, 400 MHz): δ 7.94-7.91 (m, 2H, Ar), 7.66-7.46 (m, 3H, Ar), 7.40-7.37 (m, 3H, Ar), 7.35-7.35 (m, 2H, Ar), 7.34-7.33 (m, 2H, Ar), 7.27-7.24 (m, 3H, Ar), 5.27 (dd, 1H, ³J_{HH} = 13.88 Hz, ³J_{HH} = 11.96 Hz, AsCH), 5.00 (dd, 1H, ³J_{HH} = 11.90 Hz, ²J_{HH} = 4.18 Hz, NCH), 4.85 (dd, 1H ³J_{HH} = 13.92 Hz, ²J_{HH} = 4.2 Hz, NCH); ¹³C NMR (CD₃CN, 100 MHz): δ 134.5-128.1 (15C, Ar), 76.9 (s, 1C, AsC), 43.8 (s, 1C, NC). HRMS (+ESI) *m/z*: (M + H)⁺ calcd for C₂₀H₁₉NO₂AsAuCl, 613.9956; found, 613.9951. Anal. Calcd for C₂₀H₁₈NO₂AsAuCl: C, 39.27; H, 2.97; N, 2.29. Found: C, 39.73; H, 3.36; N, 2.27 %.

Racemic synthesis of arsine 150a and phosphine 154 (Scheme 68). Nitrostyrene **127a** (7.46 mg, 0.05 mmol, 1.0 equiv.) was added to a solution of HEPPh₂ (0.06 mmol, 1.2 equiv.) in methanol (2 mL). Water (10% v/v, 200 μ L) was added under vigorous stirring at room temperature. Reaction progress was monitored by TLC. Upon completion (**150a**: 2 days, **154**: 10 mins), the white precipitate formed was redissolved in a minimal amount of DCM and was allowed to crystallize from DCM/MeOH to afford colourless fine needles of arsine **150a** and phosphine **154**.

154 White solid. Yield: 15.09 mg, 0.05 mmol, 90%. ¹H NMR (CD₃CN, 400 MHz): δ 7.74-7.73 (m, 2H, Ar), 7.50-7.50 (m, 3H, Ar), 7.40-7.37 (m, 2H, Ar), 7.25-7.18 (m, 8H, Ar), 4.92 (m, 1H,

PCH), 4.55 (m, 2H NCH); ^{13}C NMR (CD_3CN , 100 MHz): δ 134.9-18.5 (18C, Ar), 79.7 (d, 1C, $^1J_{\text{CP}} = 33.0$ Hz, AsC), 44.2 (d, 1C, $^2J_{\text{CP}} = 15.0$ Hz, NC); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_3CN , 162 MHz): δ -6.38 (s, 1P).

Synthesis of complexes 153 and 155 (Scheme 68). AuCl(SMe₂) (0.35 g, 1.2 mmol, 1.2 equiv.) was added to a solution of ligand (1.00 mmol, 1.0 equiv.) in DCM (6 mL) and stirred in the dark overnight at RT. Pure colourless crystals of gold(I) chloride complexes **153** and **155** could be obtained by direct recrystallization of the crude reaction mixture with ACN.

155 White solid. Yield: 0.45 g, 0.79 mmol, 79%. Mp: 208-209 (*dec.*)- °C. ^1H NMR (CD_3CN , 400 MHz): δ 8.14-8.09 (m, 2H, Ar), 7.70-7.68 (m, 3H, Ar), 7.64-7.58 (m, 2H, Ar), 7.50-7.50 (m, 1H, Ar), 7.44-7.39 (m, 4H, Ar), 7.28-7.26 (m, 3H, Ar), 5.28 (ddd, 1H, $^3J_{\text{HH}} = 13.6$ Hz, $^3J_{\text{HH}} = 11.6$ Hz, $^2J_{\text{HP}} = 5.4$ Hz, PCH), 5.08 (ddd, 1H, $^3J_{\text{HP}} = 15.6$ Hz, $^3J_{\text{HH}} = 11.6$ Hz, $^2J_{\text{HH}} = 3.7$ Hz, NCH), 4.83 (ddd, 1H, $^3J_{\text{HH}} = 13.6$ Hz, $^3J_{\text{HP}} = 6.0$ Hz, $^2J_{\text{HH}} = 3.7$ Hz, NCH); ^{13}C NMR (CD_3CN , 100 MHz): δ 135.4-129.7 (18C, Ar), 76.9 (d, 1C, $^1J_{\text{CP}} = 19.1$ Hz, PC), 43.0 (d, 1C, $^2J_{\text{CP}} = 34.5$ Hz, NC); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_3CN , 162 MHz): δ 40.30 (s, 1P). HRMS (+ESI) m/z : ($\text{M} + \text{H}$)⁺ calcd for C₂₀H₁₉NO₂PAuCl, 568.0508; found, 568.0504.

References

- [1] (a) Sadow, A. D.; Togni, A. *J. Am. Chem. Soc.* **2005**, *127*, 17012, (b) Sadow, A. D.; Haller, I.; Fadini, L.; Togni, A. *J. Am. Chem. Soc.* **2004**, *126*, 14704, (c) Eller, J. J.; Downey, K. *J. Comput. Chem.* **2015**, *36*, 1947.
- [2] Ananikov, V. P. *ACS Catal.* **2015**, *5*, 1964.
- [3] Cullen, W. R.; Leeder, W. R. *Can. J. Chem.* **1970**, *48*, 3757.
- [4] (a) Issleib, K.; Kümmel, R. *J. Organomet. Chem.* **1965**, *3*, 84, (b) Li, J.-N.; Liu, L.; Fu, Y.; Guo, Q.-X. *Tetrahedron* **2006**, *62*, 4453.
- [5] Yang, X.-Y.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Organometallics*, **2015**, *34*, 1582.
- [6] (a) Duncan, D.; Hope, E. G.; Singh, K.; Stuart, A. M. *Dalton Trans.* **2011**, *40*, 1998, (b) Standley, E. A.; Smith, S. J.; Muller, P.; Jamison, T. F. *Organometallics*, **2014**, *33*, 2012, (c) Li, J.-Y.; Sun, H.-J. *Jiegou Huaxue* **2015**, *34*, 1735, (d) Cornella, J.; Gómez-Bengoa, E.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997, (e) Thangavadivale, V.; Aguiar, P. M.; Jasim, N. A.; Pike, S. J.; Smith, D. A.; Whitwood, A. C.; Brammer, L.; Perutz, R. N. *Chem. Sci.* **2018**, *9*, 3767, (f) Liu, Y.-H.; Chen, C.; Yang, L.-M. *Acta Cryst. E* **2008**, *64*, m1225, (g) Yang, Z.; Liu, D.; Liu, Y.; Sugiya, M.; Imamoto, T.; Zhang, W. *Organometallics* **2015**, *34*, 1228, (h) Weber, J. M.; Longstreet, A. R.; Jamison, T. F. *Organometallics* **2018**, *37*, 2716, (i) Zheng, X.; Yang, Q.; Li, Z.; Zhu, Z.; Cui, X.; Fu, H.; Chen, H.; Li, R. *Catal. Commun.* **2014**, *57*, 143, (j) Boro, B. J.; Dickie, D. A.; Goldberg, K. I.; Kemp, R. A. *Acta Cryst. E* **2008**, *64*, m1304, (k) Zeller, A.; Herdtweck, E.; Strassner, T. *Eur. J. Inorg. Chem.* **2003**, 2003, 1802.
- [7] (a) Tanaka, S.; Imoto, H.; Yumura, T.; Naka, K. *Organometallics* **2017**, *36*, 1684, (b) Pennington, W. T.; Cordes, A. W.; Graham, J. C.; Jung, Y. W. *Acta Cryst. C* **1983**, *39*, 1010, (c) Stuckey, J. E.; Cordes, A. W.; Handy, L. B.; Perry, R. W.; Fair, C. K. *Inorg. Chem.* **1972**, *11*, 1846, (d) Camerman, A.; Trotter, J. *J. Chem. Soc.* **1965**, 730, (e) Fukuyo, M.; Nakatsu, K.;

Shimada, A. *Bull. Chem. Soc. Jpn* **1966**, *39*, 1614, (f) Trotter, J. *Can. J. Chem.* **1962**, *40*, 1590, (g) Burford, N.; MacDonald, C. L. B.; LeBlanc, D. J.; Cameron, T. S. *Organometallics* **2000**, *19*, 152, (h) Kilah, N. L.; Wild, S. B. *Organometallics* **2012**, *31*, 2658, (i) Batsanov, A. S.; Cornet, S. M.; Dillon, K. B.; Goeta, A. E.; Hazendonk, P.; Thompson, A. L. *J. Chem. Soc., Dalton Trans.* **2002**, 4622, (j) Dostal, L.; Jambor, R.; Ruzicka, A.; Jirasko, R.; Holecck, J.; de Proft, F. *Dalton Trans.* **2011**, *40*, 8922.

[8] Murugesan, S.; Kirchner, K. *Dalton Trans.* **2016**, *45*, 416.

[9] (a) Koshti, V.; Gaikwad, S.; Chikkali, S. H. *Coord. Chem. Rev.* **2014**, *265*, 52, (b) Glueck, D. S. *Synlett* **2007**, *17*, 2627, (c) Pullarkat, S. A.; Leung, P.-H. *Top. Organomet. Chem.* **2013**, *43*, 145.

[10] Brunet, J. J.; Neibecker, D. *Catalytic Heterofunctionalization: From Hydroamination to Hydrozirconization*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2001; p 91-141.

[11] Bodner, G. M.; May, M. P.; McKinney, L. E. *Inorg. Chem.* **1980**, *19*, 1951.

[12] For selected examples, see (a) Monkowius, U. V.; Nogai, S. D.; Schmidbaur, H. Z. *Naturforsch* **2003**, *58b*, 751, (b) Einstein, F. W. B.; Restivo, R. *Acta Cryst.* **1975**, *B31*, 624, (c) Balch, A. L.; Oram, D. E.; Reedy Jr, P. E. *Inorg. Chem.* **1987**, *26*, 1836, (d) Balch, A. L.; Nagle, J. K.; Oram, D. E.; Reedy Jr, P. E. *J. Am. Chem. Soc.* **1988**, *110*, 454, (e) Alvarez, B.; Fernández, E. J.; Gimeno, M. C.; Jones, P. G.; Laguna, A.; López-de-Luzuriaga, J. M. *Polyhedron* **1998**, *17*, 2029, (f) Marques, L. L.; Lang, E. S.; Burrow, R. A. *Acta Cryst.* **2003**, *E59*, m707.

[13] Ferraro, A.; Bernardi, L.; Fochi, M. *Adv. Synth. Catal.* **2016**, *358*, 1561.

[14] Maity, S.; Naveen, T.; Sharma, U.; Maiti, D. *Org. Lett.* **2013**, *15*, 3384.

[15] Yang, X.-Y.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Organometallics* **2015**, *34*, 5196.

[16] Gaussian 09, Revision E.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li,

X.; Caricato, M.; Marenich, A.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.

[17] Chai, J.-D.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615.

[18] Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297.

[19] Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327.

[20] Tay, W. S.; Lu, Y.; Yang, X.-Y.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Chem. Eur. J.* **2019**, *25*, 11308.

Chapter 4

Organocatalyzed hydroarsination reactions

4.1 Introduction

Organocatalysis, a portmanteau of the terms "organic" and "catalyst", refers to the use of small organic molecules to catalyze a chemical transformation.¹ As a subset of the umbrella field, asymmetric organocatalysis can be thematically classified into several areas: 1) iminium/enaminium/amine enolate catalysis,² 2) Brønsted/Lewis base catalysis,³ 3) phase-transfer catalysis,⁴ 4) catalysis involving hydrogen bond-donors,⁵ 5) and strong Brønsted acid catalysis.⁶ Chiral induction has been well-explored by most types of organocatalysts to great success as well and, together with biocatalysts and transition metal catalysts, form the three pillars of effective asymmetric synthesis.

Generally, organocatalysts are favoured over transition metal catalysts because of their low molecular weights, higher natural elemental abundance and well-defined reactivities. Unlike transition metal catalysts, organocatalysts are also less prone to deactivation and catalyst poisoning especially for reactions involving potentially-coordinating compounds such as amines, phosphines and thiols. Instead, organocatalysts are more commonly challenged by chemoselectivity concerns. For instance, nucleophilic organocatalysts must be selective for a single electrophilic site in order to ensure high yields of the targeted product and good stereoselectivity of the transformation (Scheme 69). To maintain high turnover numbers,

Scheme 69. Catalyst activation of electrophilic substrates.

organocatalysts must also resist irreversible addition to the activated substrate despite their close structural similarity to the reactants themselves (Scheme 70).

Scheme 70. Competing nucleophilic addition to activated substrates.

Their high natural abundance (in particular for enantiopure organocatalysts derived directly from the chiral pool) and well-defined chemical structures make organocatalysts readily-available from many commercial sources. Targeted design of organocatalysts based on amino acids, phosphoric acids, thioureas, diols, aldehydes and alkaloids can be significantly simplified by the ready availability of suitable building blocks. The abundance of enantiopure organic compounds from the chiral pool such as saccharides, amino acids, cinchona alkaloids and terpenes allows convenient access to asymmetric organocatalysts as well.⁷ Unlike transition metal catalysts which can be difficult to synthesize or handle, organocatalysis holds great potential in translating the utility of hydroarsination reactions to the general synthetic community. Due to the enormous amount of literature available, related organocatalyzed hydro-phosphination and -amination reactions are first reviewed as a reference point for the hydroarsination reaction.

4.1.1 Hydrofunctionalization reactions of Group V nucleophiles

Iminium activation was employed for the addition of secondary phosphines⁸ and amines⁹ to α,β -unsaturated aldehydes (Scheme 71). Benzoic acid additives were proposed to speed up the reaction by promoting iminium formation although no further evidence was furnished. Despite concerns of chemoselectivity, iminium activation was demonstrated to be effective in the presence of multiple reactive sites and could catalyze the domino aza-Michael/Aldol reaction towards the one-pot synthesis of 1,2-dihydroquinolidines **161** (Scheme 72).¹⁰

Scheme 71. Proline-catalyzed hydrofunctionalization of α,β -unsaturated aldehydes.

Scheme 72. Amine-catalyzed domino aza-Michael/Aldol reaction.

Brønsted base catalysis promoted by cinchona alkaloids were applicable to hydrophosphination reactions (Scheme 73).¹¹ Instead of substrate activation, base catalysis

Scheme 73. Asymmetric hydrophosphination catalysed by cinchona alkaloids.

increased the nucleophilicity of the secondary phosphine by initial deprotonation to generate a reactive anionic intermediate. In this manner, chiral quinine **162a** catalyzed the addition of diphenylphosphine to nitrostyrene **127a** to afford racemic adduct **128b** in 85% yield. However,

asymmetric induction was only achieved with thiourea catalyst **162b** upon simultaneous activation of both the electrophilic and nucleophilic reactants by the bifunctional organocatalyst.

Lastly, an aldehyde-tethering strategy was utilized for the nucleophilic activation of hydroxylamines in the Cope-type hydroamination reaction (Scheme 74).¹² The temporary

Scheme 74. Aldehyde-catalyzed Cope-type hydroamination reaction.

intramolecularity of intermediate **B** was key in achieving rate acceleration, especially in solutions of low concentrations. However, this tethering strategy was sensitive to steric hindrance of the reactants, could only proceed with terminal allylic amines and was prone to an irreversible catalyst inhibition step due to the presence of permanent covalent interactions between the catalyst and reagents. This, coupled with the use of hydroxyamines, made this example less relevant for hydroarsination reactions involving unfunctionalized secondary arsines.

4.1.2 Phosphine organocatalysts in Michael additions

As described in the previous section, both the nucleophilicity (in imine-activation of the olefin) and basicity (in the deprotonation of secondary phosphines) of amines were crucial aspects of amine organocatalysis. However, their potential compatibility with secondary arsine reagents of the targeted hydroarsination reaction was questionable given the homo-coupling of diphenylarsine previously observed with organic amine bases (Chapter 2). Phosphines, being more nucleophilic and less basic than amines,¹³ were proposed to be a plausible avenue for

exploration. Herein, the activity of nucleophilic phosphine organocatalysts in related Michael addition reactions is reviewed.

Tertiary phosphines were catalytically active in the Michael addition of carbon nucleophiles.¹⁴ Since the reaction proceeded in the absence of strong bases typically required to generate the carbanion nucleophile,¹⁵ it was proposed that phosphine organocatalysts initiated the reaction by generating zwitteranionic adduct **A** upon initial nucleophilic addition to olefin **166** (Scheme 75). Intermediate **A** then deprotonated the carbon acid to generate the

Scheme 75. Proposed mechanism of phosphine-catalyzed Michael additions.

active carbanion nucleophile. Subsequent C–C bond formation with intermediate **B** led to product generation with a concomitant release of the phosphine catalyst. Unlike the limited scope of amine nucleophilic activation (compatible only with carbonyl substrates), the greater nucleophilicity of tertiary phosphines allowed an alternative nucleophilic activation mode proceeding by catalyst addition at the 1,4-position instead.¹⁶

The same base-generation mechanism (Scheme 75) was recently revisited by Bergman and Toste.¹⁷ Whilst investigating the phosphine-catalyzed hydration of activated olefins, initial formation of the zwitteranionic phosphine-olefin adduct was conclusively established by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy. The zwitterion intermediate was observed to be the resting state of the catalyst and the $^{31}\text{P}\{^1\text{H}\}$ NMR signal matched that of the independently-synthesized phosphonium salt **168** (Scheme 76). It was promising to note that phosphine

Scheme 76. Generation of key phosphonium ion intermediate.

organocatalysis proceeding by the base-generation mechanism was applicable in carbon-heteroatom bond formations as well. Similar to alcohols used by Bergman and Toste in their investigation, secondary arsines exhibit an extent of As–H bond lability under polar protic conditions which may suggest that similar mechanism(s) are applicable for phosphine-organocatalyzed hydroarsination reactions.

4.2 Results and discussion

Research questions

- 1) *Are the proposed mechanisms for organocatalyzed hydro-phosphination/-amination reactions relevant to the hydroarsination reaction?*
- 2) *How is organocatalysis fundamentally different from transition metal-catalysis in the hydroarsination reaction?*

4.2.1 With triarylphosphine catalysts

Overview

For their air-stability and ease of handling, triarylphosphines were selected to undergo preliminary screening. Catalytic activity was benchmarked against the best-developed hydroarsination methodology thus far (Chapter 3: Ni(II)-pincer catalyzed). An examination of the phosphine catalyst was conducted, encompassing its interaction with reagents and deactivation pathways. Spectroscopic evidence suggested that existing mechanisms proposed for phosphine-catalyzed Michael additions were inapplicable in this instance. Instead, relevant examples in supporting literature prompted a consideration of an alternative mechanism involving the interaction between the phosphine organocatalysts with energetically low-lying

LUMOs of As. Notably, phosphine organocatalysis was superior with respect to solvent compatibility and demonstrated good catalytic activity in solvents previously incompatible with transition metal catalysts. Upon complete conversion, the arsine product was isolated in 99% yield while up to 48% of the phosphine catalyst (at 30 mol % loadings) was still active.

Catalyst screening

Triarylphosphines were first benchmarked against the best-developed Ni(II)-pincer catalyst with the use of nitrostyrene **151a**. Arsine loadings were comparable to existing protocols while catalyst loadings were referenced from other organocatalytic hydrofunctionalization reactions.^{8,9b,10,11} Excellent reactivity was immediately evident upon solvent screening with triphenylphosphine **170a** as catalyst (Table 22). A variety of solvents

Table 22. Solvent screening for the PPh₃-catalyzed hydroarsination of nitrostyrenes.^a

$ \begin{array}{ccc} \begin{array}{c} \text{R}_2 \\ \diagup \\ \text{C} = \text{C} \\ \diagdown \\ \text{R}_1 \quad \text{NO}_2 \end{array} & \xrightarrow[\text{solvent, 35}^\circ\text{C, } t]{\text{HAsPh}_2 \text{ (1.2 equiv.),} \\ \text{PPh}_3 \text{ (170a) (30 mol \%)} \\ \text{151a R}_1 = \text{Ph, R}_2 = \text{H,} \\ \text{127a R}_1 = \text{H, R}_2 = \text{Ph,} \\ \text{127c R}_1 = \text{H, R}_2 = 4\text{-Cl-C}_6\text{H}_4} & & \begin{array}{c} \text{R}_2 \\ \\ \text{C} - \text{AsPh}_2 \\ \\ \text{R}_1 \quad \text{NO}_2 \end{array} \\ \text{152a R}_1 = \text{Ph, R}_2 = \text{H,} & & \text{152a R}_1 = \text{Ph, R}_2 = \text{H,} \\ \text{150a R}_1 = \text{H, R}_2 = \text{Ph,} & & \text{150a R}_1 = \text{H, R}_2 = \text{Ph,} \\ \text{150c R}_1 = \text{H, R}_2 = 4\text{-Cl-C}_6\text{H}_4 & & \text{150c R}_1 = \text{H, R}_2 = 4\text{-Cl-C}_6\text{H}_4 \end{array} $				
Entry	Product	Solvent	<i>t</i> (h)	Yield ^b (%)
1	152a	toluene	24	78
2	152a	DCM	24	99
3	152a	DEE	24	54
4	152a	CHCl ₃	24	79
5	152a	EA	24	69
6	152a	Hexane	24	54
7	152a	THF	24	79
8	152a	Acetone	24	92
9	152a	MeOH	24	68
10	150a	DCM	48	61 ^c
11	150c	DCM	48	49

^aReaction conditions: nitrostyrene (4.47 mg, 0.03 mmol, 1.0 eq.), HAsPh₂ (8.28 mg, 0.04 mmol, 1.2 eq.), cat. PPh₃ (2.36 mg, 0.01 mmol, 30 mol %), solvent (1 mL). ^bIsolated yield. ^cDue product instability, conversion was reported instead.

afforded 1,4-arsine adduct **152a** in good to excellent yields with up to quantitative conversion in DCM (Entry 2). The catalysis also proceeded smoothly for internal olefins and furnished structural isomer **150a** in 64% yield (Entry 10). Aryl substituents, even at distal *para*-positions,

was observed to influence the reaction (Entry 11) while less-activated enones achieved <10% conversion after 24 h, suggesting the phosphine-catalyzed hydroarsination was less versatile in terms of substrate scope than transition metal-catalyzed variants. However, it was worth noting that excellent yields were observed when the reaction was conducted in THF (79% yield, Entry 7) and acetone (92% yield, Entry 8)- solvents for which the Ni(II) pincer complex was catalytically inactive. This prompted a consideration of fundamental reactivity differences between the phosphine organocatalyst and transition metal catalysts.

An investigation regarding the role of the phosphine was conducted by first screening a series of functionalized triarylphosphines **170** (Table 23).¹⁸ For phosphines with the same

Table 23. Catalyst screening for the phosphine-catalyzed hydroarsination of nitrostyrene **151a**.^a

Entry	R	Cone angle	Yield of 152a ^b (%)
1	C ₆ H ₅ (170a)	129	99
2	4-CH ₃ OC ₆ H ₄ (170b)	139	85
3	4-ClC ₆ H ₄ (170c)	129	81
4	3-CH ₃ C ₆ H ₄ (170d)	140	88
5	4-FC ₆ H ₄ (170e)	129	55
6	2-CH ₃ C ₆ H ₄ (170f)	142	51
7	Mesityl (170g)	212	30

^aReaction conditions: nitrostyrene **151a** (4.47 mg, 0.03 mmol, 1.0 eq.), HAsPh₂ (8.28 mg, 0.04 mmol, 1.2 eq.), cat. PR₃ **2** (0.01 mmol, 30 mol %), DCM (1 mL). ^bIsolated yield.

cone angle, catalytic activity was lower when the reaction was catalyzed by electron-deficient phosphine **170e** (Entries 1 and 5). The larger cone angle of *ortho*-substituted phosphine **170f** resulted in a moderate yield of arsine **152a** (51%, Entry 6) and the use of sterically bulky trimesitylphosphine **170g** further lowered the yield (30%, Entry 7).

Other phosphine alternatives were also screened for potential catalytic activity (Table 24). Secondary/tertiary phosphine oxides (HP(O)Ph₂, P(O)Ph₃), alkyl phosphines (dppe, dppb) and triphenylamine were catalytically inactive (Entries 3-7) when compared to the control (Entry 1). The inactivity of NPh₃ (a compound characteristic for complete delocalization of the

Table 24. Screening of alternative catalysts.^a

Entry	Cat.	Yield of 152a ^b (%)
1	-	13
2	HPPPh ₂	62
3	HP(O)Ph ₂	13
4	P(O)Ph ₃	15
5	dppe	14
6	dppb	15
7	NPh ₃	13
8	AsPh ₃	26

^aReaction conditions: nitrostyrene **151a** (4.47 mg, 0.03 mmol, 1.0 eq.), HAsPh₂ (8.28 mg, 0.04 mmol, 1.2 eq.), cat. (0.01 mmol, 30 mol %), DCM (1 mL). ^b Determined by ¹H NMR with an internal standard.

lone pair) clearly demonstrated the relevance of the phosphorus lone pair for catalytic activity (Entry 7). Only 62% yield of arsine **152a** was attained when the reaction was catalyzed by HPPPh₂ due to a competing addition of HPPPh₂ to nitrostyrene **151a** (Entry 2). In terms of catalyst design, results from the screening of functionalized phosphines and phosphine alternatives were consistent with the nucleophilic nature of other phosphine-catalyzed hydrofunctionalization reactions.

Mechanistic considerations

Related organocatalyzed hydrofunctionalization reactions have proposed substrate activation *via* the nucleophilic addition of Lewis basic catalysts to the substrate (Scheme 77).^{8,9}

Scheme 77. Modes of catalyst activation.

Alternatively, transition metal-activation of the weakly-nucleophilic secondary arsine reagent was used to generate a reactive anionic arsenide species (Chapters 2 and 3). This required alcoholic solvents to stabilize the intermediate, thereby causing poor reactivity in non-polar protic solvents. Both “substrate activation” and “arsine activation” pathways were inapplicable

to the current phosphine-catalyzed reaction. Firstly, no interactions were observed between PPh_3 and nitrostyrene **151a** when monitored using ^1H and $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy.¹⁹ Secondly, the catalysis was compatible with a wide range of solvents including DCM, acetone and hexane (Table 22). The high pK_a of HAsPh_2 ($\text{pK}_\text{a} = 20.3$ in THF)²⁰ further supported the unlikely deprotonation of HAsPh_2 by weakly-basic tertiary phosphines. It remains to be seen if transient interaction between the tertiary phosphine and energetically low-lying LUMOs of the secondary arsine may have contributed to activating the secondary arsine reagent (Scheme 78). Such interactions are well-established in phosphine-stabilized arsenium salts,²¹ and have

Scheme 78. Potential catalytic pathway for phosphine-catalyzed hydroarsination of nitrostyrenes.

been studied with X-ray crystallography and variable temperature NMR spectroscopy.²² In this instance, no physical evidence could be gathered from NMR or mass spectroscopy methods which suggest that species **A**, if formed, could have manifested as a high energy transition state instead of an energetically stable intermediate.

Catalyst deactivation pathway

Over the course of investigating the presence of (or absence thereof) interactions between the organophosphine catalyst and reagents of the hydroarsination reaction, it was noted that the triarylphosphine catalysts consistently oxidized to triarylphosphine oxides in the presence of HAsPh_2 (Figure 34). No other signals were observed on the NMR timescale and $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy was consequently not effective at shedding light on this arsine-

Figure 34. $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of PPh_3 and HAsPh_2 in DCM under an inert $\text{N}_2(\text{g})$ atmosphere.

mediated phosphine oxidation. A survey of literature revealed that triarylphosphines resist accidental oxidation well and are even used to signal successful photochemical²³ and metal-catalyzed²⁴ oxygen transfer reactions. Intentional oxidation of triarylphosphines is otherwise achieved with specialized reagents/pathways such as fluorinating reagents,²⁵ phosphonium salt hydrolysis,²⁶ peroxides²⁷ and Oxone.²⁸ Under the mild reaction conditions and chemical nature of HAsPh_2 , this arsine-mediated phosphine oxidation was unprecedented and warranted further investigation. Firstly, suppressing this oxidation was crucial in improving turnover numbers since triarylphosphine oxides are catalytically inactive in the hydroarsination reaction (demonstrated in Table 24). Secondly, this may be relevant in elucidating the hitherto unresolved catalytic cycle of the phosphine-catalyzed hydroarsination reaction.

Given the careful exclusion of ambient oxygen under reaction conditions, it was hypothesized that trace amounts of water under reaction conditions could have been the oxygen donor. Previous catalytic runs were conducted with degassed AR grade solvents and glassware stored under ambient conditions (Table 22). To evaluate if trace amounts of water present could

Table 25. Investigating phosphine oxidation.^a

$\text{PPh}_3 \xrightarrow[\text{solvent, RT, 24 h}]{\text{HAsPh}_2 \text{ (1.0 equiv.)}} \text{O=PPh}_3$			
170a		171a	
Entry	PPh ₃ loading (equiv.)	Solvent	Yield ^b (%)
1	1	DCM	48
2	1	MeOH	49
3	1	Acetone	45
4	1	DEE	42
5	1	Hexane	37
6	1	THF	38
7	1	Acetonitrile	29
8	1	MeNO ₂	33
9	30 mol %	DCM	52
10	30 mol %	MeOH	76
11	30 mol %	Acetone	43
12	30 mol %	DEE	48

^aReaction conditions: Triphenylphosphine **170a** (23.08 mg, 0.088 mmol, 1.0 eq.), HAsPh₂ (59.84 mg, 0.26 mmol, 3.0 eq.), solvent (12 mL), RT, 24 h. ^bAverage isolated yield of three runs.

indeed oxidize the phosphine catalyst, a model reaction involving a stoichiometric ratio of HAsPh₂ to triphenylphosphine **170a** was set up (Table 25). Apart from the strict exclusion of atmospheric oxygen, all reactions were performed in the dark to prevent photochemical oxidation of the tertiary phosphine. In addition, isolated yields reported were averaged from three runs. Phosphine oxidation was consistent across several solvents with phosphine oxide **171a** isolated in moderate yields of 29-49% (Entries 1-8). Oxidation was more pronounced under catalytic (30 mol %) loadings of phosphine (Entries 9-12) and the highest rate of oxidation was observed in MeOH (Entry 10). Subsequently, a series of controlled experiments provided compelling evidence that H₂O was indeed the oxygen source for the arsine-mediated oxidation pathway. No such phenomenon was previously reported in literature to the best of our knowledge, although the reactivity of several distantly-related classes of compounds may be of interest in this context:

- (1) Phosphonium ions (R₄P⁺) are well-established to hydrolyze in water to generate phosphine oxides.²⁹ For transition state **A** proposed in Scheme 78, the transient 4-

coordinate phosphorus center could be susceptible to hydrolysis in manner similar to phosphonium ions due to reduced electron density of the tertiary phosphine.³⁰

- (2) As elaborated on in Chapter 2, HAsPh_2 may be hydrolyzed under elevated temperatures to form diphenylhydroxyarsine HOAsPh_2 - an unstable intermediate known to spontaneously decompose into tetraphenylarsyloxide $(\text{Ph}_2\text{As})_2\text{O}$.³¹ Prior to decomposition, HOAsPh_2 could have served as a reactive oxygen-transfer agent in the oxidation of the tertiary phosphine.

Notably, no evidence of H_2 was observed with ^1H NMR spectroscopy when HAsPh_2 and PPh_3 were stirred under inert conditions and we were unable to identify the terminal oxidant. The absence of permanent covalent bonds between the phosphine and arsine reagents allowed diphenylarsinic acid **172** to be isolated as the oxidized derivative of HAsPh_2 after conducting the reaction with 1 equivalent of PPh_3 and 0.5 equivalents of HAsPh_2 (Figure 35). It may be

Figure 35. Molecular structure of diphenylarsinic acid **172**.

worth noting that no oxidation of PPh_3 was observed when HAsPh_2 was replaced with HOAs(O)Ph_2 . Unfortunately, these insights derived thus far were unproductive in furthering any mechanistic investigations. Diphenylhydroxyarsine HOAs(O)Ph_2 is a common product for the oxidation of several arsenic species (such as HAsPh_2 , $(\text{Ph}_2\text{As})_2$, HOAsPh_2)³¹ and therefore not indicative of the formation of a single arsenic intermediate.

The phosphine-catalyzed hydroarsination of nitrostyrene **151a** was re-conducted in the presence of $\text{MS4\AA}$ to remove trace amounts of water. Unfortunately, this formed a

polymeric material of HAsPh₂, leading to isolated product yields of only 79% after several attempts. Catalyst design was proposed as an alternative solution to maintain good turnover numbers, minimize catalyst deactivation and lower catalyst loadings. To this end, a series of functionalized tertiary phosphines of various steric, electronic and chemical characters were screened under catalytic loadings (Table 26). No notable resistance to oxidation was observed

Table 26. Screening of phosphine susceptibility to oxidation.^a

Entry	170	M	Yield ^b 171 (%)	Recovered 170 ^b (%)
1	170a	-	76	16
2	170b	-	69	15
3	170c	-	76	27
4	170d	-	73	18
5	170e	-	78	12
6	170f	-	44	43
7	170h	-	37 (61)	0
8	170i	-	31 (64)	0
9	170j	-	78	15
10	170k	-	74	22
11	170l	-	72	16
12	170m	-	76	18
13 ^c	-	NiCl ₂ (PPh ₃) ₂	54	0
14 ^c	170a	NiCl ₂	68	0
15 ^c	170a	PdCl ₂	0	0

^aReaction conditions: Phosphine **170** (0.088 mmol, 1.0 eq.), HAsPh₂ (60.76 mg, 0.264 mmol, 3.0 eq.), MeOH (12 mL), RT, 24 h. ^bIsolated average yield over three runs. Yield in parentheses refers to that for the phosphine dioxide. ^cM (0.053 mmol, 0.6 eq.) was added.

for electron-deficient (**170c**, **170e**), acidic (**170l**, **170m**) and basic (**170j**, **170k**) phosphines (Entries 3, 5, 9-12). Stepwise oxidation of bisphosphines **170h** and **170i** was observed to

proceed *via* mono-oxide intermediates **171h** and **171i** (Entries 7 and 8). Sterically hindered tri(*o*-tolyl)phosphine **170f** was notably more resistant to oxidation (Entry 6). Metal additives like NiCl₂ and PdCl₂ resulted in a lower isolated yield of oxide **171a** (Entries 14-15). No phosphine **170a** was recovered in both instances, with ³¹P{¹H} NMR spectroscopy suggesting metal-phosphine coordination. From this, it was concluded that phosphines coordinated as ligands in transition metal catalysts were protected from oxidation under hydroarsination conditions. For metal-free oxidations (Entries 1-12), unreacted phosphines **170** were recovered from the crude without any appreciable presence of other byproducts. The positive steric shielding effect observed in tri(*o*-tolyl)phosphine **170f** was encouraging because large ligand scaffolds are typically employed in many well-developed phosphine organocatalysts³² especially for asymmetric transformations.³³ Sterically-bulkier phosphines could be recommended to reduce the rate of catalyst deactivation by oxidation for subsequent efforts in this area based on results from this preliminary study.

