Development of catalytic asymmetric P(III)-C bond formations in ferrocenyl, heterobicyclic & exocyclic olefins

Abdul Sadeer Abd Salam

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**Development of Catalytic Asymmetric P(III)-C Bond Formations
in Ferrocenyl, Heterobicyclic & Exocyclic Olefins**

ABDUL SADEER BIN ABD SALAM

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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in Ferrocenyl, Heterobicyclic & Exocyclic Olefins**

ABDUL SADEER BIN ABD SALAM

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

2019

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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Chapter 3 is published as “Sadeer, A., Ong, Y. J., Kojima, T., Foo, C. Q., Li, Y., Pullarkat, S. A., & Leung, P. H. (2018). Desymmetrization of Achiral Heterobicyclic Alkenes through Catalytic Asymmetric Hydrophosphination. *Chemistry–An Asian Journal*, 13(19), 2829-2833. DOI: 10.1002/asia.201801061”

The contributions of the co-authors are as follows:

- Prof Leung P.H. and Dr. Pullarkat S.A. provided the initial project directions and suggest strategies and materials required.
- I prepared the manuscript drafts. The manuscript was revised by Dr. Sumod S.A.
- I designed the experimental study through theoretical brainstorming with Foo C.Q. and reached a consensus of the array of catalysts to be utilized.
- I synthesized all enantiopure catalyst and ran all preliminary experiments.
- All substrate synthesis and purification were conducted by Ong, Y. J. and Kojima, T. with my supervision.
- Foo, C. Q. assisted me in the collection of nuclear magnetic resonance spectra and improving the experimental method.
- Dr Li Y. assisted in carrying out the X-Ray Diffraction on crystal data and also structural refinement and analysis.
- Ong, Y. J. and Kojima, T. assisted in the collection of experimental data (purification of chiral products as well as characterization data and chiral High-Performance Liquid Chromatography) with my guidance.

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- I performed the Structure Activity Relationship analysis of compound’s activity from compiled data prepared by A. Kizhakeyil and prepared discussions & rationale regarding the chemistry and activity of compounds with Dr. Pullarkat S.A.
- Dr. Verma N.K. and Dr. Pullarkat S.A. revised the manuscript drafts.
- The synthesis and purification of ferrocenyl substrates were carried out by Tay S.W. and Pang J.H with my guidance and supervision.
- The synthesis and purification of 10 ferrocenyl phosphines derivatives were carried out by Tay S.W. and Pang J.H with my guidance and supervision.
- Synthesis of gram scale of Gold derivatives compounds were done by me.
- All nuclear magnetic resonance experiment was ran by Tay S.W, Pang J.H and and me. I analyzed and compiled the spectroscopic data obtained.
- Dr. Kizhakeyil A., Chiu, Q. Y. A. and Dr. Kumar P. prepared cell cultures.
- Dr. Kizhakeyil A., Chiu, Q. Y. A. and Dr. Kumar P. organized and carried out multiple cell assays (MTS -based cell viability assay) of synthesized drugs in Lee Kong Chian School of Medicine, NTU.
- Dr. A., Kizhakeyil and Dr. Kumar P. carried out all flow cytometry experiments: Western-immunoblot analysis, cell cycle distribution analysis.

For anti-malaria study *Dalton Transactions*, 48(3), 1108-1117.:

- Dr. Chandramohanadas R. and Dr. Pullarkat S.A. designed the research directions.
- Subramanian, G. prepared the manuscript draft for data compiled from Singapore University of Technology and Design (SUTD) and Dr. Chandramohanadas R. revised the draft.
- I performed the Structure Activity Relationship analysis of compound's activity from compiled data prepared by Subramanian, G. and prepared discussions & rationale regarding the chemistry and activity of compounds with Dr. Pullarkat S.A. We proposed other targeted ferrocene derivatives to confirm our hypothesis.
- Dr. Chandramohanadas R. and Dr. Pullarkat S.A. revised the manuscript drafts.
- The synthesis and purification of ferrocenyl substrates were carried out by Tay S.W. and Pang J.H with my guidance and supervision.
- The synthesis and purification of 10 ferrocenyl phosphines derivatives were carried out by Tay S.W. and Pang J.H with my guidance and supervision.
- The synthesis and purification of additional 9 ferrocenyl phosphines derivatives were carried out by Tay S.W. , Pang J.H and Kojima T. with my guidance and supervision.
- Synthesis of gram scale of Gold derivatives and 1, 2 disubstituted ferrocenyl compounds were done by me with assistance from Kojima T.
- All nuclear magnetic resonance experiment was ran by Tay S.W, Pang J.H and Kojima T. I analyzed and compiled the spectroscopic data obtained.
- Subramanian G., Mukherjee K., Tripathi P., Naidu R. prepared blood and 3D7 strain of *P. falciparum* parasite cultures.
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- Subramanian G., Mukherjee K., Tripathi P., Naidu R. prepared and conducted cytotoxicity assay. and related flow cytometry required.
- Subramanian G. analyzed DV physiology of treated cells and stage-transition inhibition assays, evaluation of ROS levels in *P. falciparum* as well as β hematin inhibition assays.

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Abstract

This thesis aims to provide a holistic account of the synthetic methods applied and the solutions found towards achieving asymmetric P(III)-C bond constructions with ferrocenyl enones, heterobicyclic alkenes and exocyclic olefins. Chapter 1 presents the general field of metal-mediated P(III)-H additions and describes the motivation towards developing convenient protocols. In Chapter 2, asymmetric hydrophosphination (AHP) was employed in a kinetic resolution, as means to generate a series of enantioenriched ferrocenyl monophosphines imbued with both central and planar stereogenicity, in only one step, from ferrocenyl enone racemates. These enantioenriched ferrocenylphosphines could be protected with BH_3 and further recrystallized to obtain mother liquors with *e.e.s* up to 99%. The modularity of the phosphine obtained were demonstrated via derivatization of its functional handles to yield chiral bisphosphines. In Chapter 3, asymmetric addition of diarylphosphines to oxa- and azabicyclic alkenes was performed in the presence of a chiral phosphapalladacycle catalyst and a mild acid at room temperature to give exclusively bicyclic core-retained enantioenriched products in excellent yields and good selectivities. In Chapter 4, the feasibility of current AHP protocols conducted on challenging electrophilic exocyclic olefins was investigated. The study led to intriguing mechanistic insights of AHP in general, and inspired modifications to the current protocols to achieve successful asymmetric P-H addition to such substrates. The method provided the first instance in literature of catalytic enantioselective P(III)-H addition on electrophilic exocyclic olefins, albeit with modest yields and selectivities. Finally, in Chapter 5, a library of ferrocenyl phosphine derivatives, generated from the hydrophosphination protocol, was investigated as potential metallopharmaceuticals in cancer and malarial studies. Structure-activity comparisons showed that the phosphines were more active than their parent chalcones, and both studies identified a gold-based ferrocenyl phosphine as a strong candidate for future developments in medicinal research.

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Table of Contents

Abstract	i
Acknowledgements	ii
Table of Contents	iii
Chapter 1 Introduction	1
1.1 General Introduction	1
1.2 Preparation of Chiral Phosphines	2
1.2.1 Catalytic preparation of P(III) compounds	2
1.3 Origins of Stereoselectivity in Palladacycle-catalyzed Hydrophosphination ..	11
1.4 Asymmetric Hydrophosphination in its infancy	14
References.....	15
Chapter 2 Single step access to Ferrocenyl Phosphines bearing both planar and central chirality from racemic substrate	21
2.1 Introduction	21
2.2 Results & Discussion	32
2.3 Conclusions	39
2.4 Experimental	40
References.....	61
Chapter 3 Desymmetrization of Achiral Heterobicyclic Alkenes through Catalytic Asymmetric Hydrophosphination	64
3.1 Introduction	64
3.2 Results & Discussion	71

3.3	Conclusion	80
3.4	Acknowledgement	81
3.5	Experimental	82
	References.....	97

Chapter 4 Palladacycle-Catalyzed Asymmetric P(III)-H additions on Electrophilic Exocyclic Olefins 104

4.1	Introduction	104
4.2	Results & Discussion	111
4.3	Conclusion	123
4.4	Experimental	124
	References.....	139

Chapter 5 Medicinal Applications of Synthesized Ferrocenyl Phosphines 143

5.1	Introduction	143
5.2	Results & Discussion	148
5.2.1	Evaluation of Ferrocenyl-Phosphine derivatives as anticancer agents for Haematological Malignancies	151
5.2.1	Evaluation of Ferrocenyl-Phosphine derivatives as Antimalarials	155
5.3	Conclusion	162
5.4	Acknowledgement	163
5.5	Experimental	164
5.5.1	Materials & Methods for Antitumour Studies	177
5.5.2	Material & Methods for Antimalarial studies	183
	References.....	185

Chapter 1.

Introduction

1.1 General Introduction

Asymmetric catalysis mediated by transition metals remains a versatile strategy in this era of rigorous fundamental research in synthetic methodologies.¹ Many metal complexes, amongst the arsenal of synthetic tools available in asymmetric catalysis, have been developed to scale in industries for the manufacture of important chiral precursors, pharmaceutical compounds, and functional materials.² Crucial to the late transition metals catalytic capability in terms of i) reactivity, ii) chemoselectivity, iii) stereoselectivity, is its presiding ligand; whereby differences in electronics or sterics of the ligand results in starkly differing outcomes.³ Amongst the hundreds of new classes of ligands that have been developed, tertiary phosphines continue to contribute to the success in the field of the asymmetric catalysis. Seminal to this accomplishment were the prior contributions of Nobel winning works by Knowles⁴ and Noyori⁵ using monodentate chiral phosphines, and other bidentate phosphines developed in parallel by Kagan⁶ and Horner.⁷ With the conception of chiral phosphines to realize revolutionary synthetic avenues that were initially thought of as inconceivable by chemists, more novel phosphine ligands continue to be studied, redesigned and synthesized with the objectives of pushing current boundaries in the burgeoning fields of syntheses.^{3a, 8}

1.2 Preparation of chiral phosphines

A popular non-catalytic approach to synthesize phosphines is via displacement of the halide from phosphorus (e.g. PPh_2Cl) by means of organometallic reagents.⁹ While these methods have been well developed, the disadvantages associated with it includes the reduced degree of structural modularity of the targeted phosphine due to the limitations of functional group tolerance exhibited by organometallic reagents.¹⁰ Additionally, the use of stoichiometric quantities of reagents/chiral auxiliaries, in synthesizing P-stereogenic phosphines, remains to be an unsustainable approach from an environmental point of view. Thus, it is pertinent for chemists to utilize catalytic routes in the preparation of chiral phosphines. Several examples of relevant key catalytic reactions developed for this purpose will be presented the following sections. Where catalytic routes are concerned, this chapter discusses only the preparation of phosphorus(III) compounds. The preparation of phosphorus(V) ligands will be excluded in the discussions to restrict the scope to C-P(III) bond formations.

1.2.1 Catalytic preparation of P(III) compounds

i) Organocatalyst mediated

Melchiorre has documented the use of HPPH_2 to perform a phospho-Michael addition to nitroolefins to obtain C-stereogenic phosphines.¹¹ Despite success in achieving high yields, only low to medium enantioselectivities were attained catalytically (Scheme 1). The dearth of studies revolving around organocatalysts in mediating C-P(III) bond formations are attributed to two generic factors. Firstly, the reactivity of the substrate: Highly electron withdrawing groups (EWG) are required to be incorporated in the substrate (for C=C bond polarization) in order for the nucleophilic phosphine to be able to perform an addition.

Scheme 1. Bifunctional *Cinchona* alkaloid catalyst in asymmetric phospho-Michael addition.¹¹

In cases whereby the substrate is not sufficiently activated, the substrate should possess an aldehyde handle for efficient binding of the organocatalyst (forming intermediate imines) to be activated and thereafter to impart stereo discrimination. A study by Córdova and Melchiorre to synthesize phosphino-alcohols explicates that the C=O functional handle should not be sterically hindered for effective catalysis (Scheme 2).¹² The elucidated mechanism entails iminium activation of the enal substrates (*vide infra*) and as such, sterically hindered ketones are inclined to slow down or virtually eliminate the binding process with the organocatalyst.

Scheme 2. Proline-derived catalyst in asymmetric phospho-Michael addition.^{12a}

Second, is the capability of the organocatalyst to direct the phosphine nucleophile via H-bonding/ion pairing: the lack of oxygen atom/functional handle in P(III) nucleophiles severely limits their hydrogen bonding capability with the organocatalyst.¹³ This reduces the stereoinductive efficiency and hence results in low enantiomeric excesses.

Scheme 3. Synthesis of P-stereogenic phosphines via phase-transfer catalyst (PTC) derived from Cinchona alkaloid by Paquet *et al.*¹⁴

Similarly, studies on chiral organocation catalysts (Scheme 3) employed are unable to attain the robustness of metal-mediated C-P(III) bond formations. Essentially, the capabilities of organocatalysts in C-P bond formations have been well-documented,¹⁵ and transition metal-catalyzed methods seek to fill the gaps of its counterpart in terms of robustness and wide applicability for non-specialized substrates.

ii) Metal-mediated C-P(III) bond formations

C-P(III) asymmetric coupling / via substitution of leaving groups:

Asymmetric catalytic synthesis of P-stereogenic phosphines via coupling remains a challenge despite progress in the field.¹⁶ While useful due to their ability to impart chiral information closer to the reaction site (as ligands on metals) when compared to C-stereogenic phosphines, the difficulty for chemist to procure a myriad of novel enantiopure ligands for applications has been a barrier for their inclusion in high throughput screenings.¹⁷

Glueck *et al.* has documented the asymmetric synthesis of P-stereogenic phosphines via palladium-catalyzed C–P bond formation (Scheme 4).¹⁸ Subsequent studies performed allowed elucidation of the mechanism and scope/limitations of the method.¹⁹ The method involved a dynamic kinetic resolution, whereby the diastereomeric intermediate metal phosphido complexes are in equilibrium due to pyramidal inversion at the phosphide. The more reactive intermediate then performs a reductive elimination to generate P-stereogenic phosphines. This method was subsequently found to be highly applicable with the coupling of racemic silylphosphines and aryl iodides with the use of Et-FerroTANE ligand in place of Duphos.²⁰ Alternative protocols incorporating the dynamic kinetic resolution method were also applied with Pt²¹ and Ru²² metals as a means to impart greater nucleophilic strength in order to allow use of less reactive substrates.

Scheme 4. Dynamic kinetic resolution of tertiary phosphines.

Togni *et al.* first identified that ferrocenyl bisphosphine ligands such as Josiphos analogues when coordinated to palladium were able to produce excellent enantioselectivities (up to 96% *e.e*) in the allylic phosphination of 1,3-diphenyl allyl acetate, albeit with moderate yields (Scheme 5).²³ The study further emphasized the difficulty in controlling the competing side

products and yield of the allylic phosphine. In comparison, Binap and Ferrocenyl PN ligands performed poorly as compared to the Josiphos analogue.

Scheme 5. Optimized product distribution by Togni *et al.*

Asymmetric P(III)-H addition:

Asymmetric P(III)-H addition to an unsaturated bond (e.g. C=C) is also known as catalytic asymmetric hydrophosphination (AHP). Synthesis of chiral tertiary phosphines from achiral substrates via AHP is an attractive procedure due to it being atom economical, highly selective and robust.²⁴ Over the last decade, a selection of metal-complexes has been utilized as catalysts for the inter- and intramolecular addition of phosphine nucleophile to olefins. In majority of the cases, platinum,²⁵ palladium^{24a} and nickel²⁶ complexes has shown promising asymmetric catalytic capability over iron,²⁷ lanthanides²⁸ and alkaline-earth metals.²⁹ While there exist other examples of P(III)-H additions, only asymmetric versions will be discussed.

a) Bis & Tri-phosphine Metal Complexes as catalyst for AHP:

Glueck *et al.* reported the platinum-catalyzed asymmetric hydrophosphination of activated olefins using the catalyst precursor Pt(*R, R*-Me-Duphos)(*trans*-stilbene).^{25a} With this method, only modest selectivities were achieved (Scheme 6). However, it facilitated a detailed study to elucidate the mechanisms involved. Oxidative addition of the P-H bond, insertion and reductive elimination steps were found to form the key steps in the catalytic cycle. Togni has

also reported the AHP of methacrylonitrile to obtain high selectivities (Scheme 7).²⁶ Intriguingly, the Nickel-Pigiphos complex utilized was an efficient catalyst in that it activates the electrophile, methacrylonitrile, instead of facilitating a P-H oxidative addition; followed by a nucleophilic addition of the phosphine.

Scheme 6. AHP of Methacrylonitrile by $\text{Pt}(\text{R,R-Me-Duphos})(\text{trans-stilbene})$.

Scheme 7. AHP of Methacrylonitrile by Ni Complexes.

Examples of neutral ligands having facilitated AHP remains rare. Amongst the, myriad of challenges that continues to persist with metals is the inherent issue of poisoning of the catalyst by the phosphine reagents and the phosphine products themselves leading to no reactivity or poor yields. Additionally, as in the example reported by Togni (Scheme 5), the unwanted P-P

homocoupling of the secondary phosphine persists with most ligands screened. More recently, independent studies by Duan and by Leung & Pullarkat have managed to circumvent catalyst poisoning, as well as several other associated challenges, by employing chiral palladacycle and pincer complexes as catalysts.

b) Metallacycles and pincer complexes as catalyst for AHP:

Chiral palladacycles and their analogues (platinacycles) have origins rooted as chiral derivatizing agents for resolving racemic phosphines.³⁰ In more recent years, however, metallacycles have been found to facilitate a plethora of useful reactions. An array of these complexes has been synthesized and the most commonly reported instances wherein they facilitate AHP are summarized in this section.

Pivotal endeavors by Leung *et al.* have identified palladacycles (Scheme 8) as efficient catalysts for the asymmetric generation of C-stereogenic monophosphines.

Scheme 8. General synthetic paths for AHP reactions.

The enantioselective incorporation of diphenylphosphine to activated alkenes, mediated by either a C-N or C-P-based palladacycle, generally results in C-stereogenic tertiary phosphines in high yields of >90 % yield and >90 % *e.e.* (Scheme 8).^{24c, 24d, 24f, 31} These electron deficient

olefins bear electron withdrawing groups (EWG) that spans a collection of alkyl/aryl ketones, ketoesters, N-enoyl phthalimides, malonates, N-tosyl imines, 2- nitro and alkenylisooxazoles. Noteworthy is the generation of diphosphines^{24f} and *P*-heterocycles³² generated under similar conditions (Scheme 9 and Scheme 10). The diphosphines, produced in a single pot could be further derivatized to novel pincer-type palladacycles such as (*S,S*)-4 in Scheme 8.

Scheme 9. Diphosphines and *P*-heterocycles.

Pullarkat has also demonstrated a novel approach toward introducing stereoelements in ferrocenes comparable to current methodologies.³³ The procedure involves AHP on a ferrocenyl enone coupled to a subsequent cyclopalladation step resulting in the generation of ferrocenyl phosphine palladacycle (Scheme 10).

Scheme 10. Asymmetric Hydrophosphination of ferrocenyl chalcone and derivatization to chiral palladacycle.

Additionally, the palladacycle catalytic activity in arylboronic acid conjugate additions was also demonstrated. Neither thermal activation nor degradation in catalytic activity was observed under ambient conditions.³⁴ Duan has also explored the origins of AHP in parallel and found PCP pincer catalysts in similar reactions with common substrates. Wherein other PCN³⁵ and NCN³⁶ pincers could not compete as effectively, the effectiveness of PCP pincers highlights the specificity of the ligand electronic character required.

Scheme 11. Asymmetric PH addition to activated C=C bonds by Duan.^{24g, 24h}

Hayashi and Leung applied an AHP protocol to benzoquinone and found that the nucleophile adds to benzoquinone in a unique manner (Scheme 12). High selectivities could be achieved and products formed could be derivatized to more robust P-stereogenic phosphines.³⁷ However, its catalytic pathway remains to be elucidated.

Scheme 12. Asymmetric P-H addition to benzoquinones

1.3 Origins of Stereoselectivity in Palladacycle-catalyzed Hydrophosphination

Figure 1. AHP catalytic cycle

The catalytic mechanism of Pd(II)-catalyzed P-H additions to activated alkenes (see Figure 1) has been studied and was described to characteristically include phosphine coordination, phosphide addition and protonation steps.³⁸ Origins of the regio- and stereoselectivities of AHP utilizing aminopalladacycle (*S*)-**2** have been comprehensively discussed^{31a, 39} and summarized as follows:

- i) *Electronic dissymmetry of coordination sites*: Leung *et al.* verifies the hypotheses that the phosphide moiety positions itself *trans* to the nitrogen ligand donor after deprotonation due to the preferential electronic character of the coordination site *trans* to the ligand's heteroatom; 'B'.⁴⁰ The coordination site (A) *trans* to the pi-acidic naphthyl moiety can be predicted to prefer coordination to O atom, of the enone, rather than soft P donors.⁴¹ Moreover, coordination site A was found to prefer coordination to O ketone than C=C for linear enones as suggested in ¹³C NMR analysis.^{38c} Facile displacement of HPPH₂ at site A by the substrate allows the catalytic cycle to be completed.

Fig. 2. Aminopalladacycle coordination sites

- ii) The phosphide addition step is projected on a square-planar transition state which is sterically bound by the palladacycle's 5-membered ring leaning towards either the λ (gamma) or δ (delta) conformations as previously reported^{31a, 39} with the aminopalladacycle. - The (*S*)-**2** catalyst adopts an absolute λ conformation while the (*R*)-**2** catalyst adopts an absolute δ , both in solid state as well as solution (see Figure 3). From these conformations, it is easy to extrapolate that the aryl moiety on the

phosphide's substituents play a part in stereoinduction for substrate selectivity. It is also pertinent to note that the methyl moiety at the chiral carbon generates more steric influence on the phosphide's aryl group as compared to $N\text{-Me}_{\text{axial}}$ as studied by Leung.^{31a, 39} Additionally, while it is generally understood that there exists rapid inversion at the phosphide centre when it is coordinated to the metal,⁴² the aryl fragments of the phosphide is still unlikely to adequately occupy the face of the plane where the axial methyl group of the chiral carbon is present due to its rigid steric projection.

Figure 3. Respective Catalyst Conformations for Palladacycle

In essence, the stereochemical outcome of AHP are dependent upon interaction of the substrates with the above discussed features of the C_1 -symmetric catalyst.

1.4 Asymmetric Hydrophosphination in its infancy

While AHP has been a promising tool, current limitations have imposed a barrier to widespread adoption of the atom-economical method. This could be due to the synthetic level of difficulty in preparation of specific catalysts, and the undiscovered utility of the library of phosphine products being generated. This contrasts with the pervasive use of readily and commercially available ligands and complexes in the toolbox of synthetic chemists. In addition, current AHP protocols are still unable to be widely tolerant to changes in electronics of more unique substrates, as well as changes in the phosphide's aryl groups. Hence, this thesis aims to discover and tackle current limitations imposed on the current AHP protocols and provide fundamental insights for redesigning new methods. In Chapter 2, we will explore the practical aspect of using AHP to generate ferrocenyl phosphines possessing both planar and central stereogenicity in a single step. In Chapter 3 & 4, we shall uncover the limitations of current AHP methods and solutions by extending it to non-electron deficient heterobicyclic alkenes and electrophilic exocyclic olefins respectively. The final chapter will explore ferrocenyl phosphines, synthesized via hydrophosphination, as promising anti-tumor and anti-malarial drug candidates.

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Chapter 2.

Single step access to Ferrocenyl Phosphines bearing both planar and central chirality from racemic substrate

2.1 Introduction

The iron sandwich, ferrocene, has received extensive attention from the scientific community in a plethora of fields.¹ Amongst them, includes its role as ligands in asymmetric catalysis.^{1a, 1b, 2} Ferrocenyl scaffolds present in ligands not only imparts the essential structural rigidity to create unique chiral environments but also instils a crucially minute freedom of rotation or tilting via the two parallel cyclopentadienyl rings.³ Furthermore, its versatility in allowing bulky substituents to be introduced onto the cyclopentadienyl ring serves to provide directional steric hindrance or spatial environment that enhances the selectivities in asymmetric catalysis. Essentially, successful stereoselection can be achieved as a result of the ferrocene's ligand design with complementing central and planar stereogenicity; appropriately projecting a chiral cavity in proximity to the site where bond formations take place.

A plethora of privileged ferrocenyl diphosphine ligands are being applied pervasively, as chiral bidentate chelators to metals in asymmetric catalysis; especially in asymmetric hydrogenation.¹ Lotz and Blaser has classified them into 4 different types of diphosphine moieties at the cyclopentadienyl (Cp) ring⁴:

Figure 1. Types of ferrocenyl diphosphine ligands

Type A: 2 PR_2 groups are directly linked to the Cp ring

Type B: One PR_2 group is linked directly to the Cp ring; while the other is linked to the α -position of a side chain

Type C: One PR_2 group is linked directly to the Cp ring, while the other is linked to the β -position of a side chain

Type D: Both PR_2 groups are attached to the side chains

Perceivable from Figure 1 is that there is an increase in chelating ring size from type **A** to type **D** upon coordination to a transition metal. The scientific community generally views type **D** ferrocenyl diphosphines as less attractive for study due to the uncommon ring size being formed; too large a chelating ring size usually equates to inefficient control over the stereochemistry of final product.⁵ However, contrary to popular opinion, the Walphos ligand by Walter Weissensteiner,⁶ has demonstrated that an 8 membered chelate confirms its efficacy in enantioselective hydrogenations. Diverse substituents have also been incorporated into the Walphos ligand to prove its versatility.

Figure 2. Walphos Ligand

The Rh/Walphos catalyst demonstrated excellent control for enantioselectivity in the hydrogenation of alkenyl boronates, of dehydro amino and itaconic acid with enantiomeric excesses above 92%.⁷ Admirably, its first industrial application is the hydrogenation of SPP100-SyA to give the renin inhibitor SPP 100 in 95% *e.e.*^{7a} These examples as well as those mentioned in literature shows the versatility of such a ligand with a larger ring size, making it an interesting and worthy point for further exploration.

Scheme 1. Asymmetric hydrogenation of SPP100-SyA.

While Walphos ligands are proficient in facilitating asymmetric catalysis, its synthetic route bears an inherent structural limitation similar to other well-known ferrocenyl diphosphine ligands. The synthesis of 1,2-disubstituted ferrocenyl diphosphine ligands generally begins with enantiomerically pure Ugi's amine (Figure 3), giving rise to privileged ligands such as Josiphos, Bophoz, Taniaphos and even Walphos. The underlying consequence is that it involves the use of stoichiometric to excess amount of chiral source; in this case, Ugi's amine for the

introduction of planar chirality to form the 1,2-ferrocenyl diphosphine complexes.^{7a} Furthermore, this limits the resulting ligand to always bear a methyl group at its stereogenic centre, as depicted by the diagram below. The implication is that it results in a lack variation at the stereogenic centre as indicated in Figure 3.⁸

Figure 3. Ferrocenyl diphosphines derived from enantiopure Ugi amine.

To first recognize the significance of the approach to be discussed, a brief understanding of current methods to prepare planar chiral ferrocenes is required. Foremost, the generation of exclusively planar chiral compounds are usually accessible either by a diastereoselective approach⁹ and consequent abstraction of the directing ortho-metallating group (D.M.G) (Scheme 2) or by an enantioselective ortho-directed lithiation¹⁰ (E.O.M, Scheme 3). Particularly, the later protocol possesses two challenges: (i) broadening of the substrate scope and the limited range of chiral bases, (ii) developments regarding the shift towards non-stoichiometric use of chiral additives.¹¹

Chiral D.M.G:

Scheme 2. Diastereoselective *ortho*-directed metalation (D.O.M) with D.M.Gs.

Chiral Promoters / Ligand:

Scheme 3. Enantioselective *ortho*-directed metalation (E.O.M).

Quintessentially, it is desirable to be able to generate type D ferrocenyl diphosphine ligands via alternative pathways. Aside from D.O.M and E.O.M, an alternative route, towards accessing these stereogenic motifs is the resolution of ferrocenyl racemates; which has been achieved either enzymatically or by method of employing chiral catalysts. The advantage of utilizing a

classical kinetic resolution procedure over lithium reagents mainly lies on presence of functional groups intolerant to lithium bases and that it is a non-stoichiometric method. Nicolosi, Moyano, Kudo and Ogasawara has demonstrated the utility of enzyme & chiral catalysts as shown below (Scheme 4-8).¹² These studies emphasize the requirement for chiral catalysts/enzymes to discriminate between planar chiral ferrocenyl racemates with high precision, resulting in both enantioenriched product and parent compound.

Scheme 4. Lipase-Catalyzed Esterification by Nicolosi *et al.*^{12d}

Scheme 5. Asymmetric Dihydroxylation (AD) by Moyano *et al.*¹³

Scheme 6. Asymmetric 1, 4- Addition of Nitromethane by Kudo *et al.*^{12c}

Scheme 7. Ogasawara's Asymmetric Ring-Closing Metathesis (ARCM).^{12b}

During the period of this study, Ogasawara^{12a} reported further progress towards generating planar chiral ferrocenyl phosphines, which benchmarked exceptionally well as chiral ligands for catalysis (Scheme 8). Asymmetric ring-closing metathesis (ARCM) of racemic substrates with axially chiral molybdenum-based catalyst was utilized to achieve selectivity in the kinetic resolution (*vide infra*).

Scheme 8. Ogasawara's Asymmetric Ring-Closing Metathesis to generate phosphine.^{12a}

Previously, Gan¹⁴ has conducted preliminary investigations on the feasibility of kinetic resolution of 1,2-substituted ferrocenyl enone in an effort to obtain the ferrocenyl monophosphine shown in Scheme 9 and Table 1. The AHP method (Scheme 9) exclusively

produces addition product **3** , with no observable amount of product **4** and **5**, in a preliminary trial reaction; indicating promising chemoselectivity.

Scheme 9. Gan's preliminary investigation on KR of ferrocenyl enone using AHP.¹⁴

Table 1. Substrate Screening.^[a]

No.	1 : 2	Yield ^[b] (%) (3 : 1)	<i>e.e</i> ^[c] (%) 1	<i>d.e</i> ^[d] (%) 3	<i>e.e</i> ^[e] (%) 3
1	1a : 2a	46 : 52	74	91	87
2	1b : 2a	10 : 84	n.d ^f	>99	86
3	1c : 2a	46 : 50	n.d ^f	>99	82
4	1d : 2a	42 : 56	53	87	88
5	1e : 2a	50 : 42	85	90	92
6	1f : 2a	48 : 46	n.d ^f	95	88
7	1g : 2a	50 : 46	n.d ^f	94	>99
8	1h : 2a	50 : 42	n.d ^f	84	86
9	1i : 2a	46 : 52	82	>99	>99
10	1i : 2b	44 : 54	37	84	80
11	1i : 2c	46 : 52	37	93	82
12	1i : 2d	46 : 50	57	>99	90

^[a] 0.5 eqv of **2a**, 10 mol% **C1**, 1eqv *rac*-**1**, and 1 eqv NEt₃ was added in 5 ml of dry MeOH, with stirring at -60° C for 24 hrs. Thereafter 0.5 eqv of Sulphur was added and the reaction raised to room temperature. ^[b] Isolated yields from silica gel chromatography. ^[c] Determined by ³¹P{¹H} N.M.R. ^[d] Determined by ³¹P{¹H} N.M.R. ^[e] Determined by HPLC using a chiral column. ^[f] Conclusive enantiomeric excess data by HPLC was not achieved.

The study found ideal conditions with solvent being dry MeOH. The small-scale experiments conducted at -60 °C gave tertiary ferrocenyl monophosphines with excellent selectivities (up to 99% *e.e* and 99% *d.e*). The current protocol however was re-examined and found to provide challenges in that removal of the sulphur¹⁵ (used to protect the tertiary phosphine product) gave low appreciable yields and difficulties in purification and characterization. Additionally, conducting the kinetic resolution at larger scales led to reduced selectivities. Furthermore, high concentration of the substrate, catalysts and base tend to reduce the substrate selectivity making it less suitable for large scale synthesis. Nevertheless, subjecting the leftover enantioriched parent enone to AHP with (*R*)-C1 led to appreciable selectivities for its utilization as chiral ligands.

Scheme 10. Recycling of enriched parent compound

Currently, the applications of the generated monophosphine remains unexplored. The unrefined methodology bears vast possibility and untapped potential towards further functionalization of the phosphines for appreciable utility. On this basis, a preliminary investigation of catalytic kinetic resolution of 2-substituted ferrocenyl enone racemates with modifications of Gan's post kinetic resolution protocol was conducted (Scheme 11).

Scheme 11. Current study on feasibility for the subsequent transformations of the generated phosphine.

2.2 Results & Discussion

We applied the resolution procedure as in Table 2; *rac*-**1** was subjected to AHP with HPPH₂ and catalyst (*S*)-**C1**. Thereafter, the air-sensitive phosphine products were protected with BH₃, instead of sulfur, and isolated via silica gel chromatography to produce **7**. Consistent results were achieved with the ferrocenyl substrates possessing varying electronics at the aromatic (-Ar) position, with yields of enantioenriched **7** ranging from 40 to 45%, as compared to the theoretical maximum of 50 %. This was however an exception for Table 2, Entry 3, whereby electron donating *p*-MeO present on the aryl ketone group led to modest yields, likely due to reduced electrophilicity and reactivity of the substrate.