A brief comparison with transition metal-catalyzed hydroarsinations suggested that tertiary phosphines were complementary in terms of their catalytic activity. On one hand, phosphine organocatalysts required more electron-deficient olefins which limited substrate scope. Asymmetric phosphine organocatalysis was not further pursued due to the apparent lack of reactivity with less-activated Michael acceptors. On the other hand, the low solvent dependency was a notable triumph over transition metal-catalyzed methodologies. It remains to be seen if the activation of secondary arsines by tertiary organophosphines may be useful in alternative nucleophilic arsenic-carbon bond formation reactions other than hydroarsination reactions. While developments in phosphine organocatalysis were presently shelved, another transition metal-free protocol was explored to 1) advance stereoselective and atom-economical As-C bond formation, and 2) improve the accessibility of the hydroarsination reaction to the general synthetic community (Section 4.2.2).

4.2.2 Diastereoselective hydroarsination reaction

Overview

An internal asymmetric induction strategy was employed for a diastereoselective base-catalyzed hydroarsination reaction. The chiral model substrate was prepared using an established Pd-catalyzed hydrophosphination protocol for $\alpha,\beta,\gamma,\delta$ -unsaturated ketones. Subsequently, basic hydroarsination conditions led to an unexpected intramolecular Aldol addition instead, generating a cyclic bifunctionalized hydroxyphosphine in 48% yield with no arsine incorporation. The chemoselective role of the arsine reagent was systematically investigated. Chiral induction models were applied to the proposed mechanism to rationalize the relative *syn* and *anti* relationships of the three stereocentres identified with X-ray crystallography.

Rationale

Catalytic asymmetric hydrophosphination is markedly more developed than the corresponding hydroarsination reaction and many synthetic methodologies are available for highly stereoselective C–P bond formation.³⁴ In the regioselective 1,4-phosphination of $\alpha,\beta,\gamma,\delta$ -unsaturated ketones,³⁵ subsequent functionalization at the remaining C=C bond could potentially proceed with high stereoselectivity *via* internal asymmetric induction (Scheme 79).

Scheme 79. Available protocols for regioselective 1,4-hydrophosphination.

In this manner, valuable enantioenriched mixed-type P,As compounds could be generated by sequential hydrophosphination and hydroarsination reactions.³⁶ Metal-free internal asymmetric induction strategies proceeding by hydroarsination reactions were previously unattainable

because secondary arsines were routinely activated by Pd complexes in a stoichiometric manner.³⁷ However, the mechanistic developments described in previous chapters have suggested that secondary arsines could be deprotonated by mild amine bases to generate the reactive arsenide nucleophile under alcoholic conditions. Specially-designed $\alpha,\beta,\gamma,\delta$ -unsaturated ketones **176** were prepared such that the remaining C=C bond could be activated for further reaction upon acetal deprotection (Scheme 80).

Scheme 80. Retrosynthetic design of precursor **176**.

Preparation of the chiral phosphine precursor

The hydrophosphination of $\alpha,\beta,\gamma,\delta$ -unsaturated ketones **176** catalysed by PCP-Pd complex **87a** was first optimized for regio- and stereoselectivity (Table 27). Consistent with existing literature,^{35b} 1,4-adduct **177a** was furnished with excellent *ee*'s of 92-94% in DCM, acetone, DEE and EA (Entries 2-5). For the best-performing solvent (acetone, Entry 3), no further improvements to stereoselectivity was observed when the reaction was conducted below 0°C (Entry 7). Under optimized conditions of acetone at 0°C, 1,4-adduct **177a** was isolated with 97% *ee* (Entry 6). Functionalized ketones **176b** and **176c** were then used to determine if the catalysis was as tolerant to substituents on the aryl ring as previously demonstrated.^{35b} 4-phenyl-substituted ketone **177b** was furnished with almost the same *ee*

Table 27. Optimization of conditions.^a

Entry	177	Ar	Solvent	T (°C)	<i>t</i> (h)	Yield ^b (%)	<i>ee</i> ^c (%)
1	177a	Ph	Toluene	RT	7	62	82
2	177a	Ph	DCM	RT	10	45	92
3	177a	Ph	Acetone	RT	6	50	94
4	177a	Ph	DEE	RT	24	48 ^d	92
5	177a	Ph	EA	RT	24	51 ^d	93
6	177a	Ph	Acetone	0	24	48	97
7	177a	Ph	Acetone	-20	42	56	96
8	177b	4-PhC ₆ H ₄	Acetone	0	24	45	92
9	177c	4-NO ₂ C ₆ H ₄	Acetone	0	24	48	82

^aReaction conditions: Acetal **176** (0.06 mmol, 1.0 eq.), HPPPh₂ (13.0 mg, 0.07 mmol, 1.1 eq.), cat. **87a** (2.70 mg, 3.00 μmol, 5 mol %), solvent (1 mL). ^bIsolated yield. ^cDetermined by chiral HPLC. ^d85-88% conversion was observed on ³¹P{¹H} NMR spectroscopy after 24h.

(Entry 8).^{35b} The effect of a *para* nitro substituent was not previously investigated but 4-nitro ketone **177c** was still furnished with good stereoselectivity (82% *ee*, Entry 9). While it is not the intention to elaborate on the hydrophosphination methodology for α,β,γ,δ-unsaturated ketones here, the synthetic application of existing literature is clear.^{35,38} Several reasons could have contributed to the moderate yields achieved, namely 1) formation of the 1,6-adduct, and 2) premature deprotection of acetal **176** by the mildly-acidic secondary phosphine reagent. The formation of the minor 1,6-adduct (3-20% as observed with ³¹P{¹H} NMR spectroscopy) was insufficient to explain the loss in yield. On the other hand, quantitative deprotection was achieved upon workup by washing with DCM/10% HCl.

Attempted hydroarsination leading to alternative Aldol addition

Due to the modest pK_a of diphenylarsine (pK_a = 20.3 in THF),^{20,39} no direct deprotonation by simple organoamine bases have been achieved thus far. However, mechanistic investigations from previous chapters have implied that this was possible under

alcoholic conditions. A model base-assisted hydroarsination was first conducted with crotonaldehyde **157a** before attempting the metal-free hydroarsination of phosphine **177a** (Scheme 81). Racemic arsine **178** was furnished in 54% yield as expected and was stable both

Scheme 81. Metal-free hydroarsination of crotonaldehyde **157a**.

in solid state and in solution. No C–As bond cleavage was observed in the thermodynamically-stable adduct **178** when left in the crude solution after complete conversion.

It was therefore unexpected when no arsine adduct was detected from the reaction of phosphine **177a** with HAsPh₂ in the presence of DIPEA. Instead, an internal Aldol addition was observed leading to the formation of cyclopentene **179** in 48% yield (Table 28, Entry 1).

Table 28. Investigating the role of HAsPh₂ in the intramolecular Aldol cyclization of phosphine sulfide **177a**.^a

Entry	[As]	Base	Solvent	<i>t</i> (h)	Yield ^b (%)	<i>dr</i> ^c (%)
1	HAsPh ₂	DIPEA	MeOH	3.5	48	>99
2 ^d	HAsPh ₂ (cat.)	DIPEA	MeOH	3.5	51	>99
3	-	DIPEA	MeOH	120	43 ^e	>99
4	-	NEt ₃	MeOH	120	54 ^e	>99
5	HAsPh ₂	-	MeOH	24	NR	-
6	HAsPh ₂	DIPEA	DCM	24	<5	-
7	AsPh ₃	DIPEA	MeOH	3.5	49	>99
8	HOAs(O)Ph ₂	DIPEA	MeOH	24	<5	-

^aReaction conditions: Aldehyde **177** (20.2 mg, 0.05 mmol, 1.0 eq.), [As] (0.06 mmol, 1.2 eq.), base (0.055 mmol, 1.1 eq. solvent (1 mL). ^bIsolated yield. ^cDetermined by ¹H NMR spectroscopy. ^dHAsPh₂ (2.30 mg, 0.01 mmol, 20 mol %) was used instead. ^eIncomplete conversion was observed after 5 days.

Apart from the initial success of the base-assisted hydroarsination of crotonaldehyde **157a**, the Aldol addition was unprecedented because mild tertiary amine bases have limited applicability in enolate generation.⁴⁰ Unlike in primary/secondary amine-promoted Aldol reactions,^{2b,41} tertiary amines do not participate in imine-enamine catalysis which therefore prompted an investigation of the potential cooperative role of the arsine reagent (Table 28). Firstly, catalytic

loadings of HAsPh₂ afforded the cyclopentene **179** in comparable yields of 51% which indicated the transient nature of the interaction (Entry 2). In the absence of any arsine reagents, tertiary amine-assisted cyclization required >5 days for complete conversion while generating cyclopentene **179** in moderate yields (43-54%, Entries 3 and 4). Secondly, conducting the reaction in DCM furnished only trace amounts of cyclopentene **179** (Entry 6). It must be noted, however, that this does not necessarily indicate any correlation with the deprotonation of HAsPh₂ in MeOH. The reaction proceeded smoothly even when AsPh₃ was used (Entry 7), reaffirming that the H–As bond was not indispensable. Lastly, diphenylarsinic acid did not afford appreciable amounts of the cyclic phosphine product (Entry 8), suggesting that As(III) was the active oxidation state. Excellent internal asymmetric induction was demonstrated and only a single diastereomer was observed over the course of screening. The *syn/anti* relationship of substituents at the three stereocentres in the cyclopentene ring were confirmed by X-ray crystallography and the molecular structure presented in Figure 36.

Figure 36. Molecular structure of cyclopentene **179** with non-stereogenic H omitted for clarity.

Proposed mechanism

Notably, the X-ray crystal structure suggested the presence of an O–H_a⋯S=P hydrogen bond based on bond angles about the hydroxy group in the extended crystal lattice (Figure 37). The signal corresponding to H_a was also clearly observable with ¹H NMR

Figure 37. Structural formula of ketone **179** with hydrogens labelled.

spectroscopy and was unambiguously identified with a D₂O exchange and a proton decoupling NMR experiment (Figures 38 and 39). Protonation following the C–C bond formation step of the Aldol addition was clearly influenced by the -P(S)Ph₂ moiety, thereby resulting in a well-defined molecular structure of cyclopentene **179** even in solution. Interestingly, the signal corresponding to H_a was not observed from products isolated when HAsPh₂ was used as an additive (Table 28, Entries 1 and 2). Crystals of cyclopentene **179** harvested from the aforementioned reactions exhibited the H_a NMR signal again. From this, it was hypothesized that non-negligible interactions were present between HAsPh₂ and the aldehyde moiety such that the formation of an intramolecular O-H_a⋯S=P hydrogen bond was disrupted. Several

Figure 38. ¹H NMR spectrum of ketone **179** before and after the D₂O exchange.

Figure 39. ^1H NMR spectrum before and after decoupling at 3.93 ppm.

other features of the intramolecular Aldol addition was also of interest, such as 1) the unorthodox use of tertiary amines in enolate generation, 2) C=C bond isomerization under mild conditions, and 3) the excellent diastereoselectivity observed (>99% *de*).

A single isomer (*R*)-**177a** was arbitrarily chosen to portray relative stereochemistries in bond formation steps of the proposed mechanism (Scheme 82). Firstly, HAsPh_2 was proposed to activate the ketone by a transient association with the carbonyl moiety, acidifying the α -proton. Subsequent deprotonation by the tertiary amine would yield intermediate **A1** in an indeterminate mixture of *cis/trans* enolates.⁴² Alternatively, stereoselective amine conjugate addition to phosphine sulfide **177a** proceeding at the less hindered face of the olefin (relative to the bulky $-\text{P(S)Ph}_2$ moiety oriented according to the Houk model) could result in the formation of intermediate **A2**. Eventual equilibrium distribution would result in the formation of key intermediate **B1** featuring the enolate and quaternary amine motifs. The Houk model

Scheme 82. Proposed cyclization mechanism with the associated stereochemical induction models.

was applied to intermediate **B1** in the pseudo-chair conformation thus leading to the eclipsing of the enolate with the adjacent proton. The quaternary amine was deemed to be bulkier than the $-P(S)Ph_2$ motif and therefore placed at the equatorial position.⁴³ The carbonyl was also oriented in the equatorial position to minimize 1,3-diaxial interactions with $-P(S)Ph_2$ and the enolate. Enolate attack to the *Si* face of the carbonyl would generate intermediate **C** exhibiting an *anti* relationship between the ketone and alcohol and a *syn* relationship between the alcohol and phosphine. Finally, amine- H_x elimination from intermediate **C** would generate the cyclopentene ring and reinstall the isomerized $C=C$ bond. Alternative elimination of H_y to generate cyclic vinylphosphine **180** was proposed to be a significant side reaction since the characteristic vinylphosphine chemical shift was consistently observed with $^{31}P\{^1H\}$ NMR spectroscopy.⁴⁴ The formation of byproduct **180** would also explain the moderate yields observed in Table 28.

However, it should be highlighted that the pathway in Scheme 82 featured a significant limitation arising from the proposed amine elimination of intermediate **C**. Highly reminiscent of the Hoffman elimination, present RT reaction conditions were unlikely to

support such a transformation which typically proceeded under elevated temperatures. The formation of cyclopentene **179** could instead be rationalized by a another pathway in the absence of intermediate **C** (Scheme 83). Herein, arsine/base-catalyzed *E/Z*-isomerization of

Scheme 83. Alternative pathway for the formation of cyclopentene **179**.

phosphine sulfide **177a** could furnish intermediate **B2** bearing the *Z*-enone motif required for intramolecular cyclization.⁴⁵ Following the same arsine-mediated enolate formation proposed in Scheme 82, direct attack of the enolate at the 1,2-position of the enone in an intramolecular Aldol addition would then afford cyclopentene **179**. Alternatively, 1,4-Michael addition could still yield cyclopentene **179**, potentially *via* a vinylcyclopropane rearrangement of intermediate **D**. Relative to Scheme 82, such a pathway bypassing intermediate **C** would arguably be more probable, although no conclusions could be drawn in light of the absence of spectroscopic evidence (*vide infra*).

Although the arsine-carbonyl interactions were suggested experimentally (such as in Table 28, Entries 1 and 2), no further spectroscopic evidence could be gathered. No changes were observed from the ¹H NMR spectrum when phosphine **177a** was stirred with HAsPh₂ (Table 28, Entry 5). The addition of DIPEA led to the direct formation of cyclopentene **179** with no interim resting state in the proposed mechanism. In the absence of spectroscopic evidence, we were unable to conclusively establish if the arsine-carbonyl interaction were operative in the generation of intermediates **A1**, **A2**, **B2** and **C**. The experimentally-observed enolization of phosphine **177a** by weak tertiary amines suggested that an arsine-carbonyl interaction may have acidified the α-hydrogen, thereby assisting the formation of intermediate **A1/B2**. The absence of an intramolecular O-H_a⋯S=P hydrogen bond was likely a result of an

arsine-aldehyde interaction in intermediate **B1** which hindered protonation of the Aldol adduct. σ -hole interactions have been discussed in recent years as an alternative mode of non-covalent organocatalysis⁴⁶ and such interactions have been identified in tertiary arsines functionalized with highly electron-withdrawing substituents.⁴⁷ Only a single example of tertiary arsines used as organocatalysts in this manner have been reported to date,^{46a} and it was certainly intriguing to observe alternative reactivity patterns beyond Lewis base-type activity. It may be worth mentioning that no competing arsine conjugate addition leading to irreversible C–As bond formation was observed for enal **177a**, suggesting a higher affinity of HAsPh₂ for the carbonyl instead of the enal functionality.

Investigating ring lock

The mutually *syn* relationship of the hydroxy and phosphine motifs could be advantageous for potential applications of cyclopentene **179** as a bifunctional organocatalyst. For such applications, the presence of a “ring lock” phenomenon could be valuable in 1) ensuring the close proximity between active sites thereby improving reaction rates,⁴⁸ and 2) facilitating efficient stereochemical induction from the chiral catalyst to the reaction site.⁴⁹ It was of interest to evaluate if the C=C bond of cyclopentene **179** was effective at minimizing ring flipping. To this end, a 2D ¹H-¹H NOESY NMR experiment was conducted to determine the conformation of cyclopentene **179** in solution (Figure 40).

Figure 40. 2D ^1H - ^1H NOESY spectrum of cyclopentene **179**.

Aromatic protons H_f and H_g were first assigned based on integrals and splitting pattern from the ^1H NMR spectrum whereas previous D_2O exchange and proton decoupling experiments led to the unambiguous assignments of H_a and H_b . H_h and H_c were assigned next from their strong interactions with H_g and H_f respectively. H_d was distinguished from H_c by an interaction with H_f (present in the former and absent in the latter). Other through-space correlations were consistent with the signals as assigned. Notably, the absence of several interactions suggested a high degree of conformational rigidity in cyclopentene **179** (Table 29).

Table 29. Key ^1H - ^1H NOESY interactions of cyclopentene **179**.

Key interaction	Interpretation
H_b - H_g interaction	Ketone -Ph group oriented towards $-\text{OH}_\text{a}$
Absence of H_c - H_g interaction	Ketone -Ph group oriented towards $-\text{OH}_\text{a}$
Absence of H_b - H_e interaction	Minimal ring puckering in solution
Absence of H_c -aromatic interaction	Minimal ring puckering in solution
Absence of H_a - H_f interaction	Presence of $\text{O}-\text{H}_\text{a}\cdots\text{S}=\text{P}$ hydrogen bond

The presence of H_g interactions with H_b and absence thereof with H_e suggest that free rotation was limited about the $C_{\text{cyclopentene}}-C_{\text{ketone}}$ bond. The absence of an H_b-H_e interaction was also indicative of insignificant ring puckering despite occupying the same face of the cyclopentene ring. Ring puckering was also minimal at the ketone-functionalized carbon as deduced from the absence of H_c-H_f/g interactions. Lastly, the absence of H_a-H_h interactions suggest that limited rotation was present about the P–Ph bond, presumably due to an intramolecular $O-H_a \cdots S=P$ hydrogen bond. If so, this could be potentially unfavourable for the application of cyclopentene **179** as a bifunctional organocatalyst. Another 2D 1H - 1H NOESY NMR experiment was conducted on the non-hydrogen bonded conformer isolated in the presence of $HAsPh_2$ (Figure 41). The presence of all key correlations and notable absence of the H_b-H_e interaction concluded that the observed ring lock was not dependent on intramolecular hydrogen bonding.

Figure 41. 2D 1H - 1H NOESY spectrum of non-hydrogen bonded cyclopentene **179**.

While cyclopentene **179** was structurally interesting and significant developments were presented in the course of its synthesis, this diastereoselective protocol was unfortunately less relevant for the metal-free synthesis of arsine compounds. It remains to be seen if the metal/catalyst-free hydroarsination protocol under basic conditions established with crotonaldehyde can offer new avenues for asymmetric arsine synthesis by substrate or reagent control. On the other hand, the proposed arsine-carbonyl interactions encountered in the intramolecular Aldol addition were particularly noteworthy. Not only was it more facile than the competing nucleophilic addition (hydroarsination reaction), it signaled the potential application of arsines in general organic synthesis where carbonyl motifs are both widespread and well-established. Apart from not requiring the careful exclusion of moisture or additional workup procedures, only catalytic loadings of the arsine reagent were needed for a marked improvement in reaction rate. Nevertheless, the potential application of arsines in synthetic organic chemistry was not in the direct scope of this thesis, and further developments were identified as future work (see Chapter 6).

4.3 Conclusion

In conclusion, some headway was made in developing metal-free protocols for the hydroarsination reaction. Phosphine organocatalysts were first explored in place of transition metal complexes for their ready availability and relative ease of handling. A series of triarylphosphines furnished the desired arsines in excellent yields of up to 99%. Low solvent dependency was a notable triumph over existing transition metal-catalyzed methodologies. However, the innate catalyst deactivation pathway and reliance on electronically-activated substrates led to another attempt at metal-free asymmetric As–C bond formation. An internal asymmetric induction methodology was inspired by the excellent stereoselectivity of Pd-catalyzed 1,4-hydrophosphination of $\alpha,\beta,\gamma,\delta$ -unsaturated substrates. While the base-catalyzed

hydroarsination proceeded smoothly on crotonaldehyde, such conditions led to a competing intramolecular Aldol addition when applied to an enal-functionalized 1,4-phosphine adduct.

Despite not having any As–C bond formation from the second strategy, the unexpected intramolecular Aldol addition generated new interest in the potential value of arsines as an auxiliary in organic chemistry. The widespread application of arsines in this manner was arguably hindered by underdeveloped preparative protocols leading to a lack of variety. With present developments in catalytic (asymmetric) hydroarsination, it may now be worth exploring the applications of organoarsines to justify the efforts dedicated to their preparation. The arsine-carbonyl interaction observed herein is further explored in Chapter 5 alongside the fine-tuning of metal-free hydroarsination strategies.

4.4 Experimental section

General information. All reactions were carried out under a positive pressure of nitrogen using standard Schlenk techniques. Solvents were purchased from their respective companies (ACN, MeOH, DCM: VWR Chemicals, DEE: Merck, toluene, n-hexane: Avantor, Acetone: Sigma-Aldrich, THF: Tedia) and degassed prior to use by sparging with N₂ (g). A Low Temp Pairstirrer PSL-1400 was used for controlling low temperature reactions. Column chromatography was done on Silica gel 60 (Merck). Melting points were measured using SRS Optimelt Automated Point System SRS MPA100. NMR spectra were recorded on Bruker AV 300, AV 400 and AV 500 spectrometers. Chemical shifts were reported in ppm and referenced to an internal SiMe₄ standard (0 ppm) for ¹H NMR, chloroform-d (77.23 ppm) for ¹³C NMR, and an external 85% H₃PO₄ for ³¹P{¹H} NMR.

HAsPh₂ was prepared according to literature methods.⁵⁰ All other reactants and reagents were used as supplied.

Synthesis of terminal nitroolefin 151a. To a solution of NaNO₂ (1.32 g, 19.2 mmol, 4.0 equiv.) and ethylene glycol (0.80 mL, 14.4 mmol, 3 equiv.) in water (2 mL) was added a solution of arylefin (4.8 mmol, 1.0 equiv.) in EA (15 mL). Iodine (1.83 g, 7.2 mmol, 1.5 equiv.) was added portion wise at 0°C and the mixture was gradually allowed to RT and stirred for 48 h under an inert atmosphere. The crude solution was extracted with EA (3 X 30 mL), organic layers were combined and washed with 10% aq. Na₂S₂O₃ (1 X 30 mL) and brine (1 X 30 mL), then dried over MgSO₄. Volatiles were removed and the crude product was purified by silica gel chromatography (3 n-hexanes : 1 EA) to afford compound **151** as a yellow solid. Yield: 0.56 g, 3.74 mmol, 78%. Mp: 41- 42°C. ¹H NMR (CDCl₃, 500 MHz): δ 8.03-8.00 (d, 1H, ²J_{HH}=13.65 Hz, NCCH), 7.61-7.58 (d, 1H, ²J_{HH}=13.65 Hz, NCCH), 7.56-7.44 (m, 5H, Ar); ¹³C NMR (CDCl₃, 126 MHz): δ 139.3 (s, 1C, Ar), 137.3 (s, 1C, Ar), 132.3 (s, 1C, Ar), 130.2 (s, 1C, Ar), 129.5 (1C, Ar), 129.3 (s, 1C, Ar). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₈H₈NO₂, 150.0555; found, 150.0557.

General procedure for catalytic hydroarsination of nitroolefins (Table 22, 23 and 24).

Nitrostyrene (0.03 mmol, 1.0 equiv.), HAsPh₂ (8.28 mg, 0.04 mmol, 1.2 equiv.) and catalyst (0.01 mmol, 30 mol %) were dissolved in the stated solvent (1 mL) The reaction was stirred in the dark at RT and volatiles were removed under reduced pressure after 24 h. The crude product was purified by silica gel chromatography (DCM) to afford compounds **150a**, **150c** and **152a** as white solids. The data obtained for compounds **150a/c** were consistent with the data obtained in Chapter 3.

152a White solid. Mp: 41- 42°C. ¹H NMR (CDCl₃, 400 MHz): δ 7.61-7.59 (m, 2H, Ar), 7.45-7.45 (m, 3H, Ar), 7.24-7.18 (m, 6H, Ar), 7.12-7.09 (m, 4H, Ar), 4.86 (dd, 1H, ³J_{HH}=12.9 Hz, ³J_{HH}=12.9 Hz, NCH), 4.53 (dd, 1H, ³J_{HH} = 13.1 Hz, ²J_{HH} = 3.8 Hz, AsCH), 4.26 (dd, 1H, ³J_{HH} = 12.7 Hz, ²J_{HH} = 3.8 Hz, AsCH); ¹³C NMR (CDCl₃, 100 MHz): δ 134.1-127.5 (18C, Ar), 78.7 (s, 1C, NC), 43.2 (s, 1C, AsC). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₂₀H₁₉NO₂As, 380.0632;

found, 380.0630. Anal. Calcd for C₂₀H₁₈NO₂As: C, 63.33; H, 4.78; N, 3.69. Found: C, 63.34; H, 5.09; N, 3.95 %.

General procedure for the metal-free oxidation of tertiary phosphines (Table 25 and 26).

HAsPh₂ (60.76 mg, 0.264 mmol, 3.0 equiv.) was charged to a pre-weighed Schlenk flask and dissolved in the stated solvent (6 mL). Tertiary phosphine **170** (0.088 mmol, 1.0 equiv.) was subsequently added, washed down with the stated solvent (6 mL) and the reaction was stirred for 24 h at RT in the dark. Volatiles were removed and pure phosphine oxide **171** was obtained upon recrystallization from DCM/H.

171a White solid. Mp: 160.1-160.8°C. ¹H NMR (CDCl₃, 400 MHz): δ 7.70-7.64 (m, 2H, Ar), 7.57-7.53 (m, 1H, Ar), 7.48-7.44 (m, 2H, Ar); ¹³C NMR (CDCl₃, 100 MHz): δ 132.8 (d, 3C, ¹J_{PC}=103.6 Hz, PC), 132.3 (d, 6C, ³J_{PC}=9.9 Hz, PCCC), 132.1 (d, 3C, ⁴J_{PC}=2.7 Hz, PCCCC), 128.7 (d, 6C, ²J_{PC}=12.1 Hz, PCC); ³¹P{¹H} NMR (CDCl₃, 161 MHz): δ 29.1 (s, 1P). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₁₈H₁₆OP, 279.0939; found, 279.0951.

171b White solid. Mp: 145.9-146.4°C. ¹H NMR (CDCl₃, 400 MHz): δ 7.59-7.54 (m, 6H, Ar), 6.96-6.94 (m, 6H, Ar), 3.84 (s, 3H, OCH₃); ¹³C NMR (CDCl₃, 75 MHz): δ 162.7 (d, 3C, ⁴J_{PC}=2.7 Hz, PCCCC), 134.2 (d, 6C, ³J_{PC}=11.6 Hz, PCCC), 124.3 (d, 3C, ¹J_{PC}=115.6 Hz, PC), 114.3 (d, 6C, ²J_{PC}=13.2 Hz, PCC), 55.6 (s, 3C, OCH₃); ³¹P{¹H} NMR (CDCl₃, 161 MHz): δ 28.8 (s, 1P). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₂₁H₂₂O₄P, 369.1256; found, 369.1256.

171c White solid. Mp: 173.9-174.6°C. ¹H NMR (CDCl₃, 400 MHz): δ 7.60-7.55 (m, 6H, Ar), 7.48-7.445 (m, 6H, Ar); ¹³C NMR (CDCl₃, 75 MHz): δ 139.4 (s, 3C, ClC), 133.7-133.6 (m, 9C, PC + PCC), 129.4 (d, 6C, ³J_{PC}=10.3 Hz, PCCC); ³¹P{¹H} NMR (CDCl₃, 161 MHz): δ 26.9 (s, 1P). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₁₈H₁₃³⁵Cl₃OP, 380.9770; found, 380.9769; calcd for C₁₈H₁₃³⁵Cl₂³⁷ClOP, 382.9740; found, 382.9742; calcd for C₁₈H₁₃³⁵Cl³⁷Cl₂OP, 384.9711; found, 384.9715; calcd for C₁₈H₁₃³⁷Cl₃OP, 386.9681; found, 386.9698.

171d White solid. Mp: 112.0-113.1°C. ^1H NMR (CDCl_3 , 400 MHz): δ 7.59-7.56 (m, 3H, Ar), 7.39-7.29 (m, 9H, Ar), 2.36 (s, 9H, CH_3); ^{13}C NMR (CDCl_3 , 100 MHz): δ 138.6 (d, 3C, $^3J_{\text{HH}}=12.0$ Hz, CCH_3), 132.9 (d, 3C, $^4J_{\text{PC}}=2.8$ Hz, PCCCC), 132.7 (d, 3C, $^1J_{\text{PC}}=102.7$ Hz, PC), 132.7 (d, 3C, $^2J_{\text{PC}}=9.5$ Hz, PCC), 129.4 (d, 6C, $^2J_{\text{PC}}=10.1$ Hz, PCC), 128.4 (d, 3C, $^3J_{\text{PC}}=12.7$ Hz, PCCC), 21.6 (s, 3C, CH_3); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161 MHz): δ 29.4 (s, 1P). HRMS (+ESI) m/z : ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{21}\text{H}_{22}\text{OP}$, 321.1408; found, 321.1406.

171e White solid. Mp: 120.8- 121.3°C. ^1H NMR (CDCl_3 , 400 MHz): δ 7.67-7.60 (m, 6H, Ar), 7.19-7.15 (m, 6H, Ar); ^{13}C NMR (CDCl_3 , 100 MHz): δ 165.2 (dd, 3C, $^1J_{\text{FC}}=252.8$ Hz, $^4J_{\text{PC}}=2.9$ Hz, FC), 134.5 (dd, 6C, $^2J_{\text{PC}}=8.98$ Hz, $^3J_{\text{FC}}=11.3$ Hz, PCC), 128.2 (d, 3C, $^1J_{\text{PC}}=8.0$ Hz, PC), 116.1 (dd, 6C, $^2J_{\text{FC}}=21.2$ Hz, $^3J_{\text{PC}}=13.2$ Hz, PCCC); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161 MHz): δ 26.9 (s, 1P); ^{19}F NMR (CDCl_3 , 376 MHz): δ -106.0 (brs, 3F). HRMS (+ESI) m/z : ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{18}\text{H}_{13}\text{F}_3\text{OP}$, 333.0656; found, 333.0658.

171f White solid. Mp: 154.4-155.1°C. ^1H NMR (CDCl_3 , 400 MHz): δ 7.45-7.41 (m, 3H, Ar), 7.33-7.30 (m, 3H, Ar), 7.17-7.14 (m, 3H, Ar), 7.12-7.07 (m, 3H, Ar), 2.50 (s, 9H, CH_3); ^{13}C NMR (CDCl_3 , 100 MHz): δ 143.8 (d, 3C, $^2J_{\text{PC}}=7.6$ Hz, H_3CC), 133.2-131.5 (m, 12C, Ar), 125.7 (d, 3C, $^3J_{\text{PC}}=12.6$ Hz, PCCC), 22.2 (d, 3C, $^3J_{\text{PC}}=3.8$ Hz, H_3C); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161 MHz): δ 37.1 (s, 1P). HRMS (+ESI) m/z : ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{21}\text{H}_{22}\text{OP}$, 321.1408; found, 321.1411.

171h White solid. Mp: 270.3-271.1°C. ^1H NMR (CDCl_3 , 400 MHz): δ 7.73-7.70 (m, 8H, Ar), 7.69-7.50 (m, 4H, Ar), 7.47-7.44 (m, 8H, Ar), 2.53 (d, 4H, $^2J_{\text{PH}}=1.6$ Hz, CH_2); ^{13}C NMR (CDCl_3 , 100 MHz): δ 132.3 (s, 4C, Ar), 131.1-129.0 (m, 10C, Ar), 21.9 (dd, 2C, $^1J_{\text{PC}}=40.0$ Hz, $^2J_{\text{PC}}=34.2$ Hz, PCH_2); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161 MHz): δ 33.2 (s, 2P). HRMS (+ESI) m/z : ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{26}\text{H}_{25}\text{O}_2\text{P}_2$, 431.1330; found, 431.1340.

171i Yellow solid. Mp: 244.2- 245.5°C. ^1H NMR (CDCl_3 , 400 MHz): δ 7.60-7.55 (m, 8H, Ar), 7.49-7.45 (m, 4H, Ar), 7.40-7.39 (m, 8H, Ar), 4.70 (brs, 4H, Fc), 4.26 (brs, 4H, Fc); ^{13}C NMR

(CDCl₃, 100 MHz): δ 133.9 (d, 4C, $^1J_{\text{PC}}=105.7$ Hz, PC_{Ar}), 131.8 (s, 4C, PCCCC), 131.4 (d, 8C, $^2J_{\text{PC}}=9.8$ Hz, PCC_{Ar}), 128.4 (d, 8C, $^3J_{\text{PC}}=12.0$ Hz, PCCC_{Ar}), 74.5 (d, 2C, $^1J_{\text{PC}}=1114.5$ Hz, PC_{Fe}), 74.2 (d, 4C, $^1J_{\text{PC}}=114.5$ Hz, PC_{Fe}), 74.2 (d, 8C, $^3J_{\text{PC}}=10.1$ Hz, PCCC_{Fe}), 74.6 (d, 8C, $^2J_{\text{PC}}=12.5$ Hz, PCC_{Fe}); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl₃, 161 MHz): δ 28.2 (s, 1P). HRMS (+ESI) m/z : (M + H)⁺ calcd for C₃₄H₂₉FeO₂P₂, 587.0992; found, 587.0995.

171j White solid. Mp: 106.9- 107.7°C. ^1H NMR (CDCl₃, 400 MHz): δ 8.78-8.29 (m, 1H, NCH), 7.90-7.82 (m, 1H, Ar), 7.53-7.49 (m, 5H, Ar), 7.46-7.45 (m, 2H, Ar), 7.44-7.41 (m, 2H, Ar), 7.40-7.38 (m, 1H, Ar); ^{13}C NMR (CDCl₃, 100 MHz): δ 156.6 (d, 1C, $^1J_{\text{PC}}=130.0$ Hz, NCP), 150.3 (d, 1C, $^3J_{\text{PC}}=19.0$ Hz, NCH), 136.5 (d, 1C, $^2J_{\text{PC}}=9.1$ Hz, PCC), 132.4 (d, 2C, $^1J_{\text{PC}}=103.7$ Hz, PC), 132.3 (d, 2C, $^2J_{\text{PC}}=9.4$ Hz, PCC), 132.1 (d, 1C, $^4J_{\text{PC}}=2.3$ Hz, PCCCC), 128.7-128.5 (m, 7C, Ar), 125.4 (d, 2C, $^4J_{\text{PC}}=2.14$ Hz, PCCCC); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl₃, 161 MHz): δ 20.8 (s, 1P). HRMS (+ESI) m/z : (M + H)⁺ calcd for C₁₇H₁₅NOP, 280.0891; found, 280.0892.

171k White solid. Mp: 93.4- 94.4°C. ^1H NMR (CDCl₃, 400 MHz): δ 8.53-8.51 (m, 1H, Ar), 7.65-7.45 (m, 11H, Ar), 7.40-7.36 (m, 1H, Ar), 7.11-7.06 (m, 1H, Ar), 4.93 (s, 2H, NCH₂), 3.19 (s, 6H, NCH₃); ^{13}C NMR (CDCl₃, 100 MHz): δ 136.2 (d, 1C, $^2J_{\text{PC}}=9.28$ Hz, PCCCH₂), 133.7-128.8 (m, 17C, Ar), 70.1 (s, 1C, NCH₂), 59.4 (s, 2C, NCH₃); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl₃, 161 MHz): δ 33.1 (s, 1P). HRMS (+ESI) m/z : (M + H)⁺ calcd for C₂₂H₂₂NOP, 347.1439; found, 347.1433.

171l White solid. Mp: 270.6-271.0°C. ^1H NMR (CDCl₃, 400 MHz): δ 8.17-8.14 (m, 2H, HOCCCC_H), 7.80-7.75 (m, 2H, HOCCCC_H), 7.71-7.66 (m, 4H, Ar), 7.59-7.55 (m, 2H, Ar), 7.51-7.46 (m, 4H, Ar); ^{13}C NMR (CDCl₃, 100 MHz): δ 168.7 (s, 1C, HOOC), 133.3-129.0 (18C, Ar); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl₃, 161 MHz): δ 31.0 (s, 1P). HRMS (+ESI) m/z : (M + H)⁺ calcd for C₁₉H₁₆O₃P, 323.0837; found, 323.0840.

171m White solid. Mp: 110.2-110.8°C. ^1H NMR (CDCl₃, 300 MHz): δ 7.76-7.80 (m, 4H, Ar), 7.57-7.48 (m, 6H, Ar), 2.68 (m, 4H, CH₂CH₂COOH + CH₂CH₂COOH); ^{13}C NMR (CDCl₃, 75

MHz): δ 174.1 (d, 1C, $^3J_{\text{PC}}=12.7$ Hz, COOH), 132.6 (d, 2C, $^4J_{\text{PC}}=2.1$ Hz, PCCCC), 131.3 (d, 2C, $^1J_{\text{PC}}=101.2$ Hz, PC), 131.0 (d, 4C, $^2J_{\text{PC}}=9.6$ Hz, PCC), 129.2 (d, 4C, $^3J_{\text{PC}}=11.8$ Hz, PCCC), 27.0 (d, 1C, $^2J_{\text{PC}}=2.2$ Hz, HOCCC), 24.9 (d, 1C, $^1J_{\text{PC}}=72.5$ Hz, PCH); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161 MHz): δ 35.7 (s, 1P). HRMS (+ESI) m/z : $(\text{M} + \text{H})^+$ calcd for $\text{C}_{15}\text{H}_{16}\text{O}_3\text{P}$, 275.0837; found, 275.0842.

General procedure for the oxidation of tertiary phosphines with addition of metal salts (Table 26). Tertiary phosphine **170** (0.088 mmol, 1.0 eq.) and the stated metal (0.053 mmol, 0.6 equiv.) were dissolved in MeOH (6 mL) and stirred at RT for 15 mins in the dark. Subsequently, a solution of HAsPh_2 (60.76 mg, 0.264 mmol, 3.0 equiv.) in MeOH (6 mL) was added and the reaction was stirred for 24 h at RT in the dark. Volatiles were removed and pure phosphine oxide **171** was obtained upon recrystallization from DCM/H.

Investigating catalyst 170a-substrate 151a interaction (Scheme 78 and Figure 34). Phosphine **170a** (12.00 μmol , 3.15 mg, 1.0 equiv.) and nitrostyrene **151a** (36.00 μmol , 5.37 mg, 3.0 equiv.) were stirred in dry DCM (1 mL) in the dark at 35°C for 1 h before a sample was prepared $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy.

Investigating oxygen source (Table 25). Phosphine **170a** (12.00 μmol , 3.15 mg, 1.0 equiv.) and HAsPh_2 (36.00 μmol , 8.28 mg, 3.0 equiv.) were stirred in dry DCM (1 mL) in the dark under stated conditions (Table 30) at RT for 24 h. Reactions were monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy after 24 h.

Table 30. Investigating the arsine-mediated oxidation of PPh_3 .^a

Entry	HAsPh_2	Conditions	P(III) : P(V)
1	Nil	Flame dried glassware, inert (dry) gas	100 : 0
2	3 equiv.	Flame dried glassware, moisturized gas	1 : 0.3718
3	3 equiv.	Air dried glassware, inert (dry) gas	1 : 0.4378
4	3 equiv.	Air dried glassware, moisturized gas, MS4A	100 : 0

^aReaction conditions: triphenylphosphine (12.00 μmol , 3.15 mg, 1.0 equiv), HAsPh_2 (36.00 μmol , 8.28 mg, 3.0 equiv), DCM (1 mL), RT, 24 h in dark.

General procedure for the synthesis of $\alpha,\beta,\gamma,\delta$ -unsaturated ketones **176 (Scheme 84).**

Aldehyde **A** (0.20g, 1.5 mmol, 1.0 equiv.) and ylide **B** (0.57g, 1.65 mmol, 1.1 equiv.) were refluxed in toluene (10 mL) for 16 h. Upon complete conversion as determined by thin-layer chromatography, volatiles were removed and the crude product was purified by silica gel chromatography (DCM) to afford compounds **176**.

Scheme 84. Synthesis of $\alpha,\beta,\gamma,\delta$ -unsaturated ketones **176**.

176a Yellow oil. Yield: 0.16 g, 0.69 mmol, 45%. ¹H NMR (CDCl₃, 400 MHz): δ 7.95-7.93 (m, 2H, Ar), 7.59-7.55 (m, 1H, Ar), 7.50-7.46 (m, 2H, Ar), 7.41 (dd, 1H, ³J_{HH} = 15.1 Hz, ³J_{HH} = 11.2 Hz, C(O)CHCH), 7.04 (d, 1H, ³J_{HH} = 15.1 Hz, C(O)CH), 6.63 (dd, 1H, ³J_{HH} = 15.5 Hz, ³J_{HH} = 11.2 Hz, C(O)CHCHCH), 6.11 (dd, 1H, ³J_{HH} = 15.5 Hz, ³J_{HH} = 4.3 Hz, C(O)CHCHCHCH), 4.96 (d, 1H, ³J_{HH} = 4.3 Hz, CH(OMe)₂), 3.35 (s, 6H, OCH₃); ¹³C NMR (CD₃CN, 100 MHz): δ 190.0 (s, 1C, C(O)), 142.5-127.2 (10C, Ar and vinylic), 101.9 (s, 1C, C(OMe)₂), 52.4 (s, 2C, OCH₃). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₁₄H₁₇O₃, 233.1178; found, 233.1174.

176b Light yellow solid. Yield: 0.13 g, 0.43 mmol, 28%. Mp: 133-134°C. ¹H NMR (CDCl₃, 400 MHz): δ 8.03-8.02 (m, 2H, Ar), 7.72-7.70 (m, 2H, Ar), 7.65-7.63 (m, 2H, Ar), 7.50-7.39 (m, 4H, Ar and C(O)CHCH), 7.09 (d, 1H, ³J_{HH} = 15.1 Hz, C(O)CH), 6.65 (dd, 1H, ³J_{HH} = 15.4 Hz, ³J_{HH} = 11.0 Hz, C(O)CHCHCH), 6.13 (dd, 1H, ³J_{HH} = 15.6 Hz, ³J_{HH} = 4.3 Hz, C(O)CHCHCHCH), 4.97 (d, 1H, ³J_{HH} = 4.2 Hz, CH(OMe)₂), 3.36 (s, 6H, OCH₃); ¹³C NMR (CD₃CN, 100 MHz): δ 189.4 (s, 1C, C(O)), 145.2-127.1 (16C, Ar and vinylic), 101.8 (s, 1C, C(OMe)₂), 52.3 (s, 2C, OCH₃). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₂₀H₂₁O₃, 309.1491; found, 309.1484.

176c Yellow solid. Yield: 0.10 g, 0.37 mmol, 24%. Mp: 64-65°C. ^1H NMR (CDCl_3 , 400 MHz): δ 8.76-8.75 (m, 1H, $\text{C}(\text{OCCHCNO}_2)$), 8.43 (d, 1H, $^3J_{\text{HH}} = 7.8$ Hz, O_2NCCHCH), 8.27 (d, 1H, $^3J_{\text{HH}} = 7.7$ Hz, $\text{C}(\text{O})\text{CCHCH}$), 7.69 (t, 1H, $^3J_{\text{HH}} = 8.0$ Hz, $\text{C}(\text{O})\text{CCHCH}$), 7.48 (dd, 1H, $^3J_{\text{HH}} = 15.0$ Hz, $^3J_{\text{HH}} = 11.3$ Hz, $\text{C}(\text{O})\text{CHCH}$), 7.05 (d, 1H, $^3J_{\text{HH}} = 15.0$ Hz, $\text{C}(\text{O})\text{CH}$), 6.67 (dd, 1H, $^3J_{\text{HH}} = 15.4$ Hz, $^3J_{\text{HH}} = 11.3$ Hz, $\text{C}(\text{O})\text{CHCHCH}$), 6.18 (dd, 1H, $^3J_{\text{HH}} = 15.5$ Hz, $^3J_{\text{HH}} = 4.2$ Hz, $\text{C}(\text{O})\text{CHCHCHCH}$), 4.98 (d, 1H, $^3J_{\text{HH}} = 4.1$ Hz, $\text{CH}(\text{OMe})_2$), 3.36 (s, 6H, OCH_3); ^{13}C NMR (CD_3CN , 100 MHz): δ 188.1 (s, 1C, $\text{C}(\text{O})$), 148.6 (s, 1C, CNO_2), 144.0-122.9 (9C, Ar and vinylic), 101.7 (s, 1C, $\text{C}(\text{OMe})_2$), 52.4 (s, 2C, OCH_3). HRMS (+ESI) m/z : $(\text{M} + \text{H})^+$ calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_5$, 278.1028; found, 278.1032.

General procedure for catalytic hydrophosphination reaction (Table 27). Acetal **176** (0.06 mmol, 1.0 equiv.) and complex (*R,R*)-**87a** (2.70 mg, 3.00 μmol , 5 mol %) were dissolved in the stated solvent (1 mL) and brought to the desired temperature. HPPH_2 (13.0 mg, 0.07 mmol, 1.1 equiv.) was added and the mixture was stirred for the stated time. The mixture was allowed to RT upon which S_8 (2.24 mg, 0.07 mmol, 1.1 equiv.) was added and stirred for another 45 mins. Volatiles were removed and the crude was redissolved in DCM (16 mL) and 10% v/v aq. HCl (1.3 mL). After stirring for 1.5 h at RT, the solution was extracted with DCM (3 X 10 mL), washed with water (3 X 10 mL) and dried over MgSO_4 . Purification by silica gel chromatography (DCM) afforded the pure phosphine sulfides **177**.

177a Pale yellow oil. Yield: 11.65 mg, 0.02 mmol, 48%. The *ee* was determined on a Daicel Chiralpak IC column with n-hexane/2-propanol = 75/25, flow = 1.0 mL/min, wavelength = 210 nm. Retention times: 14.2 min (minor), 25.9 min (major). $[\alpha]_{\text{D}}^{25} = +118.0$ (c 0.35, CHCl_3) (based on 97% *ee*). ^1H NMR (CDCl_3 , 400 MHz): δ 9.31 (d, 1H, $^3J_{\text{HH}} = 7.7$ Hz, $\text{C}(\text{O})\text{H}$), 8.05-7.99 (m, 2H, Ar), 7.94-7.87 (m, 4H, Ar), 7.58-7.42 (m, 9H, Ar), 6.74 (ddd, 1H, $^3J_{\text{HH}} = 15.7$ Hz, $^3J_{\text{HP}} = 8.8$ Hz, $^3J_{\text{HH}} = 6.8$ Hz, $\text{C}(\text{O})\text{CHCH}$), 6.03 (ddd, 1H, $^3J_{\text{HH}} = 15.7$ Hz, $^3J_{\text{HH}} = 7.7$ Hz, $^4J_{\text{HP}} = 4.3$ Hz, $\text{C}(\text{O})\text{CH}$), 4.64-4.57 (m, 1H, PCH), 3.75 (ddd, 1H, $^2J_{\text{HH}} = 18.2$ Hz, $^3J_{\text{HP}} = 10.1$ Hz,

$^3J_{\text{HH}} = 5.1$ Hz, PCHCH_2), 3.19 (ddd, 1H, $^2J_{\text{HH}} = 18.2$ Hz, $^3J_{\text{HP}} = 12.8$ Hz, $^3J_{\text{HH}} = 2.3$ Hz, PCHCH_2); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 162 MHz): δ 48.4; ^{13}C NMR (CDCl_3 , 100 MHz): δ 195.8 (d, 1C, $^3J_{\text{CP}} = 13.8$ Hz, $\text{CC}(\text{O})\text{C}$), 192.6 (d, 1C, $^4J_{\text{CP}} = 2.8$ Hz, $\text{C}(\text{O})\text{H}$), 150.9 (d, 1C, $^2J_{\text{CP}} = 5.4$ Hz, PCHCH), 136.4-128.1 (19C, Ar and CHCHO), 39.6 (d, 1C, $^1J_{\text{CP}} = 53.5$ Hz, PCH), 37.6, (s, 1C, $\text{CC}(\text{O})\text{CH}_2$). HRMS (+ESI) m/z : $(\text{M} + \text{H})^+$ calcd for $\text{C}_{24}\text{H}_{22}\text{O}_2\text{PS}$, 405.1078; found, 405.1078.

177b Pale yellow oil. Yield: 12.98 mg, 0.02 mmol, 45%. The *ee* was determined on a Daicel Chiralpak IC column with n-hexane/2-propanol = 75/25, flow = 1.0 mL/min, wavelength = 210 nm. Retention times: 21.7 min (minor), 35.2 min (major). $[\alpha]_{\text{D}}^{25} = +133.8$ (c 0.86, CHCl_3) (based on 92% *ee*). ^1H NMR (CDCl_3 , 400 MHz): δ 9.33 (d, 1H, $^3J_{\text{HH}} = 7.7$ Hz, $\text{C}(\text{O})\text{H}$), 8.07-8.01 (m, 2H, Ar), 7.97-7.90 (m, 4H, Ar), 7.66-7.64 (m, 2H, Ar), 7.61-7.59 (m, 2H, Ar), 7.54-7.38 (m, 9H, Ar), 6.76 (ddd, 1H, $^3J_{\text{HH}} = 15.7$ Hz, $^3J_{\text{HP}} = 8.8$ Hz, $^3J_{\text{HH}} = 6.8$ Hz, $\text{C}(\text{O})\text{CHCH}$), 6.06 (ddd, 1H, $^3J_{\text{HH}} = 15.7$ Hz, $^3J_{\text{HH}} = 7.7$ Hz, $^4J_{\text{HP}} = 4.3$ Hz, $\text{C}(\text{O})\text{CH}$), 4.67-4.59 (m, 1H, PCH), 3.78 (ddd, 1H, $^2J_{\text{HH}} = 18.1$ Hz, $^3J_{\text{HP}} = 10.1$ Hz, $^3J_{\text{HH}} = 5.1$ Hz, PCHCH_2), 3.23 (ddd, 1H, $^2J_{\text{HH}} = 18.1$ Hz, $^3J_{\text{HP}} = 12.8$ Hz, $^3J_{\text{HH}} = 2.3$ Hz, PCHCH_2); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 162 MHz): δ 48.5; ^{13}C NMR (CDCl_3 , 100 MHz): δ 195.4 (d, 1C, $^3J_{\text{CP}} = 13.8$ Hz, $\text{CC}(\text{O})\text{C}$), 192.5 (d, 1C, $^4J_{\text{CP}} = 2.9$ Hz, $\text{C}(\text{O})\text{H}$), 150.9-127.3 (26C, Ar and vinylic), 39.8 (d, 1C, $^1J_{\text{CP}} = 53.6$ Hz, PCH), 37.6 (s, 1C, $\text{CC}(\text{O})\text{CH}_2$). HRMS (+ESI) m/z : $(\text{M} + \text{H})^+$ calcd for $\text{C}_{30}\text{H}_{26}\text{O}_2\text{PS}$, 481.1393; found, 481.1391.

177c Pale yellow oil. Yield: 7.28 mg, 0.02 mmol, 48%. The *ee* was determined on a Daicel Chiralpak IC column with n-hexane/2-propanol = 60/40, flow = 1.0 mL/min, wavelength = 210 nm. Retention times: 30.3 min (minor), 71.2 min (major). $[\alpha]_{\text{D}}^{25} = +88.7$ (c 0.46, CHCl_3) (based on 82% *ee*). ^1H NMR (CDCl_3 , 400 MHz): δ 9.33 (d, 1H, $^3J_{\text{HH}} = 7.7$ Hz, $\text{C}(\text{O})\text{H}$), 8.67-8.66 (m, 1H, Ar), 8.43-8.42 (m, 1H, Ar), 8.21-8.18 (m, 1H, Ar), 8.05-7.99 (m, 2H, Ar), 7.95-7.89 (m, 2H, Ar), 7.66 (m, 1H, Ar), 7.56-7.46 (m, 6H, Ar), 6.75 (ddd, 1H, $^3J_{\text{HH}} = 15.7$ Hz, $^3J_{\text{HP}} = 8.9$

Hz, $^3J_{\text{HH}} = 6.7$ Hz, C(O)CHCH), 6.04 (ddd, 1H, $^3J_{\text{HH}} = 15.8$ Hz, $^3J_{\text{HH}} = 7.7$ Hz, $^4J_{\text{HP}} = 4.2$ Hz, C(O)CH), 4.63-4.56 (m, 1H, PCH), 3.73 (ddd, 1H, $^2J_{\text{HH}} = 18.4$ Hz, $^3J_{\text{HP}} = 9.7$ Hz, $^3J_{\text{HH}} = 5.9$ Hz, PCHCH₂), 3.29 (ddd, 1H, $^2J_{\text{HH}} = 18.3$ Hz, $^3J_{\text{HP}} = 12.6$ Hz, $^3J_{\text{HH}} = 2.7$ Hz, PCHCH₂); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl₃, 162 MHz): δ 48.3; ^{13}C NMR (CDCl₃, 100 MHz): δ 193.9 (d, 1C, $^3J_{\text{CP}} = 13.4$ Hz, CC(O)C), 192.3 (d, 1C, $^4J_{\text{CP}} = 2.7$ Hz, C(O)H), 150.2-123.0 (20C, Ar and vinylic), 39.7 (d, 1C, $^1J_{\text{CP}} = 53.1$ Hz, PCH), 38.0 (s, 1C, CC(O)CH₂). HRMS (+ESI) m/z : (M + H)⁺ calcd for C₂₄H₂₁NO₄PS, 450.0935; found, 450.0929.

General procedure for the hydroarsination of crotonaldehyde **157a (Scheme 81).** HAsPh₂ (34.5 mg, 0.15 mmol, 1.5 equiv.), crotonaldehyde **157a** (8.28 μL , 0.10 mmol, 1.0 equiv.) and DIPEA (19.2 μL , 0.11 mmol, 1.1 equiv.) were stirred in MeOH (3 mL) at RT for 2 h. Volatiles were removed and the crude was purified by silica gel chromatography (1 DCM : 1 H) to afford arsine **178** as a colourless oil in 54% yield. ^1H NMR (CDCl₃, 400 MHz): δ 9.71 (d, 1H, $^3J_{\text{HH}} = 1.2$ Hz, C(O)H), 7.51-7.46 (m, 4H, Ar), 7.37-7.34 (m, 6H, Ar), 2.93-2.87 (m, 1H, AsCH), 2.57 (dd, 1H, $^2J_{\text{HH}} = 17.2$ Hz, $^3J_{\text{HH}} = 3.6$ Hz, AsCHCH), 2.42 (ddd, 1H, $^2J_{\text{HH}} = 17.2$ Hz, $^3J_{\text{HH}} = 10.4$ Hz, $^3J_{\text{HH}} = 2.4$ Hz, AsCHCH), 1.19 (d, 3H, $^3J_{\text{HH}} = 7.0$ Hz, CH₃); ^{13}C NMR (CDCl₃, 100 MHz): δ 201.9 (s, 1C, C(O)H), 138.7-128.9 (10C, Ar), 48.19 (s, 1C, AsCHCH), 25.9 (s, 1C, AsCH), 17.7 (s, 1C, CH₃). HRMS (+ESI) m/z : (M + H)⁺ calcd for C₁₆H₁₇AsO, 300.0495; found, 300.0492.

General procedure for the intramolecular Aldol addition (Table 28). Arsine (0.06 mmol, 1.2 equiv.) aldehyde **177a** (20.2 mg, 0.05 mmol, 1.0 equiv.) and base (0.055 mmol, 1.1 equiv.) were stirred in the stated solvent (1 mL) until complete conversion of aldehyde **177a** was observed by thin-layer chromatography. Volatiles were removed and the crude product was purified by silica gel chromatography (2 Hexane : 1 EA) to afford pure cyclopentene **179** as a colourless oil. Colourless needles of cyclopentene **179** could be recrystallized from DCM/H at -15°C. $[\alpha]_{\text{D}}^{25} = +305.0$ (c 0.1, CHCl₃)(based on 97% *ee*). ^1H NMR (CDCl₃, 400 MHz): δ

8.05-8.02 (m, 2H, Ar), 7.96-7.86 (m, 4H, Ar), 7.58-7.39 (m, 9H, Ar), 6.07-6.03 (m, 1H, C(OH)CHCH=CH), 5.53-5.50 (m, 1H, C(OH)CHCH=CH), 5.06-5.02 (m, 1H, PCH), 4.81-4.77 (m, 1H, C(OH)CH), 4.00 (d, 1H, $^3J_{\text{HH}} = 16.8$ Hz, C(O)CH), 3.91 (d, 1H, $^3J_{\text{HH}} = 12.8$ Hz, OH); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 162 MHz): δ 48.0; ^{13}C NMR (CDCl_3 , 75 MHz): δ 196.9 (d, 1C, $^3J_{\text{CP}} = 8.3$ Hz, C(O)), 136.3-129.0 (17C, Ar and vinylic), 80.7 (d, 1C, $^3J_{\text{CP}} = 2.25$ Hz, C(OH)), 56.8 (d, 1C, $^2J_{\text{CP}} = 2.3$ Hz, C(O)CH), 47.3 (d, 1C, $^1J_{\text{CP}} = 52.5$ Hz, PCH). HRMS (+ESI) m/z : (M + H) $^+$ calcd for $\text{C}_{24}\text{H}_{22}\text{O}_2\text{PS}$, 405.1078; found, 405.1073.

References

- [1] MacMillan, D W. C. *Nature* **2008**, *455*, 304.
- [2] (a) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416, (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471, (c) Gaunt, M. J.; Johansson, C. C. C. *Chem. Rev.* **2007**, *107*, 5596.
- [3] (a) Wurzb, R. P. *Chem. Rev.* **2007**, *107*, 5570, (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.
- [4] Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656.
- [5] Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.
- [6] Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.
- [7] (a) Blaser, H.-U. *Chem. Rev.* **1992**, *92*, 935, (b) Brill, Z. G.; Condakes, M. L.; Ting, C. P.; Maimone, T. J. *Chem. Rev.* **2017**, *117*, 11753.
- [8] (a) Ibrahim, I.; Rios, R.; Vesely, J.; Hammar, P.; Eriksson, L.; Himo, F.; Córdova, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 4507, (b) Ibrahim, I.; Hammar, P.; Vesely, J.; Rios, R.; Eriksson, L.; Córdova, A. *Adv. Synth. Catal.* **2008**, *350*, 1875.
- [9] (a) Dinér, P.; Nielsen, M.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 1983, (b) Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328.
- [10] Sundén, H.; Rios, R.; Ibrahim, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Adv. Synth. Catal.* **2007**, *349*, 827.
- [11] Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Mazzanti, A.; Sambri, L.; Melchiorre, P. *Chem. Commun.* **2007**, 722.
- [12] Li, B.-J.; El-Nachef, C.; Beauchemin, A. M. *Chem. Commun.* **2017**, *53*, 13192.
- [13] Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035.
- [14] (a) White, D. A.; Baizer, M. M. *Tetrahedron Lett.* **1973**, *14*, 3597, (b) Fan, Y. C.; Kwon, O. *Chem. Commun.* **2013**, *49*, 11588.

- [15] Bergman, E. D.; Ginsburg, D. *Organic Reactions*; Wiley: New York, 1959, Vol. 10, p 179.
- [16] Davies, W. C.; Lewis, W. P. G. *J. Chem. Soc.* **1934**, 1599.
- [17] Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696.
- [18] (a) Billbrey, J. A.; Kazez, A. H.; Locklin, J.; Allen, W. D. *J. Comput. Chem.* **2013**, *34*, 1189, (b) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.
- [19] In the event of phosphine-substrate interaction, the appearance of a signal corresponding to the zwitteranionic phosphine-olefin adduct was expected to be observable with $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy. See reference [14a] and [17].
- [20] (a) Issleib, K.; Kümmel, R. *J. Organomet. Chem.* **1965**, *3*, 84, (b) Li, J.-N.; Liu, L.; Fu, Y.; Guo, Q.-X. *Tetrahedron* **2006**, *62*, 4453.
- [21] (a) Summers, J. C.; Sisler, H. H. *Inorg. Chem.* **1970**, *9*, 862, (b) Payraastre, C.; Madaule, Y.; Wolf, J. G.; Kim, T. C.; Mazières, M. R.; Wolf, R.; Sanchez, M. *Heteroat. Chem.* **1992**, *3*, 157.
- [22] Porter, K. A.; Willis, A. C.; Zank, J.; Wild, S. B. *Inorg. Chem.* **2002**, *41*, 6380.
- [23] (a) Tanabe, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Eur. J.* **2018**, *24*, 18618, (b) Ding, A.; Li, S.; Chen, Y.; Jin, R.; Ye, C.; Hu, J.; Guo, H. *Tetrahedron Lett.* **2018**, *59*, 3880, (c) Zhang, Y.; Ye, C.; Li, S.; Ding, A.; Gu, G.; Guo, A. *RSC Adv.* **2017**, *22*, 13240, (d) Avenier, F.; Herrero, C.; Leibl, W.; Desbois, A.; Guillot, R.; Mahy, J.-P.; Aukauloo, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 3634, (e) Prokop, K. A.; Goldberg, D. P. *J. Am. Chem. Soc.* **2012**, *134*, 8014, (f) Yasui, S.; Tojo, S.; Majima, T. *J. Org. Chem.* **2005**, *70*, 1276, (g) Somasundaram, N.; Srinivasan, C. *J. Org. Chem.* **1996**, *61*, 2895.
- [24] (a) Rettig, I. D.; Van, J.; Brauer, J. B.; McCormick, T. M. *Dalton Trans.* **2019**, *48*, 5665, (b) Lee, Y.-M.; Yoo, M.; Yoon, H.; Li, X.-X.; Nam, W.; Fukuzumi, S. *Chem. Commun.* **2017**, *53*, 9352, (c) Dobrovetsky, R.; Stephan, D. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 2516, (d) Cervilla, A.; Pérez-Pla, F.; Llopis, E.; Plies, M. *Inorg. Chem.* **2006**, *45*, 7357, (e) Du, G.;

Espenson, J. H. *Inorg. Chem.* **2005**, *44*, 2465, (f) Levason, W.; Patel, R.; Reid, G. *J. Organomet. Chem.* **2003**, 688, 280, (g) Jacobi, B. G.; Laitar, D. S.; Pu, L.; Wargocki, M. F.; DiPasquale, A. G.; Fortner, K. C.; Schuck, S. M.; Brown, S. N. *Inorg. Chem.* **2002**, *41*, 4815, (h) Grushin, V. V. *Organometallics* **2001**, *20*, 3950.

[25] (a) Chen, Q.; Zeng, J.; Yan, X.; Huang, Y.; Du, Z.; Zhang, K.; Wen, C. *Tetrahedron Lett.* **2016**, *57*, 3379, (b) Peng, W.; Shreeve, J. M. *J. Fluorine. Chem.* **2005**, *126*, 1054.

[26] (a) Byrne, P. A.; Ortin, Y.; Gilheany, D. G. *Chem. Comm.* **2015**, *51*, 1147, (b) Johnson, A. *J. Org. Chem.* **1959**, *24*, 282.

[27] (a) Sasaki, S.; Sutoh, K.; Shimizu, Y.; Kato, K.; Yoshifuji, M. *Tetrahedron Lett.* **2014**, *55*, 322, (b) Boéré, R. T.; Zhang, Y. *J. Organomet. Chem.* **2005**, *690*, 2651, (c) Bach, R. D.; Glukhovstev, M. N.; Canepa, C. *J. Am. Chem. Soc.* **1998**, *120*, 775.

[28] Woźniak, L. A.; Stec, W. J. *Tetrahedron Lett.* **1999**, *40*, 2637.

[29] (a) Sisler, H. H.; Sarkis, A.; Ahuja, H. S.; Drago, R. J.; Smith, N. L. *J. Am. Chem. Soc.* **1959**, *81*, 2982, (b) Berlin, K. D.; Butler, G. B. *Chem. Rev.* **1960**, *60*, 243.

[30] (a) Bergin, E.; O'Connor, C. T.; Robinson, S. B.; McGarrigle, E. M.; O'Mahony, C. P.; Gilheany, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 9566, (b) Rajendran, K. V.; Gilheany, D. G. *Chem. Commun.* **2012**, *48*, 10040, (c) Nikitin, K.; Rajendran, K. V.; Müller-Bunz, H.; Gilheany, D. G. *Angew. Chem. Int. Ed.* **2014**, *53*, 1906, (d) Rajendran, K. V.; Kennedy, L.; Gilheany, D. G. *Eur. J. Org. Chem.* **2010**, 5642.

[31] Blicke, F. F.; Powers, L. D. *J. Am. Chem. Soc.* **1933**, *55*, 1161

[32] Zhou, Z.; Wang, Y.; Tang, C. *Curr. Org. Chem.* **2011**, *15*, 4083 and references therein.

[33] For examples of bulky chiral phosphine organocatalysts, see (a) Xiao, Y.; Sun, Z.; Guo, H.; Kwon, O. *Beilstein J. Org. Chem.* **2014**, *10*, 2089, (b) Marinetti, A.; Voituriez, A. *Synlett* **2010**, *2*, 174, (c) Ni, H.; Chan, W.-L.; Lu, Y. *Chem. Rev.* **2018**, *118*, 9344.

- [34] For an overview of transition metal-catalyzed hydrophosphination reactions, see (a) Koshti, V.; Gaikwad, S.; Chikkali, S. H. *Coord. Chem. Rev.* **2014**, *265*, 52, (b) Rodriguez-Ruiz, V.; Carlino, R.; Bezzenine-Lafollée, S.; Gil, R.; Prim, D.; Schulz, E.; Hannedouche, J. *Dalton Trans.* **2015**, *44*, 12029, (c) Pullarkat, S. A.; Leung, P.-H. *Top. Organomet. Chem.* **2013**, *48*, 493, (d) Glueck, D. S. *Chem. Eur. J.* **2008**, *14*, 7108.
- [35] (a) Lu, J.; Ye, J.; Duan, W.-L. *Chem. Commun.* **2014**, *50*, 698, (b) Yang, X.-Y.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Organometallics* **2015**, *34*, 5196, (c) Yang, X.-Y.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Chem. Commun.* **2016**, *52*, 4211, (d) Feng, J.-J.; Chen, X.-F.; Shi, M.; Duan, W.-L. *J. Am. Chem. Soc.* **2010**, *132*, 5562.
- [36] For selected examples, see (a) Ma, M.; Lu, R.; Pullarkat, S. A.; Deng, W.; Leung, P.-H. *Dalton Trans.* **2010**, *39*, 5453, (b) Werner, H.; Manger, M.; Schmidt, U.; Laubender, M.; Weberndörfer, B. *Organometallics* **1998**, *17*, 2619, (c) Gugger, P. A.; Willis, A. C.; Wild, S. B.; Heath, G. A.; Webster, R. D.; Nelson, J. H. *J. Organomet. Chem.* **2002**, *643-644*, 136, (d) Aw, B.-H.; Leung, P.-H.; White, A. J. P.; Williams, D. J. *Organometallics* **1996**, *15*, 3640, (e) Doyle, R. J.; Salem, G.; Willis, A. C. *J. Chem. Soc., Dalton Trans.* **1995**, *0*, 1867, (f) Cho, S. Y.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 1773.
- [37] (a) Bungabong, M. L.; Tan, K. W.; Li, Y.; Selvaratnam, S. V.; Dongol, K. G.; Leung, P.-H. *Inorg. Chem.* **2007**, *46*, 4733, (b) Cheow, Y. L.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. *J. Organomet. Chem.* **2012**, *696*, 4215.
- [38] Yang, X.-Y.; Gan, J. H.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Dalton Trans.* **2015**, *44*, 1258.
- [39] (a) Birchall, T.; Jolly, W. L. *Inorg. Chem.* **1966**, *5*, 2177, (b) Wyatt, R. H.; Holtz, D.; McMahon, T. B.; Beauchamp, J. L. *Inorg. Chem.* **1974**, *13*, 1511.
- [40] (a) Gutsche, C. D.; Buriks, R. S.; Nowotny, K.; Grassner, H. *J. Am. Chem. Soc.* **1962**, *84*, 3775, (b) Markert, M.; Mulzer, M.; Schetter, B.; Mahrwald, R. *J. Am. Chem. Soc.* **2007**, *129*,

7258, (c) Calter, M. A.; Orr, R. K. *Tetrahedron Lett.* **2003**, 44, 5699, (d) Markert, M.; Mahrwald, R. *Synthesis* **2004**, 9, 1429, (e) Arnold, A.; Markert, M.; Mahrwald, R. *Synthesis* **2006**, 7, 1099, (f) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, 39, 1600.

[41] Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, 37, 558.

[42] The geometric conformation of the enolate was inconclusive in this instance due to the internal Aldol reaction proceeding by a 5-membered pseudo-chair transition state instead of a 6-membered transition state.

[43] Belot, V.; Farran, D.; Jean, M.; Albalat, M.; Vanthuyne, N.; Roussel, C. *J. Org. Chem.* **2017**, 82, 10188.

[44] Baccolini, G.; Boga, C.; Mazzacurati, M. *J. Org. Chem.* **2005**, 70, 4774.

[45] In a similar manner, tertiary phosphines have been employed to assist in the *E/Z* isomerization of enone motifs. (a) Wang, Z.; Chen, Z.; Bai, S.; Li, W.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2012**, 51, 2776, (b) Chen, Z.; Furutachi, M.; Kato, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2009**, 48, 2218.

[46] (a) Benz, S.; Poblador-Bahamonde, A. I.; Low-Ders, N.; Matile, S. *Angew. Chem. Int. Ed.* **2018**, 57, 5408, (b) Angarov, V.; Kozuch, S. *New J. Chem.* **2018**, 42, 1413, (c) Pascoe, D. J.; Ling, K. B.; Cockroft, S. L. *J. Am. Chem. Soc.* **2017**, 139, 15160.

[47] Emerson, K.; Britton, D. *Acta Cryst.* **1963**, 16, 113.