With the modified method, decrease in enantioselectivity by as much as 19% *e.e* could be observed (Table 2, Entry 7 and Table 1, Entry 7) likely due to the precipitation of the parent compound which was observed at low temperatures, leading to less efficient kinetic resolutions (Table 2, No. 7). - (*d.e* comparisons could not be obtained due to broadening of the new phosphorus peaks in NMR spectroscopy). Nevertheless, a single recrystallization of the phosphine-boranes led to enantioenrichment of its mother liquor up to 99% *e.e*. The synthetic procedure was generally tolerant to the substrates bearing different aromatic derivatives. Electron withdrawing group (*p*-ClC₆H₄), electron donating group (*p*-MeOC₆H₄, *p*-TolC₆H₄) and heterocycles (2-furyl, 2-thienyl) present on the aryl ketone would similarly provide convenient removal of the substrate by eluting the product from the crude applied on a silica plug with DCM.

Table 2. Kinetic Resolution of 2-substituted ferrocenyl enones, followed by protection of ferrocenyl phosphine with BH₃.THF. ^[a]

Entry	Substrate	Ar	yield ^[b] (%) (7 : 1)	<i>e.e.</i> ^[c] (%) 7 ^[b]
1	2a	Ph	43: 51	99 ^[d]
2	2b	<i>p</i> -Tol	42: 51	90 ^[d]
3	2c	<i>p</i> -OMe	30: 62	97 ^[d]
4	2d	<i>p</i> -Cl	43: 55	94 ^[d]
5	2e	2-naphthyl	43: 52	96 ^[d]
6	2f	2-thienyl	40: 55	98 ^[d]
7	2g	2-furyl	40: 57	80

[a] Reaction conditions: An oven-dried storage tube was charged with **1** (132 mg, 123.5 μ L, 0.71 mmol, 0.50 eq.), (*S*)- **C1** (10mol % of **1**) along with 20 mL of dry MeOH. After leaving the solution to stir for 10 mins at -60 °C, *rac*-**1** (500 mg, 1.42 mmol, 1 eq.) in 10 mL dry MeOH was added. After 5 minutes, NEt₃ (5.4 mg, 98.9 μ L, 0.71 mmol, 0.5 eqv.), dissolved along with 5 mL of methanol. The vessel was sealed, leaving to stir at -60 °C for 24 hrs after which, the solvent was concentrated under vacuum. Thereafter, the purple crude was applied on silica column and flashed with degassed DCM. The yellow effluent was collected and subsequently evaporated to dryness. The resulting yellow oil obtained was dissolved in 1mL of THF followed by addition of 1.2 eqv. of 1M BH₃.THF at -40°C. It was left to be warmed up to 0°C overnight after which 1mL of MeOH was added and left to stir for 0.5 hr. The non-air sensitive orange solution was concentrated and chromatographed on silica gel (7 - 5 hexanes: 1 EA) to obtain **7aa** - (R_f0.30) as orange foam. [b] Determination of *d.e* by ³¹P{¹H} of **7** not achieved due to broad peaks. [c] determined via HPLC using a chiral column. [d] mother liquor from single recrystallization.

Scheme 12. Overall Synthesis.

Upon complete consumption of the HPPH_2 at the kinetic resolution stage, the air-sensitive product could easily be separated from the parent compound with an inert silica plug via elution with DCM. This step was essential to prevent competing hydroboration of the alkene functionality in the substrate in the next step. Subsequently, addition of $\text{BH}_3\cdot\text{THF}$ furnished the protected ferrocenyl phosphines **7**, permitting non air-sensitive manipulation and characterization (Scheme 12).

The adjacent $-\text{CH}_2\text{OH}$ group present on ferrocenyl ring in **7** serves as a versatile functional handle. Thus, following Hu's report of phosphine substitution of ferrocenyl alcohols under mild conditions, we likewise conducted the substitution of the hydroxyl group to diphenylphosphine in acetic acid at room temperature.

The addition of 1.2 eq. **HPPh₂** to isolated **7** afforded the corresponding diphosphine **8** in >97 % yield (w.r.t **7**) with marginal difference in *e.e.s* (Table 3). The derivatization procedure was tolerant to the various aryl groups (of the ketone), despite being dissolved in glacial acetic acid, demonstrating the feasibility of this protocol. It was observed (by NMR spectroscopy) that conducting the derivatization at room temperature, as recommended in literature, was insufficient for achieving complete conversions. Hence, raising the temperature hastened the process and resulted in complete conversions.

Table 3. Derivatization of chiral phosphine-boranes.

No.	7 ^[a]	Ar	7 ^[b] <i>e.e</i> ^[c] (%)	8 <i>e.e</i> ^[c] (%)	8 Yield ^[d] (%)
1	7aa	Ph	99 ^[f]	97	98
2	7ba	<i>p</i> -Tol	90 ^[f]	88	97
3	7ca	<i>p</i> -OMe	97 ^[f]	98	97
4	7da	<i>p</i> -Cl	94 ^[f]	93	99
5	7ea	2-nap	96 ^[f]	98	97
6	7fa	2-thienyl	98 ^[f]	97	98
7	7ga	2-furyl	80	80	99

^[a] Reaction conditions: to isolated **7** in AcOH (1mL) was added HPPh₂ (1.2 eqv.) at rt and heated to 35°C for 12 hr. The solvent was evaporated and 1.2 eqv. of 1M BH₃.THF was added at -40°C and warmed up to 0°C overnight.

^[b] Determination of *d.e* by ³¹P{¹H} of **7** not achieved due to broad peaks. ^[c] determined via HPLC using a chiral column. ^[d] Isolated yield.

Deprotection of phosphine-boranes are typically done by using diethylamine, TMEDA, pyrrolidines, morpholine, DABCO.¹⁶ For the diphosphine to be generated *in situ*, convenient removal of the amines *in vacuo* will be a critical step. Initial trial of stirring diphosphine-borane **8ca** in excess of volatile NEt₃ failed to generate the diphosphine of interest. Further heating to 40°C proved the diphosphine-borane to be stable and heat tolerant. Lloyd-Jones *et al.* found diethylamine, morpholine and pyrrolidines to be among the most efficient bases for deprotection of phosphine-borane.¹⁷ However, morpholine, albeit a strong base, is difficult to remove due to its low volatility. Diethylamine, on the other hand, might prove to be too nucleophilic and be intolerant towards the carbonyl functionality present in the synthesized ferrocenyl bis(phosphine-borane). Pyrrolidine was an obvious choice due to its the balance between its nucleophilicity and volatility but however was not robust at room temperature (50% conversion) and required heating up to 40 °C before an *in situ* addition of Ru precursor for the purpose of coordination. Nevertheless, the synthesis of the ruthenium complex proceeded to furnish the corresponding bisphosphine complex Ru-**9ca**. This was indicated by the ³¹P{¹H} NMR where presence of 2 doublets observed at 56.5 ppm and 43.7 ppm due to the coupling of the phosphorus atoms.

Scheme 13. Deprotection of **8ca** with Pyrrolidine, and coordination to Ruthenium dimer.

In comparison to pyrrolidine, we utilized an alternative deprotection reagent with 2.1 equivalents of DABCO in THF to attempt to liberate the diphosphine **8fa**. Since the byproduct

and excess DABCO, could not be removed under evacuation, the crude had to be purified via a silica gel plug to remove the excess reagent. Thereafter, the liberated phosphine could be utilized for benchmarking in asymmetric catalysis after coordination to Pd (Scheme 14). X-ray crystallography performed on **10fa** provided the absolute configuration as (*R_c R_{pl}*)-**10fa** (see experimental for ORTEP structure).

Scheme 14. Deprotection of **8fa** and Coordination to Pd.

We targeted known transition metal-catalyzed reaction with prepared **10fa** (Scheme 15) as well as attempted an organocatalytic annulation using the deprotected **7aa** (Scheme 16). While the ligand facilitated good reactivities, we found that it could not enforce good selectivities in the reactions conducted.- Asymmetric Suzuki-Miyaura coupling between 2-bromo-1-methoxynaphthalene (**12a**) and 2-naphthyl boronic acid (**12b**) conducted at room temperature for 18 hours, could furnish **12c** in only 50% yield and 13% *e.e.* In comparison, few bisphosphine-Pd-catalyzed methodologies could achieve conversions at room temperature.¹⁸ In another experiment, utilizing monophosphine **6aa** as an organocatalyst in a base-free annulation between 2,6-dibenzylidene-4-*tert*-butyl-cyclohexanone (**13a**) and ethyl allenolate (**13b**) could notably provide full conversion to spiro compound **13c** but resulted in only 2% *e.e.*¹⁹

Scheme 15. Asymmetric Suzuki-Miyaura coupling.^{18b}

Scheme 16. Desymmetrization via [3+2] annulation.¹⁹

In these cases, while we find that the reactions could indeed be catalyzed, the capability of the ligand to provide a highly asymmetric environment at the reaction centre might be impeded by the larger bite angle of the bis-phosphine ligand. Similarly, the difference between the phosphines present ($\text{Ph}_2\text{P}-$), in terms of stereo & electronic effects on **10fa**, might not have provided a good projection of chirality on the Pd centre. As such, providing better stereo & electronic difference in character of the two phosphines in **10fa** might provide better electronically dissimilar vacant sites on the Pd centre for better stereocontrol in the asymmetric Suzuki-Miyaura coupling. Nevertheless, we find that the applications of these ligands are not limited to the few reactions and its unique characteristics might be of relevance in other areas of catalysis.

2.3 Conclusions

This study showed that in a single step asymmetric hydrophosphination, enantioenriched ferrocenyl monophosphines possessing both planar and central chiral elements could be obtained catalytically from their parent racemates using asymmetric hydrophosphination. We have also refined the method towards a synthetically more practical aspect from the initial stage and were able to further transform the products into diphosphines as proof-of-concept for further derivatization of the kinetically resolved adducts. Furthermore, these phosphines could be applied as ligands in transition metal catalysis as well as organocatalysts. Studies on widening the derivatization scope to P-Imidazoline ligands and TRAP type ligands as an extension of the method are currently are to be explored in the future.

2.4 Experimental

Low temperature experiments were conducted in a PSL-1800 low-temperature pair stirrer machine. Silica gel chromatography was carried out using Merck silica gel 60. Nuclear Magnetic Resonance experiments (NMR) were conducted on Bruker AV spectrometers as stated in data. ^1H spectra were referenced to residual solvent signal of CDCl_3 at δ 7.26. HPLC spectra were procured using a Daicel CHIRALPAK® ID and IF column. Specific rotation values are as the specified solvent and temperature. Mass spectrometry was conducted in ElectroSpray Ionization mode on a Thermo Finnigan LCQ Deca XP MAX system. Substrates **1a-g** was synthesized according to procedures reported by Gan¹⁴:

Preparation of substrates **1a-g**:¹⁴

Scheme 17. General synthetic route for preparation of Substrate

Racemic-1-formyl-2-hydroxymethyl ferrocene

The procedures are reported in literature.¹⁴

Rac-**1a-g**¹⁴ characterization data has been reported by Gan.¹⁴

To *racemic*-1-formyl-2-hydroxymethyl ferrocene (1.96 g, 8 mmol) in a 50 mL reaction flask was dissolved with 10 ml of EtOH to form a solution. Thereafter, respective acetyl-aromatic

variants (8 mmol) and 20 % KOH (0.5 ml) was added to the reaction flask dropwise at room temperature. After 3 hours of further stirring, H₂O (0.5 ml) was introduced and further concentrated using rotary evaporation. The crude oil acquired was chromatographed on silica gel (5 DCM : 1 EA) to provide purple oils of **1a-i**.

Kinetic resolution procedure to obtain **7aa – 7ag** (Table 2):

Reaction conditions: An oven-dried storage tube was charged with **2** (132 mg, 123.5 μ L, 0.71 mmol, 0.50 eq.), **C1** (10 mol % of **1**) and 20 mL of dry MeOH. After leaving the solution to stir for 10 mins at -60 °C, rac-**1** (500 mg, 1.42 mmol, 1 eq.) in 10 mL dry MeOH was added. After 5 minutes, NEt₃ (5.4 mg, 98.9 μ L, 0.71 mmol, 0.50 eq.) in 5 mL of dry MeOH was added dropwise. The vessel was sealed and left to stir at -60 °C for 24 hrs after which, the solvent was concentrated under vacuum. Thereafter, the purple crude was applied on a silica column and eluted with degassed DCM. The yellow effluent was collected and subsequently evaporated to dryness. The resulting yellow oil obtained was dissolved in 1mL of THF followed by 1.2 eqv. of 1M BH₃.THF at - 40°C. It was left to be warmed up to 0°C overnight after which 1mL of MeOH was added and left to stir for 0.5 hr. The non-air sensitive orange solution was concentrated and chromatographed on silica gel (7 - 5 hexanes: 1 EA) to obtain **7aa - 7ag** (R_f 0.30) as orange foam.

(*R_c R_{pl}*)-7aa

Dark orange foam. ^1H NMR (CDCl_3 , 400 MHz): δ 0.86 – 1.30 (broad m, 3H, $-\text{BH}_3$), 3.48 – 3.63 (m, 3H, $-\text{CH}_2\text{OH}$ and $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.93 (s, 6H, $-\text{Cp}$ and $-\text{CH}_2\text{OH}$ or $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 4.11 (s, 1H, $-\text{Cp}$), 4.26 (s, 1H, $-\text{Cp}$), 4.52 (s, 1H, $-\text{Cp}$), 4.76 – 4.81 (m, 1H, $-\text{CH}(\text{PPh}_2)$), 7.14 – 7.23 (m, 3H, $-\text{Ar}$), 7.34 – 7.59 (m, 8H, $-\text{Ar}$), 7.91 – 8.01 (m, 4H, $-\text{Ar}$); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 162 MHz): δ 29.29. $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl_3 , 96.3 MHz): δ -41.05. ^{13}C NMR (CDCl_3 , 100 MHz): δ 27.3 (d, $-\text{CHPPh}_2$, $^1J_{\text{CP}} = 34.3$ Hz), 42.0 (d, $-\text{CH}(\text{PPh}_2)\text{CH}_2\text{C}=\text{O}$, $^2J_{\text{CP}} = 8.9$ Hz), 58.8 ($-\text{CH}_2\text{OH}$), 67.7 (*m*-Cp), 68.1 (*o*-Cp), 68.8 (d, *m*-Cp, $^4J_{\text{CP}} = 2.1$ Hz), 69.0 (5-Cp), 86.4 (d, *i*-Cp, $^2J_{\text{CP}} = 5.5$ Hz), 87.2 (d, *i*-Cp, $^2J_{\text{CP}} = 1.5$ Hz), 126.5 (d, *i*-Ar, $^1J_{\text{CP}} = 51.5$ Hz), 128.2 (Ph Ar), 128.2 (d, *m*-Ar, $^3J_{\text{CP}} = 9.8$ Hz), 128.7 (d, *i*-Ar, $^1J_{\text{CP}} = 53.2$ Hz), 129.0 (Ph Ar), 129.1 (d, *m*-Ar, $^3J_{\text{CP}} = 9.7$ Hz), 131.2 (d, *p*-Ar, $^4J_{\text{CP}} = 2.4$ Hz), 132.0 (d, *p*-Ar, $^4J_{\text{CP}} = 2.2$ Hz), 133.2 (d, *o*-Ar, $^2J_{\text{CP}} = 8.9$ Hz), 133.6 (d, *o*-Ar, $^2J_{\text{CP}} = 8.4$ Hz), 133.8 (Ph Ar), 136.2 (Ph Ar), 197.1 (d, $\text{C}=\text{O}$, $^3J_{\text{CP}} = 8.6$ Hz). HRMS (+ESI) calcd for $\text{C}_{32}\text{H}_{33}^{11}\text{B}_1\text{Fe}_1\text{O}_2\text{P}_1$ $[\text{M} + \text{H}]^+$: 547.1661, found: 547.1663. $[\alpha]_{\text{D}}^{22} = -49.9$ (c 0.4, DCM). *Enantiomeric excess resolved using IF Column; n-Hexanes : IPA = 90 : 10, 0.5 ml / min, 254 nm, 44.2 mins (major), 47.6 mins (minor) for 99 % e.e.*

(*R_c R_{pl}*)-7ba

Orange foam. ^1H NMR (CDCl_3 , 300 MHz): δ 0.69 – 1.30 (broad m, 3H, $-\text{BH}_3$), 2.40 (s, 3H, Ar- CH_3), 3.41 – 3.53 (m, 1H, $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.57 – 3.63 (m, 2H, $-\text{CH}_2\text{OH}$), 3.85 – 3.97 (s, 6H, $-\text{Cp}$ and $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 4.09 (s, 1H, $-\text{Cp}$), 4.24 – 4.25 (m, 1H, $-\text{Cp}$), 4.50 (s, 1H, $-\text{Cp}$), 4.74 – 4.81 (m, 1H, $-\text{CH}(\text{PPh}_2)$), 7.14 – 7.25 (m, 5H, $-\text{Ar}$), 7.27 – 7.37 (m, 2H, $-\text{Ar}$), 7.46 – 7.48 (m, 3H, $-\text{Ar}$), 7.90 – 7.95 (m, 4H, $-\text{Ar}$); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 121 MHz): δ 28.68. $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl_3 , 96.3 MHz): δ -40.69. ^{13}C NMR (CDCl_3 , 100 MHz): δ 21.8 (*p*-tol Ph $-\text{CH}_3$), 27.1 (d, $-\text{CHPPh}_2$, $^1J_{\text{CP}} = 34.4$ Hz), 41.8 (d, $-\text{CH}(\text{PPh}_2)\text{CH}_2\text{C}=\text{O}$, $^2J_{\text{CP}} = 8.7$ Hz), 58.8 ($-\text{CH}_2\text{OH}$), 67.6 (*m*-Cp), 68.0 (*o*-Cp), 68.8 (*m*-Cp), 69.0 (5-Cp), 86.4 (d, *i*-Cp, $^3J_{\text{CP}} = 5.6$ Hz), 87.8 (*i*-Cp), 126.5 (d, *i*-Ar, $^1J_{\text{CP}} = 51.5$ Hz), 128.2 (d, *m*-Ar, $^3J_{\text{CP}} = 9.9$ Hz), 128.5 (*p*-tol Ph Ar), 128.8 (d, *i*-Ar, $^3J_{\text{CP}} = 53.0$ Hz), 129.1 (d, *m*-Ar, $^3J_{\text{CP}} = 9.5$ Hz), 129.6 (*p*-tol Ph -Ar), 131.2 (*p*-Ar), 131.9 (*p*-Ar), 133.1 (d, *o*-Ar, $^2J_{\text{CP}} = 8.7$ Hz), 133.6 (d, *o*-Ar, $^2J_{\text{CP}} = 8.3$ Hz), 133.7 (*p*-tol Ph Ar), 144.7 (*p*-tol Ph Ar), 196.7 (d, $\text{C}=\text{O}$, $^3J_{\text{CP}} = 8.8$ Hz). HRMS (+ESI) calcd for $\text{C}_{33}\text{H}_{35}^{11}\text{B}_1\text{Fe}_1\text{O}_2\text{P}_1$ [$\text{M} + \text{H}$] $^+$: 561.1817, found: 561.1823. $[\alpha]_{\text{D}}^{22} = +28.7$ (c 0.2, DCM). Enantiomeric excess resolved using IF Column;; *n*-Hexanes : IPA = 90 : 10, 0.75 ml / min, 220 nm, 26.4 mins (major), 30.7 mins (minor) for 90 % *e.e.*

(*R_c* *R_{pl}*)-7ca

Dark orange foam. ^1H NMR (CDCl_3 , 400 MHz): δ 0.89 – 1.40 (broad m, 3H, $-\text{BH}_3$), 3.43 – 3.52 (m, 1H, $-\text{CH}_2\text{OH}$ or $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.66 (m, 2H, $-\text{CH}_2\text{OH}$ and $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.85 – 3.92 (m, 4H, Ar- OCH_3 and $-\text{CH}_2\text{OH}$ or $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.95 (s, 5H, -Cp), 4.12 (s, 1H, -Cp), 4.26 (m, 1H, -Cp), 4.52 (s, 1H, -Cp), 4.78 – 4.83 (m, 1H, $-\text{CH}(\text{PPh}_2)$), 6.95 (d, 2H, $^3J = 8.8$ Hz, -Ar), 7.09 – 7.13 (m, 2H, -Ar), 7.18 – 7.28 (m, 3H, -Ar), 7.35 – 7.37 (m, 3H, -Ar), 7.48 – 7.52 (m, 2H, -Ar), 7.99 (d, 2H, $^3J = 8.8$ Hz, -Ar); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 162 MHz): δ 27.81. $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl_3 , 96.3 MHz): δ -40.88. ^{13}C NMR (CDCl_3 , 100 MHz): 27.2 (d, $-\text{CHPPh}_2$, $^1J_{\text{CP}} = 34.4$ Hz), 41.5 (d, $-\text{CH}(\text{PPh}_2)\text{CH}_2\text{C}=\text{O}$, $^2J_{\text{CP}} = 8.9$ Hz), 55.7 (*p*- OCH_3), 58.8 ($-\text{CH}_2\text{OH}$), 67.6 (*m*-Cp), 68.0 (*o*-Cp), 68.8 (d, *m*-Cp, $^4J_{\text{CP}} = 2.0$ Hz), 69.0 (5-Cp), 86.5 (d, *i*-Cp, $^2J_{\text{CP}} = 5.6$ Hz), 88.2 (d, *i*-Cp, $^2J_{\text{CP}} = 2.4$ Hz), 114.1 (*p*-OMe Ph), 126.6 (d, *i*-Ar, $^1J_{\text{CP}} = 51.6$ Hz), 128.2 (d, *m*-Ar, $^3J_{\text{CP}} = 9.6$ Hz), 128.9 (d, *i*-Ar, $^1J_{\text{CP}} = 53.4$ Hz), 129.1 (d, *m*-Ar, $^3J_{\text{CP}} = 9.6$ Hz), 129.3 (*p*-OMe Ph -Ar), 130.6 (*p*-OMe Ph -Ar), 131.2 (d, *p*-Ar, $^4J_{\text{CP}} = 2.3$ Hz), 131.9 (d, *p*-Ar, $^4J_{\text{CP}} = 2.2$ Hz), 133.2 (d, *o*-Ar, $^2J_{\text{CP}} = 8.8$ Hz), 133.6 (d, *o*-Ar, $^2J_{\text{CP}} = 8.3$ Hz), 164.1 (*p*-OMe Ph Ar), 195.6 (d, $\text{C}=\text{O}$, $^3J_{\text{CP}} = 8.8$ Hz). HRMS (+ESI) calcd for $\text{C}_{33}\text{H}_{35}^{11}\text{B}_1\text{Fe}_1\text{O}_3\text{P}_1$ $[\text{M} + \text{H}]^+$: 577.1766, found: 577.1783. $[\alpha]_{\text{D}}^{22} = +10.5$ (c 0.1, DCM). Enantiomeric excess resolved using IF Column; *n*-Hexanes : IPA = 90 : 10, 1.0 ml / min, 254 nm, 37.0 mins (major), 50.3 mins (minor) for 98 % *e.e.*

(*R_c R_{pl}*)-7da

Orange foam. ^1H NMR (CDCl_3 , 300 MHz): δ 0.83 – 1.35 (broad m, 3H, $-\text{BH}_3$), 3.46 – 3.66 (m, 3H, $-\text{CH}_2\text{OH}$ and $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.81 – 3.88 (m, 1H, $-\text{CH}_2\text{OH}$ or $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.92 (s, 5H, $-\text{Cp}$), 4.10 (s, 1H, $-\text{Cp}$), 4.25 – 4.27 (m, 1H, $-\text{Cp}$), 4.49 (s, 1H, $-\text{Cp}$), 4.72 – 4.79 (m, 1H, $-\text{CH}(\text{PPh}_2)$), 7.12 – 7.23 (m, 6H, $-\text{Ar}$), 7.33 – 7.38 (m, 1H, $-\text{Ar}$), 7.42 – 7.48 (m, 4H, $-\text{Ar}$), 7.89 – 7.95 (m, 3H, $-\text{Ar}$); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 121 MHz): δ 28.68. $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl_3 , 96.3 MHz): δ -41.20. ^{13}C NMR (CDCl_3 , 100 MHz): δ 27.5 (d, $-\text{CHPPh}_2$, $^1J_{\text{CP}} = 34.1$ Hz), 41.9 (d, $-\text{CH}(\text{PPh}_2)\text{CH}_2\text{C}=\text{O}$, $^2J_{\text{CP}} = 9.1$ Hz), 58.8 ($-\text{CH}_2\text{OH}$), 67.7 (*m*-Cp), 68.1 (*o*-Cp), 68.8 (*m*-Cp), 68.9 (5-Cp), 86.9 (d, *i*-Cp, $^2J_{\text{CP}} = 5.5$ Hz), 88.1 (*i*-Cp), 126.3 (d, *i*-Ar, $^1J_{\text{CP}} = 51.5$ Hz), 128.3 (d, *m*-Ar, $^3J_{\text{CP}} = 9.8$ Hz), 128.4 (d, *i*-Ar, $^2J_{\text{CP}} = 53.6$ Hz), 129.1 (d, *m*-Ar, $^3J_{\text{CP}} = 9.5$ Hz), 129.3 (*p*-Cl Ph -Ar), 129.6 (*p*-Cl Ph -Ar), 131.3 (d, *p*-Ar, $^4J_{\text{CP}} = 2.2$ Hz), 132.0 (d, *p*-Ar, $^4J_{\text{CP}} = 2.1$ Hz), 133.2 (d, *o*-Ar, $^2J_{\text{CP}} = 8.7$ Hz), 133.6 (d, *o*-Ar, $^2J_{\text{CP}} = 8.4$ Hz), 134.5 (*p*-Cl Ph Ar), 140.3 (*p*-Cl Ph Ar), 196.0 (d, $\text{C}=\text{O}$, $^3J_{\text{CP}} = 8.2$ Hz). HRMS (+ESI) calcd for $\text{C}_{32}\text{H}_{32}^{11}\text{B}_1^{35}\text{Cl}_1\text{Fe}_1\text{O}_2\text{P}_1$ [$\text{M} + \text{H}$] $^+$: 581.1271, found: 581.1286. $[\alpha]_{\text{D}}^{22} = +20.0$ (c 0.1, DCM). *Enantiomeric excess resolved using IF Column; n*-Hexanes : IPA = 90 : 10, 1.0 ml / min, 210 nm, 23.0 mins (major), 26.7 mins (minor) for 94 % *e.e.*

(*R_c R_{pl}*)-7ea

Orange foam. ^1H NMR (CDCl_3 , 300 MHz): δ 0.86 – 1.30 (broad m, 3H, $-\text{BH}_3$), 3.60 – 3.73 (m, 3H, $-\text{CH}_2\text{OH}$ and $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.92 (s, 5H, $-\text{Cp}$), 4.02 – 4.12 (m, 2H, $-\text{Cp}$ and $-\text{CH}_2\text{OH}$ or $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 4.26 – 4.28 (m, 1H, $-\text{Cp}$), 4.57 (s, 1H, $-\text{Cp}$), 4.81 – 4.90 (m, 1H, $-\text{CH}(\text{PPh}_2)$), 7.14 – 7.24 (m, 4H, $-\text{Ar}$), 7.33 – 7.39 (m, 1H, $-\text{Ar}$), 7.45 – 7.47 (m, 3H, $-\text{Ar}$), 7.55 – 7.64 (m, 2H, $-\text{Ar}$), 7.85 – 8.08 (m, 6H, $-\text{Ar}$), 8.53 (s, 1H, $-\text{Ar}$); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 121 MHz): δ 28.43. $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl_3 , 96.3 MHz): δ -41.00. ^{13}C NMR (CDCl_3 , 100 MHz): δ 27.4 (d, $-\text{CHPPh}_2$, $^1J_{\text{CP}} = 34.2$ Hz), 42.0 (d, $-\text{CH}(\text{PPh}_2)\text{CH}_2\text{C}=\text{O}$, $^2J_{\text{CP}} = 9.0$ Hz), 58.8 ($-\text{CH}_2\text{OH}$), 67.7 ($m\text{-Cp}$), 68.1 ($o\text{-Cp}$), 68.9 ($m\text{-Cp}$), 69.0 (5-Cp), 86.4 (d, $i\text{-Cp}$, $^2J_{\text{CP}} = 5.9$ Hz), 88.9 ($i\text{-Cp}$), 123.8 (naphthyl Ar), 126.5 (d, $i\text{-Ar}$, $^1J_{\text{CP}} = 53.1$ Hz), 127.2 (naphthyl Ar), 128.0 (naphthyl Ar), 128.3 (d, $m\text{-Ar}$, $^3J_{\text{CP}} = 9.8$ Hz), 128.8 (d, $i\text{-Ar}$, $^1J_{\text{CP}} = 52.4$ Hz), 128.9 (naphthyl Ar), 129.0 (naphthyl Ar), 129.2 (d, $m\text{-Ar}$, $^3J_{\text{CP}} = 9.5$ Hz), 129.9 (naphthyl Ar), 130.0 (naphthyl Ar), 131.3 (d, $p\text{-Ar}$, $^4J_{\text{CP}} = 2.4$ Hz), 132.0 (d, $p\text{-Ar}$, $^4J_{\text{CP}} = 2.1$ Hz), 132.6 (naphthyl Ar), 133.2 (d, $o\text{-Ar}$, $^2J_{\text{CP}} = 8.6$ Hz), 133.6 (naphthyl Ar), 133.6 (d, $o\text{-Ar}$, $^2J_{\text{CP}} = 8.2$ Hz), 136.0 (naphthyl Ar), 197.1 (d, $\text{C}=\text{O}$, $^3J_{\text{CP}} = 8.6$ Hz). HRMS (+ESI) calcd for $\text{C}_{36}\text{H}_{35}^{11}\text{B}_1\text{Fe}_1\text{O}_2\text{P}_1$ $[\text{M} + \text{H}]^+$: 597.1817, found: 597.1823. $[\alpha]_{\text{D}}^{22} = -19.2$ (c 0.3, DCM). Enantiomeric excess resolved using IF Column; *n*-Hexanes : IPA = 90 : 10, 1.0 ml / min, 230 nm, 34.1 mins (major), 37.8 mins (minor) for 96 % *e.e.*

(*R_c R_{pl}*)-7fa

Dark orange foam. ^1H NMR (CDCl_3 , 300 MHz): δ 0.83 – 1.30 (broad m, 3H, $-\text{BH}_3$), 3.43 – 3.59 (m, 3H, $-\text{CH}_2\text{OH}$ and $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.79 – 3.90 (m, 1H, $-\text{CH}_2\text{OH}$ or $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.98 (s, 5H, $-\text{Cp}$), 4.10 (s, 1H, $-\text{Cp}$), 4.26 – 4.27 (m, 1H, $-\text{Cp}$), 4.49 (s, 1H, $-\text{Cp}$), 4.68 – 4.77 (m, 1H, $-\text{CH}(\text{PPh}_2)$), 7.11 – 7.20 (m, 4H, $-\text{Ar}$), 7.33 – 7.37 (m, 1H, $-\text{Ar}$), 7.46 – 7.48 (m, 3H, $-\text{Ar}$), 7.64 (d, 1H, $^3J = 4.1$ Hz, $-\text{Ar}$), 7.79 (d, 1H, $^3J = 4.6$ Hz, $-\text{Ar}$), 7.90 – 7.97 (m, 2H, $-\text{Ar}$); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 121 MHz): δ 28.26. $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl_3 , 96.3 MHz): δ -41.01. ^{13}C NMR (CDCl_3 , 100 MHz): δ 27.7 (d, $-\text{CHPPh}_2$, $^1J_{\text{CP}} = 34.3$ Hz), 42.2 (d, $-\text{CH}(\text{PPh}_2)\text{CH}_2\text{C}=\text{O}$, $^2J_{\text{CP}} = 8.7$ Hz), 58.7 ($-\text{CH}_2\text{OH}$), 67.6 (*m*-Cp), 68.0 (*o*-Cp), 68.7 (*m*-Cp), 69.0 (5-Cp), 86.2 (*i*-Cp), 88.8 (*i*-Cp), 126.2 (d, *i*-Ar, $^1J_{\text{CP}} = 52.7$ Hz), 128.2 (d, *m*-Ar, $^3J_{\text{CP}} = 9.3$ Hz), 128.4 (thienyl Ar), 128.5 (d, *i*-Ar, $^1J_{\text{CP}} = 51.0$ Hz), 129.1 (d, *m*-Ar, $^3J_{\text{CP}} = 9.0$ Hz), 131.2 (*p*-Ar), 132.0 (*p*-Ar), 132.5 (thienyl Ar), 133.1 (d, *o*-Ar, $^2J_{\text{CP}} = 8.2$ Hz), 133.7 (d, *o*-Ar, $^2J_{\text{CP}} = 7.9$ Hz), 134.5 (thienyl Ar), 143.3 (thienyl Ar), 190.2 (d, $\text{C}=\text{O}$, $^3J_{\text{CP}} = 6.6$ Hz). HRMS (+ESI) calcd for $\text{C}_{30}\text{H}_{31}^{11}\text{BFe}_1\text{O}_2\text{P}_1\text{S}_1$ $[\text{M} + \text{H}]^+$: 553.1225, found: 553.1234. $[\alpha]_{\text{D}}^{22} = +43.1$ (c 0.4, DCM). Enantiomeric excess resolved using IF Column; *n*-Hexanes : IPA = 90 : 10, 1.0 ml / min, 210 nm, 33.6 mins (major), 43.5 mins (minor) for 98 % *e.e.*

(R_c R_{pl})-7ga

Dark orange foam. ^1H NMR (CDCl_3 , 300 MHz): δ 0.86 – 1.34 (broad m, 3H, $-\text{BH}_3$), 3.31 – 3.44 (m, 1H, $-\text{CH}_2\text{OH}$ or $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.59 – 3.60 (m, 2H, $-\text{CH}_2\text{OH}$ and $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.76 – 3.87 (m, 1H, $-\text{CH}_2\text{OH}$ or $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.98 (s, 5H, $-\text{Cp}$), 4.11 (s, 1H, $-\text{Cp}$), 4.26 (m, 1H, $-\text{Cp}$), 4.47 (s, 1H, $-\text{Cp}$), 4.65 – 4.74 (m, 1H, $-\text{CH}(\text{PPh}_2)$), 6.45 – 6.53 (m, 1H, $-\text{Ar}$), 7.14 – 7.23 (m, 5H, $-\text{Ar}$), 7.32 – 7.53 (m, 4H, $-\text{Ar}$), 7.59 (s, 1H, $-\text{Ar}$), 7.68 – 7.96 (m, 2H, $-\text{Ar}$); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 121 MHz): δ 28.24. $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl_3 , 96.3 MHz): δ -41.20. ^{13}C NMR (CDCl_3 , 100 MHz): δ 27.2 (d, $-\text{CHPPh}_2$, $^1J_{\text{CP}} = 34.0$ Hz), 41.5 (d, $-\text{CH}(\text{PPh}_2)\text{CH}_2\text{C}=\text{O}$, $^2J_{\text{CP}} = 8.7$ Hz), 58.8 ($-\text{CH}_2\text{OH}$), 67.7 ($m\text{-Cp}$), 68.0 ($o\text{-Cp}$), 68.9 (d, $m\text{-Cp}$, $^4J_{\text{CP}} = 2.0$ Hz), 69.0 (5-Cp), 86.3 (d, $i\text{-Cp}$, $^2J_{\text{CP}} = 5.5$ Hz), 88.7 (d, $i\text{-Cp}$, $^2J_{\text{CP}} = 2.0$ Hz), 112.6 (furyl Ar), 117.8 (furyl Ar), 126.3 (d, $i\text{-Ar}$, $^1J_{\text{CP}} = 51.5$ Hz), 128.3 (d, $m\text{-Ar}$, $^3J_{\text{CP}} = 9.8$ Hz), 128.6 (d, $i\text{-Ar}$, $^1J_{\text{CP}} = 53.5$ Hz), 129.1 (d, $m\text{-Ar}$, $^3J_{\text{CP}} = 9.7$ Hz), 131.3 (d, $p\text{-Ar}$, $^4J_{\text{CP}} = 2.4$ Hz), 132.0 (d, $p\text{-Ar}$, $^4J_{\text{CP}} = 2.2$ Hz), 133.2 (d, $o\text{-Ar}$, $^2J_{\text{CP}} = 8.6$ Hz), 133.7 (d, $o\text{-Ar}$, $^2J_{\text{CP}} = 8.4$ Hz), 146.9 (furyl Ar), 152.3 (furyl Ar), 186.5 (d, $\text{C}=\text{O}$, $^3J_{\text{CP}} = 8.9$ Hz). HRMS (+ESI) calcd for $\text{C}_{30}\text{H}_{31}^{11}\text{B}_1\text{Fe}_1\text{O}_3\text{P}_1$ $[\text{M} + \text{H}]^+$: 537.1453, found: 537.1447. $[\alpha]_{\text{D}}^{22} = -38.0$ (c 0.8, DCM). *Enantiomeric excess resolved using IF Column; n-Hexanes : IPA = 90 : 10, 1.0 ml / min, 250 nm, 43.9 mins (major), 72.7 mins (minor) for 80 % e.e.*

General procedure for derivatization of **7aa-ga** to **8aa-ga**:

Reaction conditions: A 2-neck Schlenk tube was charged with isolated **7** and AcOH (1mL). Thereafter, HPPh₂ (1.2 eqv.) was added and warmed up to 35°C for 12 – 15 hrs (monitored by TLC). Subsequently, the solvent was evaporated under *vacuo* and the obtained orange crude was redissolved in 1 mL of THF at - 40°C. 1.2 eqv. of 1M BH₃.THF was then added and left to warm up to 0°C overnight. Following that, 1mL of MeOH was added and vessel left to stir for an hour before being concentrated. The resulting orange crude was then chromatographed on silica gel (5 hexanes: 1EA) to give **8** (R_f 0.40) as orange oils.