[48] For selected examples, see (a) Xu, L.-W. *ChemCatChem* **2013**, 5, 2775, (b) Wang, T.; Han, X.; Zhong, F.; Yao, W.; Lu, Y. *Acc. Chem. Res.* **2016**, 49, 1369, (c) Cao, D.; Chai, Z.; Zhang, J.; Ye, Z.; Xiao, H.; Wang, H.; Chen, J.; Yu, X.; Zhao, G. *Chem. Commun.* **2013**, 49, 5972, (d) Jin, Q.-W.; Chai, Z.; Huang, Y.-M.; Zou, G.; Zhao, G. *Beilstein J. Org. Chem.* **2016**, 12, 725, (e) Warner, C. J. A.; Berry, S. S.; Jones, S. *Tetrahedron* **2019**, 75, 130733, (f) Miyaji, R.; Wada, Y.; Matsumoto, A.; Asano, K.; Matsubara, S. *Beilstein J. Org. Chem.* **2017**, 13, 1518,

(g) Jiménez, E. I.; Narváez, W. E. V.; Rocha-Rinza, T.; Hernández-Rodríguez, M. *Catal. Sci. Tech.* **2017**, *7*, 4470, (h) Yuan, Y.-H.; Han, X.; Zhu, F.-P.; Tian, J.-M.; Zhang, F.-M.; Tu, Y.-Q.; Wang, S.-H.; Guo, X. *Nature Comm.* **2019**, *10*, 3394 DOI: 10.1038/s41467-019-11382-8, (i) Baslé, O.; Porcel, S.; Ladeira, S.; Bouhadir, G.; Bourissou, D. *Chem. Commun.* **2012**, *48*, 4495.

[49] For selected examples, see (a) Gladiali, S.; Alberico, E.; Junge, K.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 3744, (b) Ohta, T.; Takaya, H.; Noyori, R. *Inorg. Chem.* **1988**, *27*, 566, (c) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 12579, (d) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 11038, (e) Braje, W.; Frackenpohl, J.; Langer, P.; Hoffmann, H. M. R. *Tetrahedron* **1998**, *54*, 3495, (f) Tanzer, E. M.; Schweizer, W. B.; Ebert, M. O.; Gilmour, R. *Chem. Eur. J.* **2012**, *18*, 2006, (g) Crawford, J. M.; Sigman, M. S. *Synthesis* **2019**, *51*, 1021, (h) Chen, H. J.; Teo, R. H. X.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Organometallics* **2018**, *37*, 99, (i) Wild, S. B. *Coord. Chem. Rev.* **1997**, *166*, 291.

[50] Ng, J. K.-P.; Tan, G.-K.; Vittal, J. J.; Leung, P.-H. *Inorg. Chem.* **2003**, *42*, 7674.

Chapter 5

Application of hydroarsination reactions

5.1 Introduction

As mentioned in Chapter 1, ongoing emphasis has been placed on greener and more efficient organoarsenic synthetic strategies. While the catalytic hydroarsination reaction utilizes secondary arsines in a highly atom-economical manner, the use of air-sensitive secondary arsines and designer organometallic catalysts can make such protocols difficult to apply in certain synthetic scenarios. Apart from secondary arsines, less-hazardous arylarsine oxides,¹ cyclooligoarsines,² and tertiary arsines³ have been developed for As–C bond formation (Figure 42). However, such reagents generally rely on harsh reagents (eg. organolithium,

Figure 42. Alternative precursors to secondary arsines.

Grignard reagents) and conditions (eg. high temperatures), thus leading to poor scope and functional group tolerance. The availability of a highly-functionalized, yet air-stable organoarsine precursor may expand the current utility of arsines in the fields of coordination chemistry,⁴ material science,⁵ agriculture⁶ and even chemotherapy.⁷

It was envisioned that the hydroarsination reaction could be exploited to prepare functionalized arsenic precursors by installing an arsine motif within a well-recognized organic scaffold. The affinity of arsines to carbonyl motifs described in Chapter 4 was of particular interest and ynone **181** was specially selected as a model substrate to achieve two objectives (Scheme 85). Firstly, controlled addition of a secondary arsine to ynone **181** would generate arsine-functionalized Michael acceptors **182/183** bearing multiple reactive sites. Secondly,

Scheme 85. Synthetic strategy to access β -oxovinylarsines **182/183**.

hydroarsination of ynone **181** would potentially provide an opportunity to investigate the aforementioned arsine-carbonyl interaction.

Unlike other notable main group elements such as boron, silicon and even phosphorus, applications of organoarsenic(III) chemistry are scarce. Tertiary arsines are most commonly utilized as alternative ligands to their popular phosphine counterparts.⁸ In place of phosphine organocatalysts and ylides, arsines have been explored as organocatalysts for the Wittig olefination⁹ and as arsonium ylides.¹⁰ Lastly, arsonium cations derived from tertiary arsines have been investigated as therapeutics,¹¹ inspired by the lipophilic character of organic phosphonium salts.¹² Recently, highly electron-deficient triarylarsines have been demonstrated to display excellent organocatalytic activity *via* σ -hole interactions in the Reissert-type substitution of isoquinoline, far surpassing the activity of analogous phosphines due to their increased polarizability.¹³ Not only were the pnictogen σ -hole interactions stronger than halogen- and chalcogen-based σ -hole interactions (Table 31), Matile furnished compelling

Table 31. Relative pnictogen, chalcogen and halogen bond strength based on σ -hole interaction.^a

	Pnictogen/a.u.	Chalcogen/a.u.	Halogen/a.u.
	P	S	Cl
Period 3	25.0	19.3	14.3
Period 4	As	Se	Br
	29.7	25.4	20.5

^aD: donor, EWG: electron-withdrawing substituent, LB: Lewis base. Computational values based on MP2 calculations in a.u.

evidence that the depth of pnictogen σ -holes (and corresponding binding strengths) were easily modulated with varying the electron-withdrawing nature of the substituents.^{13a} While electronic fine-tuning was convenient, it must be noted that such interactions have only been functional for arsines bearing highly electron-deficient substituents thus far.¹³ If σ -hole

interactions were indeed operative in the arsine-carbonyl interactions involving electronically-neutral HAsPh_2 , this observation would represent a remarkable development with respect to the structural and electronic requirements of arsine σ -hole organocatalysis. The synthesis of β -oxovinylarsines **182/183** was an ideal model in this instance to 1) exploit advances in the hydroarsination reaction in designing improved arsenic precursors, and concurrently 2) experimentally observe the intramolecular interaction between arsine and carbonyl motifs in close proximity.

5.2 Results and discussion

Research questions

- 1) *Can β -oxovinylarsines be used in general synthesis as a reactive yet bench-stable arsenic precursor?*
- 2) *Can arsine-carbonyl interactions be used in chemically-significant applications?*

Overview

Herein, we report the development of β -oxovinylarsines as a new arsenic synthetic precursor. These compounds 1) are stable to air and moisture, 2) possess multiple reactive sites, 3) are resistant to self-quenching or polymerization, 4) are amenable to functionalization and 5) exhibit high atom economy when used. Arsine-carbonyl interactions were operative in the stereoselective synthesis of the thermodynamically less-favoured *Z*-isomer. Representative nucleophilicity, electrophilicity and reactivity to transition metals was demonstrated by reacting β -oxovinylarsines with prototypical reagents of complementary reactivity.

Synthesis of β -oxovinylarsines

Unlike the hydroarsination of alkenes, the hydroarsination of alkynes was successfully demonstrated by Waterman with a Zr-based catalyst which furnished unsaturated vinylarsines in a mixture of geometric isomers.¹⁵ The poor *E/Z*-selectivity and overall atom-economy were two aspects targeted for further improvement. It was envisioned that the use of specially-designed organometallic catalysts could be circumvented by exploiting the ionization equilibria of secondary arsines in polar protic solvents described in Chapter 3. In the absence of catalytic control, thermodynamically-favourable *trans*- β -oxovinylarsine **183a** was expected as the major product for the uncatalyzed conjugate addition of secondary arsines to ynone **181a** (Scheme 86).

Scheme 86. Proposed key conjugate addition intermediate **A**.

The addition of HAsPh₂ to ynone **181a** was first attempted in a semi-aqueous solvent system of MeOH/H₂O (10% v/v). Remarkably, such conditions exclusively afforded *cis*- β -oxovinylarsine **182a** in 87% isolated yield while no thermodynamically-favourable *trans*-isomer **183a** was observed (Scheme 87). *Cis*- β -oxovinylarsine **182a** was recrystallized from

Scheme 87. Synthesis of *cis*- β -oxovinylarsine **182a**.

DCM/EA and its molecular structure was confirmed by X-ray crystallography (Figure 43). A cursory literature review revealed that targeted synthesis of the *Z*-isomer typically required catalytic control.¹⁶ For instance, organometallic catalysts have been employed to enforce a co-

Figure 43. Molecular structure of *cis*-β-oxovinylarsine **182a** with hydrogen atoms omitted for clarity.

facial arrangement upon simultaneous coordination of the bulkier olefin substituents.¹⁷ Alternatively, non-chelating chiral organic catalysts have promoted the formation of the *Z* isomer by substituent-directed shielding of a single prochiral olefin face.¹⁸ Insights regarding the *Z*-selectivity of arsine **182a** were of interest considering the elusiveness of absolute *E/Z* selectivity and the unestablished nature of organoarsenic chemistry.

Clearly, protonation of intermediate **A** favoured the face opposite to the -AsPh₂ motif. Under the highly protic environment of MeOH/H₂O (10% v/v), it was irrational to propose *Z*-selectivity arising from charge-charge or steric repulsion between -AsPh₂ and the incoming proton. Recent computational evidence for the presence of hydrogen bonding between arsines and water suggested that hydrogen bonding could have promoted the co-facial arrangement between the arsine and enolate functionalities in intermediate **A**.¹⁹ To validate this hypothesis, the reaction was repeated in non-protic solvents (Table 32). Experimental results suggested that good *E/Z*-selectivity was achievable without hydrogen bonding in this instance (Entries 2-6). Even in the presence of electron-withdrawing and -donating substituents, only a single *Z* isomer was observed when the reaction was conducted in hexane (Entries 5, 7 and 8). Alternatively, *Z*-selectivity arising from direct interaction between the carbonyl and arsine motifs *via* σ-hole interaction was plausible despite existing literature evidence suggesting the need for highly electron-withdrawing substituents.¹³ While this may not be immediately obvious given the allenic structure of intermediate **A**, O---As interactions may have manifested

Table 32. Optimization of conditions.^a

Entry	181	R	Solvent	Yield ^b (%)	182 : 183^c
1	181a	H	MeOH/H ₂ O (10%)	87	>99 : 1
2	181a	H	DCM	69	87 : 13
3	181a	H	THF	72	77 : 23
4	181a	H	DEE	78	83 : 17
5	181a	H	Hexane	89	>99 : 1
6	181a	H	Toluene	65	76 : 24
7	181b	CH ₃	Hexane	76	>99 : 1
8	181c	Cl	Hexane	78	>99 : 1

^aReaction conditions: ynone **181** (1.0 mmol, 1.0 equiv.) and HAsPh₂ (0.28 g, 1.2 mmol, 1.2 equiv.), solvent (18 mL), RT, 24 h. ^bIsolated yield. ^cDetermined by the ¹H NMR integrals of olefinic protons.

in the high energy transition state of the kinetic pathway, thus favouring the formation of *Z*-isomer **182** (Scheme 88). An O---As interatomic distance of 2.764 Å was observed from the

Scheme 88. Energy level diagram illustrating the effect of O-As interactions.

X-ray crystal structure of *cis*-β-oxovinylarsine **182a** (Figure 43) which was significantly less than the sum of their van der Waals radii (3.44 Å).²⁰ In addition, the solid state structure of *cis*-β-oxovinylarsine **182a** indicated an alignment of the σ* As-C orbital with the O lone pair (Figure 43). Bond lengths determined *via* X-ray crystallography also indicated a longer As1–C10 bond length relative to the As1–C16 bond (1.9663(15) Å and 1.9631(15) Å respectively). If so, this holds remarkable potential for the routine application of organoarsine compounds to carbonyl motifs ubiquitous in general synthetic chemistry and undoubtedly deserves further

specialized work to elucidate the nature of the proposed interaction (see Chapter 6). In addition, we are unable to rule out the influence of molecular orbital effects in the transition states of intermediate **A** due to the allene having two sets of π orbitals orthogonal to each other.²¹ For example, the addition of iodides and thiols to activated alkynes consistently yielded the *Z*-isomer as the major product under various reaction conditions.²²

The preparation of β -oxovinylarsines **182** was attractive in terms of energy requirements and environmental cost. No additives, catalysts or base were required for obtaining good isolated yields. Excellent *E/Z* selectivity conferred high atom economy which was crucial in reducing potentially-toxic arsenic waste. In addition, benign energy requirements for the reaction (room temperature) and post-reaction treatment (of the MeOH/water mixture) was favourable for industrial scalability.²³ β -oxovinylarsines **182** were resistant to oxidation under ambient conditions for a prolonged period of time. In fact, the non-volatile solids could be handled as a benchtop reagent without specialized equipment unlike HAsPh₂, for which a well-ventilated fume hood was necessary to contain any vapor emitted.

Simple modifications to the conjugate addition methodology allowed for the formation of the *E* isomer in high yields as well (Scheme 89). Instead of deriving the *E* isomer

Scheme 89. Synthesis of *trans*- β -oxovinylarsine **183a**.

via isomerization,²⁴ physical separation of geometric isomers of arsines **182** and **183** was avoided by employing vinyl iodide **184** as an intermediate. An addition-elimination pathway successfully afforded *trans*- β -oxovinylarsine **183a** in overall yield of 62%. No *cis*- β -oxovinylarsine **182a** was observed in the crude under these conditions and the straightforward

isolation of *trans*- β -oxovinylarsine **183a** was accomplished by column chromatography. Olefin proton coupling constants of β -oxovinylarsines **182/183** were also in good agreement with the proposed structures at $^3J_{\text{HH}} = 11.2\text{--}11.3$ Hz for *Z*-isomers **182** and $^3J_{\text{HH}} = 16.9$ Hz for the *E*-isomer **183**. It may be worth noting that other non-acidic methods to generate vinyl iodide **184** are available which may be beneficial for acid-sensitive analogues of ynone **181**.²⁵ The thermodynamically-favourable *trans*- β -oxovinylarsine **183b** could also be isolated from the ethanolic mother liquor of *cis*-isomer **182a** (5-18% yield) upon thermal equilibration.

It is worth highlighting that the general scaffold of β -oxovinylarsines **182/183** resemble that of enaminones.²⁶ However, both their syntheses and properties differ greatly.²⁷ For example, hydrolysis of enaminones is widely used in the syntheses of nitrogen-containing heterocycles whereas vinylarsine motifs are exceptionally stable to hydrolysis.²⁸ Arguably, β -oxovinylphosphines bear a closer resemblance to β -oxovinylarsines **182/183** by virtue of their group relationship. To the best of our knowledge, such phosphines have not been isolated successfully before, although they have been observed in situ by ^1H NMR spectroscopy as a catalytic intermediate.²⁹ The attempted syntheses of corresponding β -oxovinylphosphines with several different methods were unsuccessful, including routes used to successfully synthesize the aforementioned β -oxovinylarsines **182/183**.

Evaluating the reactivity of β -oxovinylarsines

By design, β -oxovinylarsines **182/183** offer an abundance of potential reactive sites within the highly functionalized molecule. The classical Michael acceptor motif is easily recognizable in the β -oxovinylarsine scaffold with electrophilic sites at the 1,2- and 1,4-positions. Nucleophilic sites at the arsenic atom of β -oxovinylarsines **182/183** parallel those of other arsenic nucleophiles such as HAsPh_2 . Lastly, neutral As–C bonds resemble other neutral arsenic reagents such as cyclooligoarsines and tertiary arsines which have been employed in

transition metal-catalyzed reactions. Other miscellaneous reactivity include potential Diels Alder reactions at the activated C=C bond in place of diphenylvinylarsine reagents.^{3c,30} The structural similarity of β -oxovinylarsines **182/183** to chalcone also potentially allows exploration in annulation methodologies which have utilized the latter as a well-defined model substrate.³¹ Of the different reactivities outlined, the chemical reactivity of β -oxovinylarsines **182/183** with transition metals, nucleophiles and electrophiles are demonstrated as follows.

Two aspects of reactivity with transition metals were of interest. Firstly, β -oxovinylarsines **182/183** were proposed to resolve the existing incompatibility of bidentate palladacycles with conjugate addition methodologies involving secondary arsines. As illustrated in Chapter 2, HAsPh₂ decomposed a series of bi- and tri-dentate palladacycles, thus limiting catalysts to only robust PCP-type pincer complexes. Consequently, highly stereoselective hydrophosphination catalysts such as palladacycle **78** could not be applied to the analogous hydroarsination reaction.³² By first trapping HAsPh₂ within the Michael acceptor scaffold, β -oxovinylarsine-based methodologies retain all the advantages of using HAsPh₂ while avoiding undesired decomposition of the catalyst.

Indeed, the structural integrity and catalytic activity of palladacycle **78** was maintained under an excess of β -oxovinylarsine **182a**. In the presence of HPPH₂, the electrophilicity of *cis*- β -oxovinylarsine **182a** at the 1,4-position was also clearly demonstrated with the conjugate addition of HPPH₂ (Scheme 90). While complete conversion of the secondary

Scheme 90. Pd-catalyzed hydrophosphination on *cis*- β -oxovinylarsine **182a**

phosphine reagent was observed, isolation of arsinophosphine **185a** was complicated by the unprecedented formation of 1,1-diphosphine **185b**. Both compounds co-crystallized in

Figure 44. Molecular structure of arsinophosphine **185a** with hydrogen atoms omitted for clarity.

DCM/EtOH and their structures were confirmed by X-ray crystallography (Figure 44). The formation of 1,1-diphosphine **185b** was a surprise since ynone **181a** did not afford appreciable yields of diphosphine **185b** under the same conditions, suggesting that diphosphine **185b** was possibly formed from migratory scrambling of P/As bonds instead of an addition-elimination reaction from arsinophosphine **185a**.³³ The significance of synthesizing arsinophosphine **185a** from β -oxovinylarsine **182a** was best highlighted by the recent catalytic synthesis of 1,1-diphosphines reported by Webster.²⁹ With β -oxovinylarsines **182**, this challenging yet synthetically-useful transformation could now be extended to unsymmetrical 1,1-P,As ligands such as arsinophosphine **185a**. Narrow bite angle diphosphines have been used with great success as ligands in transition metal catalysis,³⁴ and the different bite angles of unsymmetrical 1,1-P,As ligands are expected to facilitate the rational modulation of catalytic activity.³⁵ In addition, the potential for the asymmetric synthesis of arsinophosphine **185a** (currently isolated as a racemate) may be further explored by using the chiral version of palladacycle **78**.

Secondly, neutral As–C bonds in β -oxovinylarsines **182/183** were proposed to be activated by transition metals as a handle for further functionalization.^{3a,b} Being a more

challenging substrate due to its potential to form an As,O-chelate, *cis*- β -oxovinylarsine **182a** was selected for preliminary investigations (Scheme 91). Elimination of the arsine moiety was

Scheme 91. Rh-catalyzed arylation on β -oxovinylarsines **182a**.

observed for β -oxovinylarsine **182a** under Rh-catalyzed arylation conditions,³⁶ furnishing *trans*-chalcone **75b** in 67% isolated yield. Even under unoptimized conditions, the chemoselectivity of Rh for the C–As bond in the highly-functionalized β -oxovinylarsine scaffold was promising in terms of subsequent methodology development. It remains to be seen if the formation of chalcone **75b** proceeded *via* an addition-elimination reaction involving initial arylation of arsine **182a** or the direct substitution of arsine **182a** (bypassing a saturated addition intermediate). On the other hand, trace amounts of arylation adducts were observed when Pd-catalyzed arylation conditions were applied (Scheme 92),^{32b} suggesting that arsines

Scheme 92. Pd-catalyzed arylation on β -oxovinylarsines **182a**.

derived from the alternative hydroarsination reaction could be generated 1) without the use of air-sensitive secondary arsines, and consequently, 2) without decomposition of the bidentate palladacycle catalyst.

Lastly, nucleophilicity of β -oxovinylarsine **182a** was investigated with prototypical electrophiles such as alkyl iodides (MeI, EtI and *i*PrI) and benzyl bromide. Nucleophilicity was poor and conversion was observed only in a large excess of MeI after preliminary optimization. While methylation of the As lone pair leading to the formation of arsonium salt **186** was expected (Scheme 93), it was unfortunate that attempts to isolate the methylated products

Scheme 93. Proposed formation of arsonium salt **186**.

were unsuccessful. A mixture of methylated products were observed with ^1H NMR spectroscopy under neat conditions (Figures 45 and 46)³⁷ whereas no conversion was observed

Figure 45. ^1H NMR spectrum of the methylation of β -oxovinylarsine **182a** in CDCl_3 .

Figure 46. ^{13}C NMR spectrum of the methylation of β -oxovinylarsine **182a** in CDCl_3 .

when a stoichiometric amount of MeI was used instead. It was concluded that some part of β -oxovinylarsine **182a** was nucleophilic at best, and certainly of lower reactivity than the other reactive sites demonstrated above in Schemes 90 and 91.

5.3 Conclusion

β -oxovinylarsines were furnished with excellent atom economy in the first synthetic application of the hydroarsination reaction. Incorporating an arsine motif into a recognizable organic backbone allowed β -oxovinylarsines to be handled as a benchtop reagent without any specialized techniques or equipment. *Cis*- and *trans*- β -oxovinylarsines were synthesized from the same substrate and both isomers were isolated without employing cumbersome physical separation methods. Notably, this was a result of the proposed arsine-carbonyl interaction which resulted in high *Z*-selectivity in the absence of any external stereochemical control. It remains to be seen if this phenomenon may be applied to the broader field of general synthetic chemistry where carbonyl functionalities are both widespread and well-established.

Both the synthesis and application of β -oxovinylarsines demonstrated excellent compliance with the 12 Design Principles of Green Chemistry. This was a notable improvement from the catalytic hydroarsination reaction in terms of re-designing chemicals to retain function while reducing toxicity. Coupled with the benefits of the hydroarsination reaction which was preserved during the synthesis of β -oxovinylarsines, subsequent applications fulfilled up to 8 out of the 12 design principles especially when β -oxovinylarsines were employed in catalytic asymmetric hydrofunctionalization (hydrophosphination) reactions. These preliminary developments suggest that further work should be undertaken to evaluate if β -oxovinylarsines are better than secondary arsines in terms of reactivity, versatility and reduced toxicity.

5.4 Experimental section

General information. All reactions were carried out under a positive pressure of nitrogen using standard Schlenk techniques. Solvents were purchased from their respective companies (ACN, MeOH, DCM: VWR Chemicals, DEE: Merck, toluene, n-hexane: Avantor, Acetone: Sigma-Aldrich, THF: Tedia) and distilled under an atmosphere of nitrogen prior to use. A Low Temp Pairstirrer PSL-1400 was used for controlling low temperature reactions. Column chromatography was done on Silica gel 60 (Merck). Melting points were measured using SRS Optimelt Automated Point System SRS MPA100. NMR spectra were recorded on Bruker AV 300, AV 400 and AV 500 spectrometers. Chemical shifts were reported in ppm and referenced to an internal SiMe₄ standard (0 ppm) for ¹H NMR, chloroform-d (77.23 ppm) for ¹³C NMR, and an external 85% H₃PO₄ for ³¹P{¹H} NMR.

The ynones **181**³⁸ and complex **78**³⁹ were prepared according to literature methods. All other reactants and reagents were used as supplied.

Caution! All the complexes described as perchlorate salts should be handled as potentially explosive compounds.

Synthesis of *cis*-β-oxovinylarsines **182a, **182b** and **182c** (Table 32).** HAsPh₂ (0.28 g, 1.2 mmol, 1.2 equiv.) was added to a solution of ynone **181** (1.0 mmol, 1.0 equiv.) in the stated solvent (18 mL). The solution was stirred at RT for 24 h. Volatiles were removed and the crude solution was purified by column chromatography (2 hexane : 1 DCM) to afford the pure *cis*-β-oxovinylarsines **182a**, **182b** and **182c** as yellow solids. *Cis*-β-oxovinylarsine **182a** was recrystallized from DCM/EA.

182a. Yellow solid. 87% yield. Mp: 139.2-140.2°C. ¹H NMR (CDCl₃, 400 MHz): δ 8.02-8.00 (m, 2H, Ar), 7.96 (d, 1H, ³J_{HH} = 11.2 Hz, C(O)CCH), 7.67 (d, 1H, ³J_{HH} = 11.2 Hz, AsCCH), 7.60-7.55 (m, 1H, Ar), 7.50-7.46 (m, 6H, Ar), 7.34-7.31 (m, 6H, Ar); ¹³C NMR (CDCl₃, 100 MHz): δ 189.4 (1C, C(O)), 156.9 (s, 1C, C(O)CC), 142.3 (s, 1C), 137.5 (s, 1C), 133.9-133.1

(7C), 128.9-128.4 (10C). HRMS (+ESI) m/z : $(M + H)^+$ calcd for $C_{21}H_{18}AsO$, 361.0574; found, 361.0586. Anal. Calcd for $C_{21}H_{17}AsO$: C, 70.01; H, 4.76. Found: C, 69.79; H, 4.90%.

182b. Yellow solid. 80% yield. Mp: 145.3-145.8°C. 1H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, 1H, $^3J_{HH} = 11.2$ Hz, $C(O)CCH$), 7.90-7.88 (m, 1H, Ar), 7.60 (d, 1H, $^3J_{HH} = 11.2$ Hz, $AsCCH$), 7.45-7.43 (m, 4H, Ar), 7.31-7.24 (m, 8H, Ar), 2.40 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.0 (1C, $C(O)$), 156.2 (s, 1C, $C(O)CC$), 144.2 (s, 1C), 142.5 (s, 1C), 135.1-133.1 (7C), 129.6-128.3 (10C), 21.9 (s, 1C, CH_3). HRMS (+ESI) m/z : $(M + H)^+$ calcd for $C_{22}H_{20}AsO$, 375.0730; found, 375.0714. Anal. Calcd for $C_{22}H_{19}AsO$: C, 70.59; H, 5.12. Found: C, 70.14; H, 4.96%.

182c. Yellow solid. 82% yield. Mp: 158.8-159.2°C. 1H NMR ($CDCl_3$, 400 MHz): δ 7.94-7.91 (m, 2H, Ar), 7.89 (d, 1H, $^3J_{HH} = 11.3$ Hz, $C(O)CCH$), 7.69 (d, 1H, $^3J_{HH} = 11.3$ Hz, $AsCCH$), 7.46-7.43 (m, 6H, Ar), 7.34-7.30 (m, 6H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.2 (1C, $C(O)$), 157.8 (s, 1C, $C(O)CC$), 142.2 (s, 1C), 139.8 (s, 1C), 135.9 (s, 1C), 133.5-133.1 (6C), 130.2-128.5 (10C). HRMS (+ESI) m/z : $(M + H)^+$ calcd for $C_{21}H_{17}As^{37}ClO$, 397.0154; found, 397.0161; calcd for $C_{21}H_{17}As^{35}ClO$, 395.0184; found, 395.0181. Anal. Calcd for $C_{21}H_{16}AsClO$: C, 63.90; H, 4.09. Found: C, 64.15; H, 3.89%.

Synthesis of *trans*- β -oxovinylarsine **183 (Scheme 89).** $HAsPh_2$ (0.23 g, 1.0 mmol, 1.0 equiv.) was added to a solution of iodide **184** (0.26 g, 1.0 mmol, 1.0 equiv.) in MeOH (23 mL). CsF (1.51 g, 10.0 mmol, 10.0 equiv.) was subsequently added and the solution was stirred at RT for 24 h. Volatiles were removed and the crude solution was redissolved in DCM (15 mL). The organic layer was washed with H_2O (3 X 15 mL), dried over $MgSO_4$, then concentrated to give a yellow oil. The crude oil was purified by column chromatography (1 hexane : 1 DCM) to afford *trans*- β -oxovinylarsine **183** as a pale yellow oil in 62% yield. 1H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, 1H, $^3J_{HH} = 16.9$ Hz, $C(O)CCH$), 7.89- 7.86 (m, 2H, Ar), 7.57-7.54 (m, 1H, Ar), 7.49-7.43 (m, 6H, Ar), 7.39-7.37 (m, 6H, Ar), 7.19 (d, 1H, $^3J_{HH} = 16.9$ Hz, $AsCCH$); ^{13}C

NMR (CDCl₃, 100 MHz): δ 189.0 (1C, C(O)), 151.3 (s, 1C, C(O)CC), 138.7 (s, 1C), 137.6 (s, 1C), 136.6 (s, 1C), 133.8 (s, 4C), 133.2 (s, 2C), 129.2 (s, 6C), 129.0 (s, 2C), 238.8 (s, 2C). HRMS (+ESI) m/z: (M + H)⁺ calcd for C₂₁H₁₈AsO, 361.0574; found, 361.0579.

Synthesis of vinyliodide 184 (Scheme 89). Ynone **181a** (0.13 g, 1.0 mmol, 1.0 equiv.) and NaI (0.15 g, 1.0 mmol, 1.0 equiv.) were stirred in trifluoroacetic acid (4 mL) at RT for 30 mins. The solution was diluted with H₂O (15 mL) and solid K₂CO₃ was added until no more evolution of CO₂ (g) was observed. The solution was extracted with DEE (3 X 15 mL) and organic layers were combined, dried over MgSO₄ and concentrated. Column chromatography (1 hexane : 1 DCM) afforded vinyliodide **184** as a colourless oil which was directly used for the subsequent synthesis of *trans*- β -oxovinylarsine **183**.⁴⁰

Synthesis of arsinophosphine 185a (Scheme 90). Catalyst **78** (1.25 mg, 2.0 nmol, 5 mol %) was added to a solution of HPPH₂ (20.4 mg, 0.11 mmol, 1.1 equiv.) in toluene (1.7 mL). Subsequently, *cis*- β -oxovinylarsine **182a** (36.0 mg, 0.10 mmol, 1.0 equiv.) and NEt₃ (15.3 μ L, 0.11 mmol, 1.1 equiv.) were added and the solution was stirred at RT for 2 h. The solution was concentrated and arsinophosphine **185a** was crystallized from DCM/EtOH under an atmosphere of N₂ (g). Isolation of the air-sensitive arsinophosphine **185a** was unsuccessful due to the observed co-crystallization of 1,1-diphosphine **185b** after repeated attempts.

Rh-catalyzed arylation of *cis*- β -oxovinylarsine 182a (Scheme 91). *Cis*- β -oxovinylarsine **182a** (36.0 mg, 0.10 mmol, 1.0 equiv.), phenylboronic acid (24.4 mg, 0.2 mmol, 2.0 equiv.) and [RhCl(cod)]₂ (6.16 mg, 5.0 nmol, 5 mol %) were dissolved in THF (1 mL). Following which, a solution of K₂CO₃ in H₂O (0.15 mM, 130 μ L, 20 mol %) was added and the mixture was stirred at 50°C for 15 h. The crude was filtered through short pad of silica and concentrated. The crude was purified by column chromatography (1 hexane : 1 DCM) to afford *trans*-chalcone **75b** as an off-white solid in 67% yield. The spectroscopic data obtained was consistent with literature.⁴¹

Pd-catalyzed arylation of β -oxovinylarsine **182a (Scheme 92).** Catalyst **78** (0.24 mg, 0.25 nmol, 2.5 mol %), triphenylphosphine (0.13 mg, 0.5 nmol, 5 mol %) and K_3PO_4 (10.6 mg, 0.05 mmol, 0.5 equiv.) were dissolved in toluene (2 mL). Upon complete solvation, β -oxovinylarsine **182a** (36.0 mg, 0.10 mmol, 1.0 equiv.) and phenylboronic acid (61.0 mg, 0.5 mmol, 5.0 equiv.) were added and the mixture was stirred at RT for 16 h. Volatiles were removed and the crude was redissolved in $CDCl_3$ (0.6 mL) for 1H NMR spectroscopy. Insignificant amounts of arsine **142b** was observed from the crude with 1H NMR spectroscopy when compared to data from Chapter 2.

Reaction of β -oxovinylarsine **182a with MeI (Scheme 93).** β -oxovinylarsine **182a** (8.7 mg, 24.1 nmol, 1 equiv.) was dissolved and stirred in MeI (0.7 mL) at RT for 16 h. The solution was dried and redissolved in $CDCl_3$ (0.6 mL) for 1H and ^{13}C NMR spectroscopy.