(*R_c R_{pl}*)-8aa

Orange oil. ¹H NMR (CDCl₃, 300 MHz): δ 0.83 – 1.36 (broad m, 6H, -BH₃), 2.36 – 2.46 (m, 1H, -CH₂PPh₂), 3.25 – 3.34 (m, 1H, -CH₂PPh₂), 3.64 – 3.69 (m, 1H, -CH(PPh₂)CH₂), 3.93 (s, 5H, -Cp), 3.94 – 4.05 (m, 2H, -Cp and -CH(PPh₂)CH₂), 4.17 (s, 1H, -Cp), 4.29 (s, 1H, -Cp), 4.66 – 4.74 (m, 1H, -CH(PPh₂)), 7.16 – 7.22 (m, 2H, -Ar), 7.29 - 7.59 (m, 17H, -Ar), 7.69 – 7.84 (m, 4H, -Ar), 7.94 – 7.97 (m, 2H, -Ar); ³¹P{¹H} NMR (CDCl₃, 162 MHz): δ 13.88 (-CH₂PPh₂), 27.40 (-CH(PPh₂)CH₂C=O). ¹¹B{¹H} NMR (CDCl₃, 96.3 MHz): δ -39.61 ((CH)PPh₂→BH₃), -37.56 (CH₂PPh₂→BH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 25.1 (d, -CH₂PPh₂, ¹J_{CP} = 35.3 Hz), 27.9 (d, -CHPPh₂, ¹J_{CP} = 33.6 Hz), 43.6 (d, -CH(PPh₂)CH₂C=O, ²J_{CP} = 7.6 Hz), 66.7 (*m*-Cp), 68.0 (*o*-Cp), 69.1 (*m*-Cp), 70.0 (5-Cp), 80.2 (*i*-Cp), 87.2 (*i*-Cp), 127.5 (d, *i*-Ar, ¹J_{CP} = 51.2 Hz), 128.1 (Ph Ar), 128.5 (d, *m*-Ar, ³J_{CP} = 11.9 Hz), 128.6 (d, *i*-Ar, ¹J_{CP} = 53.3 Hz), 128.7 (d, *m*-Ar, ³J_{CP} = 10.7 Hz), 128.8 (Ph Ar), 128.8 (d, *m*-Ar, ³J_{CP} = 9.5 Hz),

128.9 (d, *m*-Ar, $^3J_{CP} = 10.1$ Hz), 129.7 (d, *i*-Ar, $^1J_{CP} = 55.3$ Hz), 130.2 (d, *i*-Ar, $^1J_{CP} = 55.1$ Hz), 131.0 (d, *p*-Ar, $^4J_{CP} = 2.3$ Hz), 131.3 (d, *p*-Ar, $^4J_{CP} = 2.2$ Hz), 131.4 (d, *p*-Ar, $^4J_{CP} = 2.1$ Hz), 131.6 (d, *p*-Ar, $^4J_{CP} = 2.0$ Hz), 132.3 (d, *o*-Ar, $^2J_{CP} = 9.0$ Hz), 132.5 (d, *o*-Ar, $^2J_{CP} = 8.7$ Hz), 133.2 (d, *o*-Ar, $^2J_{CP} = 8.8$ Hz), 133.4 (d, *o*-Ar, $^2J_{CP} = 8.5$ Hz), 133.7 (Ph Ar), 136.0 (Ph Ar), 196.9 (d, C=O, $^3J_{CP} = 6.6$ Hz). HRMS (+ESI) calcd for C₄₄H₄₅¹¹B₂Fe₁O₁P₂ [M + H]⁺: 729.2481, found: 729.2501. $[\alpha]_D^{22} = +34.9$ (c 0.4, DCM). *Enantiomeric excess resolved using IF Column; n*-Hexanes : IPA = 90 : 10, 1.0 ml / min, 210 nm, 14.3 mins (major), 19.6 mins (minor) for 98 % *e.e.*

(*R_c R_{pl}*)-8ba

Orange oil. ¹H NMR (CDCl₃, 400 MHz): δ 0.94 – 1.8 (broad m, 6H, -BH₃), 2.39 – 2.47 (m, 4H, Ar-CH₃, -CH₂PPh₂), 3.29 – 3.36 (m, 1H, -CH₂PPh₂), 3.66 – 3.79 (m, 6H, -Cp and -CH(PPh₂)CH₂), 3.96 – 4.06 (m, 2H, -Cp and -CH(PPh₂)CH₂), 4.20 (s, 1H, -Cp), 4.32 (s, 1H, -Cp), 4.71 – 4.74 (m, 1H, -CH(PPh₂)), 7.19 – 7.23 (m, 2H, -Ar), 7.27 (m, 2H, -Ar), 7.32 – 7.48 (m, 12H, -Ar), 7.55 (s, 3H, -Ar), 7.74 – 7.78 (m, 2H, -Ar), 7.82 – 7.90 (m, 3H, -Ar); ³¹P{¹H} NMR (CDCl₃, 162 MHz): δ 13.82 (-CH₂PPh₂), 27.53 (-CH(PPh₂)CH₂C=O). ¹¹B{¹H} NMR (CDCl₃, 96.3 MHz): δ -40.19 ((CH)PPh₂→BH₃), -38.19 (CH₂PPh₂→BH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 21.7 (*p*-tol Ph -CH₃), 24.9 (d, -CH₂PPh₂, $^1J_{CP} = 37.8$ Hz), 27.0 (d, -CHPPh₂, $^1J_{CP} = 33.2$ Hz), 43.3 (d, -CH(PPh₂)CH₂C=O, $^2J_{CP} = 7.3$ Hz), 66.4 (*m*-Cp), 67.7 (*o*-Cp), 68.9 (*m*-Cp), 69.8 (5-Cp), 80.0 (*i*-Cp), 87.0 (m, *i*-Cp), 127.4 (d, *i*-Ar, $^1J_{CP} = 51.0$ Hz), 128.1 (*p*-tol Ph Ar), 128.4 (d, *m*-Ar, $^3J_{CP} = 10.2$ Hz), 128.6 (d, *m*-Ar, $^3J_{CP} = 9.5$ Hz), 128.8 (d, *m*-Ar, $^3J_{CP} = 9.5$

Hz), 128.9 (d, *m*-Ar, $^3J_{CP} = 9.3$ Hz), 129.5 (*p*-tol Ph -Ar), 129.7 (d, *i*-Ar, $^1J_{CP} = 52.2$ Hz), 130.1 (d, *i*-Ar, $^1J_{CP} = 55.1$ Hz), 130.9 (*p*-Ar), 131.3 (*p*-Ar), 131.5 (*p*-Ar), 132.2 (d, *o*-Ar, $^2J_{CP} = 9.0$ Hz), 132.4 (d, *o*-Ar, $^2J_{CP} = 9.0$ Hz), 133.0 (d, *o*-Ar, $^2J_{CP} = 8.6$ Hz), 133.3 (d, *o*-Ar, $^2J_{CP} = 8.3$ Hz), 133.4 (*p*-tol Ph Ar), 144.5 (*p*-tol Ph Ar), 196.5 (d, C=O, $^3J_{CP} = 6.7$ Hz). HRMS (+ESI) calcd for C₄₅H₄₇¹¹B₂Fe₁O₁P₂ [M + H]⁺: 743.2638, found: 743.2665. $[\alpha]_D^{22} = -38.8$ (c 0.3, DCM). *Enantiomeric excess resolved using IF Column; n-Hexanes : IPA = 90 : 10, 1.0 ml / min, 240 nm, 15.7 mins (major), 22.4 mins (minor) for 88 % e.e.*

(*R_c* *R_{pl}*)-8ca

Orange oil. ^1H NMR (CDCl₃, 400 MHz): δ 0.89 – 1.56 (broad m, 6H, -BH₃), 2.36 – 2.43 (m, 1H, -CH₂PPh₂), 3.26 – 3.33 (m, 1H, -CH₂PPh₂), 3.62 – 3.72 (m, 1H, -CH(PPh₂)CH₂), 3.76 – 3.79 (m, 4H, Ar-OCH₃ and -CH(PPh₂)CH₂), 3.84 – 3.96 (m, 5H, -Cp), 4.04 (s, 1H, -Cp), 4.17 (m, 1H, -Cp), 4.30 (s, 1H, -Cp), 4.67 – 4.73 (m, 1H, -CH(PPh₂)), 6.93 (d, 2H, $^3J = 9.1$ Hz, -Ar), 7.16 – 7.20 (m, 2H, -Ar), 7.31 – 7.45 (m, 11H, -Ar), 7.51 – 7.54 (m, 3H, -Ar), 7.72 – 7.84 (m, 4H, -Ar), 7.95 (d, 2H, $^3J = 8.8$ Hz, -Ar); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl₃, 162 MHz): δ 13.82 (-CH₂PPh₂), 27.44 (-CH(PPh₂)CH₂C=O). $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl₃, 96.3 MHz): δ -40.38 ((CH)PPh₂→BH₃), -38.23 (CH₂PPh₂→BH₃). ^{13}C NMR (CDCl₃, 100 MHz): δ 25.1 (d, -CH₂PPh₂, $^1J_{CP} = 35.7$ Hz), 27.2 (d, -CHPPh₂, $^1J_{CP} = 33.4$ Hz), 43.2 (d, -CH(PPh₂)CH₂C=O, $^2J_{CP} = 7.6$ Hz), 55.6 (*p*-OCH₃), 66.6 (*m*-Cp), 67.9 (*o*-Cp), 68.9 (d, *m*-Cp, $^4J_{CP} = 3.7$ Hz), 70.0 (5-Cp), 80.0 (d, *i*-Cp, $^2J_{CP} = 2.7$ Hz), 87.3 (dd, *i*-Cp, $^2J_{CP} = 9.1$ Hz, $^3J_{CP} = 5.9$ Hz), 114.1 (*p*-OMe Ph), 127.7 (d, *i*-Ar, $^1J_{CP} = 51.2$ Hz), 128.6 (d, *m*-Ar, $^3J_{CP} = 9.8$ Hz), 128.7 (d, *m*-Ar, $^3J_{CP}$

= 10.0 Hz), 128.9 (d, *m*-Ar, $^3J_{CP}$ = 9.6 Hz), 128.9 (d, *i*-Ar, $^1J_{CP}$ = 50.0 Hz), 129.0 (d, *m*-Ar, $^3J_{CP}$ = 10.0 Hz), 129.2 (*p*-OMe Ph -Ar), 130.0 (d, *i*-Ar, $^1J_{CP}$ = 55.3 Hz), 130.3 (d, *i*-Ar, $^1J_{CP}$ = 55.0 Hz), 130.4 (*p*-OMe Ph -Ar), 131.1 (d, *p*-Ar, $^4J_{CP}$ = 2.2 Hz), 131.4 (pseudo t, *p*-Ar, $^4J_{CP}$ = 2.8 Hz), 131.6 (d, *p*-Ar, $^4J_{CP}$ = 2.1 Hz), 132.4 (d, *o*-Ar, $^2J_{CP}$ = 9.1 Hz), 132.6 (d, *o*-Ar, $^2J_{CP}$ = 9.1 Hz), 133.2 (d, *o*-Ar, $^2J_{CP}$ = 8.8 Hz), 133.5 (d, *o*-Ar, $^2J_{CP}$ = 8.3 Hz), 164.0 (*p*-OMe Ph Ar), 195.4 (d, C=O, $^3J_{CP}$ = 6.9 Hz). HRMS (+ESI) calcd for C₄₅H₄₇¹¹B₂Fe₁O₂P₂ [M + H]⁺: 759.2587, found: 759.2609. [α]_D²² = +57.1 (c 0.3, DCM). *Enantiomeric excess resolved using IF Column; n*-Hexanes : IPA = 90 : 10, 1.0 ml / min, 210 nm, 21.7 mins (major), 37.9 mins (minor) for 97 % *e.e.*

(*R_c R_{pl}*)-8da

Orange oil. ¹H NMR (CDCl₃, 400 MHz): δ 0.87 – 1.65 (broad m, 6H, -BH₃), 2.38 – 2.46 (m, 1H, -CH₂PPh₂), 3.25 – 3.32 (m, 1H, -CH₂PPh₂), 3.75 – 3.95 (m, 7H, -Cp and -CH(PPh₂)CH₂), 4.05 (s, 1H, -Cp), 4.17 (s, 1H, -Cp), 4.29 (s, 1H, -Cp), 4.66 – 4.70 (m, 1H, -CH(PPh₂)), 7.18 – 7.22 (m, 2H, -Ar), 7.31 – 7.44 (m, 13H, -Ar), 7.53 (s, 3H, -Ar), 7.68 – 7.73 (m, 2H, -Ar), 7.78 – 7.82 (m, 2H, -Ar), 7.87 – 7.90 (m, 2H, -Ar); ³¹P{¹H} NMR (CDCl₃, 162 MHz): δ 13.91 (-CH₂PPh₂), 27.18 (-CH(PPh₂)CH₂C=O). ¹¹B{¹H} NMR (CDCl₃, 96.3 MHz): δ -39.96 ((CH)PPh₂→BH₃), -38.15 (CH₂PPh₂→BH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 25.2 (d, -CH₂PPh₂, $^1J_{CP}$ = 36.2 Hz), 27.6 (d, -CHPPh₂, $^1J_{CP}$ = 32.8 Hz), 43.6 (d, -CH(PPh₂)CH₂C=O, $^2J_{CP}$ = 7.7 Hz), 66.6 (*m*-Cp), 67.9 (*o*-Cp), 69.1 (d, *m*-Cp, $^4J_{CP}$ = 3.7 Hz), 69.9 (5-Cp), 80.1 (*i*-Cp), 87.1 (dd, *i*-Cp, $^2J_{CP}$ = 9.0 Hz, $^3J_{CP}$ = 5.5 Hz), 127.5 (d, *i*-Ar, $^1J_{CP}$ = 50.8 Hz), 128.4 (d, *i*-Ar, $^1J_{CP}$ = 54.1 Hz), 128.6 (d, *m*-Ar, $^3J_{CP}$ = 10.6 Hz), 128.7 (d, *m*-Ar, $^3J_{CP}$ = 10.0 Hz), 128.9 (d,

m-Ar, $^3J_{CP} = 8.7$ Hz), 129.0 (d, *m*-Ar, $^3J_{CP} = 9.2$ Hz), 129.2 (*p*-Cl Ph -Ar), 129.5 (*p*-Cl Ph -Ar), 129.6 (d, *i*-Ar, $^1J_{CP} = 53.6$ Hz), 130.2 (d, *i*-Ar, $^1J_{CP} = 53.4$ Hz), 131.1 (d, *p*-Ar, $^4J_{CP} = 2.4$ Hz), 131.4 (d, *p*-Ar, $^4J_{CP} = 2.5$ Hz), 131.5 (d, *p*-Ar, $^4J_{CP} = 2.5$ Hz), 131.7 (d, *p*-Ar, $^4J_{CP} = 2.6$ Hz), 132.3 (d, *o*-Ar, $^2J_{CP} = 9.1$ Hz), 132.5 (d, *o*-Ar, $^2J_{CP} = 9.2$ Hz), 133.3 (d, *o*-Ar, $^2J_{CP} = 8.8$ Hz), 133.4 (d, *o*-Ar, $^2J_{CP} = 8.5$ Hz), 134.3 (*p*-Cl Ph Ar), 140.2 (*p*-Cl Ph Ar), 195.8 (d, C=O, $^3J_{CP} = 6.3$ Hz). HRMS (+ESI) calcd for C₄₄H₄₄¹¹B₂Cl₁Fe₁O₁P₂ [M + H]⁺: 763.2091, found: 763.2108. $[\alpha]_D^{22} = +5.0$ (c 0.4, DCM) *Enantiomeric excess resolved using IF Column; n*-Hexanes : IPA = 95 : 5, 1.0 ml / min, 240 nm, 21.9 mins (major), 30.6 mins (minor) for 93 % *e.e.*

(*R_c* *R_{pl}*)-8ea

Orange oil. ¹H NMR (CDCl₃, 400 MHz): δ 0.89 – 1.36 (m, 6H, -BH₃), 2.38 – 2.46 (m, 1H, -CH₂PPh₂), 3.29 – 3.35 (m, 1H, -CH₂PPh₂), 3.79 – 4.13 (m, 6H, -Cp and -CH(PPh₂)CH₂), 4.08 – 4.13 (m, 2H, -Cp and -CH(PPh₂)CH₂), 4.20 (s, 1H, -Cp), 4.39 (s, 1H, -Cp), 4.74 – 4.80 (m, 1H, -CH(PPh₂)), 7.19 – 7.22 (m, 2H, -Ar), 7.31 – 7.46 (m, 11H, -Ar), 7.53 – 7.63 (m, 5H, -Ar), 7.72 – 7.77 (m, 2H, -Ar), 7.83 – 7.90 (m, 4H, -Ar), 7.99 – 8.03 (m, 2H, -Ar), 8.45 (s, 1H, -Ar); ³¹P{¹H} NMR (CDCl₃, 162 MHz): δ 13.94 (-CH₂PPh₂), 27.27 (-CH(PPh₂)CH₂C=O). ¹¹B{¹H} NMR (CDCl₃, 96.3 MHz): δ -40.17 ((CH)PPh₂→BH₃), -38.02 (CH₂PPh₂→BH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 25.2 (d, -CH₂PPh₂, $^1J_{CP} = 35.6$ Hz), 27.5 (d, -CHPPh₂, $^1J_{CP} = 33.2$ Hz), 43.7 (d, -CH(PPh₂)CH₂C=O, $^2J_{CP} = 7.8$ Hz), 66.7 (*m*-Cp), 68.0 (*o*-Cp), 69.1 (d, *m*-Cp, $^4J_{CP} = 3.8$ Hz), 70.0 (5-Cp), 80.2 (d, *i*-Cp, $^2J_{CP} = 2.3$ Hz), 87.2 (dd, *i*-Cp, $^2J_{CP} = 9.2$ Hz, $^3J_{CP} = 5.9$ Hz), 123.7 (naphthyl Ar), 127.1 (naphthyl Ar), 127.6 (d, *i*-Ar, $^1J_{CP} = 51.3$ Hz), 127.9 (naphthyl Ar),

128.6 (d, *m*-Ar, $^3J_{CP} = 10.3$ Hz), 128.7 (d, *i*-Ar, $^1J_{CP} = 52.3$ Hz), 128.7 (d, *m*-Ar, $^3J_{CP} = 9.6$ Hz), 128.8 (naphthyl Ar), 128.9 (d, *m*-Ar, $^3J_{CP} = 8.8$ Hz), 128.9 (naphthyl Ar), 129.0 (d, *m*-Ar, $^3J_{CP} = 9.2$ Hz), 129.8 (naphthyl Ar), 129.9 (naphthyl Ar), 129.9 (d, *i*-Ar, $^1J_{CP} = 55.3$ Hz), 130.3 (d, *i*-Ar, $^1J_{CP} = 55.3$ Hz), 131.1 (d, *p*-Ar, $^4J_{CP} = 2.2$ Hz), 131.4 (d, *p*-Ar, $^4J_{CP} = 2.2$ Hz), 131.5 (d, *p*-Ar, $^4J_{CP} = 2.1$ Hz), 131.7 (d, *p*-Ar, $^4J_{CP} = 2.1$ Hz), 132.3 (d, *o*-Ar, $^2J_{CP} = 9.0$ Hz), 132.5 (naphthyl Ar), 132.6 (d, *o*-Ar, $^2J_{CP} = 9.1$ Hz), 133.3 (d, *o*-Ar, $^2J_{CP} = 8.7$ Hz), 133.4 (d, *o*-Ar, $^2J_{CP} = 8.1$ Hz), 135.9 (naphthyl Ar), 196.9 (d, C=O, $^3J_{CP} = 6.9$ Hz). HRMS (+ESI) calcd for C₄₈H₄₇¹¹B₂Fe₁O₁P₂ [M + H]⁺: 779.2638, found: 779.2628. $[\alpha]_D^{22} = +24.4$ (c 0.3, DCM). *Enantiomeric excess resolved using IF Column; n-Hexanes : IPA = 90 : 10, 1.0 ml / min, 210 nm, 19.0 mins (major), 29.7 mins (minor) for 98 % e.e.*

(*R_c R_{pl}*)-8fa

Orange oil. ^1H NMR (CDCl₃, 400 MHz): δ 0.92 – 1.65 (broad m, 6H, -BH₃), 2.37 – 2.45 (m, 1H, -CH₂PPh₂), 3.24 – 3.31 (m, 1H, -CH₂PPh₂), 3.70 – 3.76 (m, 1H, -CH(PPh₂)CH₂), 3.84 (s, 5H, -Cp), 3.88 – 3.99 (m, 1H, -CH(PPh₂)CH₂), 4.05 (m, 1H, -Cp), 4.19 (m, 1H, -Cp), 4.29 (s, 1H, -Cp), 4.60 – 4.66 (m, 1H, -CH(PPh₂)), 7.10 – 7.12 (m, 1H, -Ar), 7.16 – 7.21 (m, 2H, -Ar), 7.30 – 7.46 (m, 11H, -Ar), 7.51 – 7.53 (m, 3H, -Ar), 7.64 (d, 1H, $^3J = 4.8$ Hz, -Ar), 7.68 – 7.73 (m, 3H, -Ar), 7.78 – 7.83 (m, 2H, -Ar); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl₃, 162 MHz): δ 13.99 (-CH₂PPh₂), 27.08 (-CH(PPh₂)CH₂C=O). $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl₃, 96.3 MHz): δ -39.82 ((CH)PPh₂→BH₃), -38.02 (CH₂PPh₂→BH₃). ^{13}C NMR (CDCl₃, 100 MHz): δ 25.1 (d, -CH₂PPh₂, $^1J_{CP} = 35.6$ Hz), 27.6 (d, -CHPPh₂, $^1J_{CP} = 33.0$ Hz), 44.0 (d, -CH(PPh₂)CH₂C=O, $^2J_{CP} = 7.7$ Hz), 66.6 (*m*-Cp), 67.9 (d, *o*-Cp, $^3J_{CP} = 2.2$ Hz), 69.0 (d, *m*-Cp, $^4J_{CP} = 3.8$ Hz), 70.0 (5-Cp), 80.0 (d, *i*-Cp, $^2J_{CP} =$

2.6 Hz), 87.1 (dd, *i*-Cp, $^2J_{CP} = 8.9$ Hz, $^3J_{CP} = 5.8$ Hz), 127.4 (d, *i*-Ar, $^1J_{CP} = 51.2$ Hz), 128.4 (thienyl Ar), 128.5 (d, *i*-Ar, $^1J_{CP} = 53.5$ Hz), 128.6 (d, *m*-Ar, $^3J_{CP} = 9.7$ Hz), 128.7 (d, *m*-Ar, $^3J_{CP} = 9.8$ Hz), 128.9 (d, *m*-Ar, $^3J_{CP} = 9.7$ Hz), 129.0 (d, *m*-Ar, $^3J_{CP} = 9.8$ Hz), 129.7 (d, *i*-Ar, $^1J_{CP} = 55.2$ Hz), 130.2 (d, *i*-Ar, $^1J_{CP} = 55.1$ Hz), 131.1 (d, *p*-Ar, $^4J_{CP} = 2.1$ Hz), 131.3 (d, *p*-Ar, $^4J_{CP} = 2.1$ Hz), 131.4 (d, *p*-Ar, $^4J_{CP} = 2.1$ Hz), 131.7 (d, *p*-Ar, $^4J_{CP} = 2.1$ Hz), 132.3 (d, *o*-Ar, $^2J_{CP} = 9.1$ Hz), 132.3 (thienyl Ar), 132.5 (d, *o*-Ar, $^2J_{CP} = 9.1$ Hz), 133.2 (d, *o*-Ar, $^2J_{CP} = 8.8$ Hz), 133.5 (d, *o*-Ar, $^2J_{CP} = 8.4$ Hz), 134.4 (thienyl Ar), 143.0 (thienyl Ar), 189.9 (d, C=O, $^3J_{CP} = 6.7$ Hz). HRMS (+ESI) calcd for C₄₂H₄₃¹¹B₂Fe₁O₁P₂S [M + H]⁺: 735.2045, found: 735.2076. $[\alpha]_D^{22} = +26.5$ (c 0.3, DCM) *Enantiomeric excess resolved using IF Column; n*-Hexanes : IPA = 90 : 10, 1.0 ml / min, 230 nm, 17.2 mins (major), 25.9 mins (minor) for 98 % *e.e.*

(*R_c R_{pl}*)-8ga

Orange oil. ^1H NMR (CDCl₃, 300 MHz): δ 0.86 – 1.55 (broad m, 6H, -BH₃), 2.46 – 2.57 (m, 1H, -CH₂PPh₂), 3.22 – 3.31 (m, 1H, -CH₂PPh₂), 3.42 – 3.74 (m, 2H, -CH(PPh₂)CH₂), 3.84 (s, 5H, -Cp), 4.03 (m, 1H, -Cp), 4.18 (m, 1H, -Cp), 4.25 (s, 1H, -Cp), 4.55 – 4.63 (m, 1H, -CH(PPh₂)), 6.50 – 6.52 (m, 1H, -Ar), 7.17 - 7.22 (m, 3H, -Ar), 7.29 – 7.32 (m, 2H, -Ar), 7.34 – 7.46 (m, 9H, -Ar), 7.49 – 7.52 (m, 3H, -Ar), 7.57 (m, 1H, -Ar), 7.65 – 7.72 (m, 2H, -Ar), 7.75 – 7.82 (m, 2H, -Ar); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl₃, 121 MHz): δ 14.65 (-CH₂PPh₂), 27.76 (-CH(PPh₂)CH₂C=O). $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl₃, 96.3 MHz): δ -39.92 ((CH)PPh₂→BH₃), -38.27 (CH₂PPh₂→BH₃). ^{13}C NMR (CDCl₃, 100 MHz): δ 25.2 (d, -CH₂PPh₂, $^1J_{CP} = 35.6$ Hz), 27.2 (d, -CHPPh₂, $^1J_{CP} = 32.9$ Hz), 43.1 (d, -CH(PPh₂)CH₂C=O, $^2J_{CP} = 7.2$ Hz), 66.6 (*m*-Cp), 68.0 (d, *o*-Cp, $^3J_{CP} = 1.9$ Hz), 69.2 (d, *m*-Cp, $^4J_{CP} = 3.9$ Hz), 70.0 (5-Cp), 79.9 (d, *i*-Cp, $^2J_{CP} = 2.7$ Hz),

87.1 (dd, *i*-Cp, $^2J_{CP} = 9.7$ Hz, $^3J_{CP} = 5.5$ Hz), 112.6 (furyl Ar), 117.8 (furyl Ar), 127.5 (d, *i*-Ar, $^1J_{CP} = 50.9$ Hz), 128.6 (d, *i*-Ar, $^1J_{CP} = 54.4$ Hz), 128.6 (d, *m*-Ar, $^3J_{CP} = 9.5$ Hz), 128.7 (d, *m*-Ar, $^3J_{CP} = 9.2$ Hz), 128.8 (d, *m*-Ar, $^3J_{CP} = 9.8$ Hz), 129.0 (d, *m*-Ar, $^3J_{CP} = 9.9$ Hz), 129.6 (d, *i*-Ar, $^1J_{CP} = 55.2$ Hz), 130.3 (d, *i*-Ar, $^1J_{CP} = 55.1$ Hz), 131.1 (d, *p*-Ar, $^4J_{CP} = 2.2$ Hz), 131.3 (d, *p*-Ar, $^4J_{CP} = 2.1$ Hz), 131.4 (d, *p*-Ar, $^4J_{CP} = 2.2$ Hz), 131.6 (d, *p*-Ar, $^4J_{CP} = 2.1$ Hz), 132.4 (d, *o*-Ar, $^2J_{CP} = 9.1$ Hz), 132.5 (d, *o*-Ar, $^2J_{CP} = 9.1$ Hz), 133.2 (d, *o*-Ar, $^2J_{CP} = 8.8$ Hz), 133.5 (d, *o*-Ar, $^2J_{CP} = 8.4$ Hz), 146.8 (furyl Ar), 152.0 (furyl Ar), 186.2 (d, C=O, $^3J_{CP} = 6.4$ Hz). HRMS (+ESI) calcd for C₄₂H₄₃¹¹B₂Fe₁O₂P₂ [M + H]⁺: 719.2274, found: 719.2288. $[\alpha]_D^{22} = -92.3$ (c 1.4, DCM)

Enantiomeric excess resolved using IF Column; n-Hexanes : IPA = 90 : 10, 1.0 ml / min, 254 nm, 19.0 mins (major), 28.4 mins (minor) for 80 % e.e.