References

- [1] (a) Gregson, A. M.; Wales, S. M.; Bailey, S. J.; Keller, P. A. *J. Organomet. Chem.* **2015**, 785, 77, (b) Wada, M.; Natsume, S.; Suzuki, S.; Uo, A.; Nakamura, M.; Hayase, S.; Erabi, T. *J. Organomet. Chem.* **1997**, 548, 223, (c) Blicke, F. F.; Smith, F. D. *J. Am. Chem. Soc.* **1929**, 51, 1558, (d) Blicke, F. F.; Smith, F. D. *J. Am. Chem. Soc.* **1929**, 51, 3479, (e) Blicke, F. F.; Cataline, E. L. *J. Am. Chem. Soc.* 1938, **60**, 419.
- [2] (a) Tanaka, S.; Imoto, H.; Kato, T.; Naka, K. *Dalton Trans.* **2016**, 45, 7937, (b) Nakahashi, A.; Naka, K.; Chujo, Y. *Organometallics* **2007**, 26, 1827, (c) Arita, M.; Naka, K.; Morisaki, Y.; Nakahashi, A.; Chujo, Y. *Organometallics* **2009**, 28, 6109, (d) Ishidoshiro, M.; Matsumura, Y.; Imoto, H.; Irie, Y.; Kato, T.; Watase, S.; Matsukawa, K.; Inagi, S.; Tomita, I.; Naka, K. *Org. Lett.* **2015**, 17, 4854, (e) Kato, T.; Tanaka, S.; Naka, K. *Chem. Lett.* **2015**, 44, 1476.
- [3] (a) Kwong, F. Y.; Lai, C. W.; Yu, M.; Tan, D.-M.; Lam, F. L.; Chan, A. S. C.; Chan, K. S. *Organometallics* **2005**, 24, 4170, (b) Kwong, F. Y.; Lai, C. W.; Chan, K. S. *J. Am. Chem. Soc.* **2001**, 123, 8864, (c) Yao, W.; Ma, M.; Wang, W.; Cheng, J.; Xu, L.; Pullarkat, S. A.; Leung, P.-H. *Tetrahedron: Asymmetry* **2014**, 25, 1100.
- [4] (a) Werner, H. *Angew. Chem. Int. Ed.* **2004**, 43, 938, (b) Mohr, F.; Priver, S. H.; Bhargava, S. K.; Bennett, M. A. *Coord. Chem. Rev.* **2006**, 250, 1851, (c) Lu, D.; Salem, G. *Coord. Chem. Rev.* **2013**, 257, 1026, (d) Burt, J.; Levason, W.; Reid, G. *Coord. Chem. Rev.* **2014**, 260, 65, (e) Roodt, A.; Otto S.; Steyl, G. *Coord. Chem. Rev.* **2003**, 245, 121.
- [5] Williams, J. O. *Angew. Chem. Int. Ed.* **1989**, 28, 1110.
- [6] Bencko, V.; Foong, Y. L. *Ann. Agric. Environ. Med.* **2017**, 24, 312.
- [7] Lu, D.; Coote, M. L.; Ho, J. Kilah, N. L.; Lin, C.-Y.; Salem, G.; Weir, M.L.; Willis, A. C.; Wild, S. B.; Dilda, P. J. *Organometallics* **2012**, 31, 1808.
- [8] (a) Dube, J. W.; Zheng, Y.; Thiel, W.; Alcarazo, M. *J. Am. Chem. Soc.* **2016**, 138, 6869, (b) Quinteros, G. J.; Uberman, P. M.; Martín, S. E. *Eur. J. Org. Chem.* **2015**, 2698, (c) Bedford,

- R. B.; Betham, M.; Bruce, D. W.; Danopoulos, A. A.; Frost, R. M.; Hird, M. *J. Org. Chem.* **2006**, *71*, 1104.
- [9] Wang, P.; Liu, C.-R.; Sun, X.-L.; Chen, S.-S.; Li, J.-F.; Xie, Z.; Tang, Y. *Chem. Commun.* **2012**, *48*, 290.
- [10] (a) Ren, Z.; Cao, W.; Ding, W.; Wang, Y. *Synthesis* **2005**, *16*, 2718, (b) He, H. S.; Chung, C. W. Y.; But, T. Y. S.; Toy, P. H. *Tetrahedron* **2005**, *61*, 1385, (c) Huang, Y.; Shen, Y. *Adv. Organomet. Chem.* **1982**, *20*, 115, (d) Gosney, I.; Lillie, T. J.; Lloyd, D. *Angew. Chem. Int. Ed.* **1977**, *16*, 487.
- [11] (a) Lalwani, N.; Chen, Y.-S.; Brooke, G.; Cross, N. A.; Allen, D. W.; Reynolds, A.; Ojeda, J.; Tizzard, G. J.; Coles, S. J.; Bricklebank, N. *Chem. Commun.* **2015**, *51*, 4109, (b) Picquet, E.; Ny, K. L.; Delépine, P.; Montier, T.; Yaouanc, J.-J.; Cartier, D.; des Abbayes, H.; Férec, C.; Clément, J.-C. *Bioconjugate Chem.* **2005**, *16*, 1051, (c) Gall, T. L.; Loizeau, D.; Picquet, E.; Carmoy, N.; Yaouanc, J.-J.; Burel-Deschamps, L.; Delépine, P.; Giamarchi, P.; Jaffrès, P.-A.; Lehn, P.; Montier, T. *J. Med. Chem.* **2010**, *53*, 1496, (d) Wang, J.; Yang, C.-T.; Kim, Y.-S.; Sreerama, S. G.; Cao, Q.; Li, Z.-B.; He, Z.; Chen, X.; Liu, S. *J. Med. Chem.* **2007**, *50*, 5057.
- [12] Hoyle, A. T.; Davoren, J. E.; Wipf, P.; Fink, M. P.; Kagan, V. E. *Acc. Chem. Res.* **2008**, *41*, 87.
- [13] (a) Benz, S.; Poblador-Bahamonde, A. I.; Low-Ders, N.; Matile, S. *Angew. Chem. Int. Ed.* **2018**, *57*, 5408, (b) Emerson, K.; Britton, D. *Acta Cryst.* **1963**, *16*, 113.
- [14] Bauzá, A.; Mooibroek, T. J.; Frontera, A. *ChemPhysChem* **2015**, *16*, 2496.
- [15] Roering, A. J.; Davidson, J. J.; MacMillan, S. N. ; Tanski, J. M.; Waterman, R. *Dalton Trans.* **2008**, 4488.
- [16] (a) Mueller, A. J.; Jennings, M. P. *Org. Lett.* **2007**, *9*, 5327, (b) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669, (c) Grossman, R. B.; Comesse, S.; Rasne, R. M.; Hattori, K.; Delong,

- M. N. *J. Org. Chem.* **2003**, 68, 871, (d) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, 122, 7252.
- [17] Wang, Z.; Chen, Z.; Bai, S.; Li, W.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2012**, 51, 2776.
- [18] Misaki, T.; Kawano, K.; Sugimura, T. *J. Am. Chem. Soc.* **2011**, 133, 5695.
- [19] Zhang, J.; Li, X. *Chem. Phys. Lett.* **2019**, 735, 136767.
- [20] Mantina, M.; Chamberlin, A. C.; Valero, R.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. A.* **2009**, 113, 5806.
- [21] Fleming, I. *Molecular Orbitals and the Structures of Organic Molecules, Reference Edition*. 2010 John Wiley & Sons, Ltd, **2010**.
- [22] (a) Bowden, K.; Price, M. J. *J. Chem. Soc. (B)* **1970**, 1466, (b) Winterfeldt, E. *Angew. Chem. Int. Ed.* **1967**, 6, 423, (c) Truce, W. E.; Klein, H. G.; Kruse, R. B. *J. Am. Chem. Soc.* **1961**, 83, 4636, and references therein.
- [23] Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehadeh, S.; Dunn, P. *J. Green Chem.* **2016**, 18, 288.
- [24] For selected examples, see (a) Chen, Z.; Furutachi, M.; Kato, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2009**, 48, 2218, (b) Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, 126, 5672.
- [25] Feray, L.; Perfetti, P.; Bertrand, M. P. *Synlett* **2009**, 1, 89.
- [26] For an overview of enaminones, see (a) Lue, P.; Greenhill, J. V. *Adv. Heterocycl. Chem.* **1996**, 67, 207, (b) Elassar, A.-Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, 59, 8463.
- [27] It must be noted that the presence of energetically-available d orbitals in As (and absence thereof in N) cannot be used to directly explain differences in the chemical bonding of β -oxovinylarsines and enaminones. (a) Zhao, L.; Pan, S.; Holzmann, N.; Schwerdtfeger, P.; Frenking, G. *Chem. Rev.* **2019**, 119, 8781, (b) von Szentpály, L.; Schwerdtfeger, P. *Chem. Phys.*

Lett. **1990**, *170*, 555, (c) Kaupp, M.; Schleyer, P. V. R.; Stoll, H.; Preuss, H. *J. Am. Chem. Soc.* **1991**, *113*, 6012.

[28] (a) Raslan, M. A.; Omran, O. A. *J. Heterocycl. Chem.* **2016**, *53*, 1121, (b) El-Hameed Hassan, A. A. *Int. J. Org. Chem.* **2014**, *4*, 68.

[29] Coles, N. T.; Mahon, M. F.; Webster, R. L. *Chem. Commun.* **2018**, *54*, 10443.

[30] Yeo, W.-C.; Vittal, J. J.; White, A. J. P.; Williams, D. J.; Leung, P.-H. *Organometallics* **2001**, *20*, 2167.

[31] (a) Wilson, J. E.; Fu, G. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1426, (b) Ni, H.; Chan, W.-L.; Lu, Y. *Chem. Rev.* **2018**, *118*, 9344.

[32] For selected examples of palladacycle **78** as a chiral catalyst, see (a) Huang, Y.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. *Inorg. Chem.* **2012**, *51*, 2533, (b) Wong, J.; Gan, K.; Chen, H. J.; Pullarkat, S. A. *Adv. Synth. Catal.* **2014**, *356*, 3391, (c) Yang, X.-Y.; Jia, Y.-X.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Dalton Trans.* **2016**, *45*, 13449, (d) Huang, Y.; Li, Y.; Leung, P.-H.; Hayashi, T. *J. Am. Chem. Soc.* **2014**, *136*, 4865, (e) Sadeer, A.; Ong, Y. J.; Kojima, T.; Foo, C. Q.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Chem. Asian J.* **2018**, *13*, 2829.

[33] Migratory scrambling of E–C (E = P, As) bonds have been reported, although no satisfactory explanation has been offered to date. Gupta, A. K.; Green, J. P.; Orthaber, A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2019**, *194*, 967.

[34] For instances of 1,1-diphosphines as ligands in catalysis, see (a) Grutters, M. M. P.; Müller, C.; Vogt, D. *J. Am. Chem. Soc.* **2006**, *128*, 7414, (b) Chaplin, A. B.; Hooper, J. F.; Weller, A. S.; Willis, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 4885, (c) Pernik, I.; Hooper, J. F.; Chaplin, A. B.; Weller, A. S.; Willis, M. C. *ACS Catal.* **2012**, *2*, 2779, (d) Murphy, S. K.; Bruch, A.; Dong, V. M. *Chem. Sci.* **2015**, *6*, 174, (e) Gridnev, I. D.; Liu, Y.; Imamoto, T. *ACS Catal.* **2014**, *4*, 203, (f) Cybulski, M. K.; Nicholls, J. E.; Lowe, J. P.; Mahon, M. F.; Whittlesey, M. K. *Organometallics* **2017**, *36*, 2308.

- [35] 1,1-P,As bidentate ligands are expected to possess significantly different bite angles from their 1,1-diphosphine analogues because of different hybridizations of the P and As atoms. See Chapter 3 for the discussion on hybridization of E(III) (E = P, As) atoms.
- [36] For an overview of Rh-catalyzed arylations, see (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169, (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.
- [37] Scrambling and elimination of the arsonium intermediate could have given rise to the observed mixture of methylated products. (a) Mann, F. G.; Baker, F. C. *J. Chem. Soc.* **1952**, 4142, (b) Jones, E. R. H.; Mann, F. G. *J. Chem. Soc.* **1955**, 411.
- [38] Wang, Z.; Shi Y.; Luo, X.; Han, D.-M.; Deng, W.-P. *New J. Chem.* **2013**, *37*, 1742.
- [39] (a) Ng, J. K.-P.; Tan, G.-K.; Vittal, J. J.; Leung, P.-H. *Inorg. Chem.* **2003**, *42*, 7674, (b) Huang, Y.; Chew, R. J.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Org. Lett.* **2011**, *13*, 5862.
- [40] (a) Taniguchi, M.; Kobayashi, S.; Nakagawa, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986** *27*, 4763, (b) Fischer, G. W.; Schneider, P. *Chem. Ber.* **1973**, *106*, 435.
- [41] Schmink, J. R.; Holcomb, J. L.; Leadbeater, N. E. *Org. Lett.* **2009**, *11*, 365.

Chapter 6

Conclusion and Future Work

6.1 Evaluating the hydroarsination reaction

As mentioned in Chapter 1, the toxicity and speciation of arsenic compounds has played an influential role in directing progress in the field. This thesis summarizes the work conducted to minimize the impact of arsenic on human health and the environment during certain synthetic protocols involving arsenic species. The catalytic asymmetric hydroarsination reaction was identified as a suitable avenue for exploration after a thorough review of various arsenic bond formation strategies. Inspired by the well-established hydrophosphination reaction, various catalytic systems were designed and evaluated for their efficacy at promoting C–As bond formation. The 12 Design Principles of Green Chemistry was also adopted as a metric to evaluate the overall impact of the synthetic protocols on the environment.¹

Key parameters of the developed catalytic systems are summarized in Table 33. The

Table 33. Overview of conditions for the catalytic hydroarsination reactions under optimized conditions.

	Pd-catalyzed	Ni-catalyzed	Phosphine-catalyzed
Solvent	EtOH	MeOH/H ₂ O (10%)	DCM
Temperature	RT	-20°C to RT	35°C
Highest yield and <i>ee</i>	91% yield, 85% <i>ee</i>	95% yield, 80% <i>ee</i>	99% yield, ND <i>ee</i>
Reaction time	24 h	<5 mins to 24 h	24 to 48 h
Catalyst loading	5 mol %	2 mol %	30 mol %
Arsine activation mode	(<i>R,R</i>)- 87b'	(<i>R,R</i>)- 97a'	170'
Byproduct formation	143	Nil	171

palladium, nickel and organophosphine catalytic systems offered complementary options for C–As bond formation under different conditions. Modifying the analogous palladium-

catalyzed hydrophosphination methodology led to the first successful attempt at the corresponding hydroarsination reaction. Subsequently, nickel catalysis was observed to minimize byproduct formation, boost turnover numbers and increase the overall rate of reaction. Lastly, tertiary phosphine organocatalysts brought about a significant improvement in terms of solvent compatibility but was limited by poor reactivity and substrate scope. Secondary contributions to arsenic chemistry discovered over the course of methodology development have also been highlighted in the following subsections accordingly.

6.1.1 Pd-catalyzed hydroarsination reactions

Up to 91% yield and 85% *ee* were obtained in the hydroarsination of *trans*-chalcones **75** catalyzed by PCP-PdCl pincer complex **87b** (Scheme 94). While it was gratifying that the

Scheme 94. Pd-catalyzed hydroarsination of enones **75**.

reaction proceeded with good stereoselectivity at room temperature, no further improvement to *ee*'s was achievable because yields were adversely affected with a decrease in temperature. Three aspects were identified for further improvement: to 1) minimize the use of excess base (10.0 equiv. of CsF) and arsine (3.0 equiv. of HAsPh₂), 2) improve the tolerance for electron-rich substrates, and 3) expand the scope of compatible solvents beyond alcohols. Nevertheless, this being the first successful instance of the catalytic asymmetric hydroarsination reaction was a significant milestone in methodology development. 7 out of 12 of the design principles of green chemistry were also addressed as evidenced in Table 34.

Table 34. Evaluating against the 12 Design Principles of Green Chemistry.

Principle	Description	Evidence
2	Designing reactions towards 100% atom-economy	Catalytic addition reaction with up to 100% product incorporation and catalyst regeneration (by design)
3	To use and generate the least toxic substances possible	The use of less-toxic secondary arsine reagents as opposed to arsenic halides
5	Minimizing the use of solvents and auxiliaries	Asymmetric catalysis avoiding the stoichiometric use of chiral auxiliaries
6	Minimizing energy requirements in terms of heat and pressure	Optimized conditions at room temperature and pressure
8	Reducing derivatives such as protecting/blocking groups	No competing transformation of the substrate
9	Using catalytic amounts of reagents	Catalytic loadings of chiral auxiliary employed
12	Choosing safer substance/conditions/processes for accident prevention	Secondary arsine of high molecular weight (HAsPh ₂) was selected as a model arsine reagent

Mechanistic investigations were conducted which led to complex **87b'** being identified as the key catalytic intermediate (Scheme 95). Three pathways were proposed for

Scheme 95. Generation of key intermediate **87b'**.

the formation of complex **87b'** and ³¹P{¹H} NMR experiments furnished evidence that an alcoholic environment was crucial in promoting the base-assisted equilibrium deprotonation of HAsPh₂. The reactive arsenide anion was proposed to displace the counteranion of PdCl complex **87b** upon closely monitoring a series of controlled experiments with ³¹P{¹H} NMR spectroscopy. Non-alcoholic solvents such as MeCN, DMSO, MeNO₂, DCM, THF, toluene

and hexane resulted in no conversion after 24 h and it was evident that new catalytic systems had to be developed to improve solvent compatibility.

Most notably, the process of adapting the Pd-catalyzed hydrophosphination methodology for hydroarsination led to the salient conclusion that secondary arsines were not direct substitutes for secondary phosphines. Comparing the proposed hydroarsination mechanism to existing hydrophosphination literature clearly rationalized the dependence on alcoholic solvents observed only in the former. In addition, typical hydrophosphination workup procedures largely led to the decomposition of hydroarsination adducts due to the relative stability of arsenic in the As(III) state. A summary of the various differences between the two reactions has been provided in Chapter 2.

Finally, the guiding research questions were satisfactorily answered from the experiments conducted. Hydroarsination reactions were somewhat accessible by adapting hydrophosphination methodologies, but care had to be taken in terms of reaction design and during workup. Electron-withdrawing substrates, polar protic solvents and higher arsine loadings were favourable adaptations to increase overall yields and stereoselectivities. Accidental product degradation upon employing unsuitable workup procedures may have also contributed to the delay in developing the palladium-catalyzed hydroarsination reaction.

6.1.2 Ni-catalyzed hydroarsination reactions

In a bid to improve mechanistic variety yet build on the insights derived from palladium catalysis, the third-row Group 10 metal Nickel was selected for investigation. Up to 95% yield and 80% *ee* was achieved from the hydroarsination of nitrostyrenes **127/151** catalyzed by PCP NiCl complex **97a** (Scheme 96). Notable improvements from the palladium-catalyzed protocol included lower catalyst and arsine loadings, faster reaction time and wider substrate scope. In a standalone evaluation, this methodology was also remarkable in terms of reaction times (<5 mins) and environmental cost (semi-aqueous solvent mixture). This led to

Scheme 96. PCP NiCl pincer-catalyzed hydroarsination of nitrostyrenes **127** and **151**.

another design principle addressed in addition to those previously realized with the palladium-catalyzed hydroarsination reaction (Table 35).

Table 35. Evaluating against the 12 Design Principles of Green Chemistry.

Principle	Description	Evidence
1	Preventing waste instead of cleaning up after it has been generated	External base not required, almost-stoichiometric arsine loadings employed

Due to the short reaction times (<5 mins), computational calculations were employed to provide insights regarding plausible mechanisms. A Ni-Cl-As interaction was identified in key intermediate **97a'** which was supported by empirical evidence (Scheme 97). Notably, the

Scheme 97. Generation of key intermediate **97a'**.

presence of free arsenide anions was required for the thermodynamically-favourable formation of intermediate **97a'**. It was determined that MeOH significantly decreased the $\Delta_r G$ of H-AsPh₂ bond dissociation and was therefore crucial in facilitating an overall exothermic reaction ($\Delta_r G = -10.9 \text{ kcal mol}^{-1}$). Observing a dependence on polar protic solvents again led to the first instance of considering non-negligible arsine-alcohol interactions (see section 6.2 for further discussion on the novel reactivity of arsines).

From the products of the Ni-catalyzed hydroarsination of nitrostyrenes, a library of structurally-analogous arsines and phosphines was also synthesized and subjected to X-ray crystallographic analysis. A systematic comparison of solid-state bond lengths and angles suggested that a lower degree of orbital hybridization was present in the lone pair of tertiary arsines. Computational calculations further reaffirmed the higher *s*-character of the arsine lone pair, in good agreement with the observed air-stability of tertiary arsine products of the hydroarsination reaction.

The guiding research questions raised in the introduction of Chapter 3 were definitively addressed. Firstly, mechanisms proposed for literature examples of Ni-catalyzed hydrophosphination reactions were not applicable to the hydroarsination reaction in this instance. These mechanisms were disproven after a series of ^1H and $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopic observations which highlighted the “same but different” aspect often encountered when dealing with phosphines and arsines. Secondly, nickel catalysis was unable to relieve the strong dependence of the hydroarsination reaction on alcoholic solvents despite intrinsic mechanistic differences from palladium. On hindsight, this phenomenon alluded briefly to the arsenic-oxygen interactions explored in Chapters 4 and 5.

6.1.3 Organocatalyzed hydroarsination reactions

Solvent compatibility in a wide range of solvents was eventually achieved with phosphine organocatalysis. Under optimized conditions, the hydroarsination of nitrostyrenes **127/151** catalyzed by tertiary phosphines **170** led to the isolation of arsine adducts in 49-99% yield (Scheme 98). On the other hand, phosphine organocatalysis fared poorer than transition

Scheme 98. Tertiary phosphine-catalyzed hydroarsination of nitrostyrenes.

metal-catalyzed variants for the hydroarsination reaction. Higher reaction temperature, longer reaction times and lower turnover numbers were observed when simple triarylphosphines were employed as catalyst.

A significant catalyst deactivation pathway was observed which was proposed to be a result of transitional species **170'** (Scheme 99). The interaction of the phosphine organocatalyst

Scheme 99. Generation of key intermediate **170'**.

with energetically low-lying LUMOs of As was proposed to concomitantly increase overall arsine nucleophilicity and heighten the susceptibility of phosphine **170** to oxidation. The directionality of the interaction (phosphine donor and arsine acceptor, not *vice versa*) was reaffirmed by the higher product yields observed when electron-rich triarylphosphines were employed as catalyst instead. Notably, species **170'** was generated in the absence of H–AsPh₂ bond dissociation which rationalized the compatibility of the hydroarsination reaction with non-polar protic solvents such as DCM, DEE, EA, THF, toluene, acetone and hexane. Nevertheless, this proposed mode of activating HAsPh₂ remains inconclusive in the absence of any physical evidence supporting the formation of species **170'**.

Asymmetric catalysis was not explored for phosphine-organocatalyzed hydroarsination because of the poor reactivity relative to transition metal-catalyzed variants. It remains to be seen if phosphine-activated secondary arsines may be applicable in nucleophilic reactions other than the addition of arsines to electron-deficient substrates. Clearly, organocatalysis was fundamentally different from transition metal-catalyzed hydroarsination

reactions in terms of arsine activation. In fact, the proposed mechanism did not resemble any literature examples of related organocatalyzed hydrophosphination or hydroamination reactions, thereby representing a noteworthy contribution to the field in terms of significance and novelty.

6.2 Novel reactivity of As(III)

Due to their group relationship, it is unsurprising that the reactivity of arsine is often regarded as an extension of that of phosphine. Collective evidence across the work done herein suggests otherwise. The unexpected decomplexation of bidentate palladacycles by HAsPh_2 presented in Chapter 2 was unprecedented considering the well-established use of palladacycles as catalysts for the hydrophosphination reaction. Instead of H–As bond acidification, an alternative intramolecular insertion of the H–As bond led to protonation and decomplexation of the anionic carbon ligand (Scheme 100). This quantitative transformation

Scheme 100. Decomplexation of bidentate palladacycles by protonation.

proceeded rapidly for monomeric and dimeric complexes of various ligand steric bulks and even for weakly-coordinated complexes bearing tridentate pincer ligands. Proof-of-concept experiments suggested that such unprecedented reactivity of arsines may be applicable in deuteration by directed *ortho*-metalation and decomplexation strategies. It may be interesting to note that such synthetic applications have never been conceived of secondary arsine (nor phosphine) reagents before and it remains to be seen if such main group chemistry can be routinely applied to general synthesis (see section 6.3 for future work).

Mechanistic investigation conducted for the hydroarsination reaction also highlighted several unexpected interaction modes (Figure 47). Interaction of an arsenide anion with a

Figure 47. Key interactions operative in the proposed hydroarsination mechanisms.

stable NiCl pincer complex **97a** led to the thermodynamically favourable formation of charged species **97a'** ($\Delta_r G = -46.6 \text{ kcal mol}^{-1}$). Molecular orbital surface plots for intermediate **97a'** suggest σ -type bonding between Ni–Cl and Cl–As, although it appeared that no delocalized bonding over the Ni–Cl–As motif was present. On the other hand, intermediate **170'** could not be observed spectroscopically despite our best efforts which suggested that the interaction between the phosphine lone pair and energetically low-lying LUMOs of arsenic could be essentially non-covalent in nature.² Unlike the undetermined directionality of the Cl–As interaction in intermediate **97a'**,³ catalyst screening involving phosphines of various electronic profiles led to the conclusion that the arsenic center was the electrophilic partner in this instance. This most closely resembled “pnictogen bonding”- an interaction involving σ/π -hole interactions originating from an anisotropic distribution of electron density around a main group atom.⁴ Such non-covalent bonding has only been observed for arsenic centers bearing highly electron-withdrawing substituents,^{4a,5} and computational studies were in agreement with the electronic nature of substituents required for such bonding.⁶

Non-negligible interactions were also apparent in subsequent developments involving the reactivity of secondary arsines in the presence of oxygen-bearing moieties such as alcohol and carbonyl groups. This was observed to interrupt intramolecular hydrogen bonding and facilitate enolate formation in the presence of weak tertiary amine bases (Scheme 101, Chapter

Scheme 101. Intramolecular Aldol addition facilitated by HAsPh₂.

4). Arsine-carbonyl interactions could also have contributed to the *Z*-selective formation of the thermodynamically-unfavourable β -oxovinylarsines **182** in the absence of any additives (Scheme 102, Chapter 5). Clearly, such arsine-oxygen interactions in the absence of strongly

Scheme 102. *Z*-selective synthesis of β -oxovinylarsine **182**.

electron-withdrawing substituents were of significant influence to various reaction outcomes. It also remains to be seen if similar interactions assisted the metal-free bond dissociation of H–AsPh₂ observed in Pd- and Ni-catalyzed hydroarsination reactions which were notably absent even for other polar (but non-protic) solvents such as THF.

6.3 Future work

Several leads generated in the interim were shelved as future work unless directly related to the hydroarsination reaction. These ideas have been compiled and presented as follows, each with supporting literature to substantiate the feasibility of the proposed work.

Application of non-covalent arsine interactions

As mentioned in Chapter 4, secondary arsines were observed to promote the use of weakly-basic tertiary amines in enolate generation. Further optimization could potentially lead to developing a general method to utilize tertiary amine bases in direct Aldol additions. Presently, weakly-basic tertiary amines are more commonplace in the preparation of boron enolates which incur additional purification and workup steps.⁷ An arsine-catalyzed Aldol

addition was proposed as a preliminary model to investigate the effect of arsine additives on enolate generation by tertiary amines (Scheme 103). A comprehensive screening of tertiary

Scheme 103. Proposed arsine-catalyzed Aldol addition involving tertiary amines.

amines with respect to their steric profile and basicity may be desirable to improve reaction times and yield. Reaction conditions such as temperature, solvent and concentration were also only briefly investigated in Chapter 4 and further optimization may be useful in elucidating key features of the reaction (such as potential side reactions and kinetics). Based on the tentative non-covalent arsine interactions presumed to be a significant aspect in enolate generation, screening arsines bearing substituents of various electronic characters may also offer insights regarding the nature of the pnictogen bonding. For instance, the depth of σ -holes (and corresponding binding strengths) has been reported to be easily modulated by varying the electron-withdrawing nature of the substituents.^{4a} As with cross-Aldol reactions, varying the substituents of the ketone and aldehyde partners may be required to maximize the cross-Aldol efficiency. Lastly, while initial investigations involve stoichiometric loadings of base, reducing base loadings to catalytic quantities is also ideal to maximize efficiency and lower reagent wastage and overall cost of the reaction.⁸

Non-covalent interactions may also be useful in the application of chiral arsines as organocatalysts. As an extension of the Aldol reaction proposed, asymmetric variants can also be explored with chiral arsine products of the hydroarsination reaction. Stoichiometric amounts of chiral boron reagents derived from menthone and isopinocampheol have been effective at conferring high stereoselectivity to Aldol additions *via* covalently-bonded boron enolates **190** and **191** (Figure 48).⁹ On the other hand, non-covalent interactions have been exploited by phosphoramidate catalysts in the Mukaiyama Aldol reaction although this required an additional

Figure 48. Existing and proposed chiral organocatalysts for the Aldol reaction.

step in pre-forming the silyl enol ether **192**.¹⁰ Non-covalent chiral arsine organocatalysts would offer a notable edge in terms of atom economy (over the stoichiometric use of chiral boron reagents) and synthetic convenience (compared to the need for pre-formed silyl enol ethers). Despite the transient nature of the arsine-enolate interaction surmised in Chapter 4, potential for effective asymmetric induction arguably exists based on several successful examples of stereoselectivity directed by non-covalent interactions (such as in asymmetric counteranion-directed catalysis).¹¹ Indeed, the arsine-mediated synthesis of the thermodynamically less-favoured *Z*-isomer reported in Chapter 5 suggest that such non-covalent interactions may possess untapped synthetic utility. C*-chiral arsines **142a** and **150a** have been selected for preliminary screening on account of their high enantio-enrichment derived directly from catalysis. Prior to routine application as asymmetric catalysts, optical resolution of the enantioenriched arsines **142a** and **150a** will have to be conducted by diastereomeric separation since slow recrystallization only yielded racemic crystals after repeated attempts.

Application of arsines in organometallic chemistry

Protecting groups, while well-established in organic chemistry, is sparingly featured in organometallic chemistry. Varying the choice of ligand and an astute control of reaction conditions are more commonly utilized to favour a desired reaction pathway although such strategies require precise and delicate control over the reaction environment. Deuterium as a

protecting group for carbon has been applied in organic synthesis to acidic protons (eg. in amides and carbamates) under strongly basic conditions (eg. *t*BuLi, then quenching with D₂O).¹² Herein, the use of secondary arsines as an effective deuterium shuttle is proposed to increase the applicability of deuterium protecting groups in organometallic chemistry. The decomplexation of palladacycles by deuterated secondary arsines reported in Chapter 2 was remarkably mild, rapid and facile, affording the deuterated preligands within 30 mins at room temperature. The quantitative decomplexation was exceptionally advantageous since loss in overall yield is often cited as a main drawback in protection-deprotection strategies. Coupled with the ubiquitous nature of palladacycle intermediates in modern organometallic chemistry, this deuteration-decomplexation strategy could potentially offer solutions to existing problems in literature. For example, palladation resulted in the formation of bimetallic NCE-Pd pincer complex **105** instead of the less-favourable 6-membered bicyclic ECE-Pd complex **195** (Scheme 104).¹³ Subjecting bimetallic NCE-Pd complex **105** to an excess of deuterated

Scheme 104. Proposed deuterium protection leading to palladation at alternative site.

secondary arsines could potentially afford the protected preligand **194**, thereby promoting formation of the desired ECE-Pd complex **195** upon exploiting the kinetic isotope effect.¹⁴ If required, reinstalling the original C–H bond should also be feasible through another

cyclopalladated intermediate derived from C–D bond activation in the presence of excess protonated secondary arsines.

Deuteration leading to rapid decomplexation of palladacycles may also be relevant in advancing current efforts in palladium-catalyzed deuteration. Only two examples exist to date, both featuring specially-designed palladacycles to combat the difficulty of deutrating strongly-coordinated palladacycles under acidic conditions.¹⁵ Azapalladacycle **196** was an example of such a “strongly-coordinating palladacycle” which resisted protonation (deuteration) even when stirred in acetic acid at 120°C (Scheme 105).^{15a} The ability of

Scheme 105. Proposed deuteration of strongly-coordinated palladacycle **196**.

secondary arsines to rapidly afford phosphapalladacycle preligands, arguably more strongly-coordinating than amine ligands, suggest that secondary arsines may significantly broaden the scope of palladacycle intermediates compatible with Pd-catalyzed deuteration. As a proof of concept, secondary arsines can first be investigated with azapalladacycle **196** to determine if deuteration can indeed occur more rapidly under milder (room temperature, neutral environment) conditions (Scheme 104). Subsequently, catalytic loadings of palladium can be introduced with a focus on catalytic efficiency and turnover numbers (Scheme 106). Reagents

Scheme 106. Proposed catalytic deuteration with DAsPh₂.

for in-situ palladation (Pd(OAc)₂ and Na₂CO₃) were adapted from existing literature whereas the deuterium source and reaction conditions reflected the optimized conditions reported in Chapter 2.^{15a} It may be worth noting that a liberating agent (S₈) was required under

stoichiometric conditions and no free phosphine preligand was previously observed in the absence of S₈. Deuteration under catalytic conditions may assist palladium turnover by ligand displacement, thereby driving the catalytic cycle forward. Optimization is likely to be required for more challenging substrates with both *ortho* positions available for deuteration (Scheme 106).¹⁶ The Pd-catalyzed formation of tetraphenyldiarsine may also be observed (see control reactions conducted in Chapter 2) and loadings of the secondary arsine reagent should be modified accordingly. It remains to be seen if primary arsines bearing two As–D bonds can function as atom-economical alternatives to secondary arsines- although their lower molecular weights present a larger safety hazard due to their increased volatility.

Fine-tuning the synthesis of chiral arsines *via* addition methodologies

The phosphine-organocatalyzed hydroarsination methodology presented in Chapter 4 was a promising avenue for a general strategy featuring good solvent compatibility. Unfortunately, progress was hindered by low turnover numbers which was attributed to catalyst oxidation. Several new phosphine scaffolds **201–205** were identified for exploration on account of their exceptional air-stability arising out of unusually high SOMO energy levels (Scheme 107).¹⁷ It was suggested that phosphine radical cation intermediates (derived from reacting with

Scheme 107. Proposed catalyst screening for phosphine-organocatalyzed hydroarsination of nitrostyrenes.

elemental oxygen) bearing SOMOs of lower stabilities would be less reactive, thereby conferring oxidative resistance.¹⁸ While oxidation by elemental oxygen has been definitively

ruled out for the phosphine-organocatalyzed hydroarsination reaction, radical pathways remain a possibility. Catalyst screening involving phosphines **201-205** can be monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy to conveniently determine their susceptibility to arsine-mediated oxidation. Importantly, air-stable primary phosphines **201-205** arguably offers comparable synthetic convenience to triarylphosphine catalysts by bypassing the need for inert environments (particularly during the weighing of small catalyst quantities). Primary phosphines **201-205** may even offer an edge over triarylphosphines for their increased nucleophilicities, although a competing addition of the secondary phosphine to the activated olefin substrate (hydrophosphination) may occur. If desired, triaryl analogues of primary phosphines **201-205** can also be prepared by base-assisted $\text{P}-\text{C}_{\text{Ar}}$ bond formation to minimize side reactions and increase the steric bulkiness around the reaction site.¹⁹

Aside from hydroarsination reactions, other addition methodologies can be as favourable for the synthesis of arsenic compounds in terms of atom economy. Electrophilic β -oxovinylarsines **182/183** developed in Chapter 5 offer an excellent avenue for a myriad of reactions to the activated olefin moiety. For instance, the hydrophosphination of β -oxovinylarsine **182** yielding 1,2-arsinophosphine **185a** was attractive for its ability to furnish mixed P,As narrow bite angle ligands (Scheme 108).²⁰ Since the reaction was previously

Scheme 108. Proposed catalytic asymmetric hydrophosphination of β -oxovinylarsine **182/183**.

conducted only as a probe for electrophilicity, several shortfalls remain to be addressed. Firstly, the undesired formation of 1,1-diphosphine **185b** was observed to affect product purification

and overall yield. Catalyst screening (starting with well-established hydrophosphination catalysts **70**, **78**, **87a** and **104b**) and condition optimization may suppress such side reactions and even offer insights for key catalytic processes. It may be worth noting that tridentate pincer complexes such as **87a** and **104b** may be more resistant to catalyst poisoning in the presence of potentially chelating products. Secondly, workup procedures have yet to be developed for 1,2-arsinophosphine **185a**. Phosphine oxidation and C–As bond instability made column chromatography unsuitable for purifying the crude product mixture. Previous attempts to protect the phosphine by sulfurization led to product decomposition; phosphine protection was also arguably unfavourable for the application of 1,2-arsinophosphines **185a** as ligands. A one-pot coordination of the crude 1,2-arsinophosphines **185a** could be explored in light of successful precedents in purifying the organometallic derivative instead.²¹ Finally, achieving excellent stereoselectivity remains a critical yet elusive aspect of asymmetric catalysis. Determining the absolute product configuration, a sizable substrate scope and consistently-isolable products also pose additional hurdles before the hydrophosphination of β -oxovinylarsines **182/183** can be regarded as a viable methodology for the synthesis of chiral narrow bite angle arsinophosphines.

Lastly, it must be highlighted that β -oxovinylarsines **182/183** are not limited to hydrofunctionalization reactions at the activated C=C bond. Annulation reactions such as the [3+2] cycloaddition of allene **206** to β -oxovinylarsines **182/183** can be an alternative addition strategy as well (Scheme 109).²² This reaction was not previously explored due to the lack of suitable alternatives to the highly air-sensitive trialkylphosphine (*R*)-**208**. Expected annulation

Scheme 109. Proposed asymmetric [3+2] cycloaddition of allene **206** with β -oxovinylarsine **183**.

products **207** were particularly reminiscent of the cyclopentene-based hydroxyphosphine **179** presented in Chapter 4 which may be of value as structurally-rigid chiral arsine organocatalysts in future applications.

Miscellaneous

Cyclopentene **179** was isolated and characterized in Chapter 5 but applications were not further pursued since it was deemed as out of the scope. The excellent potential of cyclopentene **179** as an organocatalyst was suggested by an excellent control over the formation of all three chiral centres, the presence of several functional groups and a low degree of conformational freedom. Several transformations were proposed for the highly-functionalized cyclopentene **179** to improve its viability in organocatalysis (Scheme 110).

Scheme 110. Proposed transformations of phosphine sulfide **179**.