(*R_c R_{pl}*)-10fa

Glassy orange solid flakes. ¹H NMR (CDCl₃, 500 MHz): δ 3.02 (s, 1H, *Cp*), 3.09 (ddd, 1H, $^3J_{HH} = 1.6$ Hz, $^3J_{HP} = 12.3$ Hz, $^2J_{HH} = 17.3$ Hz), 3.24 (ddd, 1H, $^3J_{HH} = 3.4$ Hz, $^3J_{HP} = 6.8$ Hz, $^2J_{HH} = 17.6$ Hz), 3.36 (pseudo td, 1H, $^3J_{HH} = 1.9$ Hz, $^1J_{HP} = 22.0$ Hz, -CHPPh₂), 3.46 (s, 1H, -Cp), 3.74 (s, 5H, -Cp), 3.83 (m, 1H, -Cp), 3.36 (pseudo dd, 1H, $^3J_{HH} = 4.9$ Hz, $^2J_{HP} = 14.4$ Hz, -CHPPh₂), 4.89 (m, 1H, -CH(PPh₂)), 3.36 (pseudo t, 1H, $^3J_{HH} = 4.4$ Hz, thienyl-*H*), 7.34 – 7.41 (m, 3H, -Ar), 7.42 - 7.59 (m, 9H, -Ar), 7.62 (d, 1H, $^3J_{HH} = 3.7$ Hz, Ar), 7.67 (d, 1H, $^3J_{HH} = 5.2$ Hz, Ar), 7.73 (d, 1H, $^3J_{PH} = 11.5$ Hz, Ar), 7.75 (d, 1H, $^3J_{PH} = 11.5$ Hz, Ar), 7.83 – 7.94 (m, 4H, -Ar), 8.00 (d, 1H, $^3J_{PH} = 11.3$ Hz, Ar), 8.02 (d, 1H, $^3J_{PH} = 11.1$ Hz, Ar); ³¹P{¹H} NMR (CDCl₃, 162 MHz): δ 22.0 (-CH₂PPh₂), 34.6 (-CH(PPh₂)CH₂C=O). ¹³C NMR (CDCl₃, 100 MHz): δ

31.7 (dd, -CH₂PPh₂, $^3J_{CP} = 4.4$ Hz, $^1J_{CP} = 21.4$ Hz), 32.8 (d, -CHPPh₂, $^3J_{CP} = 3.5$ Hz, $^1J_{CP} = 23.8$ Hz), 40.3 (d, -CH(PPh₂)CH₂C=O, $^2J_{CP} = 3.1$ Hz), 66.5 (s, *m*-Cp), 66.6 (s, *o*-Cp), 69.1 (s, *m*-Cp), 69.6 (s, 5-Cp), 78.4 (m, *i*-Cp), 85.0 (m, *i*-Cp), 127.4 (d, *i*-Ar, $^1J_{CP} = 51.2$ Hz), 127.6 (d, *i*-Ar, $^1J_{CP} = 55.4$ Hz), 127.7 (d, *m*-Ar, $^3J_{CP} = 11.4$ Hz), 128.1 (d, *m*-Ar, $^3J_{CP} = 11.4$ Hz), 128.5 (s, thienyl Ar), 128.7 (d, *m*-Ar, $^3J_{CP} = 10.2$ Hz), 128.8 (d, *m*-Ar, $^3J_{CP} = 10.7$ Hz), 128.9 (d, *i*-Ar, $^1J_{CP} = 49.1$ Hz), 130.5 (d, *i*-Ar, $^1J_{CP} = 50.1$ Hz), 130.9 (d, *p*-Ar, $^4J_{CP} = 2.5$ Hz), 131.1 (d, *p*-Ar, $^4J_{CP} = 2.1$ Hz), 131.3 (d, *p*-Ar, $^4J_{CP} = 3.0$ Hz), 131.6 (d, *p*-Ar, $^4J_{CP} = 2.0$ Hz), 132.2 (s, thienyl Ar), 132.7 (d, *o*-Ar, $^2J_{CP} = 8.5$ Hz), 132.7 (d, *i*-Ar, $^1J_{CP} = 58.8$ Hz), 133.6 (d, *o*-Ar, $^2J_{CP} = 9.9$ Hz), 134.4 (d, *o*-Ar, $^2J_{CP} = 10.6$ Hz), 134.9 (s, thienyl Ar), 134.8 (d, *o*-Ar, $^2J_{CP} = 10.8$ Hz), 143.1 (s, thienyl Ar), 189.4 (d, C=O, $^3J_{CP} = 6.2$ Hz). HRMS (+ESI) calcd for C₄₂H₃₇O₁P₂S₁³⁵Cl₂⁵⁶Fe₁Pd₁ [M + H]⁺: 884.9375, found: 884.9900. [α]_D²² = -26.3 (c 0.5, DCM)

(*R_c* *R_{pl}*)-10fa: X-Ray Crystallographic Data

Crystal Structure Report for leung1151m

Table 1. Sample and crystal data for leung1151m.

Identification code	leung1151m
Chemical formula	C _{44.50} H ₄₃ Cl ₂ FeO ₂ P ₂ PdS
Formula weight	936.94 g/mol
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal size	0.040 x 0.200 x 0.220 mm
Crystal habit	orange plate

Crystal system	monoclinic
Space group	P 1 21 1
Unit cell dimensions	a = 15.2788(4) Å $\alpha = 90^\circ$ b = 12.9206(4) Å $\beta = 91.6982(9)^\circ$ c = 21.1519(5) Å $\gamma = 90^\circ$
Volume	4173.8(2) Å ³
Z	4
Density (calculated)	1.491 g/cm ³
Absorption coefficient	1.070 mm ⁻¹
F(000)	1912

Table 2. Data collection and structure refinement for leung1151m.

Theta range for data collection	2.29 to 32.04°
Index ranges	-22 ≤ h ≤ 22, -15 ≤ k ≤ 19, -26 ≤ l ≤ 31
Reflections collected	46213
Independent reflections	24778 [R(int) = 0.0634]
Absorption correction	Multi-Scan
Max. and min. transmission	0.9580 and 0.7990
Refinement method	Full-matrix least-squares on F ²
Refinement program	SHELXL-2018/3 (Sheldrick, 2018)
Function minimized	$\sum w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	24778 / 2551 / 1255
Goodness-of-fit on F²	1.020
$\Delta/\sigma_{\max}$	0.001

Final R indices	17894 data; $I > 2\sigma(I)$	$R1 = 0.0660$, $wR2 = 0.1599$
	all data	$R1 = 0.0947$, $wR2 = 0.1873$
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0770P)^2 + 2.8855P]$ where $P = (F_o^2 + 2F_c^2)/3$	
Absolute structure parameter	0.02(2)	
Largest diff. peak and hole	1.175 and -0.967 eÅ ⁻³	
R.M.S. deviation from mean	0.114 eÅ ⁻³	

2.5 References

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Chapter 3

Desymmetrization of Achiral Heterobicyclic Alkenes through Catalytic Asymmetric Hydrophosphination

3.1 Introduction

Desymmetrizing transformations of achiral heterobicyclic alkenes are important towards the development of chiral scaffolds prominent in various natural products and molecules with pharmacological attributes.¹ The application of transition metals as catalysts in this methodology has been well-studied with carbon,² oxygen,³ nitrogen,⁴ sulphur,⁵ boron⁶ and fluorine⁷ based nucleophiles thereby producing molecules with unique spatial dissymmetry owing to the tandem realization of multiple stereogenic centres. (Scheme 1) Advances by Lautens *et al.*, and several others have demonstrated the potential of this strategy in asymmetric ring opening reactions (ARO) with oxa- and azabicyclic alkenes and various nucleophiles.⁸

Scheme 1. Generic reaction scheme for desymmetrization of bicyclic alkenes.

In parallel, heterobicyclic core-retained additions (simple addition) are less well-explored due to the inclination for the molecule to relieve ring strain with transition metal catalysts. The motivation for developing methods for the retention of the heteroatom bridgehead is borne from the intricate syntheses of natural analgesic analogues usually leading to low yields.^{1j-s}

Figure 1. Highly potent analgesics with heterobicyclic scaffolds found in nature.

Some examples of effective analgesics with heterobicyclic scaffolds found in nature include samandarine (isolated from secretions of skin glands of the fire salamander, *Salamandra salamandra*) and epibatidine (isolated from secretions of skin glands of the endangered frog, *Epipedobates tricolor*) that targets numerous neuronal nicotinic acetylcholine receptor subtypes.^{1t-v} As such, studying analogues of such molecules becomes imperative, in the analysis for structure activity relationships, to design drugs with desired level of potencies and targeting mechanisms. In essence, developing catalytic methods to directly generate unexplored derivatives of the heterobicyclic scaffold brings great value to the scientific community.

An example of asymmetric hydroarylation with retention of the bicyclic core was demonstrated by Lautens *et al.* using a chiral rhodium N-heterocyclic carbene catalyst (Scheme 2).^{2ap} The method facilitated addition in high yields using arylboronic acids with non-electron withdrawing groups. Subsequently, the protocol was applied in the catalytic synthesis of the *N*-protected epibatidine resulting in high enantioselectivities and diastereoselectivities albeit with modest yield.

Scheme 2. Hydroarylation of azabicycles by Lautens *et al.*^{2ap}

Scheme 3. Hydrothiolation of oxabicycles by Wang *et al.*^{5b}

Scheme 4. Hydroamination of heterobicycles by Hirano & Miura *et al.*^{4j}

Further successful examples of exclusive heterobicyclic core-retained hydrothiolation and hydroamination was also demonstrated by Wang *et al.*^{5b} and Hirano & Miura *et al.*^{4j} respectively using commercially available catalysts (Scheme 3 and 4). High yields and selectivities were achieved with tolerance to various electronics imposed on both substrate and nucleophile.

Hou *et al.*, recently highlighted the capability of phosphapalladacycles to selectively access either "ring opening" or "addition" adducts by switching the electronic effects imparted by the ligand to the metal center (Scheme 5).⁹ In a series of palladacycles screened for hydroalkynylation, the use of palladacycles possessing more sp^3 character at the carbon adjacent to the palladium consistently provided a major amount of addition product (via hydrolysis) while those possessing sp^2 character would facilitate the β -oxygen elimination to give ring-opening products.

Scheme 5. Hou's application of palladacycles in hydroalkynylation resulting in either "ring opening" or "addition" adducts.⁹

Figure 2. Comparison of transition states for hydroalkynylation.

It was rationalized by "hard and soft acids-bases" principle and anti-symbiotic effects, that the energy of the transition state will depend on the electronic character of the ligated carbon in

the palladacycle. In the case of using **6** as the catalyst, the Csp³ (sp³ hybridized carbon atom) of the ligand exhibits a ‘soft’ character and hence introduces better stability in **TS2** as compared to **TS1**. This is due to the palladacycle’s Csp³ carbon being positioned *trans* to the oxabicyclic alkene’s Csp³ carbon instead of the oxygen atom which possesses a ‘hard’ character. It is pertinent to note that the Csp³ carbon possesses softer electronic character than tertiary phosphine donor in phosphapalladacycle **6**. However, the study conducted did not elaborate on the enantioselectivity of the hydroalkynylation reaction but only focused upon the influence of electronics on the palladacycle as described.

Scheme 6. Hou’s application of (*R*)-**4a** in boronic acid addition to oxabicyclic alkenes.^{2q}

Hou has also demonstrated a boronic acid addition with oxabicyclic alkenes with the discussed palladacycle **4a**.^{2q} The Mop-H derived palladacycle **4a** furnished ring-opening products in high yields and enantioselectivities. Functional groups on the oxabicyclic alkene was found to impact selectivities to small extent. Enantiomeric excess of the product increased to 83% when an electron-withdrawing group R¹ = Br, while electron donating R¹ = CH₃ and -OCH₃ groups reduced *e.e* value of the products.

In the wider context of nucleophilic additions and in view of the synthetic difficulty inherent in the aforementioned transformations,¹⁰ there also exists a dearth of reports on the catalytic

enantioselective addition of phosphorus(III) nucleophiles to cyclic alkenes. This is unfortunate in view of the synthetic utility of the potential products that can be obtained via such transformations. In our hands (Scheme 8), air-stable palladacycles have proven to be efficient for conducting catalytic P-H additions to activated linear conjugated and non-conjugated alkenes (Scheme 7).¹¹

Scheme 7. General catalytic Asymmetric Hydrophosphination (AHP)

Motivated by this potential of palladacycles, we hypothesized that extending the asymmetric hydrophosphination (AHP) methodology to oxabicyclic alkenes via a desymmetrization pathway would prove to be of immense value towards broadening the access to novel and otherwise synthetically challenging chiral phosphine frameworks. Hence, as part of our ongoing efforts to further develop the Pd-catalyzed Asymmetric Hydrophosphination (AHP) reaction, we examined the catalytic activity of a selection of established palladacycles for the protocol (Scheme 8). Palladacycles (*S*)-**1/2** and (*S,S*)-**3** were initially shortlisted based on their performance in previous AHP scenarios^{11a, 11b} whereas phospho-palladacycles (*R*)-**4** and **5** were selected for their documented stability in catalyzing hydroalkynylations of oxabicyclic alkenes.⁹

Scheme 8. AHP of 1,4 – Epoxydihydronaphthalene (**1a**)

3.2 Results & Discussion

Initial trials conducted by mixing 1.2 equivalents of 1,4-dihydro-1,4-epoxynaphthalene (**1a**) and 1 equivalent diphenylphosphine along with 5 % of catalyst in toluene (Scheme 5, Table 1) showed that (*S*)-**1** gave trace conversions whereas (*R*)-**4a** provided full conversion after 60h at room temperature with the reaction producing solely the oxabicyclic core-retained addition product **2a** with high diastereoselectivity. This clear preference for the addition product was in stark contrast to boronic acid additions and hydroalkynylation reactions demonstrated by Hou using the same catalyst (*R*)-**4a** that provided the ring-opening product.^{2q,9} This could be attributed to the Pd core's preference for the phosphine lone pair over that of the oxygen in the expected carbometallated state thus averting β -oxygen elimination (see Figure 3).

Table 1. Catalyst screening for AHP of 1, 4 -epoxydihydronaphthalene (**1a**) in Scheme 8.

Entry ^[a]	Catalyst	Conversion ^[b] (%)	<i>d.e</i> ^[c] (%)	<i>e.e</i> ^[d] (%)
1	(<i>S</i>)- 1	trace	-	-
2	(<i>S</i>)- 2	n.r	-	-
3 ^[e]	(<i>S, S</i>)- 3	n.r	-	-
4	(<i>R</i>)- 4a	>99	>99	56
5 ^[e, f]	(<i>R</i>)- 5	n.r	-	-
6	(<i>S</i>)-Binap/ PdOAc ₂	trace	-	-

[a] Reaction conditions: 1.2 eqv **1a**, 5 μ L (1 eqv) HPPH₂, 5 mol% catalyst, 2.5 mL toluene for 60 hr. [b] Determined by ³¹P{¹H} NMR [c] Determined by ³¹P{¹H} NMR & ¹H NMR. [d] *e.e* determined via HPLC on a stationary chiral phase after isolation of sulphurized product. [e] 10 mol% catalyst used. [f] 1 eqv of NEt₃ added.

Figure 3. General catalytic Asymmetric Hydrophosphination (AHP)

The aza-palladacycle (*S*)-**2** gave no product while phosphapalladacycles (*S*)-**1** and (*R*)-**4a** performed better when compared to the pincer type catalyst (*S, S*)-**3**. The latter observation can be attributed to the well-established requirement for two potential vacant sites on the Pd core for simultaneous activation of both the phosphine and substrate in this class of metallacycle catalysts when involved in the hydrophosphination reaction.^{11a,b,12} Increasing the reaction temperature whilst employing (*R*)-**4a** improved conversion rates but resulted in significant decline in enantioselectivity. Notably, the use of triethylamine as an external base resulted in no conversions for (*S*)-**1**, (*R*)-**4a** and **5**. Additionally, modulating the pi-acidity of phosphine donor as done in the case of (*R*)-**4b** and **4c** resulted in poor selectivities but gave similar conversion rates. Effect of solvents were subsequently studied (Table 2) and it was found that protic solvents such as methanol would result in no conversion whereas dichloromethane (DCM) reduced conversion rates significantly with concomitant poor enantioselectivity. Surprisingly, non-polar solvents such as cyclohexane and hexane gave higher enantioselectivities albeit with moderate conversion. Moreover, precipitation of the product **2a** out of the reaction solution was also observed. Solvent mixture of hexanes: dichloromethane (1:1) provided slightly better conversion than DCM alone; implying the need for product precipitation for improved conversion. As the product precipitates out of solution during the course of the reaction, vacant sites on the palladacycle are more readily accessible by the reactants, thereby improving the catalyst regeneration rate. Moreover, doubling the amount of

HPPH₂ or alkene did not improve conversion. Further highlighting the importance of the acetate bridged complexes, separate trials with the bis-acetonitrile ligated versions of palladacyclic complexes (*S*)-**1** and **2**, commonly successful for facilitating AHPs, yielded no products. Similarly, as aforementioned, no product was detected with (*R*)-**5**; the bis-acetonitrile variant of (*R*)-**4a**.

Figure 4. Role of acetate in catalytic AHP

This brought to our attention the pertinent role of the acetate anion in this protocol. Probing a plausible mechanism^{2g,2q,11d} (Figure 4), we hypothesized that the acetate anion would fulfil two purposes in the catalytic cycle. Firstly, to facilitate the protonolysis step and secondly, to compete with the higher amounts of coordinative species (HPPH₂ and product **2a**) present in solution for a vacant site on Pd to regenerate the acetate-based catalyst complex; consequently allowing product elimination. The acetate would be expected to have better affinity for the Pd vacant site with a "hard" character as compared to phosphines.¹³ In addition, coordination of

HPPh₂ *trans* to the P(Ar)₂ moiety of the phosphapalladacycle provides better steric relief as compared to the *cis* position. Similar preference has been previously observed in various AHP protocols¹⁴ involving phosphapalladacycles. The aforementioned character also congruently manifests in Hou's study involving the (*S*)-proline variant of (*S*)-**4a**, whereby the carboxyl oxygen of the proline is coordinated *trans* to the naphthyl moiety of the phosphapalladacycle while the "softer" N atom is positioned *trans* to the phosphine exclusively (Figure 5).²⁴

Figure 5. (*S*)-proline variant of (*S*)-**4a**

Table 2. Optimization for solvents & additives

Entry ^[a]	Solvent	Acid	Time(d)	Conv. ^[c] (%)	e.e ^[d] (%)
1	Toluene	-	2.5	>99	56
2	DCM	-	2.5	10	-
3	MeOH	-	2.5	0	-
4	Cyclohexane	-	2.5	70	59
5	Hexane	-	2.5	52	84
6	1 DCM: 1 Hex	-	2.5	20	-
7	Hexane	Acetic	1.5	>99	77
8	Hexane	Acetic ^[b]	1.5	>99	60
9	Hexane	Propionic	1.5	>99	80
10	Hexane	Benzoic	1.5	>99	51
11	Hexane	Cyclohexyl	1.5	<5	-
12	Hexane	Formic	1.5	<5	-
13	Hexane	Glycolic	1.5	<5	-
14	Hexane	10% HCl _(aq)	4.0	0	-

[a] Reaction conditions: 1.2 eqv **1a**, 5 μ L (1 eqv) HPPH₂, 5 mol% (*R*)-**4a**, 2.5 mL solvent & 1 equivalent acid for up to the time indicated. [b] 2 eqv acid added. [c] Determined by ³¹P{¹H} NMR. [d] *e.e* determined via HPLC on a stationary chiral phase after isolation of sulphurized product.

Recognizing that the disparity in acetic acid concentration relative to the phosphine species in solution might have led to low conversion rates, our optimization trials subsequently focussed on this aspect. As seen in Table 2, Entry 7, reaction time could indeed be reduced with 1 equivalent of acid but however led to partial sacrifice of enantioselectivity. Increasing the amount of acid further would result in loss of enantioselectivity. Subsequent experiments with organic acids with pKa's in range of acetic acid singled out propionic acid as the optimum additive providing similar reaction times but with improved enantioselectivity. On another note, utilizing 1 equivalent of aqueous mineral acid HCl provided no conversions as expected due to the high binding affinity of chloride anion to the Pd core; concurrently displacing acetate anion as acid and permanently hindering a vacant site on the Pd core intended for substrate activation. Nevertheless, this experiment further supports the prerequisite that two adjacent vacant sites on Pd are required for the intramolecular AHP reaction to proceed with stereocontrol.

The substrate scope of the newly developed protocol was then assessed with several bis-aromatic phosphine nucleophiles as well as heterobicyclic olefins possessing homo-conjugative induction capabilities (Table 3). It was apparent that the methodology tolerated phosphines with electron-donating derivatives (Table 3, Entry 2, 3.). Use of *p*-MeO Phosphine gave excellent conversions but poor *e.e.s* whereas *p*-CF₃ bearing phosphine provided trace conversions. For the heterobicyclic substrates with non-proton substituents present at R¹ and R², positive tolerance was observed except at R³, wherein no addition product was obtained. In most cases, the polar substrates were only partially soluble in the reaction mixture but nevertheless, could achieve full conversion when the reaction was conducted up to 7 days. Utilizing more polar solvents to homogenize the reaction mixture led to significant decrease in *e.e* and incomplete conversion. Retrospectively, it could be deduced from these experiments that limiting the solubility of the phosphine product lowered the competition faced by

phosphine nucleophile towards coordination to the catalyst thus circumventing possible catalyst poisoning by the product. Additionally, a preliminary test to explore the extension of this methodology to azabenzonorbornadiene gave the product in excellent conversion and good enantioselectivity (Table 3, Entry 10). The absolute configuration of **2a** was confirmed upon its coordination to gold(I) chloride to be 1*R*, 2*S*, 4*R* from the single crystal X-ray diffraction analysis (Figure 6).¹⁵ The high diastereocontrol observed could be further rationalized from the ORTEP. Formation of an endo adduct is impeded by unfavourably high steric congestion between the bulky diarylphosphine and substrate's aryl moiety.

Table 3. AHP of heterobicyclic alkenes with the optimized protocol

Ent ^[a]	-Ar	Substrate	Time (d)	Pdt ^[d]	Conv. ^[b] (%)	<i>e.e</i> ^[c] (%)
1	Ph		1.5	2a	>99	80
2	<i>p</i> -MeO(C ₆ H ₄)		7	2b	>99	59
3	<i>p</i> -CF ₃ (C ₆ H ₄)		7	-	trace	-
4	Ph		7	2d	87	80
5			6	2e	>99	74
6			7	2f	>99	79
7			7	2g	95	79
8			6	2h	>99	67
9			~	-	n.r	-
10			7	2j	>99	80

[a] Reaction Conditions: 1.2 eqv **1a**, 5 μ L (1 eqv) HPPH₂, 5 mol% (*R*)-**4a**, 2.5 mL hexanes & 1 eqv propionic acid for up to the time indicated. [b] Determined by ³¹P{¹H} NMR. [c] *e.e* determined via HPLC on stationary chiral phase after isolation of sulphurized product. [d] Isolated yields & characterization data are available in the Experimental.

Figure 6. ORTEP of gold complex of **2a** with thermal ellipsoids drawn at the 50% probability level.

3.2 Conclusions

In summary, we have developed an optimized protocol, leveraging on a rational catalyst selection in conjunction with key solvent and additive effects, for the first instance in literature of an asymmetric catalytic addition of P-nucleophiles to achiral oxa- and aza-bicyclic alkenes. This grants access to new and synthetically challenging hitherto inaccessible phosphine addition products in excellent yields and good selectivities. This is also the very first instance in literature wherein up to three new stereogenic centers are generated through an AHP reaction.

3.4 Acknowledgement

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3.5 Experimental

All air-sensitive manipulations were carried out under positive pressure of nitrogen by utilizing Schlenk techniques unless otherwise stated. Solvents procured were left to sit over 4 Å / 3 Å molecular sieves for 24 hrs before being degassed / distilled and stored in storage tubes. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F254 aluminium backed plates and visualized under UV light. Flash column chromatography was accomplished using Merck silica gel 60. NMR spectra were obtained using a Bruker AV 300 spectrometer (^1H at 300 MHz, $^{13}\text{C}\{^1\text{H}\}$ at 75 MHz, $^{31}\text{P}\{^1\text{H}\}$ at 121 MHz), Bruker AV 400 spectrometer (^1H at 400 MHz, $^{13}\text{C}\{^1\text{H}\}$ at 100 MHz, $^{31}\text{P}\{^1\text{H}\}$ at 162 MHz) or Bruker AV 500 spectrometer (^1H at 500 MHz, $^{13}\text{C}\{^1\text{H}\}$ at 125 MHz, $^{31}\text{P}\{^1\text{H}\}$ at 202 MHz). ^1H spectra were referenced to an internal SiMe_4 standard at δ 0 ppm or to the targeted residual proton solvent signal (CDCl_3 at δ 7.26 ppm). Chiral HPLC data was obtained using Agilent Technologies 1200 Series HPLC coupled with a Daicel CHIRALPAK[®] ID column. Melting points were measured using SRS Optimeit Automated Point System SRS MPA100. Specific rotation values were measured with JASCO P-1030 Polarimeter in the specified solvent and temperature in a 0.1 dm cell³.

Materials:

1a was purchased from Alfa Aesar, while substrates **1d**¹⁶, **1e**¹⁷, **1f**¹⁸, **1g**¹⁷, **1h**¹⁸, **1i**¹⁹, **1j**²⁰ were synthesized according to respective literature procedures. Catalysts **1** - **5** were similarly synthesized from literature procedures.^{2q} HPPPh_2 was synthesized using literature procedures²¹ and, $\text{HP}(\text{p-Tol})_2$ & $\text{HP}(\text{p-OMeC}_6\text{H}_4)_2$ was procured from Sigma Aldrich.

General procedure for Asymmetric Hydrophosphination of Bicyclic Olefins (Table 3.):

To an oven-dried 25 mL storage tube, charged with N₂, was added (*S*)-**4a** (0.0112 mmol, 6.8 mg) and substrates **1a - j** (0.136 mmol). 8.0 mL of Hexanes was added and subsequently propionic acid (0.112 mmol, 10.4 μ L) was micropipetted, leaving to stir for one minute. **HPP_h2** (0.112 mmol, 20 μ L) was then added to the suspension and subsequently washed down with an additional 2.0 mL of hexanes; allowing the suspension to turn into a semi-homogenous reddish-brown solution. The tube was then sealed, and reaction left to stir vigorously for the indicated reaction time or until all HPP_h2 was consumed. Subsequently, sulfur (0.136 mmol, 4.3 mg) and 5.0 mL dichloromethane was added and the resulting red homogenous solution was further left to stir for 2 hours. Thereafter, the resultant clear yellow solution was concentrated via rotary evaporation at room temperature and the crude obtained further purified via flash column chromatography on silica gel (hexanes: ethyl acetate; 10: 1 – 4: 1) to give sulfurized **2a – j**.

Procedure for Syntheses of **2a-AuCl**:

Similar procedures were employed as above, in General procedure for Asymmetric Hydrophosphination of Bicyclic Olefins, but with the addition of 1.1 equivalent Me₂S.AuCl in substitute of sulfur and the reaction solution kept in the dark overnight. Thereafter, the resultant solution was concentrated via rotary evaporation at room temperature and the crude obtained further purified via flash column chromatography on silica gel (hexanes: ethyl acetate; 5: 1 – 2: 1) to give **2a-AuCl**.

Characterization Data of Products:

General Labelling of Carbon Atoms of Sulfurized Products

2a:

Isolated yield = 93%. White solid. m.p. 165°C; $[\alpha]_D^{22} = +24.4 \text{ deg cm}^3 \text{ g}^{-1} \text{ dm}^{-1}$ (c 0.2, DCM); ^1H NMR (400 MHz, CDCl_3 , 25°C, TMS): δ = 1.76 (pseudo dt, $^2J(\text{H,H}) = 11.7 \text{ Hz}$, $^3J(\text{H,P} \& \text{H}) = 8.2 \text{ Hz}$, 1H; CH), 2.45 (pseudo ddt, $^3J(\text{H,P}) = 22.5 \text{ Hz}$, $^2J(\text{H,H}) = 11.7 \text{ Hz}$, $^3J(\text{H,H}) = 5.0 \text{ Hz}$, 1H; CH), 2.79 (pseudo dt, $^3J(\text{H,H}) = 8.3 \text{ Hz}$, $^2J(\text{H,P}) = 4.9 \text{ Hz}$, $^3J(\text{H,H}) = 4.9 \text{ Hz}$, 1H; CH), 5.47 (d, $^3J(\text{H,H}) = 4.9 \text{ Hz}$, 1H; CH), 5.56 (d, $^3J(\text{H,P}) = 8.6 \text{ Hz}$, 1H; CH), 7.16 – 7.21 (m, 3H; ArH), 7.26 – 7.29 (m, 1H; ArH), 7.38 – 7.60 (m, 6H; ArH), 7.73 – 7.80 (m, 2H; ArH), 7.92 – 8.00 (m, 2H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3 , 25°C, H_3PO_4): δ = 48.4; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3 , 25°C) 30.5 (s, 1C; C1), 42.7 (d, $^1J(\text{C,P}) = 56.1 \text{ Hz}$, 1C; C2), 79.4 (d, $^2J(\text{C,P}) = 2.4 \text{ Hz}$, 1C; C3), 79.7 (s, 1C; C10), 118.1 (s, 1C; C8), 119.6 (s, 1C; C5), 127.0 (s, 1C; C6), 127.1 (s, 1C; C7), 128.6 (d, $^3J(\text{C,P}) = 12.0 \text{ Hz}$, 2C; Ca^{meta}), 128.8 (d, $^3J(\text{C,P}) = 11.8 \text{ Hz}$, 2C; Cb^{meta}), 131.4 (d, $^2J(\text{C,P}) = 10.2 \text{ Hz}$, 2C; Ca^{ortho}), 131.5 (d, $^4J(\text{C,P}) = 2.9 \text{ Hz}$, 1C; Ca^{para}), 131.8 (d, $^4J(\text{C,P}) = 2.9 \text{ Hz}$, 1C; Cb^{para}), 131.9 (d, $^1J(\text{C,P}) = 9.7 \text{ Hz}$, 2C; Cb^{ortho}), 132.5 (d, $^1J(\text{C,P}) = 80.5 \text{ Hz}$, 1C; Ca^{ipso}),

133.0 (d, $^2J(\text{C},\text{P})=79.7$ Hz, 1C; Cb^{ipso}), 145.4 (s, 1C; C9), 146.0 (d, $^3J(\text{C},\text{P})=12.0$ Hz, 1C; C4).

HRMS m/z (+ESI) ($\text{M} + \text{H}$)⁺ calcd for C₂₂H₂₀O₁P₁S₁: 363.0973, found: 363.0972.

2b:

Isolated yield = 90%. White solid. m.p. 177°C; $[\alpha]_{\text{D}}^{22}=+32.6$ (c 0.2, DCM); ^1H NMR (300 MHz, CDCl₃, 25°C, TMS): δ =1.73 (pseudo dt, $^2J(\text{H},\text{H})=11.6$ Hz, $^3J(\text{H},\text{P} \ \& \ \text{H})=8.2$ Hz, 1H; CH), 2.43 (pseudo ddt, $^3J(\text{H},\text{P})=22.3$ Hz, $^2J(\text{H},\text{H})=11.6$ Hz, $^3J(\text{H},\text{H})=4.7$ Hz, 1H; CH), 2.71 (pseudo dt, $^3J(\text{H},\text{H})=8.7$ Hz, $^2J(\text{H},\text{P})=5.0$ Hz, $^3J(\text{H},\text{H})=5.0$ Hz, 1H; CH), 3.82 (s, 3H; CH₃), 3.87 (s, 3H; CH₃), 5.45 (d, $^3J(\text{H},\text{H})=4.7$ Hz, 1H; CH), 5.55 (d, $^3J(\text{H},\text{P})=8.7$ Hz, 1H; CH), 6.86 – 7.10 (m, 4H; ArH), 7.12 – 7.23 (m, 3H; ArH), 7.24 – 7.28 (m, 1H; ArH), 7.60 – 7.75 (m, 2H; ArH), 7.80 – 7.94 (m, 2H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, CDCl₃, 25°C, H₃PO₄): δ = 47.5; $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl₃, 25°C): δ = 30.6 (s, 1C; C1), 43.4 (d, $^1J(\text{C},\text{P})=55.2$ Hz, 1C; C2), 56.4 (s, 1C; OCH₃), 55.5 (s, 1C; OCH₃), 79.5 (d, $^2J(\text{C},\text{P})=2.5$ Hz, 1C; C3), 79.8 (s, 1C; C10), 114.1 (d, $^3J(\text{C},\text{P})=13.3$ Hz, 2C; Ca^{meta}), 114.3 (d, $^3J(\text{C},\text{P})=13.2$ Hz, 2C; Cb^{meta}), 118.1 (s, 1C; C8), 119.6 (s, 1C; C5), 123.6 (d, $^1J(\text{C},\text{P})=86.9$ Hz, 1C; Ca^{ipso}), 124.3 (d, $^1J(\text{C},\text{P})=86.0$ Hz, 1C; Cb^{ipso}), 127.0 (s, 2C; C6 & C7), 133.3 (d, $^2J(\text{C},\text{P})=11.3$ Hz, 2C; Ca^{ortho}), 133.6 (d, $^2J(\text{C},\text{P})=11.1$ Hz, 2C; Cb^{ortho}), 145.5 (s, 1C; C9), 146.2 (d, $^3J(\text{C},\text{P})=11.8$ Hz, 1C; C4), 162.1 (d, $^4J(\text{C},\text{P})=2.8$ Hz, 1C; Ca^{para}), 162.3 (d, $^4J(\text{C},\text{P})=2.9$ Hz, 1C; Cb^{para}). HRMS m/z (+ESI) ($\text{M} + \text{H}$)⁺ calcd for C₂₄H₂₄O₃P₁S₁: 423.1184, found: 423.1185.

2d:

Isolated yield = 80%. White solid. m.p. 96°C(decomp.); $[\alpha]_D^{22} = +34.1$ (c 0.2, DCM); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 1.73$ (pseudo dt, $^2J(\text{H,H}) = 11.5$ Hz, $^3J(\text{H,P} \ \& \ \text{H}) = 8.4$ Hz, 1H; CH), 2.42 ppm (m, 1H; CH), 2.72 (pseudo dt, $^3J(\text{H,H}) = 8.9$ Hz, $^2J(\text{H,P}) = 4.6$ Hz, $^3J(\text{H,H}) = 4.6$ Hz, 1H; CH), 3.86 (s, 6H; CH_3), 5.41 (d, $^3J(\text{H,H}) = 4.5$ Hz, 1H; CH), 5.58 (d, $^3J(\text{H,P}) = 8.3$ Hz, 1H; CH), 6.79 (s, 1H; ArH), 6.87 (s, 1H; ArH), 7.35 – 7.65 (m, 6H; ArH), 7.70 – 7.86 (m, 2H; ArH), 7.88 – 7.80 (m, 2H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3 , 25°C, H_3PO_4): $\delta = 48.6$; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3 , 25°C): $\delta = 31.2$ (s, 1C; C1), 43.4 (d, $^1J(\text{C,P}) = 57.1$ Hz, 1C; C2), 56.4 (s, 1C; OCH_3), 56.5 (s, 1C; OCH_3), 79.8 (d, $^2J(\text{C,P}) = 2.4$ Hz, 1C; C3), 80.0 (s, 1C; C10), 103.1 (s, 1C; C5), 104.4 (s, 1C; C8), 128.6 (d, $^3J(\text{C,P}) = 12.0$ Hz, 2C; Ca^{meta}), 128.8 (d, $^3J(\text{C,P}) = 11.8$ Hz, 2C; Cb^{meta}), 131.5 (d, $^4J(\text{C,P}) = 3.0$ Hz, 1C; Ca^{para}), 131.6 (d, $^2J(\text{C,P}) = 10.0$ Hz, 2C; Ca^{ortho}), 131.7 (d, $^4J(\text{C,P}) = 2.5$ Hz, 1C; Cb^{para}), 131.8 (d, $^2J(\text{C,P}) = 9.6$ Hz, 2C; Cb^{ortho}), 132.6 (d, $^1J(\text{C,P}) = 80.5$ Hz, 1C; Ca^{ipso}), 132.8 (d, $^1J(\text{C,P}) = 79.3$ Hz, 1C; Cb^{ipso}), 137.9 (s, 1C; C9), 138.3 (d, $^3J(\text{C,P}) = 11.8$ Hz, 1C; C4), 148.3 (s, 1C; C6), 148.3 (s, 1C; C7). HRMS m/z (+ESI) $(\text{M} + \text{H})^+$ calcd for $\text{C}_{24}\text{H}_{24}\text{O}_3\text{P}_1\text{S}_1$: 423.1184, found: 423.1183.

2e:

Isolated yield = 87%. White solid. m.p. 244°C(decomp.); $[\alpha]_D^{22} = +24.4$ (c 0.9, DCM); ^1H NMR (400 MHz, CDCl_3 , 25°C, TMS): $\delta = 1.76$ (pseudo dt, $^2J(\text{H,H}) = 11.8$ Hz, $^3J(\text{H,P} \& \text{H}) = 8.2$ Hz, 1H; CH), 2.49 (pseudo ddt, $^3J(\text{H,P}) = 22.6$ Hz, $^2J(\text{H,H}) = 11.4$ Hz, $^3J(\text{H,H}) = 5.4$ Hz, 1H; CH), 2.78 (pseudo dt, $^3J(\text{H,H}) = 9.4$ Hz, $^2J(\text{H,P}) = 4.7$ Hz, $^3J(\text{H,H}) = 4.7$ Hz, 1H; CH), 5.43 (d, $^3J(\text{H,H}) = 4.8$ Hz, 1H; CH), 5.51 (d, $^3J(\text{H,P}) = 8.5$ Hz, 1H; CH), 7.38 – 7.64 (m, 8H; ArH), 7.70 – 7.81 (m, 2H; ArH), 7.88 – 7.98 (m, 2H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3 , 25°C, H_3PO_4): $\delta = 48.1$. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3 , 25°C): $\delta = 30.3$ (s, 1C; C1), 42.5 (d, $^1J(\text{C,P}) = 56.1$ Hz, 1C; C2), 79.0 (d, $^2J(\text{C,P}) = 2.3$ Hz, 1C; C3), 79.2 (s, 1C; C10), 123.0 (s, 1C; C6), 123.1 (s, 1C; C7), 123.5 (s, 1C; C5), 125.1 (s, 1C; C8), 128.7 (d, $^3J(\text{C,P}) = 11.9$ Hz, 2C; Ca^{meta}), 128.9 (d, $^3J(\text{C,P}) = 11.9$ Hz, 2C; Cb^{meta}), 131.4 (d, $^2J(\text{C,P}) = 10.0$ Hz, 2C; Ca^{ortho}), 131.6 (d, $^4J(\text{C,P}) = 2.6$ Hz, 1C; Ca^{para}), 131.7 (d, $^2J(\text{C,P}) = 9.5$ Hz, 2C; Cb^{ortho}), 131.9 (d, $^4J(\text{C,P}) = 2.8$ Hz, 1C; Cb^{para}), 132.2 (d, $^1J(\text{C,P}) = 80.6$ Hz, 1C; Ca^{ipso}), 132.5 (d, $^1J(\text{C,P}) = 79.7$ Hz, 1C; Cb^{ipso}), 146.4 (s, 1C; C9), 146.9 (d, $^3J(\text{C,P}) = 11.7$ Hz, 1C; C4). HRMS m/z (+ESI) (M + H)⁺ calcd for $\text{C}_{22}\text{H}_{18}\text{O}_1\text{P}_1\text{S}_1^{79}\text{Br}_1^{81}\text{Br}_1$: 520.9162, found: 520.9166.

2f:

Isolated yield = 91%. White solid. m.p. 184°C; $[\alpha]_D^{22} = +39.6$ (c 0.8, DCM); ^1H NMR (400 MHz, CDCl_3 , 25°C, TMS): $\delta = 1.72$ (pseudo dt, $^2J(\text{H,H}) = 11.5$ Hz, $^3J(\text{H,P} \& \text{H}) = 8.3$ Hz, 1H; CH), 2.24 (s, 6H; CH_3), 2.44 (pseudo ddt, $^3J(\text{H,P}) = 22.4$ Hz, $^2J(\text{H,H}) = 11.5$ Hz, $^3J(\text{H,H}) = 5.6$ Hz, 1H; CH), 2.77 (pseudo dt, $^3J(\text{H,H}) = 8.3$ Hz, $^2J(\text{H,P}) = 4.6$ Hz, $^3J(\text{H,H}) = 4.6$ Hz, 1H; CH), 5.41 (d, $^3J(\text{H,H}) = 4.7$ Hz, 1H; CH), 5.50 (d, $^3J(\text{H,P}) = 8.5$ Hz, 1H; CH), 6.97 (s, 1H; ArH), 7.05 (s, 1H; ArH), 7.36 – 7.63 (m, 6H; ArH), 7.70 – 7.86 (m, 2H; ArH), 7.88 – 8.03 (m, 2H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3 , 25°C, H_3PO_4): $\delta = 48.5$; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3 , 25°C): $\delta = 19.9$ (s, 2C; CH_3), 30.8 (s, 1C; C1), 43.0 (d, $^1J(\text{C,P}) = 55.7$ Hz, 1C; C2), 79.3 (d, $^2J(\text{C,P}) = 2.6$ Hz, 1C; C3), 79.5 (s, 1C; C10), 119.4 (s, 1C; C5), 120.9 (s, 1C; C8), 128.5 (d, $^3J(\text{C,P}) = 11.9$ Hz, 2C; Ca^{meta}), 128.7 (d, $^3J(\text{C,P}) = 11.9$ Hz, 2C; Cb^{meta}), 131.4 (d, $^4J(\text{C,P}) = 2.9$ Hz, 1C; Ca^{para}), 131.4 (d, $^2J(\text{C,P}) = 9.5$ Hz, 2C; Ca^{ortho}), 131.7 (d, $^4J(\text{C,P}) = 2.9$ Hz, 1C; Cb^{para}), 131.8 (d, $^2J(\text{C,P}) = 9.5$ Hz, 2C; Cb^{ortho}), 132.6 (d, $^1J(\text{C,P}) = 79.9$ Hz, 1C; Ca^{ipso}), 133.0 (d, $^1J(\text{C,P}) = 79.7$ Hz, 1C; Cb^{ipso}), 135.1 (s, 1C; C6), 135.2 (s, 1C; C6), 143.3 (s, 1C; C9), 143.9 (d, $^3J(\text{C,P}) = 11.8$ Hz, 1C; C4). HRMS m/z (+ESI) ($\text{M} + \text{H}$)⁺ calcd for $\text{C}_{24}\text{H}_{24}\text{O}_1\text{P}_1\text{S}_1$: 391.1286, found: 391.1287.

2g:

Isolated yield = 88%. White solid. m.p. 94°C; $[\alpha]_D^{22} = +25.8$ (c 1.0, DCM); ^1H NMR (500 MHz, CDCl_3 , 25°C, TMS): $\delta = 1.71$ (pseudo dt, $^2J(\text{H,H}) = 11.4$ Hz, $^3J(\text{H,P} \ \& \ \text{H}) = 8.0$ Hz, 1H; CH), 2.47 (pseudo ddt, $^3J(\text{H,P}) = 22.1$ Hz, $^2J(\text{H,H}) = 11.4$ Hz, $^3J(\text{H,H}) = 4.5$ Hz, 1H; CH), 2.81 (pseudo dt, $^3J(\text{H,H}) = 8.0$ Hz, $^2J(\text{H,P}) = 4.6$ Hz, $^3J(\text{H,H}) = 4.6$ Hz, 1H; CH), 3.77 (s, 3H; CH_3), 3.79 (s, 3H; CH_3), 5.63 (d, $^3J(\text{H,H}) = 4.6$ Hz, 1H; CH), 5.71 (d, $^3J(\text{H,P}) = 8.1$ Hz, 1H; CH), 6.66 (AB, $^3J(\text{H,H}) = 8.8$ Hz, 1H; ArH), 6.68 (AB, $^3J(\text{H,H}) = 8.8$ Hz, 1H; ArH), 7.35 – 7.60 (m, 6H; ArH), 7.72 – 7.81 (m, 2H; ArH), 7.93 – 8.02 (m, 2H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3 , 25°C, H_3PO_4): $\delta = 47.3$; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3 , 25°C): $\delta = 29.7$ (s, 1C; C1), 41.9 (d, $^1J(\text{C,P}) = 56.3$ Hz, 1C; C2), 56.1 (s, 1C; OCH_3), 56.2 (s, 1C; OCH_3), 77.2 – 77.3 (m, 1C; C3), 77.9 (s, 1C; C10), 111.5 (s, 1C; C6), 111.7 (s, 1C; C7), 128.5 (d, $^2J(\text{C,P}) = 8.2$ Hz, 2C; Ca^{ortho}), 128.6 (d, $^2J(\text{C,P}) = 8.5$ Hz, 2C; Cb^{ortho}), 131.3 (d, $^3J(\text{C,P}) = 11.2$ Hz, 2C; Ca^{meta}), 131.3 (d, $^4J(\text{C,P}) = 3.0$ Hz, 1C; Ca^{para}), 131.6 (d, $^4J(\text{C,P}) = 2.9$ Hz, 1C; Cb^{para}), 132.0 (d, $^3J(\text{C,P}) = 9.8$ Hz, 2C; Cb^{meta}), 132.6 (d, $^1J(\text{C,P}) = 80.7$ Hz, 1C; Ca^{ipso}), 133.5 (d, $^1J(\text{C,P}) = 79.7$ Hz, 1C; Cb^{ipso}), 134.4 (s, 1C; C9), 135.2 (d, $^3J(\text{C,P}) = 11.5$ Hz, 1C; C4), 145.7 (s, 1C; C5), 147.1 (s, 1C; C8). HRMS m/z (+ESI) ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{24}\text{H}_{24}\text{O}_3\text{P}_1\text{S}_1$: 423.1184, found: 423.1187.

2h:

Isolated yield = 85%. White solid. m.p. 75°C; $[\alpha]_{\text{D}}^{22} = +12.8$ (c 0.5, DCM); ^1H NMR (400 MHz, CDCl_3 , 25°C, TMS): δ = 1.81 (pseudo dt, $^2J(\text{H,H}) = 11.0$ Hz, $^3J(\text{H,P \& H}) = 7.7$ Hz, 1H; CH), 2.61 – 2.80 (m, 2H; CH), 6.08 (d, $^3J(\text{H,H}) = 8.3$ Hz, 1H; CH), 6.11 (d, $^3J(\text{H,P}) = 4.3$ Hz, 1H; CH), 7.34 – 7.70 (m, 11H; ArH), 7.72 – 7.82 (m, 2H; ArH), 7.87 – 7.94 (m, 1H; ArH), 7.99 – 8.08 (m, 2H; ArH), 8.70 – 8.77 (m, 2H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (202 MHz, CDCl_3 , 25°C, H_3PO_4): δ = 47.8; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3 , 25°C): δ = 30.5 (s, 1C; C1), 43.1 (d, $^1J(\text{C,P}) = 55.8$ Hz, 1C; C2), 79.1 (d, $^2J(\text{C,P}) = 2.2$ Hz, 1C; C3), 79.4 (s, 1C; C10), 123.6 (s, 1C; Ar), 123.7 (s, 1C; Ar), 124.1 (s, 1C; Ar), 124.2 (s, 1C; Ar), 124.7 (s, 1C; C6), 125.9 (s, 1C; C7), 126.5 (s, 2C; Ar), 127.0 (s, 1C; Ar), 127.1 (s, 1C; Ar), 128.6 (d, $^3J(\text{C,P}) = 12.0$ Hz, 2C; Ca^{meta}), 128.8 (d, $^3J(\text{C,P}) = 11.8$ Hz, 2C; Cb^{meta}), 130.2 (s, 1C; C5), 130.4 (s, 1C; C8), 131.3 (d, $^2J(\text{C,P}) = 10.1$ Hz, 2C; Ca^{ortho}), 131.5 (d, $^4J(\text{C,P}) = 2.9$ Hz, 1C; Ca^{para}), 131.8 (br s, 1C; Cb^{para}), 131.9 (d, $^1J(\text{C,P}) = 9.5$ Hz, 2C; Cb^{ortho}), 132.6 (d, $^1J(\text{C,P}) = 80.2$ Hz, 1C; Ca^{ipso}), 133.1 (d, $^2J(\text{C,P}) = 79.7$ Hz, 1C; Cb^{ipso}), 140.7 (s, 1C; C9), 141.1 (d, $^3J(\text{C,P}) = 11.2$ Hz, 1C; C4). HRMS m/z (+ESI) ($\text{M} + \text{H}$)⁺ calcd for $\text{C}_{30}\text{H}_{24}\text{O}_1\text{P}_1\text{S}_1$: 463.1286, found: 463.1291.

2J:

Isolated yield = 80%. Colourless oil.; $[\alpha]_D^{22} = +89.0$ (c 0.2, DCM); ^1H NMR (500 MHz, CDCl_3 , 25°C, TMS): $\delta = 1.70$ (pseudo dt, $^2J(\text{H,H}) = 11.8$ Hz, $^3J(\text{H,P} \& \text{H}) = 8.3$ Hz, 1H; CH), 2.49 (pseudo ddt, $^3J(\text{H,P}) = 21.9$ Hz, $^2J(\text{H,H}) = 11.8$ Hz, $^3J(\text{H,H}) = 5.1$ Hz, 1H; CH), 2.68 (pseudo dt, $^3J(\text{H,H}) = 8.3$ Hz, $^2J(\text{H,P}) = 5.1$ Hz, $^3J(\text{H,H}) = 5.1$ Hz, 1H; CH), 5.11 (br s, 1H; CH), 5.32 (d, $^3J(\text{H,P}) = 8.0$ Hz, 1H; CH), 7.10 – 7.12 (m, 2H; ArH), 7.20 – 7.30 (m, 2H; ArH), 7.39 – 7.60 (m, 6H; ArH), 7.70 – 7.83 (m, 2H; ArH), 7.83 – 8.02 (br s, 2H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (202 MHz, CDCl_3 , 25°C, H_3PO_4): $\delta = 48.3$; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3 , 25°C): $\delta = 28.2$ (s, 3C; CH_3), 31.0 (s, 1C; C1), 43.5 (br s, 1C; C2), 60.9 (br s, 1C; C3), 80.2 (s, 1C; tBu), 119.0 (br s, 2C; C7 & C8), 120.4 (br s, 2C; C5 & C6), 126.8 (d, $^2J(\text{C,P}) = 6.6$ Hz, 2C; Ca^{ortho}), 126.8 (br s, 2C; Cb^{ortho}), 128.5 (br s, 2C; Cb^{meta}), 128.6 (d, $^3J(\text{C,P}) = 11.7$ Hz, 2C; Ca^{meta}), 131.5 (d, $^4J(\text{C,P}) = 2.8$ Hz, 1C; Cb^{para}), 131.7 (d, $^4J(\text{C,P}) = 2.9$ Hz, 1C; Cb^{para}), 132.0 (br s, 2C; Ca^{ipso} & Cb^{ipso}), 145.9 (br s, 2C; C4 & C9), 153.7 (s, 1C; C=O). HRMS m/z (+ESI) ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{27}\text{H}_{29}\text{N}_1\text{O}_2\text{P}_1\text{S}_1$: 462.1657, found: 462.1678.

2a-AuCl:

Isolated yield = 87%. White solid. m.p 263°C(decomp.); $[\alpha]_{385\text{nm}}^{25} = -78.3$ (c 0.4, DCM); ^1H NMR (400 MHz, CDCl_3 , 25°C, TMS): $\delta=1.77$ (pseudo dt, $^2J(\text{H,H})=11.8$ Hz, $^3J(\text{H,P} \ \& \ \text{H})=9.0$ Hz, 1H; CH), 2.28 (pseudo ddt, $^3J(\text{H,P})=23.7$ Hz, $^2J(\text{H,H})=11.9$ Hz, $^3J(\text{H,H})=5.1$ Hz, 1H; CH), 2.79 (pseudo dt, $^3J(\text{H,H})=8.4$ Hz, $^2J(\text{H,P})=5.0$ Hz, $^3J(\text{H,H})=4.9$ Hz, 1H; CH), 5.30 (d, $^3J(\text{H,H})=4.8$ Hz, 1H; CH), 5.55 (d, $^3J(\text{H,P})=8.8$ Hz, 1H; CH), 7.14 – 7.24 (m, 3H; ArH), 7.26 – 7.29 (m, 1H; ArH), 7.39 – 7.61 (m, 6H; ArH), 7.63 – 7.71 (m, 2H; ArH), 7.77 – 7.86 (m, 2H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3 , 25°C, H_3PO_4): $\delta= 40.5$. HRMS m/z (+ESI) ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{22}\text{H}_{20}\text{O}_1\text{P}_1^{35}\text{Cl}_1\text{Au}_1$: 563.0606, found: 563.0780.

Single Crystal X-Ray Diffraction Data of **2a.AuCl**:

Figure 7. ORTEP of compound **2a-AuCl** with thermal ellipsoids drawn at the 50% probability level. Only protons at chiral centres were included for clarity.

A colorless plate-like specimen of $C_{22}H_{19}AuClOP$, approximate dimensions 0.020 mm x 0.120 mm x 0.220 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

The total exposure time was 0.09 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 11051 reflections to a maximum θ angle of 29.00° (0.73 Å resolution), of which 4795 were independent (average redundancy 2.305, completeness = 99.8%, $R_{int} = 10.53\%$, $R_{sig} = 16.96\%$) and 3105 (64.75%) were greater than $2\sigma(F^2)$. The final cell constants of $a = 16.171(2)$ Å, $b = 11.0972(12)$ Å, $c = 11.0811(15)$ Å, $\beta = 109.413(6)^\circ$, volume = $1875.5(4)$ Å³, are based upon the refinement of the XYZ-centroids of 2385 reflections above $20\sigma(I)$ with $5.341^\circ < 2\theta < 52.81^\circ$. Data were corrected for absorption effects

using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.511. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.2690 and 0.8550.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $C 1 2 1$, with $Z = 4$ for the formula unit, $C_{22}H_{19}AuClOP$. The final anisotropic full-matrix least-squares refinement on F^2 with 199 variables converged at $R1 = 6.12\%$, for the observed data and $wR2 = 13.39\%$ for all data. The goodness-of-fit was 1.011. The largest peak in the final difference electron density synthesis was $1.926 \text{ e}^-/\text{\AA}^3$ and the largest hole was $-2.269 \text{ e}^-/\text{\AA}^3$ with an RMS deviation of $0.312 \text{ e}^-/\text{\AA}^3$. On the basis of the final model, the calculated density was 1.993 g/cm^3 and $F(000)$, 1080 e^- .

Table 1. Sample and crystal data for 2a-AuCl.

Identification code	leung1074m
Chemical formula	$C_{22}H_{19}AuClOP$
Formula weight	562.76 g/mol
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal size	0.020 x 0.120 x 0.220 mm
Crystal habit	colorless plate
Crystal system	monoclinic
Space group	$C 1 2 1$
Unit cell dimensions	$a = 16.171(2) \text{ Å}$ $\alpha = 90^\circ$

	$b = 11.0972(12) \text{ \AA}$	$\beta = 109.413(6)^\circ$
	$c = 11.0811(15) \text{ \AA}$	$\gamma = 90^\circ$
Volume	$1875.5(4) \text{ \AA}^3$	
Z	4	
Density (calculated)	1.993 g/cm^3	
Absorption coefficient	8.080 mm^{-1}	
F(000)	1080	

Table 2. Data collection and structure refinement for 2a-AuCl.

Theta range for data collection	2.67 to 29.00°
Index ranges	$-22 \leq h \leq 22$, $-15 \leq k \leq 14$, $-15 \leq l \leq 15$
Reflections collected	11051
Independent reflections	4795 [R(int) = 0.1053]
Coverage of independent reflections	99.8%
Absorption correction	Multi-Scan
Max. and min. transmission	0.8550 and 0.2690
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	$\sum w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	4795 / 223 / 199

Goodness-of-fit on F^2	1.011
Final R indices	3105 data; $R_1 = 0.0612$, $wR_2 =$
	$I > 2\sigma(I)$ 0.1104
	$R_1 = 0.1182$, $wR_2 =$
	all data 0.1339
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0334P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
Absolute structure parameter	0.015(15)
Largest diff. peak and hole	1.926 and -2.269 $e\text{\AA}^{-3}$
R.M.S. deviation from mean	0.312 $e\text{\AA}^{-3}$

3.6 References

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Chapter 4

Palladacycle-Catalyzed Asymmetric P-H additions on Electrophilic Exocyclic Olefins

4.1 Introduction

Asymmetric catalytic conjugate addition of nucleophiles to electrophilic Michael-acceptor substrates has been well documented as a synthetically practical method for the generation of enantioenriched compounds.¹ The 21st century had the asymmetric catalysis community's research efforts heavily invested in the motive towards advancement of highly selective and competent catalytic protocols facilitating stereo-controlled reactions with various α,β -unsaturated acceptors, including α,β -unsaturated esters,² β -aryl nitroalkenes,³ α,β -unsaturated ketones,⁴ arylidene malonates,⁵ and alkylidene bisphosphonates⁶ in conjugate addition reactions (CA).^{1a-c} Amongst these methodologies, the extensive range of nucleophiles and coupling reagents include boronic acids, organometallic species (Grignard reagents, Organozinc, organocopper, organozirconium), amines, carboanions and more.^{1a-f, 1h, 1i} Spectacular enantioselectivities, accompanied with high yields have been achieved with both cyclic and linear-type alkenes with a plethora of chiral-ligand metal catalysts and organocatalysts (Scheme 1).

Scheme 1. General conjugate addition of nucleophiles onto activated alkenes.

Furthermore, subsequent transformations of majority of these chiral adducts provide robust access to highly functionalized synthetic precursors for the preparation of a plethora of natural products and biologically active compounds.⁷ Examples include, the synthesis of all-*syn*-1,3-methyl fragments reported by ter Horst *et al.* where the total synthesis of (–)-lardolure, mycocerosic acid and phthioceranic acid was demonstrated (Scheme 2).^{7f, 7g} Catalytic Asymmetric CA (ACA) of MeMgBr to α , β -unsaturated thioesters, followed by DIBAL-H reduction of the thioester to an aldehyde and subsequent Wittig olefination to incorporate the next electrophilic acceptor fragment for a successive cycle.

Scheme 2. Total syntheses of biologically active chiral acids.

In another example, Alexakis *et al.* described a formal synthesis of a direct (+)-naproxen precursor (Scheme 3), the enantiomer of the commercial nonsteroidal anti-inflammatory drug. High enantioselectivity of 93% *e.e* could be achieved based on their Cu/phosphoramidite-catalyzed protocol.^{7b}

Scheme 3. Synthetic route to a direct (+)-Naproxen precursor.^{7b}

Despite promising advances made in this field, asymmetric conjugate addition to exocyclic olefin acceptors remains exceptionally rare. Few studies to date have been focused on electrophilic exocyclic acceptor substrates possessing adjacent α -alkyl groups or the α -alkyl/arylidene alkanone class. The most recent study, by Alexakis *et al.*, utilized chiral Copper phosphoramidite catalyst for the addition of alkyl groups from trialkylaluminium.⁸ The study revealed a challenging prospect in effectively controlling the diastereoselective protonation step where the α -carbon stereogenic centre is produced. This led to a broad range of diastereoselective ratios obtained (Scheme 4).

Scheme 4. Asymmetric Conjugate addition to aryl/alkylidene cycloalkanones.⁸

Furthermore, only a handful of examples exist that mentions asymmetric control of arylidene - 1-tetralones and arylidene-1-indanones. Ma-Jun An *et al.* demonstrated the efficacy of tandem conjugate addition of glycine imine to arylidene-1-tetralones utilizing phase transfer catalysts (Scheme 5).⁹ Impressive selectivities were achieved albeit with extended reaction times.

Scheme 5. Phase transfer catalysis of glycine imine onto electrophilic exocyclic olefin acceptors.

White *et al.* also provided a singular example of utilizing a chiral iron salen catalyst in the addition of a thiol (Scheme 6).¹⁰ Spectacularly, the product was furnished with high *d.r.* and *e.e.s.* However, the scope of the study mainly includes linear acyclic olefins.

Scheme 6. White's asymmetric conjugate addition to aryl/alkylidene cycloalkanones¹⁰.

Other earlier examples by Sarkar *et al.* relied upon the enone being anchored onto chromium in order to activate the enone for improved reactivity (Scheme 7).¹¹ However, these non-asymmetric methods did not address the planar chirality inherent in the products. Nevertheless, these reported studies indicate that electrophilic exocyclic olefins remain an interesting challenge for catalytic asymmetric additions.

Scheme 7. Conjugate addition to arylidene-1-tetralones anchored onto Chromium.

Our interest in asymmetric hydrophosphination has had initial success towards exocyclic olefins such as **8** in Scheme 8. Specifically, a phosphination protocol was developed incorporating a conjugate addition-elimination procedure (see Scheme 8). This relied upon introducing a leaving group adjacent to the alkene such as bromide (**8a**).¹² However, the drawback of this method was that any electronic incorporation of electron withdrawing or electron donating groups to the aryl rings of the β -carbon would lead to unsuccessful conversions. In addition, the synthetic difficulty of varying the leaving groups also compounded to the narrow substrate scope; rendering the protocol less attractive.

Scheme 8. AHP utilizing Phosphapalladacycle (*S*)-2.

Unperturbed by this result and intrigued by the limitations, this work aims to examine the hydrophosphination protocol's feasibility on electrophilic exocyclic olefins (Figure 1) and shed light on the limitations on current methods.

Figure 1. Electrophilic exocyclic olefin substrates.

4.2 Results & Discussion

Scheme 9. AHP to benzylidene, 1,3-indandione.

The hydrophosphination method was firstly applied to 2-benzylidene-indene-1,3-dione (**9a**) utilizing 5 mol% (S)-**3** as catalyst. Despite excellent yield, the isolated product **9b** was found to racemize over time in isopropyl alcohol solution at room temperature. The significant reduction in enantiomeric excess could be observed over 24 hours. Noticeably, the presence of three electron withdrawing groups on the substrate **9a** causes the β_C proton to be highly acidic, hence racemizing the product in solution. As a result, due to the characteristics of the compound, we find that the product would not possess the desired capability to be an efficient chiral ligand. In order to plausibly circumvent the racemization issue, we shifted the focus toward arylidene-1-tetralones and arylidene-1-indanones. These substrates contain a singular ketone function in that they may impart less electron withdrawing effect on the conjugate product's chiral proton. However, this also entails that the hydrophosphination would require control over two stereogenic centres (Scheme 10).

A standard asymmetric hydrophosphination protocol (see Scheme 10) was applied to benzylidene-1-tetralone (**1**) due to its similarity to aryl chalcones as in previous works (see Figure 2 for comparison).¹³

Scheme 10. AHP to benzylidene 1-tetralone

Figure 2. Comparison of skeletal structures of the exocyclic and linear chalcone

Intriguingly, the presence of two carbons tethered to the alpha carbon completely prevents the phosphination to proceed even with extended reaction times. With the plausibility that the catalyst may be trapped in an enolate state (Figure 3), the reaction was conducted in protic solvents to facilitate hydrolysis. Despite this, no conversion was achieved with (S)-**1** and (S)-**2**.

Figure 3. Hydrolysis step of AHP

Further trials with pincer catalyst (*S, S*)-**3** was conducted due to its differing catalytic mechanism as proposed by Leung^{1d, 14} and Duan.¹⁵ Disappointingly, the reaction outcome was similar. Upon re-examination of the generic catalytic cycle proposed by the naphthyl-based palladacycles, it was rationalized that the *S-cis* locked enone could be generating sufficient steric hindrance toward the Pd centre for successful activation of the enone by means of the β_C hydrogen's proximity (Figure 4). Based on this rationale, the enone would experience difficulty displacing the diphenylphosphine *trans* to the naphthyl moiety in the catalyst (Figure 4).

Figure 4. Lewis acid coordination possibilities

Figure 5. Displacement of HPPH₂ in comparison to ⁻OAc for coordination to Pd

Hypothesizing that incorporating an oxygen based anionic ligand might prevent the diphenylphosphine to remain coordinated onto the intended coordination site on Pd (*trans* to the naphthyl moiety), the reaction was repeated with acetate bridged palladacycle catalyst in precise order of reactant/reagent addition with non-coordinating solvents (Table 1) .

Table 1. AHP with acetate-based palladacycles and pincer.

Entry ^a	Catalyst	Solvent	Time (hr)	Conversion (%)	<i>d.r.</i> ^b	<i>e.e.</i> ^c of Major (%)
1	(<i>S</i>)- 4	DCM	24	-	-	-
2	(<i>S</i>)- 5	DCM	24	33	25:8	69
3	(<i>S, S</i>)- 3	DCM	24	-	-	-
4	(<i>S</i>)- 5	Tol	24	-		
5	(<i>S</i>)- 5	THF	24	-		

[a] An evacuated flask under inert atmosphere was charged with **1** (0.0071g, 1.1eqv). 1.5mL of solvent was added and subsequently HPPH₂ (4.7μL, 1.0eqv) & DIPEA (4.7 μL, 1.0eqv) was micropipetted. 5 mol% catalyst was then added; washing down with 1mL of solvent. [b] determined by crude ³¹P {¹H}NMR after oxidation. [c] determined via chiral HPLC on an ID column.

Intriguingly, the reaction proceeded up to 33% conversion within 24 hours, but however did not progress further even with extended reaction times. The stagnation in reactivity suggests that the acetate ligand is eventually excluded from the coordination sphere due to much higher concentration of diphenylphosphine in solution. It was also observed that only the aminopalladacycle (*S*)-**5** catalyzed the reaction. This suggests that the acetate ligand in the phosphapalladacycle (*S*)-**4** is presumably either more labile than (*S*)-**5** or essentially too bulky to receive the enone within its coordination sphere.

To verify that catalyst in the bis-diphenylphosphine complex form stagnates the reaction, the bridged palladacycle (*S*)-**5** and HPPPh₂ was added first to the flask and subsequently charged with base with the final reagent to be added being the enone. As a result, conversion achieved was below 7 % and replicable.

The reaction was repeated with increment of 3 equivalents of enone, however, no improvement in conversion was achieved. Increasing the amine concentration provided poor diastereoselectivity although with similar conversions. Interestingly, the reaction condition was only specific to DCM as solvent. Other non-coordinating solvents with lower dielectric constants did not provide similar conversions. (e.g. Toluene)

We further conducted the AHP with derivatives of catalyst (*S*)-**5** by narrowing down the plausible factors (sterics & electronics on N moiety) with catalysts (*S*)-**6**, **7** & **8** and found that these palladacycles would also not facilitate the AHP process.