Firstly, phosphonium salt **209** was identified as a versatile intermediate and could be generated by treating phosphine sulfide **179** with oxalyl chloride.²³ Basic hydrolysis of phosphonium salt **209** would then furnish the corresponding phosphine oxide **210**.²⁴ Alternatively, reductive conditions involving sodium borohydride could afford the protected phosphine borane **211**,²³

from which free phosphine **212** may be isolated upon deprotection with a variety of amines (eg. morpholine, piperidine, pyrrolidine, quinuclidine, DABCO).²⁵ NMR spectroscopy would be a convenient tool to monitor potential racemization by base-catalyzed tautomerization at the chiral enolate carbon of phosphine borane **211**. Lastly, quaternary phosphonium salt **213** could also be derived from intermediate **209** by the addition of a Grignard reagent.²⁶ The presence of multiple reactive sites in cyclopentene **179** meant that protecting groups were essential in these proposed transformations. Fortunately, protecting the alcohol (eg. with ethers) or ketone (eg. with ketals) moieties is unlikely to affect the adjacent chiral centres. In fact, the increase in steric bulk derived from ketal protection could even be beneficial for catalytic activity by shielding one face of the cyclopentene ring.

The catalytic activity of hydroxy-phosphine oxide **210** was proposed to be explored in the asymmetric reduction of ketimine **214** (Scheme 111). Bifunctional catalysts (*S*)-**216** and

Scheme 111. Proposed asymmetric reduction of ketimine **214** catalysed by cyclopentene **210**.

(*R*)-**217** have been employed for the same reaction with limited success in terms of stereoselectivity.²⁷ Cyclopentene **210** may be worth exploring for the structural diversity provided in comparison to the linear and axially-chiral scaffolds of catalysts **216** and **217**. As reported by Jones, the hydroxy group was proposed to serve as a Lewis acid in activating ketimine **214** whereas the phosphine oxide moiety functioned as a chiral directing group for the silane reducing agent. No comment was made on catalyst turnover numbers despite a potential deactivation pathway involving Si–O bond formation.

Secondly, free phosphine **212** may be applicable in asymmetric Michael additions upon converting the hydroxy moiety to a boronic ester, yielding compound **212'**. Phosphinoborane **220** was previously employed as a racemic catalyst for the addition of dimethylmalonate to enone **218** (Scheme 112).²⁸ This reaction was a suitable model in this

Scheme 112. Proposed asymmetric Michael addition catalysed by cyclopentene **212'**.

instance due to the presence of a chiral centre upon C–C bond formation. Control reactions conducted by Bourisson demonstrated a cooperative effect between the borane and phosphine groups in catalyst **220**, with activation of the substrate by the borane and nucleophilic addition to the 1,4-position promoted by the phosphine. Similar Lewis acidic and basic sites were identified in compound **212'** although the boronic ester was expected to be less Lewis acidic whereas the converse was expected of the Lewis basic alkylphosphine.

Lastly, quarternary phosphonium salt **213** may be relevant as a phase-transfer catalyst in the asymmetric aza-Henry reaction (Scheme 113). Phosphonium-thiourea catalysts **223** and

Scheme 113. Proposed asymmetric aza-Henry reaction catalysed by cyclopentene **213**.

224 were reported to furnish product **222** in high yields and *ee*'s as a result of dual hydrogen bonding involving the (thio)urea hydrogens and phosphonium moieties.²⁹ Consequently, the alcohol functionality of compound **213** was likely to be of greater significance than the ketone group which may allow the protected ketal derivative to be employed in catalysis as well.

References

- [1] Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998; p 30.
- [2] (a) Zhao, Y.; Cotellet, Y.; Sakai, N.; Matile, S. *J. Am. Chem. Soc.* **2016**, *138*, 4270, (b) Wagner, J. P.; Schreiner, P. R. *Angew. Chem. Int. Ed.* **2015**, *54*, 12274, (c) Lacour, J.; Moraleda, D. *Chem. Commun.* **2009**, 7073, (d) Mahlau, M.; List, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 518, (e) Brak, K.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2013**, *52*, 534, (f) Bulfield, D.; Huber, S. M. *Chem. Eur. J.* **2016**, *22*, 14434, (g) Cavallo, G.; Metrangolo, P.; Milani, R.; Pilati, T.; Priimagi, A.; Resnati, G.; Terraneo, G. *Chem. Rev.* **2016**, *116*, 2478.
- [3] Halogen bonding involving the electrophilic halogen and nucleophilic arsenide would be distinct from σ -hole interaction involving the electrophilic arsenide anti-bonding molecular orbital and the nucleophilic chloride lone pair, for instance.
- [4] (a) Benz, S.; Poblador-Bahamonde, A. I.; Low-Ders, N.; Matile, S. *Angew. Chem. Int. Ed.* **2018**, *57*, 5408, (b) Guan, L.; Mo, Y. *J. Phys. Chem. A.* **2014**, *118*, 8911, (c) Angarov, V.; Kozuch, S. *New. J. Chem.* **2018**, *42*, 1413.
- [5] Emerson, K.; Britton, D. *Acta Cryst.* **1963**, *16*, 113.
- [6] Schmauck, J.; Breugst, M. *Org. Biomol. Chem.* **2017**, *15*, 8037.
- [7] Abiko, A. Boron Enolate Chemistry. In *Boron Reagents in Synthesis*; ACS Symposium Series, Vol. 1236; American Chemical Society, 2016, Chapter 4, p 123.
- [8] (a) Gut, B.; Mlynarski, J. *Eur. J. Org. Chem.* **2015**, 5075, (b) Paradowska, J.; Rogozińska, M.; Mlynarski, J. *Tetrahedron Lett.* **2009**, *50*, 1639.
- [9] For selected examples, see (a) Gennari, C.; Moresca, D.; Vulpetti, A.; Pain, G. *Tetrahedron Lett.* **1994**, *35*, 4623, (b) Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997, (c) Paterson, I.; Florence, G. J. *Tetrahedron Lett.* **2000**, *41*, 6935.

- [10] (a) Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837, (b) Denmark, S. E.; Pham, S. M.; Stavenger, R. A.; Su, X.; Wong, K.-T.; Nishigaichi, Y. *J. Org. Chem.* **2006**, *71*, 3904, (c) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *Tetrahedron Lett.* **1998**, *54*, 10389.
- [11] (a) Mahlau, M.; List, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 518, (b) Alvim, H. G. O.; Pinheiro, D. L. J.; Carvalho-Silva, V. H.; Fioramonte, M.; Gozzo, F. C.; da Silva, W. A.; Amarante, G. W.; Neto, B. A. D. *J. Org. Chem.* **2018**, *83*, 12143, (c) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nature Chemistry* **2012**, *4*, 603.
- [12] (a) Clayden, J.; Pink, J. H.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1998**, *39*, 8377, (b) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34, (c) Ahmed, A.; Clayden, J.; Rowley, M. *Tetrahedron Lett.* **1998**, *39*, 6103.
- [13] Tay, W. S.; Yang, X.-Y.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *RSC Adv.* **2016**, *6*, 75951.
- [14] Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. *Science* **2004**, *305*, 495.
- [15] (a) Ma, S.; Villa, G.; Thuy-Boun, P. S.; Homs, A.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2014**, *53*, 734, (b) Xu, H.; Liu, M.; Li, L.-J.; Cao, Y.-F.; Yu, J.-Q.; Dai, H.-X. *Org. Lett.* **2019**, *21*, 4887.
- [16] (a) Peng, X.; Wang, W.; Jiang, C.; Sun, D.; Xu, Z.; Tung, C.-H. *Org. Lett.* **2014**, *16*, 5354, (b) Chen, Z.; Hu, L.; Zeng, F.; Zhu, R.; Zheng, S.; Yu, Q.; Huang, J. *Chem. Commun.* **2017**, *53*, 4258.
- [17] (a) Hiney, R. M.; Higham, L. J.; Müller-Bunz, H.; Gilheany, D. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7248, (b) Brynda, M. *Coord. Chem. Rev.* **2005**, *249*, 2013.
- [18] Stewart, B.; Harriman, A.; Higham, L. J. *Organometallics* **2011**, *30*, 5338,
- [19] Maier, L. Preparation and Properties of Primary, Secondary, and Tertiary Phosphines. In *Progress in Inorganic Chemistry, Vol. 5*; Cotton, F. A., Ed.; John Wiley & Sons, Inc, 1963.
- [20] For instances of 1,1-diphosphines as ligands in catalysis, see (a) Grutters, M. M. P.; Müller, C.; Vogt, D. *J. Am. Chem. Soc.* **2006**, *128*, 7414, (b) Chaplin, A. B.; Hooper, J. F.; Weller, A.

- S.; Willis, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 4885, (c) Pernik, I.; Hooper, J. F.; Chaplin, A. B.; Weller, A. S.; Willis, M. C. *ACS Catal.* **2012**, *2*, 2779, (d) Murphy, S. K.; Bruch, A.; Dong, V. M. *Chem. Sci.* **2015**, *6*, 174, (e) Gridnev, I. D.; Liu, Y.; Imamoto, T. *ACS Catal.* **2014**, *4*, 203, (f) Cybulski, M. K.; Nicholls, J. E.; Lowe, J. P.; Mahon, M. F.; Whittlesey, M. K. *Organometallics* **2017**, *36*, 2308.
- [21] (a) Yang, X.-Y.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Organometallics* **2015**, *34*, 1582, (b) Wong, E. H. Y.; Jia, Y.-X.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *J. Organomet. Chem.* **2018**, *862*, 22.
- [22] (a) Wilson, J. E.; Fu, G. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1426, (b) Ni, H.; Chan, W.-L.; Lu, Y. *Chem. Rev.* **2018**, *118*, 9344 and references therein.
- [23] Rajendran, K. V.; Gilheany, D. G. *Chem. Commun.* **2012**, *48*, 817.
- [24] Schweizer, E. E.; Wehman, A. T. *J. Chem. Soc. C.* **1971**, 343.
- [25] Lloyd-Jones, G. C.; Taylor, N. P. *Chem. Eur. J.* **2015**, *21*, 5423.
- [26] Vetter, A. C.; Nikitin, K.; Gilheany, D. G. *Chem. Commun.* **2018**, *54*, 5843.
- [27] Warner, C. J. A.; Berry, S. S.; Jones, S. *Tetrahedron* **2019**, *75*, 130733.
- [28] Baslé, O.; Porcel, S.; Ladeira, S.; Bouhadir, G.; Bourisson, D. *Chem. Commun.* **2012**, *48*, 4495.
- [29] Cao, D.; Chai, Z.; Zhang, J.; Ye, Z.; Xiao, H.; Wang, H.; Chen, J.; Wu, X.; Zhao, G. *Chem. Commun.* **2013**, *49*, 5972.

Appendix I

Crystallographic Data

Crystallographic Data for Compound 132

Figure 49. Molecular structure of sulfurized preligand **132**.

Identification code	leung1144m
Chemical formula	C _{24.50} H ₂₂ ClPS
Formula weight	414.90 g/mol
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal size	0.020 x 0.220 x 0.280 mm
Crystal habit	colorless plate
Crystal system	orthorhombic
Space group	F d d 2
Unit cell dimensions	$a = 42.0439(13) \text{ Å}$ $\alpha = 90^\circ$ $b = 24.8421(8) \text{ Å}$ $\beta = 90^\circ$ $c = 7.9493(2) \text{ Å}$ $\gamma = 90^\circ$
Volume	8302.7(4) Å ³
Z	16
Density (calculated)	1.328 g/cm ³
Absorption coefficient	0.369 mm ⁻¹
F(000)	3472

Theta range for data collection	2.54 to 29.61°
Index ranges	-58<= <i>h</i> <=58, -31<= <i>k</i> <=34, -11<= <i>l</i> <=7
Reflections collected	18003
Independent reflections	5168 [R(int) = 0.0743]
Coverage of independent reflections	99.7%
Absorption correction	Multi-Scan
Max. and min. transmission	0.9930 and 0.9040
Structure solution technique	direct methods
Structure solution program	XT, VERSION 2014/5
Refinement method	Full-matrix least-squares on F ²
Refinement program	SHELXL-2017/1 (Sheldrick, 2017)
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	5168 / 1 / 263
Goodness-of-fit on F²	1.036
$\Delta/\sigma_{\max}$	0.001
Final R indices	3810 data; I>2σ(I) R1 = 0.0503, wR2 = 0.0809 all data R1 = 0.0828, wR2 = 0.0928
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0243P)^2+5.1751P]$ where $P=(F_o^2+2F_c^2)/3$
Absolute structure parameter	-0.04(5)
Largest diff. peak and hole	0.285 and -0.442 eÅ ⁻³
R.M.S. deviation from mean	0.060 eÅ ⁻³

Table 36. Bond lengths (Å) of phosphine sulfide **132**.

C1-C2	1.544(5)	C1-H1A	0.98
C1-H1B	0.98	C1-H1C	0.98
C2-C3	1.513(4)	C2-P1	1.847(3)
C2-H2	1.0	C3-C4	1.376(4)
C3-C8	1.439(5)	C4-C5	1.403(5)
C4-H4	0.95	C5-C6	1.368(5)
C5-H5	0.95	C6-C7	1.412(5)
C6-H6	0.95	C7-C12	1.420(5)
C7-C8	1.426(4)	C8-C9	1.420(4)
C9-C10	1.365(5)	C9-H9	0.95
C10-C11	1.401(5)	C10-H10	0.95
C11-C12	1.361(5)	C11-H11	0.95

C12-H12	0.95	C13-C14	1.391(5)
C13-C18	1.391(5)	C13-P1	1.820(3)
C14-C15	1.387(5)	C14-H14	0.95
C15-C16	1.377(5)	C15-H15	0.95
C16-C17	1.383(5)	C16-H16	0.95
C17-C18	1.394(5)	C17-H17	0.95
C18-H18	0.95	C19-C24	1.395(5)
C19-C20	1.397(5)	C19-P1	1.808(4)
C20-C21	1.387(6)	C20-H20	0.95
C21-C22	1.379(6)	C21-H21	0.95
C22-C23	1.377(5)	C22-H22	0.95
C23-C24	1.392(5)	C23-H23	0.95
C24-H24	0.95	C25-Cl1	1.729(11)
C25-Cl2	1.780(10)	C25-H25A	0.99
C25-H25B	0.99	P1-S1	1.9525(13)

Table 37. Bond angles (°) of phosphine sulfide **132**.

C2-C1-H1A	109.5	C2-C1-H1B	109.5
H1A-C1-H1B	109.5	C2-C1-H1C	109.5
H1A-C1-H1C	109.5	H1B-C1-H1C	109.5
C3-C2-C1	113.1(3)	C3-C2-P1	111.0(2)
C1-C2-P1	110.0(2)	C3-C2-H2	107.5
C1-C2-H2	107.5	P1-C2-H2	107.5
C4-C3-C8	118.4(3)	C4-C3-C2	119.3(3)
C8-C3-C2	122.3(3)	C3-C4-C5	122.5(3)
C3-C4-H4	118.8	C5-C4-H4	118.8
C6-C5-C4	120.0(3)	C6-C5-H5	120.0
C4-C5-H5	120.0	C5-C6-C7	120.1(3)
C5-C6-H6	119.9	C7-C6-H6	119.9
C6-C7-C12	120.0(3)	C6-C7-C8	120.2(3)
C12-C7-C8	119.7(3)	C9-C8-C7	117.1(3)
C9-C8-C3	124.1(3)	C7-C8-C3	118.7(3)
C10-C9-C8	121.5(3)	C10-C9-H9	119.2
C8-C9-H9	119.2	C9-C10-C11	120.9(3)
C9-C10-H10	119.5	C11-C10-H10	119.5
C12-C11-C10	119.7(4)	C12-C11-H11	120.1

C10-C11-H11	120.1	C11-C12-C7	120.9(3)
C11-C12-H12	119.5	C7-C12-H12	119.5
C14-C13-C18	118.8(3)	C14-C13-P1	118.4(3)
C18-C13-P1	122.8(3)	C15-C14-C13	120.6(3)
C15-C14-H14	119.7	C13-C14-H14	119.7
C16-C15-C14	120.1(3)	C16-C15-H15	120.0
C14-C15-H15	120.0	C15-C16-C17	120.3(3)
C15-C16-H16	119.8	C17-C16-H16	119.8
C16-C17-C18	119.6(3)	C16-C17-H17	120.2
C18-C17-H17	120.2	C13-C18-C17	120.6(3)
C13-C18-H18	119.7	C17-C18-H18	119.7
C24-C19-C20	119.3(3)	C24-C19-P1	120.5(3)
C20-C19-P1	120.1(3)	C21-C20-C19	119.7(4)
C21-C20-H20	120.2	C19-C20-H20	120.2
C22-C21-C20	120.4(4)	C22-C21-H21	119.8
C20-C21-H21	119.8	C23-C22-C21	120.7(4)
C23-C22-H22	119.6	C21-C22-H22	119.6
C22-C23-C24	119.4(4)	C22-C23-H23	120.3
C24-C23-H23	120.3	C23-C24-C19	120.5(3)
C23-C24-H24	119.8	C19-C24-H24	119.8
Cl1-C25-Cl2	110.5(6)	Cl1-C25-H25A	109.5
Cl2-C25-H25A	109.5	Cl1-C25-H25B	109.5
Cl2-C25-H25B	109.5	H25A-C25-H25B	108.1
C19-P1-C13	106.29(16)	C19-P1-C2	104.22(16)
C13-P1-C2	105.78(16)	C19-P1-S1	112.75(13)
C13-P1-S1	112.40(12)	C2-P1-S1	114.64(12)

Crystallographic Data for Compound (*S*)-141

Figure S0. Molecular structure of chiral phosphine sulfide (*S*)-141.

Identification code	leung1078m
Chemical formula	C ₂₇ H ₂₂ ClOPS
Formula weight	460.92 g/mol
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal size	0.200 x 0.220 x 0.240 mm
Crystal habit	colorless block
Crystal system	orthorhombic
Space group	P 21 21 21
Unit cell dimensions	$a = 6.4374(2) \text{ Å}$ $\alpha = 90^\circ$ $b = 17.2220(7) \text{ Å}$ $\beta = 90^\circ$ $c = 21.0699(9) \text{ Å}$ $\gamma = 90^\circ$
Volume	2335.91(16) Å ³
Z	4
Density (calculated)	1.311 g/cm ³
Absorption coefficient	0.338 mm ⁻¹
F(000)	960
Theta range for data collection	2.27 to 30.02°
Index ranges	-8 ≤ h ≤ 9, -23 ≤ k ≤ 24, -29 ≤ l ≤ 15
Reflections collected	18546
Independent reflections	6539 [R(int) = 0.0623]
Coverage of independent reflections	99.6%

Absorption correction	Multi-Scan	
Max. and min. transmission	0.9350 and 0.9230	
Structure solution technique	direct methods	
Structure solution program	XT, VERSION 2014/5	
Refinement method	Full-matrix least-squares on F ²	
Refinement program	SHELXL-2016/6 (Sheldrick, 2016)	
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	6539 / 0 / 280	
Goodness-of-fit on F²	1.018	
Final R indices	4855 data; I>2 σ (I)	R1 = 0.0537, wR2 = 0.1042
	all data	R1 = 0.0864, wR2 = 0.1224
Weighting scheme	w=1/[$\sigma^2(F_o^2)+(0.0458P)^2+0.8281P$] where P=(F _o ² +2F _c ²)/3	
Absolute structure parameter	0.03(5)	
Largest diff. peak and hole	0.333 and -0.569 eÅ ⁻³	
R.M.S. deviation from mean	0.075 eÅ ⁻³	

Table 38. Bond lengths (Å) of phosphine sulfide (S)-**141**.

C1-C6	1.388(5)	C1-C2	1.386(5)
C1-H1	0.95	C2-C3	1.375(6)
C2-H2	0.95	C3-C4	1.385(6)
C3-C11	1.742(4)	C4-C5	1.397(5)
C4-H4	0.95	C5-C6	1.386(5)
C5-H5	0.95	C6-C7	1.520(5)
C7-C8	1.531(5)	C7-P1	1.852(4)
C7-H7	1.0	C8-C9	1.518(5)
C8-H8A	0.99	C8-H8B	0.99
C9-O1	1.224(4)	C9-C10	1.487(5)
C10-C11	1.389(6)	C10-C15	1.396(5)
C11-C12	1.392(5)	C11-H11	0.95
C12-C13	1.380(6)	C12-H12	0.95
C13-C14	1.382(6)	C13-H13	0.95
C14-C15	1.388(6)	C14-H14	0.95
C15-H15	0.95	C16-C17	1.395(5)
C16-C21	1.399(5)	C16-P1	1.822(4)
C17-C18	1.389(5)	C17-H17	0.95

C18-C19	1.383(6)	C18-H18	0.95
C19-C20	1.377(5)	C19-H19	0.95
C20-C21	1.393(5)	C20-H20	0.95
C21-H21	0.95	C22-C23	1.386(5)
C22-C27	1.399(5)	C22-P1	1.815(4)
C23-C24	1.384(6)	C23-H23	0.95
C24-C25	1.373(6)	C24-H24	0.95
C25-C26	1.368(6)	C25-H25	0.95
C26-C27	1.380(6)	C26-H26	0.95
C27-H27	0.95	P1-S1	1.9535(13)

Table 39. Bond angles (°) of phosphine sulfide (*S*)-**141**.

C6-C1-C2	121.5(4)	C6-C1-H1	119.3
C2-C1-H1	119.3	C3-C2-C1	118.9(4)
C3-C2-H2	120.5	C1-C2-H2	120.5
C2-C3-C4	121.5(4)	C2-C3-Cl1	118.8(3)
C4-C3-Cl1	119.7(3)	C3-C4-C5	118.6(4)
C3-C4-H4	120.7	C5-C4-H4	120.7
C6-C5-C4	121.1(4)	C6-C5-H5	119.4
C4-C5-H5	119.4	C1-C6-C5	118.4(4)
C1-C6-C7	119.5(3)	C5-C6-C7	122.0(3)
C6-C7-C8	113.0(3)	C6-C7-P1	111.1(3)
C8-C7-P1	108.6(2)	C6-C7-H7	108.0
C8-C7-H7	108.0	P1-C7-H7	108.0
C9-C8-C7	112.5(3)	C9-C8-H8A	109.1
C7-C8-H8A	109.1	C9-C8-H8B	109.1
C7-C8-H8B	109.1	H8A-C8-H8B	107.8
O1-C9-C10	120.8(4)	O1-C9-C8	119.5(4)
C10-C9-C8	119.6(3)	C11-C10-C15	118.8(4)
C11-C10-C9	122.2(3)	C15-C10-C9	119.0(4)
C10-C11-C12	120.4(4)	C10-C11-H11	119.8
C12-C11-H11	119.8	C13-C12-C11	120.2(4)
C13-C12-H12	119.9	C11-C12-H12	119.9
C12-C13-C14	120.1(4)	C12-C13-H13	120.0
C14-C13-H13	120.0	C13-C14-C15	120.0(4)
C13-C14-H14	120.0	C15-C14-H14	120.0

C14-C15-C10	120.6(4)	C14-C15-H15	119.7
C10-C15-H15	119.7	C17-C16-C21	119.5(3)
C17-C16-P1	118.0(3)	C21-C16-P1	122.4(3)
C18-C17-C16	120.2(3)	C18-C17-H17	119.9
C16-C17-H17	119.9	C19-C18-C17	119.8(3)
C19-C18-H18	120.1	C17-C18-H18	120.1
C20-C19-C18	120.4(4)	C20-C19-H19	119.8
C18-C19-H19	119.8	C19-C20-C21	120.4(4)
C19-C20-H20	119.8	C21-C20-H20	119.8
C20-C21-C16	119.5(3)	C20-C21-H21	120.2
C16-C21-H21	120.2	C23-C22-C27	119.3(4)
C23-C22-P1	122.6(3)	C27-C22-P1	118.1(3)
C24-C23-C22	119.9(4)	C24-C23-H23	120.1
C22-C23-H23	120.1	C25-C24-C23	120.2(4)
C25-C24-H24	119.9	C23-C24-H24	119.9
C26-C25-C24	120.5(4)	C26-C25-H25	119.7
C24-C25-H25	119.7	C25-C26-C27	120.3(4)
C25-C26-H26	119.9	C27-C26-H26	119.9
C26-C27-C22	119.8(4)	C26-C27-H27	120.1
C22-C27-H27	120.1	C22-P1-C16	108.76(17)
C22-P1-C7	106.08(17)	C16-P1-C7	104.83(17)
C22-P1-S1	112.10(13)	C16-P1-S1	112.36(12)
C7-P1-S1	112.25(13)		

Crystallographic Data for Compound 143

Figure S1. Molecular structure of diarsine **143**.

Identification code	leung1028m	
Chemical formula	C ₂₄ H ₂₀ As ₂	
Formula weight	458.24 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.040 x 0.200 x 0.220 mm	
Crystal habit	colorless plate	
Crystal system	monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 6.1992(2) Å	α = 90°
	b = 7.3524(2) Å	β = 90.9970(10)°
	c = 21.2601(5) Å	γ = 90°
Volume	968.87(5) Å ³	
Z	2	
Density (calculated)	1.571 g/cm ³	
Absorption coefficient	3.453 mm ⁻¹	
F(000)	460	
Theta range for data collection	2.93 to 35.01°	
Index ranges	-9 ≤ h ≤ 10, -11 ≤ k ≤ 11, -34 ≤ l ≤ 34	
Reflections collected	21465	
Independent reflections	4263 [R(int) = 0.0650]	
Coverage of independent reflections	99.9%	
Absorption correction	Multi-Scan	

Max. and min. transmission	0.8740 and 0.5170
Structure solution technique	direct methods
Structure solution program	XT, VERSION 2014/5
Refinement method	Full-matrix least-squares on F ²
Refinement program	SHELXL-2016/6 (Sheldrick, 2016)
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	4263 / 0 / 118
Goodness-of-fit on F²	1.021
$\Delta/\sigma_{\max}$	0.001
Final R indices	3075 data; $I > 2\sigma(I)$ R1 = 0.0376, wR2 = 0.0641 all data R1 = 0.0669, wR2 = 0.0742
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0193P)^2 + 0.8255P]$ where $P = (F_o^2 + 2F_c^2)/3$
Largest diff. peak and hole	0.731 and -0.593 eÅ ⁻³
R.M.S. deviation from mean	0.126 eÅ ⁻³

Table 40. Bond lengths (Å) of tetraphenyldiarsine **143**.

As1-C1	1.9545(19)	As1-C7	1.9606(19)
As1-As1	2.4603(4)	C1-C6	1.390(3)
C1-C2	1.398(3)	C2-C3	1.389(3)
C2-H2	0.95	C3-C4	1.387(3)
C3-H3	0.95	C4-C5	1.381(3)
C4-H4	0.95	C5-C6	1.396(3)
C5-H5	0.95	C6-H6	0.95
C7-C8	1.394(3)	C7-C12	1.403(3)
C8-C9	1.394(3)	C8-H8	0.95
C9-C10	1.387(3)	C9-H9	0.95
C10-C11	1.386(3)	C10-H10	0.95
C11-C12	1.390(3)	C11-H11	0.95
C12-H12	0.95		

Table 41. Bond angles (°) of tetraphenyldiarsine **143**.

C1-As1-C7	102.54(8)	C1-As1-As1	95.03(6)
C7-As1-As1	95.46(6)	C6-C1-C2	118.97(18)
C6-C1-As1	115.80(14)	C2-C1-As1	124.99(15)
C3-C2-C1	120.79(19)	C3-C2-H2	119.6

C1-C2-H2	119.6	C4-C3-C2	119.53(19)
C4-C3-H3	120.2	C2-C3-H3	120.2
C5-C4-C3	120.38(19)	C5-C4-H4	119.8
C3-C4-H4	119.8	C4-C5-C6	120.0(2)
C4-C5-H5	120.0	C6-C5-H5	120.0
C1-C6-C5	120.28(19)	C1-C6-H6	119.9
C5-C6-H6	119.9	C8-C7-C12	119.18(18)
C8-C7-As1	124.13(15)	C12-C7-As1	116.60(14)
C7-C8-C9	120.27(19)	C7-C8-H8	119.9
C9-C8-H8	119.9	C10-C9-C8	120.15(19)
C10-C9-H9	119.9	C8-C9-H9	119.9
C11-C10-C9	119.95(19)	C11-C10-H10	120.0
C9-C10-H10	120.0	C10-C11-C12	120.40(19)
C10-C11-H11	119.8	C12-C11-H11	119.8
C11-C12-C7	120.03(19)	C11-C12-H12	120.0
C7-C12-H12	120.0		

Crystallographic Data for Compound (S)-153

Figure S2. Molecular structure of Au-coordinated arsine (S)-153.

Chemical formula	$\text{C}_{20}\text{H}_{18}\text{AsAuClNO}_2$	
Formula weight	611.69 g/mol	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal size	0.100 x 0.120 x 0.360 mm	
Crystal habit	colorless block	
Crystal system	monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	$a = 9.8186(5)$ Å	$\alpha = 90^\circ$
	$b = 9.2688(5)$ Å	$\beta = 99.2433(18)^\circ$
	$c = 10.8223(5)$ Å	$\gamma = 90^\circ$
Volume	$972.11(9)$ Å ³	
Z	2	
Density (calculated)	2.090 g/cm ³	
Absorption coefficient	9.407 mm ⁻¹	
F(000)	580	
Theta range for data collection	1.91 to 27.99°	
Index ranges	-12 ≤ h ≤ 12, -6 ≤ k ≤ 12, -14 ≤ l ≤ 14	
Reflections collected	14442	
Independent reflections	3710 [R(int) = 0.0664]	
Coverage of independent reflections	100.0%	
Absorption correction	Multi-Scan	

Max. and min. transmission	0.4530 and 0.1330
Structure solution technique	direct methods
Structure solution program	XT, VERSION 2014/5
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	3710 / 1 / 235
Goodness-of-fit on F^2	1.029
Final R indices	3401 data; $I > 2\sigma(I)$ $R1 = 0.0348$, $wR2 = 0.0675$ all data $R1 = 0.0421$, $wR2 = 0.0706$
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0198P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
Absolute structure parameter	-0.005(13)
Largest diff. peak and hole	2.361 and -2.019 $e\text{\AA}^{-3}$
R.M.S. deviation from mean	0.181 $e\text{\AA}^{-3}$

Table 42. Bond lengths ($\text{\AA}$) of complex (*S*)-153.

As1-C7	1.913(9)	As1-C1	1.923(9)
As1-C19	1.979(9)	As1-Au1	2.3309(11)
Au1-C11	2.279(3)	C1-C2	1.379(14)
C1-C6	1.410(12)	C2-C3	1.400(14)
C2-H2	0.95	C3-C4	1.392(14)
C3-H3	0.95	C4-C5	1.377(16)
C4-H4	0.95	C5-C6	1.377(13)
C5-H5	0.95	C6-H6	0.95
C7-C12	1.395(13)	C7-C8	1.398(14)
C8-C9	1.397(12)	C8-H8	0.95
C9-C10	1.372(16)	C9-H9	0.95
C10-C11	1.376(14)	C10-H10	0.95
C11-C12	1.388(12)	C11-H11	0.95
C12-H12	0.95	C13-C14	1.375(12)
C13-C18	1.394(13)	C13-H13	0.95
C14-C15	1.387(15)	C14-H14	0.95
C15-C16	1.391(15)	C15-H15	0.95
C16-C17	1.416(13)	C16-H16	0.95
C17-C18	1.402(14)	C17-H17	0.95

C18-C19	1.504(12)	C19-C20	1.508(13)
C19-H19	1.0	C20-N1	1.495(13)
C20-H20A	0.99	C20-H20B	0.99
N1-O1	1.205(14)	N1-O2	1.218(12)

Table 43. Bond angles (°) of complex (S)-**153**.

C7-As1-C1	104.9(4)	C7-As1-C19	105.3(4)
C1-As1-C19	105.2(4)	C7-As1-Au1	117.1(3)
C1-As1-Au1	112.8(3)	C19-As1-Au1	110.7(3)
Cl1-Au1-As1	176.63(7)	C2-C1-C6	119.6(9)
C2-C1-As1	121.1(7)	C6-C1-As1	119.3(7)
C1-C2-C3	119.9(9)	C1-C2-H2	120.0
C3-C2-H2	120.0	C4-C3-C2	119.5(10)
C4-C3-H3	120.3	C2-C3-H3	120.3
C5-C4-C3	120.8(10)	C5-C4-H4	119.6
C3-C4-H4	119.6	C4-C5-C6	119.8(10)
C4-C5-H5	120.1	C6-C5-H5	120.1
C5-C6-C1	120.3(10)	C5-C6-H6	119.8
C1-C6-H6	119.8	C12-C7-C8	119.5(8)
C12-C7-As1	117.7(7)	C8-C7-As1	122.5(7)
C9-C8-C7	119.2(10)	C9-C8-H8	120.4
C7-C8-H8	120.4	C10-C9-C8	120.5(12)
C10-C9-H9	119.8	C8-C9-H9	119.8
C9-C10-C11	120.5(10)	C9-C10-H10	119.7
C11-C10-H10	119.7	C10-C11-C12	120.0(9)
C10-C11-H11	120.0	C12-C11-H11	120.0
C11-C12-C7	120.2(9)	C11-C12-H12	119.9
C7-C12-H12	119.9	C14-C13-C18	121.5(9)
C14-C13-H13	119.2	C18-C13-H13	119.2
C13-C14-C15	120.4(9)	C13-C14-H14	119.8
C15-C14-H14	119.8	C14-C15-C16	119.9(9)
C14-C15-H15	120.0	C16-C15-H15	120.0
C15-C16-C17	119.5(10)	C15-C16-H16	120.3
C17-C16-H16	120.3	C18-C17-C16	120.3(10)
C18-C17-H17	119.9	C16-C17-H17	119.9
C13-C18-C17	118.3(9)	C13-C18-C19	119.5(9)

C17-C18-C19	122.1(9)	C18-C19-C20	115.8(8)
C18-C19-As1	108.9(6)	C20-C19-As1	106.7(6)
C18-C19-H19	108.4	C20-C19-H19	108.4
As1-C19-H19	108.4	N1-C20-C19	111.5(8)
N1-C20-H20A	109.3	C19-C20-H20A	109.3
N1-C20-H20B	109.3	C19-C20-H20B	109.3
H20A-C20-H20B	108.0	O1-N1-O2	122.6(11)
O1-N1-C20	119.3(10)	O2-N1-C20	118.1(10)

Crystallographic Data for Compound 172

Figure 53. Molecular structure of diphenylarsinic acid **172**.

Identification code	leung945s	
Chemical formula	C ₁₂ H ₁₁ AsO ₂	
Formula weight	262.13 g/mol	
Temperature	133(2) K	
Wavelength	1.54178 Å	
Crystal size	0.040 x 0.080 x 0.220 mm	
Crystal habit	colorless needle	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 11.46318(16) Å	α = 90°
	b = 6.04356(9) Å	β = 99.3585(6)°
	c = 15.8125(2) Å	γ = 90°
Volume	1080.88(3) Å ³	
Z	4	
Density (calculated)	1.611 g/cm ³	
Absorption coefficient	4.065 mm ⁻¹	
F(000)	528	
Theta range for data collection	3.91 to 66.70°	
Index ranges	-13 ≤ h ≤ 13, -6 ≤ k ≤ 7, -18 ≤ l ≤ 18	
Reflections collected	9223	
Independent reflections	1913 [R(int) = 0.0419]	
Coverage of independent reflections	99.6%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.8540 and 0.4680	

Structure solution technique	direct methods		
Structure solution program	XT, VERSION 2014/5		
Refinement method	Full-matrix least-squares on F2		
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)		
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$		
Data / restraints / parameters	1913 / 0 / 141		
Goodness-of-fit on F2	1.098		
$\Delta/\sigma_{\text{max}}$	0.002		
Final R indices	1825 data; $I>2\sigma(I)$	R1 = 0.0262, wR2 = 0.0702	
	all data	R1 = 0.0271, wR2 = 0.0708	
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0398P)^2+0.6140P]$		
	where $P=(F_o^2+2F_c^2)/3$		
Extinction coefficient	0.0029(3)		
Largest diff. peak and hole	0.520 and -0.572 eÅ ⁻³		
R.M.S. deviation from mean	0.108 eÅ ⁻³		

Table 44. Bond lengths (Å) of diphenylarsinic acid **172**.