Figure 6. Displacement of HPPPh₂ in comparison to ⁻OAc for coordination to Pd.

The focus was then shifted to the addition of additives to aid the phosphination (Table 2). Incorporating additives into the reaction, where metal salts are concerned, provides an avenue for the additional cations to not only activate the enone but also compete with the diphenylphosphide species in coordination to the palladium centre. This transiently vacates a coordination site on the palladium and improves the likelihood of the enone binding to the palladium center.

Table 2. AHP Screening with additives

Entry ^a	Cat.	Solvent	Amine	Additive (eqv)	Time (hr)	Conv. (%)	<i>d.r.</i> ^b	<i>e.e.</i> ^c (%)	
								2a	2b
1	(S)- 5	DCM	DIPEA	-	24	33	25:8	70	-
2	(S)- 5	DCM	DIPEA	1 NaOAc	24	9	>99:1	-	-
3	(S)- 5	DCM	3 DIPEA	-	24	38	21:17	-	-
4	(S)- 5	DCM	DIPEA	1 K ₂ CO ₃	24	31	19:12	-	-
5	(S)- 5	DCM	DIPEA	0.2 KPF ₆	24	38	28:10	-	-
6	(S)- 5	DCM	DIPEA	0.1 KOtBu	68	64	56:8	68	-
7	(S)- 5	DCM	DIPEA	0.4 KOtBu	30	76	50:12	68	90
8	(S)- 5	DCM	3 DIPEA	0.4 KOtBu	30	99	61:21	60	80
9	(S)- 5	DCM	Et ₃ N	0.4 KOtBu	30	99	60:23	60	90
10	none	DCM	DIPEA	0.4 KOtBu	30	trace	-	-	-
11	(S)- 5	THF	DIPEA	1 KOtBu	40	99	79:6	2	-
12	(S)- 5	DCM	DIPEA	0.4 KOtBu	40	trace	-	-	-
13	(S)- 5	E.A	DIPEA	1 KOtBu	40	99	-	2	-
14	(S)- 5	DCM	DIPEA	0.2 NaOEt	40	38	21:17	-	-

[a] An evacuated flask under inert atmosphere was charged with **1** (0.0071g, 1.1eqv) and additive. 1.5mL of solvent was added and subsequently HPPH₂ (4.7μL, 1.0eqv) & DIPEA (4.7 μL, 1.0eqv) was micropipetted. 5 mol% catalyst was then added; washing down with 1mL of solvent. [b] determined by crude ³¹P NMR [c] determined via chiral HPLC on ID column after oxidation.

Sodium acetate present in the reaction halted the reaction, indicating that acetate has presumably stronger binding capability with the catalyst. Tertiary butoxide however, improved the conversions significantly (up to completion) in DCM but with lower *d.r.* On top of that, the side product (associated with using *t*BuOK) found at 23ppm in crude ³¹P NMR (~20%) was later identified to be bisdiphenylphosphinomethane (BDPPM).

Nevertheless, the current results contrast the reactivity achieved merely with the incorporation of an acetate component and tertiary-butoxide as an additive. Screening with protic or ethereal solvents led to high conversions but low *e.e.s* undoubtedly due to *t*BuOK acting as a catalyst in such media. This was confirmed via a control run with no catalyst. Additional control runs to investigate *t*BuOK (catalytic capability) in DCM solvent showed no conversion to the product but with slight amount of diphenylphosphinomethylenechloride being generated.- Subsequent addition of (*S*)-**5** to the solution catalyzed the former by-product to BDDPM. This verified that very low concentrations of KPPH₂ was probably responsible for improved conversions albeit with retardation of *e.e.* It was also essential to have the amine present to better regulate the solubility of *t*BuOK and thus allow the reaction to progress within shorter periods without stagnation.

As this AHP protocol applied on the benzylidene-1-tetralone proceeded only via incorporation of an acetate bridge aminopalladacycle (*S*)-**5**, further improvement was brought about by adding a controlled amount of *t*BuOK as an additive on top of the amine present (Table 2, Entry 6 – 9). The procedure was also found to be only tolerant in DCM as a solvent. Despite the average diastereoselectivity achieved, the enantiomeric excess of up to 90% was achieved, albeit with modest yield. Having found the optimized solution, we applied the protocol to EWG and EDG derivatives of benzylidene-1-tetralone as well as heterocyclic analogues (Table 3).

Figure 7. ORTEP structure of major diastereomer of oxide of **2a** with thermal ellipsoids drawn at the 50% probability level.

Table 3. AHP tolerance with modifications of substrate

Entry ^a	Substrate 1	Amine	Additive (eqv)	Time(hr)	Conversion (%)	<i>d.r</i> ^b	<i>e.e</i> ^c (%)	
							2	3
1	a	DIPEA	0.4 KOtBu	26	76	50:12	68	90
2	b	DIPEA	0.4 KOtBu	26	64	19:45	37	50
3	c	DIPEA	0.4 KOtBu	26	51	17:34	19	55
4	d	DIPEA	0.4 KOtBu	26	66	61:5	14	-
5	e	DIPEA	0.4 KOtBu	26	99	89:11	7	-
6	f	DIPEA	0.4 KOtBu	26	61	12:49	27	14

[a] An evacuated flask under inert atmosphere was charged with **1** (0.0071g, 1.1eqv) and additive. 1.5mL of solvent was added and subsequently HPPH₂ (4.7μL, 1.0eqv) & DIPEA (4.7 μL, 1.0eqv) was micropipetted. 5 mol% catalyst was then added; washing down with 1mL of solvent. [b] determined by crude ³¹P NMR [c] oxidized adducts were determined via chiral HPLC on ID column.

From the data in Table 3, we find that in general, addition of the additive synergistically facilitates the reactions along with the palladacycle to give moderate to good yields in the AHP of exocyclic olefins. Electron donating group (*p*-MeO-) or electron drawing group (*p*-Cl-) present on the aryl ring distal to the ketone would result in diminished selectivities. Similarly, the selectivity was severely reduced when the ring is contracted by one carbon (Entry 4) or incorporated with S or O atoms (Entry 5-6). Contrastingly, as for entries 2, 3 and 6, the

diastereoselectivity is in favor of the *trans* products. The sensitivity of selectivities based on the changes in electronics and steric interactions for this substrate led to the realization that the association of the substrate and catalyst of these exocyclic alkenes starkly contrasts with that of linear alkenes. - Linear forms would furnish smooth additions even at -80°C.

As a comparison, the result sheds light on the mechanics of successful hydrophosphination of linear olefins with palladacycles. The carbonyl, C=O, and vinyl, C=C, bond of a linear α,β -unsaturated enone has their orientations plausibly locked, such that it adopts an intermediate orientation between *S-cis* and *S-trans* conformation in the transition state.

Figure 8. *S-cis*/*S-trans* equilibria of enones coordinated to Lewis Acids

Studies in standard 1,4-conjugate additions and in Diels Alder type reactions mediated by Palladacycles have suggested that *S-cis* conformation is unfavorable when coordinated to bulky Lewis acids due to high degree of sterics between the large Lewis acid moiety and the substituents on the enone.¹⁶ However, for an inner-sphere addition to occur, the phosphide P

atom should still be in relative proximity to the beta carbon of the unsaturated substrate as illustrated in Figure 8. Therefore, it can be visualized using Dreiding models that the face of the alkene C=C bond is skewed out of plane from the Palladium's square planar coordination vertices.

Figure 9. Intermediate conformation of linear substrate primed for AHP.

Figure 10. Conformation of exocyclic substrate with poor alignment for AHP

In the case of exocyclic olefins (Fig 5.), a phosphide shuttle or tether is likely required to facilitate the transfer of the phosphide nucleophile due to the lack of freedom of rotation of the alkene. Hence, the capability of *t*BuOK to form KPPh_2 via abstraction of phosphide from the palladium and perform the addition compensates for lack of reactivity in *S-cis* locked enones.

4.3 Conclusions

The hydrophosphination protocol applied on the exocyclic olefins was found to proceed only via an acetate bridged aminopalladacycle (*S*)-**5** as catalyst. Further improvement in yields was brought about by adding a controlled amount of *t*BuOK as an additive in addition to the amine. The procedure was also found to be only tolerant to DCM as a solvent. Despite poor diastereoselectivity, enantiomeric excess of up to 90% was achieved albeit with modest yields. The role of the acetate in the catalyst has been shown to be important in facilitating AHP in these cases and have prompted a re-examination of current catalysts applied in P-H additions used for future designs of asymmetric hydrophosphination.

4.5 Experimental

General Information: All equipment utilized are as stated in Chapter 2 Experimental

Materials:

Substrates **1a-f** were synthesized according to literature procedures.¹⁷ Catalysts **1-5** were similarly synthesized from literature procedures.¹⁸ HPPH₂ was synthesized from literature¹⁹.

General procedure for Asymmetric Hydrophosphination of Exocyclic Olefins (Table 3):

An evacuated flask under inert atmosphere was charged with **1** (7.10 mg, 1.1 eqv) and 40 % *t*BuOK (1.20 mg, 0.4 eqv), 0.8 mL of DCM. Subsequently HPPPh₂ (4.7 μL, 1.0eqv) & DIPEA (4.7 μL, 1.0eqv) was micropipetted and 0.3 mL of DCM was added. 5 mol% catalyst was then added; washing down with 0.4 mL of DCM. The tube was then sealed and reaction left to stir for the indicated reaction time or until all HPPPh₂ was consumed. Subsequently, the reaction mixture was flashed through a silica plug with DCM to remove the catalyst and *t*BuOK. Thereafter, the resultant clear yellow solution was concentrated via rotary evaporation at room temperature and to the crude obtained was added a 0.1 mL of 5% H₂O₂ in EtOH. The solution was left to stir in air for an hour or until all phosphine product has oxidized. Thereafter the solution was concentrated and purified via flash column chromatography on silica gel (DCM: ethyl acetate; 7: 1 – 5: 1) to give oxidized **2** and **3**.

General assignment of atoms.

2a

White solid. m.p. 199°C; $[\alpha]_D^{22} = -104.0$ (c 0.03, DCM); ^1H NMR (400 MHz, CDCl_3 , 25°C, TMS): $\delta = 1.56 - 1.75$ (m, 1H; CH), 2.84 – 3.13 (m, 4H; CH), 5.14 (d, $^3J(\text{H,P}) = 8.6$ Hz, 1H; CH), 7.03 – 7.19 (m, 4H; ArH), 7.19 – 7.32 (m, 3H; ArH), 7.34 – 7.42 (m, 1H; ArH), 7.43 – 7.54 (m, 3H; ArH), 7.59 – 7.77 (m, 4H; ArH), 7.94 – 8.06 (m, 3H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3 , 25°C, H_3PO_4): $\delta = 34.9$; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 27.1 (s, 1C; CH_2), 29.8 (s, 1C; CH_2), 41.6 (d, $^1J(\text{C,P}) = 73.0$ Hz, 1C; CH), 49.0 (s, 1C; CH), 126.6 (s, 1C; $\text{C}_{\text{c}}^{\text{para}}$), 127.2 (s, 1C; C6), 127.9 (s, 1C; C4), 128.2 (s, 2C; $\text{C}_{\text{c}}^{\text{meta}}$), 128.3 (d, $^3J(\text{C,P}) = 11.6$ Hz, 2C; $\text{C}_{\text{a}}^{\text{meta}}$), 128.9 (s, 1C; C7), 129.1 (d, $^3J(\text{C,P}) = 11.2$ Hz, 2C; $\text{C}_{\text{b}}^{\text{meta}}$), 131.0 (d, $^2J(\text{C,P}) = 8.7$ Hz, 2C; $\text{C}_{\text{a}}^{\text{ortho}}$), 131.2 (d, $^2J(\text{C,P}) = 8.3$ Hz, 2C; $\text{C}_{\text{b}}^{\text{ortho}}$), 131.3 (d, $^4J(\text{C,P}) = 2.8$ Hz, 1C; $\text{C}_{\text{b}}^{\text{para}}$), 131.8 (d, $^3J(\text{C,P}) = 8.0$ Hz, 1C; $\text{C}_{\text{c}}^{\text{ortho}}$), 131.9 (d, $^4J(\text{C,P}) = 3.6$ Hz, 1C; $\text{C}_{\text{a}}^{\text{para}}$), 132.2 (s, 1C; $\text{C}_{\text{c}}^{\text{ipso}}$), 132.9 (d, $^1J(\text{C,P}) = 95.6$ Hz, 1C; $\text{C}_{\text{a}}^{\text{ipso}}$), 133.1 (d, $^1J(\text{C,P}) = 99.8$ Hz, 1C; $\text{C}_{\text{b}}^{\text{ipso}}$), 133.7 (s, 1C; C5), 134.2 (d, $^4J(\text{C,P}) = 3.7$ Hz, 1C; C8), 144.5 (s, 1C; C3), 196.8 (d, $^3J(\text{C,P}) = 13.4$ Hz, 1C; C=O). HRMS m/z (+ESI) $(\text{M} + \text{H})^+$ calcd for $\text{C}_{29}\text{H}_{26}\text{O}_2\text{P}_1$: 437.1670, found: 437.1668.

Enantiomeric excess resolved using ID Column; n-Hexanes : IPA = 90 : 10, 1.0 ml / min, 210 nm, 42.9 mins (minor), 49.6 mins (major) for 68 % e.e.

3a

White solid. m.p. 205°C; $[\alpha]_D^{22} = +11.7$ (c 0.13, DCM); ^1H NMR (400 MHz, CDCl_3 , 25°C, TMS): δ =1.95 – 2.20 (m, 1H; CH), 2.76 – 3.03 (m, 3H; CH), 3.18 – 3.39 (m, 1H; CH), 4.78 (dd, $^3J(\text{H},\text{P})=8.0$ Hz, $^3J(\text{H},\text{H})=5.0$ Hz, 1H; CH), 7.08 – 7.34 (m, 7H; ArH), 7.35 – 7.56 (m, 8H; ArH), 7.69 – 7.76 (m, 1H; ArH), 7.89 – 7.97 (m, 2H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3 , 25°C, H_3PO_4): δ = 31.2; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 28.2 (d, $^3J(\text{C},\text{P})=5.9$ Hz, 1C; CH_2), 29.9 (s, 1C; CH_2), 44.5 (d, $^1J(\text{C},\text{P})=68.0$ Hz, 1C; CH), 53.7.0 (s, 1C; CH), 126.4 (s, 1C; $\text{C}_{\text{c}}^{\text{para}}$), 127.5 (s, 1C; C6), 127.9 (d, $^3J(\text{C},\text{P})=11.7$ Hz, 2C; $\text{C}_{\text{a}}^{\text{meta}}$), 128.3 (s, 1C; C4), 128.4 (s, 2C; $\text{C}_{\text{c}}^{\text{meta}}$), 128.4 (s, 1C; C7), 128.4 (d, $^3J(\text{C},\text{P})=11.1$ Hz, 2C; $\text{C}_{\text{b}}^{\text{meta}}$), 130.2 (d, $^2J(\text{C},\text{P})=6.2$ Hz, 2C; $\text{C}_{\text{c}}^{\text{ortho}}$), 131.0 (d, $^2J(\text{C},\text{P})=8.7$ Hz, 2C; $\text{C}_{\text{a}}^{\text{ortho}}$), 131.0 (d, $^4J(\text{C},\text{P})=2.5$ Hz, 1C; $\text{C}_{\text{b}}^{\text{para}}$), 131.4 (d, $^3J(\text{C},\text{P})=8.9$ Hz, 1C; $\text{C}_{\text{b}}^{\text{ortho}}$), 131.6 (d, $^4J(\text{C},\text{P})=2.8$ Hz, 1C; $\text{C}_{\text{a}}^{\text{para}}$), 132.3 (s, 1C; $\text{C}_{\text{c}}^{\text{ipso}}$), 133.0 (d, $^1J(\text{C},\text{P})=101.0$ Hz, 1C; $\text{C}_{\text{a}}^{\text{ipso}}$), 133.3 (s, 1C; C5 overlap), 133.3 (d, $^1J(\text{C},\text{P})=93.1$ Hz, 1C; $\text{C}_{\text{b}}^{\text{ipso}}$), 138.3 (d, $^4J(\text{C},\text{P})=4.7$ Hz, 1C; C8), 143.5 (s, 1C; C3), 197.4 (d, $^3J(\text{C},\text{P})=6.1$ Hz, 1C; C=O). HRMS m/z (+ESI) ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{29}\text{H}_{26}\text{O}_2\text{P}$: 437.1670, found: 437.1670. *Enantiomeric excess resolved using ID Column; n-Hexanes : IPA* = 90 : 10, 1.0 ml / min, 210 nm, 70.4 mins (major), 116.0 mins (minor) for 90 % *e.e.*

2b

White solid. m.p. 195°C; $[\alpha]_D^{22} = -11.5$ (c 0.16, DCM); ^1H NMR (400 MHz, CDCl_3 , 25°C, TMS): $\delta = 1.60 - 1.79$ (m, 1H; CH), 2.85 – 3.13 (m, 4H; CH), 5.09 (dd, $^3J(\text{H,P}) = 8.7$ Hz, $^3J(\text{H,H}) = 0.9$ Hz, 1H; CH), 7.06 – 7.18 (m, 3H; ArH), 7.19 – 7.24 (m, 1H; ArH), 7.28 – 7.44 (m, 4H; ArH), 7.46 – 7.53 (m, 3H; ArH), 7.57 – 7.70 (m, 4H; ArH), 7.93 – 8.04 (m, 3H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3 , 25°C, H_3PO_4): $\delta = 34.7$; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 26.9 (s, 1C; CH_2), 29.5 (s, 1C; CH_2), 40.8 (d, $^1J(\text{C,P}) = 72.8$ Hz, 1C; CH), 48.7 (s, 1C; CH), 126.5 (s, 1C; C6), 127.7 (s, 1C; C7), 128.3 (s, 2C; C^{meta}), 128.4 (d, $^3J(\text{C,P}) = 11.7$ Hz, 2C; C^{meta}), 128.7 (s, 1C; C4), 129.0 (d, $^3J(\text{C,P}) = 11.4$ Hz, 2C; C^{meta}), 130.8 (d, $^2J(\text{C,P}) = 8.8$ Hz, 2C; C^{ortho}), 130.9 (d, $^2J(\text{C,P}) = 8.5$ Hz, 2C; C^{ortho}), 131.4 (d, $^4J(\text{C,P}) = 3.3$ Hz, 1C; C^{para}), 131.9 (d, $^4J(\text{C,P}) = 4.1$ Hz, 1C; C^{para}), 132.2 (d, $^1J(\text{C,P}) = 81.4$ Hz, 1C; C^{ipso}), 132.3 (d, $^1J(\text{C,P}) = 82.0$ Hz, 1C; C^{ipso}), 133.0 (d, $^3J(\text{C,P}) = 7.9$ Hz, 2C; C^{ortho}), 132.5 (m, 1C; C^{ipso} overlap), 133.2 (s, 1C; C5), 133.2 (s, 1C; C8 overlap), 133.7 (s, 1C; C^{para}), 144.3 (s, 1C; C3), 196.4 (s, 1C; C=O). HRMS m/z (+ESI) ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{29}\text{H}_{25}\text{O}_2\text{P}^{35}\text{Cl}$: 471.1281, found: 471.1279. *Enantiomeric excess resolved using ID Column; n-Hexanes : IPA = 90 : 10, 1.0 ml / min, 210 nm, 52.7 mins (minor), 66.5 mins (major) for 37 % e.e.*

3b

White solid. m.p 221°C; $[\alpha]_D^{22} = -40.3$ (c 0.19, DCM); ^1H NMR (400 MHz, CDCl_3 , 25°C, TMS): $\delta = 1.95 - 2.20$ (m, 1H; CH), 2.78 – 3.05 (m, 3H; CH), 3.17 – 3.34 (m, 1H; CH), 4.71 (dd, $^3J(\text{H},\text{P}) = 7.6$ Hz, $^3J(\text{H},\text{H}) = 4.8$ Hz, 1H; CH), 7.10 – 7.28 (m, 5H; ArH), 7.30 – 7.56 (m, 9H; ArH), 7.69 – 7.75 (m, 1H; ArH), 7.80 – 7.97 (m, 2H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3 , 25°C, H_3PO_4): $\delta = 31.5$; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 26.9 (d, $^3J(\text{C},\text{P}) = 5.7$ Hz, 1C; CH_2), 29.8 (s, 1C; CH_2), 44.0 (d, $^1J(\text{C},\text{P}) = 68.1$ Hz, 1C; CH), 53.6 (s, 1C; CH), 126.4 (s, 1C; C6), 127.5 (s, 1C; C7), 128.1 (d, $^3J(\text{C},\text{P}) = 11.7$ Hz, 2C; C_a^{meta}), 128.5 (s, 2C; C_c^{meta}), 128.5 (s, 1C; C4 overlap), 128.6 (d, $^3J(\text{C},\text{P}) = 12.3$ Hz, 2C; C_b^{meta}), 130.9 (d, $^2J(\text{C},\text{P}) = 8.5$ Hz, 2C; $\text{C}_a^{\text{ortho}}$), 131.2 (d, $^4J(\text{C},\text{P}) = 2.5$ Hz, 1C; C_a^{para}), 131.4 (d, $^2J(\text{C},\text{P}) = 9.0$ Hz, 2C; $\text{C}_b^{\text{ortho}}$), 131.5 (d, $^3J(\text{C},\text{P}) = 6.2$ Hz, 2C; $\text{C}_c^{\text{ortho}}$), 131.7 (d, $^4J(\text{C},\text{P}) = 4.1$ Hz, 1C; C_b^{para}), 132.2 (s, 1C; C_c^{para}), 132.8 (d, $^2J(\text{C},\text{P}) = 2.5$ Hz, 1C; C_c^{ipso}), 133.0 (d, $^1J(\text{C},\text{P}) = 100.9$ Hz, 1C; C_a^{ipso}), 133.2 (d, $^1J(\text{C},\text{P}) = 93.4$ Hz, 1C; C_b^{ipso}), 133.4 (s, 1C; C5), 137.1 (d, $^4J(\text{C},\text{P}) = 5.0$ Hz, 1C; C8), 143.4 (s, 1C; C3), 197.2 (d, $^3J(\text{C},\text{P}) = 6.2$ Hz, 1C; C=O). HRMS m/z (+ESI) ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{29}\text{H}_{25}\text{O}_2\text{P}_1^{35}\text{Cl}_1$: 471.1281, found: 471.1285. *Enantiomeric excess resolved using ID Column; n-Hexanes : IPA = 80 : 20, 1.0 ml / min, 210 nm, 32.0 mins (major), 58.7 mins (minor) for 50 % e.e.*

2c

White solid. m.p 206°C; $[\alpha]_D^{22} = +10.4$ (c 0.13, DCM); ^1H NMR (400 MHz, CDCl_3 , 25°C, TMS): $\delta = 1.68 - 1.81$ (m, 1H; CH), 2.83 – 3.08 (m, 4H; CH), 3.67 (s, 3H; -OMe), 5.09 (d, $^3J(\text{H,P}) = 8.8$ Hz, 1H; CH), 6.63 – 6.78 (m, 1H; ArH), 7.10 – 7.40 (m, 7H; ArH), 7.42 – 7.51 (m, 3H; ArH), 7.53 – 7.60 (m, 2H; ArH), 7.62 – 7.69 (m, 2H; ArH), 7.91 – 8.06 (m, 3H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3 , 25°C, H_3PO_4): $\delta = 35.5$; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 26.9 (s, 1C; CH_2), 29.6 (s, 1C; CH_2), 40.5 (d, $^1J(\text{C,P}) = 73.7$ Hz, 1C; CH), 48.9 (s, 1C; CH), 55.0 (s, 1C; OCH_3), 113.5 (s, 2C; C_c^{meta}), 125.8 (d, $^2J(\text{C,P}) = 3.7$ Hz, 1C; C_c^{ipso}), 126.4 (s, 1C; C6), 127.7 (s, 1C; C7), 128.2 (d, $^3J(\text{C,P}) = 11.6$ Hz, 2C; C_a^{meta}), 128.7 (s, 1C; C4), 128.9 (d, $^3J(\text{C,P}) = 11.1$ Hz, 2C; C_b^{meta}), 130.9 (d, $^2J(\text{C,P}) = 8.7$ Hz, 2C; $\text{C}_a^{\text{ortho}}$), 131.0 (d, $^2J(\text{C,P}) = 8.2$ Hz, 2C; $\text{C}_b^{\text{ortho}}$), 131.1 (d, $^4J(\text{C,P}) = 2.5$ Hz, 1C; C_a^{para}), 131.7 (d, $^4J(\text{C,P}) = 2.7$ Hz, 1C; C_b^{para}), 132.0 (s, 1C; C5), 132.7 (d, $^1J(\text{C,P}) = 95.1$ Hz, 1C; C_a^{ipso} overlap), 132.7 (d, $^3J(\text{C,P}) = 8.2$ Hz, 2C; $\text{C}_c^{\text{ortho}}$), 132.9 (d, $^1J(\text{C,P}) = 100.1$ Hz, 1C; C_b^{ipso}), 133.5 (s, 1C; C8), 144.4 (s, 1C; C3), 158.6 (s, 1C; C_c^{para}), 196.8 (d, $^3J(\text{C,P}) = 13.8$ Hz, 1C; $\text{C}=\text{O}$). HRMS m/z (+ESI) $(\text{M} + \text{H})^+$ calcd for $\text{C}_{30}\text{H}_{28}\text{O}_3\text{P}_1$: 467.1776, found: 467.1776. *Enantiomeric excess resolved using ID Column; n-Hexanes : IPA = 90 : 10, 1.0 ml / min, 210 nm, 96.2 mins (minor), 122.8 mins (major) for 19 % e.e.*

3c

White solid. m.p 212°C; $[\alpha]_D^{22} = -40.1$ (c 0.30, DCM); ^1H NMR (400 MHz, CDCl_3 , 25°C, TMS): $\delta = 2.05 - 2.20$ (m, 1H; CH), 2.75 – 3.00 (m, 3H; CH), 3.17 – 3.30 (m, 1H; CH), 3.72 (s, 3H; -OMe), 4.72 (dd, $^3J(\text{H},\text{P}) = 8.4$ Hz, $^3J(\text{H},\text{H}) = 5.2$ Hz, 1H; CH), 6.65 – 6.78 (m, 2H; ArH), 7.10 – 7.35 (m, 6H; ArH), 7.36 – 7.55 (m, 5H; ArH), 7.47 – 7.58 (m, 2H; ArH), 7.65 – 7.75 (m, 1H; ArH), 7.80 – 7.85 (m, 2H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3 , 25°C, H_3PO_4): $\delta = 32.4$; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 28.0 (d, $^3J(\text{C},\text{P}) = 5.9$ Hz, 1C; CH_2), 29.8 (s, 1C; CH_2), 43.6 (d, $^1J(\text{C},\text{P}) = 68.8$ Hz, 1C; CH), 53.8 (s, 1C; CH), 55.1 (s, 1C; OCH_3), 113.8 (s, 2C; C^{meta}), 126.3 (s, 1C; C6), 127.5 (s, 1C; C7), 128.0 (d, $^3J(\text{C},\text{P}) = 11.6$ Hz, 2C; C^{meta}), 128.4 (s, 1C; C4 overlap), 128.4 (d, $^3J(\text{C},\text{P}) = 11.9$ Hz, 2C; C^{meta}), 130.2 (d, $^2J(\text{C},\text{P}) = 4.7$ Hz, 1C; C^{ipso}), 130.9 (d, $^4J(\text{C},\text{P}) = 2.2$ Hz, 1C; C^{para}), 131.0 (d, $^2J(\text{C},\text{P}) = 8.5$ Hz, 2C; C^{ortho}), 131.2 (d, $^3J(\text{C},\text{P}) = 6.3$ Hz, 2C; C^{ortho}), 131.5 (d, $^2J(\text{C},\text{P}) = 9.2$ Hz, 2C; C^{ortho}), 131.7 (d, $^4J(\text{C},\text{P}) = 2.5$ Hz, 1C; C^{para} overlap), 132.3 (s, 1C; C5), 133.2 (s, 1C; C8), 133.3 (d, $^1J(\text{C},\text{P}) = 100.7$ Hz, 1C; C^{ipso}), 133.5 (d, $^1J(\text{C},\text{P}) = 92.3$ Hz, 1C; C^{ipso}), 143.4 (s, 1C; C3), 158.4 (d, $^4J(\text{C},\text{P}) = 1.6$ Hz, 1C; C^{para}), 197.4 (d, $^3J(\text{C},\text{P}) = 5.7$ Hz, 1C; $\text{C}=\text{O}$). HRMS m/z (+ESI) $(\text{M} + \text{H})^+$ calcd for $\text{C}_{30}\text{H}_{28}\text{O}_3\text{P}_1$: 467.1776, found: 467.1774. *Enantiomeric excess resolved using ID Column; n-Hexanes : IPA = 80 : 20, 1.0 ml / min, 210 nm, 56.9 mins (major), 117.8 mins (minor) for 55 % e.e.*

2d

White solid. m.p 198°C (decomp.); $[\alpha]_D^{22} = -2.7$ (c 0.13, DCM); ^1H NMR (400 MHz, CDCl_3 , 25°C, TMS): $\delta = 3.03 - 3.15$ (m, 1H; CH), 3.45 – 3.55 (m, 2H; CH), 4.65 (dd, $^3J(\text{H},\text{P}) = 8.2$ Hz, $^3J(\text{H},\text{H}) = 2.3$ Hz, 1H; CH), 6.98 – 7.15 (m, 3H; ArH), 7.19 – 7.40 (m, 5H; ArH), 7.40 – 7.71 (m, 9H; ArH), 7.98 – 8.10 (m, 2H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3 , 25°C, H_3PO_4): $\delta = 35.0$; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 29.4 (s, 1C; CH_2), 43.9 (d, $^1J(\text{C},\text{P}) = 72.6$ Hz, 1C; CH), 48.0 (s, 1C; CH), 126.5 (s, 1C; C5), 126.5 (s, 1C; C6), 127.3 (s, 1C; Cc^{para}), 128.3 (s, 2C; Cc^{meta} overlap), 128.3 (d, $^3J(\text{C},\text{P}) = 11.7$ Hz, 2C; Ca^{meta}), 129.0 (d, $^3J(\text{C},\text{P}) = 11.5$ Hz, 2C; Cb^{meta}), 130.9 (d, $^2J(\text{C},\text{P}) = 8.7$ Hz, 2C; Ca^{ortho}), 131.1 (d, $^2J(\text{C},\text{P}) = 8.6$ Hz, 2C; Cb^{ortho}), 131.2 (s, 1C; C4), 131.3 (d, $^4J(\text{C},\text{P}) = 3.4$ Hz, 1C; Cb^{para}), 131.9 (d, $^4J(\text{C},\text{P}) = 2.7$ Hz, 1C; Ca^{para}), 132.3 (d, $^1J(\text{C},\text{P}) = 99.4$ Hz, 1C; Ca^{ipso}), 132.5 (d, $^1J(\text{C},\text{P}) = 96.5$ Hz, 1C; Cb^{ipso}), 133.2 (m, 1C; Cc^{ipso} overlap), 134.9 (s, 2C; Cc^{ortho}), 135.5 (s, 1C; C3), 135.6 (s, 1C; C7), 154.4 (s, 1C; C2), 206.1 (d, $^3J(\text{C},\text{P}) = 14.6$ Hz, 1C; C=O). HRMS m/z (+ESI) ($\text{M} + \text{H}$)⁺ calcd for $\text{C}_{28}\text{H}_{24}\text{O}_2\text{P}_1$: 423.1514, found: 423.1514. *Enantiomeric excess resolved using ID Column; n-Hexanes : IPA = 90 : 10, 1.0 ml / min, 210 nm, 67.0 mins (minor), 80.1 mins (major) for 14 % e.e.*

2e

White solid. m.p 205°C (decomp.); $[\alpha]_D^{22} = -0.5$ (c 0.31, DCM); ^1H NMR (400 MHz, CDCl_3 , 25°C, TMS): δ =3.28 – 3.39 (m, 1H; CH), 5.35 (dd, $^3J(\text{H,P})=11.2$ Hz, $^3J(\text{H,H})=5.4$ Hz, 1H; CH), 4.99 (dd, $^3J(\text{H,P})=8.5$ Hz, $^3J(\text{H,H})=1.7$ Hz, 1H; CH), 5.35 (dd, $^3J(\text{H,P})=11.2$ Hz, $^3J(\text{H,H})=5.38$ Hz, 1H; CH), 6.83 – 6.96 (m, 2H; ArH), 7.05 – 7.22 (m, 3H; ArH), 7.28 – 7.44 (m, 3H; ArH), 7.45 – 7.55 (m, 3H; ArH), 7.55 – 7.68 (m, 4H; ArH), 7.76 – 7.84 (m, 1H; ArH), 7.94 – 8.03 (m, 2H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3 , 25°C, H_3PO_4): δ = 35.0; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 39.9 (d, $^1J(\text{C,P})=72.2$ Hz, 1C; CH), 45.6 (s, 1C; CH_2), 69.6 (s, 1C; CH_2), 118.0 (s, 1C; C4), 120.7 (s, 1C; C8), 121.2 (s, 1C; C6), 127.5 (s, 1C; C7), 127.6 (s, 1C; C8), 127.6 (s, 1C; Cc^{para}), 128.3 (d, $^3J(\text{C,P})=11.9$ Hz, 2C; Ca^{meta}), 128.4 (s, 2C; Cc^{meta}), 129.0 (d, $^3J(\text{C,P})=11.3$ Hz, 2C; Cb^{meta}), 130.9 (d, $^2J(\text{C,P})=8.8$ Hz, 2C; Ca^{ortho}), 131.1 (d, $^2J(\text{C,P})=8.2$ Hz, 2C; Cb^{ortho}), 131.1 (d, $^2J(\text{C,P})=6.3$ Hz, 2C; Cc^{ortho} overlap), 131.4 (d, $^4J(\text{C,P})=2.7$ Hz, 1C; Ca^{para}), 132.0 (d, $^4J(\text{C,P})=2.7$ Hz, 1C; Cb^{para}), 132.0 (d, $^1J(\text{C,P})=97.0$ Hz, 1C; Ca^{ipso} overlap), 132.1 (d, $^1J(\text{C,P})=100.2$ Hz, 1C; Cb^{ipso}), 132.7 (d, $^2J(\text{C,P})=3.9$ Hz, 1C; Cc^{ipso}), 136.0 (s, 1C; C5), 161.9 (s, 1C; C3), 191.3 (d, $^3J(\text{C,P})=13.0$ Hz, 1C; C=O). HRMS m/z (+ESI) $(\text{M} + \text{H})^+$ calcd for $\text{C}_{28}\text{H}_{24}\text{O}_3\text{P}_1$: 439.1463, found: 439.1462. *Enantiomeric excess resolved using ID Column; n-Hexanes : IPA = 60 : 40, 1.0 ml / min, 210 nm, 43.3 mins (minor), 55.7 mins (major) for 7 % e.e.*

2f

White solid. m.p 190°C (decomp.); $[\alpha]_D^{22} = +165.6$ (c 0.05, DCM); ¹H NMR (400 MHz, CDCl₃, 25°C, TMS): δ =3.29 – 3.40 (m, 1H; CH), 3.69 (s, 3H; -OMe), 3.91 (dd, ³J(H,P)=13.2 Hz, ³J(H,H)=3.7 Hz, 1H; CH), 5.03 (dd, ³J(H,P)=8.8 Hz, ³J(H,H)=1.8 Hz, 1H; CH), 5.35 (dd, ³J(H,P)=11.2 Hz, ³J(H,H)=5.38 Hz, 1H; CH), 6.70 (d, ³J(H,H)=8.7 Hz, 1H; ArH) 7.05 – 7.22 (m, 2H; ArH), 7.28 – 7.38 (m, 3H; ArH), 7.45 – 7.55 (m, 3H; ArH), 7.55 – 7.68 (m, 4H; ArH), 7.90 – 8.00 (m, 1H; ArH), 8.00 – 8.010 (m, 1H; ArH); ³¹P{¹H} NMR (162 MHz, CDCl₃, 25°C, H₃PO₄): δ = 34.8; ¹³C{¹H} NMR (100 MHz, CDCl₃): 29.6 (s, 1C; CH₂), 41.0 (d, ¹J(C,P)=72.9 Hz, 1C; CH), 49.3 (s, 1C; CH), 55.2 (s, 1C; OCH₃), 113.9 (s, 2C; Cc^{meta}), 124.9 (s, 1C; C6), 125.2 (d, ²J(C,P)=3.6 Hz, 1C; Cc^{ipso} overlap), 127.7 (s, 1C; C7), 128.4 (d, ³J(C,P)=11.8 Hz, 2C; Ca^{meta}), 129.2 (d, ³J(C,P)=11.4 Hz, 2C; Cb^{meta}), 130.1 (s, 1C; C4), 131.0 (d, ²J(C,P)=8.9 Hz, 2C; Ca^{ortho}), 131.0 (s, 1C; C5 overlap), 131.2 (d, ²J(C,P)=8.5 Hz, 2C; Cb^{ortho}), 131.4 (d, ⁴J(C,P)=2.7 Hz, 1C; Cb^{para}), 132.0 (d, ⁴J(C,P)=2.8 Hz, 1C; Ca^{para}), 132.5 (d, ¹J(C,P)=97.9 Hz, 1C; Ca^{ipso} overlap), 132.6 (d, ¹J(C,P)=100.0 Hz, 1C; Cb^{ipso}), 132.7 (d, ³J(C,P)=7.8 Hz, 2C; Cc^{ortho}), 133.3 (s, 1C; C8), 142.5 (s, 1C; C3), 159.0 (s, 1C; Cc^{para}), 193.1 (d, ³J(C,P)=12.9 Hz, 1C; C=O). HRMS m/z (+ESI) (M + H)⁺ calcd for C₂₉H₂₆O₃P₁S₁: 485.1340, found: 485.1341. *Enantiomeric excess resolved using ID Column; n-Hexanes : IPA = 80 : 20, 1.0 ml / min, 210 nm, 63.7 mins (major), 110.9 mins (minor) for 27 % e.e.*

3f

White solid. m.p 201°C (decomp.); $[\alpha]_D^{22} = -12.8$ (c 0.24, DCM); ^1H NMR (400 MHz, CDCl_3 , 25°C, TMS): $\delta = 3.10 - 3.20$ (m, 1H; CH), 3.60 – 3.70 (m, 1H; CH), 3.77 – 3.80 (m, 1H; CH), 3.76 (s, 3H; -OMe), 4.72 – 4.79 (m, 1H; CH), 6.64 (d, $^3J(\text{H,H}) = 8.8$ Hz, 2H; ArH), 7.00 – 7.10 (m, 1H; ArH), 7.15 - 7.22 (m, 4H; ArH), 7.23 – 7.38 (m, 3H; ArH), 7.45 – 7.68 (m, 6H; ArH), 7.96 – 8.10 (m, 2H; ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3 , 25°C, H_3PO_4): $\delta = 30.1$; $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 30.5 (d, $^3J(\text{C,P}) = 3.6$ Hz, 1C; CH_2), 42.6 (d, $^1J(\text{C,P}) = 67.1$ Hz, 1C; CH), 50.2 (s, 1C; CH), 55.1 (s, 1C; OCH_3), 113.6 (s, 2C; C_c^{meta}), 124.6 (s, 1C; C6), 126.8 (s, 1C; C7), 127.8 (d, $^2J(\text{C,P}) = 5.2$ Hz, 1C; C_c^{ipso} overlap), 128.0 (d, $^3J(\text{C,P}) = 11.9$ Hz, 2C; C_a^{meta}), 128.7 (d, $^3J(\text{C,P}) = 11.3$ Hz, 2C; C_b^{meta}), 129.7 (s, 1C; C4), 130.9 (s, 1C; C5), 131.0 (d, $^2J(\text{C,P}) = 8.6$ Hz, 2C; $\text{C}_a^{\text{ortho}}$), 131.2 (d, $^4J(\text{C,P}) = 2.6$ Hz, 1C; C_a^{para}), 131.4 (d, $^2J(\text{C,P}) = 8.9$ Hz, 2C; $\text{C}_b^{\text{ortho}}$), 131.4 (d, $^3J(\text{C,P}) = 6.8$ Hz, 2C; $\text{C}_c^{\text{ortho}}$ overlap), 131.9 (d, $^4J(\text{C,P}) = 2.4$ Hz, 1C; C_b^{para}), 132.2 (d, $^1J(\text{C,P}) = 99.8$ Hz, 1C; C_a^{ipso}), 132.4 (d, $^1J(\text{C,P}) = 92.3$ Hz, 1C; C_b^{ipso}), 133.0 (s, 1C; C8), 140.8 (s, 1C; C3), 158.6 (s, 1C; C_c^{para}), 193.8 (d, $^3J(\text{C,P}) = 8.6$ Hz, 1C; C=O). HRMS m/z (+ESI) $(\text{M} + \text{H})^+$ calcd for $\text{C}_{29}\text{H}_{26}\text{O}_3\text{P}_1\text{S}_1$: 485.1340, found: 485.1339. *Enantiomeric excess resolved using ID Column; n-Hexanes : IPA = 70 : 30, 1.0 ml / min, 210 nm, 83.7 mins (major), 136.1 mins (minor) for 14 % e.e.*

Crystal Data of Oxide of 2a:

Figure 11. ORTEP structure of major diastereomer of oxide of **2a** with thermal ellipsoids drawn at the 50% probability level.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 2₁ 2₁ 2₁, with Z = 4 for the formula unit, C₂₉H₂₅O₂P. The final anisotropic full-matrix least-squares refinement on F² with 289 variables converged at R1 = 2.95%, for the observed data and wR2 = 7.41% for all data. The goodness-of-fit was 1.057. The largest peak in the final difference electron density synthesis was 0.159 e⁻/Å³ and the largest hole was -0.274 e⁻/Å³ with an RMS deviation of 0.044 e⁻/Å³. On the basis of the final model, the calculated density was 1.327 g/cm³ and F(000), 920 e⁻.

Table 1. Sample and crystal data for oxide of 2a.

Identification code	leung953s	
Chemical formula	$\text{C}_{29}\text{H}_{25}\text{O}_2\text{P}$	
Formula weight	436.46 g/mol	
Temperature	143(2) K	
Wavelength	1.54178 Å	
Crystal size	0.160 x 0.200 x 0.300 mm	
Crystal habit	yellow block	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.00366(6) Å	$\alpha = 90^\circ$
	b = 17.92816(18) Å	$\beta = 90^\circ$
	c = 20.2992(2) Å	$\gamma = 90^\circ$
Volume	2184.90(4) Å ³	
Z	4	
Density (calculated)	1.327 g/cm ³	
Absorption coefficient	1.302 mm ⁻¹	
F(000)	920	

Table 2. Data collection and structure refinement for Oxide of 2a.

Theta range for data collection	3.29 to 67.37°
Index ranges	-7<= <i>h</i> <=6, -21<= <i>k</i> <=21, -19<= <i>l</i> <=24
Reflections collected	8793
Independent reflections	3798 [R(int) = 0.0334]
Coverage of independent reflections	97.8%
Absorption correction	Multi-Scan
Max. and min. transmission	0.8190 and 0.6960
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	3798 / 0 / 289
Goodness-of-fit on F²	1.057
$\Delta/\sigma_{\max}$	0.001

Final R indices	3672 data;	R1 = 0.0295, wR2 =
	I>2σ(I)	0.0735
	all data	R1 = 0.0304, wR2 =
		0.0741
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0384P)^2+0.1547P]$ where $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	0.000(9)	
Largest diff. peak and hole	0.159 and -0.274 eÅ ⁻³	
R.M.S. deviation from mean	0.044 eÅ ⁻³	

4.6 References

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Chapter 5

Medicinal Applications of Synthesized Ferrocenyl Phosphines

5.1 Introduction

The field of organometallic complexes for medicinal purposes has been in a state of rapid development and has shown unprecedented progress. The structural elucidation of ferrocene in the 1950's spawned the development of a myriad of ferrocenyl compounds.¹ Due to their interesting electrochemical properties, unique redox characteristics, innate stability in aqueous media and easy functionalization, these organometallic compounds have stimulated increasing research interest for their potential applications in antifungal,² antitumor,³ antiparasitic,⁴ and antibacterial agents.⁵ The anticancer property of ferrocene derivatives was first studied in the late 1970s, when Brynes and co-workers reported antitumor activities of ferrocenyl compounds bearing amine or amide functional groups.⁶ These molecules exhibited low but significant antitumor efficacy in mice, suggesting that the incorporation of the ferrocenyl group into an appropriate carrier could provide an organometallic compound with enhanced biological activity.⁶⁻⁷ In this regard, "ferrocifen" was developed by integrating ferrocene into the tamoxifen scaffold that exhibited significant cytotoxicity in ER+ MCF-7, a breast cancer cell line resistant to common anti-estrogenic drugs.⁸ Another example conceived from the strategy is Ferroquine (FQ), an analogue of chloroquine obtained from attaching ferrocene to 4-aminoquinoline. FQ was found to demonstrate remarkable antimalarial activity; more potent against chloroquine-resistant and multidrug-resistant parasites.⁹ Essentially, the conception of

these molecules and their efficacies was sufficient to spur the scientific community to study, improve and expand the library in order to tackle and perhaps cure specific diseases faced by humanity.

Figure 1. Anticancer drug candidate ferrocifen is a tamoxifen derivative in advanced preclinical evaluation and ferroquine is a chloroquine derivative undergoing phase II clinical trials.

Amongst classes of disease that are prevalent worldwide are tumours of the haematopoietic and lymphoid (or hematolymphoid) malignancies and it categorizes diverse forms of cancers of both blood and immune systems. An example of a class of such a malignancy includes non-Hodgkin cutaneous T-cell lymphomas (CTCL) which is characterized by abnormal accumulation of malignant T-cells in the skin. These are often diagnosed in the elderly population in their 50s and account for ~9% of all cancers. In addition, 35% of childhood cancers were found to be of such malignancies. In contrast to the lowering trend in the incidence of other forms of cancer, the occurrence of hematolymphoid malignancies has dramatically increased globally in the past decade.¹⁰ Unfortunately, clinical drug-resistant types of tumours have recently surfaced and as a result, has spurred defensive measures taken by the worldwide scientific community- the development of new anticancer drugs.¹¹ Such measures are anticipated for current arsenal of pharmaceuticals to remain ahead of the rate at which drug-resistance proliferates.

Malaria is another disease which brings forth similar circumstances. Current efforts to tackle malaria has been aggressive due the emergence of multiple drug resistant strains in various regions of the world.¹² Reports of regional drug resistance are alarming as Malaria is a deadly infectious disease and having treatment protocols rendered ineffective for Malaria infected patients might be calamitous.¹³ The *World Malaria Report 2018* states that there were 219 million cases of malaria in 2017 (an increase of 2 million from the previous year) while the number of related deaths was estimated to be 435 000 in the same year.¹⁴ Furthermore, the report highlighted that there was no significant progress made in reducing global malaria cases from 2015 to 2017. Out of the 5 major species of plasmodium genus (protozoan parasites) causing malaria in humans, *Plasmodium falciparum* has been found to be the cause for majority of the aforementioned deaths (99% in 2016).¹⁴⁻¹⁵ Current antimalarials such as chloroquine, amodiaquine, mefloquine, artemisinin, doxycycline and sulfadoxine, has been concluded in reports to be amongst those in which *P. Falciparum* were observed to show resistance against.¹⁶ As such, conducting research and development of novel antimalarial candidates that are effective against drug resistant variants of plasmodium parasites is inevitable.¹⁷

Known biologically active ferrocene based compounds adhere to the general molecular design strategy, which involves the incorporation of a conjugated functional group that modulates the redox capability of the parent ferrocene moiety.^{8b, 18} Furthermore, introducing common pharmacophores capable of hydrogen bonding such as amino acid linkers or peptide chains tends to augment its pharmacological profile. The intrinsic capability of ferrocene compounds to generate the desired reactive oxygen species (ROS) is highly dependent on their physicochemical properties (*e.g.* lipophilicity, polarity and planarity).¹⁹

As a means to explore new potentially bioactive ferrocenes, our current work employed an alternative approach that deviates from the aforementioned common synthetic routes. Utilizing

a recently developed Pd catalyzed hydrophosphination protocol to remove the electronic conjugation between the ferrocene and its attached functional group, we were able to conveniently obtain an array of ferrocenyl phosphines.²⁰ Studies have described that upon removal of the electronic property of the conjugate linkers (of chalcones) the derivatives showed unexpected biological activity as compared to their parent compounds.²¹ The key advantages of this protocol include the inherent flexibility it provides in managing critical structural and electronic parameters of the target compound and the incorporation of a functional handle, which can subsequently be derivatized by either simple oxidation or coordination of the phosphines to form the desired metal complexes. The intramolecular scaffold of these compounds can be organized into 3 customizable pharmacophores: (A) metallocene, (B) phosphine, and (C) aryl ketone.

Figure 2. Customizable pharmacophores: (A) metallocene, (B) phosphine, and (C) aryl ketone.

Considering the possible plethora of derivatives that could be obtained via the hydrophosphination protocol, we narrowed the current work to the less studied oxide (**O1-7**) & sulphide derivatives (**S1-7** & **DS1-4**) as well as gold(I) chloride complexes (**G1-3**) for analysis of their anti-proliferative activities in hematolymphoid cells as well biological potential as antimalarial candidates (Figure 3).

Figure 3. Library of Ferrocenyl phosphine derivatives synthesized

5.2 Results & Discussion

A library of 19 new ferrocenyl phosphine derivatives were synthesized, in a non-asymmetric manner, from their parent ferrocenyl enones (**C1 - 4** & **C7**) via the palladacycle-catalyzed hydrophosphination reaction with diphenylphosphine and subsequently derivatized. The Michael addition based hydrophosphination protocol afforded the phosphine functionalized complexes in high regioselectivity and yields of up to 98% (Scheme 2.). As the compounds were to be subjected to preliminary evaluations only, racemic catalyst A1 was applied to obtain the ferrocenyl phosphine racemates. Subsequent derivatization of these air sensitive tertiary phosphine products to more stable oxide (**O1-4**, **O6-7**) & sulfide derivatives (**S1-5**, **S7-8**, **DS1**, **DS3-4**) was achieved by exposure to air and addition of elemental sulphur respectively. Gold(I) ferrocenyl phosphine derivatives (**G1-3**) were obtained by addition of $\text{Me}_2\text{S} \cdot \text{AuCl}$ directly to the selected tertiary phosphines (Scheme 2).

Scheme 1. Syntheses of Ferrocenyl phosphine

In general, the syntheses for most derivatives resulted in high isolated yields for all except acetyl ketone derivative **O6**, malonate derivatives **O7** & **S7** and as well as **DS1-3**. For **O6**, it was apparent that reactivity with HPPH_2 was slow due to the lack of pi-acidic conjugation by the methyl substituent as compared to the aryl groups. The malonate derivatives, however, show slight sensitivity when subjected to silica gel purification. This caused isolated yields to

be reduced. This was similar to the synthesis of **DS1** to **DS3** whereby some appear to be immobilized in the silica gel column, along with impurities; due to the alcohol group present. Selected compounds were screened for activity in hematolymphoid cells and also separately evaluated for their potential as antimalarial agents. For the purpose of clarity, we will discuss these two studies in separate sections.

Scheme 2. Derivatization to library of ferrocenyl phosphine derivatives (with % yields)

Figure 4. ORTEP of gold complex **G3** with thermal ellipsoids drawn at the 50% probability level.

5.2.1 Evaluation of Ferrocenyl-Phosphines as anticancer agents for Haematological Malignancies

10 ferrocenyl-phosphine derivatives (Table 1) were screened for their anti-proliferative activities on 4 different CTCL cell lines (HuT78, MJ, MyLa and HH). Cells (5×10^4 cells/well in 96-well plate) were treated with increasing concentrations of compounds ranging from 1 μ M to 100 μ M for 24 h and cell viability was quantified by MTS-based assay. The concentrations that inhibited cell growth by 50% (IC_{50}) were determined and results are presented in Table 1.

Table 1. IC_{50} values of ferrocenyl-phosphine derivatives on four different hematolymphoid cell lines – HuT78, HH, MJ, and MyLa.

Cell line Compound	IC_{50} (μ M)			
	HuT78	HH	MJ	MyLa
O1	>50	14.99 $\pm$ 1.04	>50	>50
O2	11.22 $\pm$ 0.47	24.07 $\pm$ 0.69	>50	>50
O4	19.20 $\pm$ 0.82	12.37 $\pm$ 0.95	30.20 $\pm$ 0.32	30.02 $\pm$ 1.07
O7	>50	>50	>50	>50
S1	>50	>50	>50	>50
S4	>50	>50	>50	>50
S8	19.62 $\pm$ 1.06	14.78 $\pm$ 1.12	>50	>50
G1	20.82 $\pm$ 6.00	16.10 $\pm$ 1.09	>50	>50
G2	>50	39.54 $\pm$ 8.05	>50	>50
G3	5.55 $\pm$ 0.20	7.80 $\pm$ 0.09	3.16 $\pm$ 0.10	6.46 $\pm$ 0.24
SAHA	2.10 $\pm$ 0.25	0.50 $\pm$ 0.15	3.01 $\pm$ 0.40	1.75 $\pm$ 0.20

Cells were treated with suberoylanilide hydroxamic acid (SAHA, also called vorinostat) as a positive control. Assay conducted by Lee Kong Chian School of Medicine.

Notably, compound **G3** showed significant anti-proliferative activity in all the four hematolymphoid cell lines with IC₅₀ values in the range of 5 μ M to 8 μ M (Table 1). The observed anti-proliferative activities of the ferrocenyl-phosphine compounds are speculated to be due to the augmentation of spatial morphology of the parent ferrocenyl compounds, as a result of the removal of a conjugate linker, providing the dual hydrophilicity (when Fc is oxidized to Fc⁺) and hydrophobicity attributed to the organic fragment. In this respect, the high anticancer activity of **G3** could be due to the presence of PPh₂-AuCl along with an aromatic furan side chain. Up to some extent, fair success to **G2** could be attributed to the presence of PPh₂-AuCl functional group and an aromatic methylbenzene side chain. Based on the cytotoxicity screening data showing the robust and consistent anti-proliferative activity of **G3**, this compound was chosen for further biological studies to investigate the mechanism of action in CTCL cells. Further investigation conducted by Lee Kong Chian School of Medicine on **G3**, to investigate the compounds capability to induce cell death by means of apoptosis showed positive induction of apoptosis in all three CTCL cells -HuT78, MJ and MyLa (see Figure 7 in Experimental - Annexin V-FITC/PI binding assay performed using flow-cytometry.).

Figure 5. Effective anticancer therapeutics agents are designed to induce apoptosis over necrosis.

Apoptosis or programmed cell death is an essential physiological process for proper homeostatic maintenance by removing injured or mutated cells. Any dysregulation in apoptosis results in high or decreased cell death, which supports the malignancy progression. The generation of reactive oxygen species (ROS) is one of the key factors that induce apoptosis under physiologic as well as pathologic conditions²² and therefore targeting ROS response pathway is a viable strategy for anticancer development. Since, ferrocene complexes have been found to elevate ROS within cancer cells,²³ it is likely that **G3** targets cellular antioxidant systems leading to intracellular ROS generation resulting in cell death *via* apoptosis.

In addition, cell cycle distribution analysis carried out showed that **G3** induces G0/G1 phase cell cycle arrest in hematolymphoid cells (see Figure 8 in Experimental). Aside from programmed cell death, cell cycle is another main biological process implicated in the

pathogenesis and progression of cancers.²⁴ Cell cycle depends upon the several checkpoints, which synchronize in different phases. Blockade of cell cycle at specific phase causes an accumulation of cells at that phase resulting into the induction of apoptosis.²⁵

Figure 6. Cell Cycle: **G3** arrests cell cycle at G₁ to S Phase

In summary, the study identified the gold-coordinated ferrocenyl-phosphine complex **G3** as a potential anticancer compound. The introduction of the gold center was in view of the proven ability of gold to amplify biological activity, as in many classes of anticancer drugs, including several instances involving phosphine based drugs.²⁶ **G3** consistently blocked cell growth, inhibited STAT3, Akt and c-Myc (see Figure 9 in Experimental), induces apoptosis and arrests the cell-cycle in hematolymphoid cells..

5.2.2 Evaluation of Ferrocenyl-Phosphine derivatives as Antimalarials

Figure 10. Lifecycle of Malaria Parasite, *Plasmodium falciparum*.

The 24 compounds **O1 – G3** were firstly subjected to growth inhibition assays against trophozoite stage *P. falciparum* (in intraerythrocytic cycle) in order to gauge its inhibitory potential. Conducted by the Singapore University of Technology & Design (SUTD), the parasites were treated with 1 in 4 serial dilutions of compounds beginning from 100µM for 52 h. Compounds (>40%) in parasitemia in the next replication cycle compared to the vehicle-alone (DMSO) treated controls were selected as potential hits. Amongst the 24, a total of 9 compounds were found to meet the hit criteria; namely **O2, S1, S4, S7, G3, S2, S3, S5** and **DS1** (Figure 11).

Figure 11. Identification of compounds from the ferrocenyl phosphine library exhibiting potential antimalarial activity.

In addition, the preliminary inhibitory potency of compounds **O1 - 4**, **S1 - 4** and **G1 – 3**, against young trophozoite stages parasites, as compared to their parent ferrocenyl chalcones **C1 – C4** clearly show improved efficacy with the structural change (Table 2).

Table 2. Preliminary determination of IC₅₀ values in comparison to their parent ferrocenyl chalcone.

O1	7.48 μ M	S1	3.82 μ M	G1	4.58 μ M	DS1	2.27 μ M	C1	12.81 μ M

O2	2.72 μ M	S2	0.792 μ M	G2	9.70 μ M			C2	12.74 μ M

O3	12.07 μ M	S3	5.19 μ M	G3	2.55 μ M	DS3	9.93 μ M	C3	17.2 μ M

O4	13.58 μ M	S4	5.10 μ M			DS4	5.34 μ M	C4	15.49 μ M

With the identified hits, inhibitory potency (IC₅₀) values were further determined with accuracy.

The growth inhibition assays were carried out against young trophozoite stage parasites (both 3D7 and K1 strain). It was found that all the identified compounds had IC₅₀ values of less than 5 μ M for 3D7 and less than 10 μ M for K1 strain (Table 3).

Table 3. Inhibitory potency of selected hits against 3D7 & K1 strain (drug-resistant) of *P. Falciparum*

Compound ID	3D7		K1		Resistance Index (RI)
	IC ₅₀ (μM)	95% Confidence Interval (μM)	IC ₅₀ (μM)	95% Confidence Interval (μM)	
O2	3.63	3.21 to 4.10	7.42	6.82 to 8.07	2.04
S1	3.96	3.46 to 4.51	5.21	4.74 to 5.72	1.32
S4	2.82	2.27 to 3.48	7.92	7.30 to 8.59	2.81
S7	2.56	1.98 to 3.31	5.30	4.85 to 5.78	2.07
G3	3.43	3.03 to 3.89	4.87	4.39 to 5.38	1.42
S2	4.40	4.06 to 4.76	2.29	2.07 to 2.53	0.52
S3	2.79	2.35 to 3.29	3.92	3.49 to 4.38	1.41
S5	4.91	4.41 to 5.46	7.23	6.35 to 8.23	1.47
DS1	3.52	3.12 to 3.96	6.34	5.55 to 7.23	1.80

Resistance Index (RI) calculated for each drug from the ratio of IC₅₀ against K1 strain to IC₅₀ against 3D7. Assays performed by SUTD.

Intriguingly, **S2**, the ferrocenyl phosphine sulfide bearing the two CF₃ moieties on the terminal aryl ring showed higher inhibitory potential against drug resistant K1 strain as compared to 3D7 strain. In addition, the analogue of **S2**, wherein the phosphine was protected via oxidation instead of sulfurization viz., **O2**, produced lower inhibitory impact on the K1 strain. The efficacy of S2 this brings forth the point that incorporation of fluorine is desirable. Fluorinated moieties in drug design view, imparts augmented intermolecular interactions (including hydrogen bond formations) as well as increased lipophilicity.

Chloroquine had been reported to have Resistance Index (RI) values of 15.4 and 23.3 estimated based on ratio of K1 to NF54 and K1 to W2 respectively. RI values are a gauge for the degree

of probable development of cross resistance of the drug in strains. All compounds except **O2**, **S4** and **S7** showed a RI values less than 2, indicating good probability of negligible resistance formation (Table 3) while **S2** had the lowest RI value of 0.5; which is a reduction of 30 times in comparison to chloroquine.

The antimalarial activities for the synthesized ferrocenyl phosphine compounds provided a general trend that the ferrocenyl phosphine sulfides (**S**) were distinctly better candidates than their corresponding phosphine oxides (**O**). The exception to this was the aforementioned bioactivity observed with **O2** and **S2** whereby the presence of -CF₃ moiety on the aromatic aryl ring distal to the ferrocene appears to weaken the pharmacological activity of P=S derivative over P=O against malarial parasites. A developed antimalarial compound, ferroquine (FQ), has been observed to accumulate in the digestive vacuole (DV) of the malarial parasite²⁸ and this was similarly observed in the assay for DV phenotypes conducted by SUTD (see Experimental Figure 12). Drug candidates that exhibit comparatively less lipophilic character has been linked to reduced vacuolar accumulation in malarial parasite as their membrane permeation capability is reduced.^{28b, 29} As such, phosphine sulfides are inherently more lipophilic than their phosphine oxide counterpart due to the presence of a less electronegative sulfur atom. Thus, the superior inhibitory activities for phosphine sulfides over the oxide analogues suggests improved membrane transport into digestive vacuoles (DV). Similarly, it was also observed in the preliminary assays that the inclusion of a hydroxy methyl group (-CH₂OH) in **S1**, **S3** & **S4** to generate the respective **DS1**, **DS3** & **DS4** derivatives generally decreased the antimalarial potency; which can be attributed to the expected reduction in lipophilicity & hydrophobicity.

Notably, the relatively higher bioactivity of **O1-4** as compared to **O6** showed that the aromatic ring adjacent to the ketone unit is critical as an antimalarial pharmacophore. Aromatic rings increase lipophilic character of the compound; likely resulting in increased bioactivity as

mentioned. Similarly, sterically bulky isopropyl ester groups adjacent to the ketone unit as seen in **S7** (compared to **S8**) provided improved antimalarial activity. On the other hand, increasing planar steric bulk further on the furyl unit in **S3** to generate **S5** showed a reduction in bioactivity whereas substituting the furyl group of **S3** to a slightly larger thienyl group to generate **S4** provided improved inhibitory capability. Antimalarial drug candidates that are too lipophilic perform poorly and has been suggested to be due to them being “bounded” within the vacuolar membrane, thereby preventing potential interaction with hemozoin.^{28b} Hence, the aforementioned results suggests that lipophilic balance is a critical parameter for these class of antimalarial compounds.

Gold(I) ferrocenyl phosphines (**G1-3**), however, did not establish definite trends in antimalarial activity as compared to their corresponding phosphine oxides and sulfides. While **S2** consistently performed better than its analogues (**O2** & **G2**), only **G3** exhibited greater antimalarial capability than its analogues (**O3** & **S3**). This suggests that antimalarial mode of action of **G3** involves either a diverse or different cell-kill mechanism as compared to the analogous phosphine oxides and sulphides and the cytotoxicity of gold maybe one of the main contributing factor although **G1** and **G2** performed relatively poorly; thus highlighting the intricate role played by complementary functionalities on drug efficacy. To emphasize this further, **G3** was also found to express significantly greater inhibitory capability in early erythrocytic stage (ring to trophozoite stage specific assay) as compared to the other screened ferrocenyl phosphine derivatives, and exclusively demonstrated inhibition of hemozoin in the β -hemozoin assay (see Experimental **Figure 15**). Additionally, the consistent inhibitory performance of **G3** in each stage specific assay suggests it to be a good lead candidate for further study (see Experimental Figure 13 & Table 4). In relation to potential modes of action, the antiparasitic activity of gold(I) incorporated drugs has characteristically been linked to the direct inhibition of *P. falciparum* thioredoxin reductase.³⁰ Additional modes of action

endowed by incorporating gold(I) further complements the intrinsic capability of ferrocenyl phosphines as antimalarial drugs.

Intriguingly, as mentioned earlier, it was observed that the parent non-functionalized compounds (**C1-4** & **C7**) of the bioactive ferrocenyl phosphine derivatives (**O3**, **S1-4**, **S7** & **G3**) exhibited negligible antimalarial capability at low concentrations. This further establishes the requirement for the incorporation of phosphine heteroatom to ferrocenyl chalcones to imbue antiplasmodial potential against *P. falciparum*. On another note, ferrocenyl antimalarial analogues have been well-studied to show that they exhibit an additional capability, as compared to their organic analogues, to generate ROS that cause oxidative stress to the malarial parasite.^{28b, 31} This was similarly evident in the ROS level evaluations primarily due to the presence of the ferrocene moiety that can produce hydroxyl radicals that are toxic for the parasite (see Experimental Figure 14).

In summary, these compounds possess excellent resistance index (RI) and were found to inhibit the intraerythrocytic development of both laboratory 3D7 strain as well as CQ resistant K1 strain of *P. falciparum*. Stage specific assays highlighted **G3** to consistently exhibit antiplasmodial activity whereas phosphine sulfides exhibited excellent activity only in the mid- and late-stages. Modification of the organic aryl/alkyl ketone moiety of the ferrocenyl phosphine was found to be influential to the antimalarial capability of the drug candidates. Further monitoring on cellular uptake and distribution as well as metabolomic studies to obtain insight into the modes action of are to be included in future studies.

5.3 Conclusions

The panel of ferrocenyl phosphine derivatives validated heterobimetallic Gold(I) ferrocenyl phosphine **G3** and several ferrocenyl phosphine sulfides/oxides, obtained via hydrophosphination protocol, to be excellent structural candidates for advancement in future studies as both anti-tumor and anti-malarial drugs. The ferrocenyl phosphine compounds subjected to the individual studies also revealed trends whereby important structural moieties (both proximal and distal to the ferrocene) within the molecule impacts their bio-active capability. Pertinently, it was also found that these ferrocenyl phosphine derivatives were more active than their parent chalcones; prior to hydrophosphination, proving that it is a powerful strategy for future drug designs.