As1-O2	1.6529(15)	As1-O1	1.7114(15)
As1-C1	1.911(2)	As1-C7	1.912(2)
C1-C2	1.388(3)	C1-C6	1.391(3)
C2-C3	1.390(4)	C2-H2	0.95
C3-C4	1.383(4)	C3-H3	0.95
C4-C5	1.383(4)	C4-H4	0.95
C5-C6	1.390(3)	C5-H5	0.95
C6-H6	0.95	C7-C12	1.387(3)
C7-C8	1.392(3)	C8-C9	1.393(3)
C8-H8	0.95	C9-C10	1.383(4)
C9-H9	0.95	C10-C11	1.381(4)
C10-H10	0.95	C11-C12	1.387(3)
C11-H11	0.95	C12-H12	0.95
O1-H1A	0.91(4)		

Table 45. Bond angles (°) of diphenylarsinic acid **172**.

O2-As1-O1	115.11(8)	O2-As1-C1	110.67(9)
O1-As1-C1	101.10(9)	O2-As1-C7	112.82(9)
O1-As1-C7	106.41(9)	C1-As1-C7	110.05(9)

C2-C1-C6	121.3(2)	C2-C1-As1	119.51(17)
C6-C1-As1	119.23(17)	C1-C2-C3	118.9(2)
C1-C2-H2	120.5	C3-C2-H2	120.5
C4-C3-C2	120.2(3)	C4-C3-H3	119.9
C2-C3-H3	119.9	C5-C4-C3	120.4(2)
C5-C4-H4	119.8	C3-C4-H4	119.8
C4-C5-C6	120.2(2)	C4-C5-H5	119.9
C6-C5-H5	119.9	C5-C6-C1	118.9(2)
C5-C6-H6	120.5	C1-C6-H6	120.5
C12-C7-C8	120.7(2)	C12-C7-As1	118.01(17)
C8-C7-As1	121.25(16)	C7-C8-C9	118.9(2)
C7-C8-H8	120.5	C9-C8-H8	120.5
C10-C9-C8	120.5(2)	C10-C9-H9	119.8
C8-C9-H9	119.8	C11-C10-C9	120.1(2)
C11-C10-H10	120.0	C9-C10-H10	120.0
C10-C11-C12	120.3(2)	C10-C11-H11	119.8
C12-C11-H11	119.8	C11-C12-C7	119.5(2)
C11-C12-H12	120.3	C7-C12-H12	120.3
As1-O1-H1A	112.(2)		

Crystallographic Data for Compound 179

Figure S4. Molecular structure of cyclopentene **179** with non-stereogenic H omitted for clarity.

Identification code	leung1159m	
Chemical formula	C ₂₄ H ₂₁ O ₂ PS	
Formula weight	404.44 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.010 x 0.020 x 0.100 mm	
Crystal habit	colorless needle	
Crystal system	monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 10.6940(9) Å	α = 90°
	b = 7.2751(6) Å	β = 94.672(3)°
	c = 13.1578(11) Å	γ = 90°
Volume	1020.27(15) Å ³	
Z	2	
Density (calculated)	1.316 g/cm ³	
Absorption coefficient	0.254 mm ⁻¹	
F(000)	424	
Theta range for data collection	2.56 to 29.58°	
Index ranges	-14 ≤ h ≤ 14, -10 ≤ k ≤ 8, -18 ≤ l ≤ 18	
Reflections collected	15679	
Independent reflections	5308 [R(int) = 0.0844]	
Coverage of independent reflections	99.8%	
Absorption correction	Multi-Scan	

Max. and min. transmission	0.9970 and 0.9750
Structure solution technique	direct methods
Structure solution program	XT, VERSION 2014/5
Refinement method	Full-matrix least-squares on F ²
Refinement program	SHELXL-2018/3 (Sheldrick, 2018)
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	5308 / 1 / 254
Goodness-of-fit on F²	1.024
Final R indices	3885 data; I>2 σ (I) R1 = 0.0501, wR2 = 0.0865 all data R1 = 0.0876, wR2 = 0.1004
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0305P)^2+0.1048P]$ where $P=(F_o^2+2F_c^2)/3$
Absolute structure parameter	0.14(7)
Largest diff. peak and hole	0.366 and -0.365 eÅ ⁻³
R.M.S. deviation from mean	0.074 eÅ ⁻³

Table 46. Bond lengths (Å) of cyclopentene **179**.

C1-O1	1.421(5)	C1-C2	1.498(5)
C1-C5	1.565(5)	C1-H1	1.0
C2-C3	1.313(5)	C2-H2	0.95
C3-C4	1.506(5)	C3-H3	0.95
C4-C5	1.546(5)	C4-P1	1.831(4)
C4-H4	1.0	C5-C6	1.523(5)
C5-H5	1.0	C6-O2	1.221(4)
C6-C7	1.492(5)	C7-C8	1.397(5)
C7-C12	1.401(5)	C8-C9	1.381(5)
C8-H8	0.95	C9-C10	1.380(6)
C9-H9	0.95	C10-C11	1.388(6)
C10-H10	0.95	C11-C12	1.384(5)
C11-H11	0.95	C12-H12	0.95
C13-C14	1.391(5)	C13-C18	1.395(5)
C13-P1	1.819(4)	C14-C15	1.387(5)
C14-H14	0.95	C15-C16	1.381(6)
C15-H15	0.95	C16-C17	1.379(6)
C16-H16	0.95	C17-C18	1.384(5)
C17-H17	0.95	C18-H18	0.95

C19-C20	1.391(5)	C19-C24	1.395(5)
C19-P1	1.813(4)	C20-C21	1.388(5)
C20-H20	0.95	C21-C22	1.377(6)
C21-H21	0.95	C22-C23	1.378(6)
C22-H22	0.95	C23-C24	1.376(5)
C23-H23	0.95	C24-H24	0.95
O1-H1A	0.84	P1-S1	1.9534(13)

Table 47. Bond angles (°) of cyclopentene **179**.

O1-C1-C2	113.8(3)	O1-C1-C5	113.8(3)
C2-C1-C5	103.5(3)	O1-C1-H1	108.5
C2-C1-H1	108.5	C5-C1-H1	108.5
C3-C2-C1	113.0(3)	C3-C2-H2	123.5
C1-C2-H2	123.5	C2-C3-C4	112.7(3)
C2-C3-H3	123.7	C4-C3-H3	123.7
C3-C4-C5	103.9(3)	C3-C4-P1	110.9(3)
C5-C4-P1	112.3(2)	C3-C4-H4	109.9
C5-C4-H4	109.9	P1-C4-H4	109.9
C6-C5-C4	112.3(3)	C6-C5-C1	110.0(3)
C4-C5-C1	105.7(3)	C6-C5-H5	109.6
C4-C5-H5	109.6	C1-C5-H5	109.6
O2-C6-C7	120.5(3)	O2-C6-C5	121.3(3)
C7-C6-C5	118.2(3)	C8-C7-C12	118.9(4)
C8-C7-C6	118.8(3)	C12-C7-C6	122.2(3)
C9-C8-C7	120.3(4)	C9-C8-H8	119.8
C7-C8-H8	119.8	C10-C9-C8	120.4(4)
C10-C9-H9	119.8	C8-C9-H9	119.8
C9-C10-C11	119.9(4)	C9-C10-H10	120.0
C11-C10-H10	120.0	C12-C11-C10	120.2(4)
C12-C11-H11	119.9	C10-C11-H11	119.9
C11-C12-C7	120.2(4)	C11-C12-H12	119.9
C7-C12-H12	119.9	C14-C13-C18	119.2(4)
C14-C13-P1	122.4(3)	C18-C13-P1	118.4(3)
C15-C14-C13	120.1(4)	C15-C14-H14	120.0
C13-C14-H14	120.0	C16-C15-C14	120.3(4)
C16-C15-H15	119.9	C14-C15-H15	119.9

C17-C16-C15	120.0(4)	C17-C16-H16	120.0
C15-C16-H16	120.0	C16-C17-C18	120.3(4)
C16-C17-H17	119.9	C18-C17-H17	119.9
C17-C18-C13	120.2(4)	C17-C18-H18	119.9
C13-C18-H18	119.9	C20-C19-C24	119.6(3)
C20-C19-P1	121.2(3)	C24-C19-P1	119.2(3)
C21-C20-C19	119.4(4)	C21-C20-H20	120.3
C19-C20-H20	120.3	C22-C21-C20	120.4(4)
C22-C21-H21	119.8	C20-C21-H21	119.8
C21-C22-C23	120.4(4)	C21-C22-H22	119.8
C23-C22-H22	119.8	C24-C23-C22	119.9(4)
C24-C23-H23	120.0	C22-C23-H23	120.0
C23-C24-C19	120.3(4)	C23-C24-H24	119.9
C19-C24-H24	119.9	C1-O1-H1A	109.5
C19-P1-C13	106.34(16)	C19-P1-C4	104.67(16)
C13-P1-C4	105.88(17)	C19-P1-S1	113.03(12)
C13-P1-S1	113.05(13)	C4-P1-S1	113.17(13)

Crystallographic Data for Compound 182a

Figure S5. Molecular structure of *cis*-β-oxovinylarsine **182a** with hydrogen atoms omitted for clarity.

Identification code	leung1129m
Chemical formula	C ₂₁ H ₁₇ AsO
Formula weight	360.27 g/mol
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal size	0.040 x 0.120 x 0.280 mm
Crystal habit	orange plate
Crystal system	monoclinic
Space group	P 1 2 ₁ /c 1
Unit cell dimensions	a = 10.8612(2) Å α = 90° b = 5.56630(10) Å β = 99.9763(10)° c = 26.7386(7) Å γ = 90°
Volume	1592.08(6) Å ³
Z	4
Density (calculated)	1.503 g/cm ³
Absorption coefficient	2.137 mm ⁻¹
F(000)	736
Theta range for data collection	2.23 to 37.83°
Index ranges	-18 ≤ h ≤ 18, -9 ≤ k ≤ 9, -45 ≤ l ≤ 46
Reflections collected	23525
Independent reflections	8551 [R(int) = 0.0490]
Coverage of independent reflections	99.7%
Absorption correction	Multi-Scan
Max. and min. transmission	0.9190 and 0.5860
Structure solution technique	direct methods

Structure solution program	XT, VERSION 2014/5	
Refinement method	Full-matrix least-squares on F ²	
Refinement program	SHELXL-2017/1 (Sheldrick, 2017)	
Function minimized	$\Sigma w(\text{Fo}^2 - \text{Fc}^2)^2$	
Data / restraints / parameters	8551 / 0 / 208	
Goodness-of-fit on F²	1.018	
$\Delta/\sigma_{\text{max}}$	0.001	
Final R indices	6362 data; $I > 2\sigma(I)$	R1 = 0.0411, wR2 = 0.0824
	all data	R1 = 0.0668, wR2 = 0.0937
Weighting scheme	$w = 1/[\sigma^2(\text{Fo}^2) + (0.0333\text{P})^2 + 0.4282\text{P}]$ where $\text{P} = (\text{Fo}^2 + 2\text{Fc}^2)/3$	
Largest diff. peak and hole	0.659 and -0.699 eÅ ⁻³	
R.M.S. deviation from mean	0.114 eÅ ⁻³	

Table 48. Bond lengths (Å) of *cis*-β-oxovinylarsine **182a**.

As1-C9	1.9442(15)	As1-C16	1.9631(15)
As1-C10	1.9663(15)	C1-C2	1.391(2)
C1-C6	1.392(2)	C1-H1	0.95
C2-C3	1.395(2)	C2-H2	0.95
C3-C4	1.381(3)	C3-H3	0.95
C4-C5	1.395(2)	C4-H4	0.95
C5-C6	1.397(2)	C5-H5	0.95
C6-C7	1.496(2)	C7-O1	1.2299(17)
C7-C8	1.479(2)	C8-C9	1.337(2)
C8-H8	0.95	C9-H9	0.95
C10-C15	1.392(2)	C10-C11	1.397(2)
C11-C12	1.391(2)	C11-H11	0.95
C12-C13	1.385(2)	C12-H12	0.95
C13-C14	1.383(2)	C13-H13	0.95
C14-C15	1.399(2)	C14-H14	0.95
C15-H15	0.95	C16-C17	1.392(2)
C16-C21	1.398(2)	C17-C18	1.392(2)
C17-H17	0.95	C18-C19	1.386(2)
C18-H18	0.95	C19-C20	1.394(2)
C19-H19	0.95	C20-C21	1.386(2)
C20-H20	0.95	C21-H21	0.95

Table 49. Bond angles (°) of *cis*-β-oxovinylarsine **182a**.

C9-As1-C16	97.85(6)	C9-As1-C10	99.69(6)
C16-As1-C10	94.76(6)	C2-C1-C6	120.99(14)
C2-C1-H1	119.5	C6-C1-H1	119.5
C1-C2-C3	119.32(15)	C1-C2-H2	120.3
C3-C2-H2	120.3	C4-C3-C2	120.03(15)
C4-C3-H3	120.0	C2-C3-H3	120.0
C3-C4-C5	120.73(15)	C3-C4-H4	119.6
C5-C4-H4	119.6	C4-C5-C6	119.59(15)
C4-C5-H5	120.2	C6-C5-H5	120.2
C1-C6-C5	119.31(14)	C1-C6-C7	117.45(12)
C5-C6-C7	123.23(14)	O1-C7-C8	119.99(13)
O1-C7-C6	119.98(13)	C8-C7-C6	120.00(12)
C9-C8-C7	122.01(13)	C9-C8-H8	119.0
C7-C8-H8	119.0	C8-C9-As1	125.00(11)
C8-C9-H9	117.5	As1-C9-H9	117.5
C15-C10-C11	118.24(14)	C15-C10-As1	127.10(11)
C11-C10-As1	114.54(11)	C12-C11-C10	121.46(15)
C12-C11-H11	119.3	C10-C11-H11	119.3
C13-C12-C11	119.65(16)	C13-C12-H12	120.2
C11-C12-H12	120.2	C14-C13-C12	119.71(15)
C14-C13-H13	120.1	C12-C13-H13	120.1
C13-C14-C15	120.63(16)	C13-C14-H14	119.7
C15-C14-H14	119.7	C10-C15-C14	120.28(15)
C10-C15-H15	119.9	C14-C15-H15	119.9
C17-C16-C21	119.00(14)	C17-C16-As1	120.12(11)
C21-C16-As1	120.78(11)	C16-C17-C18	120.36(14)
C16-C17-H17	119.8	C18-C17-H17	119.8
C19-C18-C17	120.30(15)	C19-C18-H18	119.8
C17-C18-H18	119.8	C18-C19-C20	119.71(15)
C18-C19-H19	120.1	C20-C19-H19	120.1
C21-C20-C19	119.98(14)	C21-C20-H20	120.0
C19-C20-H20	120.0	C20-C21-C16	120.65(14)
C20-C21-H21	119.7	C16-C21-H21	119.7

Crystallographic Data for Compound **185a**

Figure S6. Molecular structure of arsinophosphine **185a** with hydrogen atoms omitted for clarity.

Identification code	leung1128m	
Chemical formula	$\text{C}_{33}\text{H}_{28}\text{As}_{0.70}\text{OP}_{1.30}$	
Formula weight	533.37 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.040 x 0.120 x 0.280 mm	
Crystal habit	orange needle	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	$a = 6.2161(2)$ Å	$\alpha = 90^\circ$
	$b = 22.3323(8)$ Å	$\beta = 93.2596(13)^\circ$
	$c = 18.8188(6)$ Å	$\gamma = 90^\circ$
Volume	$2608.20(15)$ Å ³	
Z	4	
Density (calculated)	1.358 g/cm ³	
Absorption coefficient	1.033 mm ⁻¹	
F(000)	1107	
Theta range for data collection	2.83 to 29.57°	
Index ranges	$-8 \leq h \leq 7$, $-26 \leq k \leq 30$, $-26 \leq l \leq 26$	
Reflections collected	29393	
Independent reflections	7312 [R(int) = 0.0922]	

Coverage of independent reflections	99.8%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.9600 and 0.7610	
Structure solution technique	direct methods	
Structure solution program	XT, VERSION 2014/5	
Refinement method	Full-matrix least-squares on F ²	
Refinement program	SHELXL-2017/1 (Sheldrick, 2017)	
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	7312 / 2 / 339	
Goodness-of-fit on F²	1.016	
Final R indices	4651 data; I > 2 σ (I)	R1 = 0.0466, wR2 = 0.0736
	all data	R1 = 0.0987, wR2 = 0.0881
Weighting scheme	w = 1/[$\sigma^2(F_o^2) + (0.0242P)^2 + 0.4979P$] where P = (F _o ² + 2F _c ²)/3	
Largest diff. peak and hole	0.367 and -0.370 eÅ ⁻³	
R.M.S. deviation from mean	0.081 eÅ ⁻³	

Table 50. Bond lengths (Å) of arsinophosphine **185a**.

As1-C22	1.904(8)	As1-C28	1.929(9)
As1-C9	1.986(5)	P1A-C9	1.851(11)
P1A-C22	1.936(19)	P1A-C28	1.95(2)
P1-C10	1.828(10)	P1-C9	1.856(7)
P1-C16	1.893(9)	As1A-C16	1.790(14)
As1A-C10	1.988(15)	As1A-C9	1.990(10)
C10-C15	1.391(3)	C10-C11	1.400(3)
C11-C12	1.393(3)	C11-H11	0.95
C12-C13	1.377(4)	C12-H12	0.95
C13-C14	1.380(4)	C13-H13	0.95
C14-C15	1.382(3)	C14-H14	0.95
C15-H15	0.95	C16-C17	1.389(3)
C16-C21	1.392(3)	C17-C18	1.387(3)
C17-H17	0.95	C18-C19	1.380(4)
C18-H18	0.95	C19-C20	1.372(4)
C19-H19	0.95	C20-C21	1.385(4)
C20-H20	0.95	C21-H21	0.95

C22-C27	1.385(3)	C22-C23	1.402(3)
C23-C24	1.386(3)	C23-H23	0.95
C24-C25	1.387(3)	C24-H24	0.95
C25-C26	1.382(3)	C25-H25	0.95
C26-C27	1.393(3)	C26-H26	0.95
C27-H27	0.95	C28-C29	1.392(3)
C28-C33	1.396(3)	C29-C30	1.387(3)
C29-H29	0.95	C30-C31	1.385(3)
C30-H30	0.95	C31-C32	1.382(3)
C31-H31	0.95	C32-C33	1.388(3)
C32-H32	0.95	C33-H33	0.95
C1-C2	1.383(3)	C1-C6	1.389(3)
C1-H1	0.95	C2-C3	1.385(4)
C2-H2	0.95	C3-C4	1.377(3)
C3-H3	0.95	C4-C5	1.383(3)
C4-H4	0.95	C5-C6	1.390(3)
C5-H5	0.95	C6-C7	1.504(3)
C7-O1	1.216(2)	C7-C8	1.512(3)
C8-C9	1.535(3)	C8-H8A	0.99
C8-H8B	0.99	C9-H9	1.0

Table 51. Bond angles (°) of arsinophosphine **185a**.

C22-As1-C28	100.8(4)	C22-As1-C9	100.8(3)
C28-As1-C9	99.8(3)	C9-P1A-C22	104.6(8)
C9-P1A-C28	104.0(9)	C22-P1A-C28	99.0(9)
C10-P1-C9	103.5(4)	C10-P1-C16	103.1(4)
C9-P1-C16	102.2(4)	C16-As1A-C10	100.9(7)
C16-As1A-C9	100.9(6)	C10-As1A-C9	93.3(5)
C15-C10-C11	117.7(2)	C15-C10-P1	125.4(3)
C11-C10-P1	116.9(3)	C15-C10-As1A	128.8(4)
C11-C10-As1A	113.5(4)	C12-C11-C10	121.1(2)
C12-C11-H11	119.4	C10-C11-H11	119.4
C13-C12-C11	119.7(2)	C13-C12-H12	120.1
C11-C12-H12	120.1	C12-C13-C14	119.9(2)
C12-C13-H13	120.0	C14-C13-H13	120.0
C13-C14-C15	120.4(2)	C13-C14-H14	119.8

C15-C14-H14	119.8	C14-C15-C10	121.1(2)
C14-C15-H15	119.5	C10-C15-H15	119.5
C17-C16-C21	118.5(2)	C17-C16-As1A	131.1(4)
C21-C16-As1A	110.4(4)	C17-C16-P1	124.7(3)
C21-C16-P1	116.7(3)	C18-C17-C16	120.2(2)
C18-C17-H17	119.9	C16-C17-H17	119.9
C19-C18-C17	120.5(3)	C19-C18-H18	119.8
C17-C18-H18	119.8	C20-C19-C18	119.9(3)
C20-C19-H19	120.1	C18-C19-H19	120.1
C19-C20-C21	120.0(3)	C19-C20-H20	120.0
C21-C20-H20	120.0	C20-C21-C16	120.9(3)
C20-C21-H21	119.6	C16-C21-H21	119.6
C27-C22-C23	119.0(2)	C27-C22-As1	115.2(2)
C23-C22-As1	125.8(3)	C27-C22-P1A	118.3(5)
C23-C22-P1A	122.7(5)	C24-C23-C22	120.1(2)
C24-C23-H23	119.9	C22-C23-H23	119.9
C23-C24-C25	120.3(2)	C23-C24-H24	119.8
C25-C24-H24	119.8	C26-C25-C24	119.9(2)
C26-C25-H25	120.0	C24-C25-H25	120.0
C25-C26-C27	119.9(2)	C25-C26-H26	120.0
C27-C26-H26	120.0	C22-C27-C26	120.7(2)
C22-C27-H27	119.6	C26-C27-H27	119.6
C29-C28-C33	118.0(2)	C29-C28-As1	126.7(3)
C33-C28-As1	115.1(3)	C29-C28-P1A	126.6(6)
C33-C28-P1A	115.4(6)	C30-C29-C28	121.0(2)
C30-C29-H29	119.5	C28-C29-H29	119.5
C31-C30-C29	120.2(2)	C31-C30-H30	119.9
C29-C30-H30	119.9	C32-C31-C30	119.7(2)
C32-C31-H31	120.2	C30-C31-H31	120.2
C31-C32-C33	120.1(2)	C31-C32-H32	120.0
C33-C32-H32	120.0	C32-C33-C28	121.0(2)
C32-C33-H33	119.5	C28-C33-H33	119.5
C2-C1-C6	120.2(2)	C2-C1-H1	119.9
C6-C1-H1	119.9	C1-C2-C3	120.4(2)
C1-C2-H2	119.8	C3-C2-H2	119.8
C4-C3-C2	119.6(2)	C4-C3-H3	120.2

C2-C3-H3	120.2	C3-C4-C5	120.3(2)
C3-C4-H4	119.9	C5-C4-H4	119.9
C4-C5-C6	120.5(2)	C4-C5-H5	119.8
C6-C5-H5	119.8	C1-C6-C5	119.0(2)
C1-C6-C7	123.3(2)	C5-C6-C7	117.69(19)
O1-C7-C6	120.1(2)	O1-C7-C8	120.3(2)
C6-C7-C8	119.54(18)	C7-C8-C9	114.21(18)
C7-C8-H8A	108.7	C9-C8-H8A	108.7
C7-C8-H8B	108.7	C9-C8-H8B	108.7
H8A-C8-H8B	107.6	C8-C9-P1A	110.6(6)
C8-C9-P1	106.7(3)	C8-C9-As1	110.8(3)
P1-C9-As1	105.3(4)	C8-C9-As1A	109.4(4)
P1A-C9-As1A	100.0(8)	C8-C9-H9	111.3
P1-C9-H9	111.3	As1-C9-H9	111.3

Appendix II

Computational Data for Chapter 3

Computational data for catalytic intermediates A, B and C

Table 52 summarizes the free energy values of relevant species required for the calculations involving intermediates A, B and C.

Table 52. Free energy values at 298.15 K.

Compounds	State	$\epsilon_0 + G_{corr}$ (Hartree)
HAsPh ₂	Gaseous	-2698.9141
	In MeOH	-2698.9183
H ⁺	Gaseous	-0.0100
	In MeOH	-2698.3478
AsPh ₂ ⁻	Gaseous	-2698.4267
	In MeOH	-115.9636
MeOH ₂ ⁺	Gaseous	-115.5670
	In MeOH	-115.5719
Cl ⁻	Gaseous	-460.0959
	In MeOH	-460.2132
Ni-Cl complex 97a	Gaseous	-4872.2145
	In MeOH	-4872.2662
Ni-Br complex 97c	Gaseous	-6986.0671

	In MeOH	-6986.1205
Intermediate A1	Gaseous	-7570.6511
	In MeOH	-7570.7671
Intermediate A2	Gaseous	-7071.8305
Intermediate A1'	Gaseous	-9684.4982
Intermediate B	Gaseous	-8084.1056
	In MeOH	-8084.2281
Intermediate C	Gaseous	-8084.6542
	In MeOH	-8084.7122
Nitrostyrene 127a	Gaseous	-513.4986
	In MeOH	-513.5076
Adduct 150a	Gaseous	-3212.4318
	In MeOH	-3212.4432

Derivation of values found in Tables 14 and 15

Table 53. ΔG_{rxn} in gaseous state at 298.15 K.

Compounds	$\Delta_r G$ (kcal/mol)
$\text{HAsPh}_2 (\text{g}) \rightarrow \text{H}^+ (\text{g}) + \text{AsPh}_2^- (\text{g})$	349.1
97a (g) + $\text{AsPh}_2^- (\text{g}) \rightarrow \text{A1} (\text{g})$	-55.7
97a (g) + $\text{AsPh}_2^- (\text{g}) \rightarrow \text{A2} (\text{g}) + \text{Cl}^- (\text{g})$	24244.4
97c (g) + $\text{AsPh}_2^- (\text{g}) \rightarrow \text{A1}' (\text{g})$	-52.3
97a (g) + $\text{HAsPh}_2 (\text{g}) \rightarrow \text{A1} (\text{g}) + \text{H}^+ (\text{g})$	293.4

Derivation of values found in Figure 32

Table 54. ΔG_{rxn} in methanolic state at 298.15 K.

Compounds	$\Delta_r G$ (kcal/mol)
$\text{HAsPh}_2 (\text{l}) + \text{MeOH} (\text{l}) \rightarrow \text{MeOH}_2^+ (\text{l}) + \text{AsPh}_2^- (\text{l})$	62.7
97a (l) + $\text{AsPh}_2^- (\text{l}) \rightarrow \text{A1} (\text{l})$	-46.6
A1 (l) + Nitrostyrene 127a (l) $\rightarrow \text{B} (\text{l})$	29.2
B (l) + $\text{MeOH}_2^+ (\text{l}) \rightarrow \text{C} (\text{l}) + \text{MeOH} (\text{l})$	-58.0
C (l) $\rightarrow$ Adduct 150a (l) + 97a (l)	1.8

Computational data for solvent effects of MeOH

Table 55 summarizes the free energy values of relevant species required for the calculation regarding the significance of solvent effects on the reaction: $\text{HAsPh}_2 \rightarrow \text{H}^+ + \text{AsPh}_2^-$.

Table 55. Free energy values at 298.15 K.

Compounds	State	$\varepsilon_0 + G_{\text{corr}}$ (Hartree)
HAsPh ₂	Gaseous	-2698.9141
	In MeOH	-2698.9183
	In THF	-2698.9175
H ⁺	Gaseous	-0.0100
AsPh ₂ ⁻	Gaseous	-2698.3478
	In MeOH	-2698.4267
	In THF	-2698.4167
MeOH ₂ ⁺	In MeOH	-115.9636
MeOH	In MeOH	-115.5719
THF-H ⁺	In THF	-232.5071
THF	In THF	-232.1166
Ni-Cl complex 97a	Gaseous	-4872.2145
	In MeOH	-4872.2662
Intermediate A1	Gaseous	-7570.6511
	In MeOH	-7570.7671

Derivation of values found in Table 17

Table 56. ΔG_{rxn} in gaseous and solution states.

Compounds	$\Delta_r G$ (kcal/mol)
$\text{HAsPh}_2 (\text{g}) \rightarrow \text{H}^+ (\text{g}) + \text{AsPh}_2^- (\text{g})$	349.1
$\text{HAsPh}_2 (\text{l}) + \text{MeOH} (\text{l}) \rightarrow \text{MeOH}_2^+ (\text{l}) + \text{AsPh}_2^- (\text{l})^{\text{a}}$	62.7
$\text{HAsPh}_2 (\text{l}) + \text{THF} (\text{l}) \rightarrow \text{THF-H}^+ (\text{l}) + \text{AsPh}_2^- (\text{l})^{\text{b}}$	217.5
97a (g) + AsPh ₂ ⁻ (g) → A1 (g)	-55.7
97a (l) + AsPh ₂ ⁻ (l) → A1 (l) ^a	-46.6

^aIn MeOH solution. ^bIn THF solution.

NBO plots of intermediate A1

Out of 143 bonding molecular orbitals (MOs), four MOs (MO 245, 216, 201, and 197) describe the bonding between the atoms of interest (diagrams have been included below). The atoms are coloured as follows- Nickel (blue), Chlorine (light green), Arsenic (violet). From the diagrams, σ -type bonding was observed between Ni–Cl and Cl–As while no delocalized bonding was observed across the Ni–Cl–As motif from the MOs plotted.

Figure 57. NBO plots of MO 245, 216, 201 and 197 of intermediate A1.

Coordinates of reactants and intermediates in the gas phase

A. Nitrostyrene **127a**

C	-3.081858	-1.066667	0.000036
C	-1.703806	-1.265234	-0.000024
C	-0.820665	-0.175469	-0.000050
C	-1.354958	1.124069	-0.000014
C	-2.730306	1.322124	0.000045
C	-3.597812	0.227679	0.000070
H	-3.754570	-1.926230	0.000055
H	-1.300318	-2.280631	-0.000051
H	-0.691188	1.990696	-0.000033
H	-3.131153	2.337479	0.000072
H	-4.677898	0.387170	0.000117
C	0.620555	-0.444128	-0.000111
H	0.935799	-1.491982	-0.000132
C	1.602728	0.460541	-0.000149
H	1.513686	1.544838	-0.000137
N	2.994637	0.030911	-0.000214
O	3.820205	0.921233	0.000173
O	3.247284	-1.155634	0.000175

B. Adduct **150a**

C	-0.843260	-0.860682	-0.862892
H	-0.506125	-1.732952	-1.443171
C	-2.239844	-0.521084	-1.351087

H	-2.249749	-0.286542	-2.426678
H	-2.716760	0.296297	-0.799357
N	-3.171291	-1.695946	-1.202254
O	-4.282110	-1.465145	-0.786161
O	-2.755281	-2.780939	-1.538544
C	-0.798374	-1.208436	0.601324
C	-1.297446	-0.341909	1.583924
C	-0.224662	-2.418993	1.008215
C	-1.189602	-0.663496	2.934992
H	-1.757668	0.606441	1.299830
C	-0.119718	-2.743525	2.358440
H	0.156185	-3.110446	0.252923
C	-0.594169	-1.861741	3.328112
H	-1.573853	0.030765	3.685329
H	0.336880	-3.690659	2.653399
H	-0.508629	-2.110643	4.388015
As	0.439481	0.562709	-1.504202
C	2.090774	-0.128009	-0.720389
C	2.299597	-0.417912	0.636708
C	3.132917	-0.368066	-1.625773
C	3.519123	-0.934235	1.069765
H	1.509542	-0.248879	1.369270
C	4.353136	-0.886945	-1.192279
H	2.990164	-0.148789	-2.687731
C	4.547417	-1.170399	0.157458
H	3.663364	-1.155630	2.129470
H	5.152802	-1.068624	-1.913654
H	5.501191	-1.577110	0.501194
C	-0.059262	2.025462	-0.303362
C	-1.253440	2.698559	-0.602119
C	0.692233	2.457186	0.794006
C	-1.717943	3.730163	0.211458
H	-1.833348	2.421745	-1.488145
C	0.235943	3.499212	1.601610
H	1.645864	1.983548	1.029253
C	-0.975989	4.127473	1.323703
H	-2.657568	4.231843	-0.030070
H	0.834297	3.818809	2.457789
H	-1.335892	4.935996	1.963542

C. HAsPh₂

As	-0.059692	-1.567633	0.080511
H	0.006739	-1.733561	1.594569
C	1.478056	-0.365578	-0.016443
C	2.256167	-0.031687	1.097976
C	1.818209	0.175371	-1.263205
C	3.347152	0.829288	0.969817
H	2.008606	-0.441685	2.080525
C	2.900916	1.042875	-1.390362
H	1.227554	-0.077261	-2.148877
C	3.668821	1.371258	-0.273024
H	3.944215	1.081855	1.849177
H	3.147804	1.463375	-2.367788
H	4.518457	2.050428	-0.371957
C	-1.480885	-0.210778	0.084175
C	-2.707166	-0.543625	-0.500684
C	-1.314496	1.067789	0.630158
C	-3.754250	0.379265	-0.531199
H	-2.850002	-1.533390	-0.944147
C	-2.358057	1.990060	0.598283
H	-0.358157	1.349780	1.078148
C	-3.580595	1.647151	0.018619
H	-4.706252	0.106731	-0.992326
H	-2.216124	2.984115	1.028634
H	-4.396251	2.373173	-0.007485

D. AsPh₂⁻

As	0.000024	-1.457978	0.000095
C	1.507756	-0.237670	-0.021577
C	2.746898	-0.708232	0.474018
C	1.526740	1.057201	-0.590921

C	3.913242	0.048744	0.405262
H	2.783307	-1.700491	0.936689
C	2.687589	1.824958	-0.642201
H	0.607100	1.462714	-1.021214
C	3.898220	1.332252	-0.147206
H	4.846464	-0.363494	0.803621
H	2.649176	2.822481	-1.092626
H	4.809871	1.934522	-0.191817
C	-1.507751	-0.237797	0.021853
C	-2.746719	-0.708233	-0.474383
C	-1.527002	1.056848	0.591666
C	-3.913024	0.048791	-0.406069
H	-2.783002	-1.700396	-0.937281
C	-2.687850	1.824679	0.642507
H	-0.607618	1.462102	1.022751
C	-3.898204	1.332216	0.146662
H	-4.846050	-0.363307	-0.805029
H	-2.649589	2.822039	1.093304
H	-4.809826	1.934571	0.190809

E. MeOH_2^+

C	0.786288	-0.002303	0.000056
H	1.078277	1.052392	-0.002100
H	1.107071	-0.512878	-0.913787
H	1.107034	-0.509305	0.915901
O	-0.697651	-0.000919	-0.000177
H	-1.209358	-0.828859	0.000517
H	-1.219543	0.819823	0.000549

F. MeOH

C	0.650865	-0.019767	0.000000
H	1.090048	0.988054	-0.000081

H	1.034462	-0.546479	0.895005
H	1.034448	-0.546615	-0.894930
O	-0.741177	0.122185	0.000000
H	-1.134731	-0.753841	0.000001

G. Ni-Cl complex **97a**

Ni	0.085044	-0.048561	-0.790728
C	0.051918	-0.009341	1.126441
C	1.237763	0.173989	1.856400
C	1.265022	0.141915	3.277368
C	0.062198	-0.103087	3.854170
C	-1.155035	-0.260313	3.258041
C	-1.141333	-0.209971	1.845706
C	-2.426613	-0.305743	1.059119
C	-1.628493	-2.846881	-0.210701
C	-2.341654	-3.547718	0.768066
C	-2.127985	-4.914013	0.946161
C	-1.202262	-5.586391	0.148820
C	-0.485654	-4.890528	-0.825062
C	-0.692677	-3.524906	-1.003653
C	2.537139	0.357905	1.105266
C	3.318068	-0.953011	0.807537
C	2.965309	-2.024944	1.826255
C	1.278054	-3.559250	2.364661
C	4.814065	-0.675138	0.823580
C	6.868036	-1.333318	-0.065930
C	3.436797	1.022169	-1.570458
C	4.507721	1.902085	-1.282779
C	5.648944	1.711804	-2.011933
C	5.819592	0.772033	-3.004452
C	4.723820	-0.045245	-3.320773
C	3.541957	0.071696	-2.589580
C	1.569141	2.811712	-0.242026

C	1.026566	3.492580	-1.341476
C	0.655184	4.827487	-1.219172
C	0.807282	5.485671	0.001877
C	1.331944	4.807083	1.098894
C	1.713300	3.471517	0.980644
Cl	0.128970	-0.174936	-3.004566
O	1.899845	-2.706207	1.414967
O	3.524752	-2.200145	2.875053
O	5.463273	-1.526755	0.038162
O	5.340699	0.200703	1.454755
P	-1.838452	-1.067871	-0.533650
P	1.957079	1.057219	-0.500126
H	2.217457	0.239900	3.807404
H	-2.097646	-0.388386	3.797595
H	-3.197170	-0.899043	1.569463
H	-3.071035	-3.034151	1.397890
H	-2.687524	-5.454458	1.712540
H	-1.035138	-6.656235	0.290928
H	0.244465	-5.412598	-1.446570
H	-0.129794	-2.974026	-1.762797
H	3.226304	1.018884	1.650664
H	3.048519	-1.362140	-0.176191
H	1.979379	-4.328536	2.716770
H	0.427574	-4.017197	1.849257
H	0.928271	-2.968554	3.224555
H	7.083001	-0.316983	-0.425750
H	7.224414	-2.076901	-0.786662
H	7.352459	-1.481035	0.909605
H	4.396587	2.678566	-0.516773
H	6.773581	0.634251	-3.524732
H	4.804082	-0.790570	-4.117155
H	2.680724	-0.559490	-2.819490
H	0.886857	2.966095	-2.290469
H	1.441065	5.315907	2.058492
H	2.109571	2.949265	1.853135
H	0.507549	6.531148	0.100396
H	0.235740	5.353741	-2.078998
C	-3.212781	-0.931497	-1.721010
C	-3.246630	0.184223	-2.566062
C	-4.256327	-1.863358	-1.764608
C	-4.327374	0.378486	-3.423962
H	-2.408634	0.884027	-2.573060
C	-5.329732	-1.670665	-2.628977
H	-4.237176	-2.740396	-1.114383

C	-5.368450	-0.547380	-3.456155
H	-4.344769	1.249594	-4.082012
H	-6.140482	-2.401312	-2.656028
H	-6.209617	-0.400304	-4.137615
C	-3.039129	1.077500	0.740949
H	-2.537896	1.545369	-0.118484
C	-2.824642	2.064931	1.881018
O	-2.074100	2.997561	1.844619
O	-3.566754	1.740069	2.944718
C	-3.375172	2.533216	4.107219
H	-3.556442	3.594917	3.889889
H	-4.092718	2.167246	4.849469
H	-2.346747	2.417918	4.480571
C	-4.523496	0.948545	0.424795
O	-5.211267	0.003202	0.701676
O	-4.964993	2.037252	-0.198457
C	-6.327063	2.024703	-0.601077
H	-6.989985	1.882635	0.263834
H	-6.514129	2.996305	-1.070496
H	-6.499366	1.213191	-1.322908

H. Intermediate A1

Ni	0.352669	-0.363599	-0.345810
C	1.029285	-1.645402	0.871753
C	2.250496	-1.490622	1.557548
C	2.628647	-2.405581	2.552699
C	1.943801	-3.607304	2.863314
C	0.769143	-3.748654	2.094162
C	0.274503	-2.789591	1.195307
C	-1.095459	-2.934015	0.574526
C	0.242205	-3.306375	-1.969669
C	-0.069781	-4.670406	-2.039677

C	0.773216	-5.547573	-2.717311
C	1.936063	-5.070834	-3.324692
C	2.259761	-3.718354	-3.244917
C	1.418963	-2.841155	-2.564121
C	3.133044	-0.325122	1.184512
C	4.184851	-0.631433	0.084403
C	4.707371	-2.050599	0.246382
C	4.036057	-4.278428	-0.071184
C	5.320949	0.379111	0.152143
C	6.806295	1.637545	-1.141009
C	2.748417	2.062990	-0.609247
C	3.604287	3.110563	-0.205140
C	4.181920	4.065367	-1.078487
C	3.850292	3.817045	-2.434544
C	3.085180	2.736393	-2.894405
C	2.513882	1.857357	-1.979572
C	1.262281	1.829623	1.970703
C	1.268855	3.226945	2.059068
C	0.563647	3.872057	3.076003
C	-0.148511	3.131606	4.017229
C	-0.140815	1.737185	3.949229
C	0.556269	1.089912	2.934802
Cl	-0.848120	1.343396	-1.561400
O	3.920488	-2.904217	-0.410075
O	5.669214	-2.372749	0.890287
O	5.839290	0.598169	-1.053112
O	5.700689	0.913821	1.159154
P	-0.789883	-2.117816	-1.053438
P	1.930618	0.919513	0.526768
H	3.555323	-2.156978	3.094509
H	0.148969	-4.655024	2.202668
H	-1.398474	-3.986038	0.477723
H	-0.971905	-5.052878	-1.555458
H	0.527920	-6.610979	-2.761662
H	2.600872	-5.761705	-3.848386
H	3.183866	-3.343049	-3.688039
H	1.696992	-1.789705	-2.464260
H	3.678067	0.071306	2.053665
H	3.728271	-0.573358	-0.913807
H	5.070612	-4.628468	-0.200399
H	3.358834	-4.811215	-0.749101
H	3.712063	-4.428670	0.971154
H	6.322093	2.613816	-0.972508
H	7.207601	1.590713	-2.160093

H	7.607594	1.485522	-0.403749
H	3.844467	3.160001	0.867257
H	4.223201	4.507094	-3.209900
H	2.913415	2.582315	-3.966019
H	1.882221	1.033807	-2.323563
H	1.808998	3.821426	1.322225
H	-0.701796	1.134916	4.666212
H	0.512563	0.000669	2.876035
H	-0.708474	3.640468	4.806229
H	0.569632	4.963732	3.119287
C	-2.375864	-2.008264	-1.971688
C	-3.277500	-1.007842	-1.583718
C	-2.732453	-2.851681	-3.030536
C	-4.512705	-0.868233	-2.209240
H	-3.014709	-0.314502	-0.785524
C	-3.967155	-2.711523	-3.662456
H	-2.041327	-3.624606	-3.370657
C	-4.862195	-1.724921	-3.251768
H	-5.189673	-0.075010	-1.884876
H	-4.229592	-3.381135	-4.484679
H	-5.827032	-1.615730	-3.752495
C	-2.196964	-2.184239	1.355436
H	-2.163910	-1.106013	1.143990
C	-1.937050	-2.262359	2.859080
O	-1.663159	-1.310304	3.539180
O	-2.040883	-3.507161	3.306586
C	-1.490059	-3.770124	4.594873
H	-1.880694	-3.060141	5.336781
H	-1.785213	-4.794985	4.845429
H	-0.391038	-3.696288	4.536518
C	-3.581984	-2.701018	1.014762
O	-3.835571	-3.762602	0.514723
O	-4.522263	-1.801808	1.343371
C	-5.853800	-2.157769	1.020485
H	-6.135986	-3.105449	1.500978
H	-6.489378	-1.344215	1.388339
H	-5.967795	-2.265784	-0.068885
As	-1.624344	2.454477	0.282806
C	-3.504023	2.468268	-0.242700
C	-4.372928	1.738377	0.577612
C	-4.009713	3.131578	-1.367954
C	-5.737425	1.689206	0.287621
H	-3.986572	1.194644	1.445199
C	-5.369604	3.073620	-1.660024

H	-3.333750	3.697777	-2.013666
C	-6.234996	2.357877	-0.828714
H	-6.409262	1.123236	0.935996
H	-5.759207	3.589299	-2.540485
H	-7.302682	2.318539	-1.057256
C	-1.078911	4.230158	-0.295320
C	-1.850943	5.333613	0.090876
C	0.179541	4.431702	-0.874021
C	-1.360295	6.625078	-0.099117
H	-2.835382	5.192905	0.546952
C	0.672071	5.723609	-1.049209
H	0.806115	3.590127	-1.177891
C	-0.097728	6.819735	-0.660857
H	-1.965954	7.483157	0.202474
H	1.676612	5.846510	-1.461758
H	0.292115	7.832004	-0.790826

I. Intermediate A2

Ni	0.005839	-0.167331	-0.297075
C	-0.254521	-1.753001	0.780102
C	0.796210	-2.306281	1.537989
C	0.606627	-3.442849	2.344259
C	-0.647399	-4.003399	2.331023
C	-1.718919	-3.542484	1.603511
C	-1.513777	-2.385752	0.833796
C	-2.646446	-1.772974	0.052945
C	-1.238487	-2.217043	-2.486429
C	-1.960276	-3.370098	-2.915535
C	-1.220337	-3.964745	-3.939148
C	-0.047295	-3.194628	-4.160721
C	-0.053768	-2.119760	-3.273366
C	2.165327	-1.682242	1.432517
C	3.065549	-2.317698	0.340298
C	2.647467	-3.757546	0.051274
C	0.996971	-4.939436	-1.158913

C	4.528308	-2.245928	0.735923
C	6.709034	-2.381407	-0.090244
C	3.368359	0.726493	0.310671
C	4.425037	1.120805	1.154271
C	5.594346	1.498657	0.539421
C	5.831646	1.505645	-0.817845
C	4.779339	1.087974	-1.640244
C	3.562495	0.709553	-1.076004
C	1.430028	1.000897	2.489784
C	1.801434	2.346725	2.609885
C	1.395427	3.095172	3.710976
C	0.603712	2.510851	4.698065
C	0.217246	1.177625	4.577212
C	0.622723	0.423813	3.478800
O	1.719231	-3.743763	-0.883318
O	3.070508	-4.728267	0.622243
O	5.310035	-2.420764	-0.325475
O	4.939788	-2.042133	1.847383
P	-1.751951	-0.984876	-1.370768
P	1.794203	0.073088	0.964171
H	1.436625	-3.865261	2.916102
H	-2.695935	-4.031721	1.615097
H	-3.359820	-2.529693	-0.302729
H	-2.913038	-3.719463	-2.513240
H	-1.494115	-4.877038	-4.472148
H	0.732219	-3.415247	-4.891592
H	0.709585	-1.342029	-3.185972
H	2.715073	-1.729679	2.384248
H	2.947899	-1.799669	-0.620606
H	1.679196	-5.719152	-1.525555
H	0.258941	-4.668831	-1.923431
H	0.503066	-5.289529	-0.240658
H	6.999656	-1.408252	0.331399
H	7.187085	-2.533199	-1.063881
H	7.007813	-3.174808	0.609057
H	4.319215	1.101984	2.241681
H	6.789484	1.815976	-1.242380
H	4.905196	1.064726	-2.724510
H	2.748940	0.389134	-1.730550
H	2.411262	2.818722	1.837253
H	-0.424366	0.717389	5.330442
H	0.274524	-0.605677	3.381119
H	0.277762	3.100166	5.557790
H	1.690244	4.143281	3.791301

C	-2.994804	0.108177	-2.188328
C	-3.375512	1.355636	-1.674427
C	-3.581573	-0.337262	-3.379064
C	-4.341252	2.127691	-2.318261
H	-2.934221	1.744949	-0.755081
C	-4.547510	0.434365	-4.021742
H	-3.269143	-1.297936	-3.798166
C	-4.932829	1.665578	-3.493034
H	-4.624895	3.095378	-1.898361
H	-4.999795	0.068866	-4.946122
H	-5.687293	2.270111	-4.001917
C	-3.431198	-0.703083	0.848106
H	-2.967511	0.283269	0.735939
C	-3.384427	-0.940807	2.346535
O	-2.693588	-0.312278	3.107161
O	-4.173684	-1.944944	2.717175
C	-4.104745	-2.339788	4.079911
H	-4.330807	-1.493692	4.743514
H	-4.848808	-3.133450	4.205317
H	-3.098953	-2.720793	4.310094
C	-4.862937	-0.581943	0.346506
O	-5.427804	-1.374175	-0.354124
O	-5.412440	0.550855	0.789224
C	-6.719165	0.837517	0.314426
H	-7.420019	0.034826	0.583083
H	-7.017032	1.778739	0.789145
H	-6.706082	0.949602	-0.779882
As	-0.024577	2.011981	-1.061455
C	1.435909	3.009521	-1.812059
C	1.762133	2.754169	-3.151822
C	2.236579	3.884058	-1.063559
C	2.874085	3.360811	-3.731455
H	1.146651	2.071915	-3.745710
C	3.352780	4.480182	-1.644213
H	1.997586	4.089373	-0.017702
C	3.672835	4.219703	-2.976936
H	3.116973	3.160162	-4.777054
H	3.981107	5.146198	-1.049358
H	4.549160	4.688916	-3.429134
C	-0.755093	3.122016	0.319745
C	-0.791555	4.522351	0.240036
C	-1.357188	2.482282	1.416264
C	-1.401540	5.262258	1.250413
H	-0.347574	5.036053	-0.616111

C	-1.975854	3.224242	2.416358
H	-1.326676	1.394655	1.522272
C	-1.994940	4.616523	2.336811
H	-1.424017	6.352181	1.182653
H	-2.430671	2.699198	3.258060
H	-2.476633	5.202979	3.122307

J. Intermediate **B**

Ni	0.784978	0.133315	-0.193404
C	2.364439	0.069656	0.864495
C	2.804401	1.184779	1.614826
C	3.868949	1.063853	2.525434
C	4.742062	-0.048083	2.607802
C	4.357823	-1.069902	1.717622
C	3.175969	-1.085239	0.958349
C	2.822567	-2.326394	0.168551
C	2.989592	-1.097987	-2.378947
C	3.894316	-2.028242	-2.912656
C	4.906238	-1.605030	-3.769927
C	5.035021	-0.250744	-4.086076
C	4.152353	0.679004	-3.542318
C	3.133556	0.256601	-2.690474
C	2.218083	2.544971	1.320925
C	3.058569	3.387174	0.320816
C	4.541628	3.053279	0.380632
C	6.093339	1.422015	-0.272828
C	2.860078	4.876188	0.568082
C	2.889385	6.968674	-0.480328
C	0.176886	3.490977	-0.632353
C	-0.096797	4.830600	-0.287303
C	-0.217135	5.898854	-1.212476
C	-0.006315	5.472303	-2.548208
C	0.261974	4.153874	-2.943318

C	0.350696	3.148122	-1.983925
C	-0.616730	2.365346	1.988346
C	-1.835497	3.046406	1.884877
C	-2.737150	3.045612	2.950634
C	-2.432220	2.368318	4.130614
C	-1.208816	1.705164	4.248631
C	-0.306911	1.702171	3.186446
Cl	-1.223713	-0.041327	-1.412426
O	4.811118	2.014711	-0.409765
O	5.363728	3.643927	1.028615
O	3.172994	5.575534	-0.516502
O	2.477528	5.358248	1.601830
P	1.741376	-1.591306	-1.143203
P	0.545850	2.199638	0.584380
H	4.062596	1.951366	3.149537
H	5.020783	-1.937440	1.571428
H	3.724136	-2.748522	-0.298533
H	3.818415	-3.083906	-2.635729
H	5.610677	-2.333689	-4.177706
H	5.838729	0.080946	-4.747786
H	4.265375	1.743467	-3.755430
H	2.470948	0.992629	-2.232388
H	2.114406	3.154654	2.231398
H	2.749258	3.185602	-0.714209
H	6.885277	2.158568	-0.475575
H	6.123864	0.608796	-1.008158
H	6.205088	1.015349	0.745444
H	1.795359	7.114389	-0.544881
H	3.377961	7.398964	-1.362832
H	3.287312	7.421910	0.438608
H	-0.182578	5.052765	0.786576
H	-0.049280	6.218311	-3.359259
H	0.408707	3.901971	-4.000137
H	0.545455	2.113346	-2.276896
H	-2.074578	3.594622	0.972737
H	-0.954466	1.182497	5.173275
H	0.647775	1.174466	3.281301
H	-3.140503	2.366392	4.962324
H	-3.681162	3.587643	2.851194
C	0.709793	-2.907670	-1.897126
C	-0.368001	-3.368279	-1.127223
C	0.907253	-3.455286	-3.168748
C	-1.190763	-4.391038	-1.592517
H	-0.582757	-2.913035	-0.156586

C	0.070761	-4.463883	-3.644153
H	1.721118	-3.094291	-3.799074
C	-0.972701	-4.943780	-2.853929
H	-2.013850	-4.739800	-0.966055
H	0.240643	-4.880728	-4.639414
H	-1.621724	-5.741347	-3.224313
C	2.162728	-3.460604	0.967889
H	1.125902	-3.216075	1.225501
C	2.859562	-3.676143	2.309350
O	2.361832	-3.457753	3.381854
O	4.092299	-4.147412	2.150901
C	4.926028	-4.112755	3.304728
H	4.468561	-4.672899	4.132201
H	5.874857	-4.571400	3.005811
H	5.084850	-3.065402	3.608242
C	2.157388	-4.757240	0.176873
O	2.809089	-4.990593	-0.806107
O	1.306147	-5.640163	0.713832
C	1.147563	-6.858866	0.010753
H	2.111047	-7.375151	-0.105902
H	0.458753	-7.469430	0.605760
H	0.722665	-6.669791	-0.986776
As	-3.488317	0.301051	-0.157996
C	-4.463682	-0.946457	-1.238833
C	-3.820396	-2.023052	-1.852679
C	-5.837556	-0.742966	-1.405126
C	-4.565458	-2.908416	-2.628299
H	-2.745321	-2.164622	-1.738157
C	-6.570728	-1.631249	-2.186602
H	-6.342025	0.094872	-0.917559
C	-5.935470	-2.713383	-2.795984
H	-4.060459	-3.750214	-3.106855
H	-7.643627	-1.477451	-2.315415
H	-6.514937	-3.407704	-3.408541
C	-3.802259	2.134968	-0.644715
C	-4.914937	2.787573	-0.093661
C	-2.949089	2.792562	-1.529685
C	-5.132105	4.126843	-0.401979
H	-5.606155	2.268930	0.572829
C	-3.174503	4.137765	-1.820192
H	-2.083808	2.289876	-1.958348
C	-4.251457	4.805989	-1.245746
H	-5.989331	4.643509	0.034768
H	-2.462685	4.667234	-2.454635

H	-4.396132	5.868544	-1.449760
C	-3.049559	-0.357231	1.614237
H	-2.404255	0.388690	2.091701
C	-4.468441	0.199534	1.608730
H	-4.550422	1.158580	2.121910
N	-5.718622	-0.505250	1.746100
O	-6.707963	0.203960	1.849687
O	-5.758404	-1.717011	1.697656
C	-2.516732	-1.731625	1.839159
C	-3.122933	-2.919506	1.404276
C	-1.300536	-1.810989	2.533628
C	-2.534228	-4.148625	1.687490
H	-4.065749	-2.887520	0.864615
C	-0.720619	-3.042001	2.824781
H	-0.799613	-0.895183	2.852572
C	-1.336349	-4.216573	2.397688
H	-3.025373	-5.064800	1.350795
H	0.231848	-3.079241	3.356971
H	-0.865912	-5.179615	2.603513

K. Intermediate C

Ni	1.447722	-0.525318	-0.573626
C	1.883370	-0.965700	1.246742
C	2.873734	-0.239166	1.936369
C	3.278545	-0.580210	3.250642
C	2.620732	-1.651562	3.762525
C	1.698394	-2.468047	3.192543
C	1.298219	-2.069959	1.891396
C	0.217131	-2.838831	1.163947
C	2.078297	-3.807246	-0.905599
C	2.240393	-4.991816	-0.178318
C	3.237088	-5.900413	-0.532504

C	4.079313	-5.629244	-1.610276
C	3.931702	-4.441762	-2.327084
C	2.938403	-3.530491	-1.976968
C	3.528012	0.922321	1.241030
C	4.839760	0.561856	0.483076
C	5.437265	-0.725929	1.028319
C	5.232784	-3.052726	0.947516
C	5.863122	1.678863	0.637370
C	7.650560	2.757547	-0.404895
C	3.145283	2.640241	-1.033541
C	3.864110	3.713736	-0.437229
C	4.650387	4.493644	-1.244200
C	4.794352	4.287723	-2.602713
C	4.125211	3.199132	-3.178934
C	3.296904	2.388870	-2.401362
C	1.115420	2.544026	1.050965
C	0.956153	3.915278	0.809539
C	0.185177	4.698292	1.667176
C	-0.442613	4.123821	2.771058
C	-0.337828	2.750038	2.984774
C	0.426667	1.964038	2.126571
Cl	1.222341	-0.302335	-2.780507
O	4.938603	-1.780115	0.389961
O	6.215837	-0.791875	1.941905
O	6.678783	1.719332	-0.408166
O	5.929374	2.417804	1.582238
P	0.736235	-2.610136	-0.604874
P	2.219219	1.493603	0.026536
H	4.053636	-0.004660	3.764160
H	1.254721	-3.348462	3.665130
H	0.177987	-3.892180	1.473127
H	1.586105	-5.222724	0.664931
H	3.353653	-6.825674	0.035501
H	4.856768	-6.343840	-1.888613
H	4.596305	-4.219658	-3.164276
H	2.818224	-2.600845	-2.540170
H	3.777678	1.720279	1.955520
H	4.649634	0.399296	-0.587159
H	6.315927	-3.181772	1.076919
H	4.835172	-3.792101	0.246766
H	4.739761	-3.154012	1.926224
H	7.149153	3.737002	-0.384274
H	8.219160	2.642272	-1.333793
H	8.313513	2.667023	0.466961

H	3.817566	3.866593	0.646783
H	5.392142	4.953488	-3.235018
H	4.229022	2.998175	-4.248997
H	2.761894	1.551668	-2.855351
H	1.434313	4.384655	-0.050104
H	-0.871259	2.275650	3.809627
H	0.473582	0.890708	2.304111
H	-1.045812	4.739356	3.441935
H	0.075635	5.766088	1.467864
C	-0.638806	-3.212941	-1.639543
C	-1.442219	-2.302186	-2.331474
C	-0.918849	-4.584216	-1.722760
C	-2.523555	-2.754090	-3.086618
H	-1.201684	-1.239446	-2.304621
C	-2.002132	-5.031206	-2.470724
H	-0.298369	-5.308096	-1.191554
C	-2.807237	-4.115404	-3.151558
H	-3.141245	-2.033201	-3.625160
H	-2.217076	-6.100342	-2.524613
H	-3.655453	-4.467304	-3.743395
C	-1.197348	-2.249259	1.359947
H	-1.383802	-1.414613	0.665699
C	-1.370814	-1.648128	2.745893
O	-1.489501	-0.473410	2.974884
O	-1.363788	-2.585745	3.690370
C	-1.440897	-2.130612	5.036544
H	-2.361939	-1.554176	5.198816
H	-1.438019	-3.029804	5.661516
H	-0.574165	-1.496502	5.272498
C	-2.268150	-3.311948	1.146023
O	-2.078944	-4.497049	1.117561
O	-3.463321	-2.741334	1.023849
C	-4.567632	-3.599835	0.770595
H	-4.637328	-4.380545	1.540398
H	-5.455801	-2.957410	0.791776
H	-4.455511	-4.071813	-0.216301
As	-2.281134	1.011245	-0.701872
C	-3.742302	0.358599	-1.836967
C	-4.551008	-0.682446	-1.360590
C	-3.918530	0.787856	-3.157721
C	-5.548276	-1.236347	-2.158081
H	-4.402232	-1.066086	-0.350986
C	-4.907009	0.220522	-3.964411
H	-3.281406	1.570865	-3.572953

C	-5.734541	-0.782690	-3.463468
H	-6.179808	-2.032815	-1.757998
H	-5.031012	0.572351	-4.991122
H	-6.514838	-1.216708	-4.092679
C	-1.818198	2.636358	-1.688124
C	-2.736057	3.637692	-2.038194
C	-0.481929	2.790353	-2.067768
C	-2.315979	4.783567	-2.707447
H	-3.796303	3.515794	-1.803345
C	-0.056883	3.936361	-2.741747
H	0.230894	1.988473	-1.867526
C	-0.970982	4.939598	-3.050207
H	-3.041823	5.557209	-2.967214
H	0.994986	4.036231	-3.020423
H	-0.640938	5.841341	-3.570741
C	-3.249998	1.740380	0.938087
H	-2.594092	1.352483	1.729568
C	-3.215771	3.248690	1.033399
H	-3.932528	3.767577	0.388919
N	-3.531298	3.753881	2.419191
O	-3.756628	4.940412	2.503932
O	-3.497403	2.984370	3.350708
C	-4.625613	1.163518	1.149317
C	-5.730455	1.591968	0.404281
C	-4.813500	0.152754	2.098365
C	-6.984688	1.016413	0.588116
H	-5.606726	2.363554	-0.360223
C	-6.064816	-0.432522	2.278559
H	-3.962010	-0.167443	2.700858
C	-7.155359	-0.005686	1.521161
H	-7.830439	1.358865	-0.011711
H	-6.191351	-1.218855	3.026830
H	-8.137802	-0.461200	1.664014
H	-2.221183	3.665921	0.823668

L. Ni-Br complex **97c**

Ni	-0.103148	0.080931	-0.681923
C	-0.052625	-0.024882	1.237919
C	-1.233329	-0.220271	1.971977
C	-1.245478	-0.237297	3.392070
C	-0.035830	-0.034511	3.977869
C	1.175135	0.125623	3.364360
C	1.148764	0.130340	1.952452
C	2.420885	0.242901	1.149236
C	1.598185	2.859030	0.067563
C	2.274931	3.477690	1.124619
C	2.073451	4.831874	1.388604
C	1.194766	5.575042	0.601083
C	0.509469	4.959903	-0.446611
C	0.705001	3.606688	-0.711213
C	-2.531586	-0.382518	1.215431
C	-3.269300	0.946715	0.907239
C	-2.973566	1.970201	1.992425
C	-1.335392	3.500415	2.675308
C	-4.767647	0.714532	0.795770
C	-6.751285	1.601560	-0.055268
C	-3.422652	-1.170637	-1.432208
C	-4.330343	-2.243889	-1.261191
C	-5.496366	-2.139077	-1.961898
C	-5.855349	-1.123089	-2.815166
C	-4.912755	-0.102650	-3.019160
C	-3.708753	-0.125822	-2.316075
C	-1.449745	-2.817553	-0.074354
C	-0.797835	-3.475043	-1.127315
C	-0.336159	-4.776058	-0.956787
C	-0.508972	-5.423273	0.266676
C	-1.149210	-4.769961	1.316485
C	-1.620497	-3.469320	1.149647

O	-1.909937	2.692789	1.658369
O	-3.572825	2.071077	3.029251
O	-5.349209	1.716286	0.142388
O	-5.353637	-0.238606	1.231386
P	1.815560	1.106791	-0.382617
P	-1.931489	-1.093580	-0.378484
H	-2.194762	-0.346453	3.925874
H	2.126357	0.220511	3.896369
H	3.215340	0.790590	1.673956
H	2.965813	2.908781	1.749728
H	2.605208	5.306999	2.215667
H	1.038797	6.635974	0.808088
H	-0.185205	5.536211	-1.060763
H	0.165220	3.122723	-1.530322
H	-3.242651	-1.033551	1.744366
H	-2.913142	1.387513	-0.035082
H	-2.064189	4.231089	3.053023
H	-0.482860	4.006567	2.211063
H	-0.993879	2.865216	3.506244
H	-6.981013	0.687615	-0.621711
H	-7.053462	2.489070	-0.621590
H	-7.277054	1.565917	0.909125
H	-4.075975	-3.088185	-0.610903
H	-6.830517	-1.081376	-3.311361
H	-5.130097	0.716589	-3.710265
H	-2.970000	0.663618	-2.469256
H	-0.644186	-2.957959	-2.079403
H	-1.276200	-5.270195	2.278404
H	-2.104960	-2.964237	1.987001
H	-0.132801	-6.439102	0.404772
H	0.170785	-5.283056	-1.780333
C	3.206446	1.076618	-1.560660
C	3.295330	0.017140	-2.471613
C	4.224445	2.036573	-1.518639
C	4.400672	-0.089999	-3.313848
H	2.486141	-0.712833	-2.538679
C	5.323477	1.929963	-2.365106
H	4.166214	2.868630	-0.814106
C	5.414145	0.865160	-3.261903
H	4.458814	-0.916358	-4.025091
H	6.113556	2.682223	-2.324149
H	6.274725	0.786039	-3.930251
C	2.996355	-1.132493	0.738600
H	2.477942	-1.535880	-0.143090

C	2.763642	-2.181451	1.818813
O	2.001222	-3.100713	1.725728
O	3.504270	-1.927046	2.901854
C	3.286223	-2.771415	4.022748
H	3.450134	-3.824863	3.756789
H	4.002919	-2.454645	4.788000
H	2.256522	-2.652897	4.391579
C	4.481861	-1.024903	0.419053
O	5.198163	-0.117056	0.744085
O	4.889715	-2.089043	-0.267719
C	6.251507	-2.093635	-0.670507
H	6.917497	-2.014227	0.200142
H	6.412619	-3.045037	-1.188479
H	6.447370	-1.250807	-1.349204
Br	-0.216975	0.315563	-3.011631

M. Intermediate A1'

Ni	0.504321	-0.341365	-0.348046
C	1.439155	-1.484029	0.842767
C	2.621210	-1.102764	1.508660
C	3.207011	-1.951751	2.461081
C	2.798446	-3.281273	2.733574
C	1.652030	-3.634775	1.990785
C	0.938682	-2.765241	1.149946
C	-0.411829	-3.153317	0.591123
C	0.845402	-3.285074	-1.984046
C	0.648642	-4.661465	-2.159921
C	1.585339	-5.419780	-2.856446
C	2.728583	-4.810790	-3.377237
C	2.937412	-3.446258	-3.191062
C	2.001724	-2.686532	-2.491495

C	3.230987	0.234411	1.165665
C	4.296132	0.187196	0.037078
C	5.126916	-1.081024	0.161401
C	4.977258	-3.397115	-0.190374
C	5.178827	1.425787	0.098570
C	6.268638	3.032274	-1.200307
C	2.321831	2.574189	-0.499823
C	2.886557	3.781901	-0.032902
C	3.198311	4.897284	-0.849117
C	2.949129	4.641323	-2.220890
C	2.500278	3.421390	-2.745708
C	2.163006	2.383770	-1.882881
C	0.922640	1.885927	2.048595
C	0.621973	3.244765	2.203978
C	-0.210106	3.670719	3.239975
C	-0.745112	2.748748	4.136847
C	-0.431595	1.395092	4.004234
C	0.393287	0.965811	2.969933
O	4.544145	-2.080459	-0.503616
O	6.146594	-1.189061	0.787339
O	5.572747	1.794859	-1.117472
O	5.478670	2.001344	1.109601
P	-0.326644	-2.269696	-1.028630
P	1.779583	1.218740	0.568467
H	4.073557	-1.532100	2.996741
H	1.231536	-4.650942	2.080499
H	-0.514979	-4.240937	0.470297
H	-0.240581	-5.143925	-1.745119
H	1.427606	-6.492753	-2.985527
H	3.466567	-5.408096	-3.917896
H	3.844038	-2.968417	-3.566769
H	2.191233	-1.627398	-2.306698
H	3.703276	0.707386	2.039231
H	3.812204	0.154414	-0.949445
H	6.059084	-3.504454	-0.356163
H	4.414421	-4.062174	-0.855668
H	4.728103	-3.627165	0.858096
H	5.607479	3.857349	-0.890250
H	6.541698	3.153872	-2.254792
H	7.168261	3.015889	-0.567740
H	3.106356	3.836686	1.043328
H	3.127909	5.443993	-2.955905
H	2.385523	3.279370	-3.826523
H	1.772806	1.441630	-2.277722

H	1.018535	3.978988	1.503558
H	-0.843719	0.648909	4.685925
H	0.592291	-0.102060	2.866629
H	-1.406206	3.084149	4.940214
H	-0.442233	4.734213	3.333044
C	-1.927293	-2.390360	-1.921375
C	-3.015927	-1.667337	-1.411951
C	-2.099510	-3.089241	-3.121671
C	-4.248262	-1.669285	-2.056758
H	-2.907016	-1.077278	-0.501187
C	-3.332609	-3.089387	-3.773593
H	-1.263099	-3.635319	-3.560800
C	-4.410750	-2.385605	-3.242150
H	-5.072185	-1.087398	-1.637964
H	-3.445691	-3.640226	-4.710106
H	-5.373551	-2.382173	-3.758191
C	-1.579728	-2.650533	1.464926
H	-1.735207	-1.570056	1.334293
C	-1.236448	-2.789632	2.948989
O	-1.117278	-1.858765	3.699065
O	-1.082053	-4.061379	3.294450
C	-0.439468	-4.308312	4.542750
H	-0.933900	-3.752580	5.351412
H	-0.517228	-5.387761	4.712622
H	0.619889	-4.010325	4.467008
C	-2.874742	-3.374840	1.147796
O	-2.971721	-4.444961	0.612439
O	-3.935749	-2.655319	1.545316
C	-5.203802	-3.213986	1.255555
H	-5.316589	-4.201909	1.724832
H	-5.946548	-2.516505	1.659447
H	-5.335657	-3.322424	0.168357
As	-2.101457	2.038087	0.388301
C	-3.956902	1.721210	-0.142886
C	-4.696283	0.855108	0.671350
C	-4.563156	2.293983	-1.268221
C	-6.033035	0.580214	0.374829
H	-4.228444	0.381181	1.539809
C	-5.892102	2.009918	-1.568423
H	-3.988305	2.966218	-1.910296
C	-6.630525	1.158068	-0.743193
H	-6.607116	-0.088076	1.020160
H	-6.357250	2.456891	-2.449783
H	-7.676157	0.943526	-0.976045

C	-1.923020	3.921672	-0.080180
C	-2.926203	4.818175	0.310446
C	-0.712722	4.414545	-0.583291
C	-2.713821	6.191986	0.197387
H	-3.876430	4.451436	0.709351
C	-0.497523	5.787820	-0.679653
H	0.091807	3.742440	-0.890653
C	-1.499338	6.676513	-0.289586
H	-3.500261	6.887062	0.501243
H	0.477045	6.137461	-1.031407
H	-1.330537	7.753467	-0.361226
Br	-1.074792	1.148885	-1.614400