5.4 Acknowledgement

The studies were published and reused / reproduced by permission of The Royal Society of Chemistry. <https://doi.org/10.1039/C8RA05224G> & <http://dx.doi.org/10.1039/C8DT04263B>.

5.5 Experimental

General information for syntheses and physicochemical measurements

Reagents and solvents were obtained from commercial sources and used without further purification. The compounds were characterized by standard spectroscopic techniques. Air-sensitive manipulations were carried out under dry nitrogen by Schlenk techniques unless otherwise stated. Solvents were degassed and/or distilled and stored over 3 Å molecular sieves prior to use. Glassware were oven-dried and placed under vacuum for 30 minutes prior to use. The progress of reactions was monitored by thin-layer chromatography (TLC) on silica gel 60 F₂₅₄ aluminium-backed plates (Merck). Chromatograms were visualized under ultraviolet radiation (UV) or I₂. Flash column chromatography was conducted using silica gel 60 (Merck). Nuclear magnetic resonance (NMR) spectra were obtained using a Bruker AV 300 spectrometer (¹H at 300 MHz, ¹³C at 75 MHz, ¹⁹F{¹H} at 282 MHz, ³¹P{¹H} at 121 MHz), Bruker AV 400 spectrometer (¹H at 400 MHz, ¹³C at 100 MHz, ³¹P{¹H} at 161 MHz) or Bruker AV 500 spectrometer (¹H at 500 MHz, ¹³C at 125 MHz, ³¹P{¹H} at 202 MHz). ¹H spectra were referenced to an internal SiMe₄ standard at δ 0 or CDCl₃ at δ 7.26. All ¹³C spectra were referenced to CDCl₃ at δ 77.16.

Synthetic methodology

The racemic ferrocenyl-phosphines were obtained from their respective ferrocenyl enones³² via the air-sensitive hydrophosphination protocol (Scheme 1) as follows: A Schlenk flask was first charged with diphenylphosphine (50.0 mg, 0.27 mmol) and degassed methanol (2 mL). Thereafter, racemic catalyst **A1**³³ (13.1 mg, 0.027 mmol) was added and the yellow solution was stirred at the stipulated temperature for 5 minutes. Following that, the respective ferrocenyl enone (0.27 mmol) and triethylamine (27.3 mg, 37.6 μ L, 0.27 mmol), diluted with degassed methanol (2 mL), was introduced. The mixture was stirred at room temperature for 24 h.

Subsequently, the reaction mixture was oxidized/sulphurized and coordinated to $\text{SMe}_2\cdot\text{AuCl}$. NMR structural confirmation and mass spectrometry characterization for purity analysis of the compounds were performed. All the compounds are soluble in polar organic solvents, including dimethyl sulfoxide (DMSO), and are bench stable. All compounds were purified *via* silica gel column chromatography under ambient conditions.

Characterization data of Ferrocenyl-phosphine derivatives

O1: HP procedure of the respective enone produced orange-yellow precipitates. The reaction solvent was removed *via* cannula and solids washed with cold hexanes. Subsequently, the solids were dissolved in 5 mL non-degassed dichloromethane (DCM) and left to stir at ambient atmosphere for 24 h. Thereafter, the solvent was removed under reduced pressure and crude purified on SiO_2 ; silica gel column chromatography (DCM/E.A) to give FD1 as dull orange powder; yield: 98%. m.p. 191°C (decomp.); ^1H NMR (CDCl_3 , 400 MHz): δ 2.39 (s, 3H, - Me), 3.54 (s, 1H, Cp), 3.61 - 3.85 (m, 2H, - CH_2), 3.89 (s, 1H, Cp), 3.92 (s, 5H, Cp), 4.11 (s, 1H, Cp), 4.23 (s, 1H, Cp), 4.42 (m, 1H, - CHPh_2), 7.22 - 7.26 (m, 2H, - Ar), 7.28 – 7.34 (m, 2H, - Ar), 7.35 – 7.44 (m, 4H, - Ar), 7.47 – 7.55 (m, 2H, - Ar), 7.83 – 7.90 (m, 4H, - Ar). $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161.6 MHz): δ 34.0 (s). ^{13}C NMR (CDCl_3 , 100 MHz): δ 21.8 (-Me), 34.2 (d, - CHPh_2 , $^1J_{\text{CP}} = 67.0$ Hz), 38.7(- CH_2), 67.2 (*m*-Cp), 67.7 (d, *o*-Cp, $^3J_{\text{CP}} = 1.6$ Hz), 68.4 (*m*-Cp), 68.6 (5Cp), 70.3 (d, *o*-Cp, $^3J_{\text{CP}} = 2.0$ Hz), 85.7 (*i*-Cp), 128.1 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 11.5$ Hz), 128.4(2 *m*-Ar), 128.6 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 11.2$ Hz), 129.5 (2 *o*-Ar), 131.5 (d, 2 *o*-Ar, $^2J_{\text{CP}} = 8.7$ Hz), 131.5 (*p*-Ar), 131.6 (d, 2 *o*-Ar, $^2J_{\text{CP}} = 8.7$ Hz), 131.6 (d, *i*-Ar, $^1J_{\text{CP}} = 95.0$ Hz), 131.7 (d, *i*-Ar, $^1J_{\text{CP}} = 96.0$ Hz), 131.9 (d, *p*-Ar, $^4J_{\text{CP}} = 3.1$ Hz), 134.1 (*p*-Ar), 144.4 (*i*-Ar), 196.9 (d, C=O, $^3J_{\text{CP}} = 7.2$ Hz). HRMS m/z (+ESI) ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{32}\text{H}_{30}\text{O}_2\text{P}_1\text{Fe}_1$: 533.1333, found: 533.1334.

O2: Similar procedure to O1; dull-orange powder; yield: 90%. m.p. 180°C (decomp.); ^1H NMR (CDCl_3 , 400 MHz): δ 3.50 – 3.58 (m, 1H, - CH), 3.62 (m, 1H, Cp), 3.73 - 3.86 (m, 1H, - CH),

3.90 (s, 1H, Cp), 3.98 (m, 1H, Cp), 4.06 – 4.12 (m, 6H, Cp), 4.52 (m, 1H, -CHPPh₂), 7.31 - 7.39 (m, 3H, - Ar), 7.43 – 7.58 (m, 6H, - Ar), 7.75 – 7.84 (m, 2H, - Ar), 7.86 – 7.94 (m, 2H, - Ar). ¹⁹F{¹H} NMR (CDCl₃, 282.2 MHz): δ -62.99 (s), -58.41 (s). ³¹P{¹H} NMR (CDCl₃, 161.6 MHz): δ 32.5 (s). ¹³C NMR (CDCl₃, 100 MHz): δ 35.7 (d, -CHPPh₂, ¹J_{CP} = 64.6 Hz), 43.9(-CH₂), 67.7 (*m*-Cp), 67.9 (*o*-Cp), 68.4 (*m*-Cp), 68.8 (5Cp), 69.9 (d, *o*-Cp, ³J_{CP} = 1.7 Hz), 85.1 (*i*-Cp), 122.9 (q, CF₃, ¹J_{CF} = 273.2 Hz), 123.1 (q, CF₃, ¹J_{CF} = 273.9 Hz), 125.2(m, *p*-Ar), 127.0 (q, *m*-Ar, ³J_{CF} = 3.9 Hz), 127.3 (q, *m*-Ar, ³J_{CF} = 5.1 Hz), 128.1 (d, 2 *m*-Ar, ³J_{CP} = 11.5 Hz), 128.8 (d, 2 *m*-Ar, ³J_{CP} = 11.3 Hz), 129.7 (d, *i*-Ar, ¹J_{CP} = 97.7 Hz), 130.4 (d, *i*-Ar, ¹J_{CP} = 100.3 Hz), 131.5 (d, 2 *o*-Ar, ²J_{CP} = 9.0 Hz), 132.0 (m, *p*-Ar), 132.3 (d, 2 *o*-Ar, ²J_{CP} = 8.8 Hz), 132.4 (d, *p*-Ar, ⁴J_{CP} = 2.2 Hz), 134.3 (q, 2 *m*-Ar, ²J_{CF} = 33.0 Hz), 141.2 (*i*-Ar), 200.1 (s, C=O). HRMS *m/z* (+ESI) (M + H)⁺ calcd for C₃₃H₂₆O₂F₆P₁Fe₁: 655.0924, found: 655.0927.

O3: Similar procedure to O1; dull-orange powder; yield: 90%; m.p. 178°C(decomp.); ¹H NMR (CDCl₃, 300 MHz): δ 3.54 (s, 1H, Cp), 3.57 - 3.62 (dd, 2H, -CH₂), 3.90 (s, 1H, Cp), 3.97 (s, 4H, Cp), 4.11 (s, 1H, Cp), 4.20 (s, 1H, Cp), 4.29 - 4.33 (m, 1H, -CHPPh₂), 6.50 - 6.52 (m, 1H, - furyl CH), 7.20 (d, 1H, - furyl CH), 7.29 – 7.46 (m, 5H, - Ar), 7.47 – 7.62 (m, 3H, - Ar), 7.79 – 7.92 (m, 2H, - Ar). ³¹P{¹H} NMR (CDCl₃, 161.6 MHz): δ 33.9 (s); ¹³C NMR (CDCl₃, 100 MHz): δ 34.5 (d, -CHPPh₂, ¹J_{CP} = 67.1 Hz), 38.1 (s, -CH₂), 67.2 (*m*-Cp), 68.2 (*m*-Cp), 67.6 (d, *o*-Cp, ³J_{CP} = 1.7 Hz), 68.6 (5Cp), 70.0 (d, *o*-Cp, ³J_{CP} = 2.0 Hz), 85.2 (*i*-Cp), 112.4 (furyl Ar), 117.7 (furyl Ar), 128.0 (d, 2 *m*-Ar, ³J_{CP} = 11.7 Hz), 128.5 (d, 2 *m*-Ar, ³J_{CP} = 11.2 Hz), 131.1 (d, *i*-Ar, ¹J_{CP} = 83.5 Hz), 131.3 (d, *i*-Ar, ¹J_{CP} = 93.2 Hz), 131.4 (d, *o*-Ar, ²J_{CP} = 8.8 Hz), 131.5 (d, 2 *p*-Ar, ²J_{CP} = 3.0 Hz, overlap with *i*-Ar doublet), 131.6 (d, *o*-Ar, ²J_{CP} = 8.8 Hz), 131.8 (d, *p*-Ar, ⁴J_{CP} = 2.9 Hz), 146.7 (furyl Ar), 152.2 (furyl Ar), 186.4 (d, C=O, ³J_{CP} = 7.1 Hz). HRMS *m/z* (+ESI) (M + H)⁺ calcd for C₂₉H₂₆O₃P₁Fe₁: 509.0969, found: 509.0970.

O4: Similar procedure to O1; dull-orange powder; yield: 98%. m.p. 198°C(decomp.); ^1H NMR (CDCl_3 , 400 MHz): δ 3.52 (s, 1H, Cp), 3.62 - 3.71 (m, 2H, $-\text{CH}_2$), 3.90 (s, 1H, Cp), 3.97 (s, 5H, Cp), 4.12 (s, 1H, Cp), 4.22 (s, 1H, Cp), 4.30 - 4.37 (m, 1H, $-\text{CHPPH}_2$), 7.07 - 7.14 (m, 1H, -thienyl CH), 7.28 - 7.46 (m, 6H, - Ar), 7.46 - 7.56 (m, 2H, - Ar), 7.62 (dd, 1H, $^3J_{\text{HH}} = 4.9$ Hz, $^4J_{\text{HH}} = 0.7$ Hz, - thienyl CH), 7.76 (dd, 1H, $^3J_{\text{HH}} = 3.7$ Hz, $^4J_{\text{HH}} = 0.7$ Hz, - thienyl CH), 7.82 - 7.91 (m, 2H, - Ar). $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161.6 MHz): δ 33.5 (s). ^{13}C NMR (CDCl_3 , 100 MHz): δ 34.9 (d, $-\text{CHPPH}_2$, $^1J_{\text{CP}} = 67.3$ Hz), 39.3($-\text{CH}_2$), 67.3 (*m*-Cp), 67.6 (d, *o*-Cp, $^3J_{\text{CP}} = 2.3$ Hz), 68.4 (*m*-Cp), 68.7 (5Cp), 70.2 (d, *o*-Cp, $^3J_{\text{CP}} = 2.1$ Hz), 85.4 (*i*-Cp), 128.1 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 11.7$ Hz), 128.3 (thienyl Ar), 128.7 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 11.4$ Hz), 131.5 (d, 2 *i*-Ar, $^1J_{\text{CP}} = 96.9$ Hz), 131.5 (d, 2 *o*-Ar, $^2J_{\text{CP}} = 8.9$ Hz), 131.6 (d, *p*-Ar, $^4J_{\text{CP}} = 3.1$ Hz), 131.7 (d, 2 *o*-Ar, $^2J_{\text{CP}} = 9.1$ Hz), 131.9 (d, *p*-Ar, $^4J_{\text{CP}} = 2.6$ Hz), 132.4 (thienyl Ar), 134.2 (thienyl Ar), 143.7 (thienyl Ar), 190.4 (d, $\text{C}=\text{O}$, $^3J_{\text{CP}} = 7.3$ Hz). HRMS m/z (+ESI) ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{29}\text{H}_{26}\text{O}_2\text{P}_1\text{Fe}_1\text{S}_1$: 525.0741, found: 525.0746.

O6: Similar procedure to O1; dull-orange oil; yield: 60%; ^1H NMR (CDCl_3 , 400 MHz): δ 2.03 (s, 3H, $-\text{CH}_3$), 3.00 - 3.40 (m, 2H, $-\text{CH}_2$), 3.66 - 3.74 (m, 2H, $-\text{CH}_2$), 3.96 (s, 5H, Cp), 4.12 - 4.15 (m, 1H, Cp), 4.32 - 4.35 (m, 1H, Cp), 4.78 - 4.84 (m, 1H, $-\text{CH}_2$), 3.57 (s, 1H, $-\text{CpH}$), 3.92 (s, 1H, $-\text{CpH}$), 4.00 - 4.30 (m, 8H, $-\text{CpH}$ & $-\text{CHPPH}_2$), 7.28 - 7.39 (m, 2H, - Ar), 7.39 - 7.54 (m, 6H, - Ar), 7.75 - 7.90 (m, 2H, - Ar). $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161.6 MHz): δ 33.1 (s). ^{13}C NMR (CDCl_3 , 100 MHz): δ 1.0 (s, $-\text{Me}$), 30.1 (s, $-\text{CHPPH}_2$), 43.4 (s, $-\text{CH}_2$), 67.3 (*m*-Cp), 67.6 (*o*-Cp), 68.3 (*m*-Cp), 68.5 (5Cp), 69.9 (*o*-Cp), 85.4 (*i*-Cp), 125.2(m, *p*-Ar), 128.1 (m, 2 *m*-Ar), 128.6 (m, 2 *m*-Ar), 128.8, 129.0, 130.9, 129.7, 130.9, 131.6, 131.7, 131.8, 132.3, 141.2 (*i*-Ar), 205.7 (s, $\text{C}=\text{O}$). HRMS m/z (+ESI) ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{29}\text{H}_{26}\text{O}_2\text{P}_1\text{Fe}_1$: 457.1020, found: 457.1019.

O7: HP procedure gave a light purple solution. To the reaction vessel was added non-degassed DCM and left to stir under ambient atmospheric conditions for 24 h. The solvent was then removed under reduced pressure and crude purified on SiO₂; silica gel column chromatography (Hexane/E.A); orange-yellow; yield: 60%. m.p. 149°C; ¹H NMR (CDCl₃, 400 MHz): δ 1.18 (m, 6H, -Me), 1.29 (m, 6H, -Me), 3.73 (s, 1H, Cp), 3.97 – 4.00 (m, 2H, Cp), 4.05 (s, 5H, Cp), 4.07 (s, 1H, Cp), 4.32 (dd, 1H, ³J_{HH} = 3.7 Hz, ²J_{HP} = 20.0 Hz, -CHPh₂), 4.46 (dd, 1H, ³J_{HH} = 3.6 Hz, ³J_{HP} = 14.4 Hz, -CH), 4.95 (sep, 1H, ³J_{HH} = 6.3 Hz, -CH), 5.08 (sep, 1H, ³J_{HH} = 5.9 Hz, -CH), 7.27 - 7.35 (m, 2H, -Ar), 7.37 - 7.55 (m, 6H, -Ar), 7.71 - 7.81 (m, 2H, -Ar). ³¹P{¹H} NMR (CDCl₃, 161.6 MHz): δ 30.5 (s). ¹³C NMR (CDCl₃, 100 MHz): δ 21.5 (-Me), 21.7 (-Me), 21.8 (-Me), 21.8 (-Me), 41.2 (d, -CHPh₂, ¹J_{CP} = 67.1 Hz), 56.0 (d, -CH), 67.7 (-CH), 68.3 (-CH), 68.6 (d, *o*-Cp, ³J_{CP} = 3.0 Hz), 67.0 (5 Cp), 69.3 (*m*-Cp), 70.0 (*m*-Cp), 69.3 (*o*-Cp), 85.0 (*i*-Cp), 127.7 (d, 2 *m*-Ar, ³J_{CP} = 11.7 Hz), 128.3 (d, 2 *m*-Ar, ³J_{CP} = 11.4 Hz), 131.2 (d, *p*-Ar, ⁴J_{CP} = 2.6 Hz), 131.5 (d, *p*-Ar, ⁴J_{CP} = 2.5 Hz), 131.6 (d, *i*-Ar, ¹J_{CP} = 99.7 Hz), 131.9 (d, 2 *o*-Ar, ²J_{CP} = 9.0 Hz), 132.7 (d, 2 *o*-Ar, ²J_{CP} = 8.6 Hz), 134.7 (d, *i*-Ar, ¹J_{CP} = 95.9 Hz), 167.7 (d, C=O, ³J_{CP} = 4.4 Hz), 168.2 (d, C=O, ³J_{CP} = 4.4 Hz). HRMS *m/z* (+ESI) (M + H)⁺ calcd for C₃₂H₃₆O₅P₁Fe₁: 587.1650, found: 587.1652.

S1: HP procedure of the respective enone produced orange-yellow precipitates. The reaction solvent was removed *via* cannula and solids washed with cold hexanes. Thereafter, 1.2 equivalent of Sulphur was added and solids dissolved in 5 mL degassed DCM. The solution was left for 24 h. Thereafter, the solvent was removed under reduced pressure and crude purified on SiO₂; silica gel column chromatography (Hexane/E.A); orange powder; yield: 90%. m.p. 190°C(decomp.); ¹H NMR (CDCl₃, 400 MHz): δ 2.40 (s, 3H, -Me), 3.38 (s, 1H, Cp), 3.61 - 3.80 (m, 2H, -CH₂), 3.85 (s, 1H, Cp), 3.92 (s, 5H, Cp), 4.12 (s, 1H, Cp), 4.33 (s, 1H, Cp), 4.82 (m, 1H, -CHPh₂), 7.22 - 7.24 (m, 2H, -Ar), 7.24 – 7.26 (m, 2H, -Ar), 7.28 – 7.43 (m, 6H, -Ar), 7.59 – 7.67 (m, 2H, -Ar), 7.87 – 7.92 (m, 2H, -Ar), 8.00 – 8.10 (m, 2H, -Ar).

$^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161.6 MHz): δ 53.5 (s). ^{13}C NMR (CDCl_3 , 100 MHz): δ 21.7 (-Me), 35.9 (d, -CHPPH₂, $^1J_{\text{CP}} = 51.7$ Hz), 39.6 (d, -CH₂, $^2J_{\text{CP}} = 4.6$ Hz), 67.1 (*m*-Cp), 68.1 (d, *o*-Cp, $^3J_{\text{CP}} = 1.7$ Hz), 68.2 (*m*-Cp), 68.6 (5Cp), 70.2 (d, *o*-Cp, $^3J_{\text{CP}} = 1.9$ Hz), 85.3 (*i*-Cp), 127.9 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 12.1$ Hz), 128.3(2 *m*-Ar), 128.5 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 11.5$ Hz), 129.4 (2 *o*-Ar), 131.0 (d, *i*-Ar, $^1J_{\text{CP}} = 74.5$ Hz), 131.2 (d, *i*-Ar, $^1J_{\text{CP}} = 79.4$ Hz), 131.3 (d, *p*-Ar, $^4J_{\text{CP}} = 2.9$ Hz), 131.6 (d, *p*-Ar, $^4J_{\text{CP}} = 2.9$ Hz), 132.0(d, 2 *o*-Ar, $^2J_{\text{CP}} = 9.4$ Hz), 132.2 (d, 2 *o*-Ar, $^2J_{\text{CP}} = 9.6$ Hz), 134.0 (*p*-Ar), 144.4 (*i*-Ar), 196.8 (d, C=O, $^3J_{\text{CP}} = 7.9$ Hz). HRMS m/z (+ESI) ($\text{M} + \text{H}$)⁺ calcd for C₃₂H₃₀O₁P₁S₁Fe₁: 549.1104, found: 533.1107.

S2: Similar procedure to S1; orange powder; yield: 90%. m.p. 151°C; ^1H NMR (CDCl_3 , 300 MHz): δ 3.45 – 3.49 (m, 1H, Cp), 3.86 - 3.98 (m, 2H, -CH₂), 3.99 – 4.09 (m, 2H, Cp), 4.11(s, 5H, Cp), 4.79 – 4.87 (m, 1H, -CHPPH₂), 7.03 (s, 1H, - Ar), 7.30 – 7.55 (m, 6H, - Ar), 7.66 – 7.85 (m, 4H, -Ar), 8.08 – 8.19 (m, 2H, - Ar). $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161.6 MHz): δ 53.4 (s). $^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 , 282.2 MHz): δ -62.96 (s), -58.29 (s). $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 121.2 MHz): δ 53.4 (s). ^{13}C NMR (CDCl_3 , 100 MHz): δ 36.7 (d, -CHPPH₂, $^1J_{\text{CP}} = 49.5$ Hz), 44.8 (d, -CH₂, $^2J_{\text{CP}} = 4.1$ Hz), 67.5 (*m*-Cp), 68.3 (*o*-Cp), 68.4 (*m*-Cp), 68.7 (5Cp), 69.9 (*o*-Cp), 85.3 (*i*-Cp), 122.7 (q, CF₃, $^1J_{\text{CF}} = 273.4$ Hz), 122.9 (q, CF₃, $^1J_{\text{CF}} = 273.9$ Hz), 124.7 (m, *p*-Ar), 127.1 (q, *m*-Ar, $^3J_{\text{CF}} = 3.47$ Hz), 127.3 (q, *m*-Ar, $^3J_{\text{CF}} = 4.9$ Hz), 128.0 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 12.0$ Hz), 128.6 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 11.5$ Hz), 129.8 (d, *i*-Ar, $^1J_{\text{CP}} = 79.6$ Hz), 130.1 (q, *m*-Ar, $^2J_{\text{CF}} = 33.4$ Hz), 130.4 (d, *i*-Ar, $^1J_{\text{CP}} = 74.4$ Hz), 131.6 (d, *p*-Ar, $^4J_{\text{CP}} = 2.7$ Hz), 132.1 (d, *p*-Ar, $^4J_{\text{CP}} = 2.6$ Hz), 132.6 (d, 2 *o*-Ar, $^2J_{\text{CP}} = 9.5$ Hz), 134.0 (q, *m*-Ar, $^2J_{\text{CF}} = 33.6$ Hz), 140.7 (*i*-Ar), 200.1 (d, C=O, $^3J_{\text{CP}} = 2.7$ Hz). HRMS m/z (+ESI) ($\text{M} + \text{H}$)⁺ calcd for C₃₃H₂₆O₁P₁S₁Fe₁F₆: 671.0696, found: 671.0693.

S3: Similar procedure to S1; orange powder; yield: 90%. m.p. 169°C; ^1H NMR (CDCl_3 , 400 MHz): δ 3.34 – 3.37 (m, 1H, Cp), 3.58 (dd, 2H, -CH₂, $^3J_{\text{CP}} = 4.98$ Hz, $^2J_{\text{HH}} = 1.98$ Hz), 3.62 (d,

1H, -CH₂, ³J_{CP} = 5.00 Hz), 3.84 - 3.88 (m, 1H, Cp), 3.96 (s, 5H, Cp), 4.12 – 4.15 (m, 1H, Cp), 4.29 - 4.32 (m, 1H, Cp), 4.66 – 4.73 (m, 1H, -CHPPH₂), 6.51 (dd, - furyl CH, ²J_{HH} = 1.52 Hz, ²J_{HH} = 3.52 Hz), 7.23 (d, - furyl CH, ²J_{HH} = 3.60 Hz), 7.28 - 7.35 (m, 2H, - Ar), 7.36 – 7.45 (m, 4H, - Ar), 7.58 (s, 1H, - thienyl CH), 7.61 – 7.69 (m, 2H, -Ar), 8.00 – 8.09 (m, 2H, -Ar). ³¹P{¹H} NMR (CDCl₃, 161.6 MHz): δ 52.8 (s). ¹³C NMR (CDCl₃, 100 MHz): δ 36.3 (d, - CHPPH₂, ¹J_{CP} = 51.4 Hz), 39.3 (d, -CH₂, ²J_{CP} = 4.6 Hz), 67.3 (*m*-Cp), 68.3 (*m*-Cp, *o*-Cp), 68.8 (5Cp), 70.1 (d, *o*-Cp, ³J_{CP} = 1.6 Hz), 85.2 (*i*-Cp), 112.6 (furyl Ar), 118.1 (furyl Ar), 128.1 (d, 2 *m*-Ar, ³J_{CP} = 11.8 Hz), 128.6 (d, 2 *m*-Ar, ³J_{CP} = 11.6 Hz), 131.0 (d, *i*-Ar, ¹J_{CP} = 74.5 Hz), 131.1 (d, *i*-Ar, ¹J_{CP} = 79.2 Hz), 131.5 (d, 2 *p*-Ar, ²J_{CP} = 2.8 Hz, overlap with *i*-Ar doublet), 131.8 (d, *p*-Ar, ⁴J_{CP} = 2.8 Hz), 132.2 (d, *o*-Ar, ²J_{CP} = 9.5 Hz), 132.4 (d, *o*-Ar, ²J_{CP} = 9.8 Hz), 146.9 (furyl Ar), 152.4 (furyl Ar), 186.6 (d, C=O, ³J_{CP} = 7.9 Hz). HRMS m/z (+ESI) (M + H)⁺ calcd for C₂₉H₂₆O₂P₁S₁Fe₁: 525.0741, found: 525.0731.

S4: Similar procedure to S1; orange powder; yield: 90%. m.p. 202°C; ¹H NMR (CDCl₃, 400 MHz): δ 3.35 (s, 1H, Cp), 3.58 - 3.76 (m, 2H, -CH₂), 3.87 (s, 1H, Cp), 3.97 (s, 5H, Cp), 4.14 (s, 1H, Cp), 4.31 (s, 1H, Cp), 4.68 – 4.76 (m, 1H, -CHPPH₂), 7.08 - 7.13 (m, 1H, - thienyl CH), 7.28 – 7.45 (m, 6H, - Ar), 7.60 – 7.69 (m, 3H, - 2Ar & - thienyl CH), 7.80 (m, 1H, - thienyl CH), 8.00 – 8.10 (m, 2H, - Ar). ³¹P{¹H} NMR (CDCl₃, 161.6 MHz): δ 53.7 (s). ¹³C NMR (CDCl₃, 100 MHz): δ 36.7 (d, -CHPPH₂, ¹J_{CP} = 51.3 Hz), 40.1 (d, -CH₂, ²J_{CP} = 4.1 Hz), 67.2 (*m*-Cp), 68.1 (d, *o*-Cp, ³J_{CP} = 1.4 Hz), 68.2 (*m*-Cp), 68.7 (5Cp), 70.1 (d, *o*-Cp, ³J_{CP} = 1.7 Hz), 85.1 (*i*-Cp), 128.0 (d, 2 *m*-Ar, ³J_{CP} = 12.1 Hz), 128.3 (thienyl Ar), 128.5 (d, 2 *m*-Ar, ³J_{CP} = 11.5 Hz), 130.8 (d, 2 *i*-Ar, ¹J_{CP} = 74.4 Hz), 131.5 (d, 2 *i*-Ar, ¹J_{CP} = 80.0 Hz), 131.4 (d, *p*-Ar, ⁴J_{CP} = 3.2 Hz), 131.7 (d, *p*-Ar, ⁴J_{CP} = 2.8 Hz), 131.2 (d, 2 *o*-Ar, ²J_{CP} = 8.9 Hz), 131.3 (d, 2 *o*-Ar, ²J_{CP} = 10.0 Hz), 132.6 (thienyl Ar), 134.4 (thienyl Ar), 143.7 (thienyl Ar), 190.4 (d, C=O, ³J_{CP} = 7.8 Hz). HRMS m/z (+ESI) (M + H)⁺ calcd for C₂₉H₂₆O₁P₁S₂Fe₁: 541.0512, found: 541.0512.

S5: Similar procedure to S1; orange powder; yield: 90%. m.p. 148°C(decomp.); ^1H NMR (CDCl_3 , 400 MHz): δ 3.39 – 3.42 (m, 1H, Cp), 3.70 – 3.81 (m, 2H, $-\text{CH}_2$), 3.87 – 3.90 (m, 1H, Cp), 3.98 (s, 5H, Cp), 4.14 – 4.17 (m, 1H, Cp), 4.33 – 4.36 (m, 1H, Cp), 4.71 – 4.78 (m, 1H, $-\text{CHPhPh}_2$), 7.28 – 7.38 (m, 6H, - Ar), 7.39 – 7.45 (m, 1H, - Ar), 7.46 – 7.52 (m, 1H, - Ar), 7.56 – 7.62 (m, 2H, - Ar), 7.63 – 7.72 (m, 3H, - 2Ar & - thienyl CH), 8.00 – 8.09 (m, 2H, - Ar). $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161.6 MHz): δ 52.9 (s). ^{13}C NMR (CDCl_3 , 100 MHz): δ 36.3 (d, $-\text{CHPhPh}_2$, $^1J_{\text{CP}} = 51.0$ Hz), 39.3 (d, $-\text{CH}_2$, $^2J_{\text{CP}} = 4.4$ Hz), 69.2 (*m*-Cp), 70.1 (*m*-Cp, *o*-Cp), 71.0(5Cp), 72.1 (*o*-Cp), 87.1 (*i*-Cp), 112.6 (furyl Ar), 113.9 (furyl Ar), 123.5 (Ar), 124.1 (Ar), 126.9 (Ar), 128.2 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 12.0$ Hz), 128.6 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 11.3$ Hz), 128.7 (Ar), 130.9 (d, *i*-Ar, $^1J_{\text{CP}} = 74.5$ Hz), 131.0 (d, *i*-Ar, $^1J_{\text{CP}} = 79.9$ Hz), 131.6 (d, *p*-Ar, $^2J_{\text{CP}} = 1.5$ Hz), 131.7 (d, *p*-Ar, $^2J_{\text{CP}} = 1.6$ Hz), 132.1 (d, *o*-Ar, $^2J_{\text{CP}} = 9.3$ Hz), 132.5 (d, *o*-Ar, $^2J_{\text{CP}} = 9.7$ Hz), 152.0 (furyl Ar), 155.8 (furyl Ar), 188.1 (d, $\text{C}=\text{O}$, $^3J_{\text{CP}} = 7.2$ Hz). HRMS m/z (+ESI) ($\text{M} + \text{H}^+$) calcd for $\text{C}_{33}\text{H}_{28}\text{O}_2\text{P}_1\text{S}_1\text{Fe}_1$: 575.0897, found: 575.0897.

S7: HP procedure gave a light purple solution. 1.2 equivalent of sulfur was added to the crude and washed with degassed DCM. Thereafter, the solution was left to stir for 24 h. The solvent was then removed under reduced pressure and crude purified on SiO_2 ; silica gel column chromatography (Hexane/E.A); orange powder; yield: 60%. m.p. 145°C; ^1H NMR (CDCl_3 , 400 MHz): δ 1.11 (d, 3H, $^3J_{\text{HH}} = 6.2$ Hz, $-\text{Me}$), 1.20 (d, 3H, $^3J_{\text{HH}} = 6.3$ Hz, $-\text{Me}$), 1.27 (d, 3H, $^3J_{\text{HH}} = 6.2$ Hz, $-\text{Me}$), 1.31 (d, 3H, $^3J_{\text{HH}} = 6.3$ Hz, $-\text{Me}$), 3.42 (s, 1H, Cp), 3.90 (s, 1H, Cp), 4.04 (s, 5H, Cp), 4.11 (s, 1H, Cp), 4.19 (s, 1H, Cp), 4.50 (dd, 1H, $^3J_{\text{HH}} = 3.6$ Hz, $^2J_{\text{HP}} = 18.8$ Hz, $-\text{CHPhPh}_2$), 4.79 (dd, 1H, $^3J_{\text{HH}} = 3.6$ Hz, $^3J_{\text{HP}} = 12.8$ Hz, $-\text{CH}$), 4.87 (sep, 1H, $^3J_{\text{HH}} = 6.3$ Hz, $-\text{CH}$), 5.10 (sep, 1H, $^3J_{\text{HH}} = 6.3$ Hz, $-\text{CH}$), 7.27 – 7.32 (m, 2H, - Ar), 7.35 – 7.49 (m, 4H, - Ar), 7.55 – 7.64 (m, 2H, - Ar), 7.88 – 7.97 (m, 2H, - Ar). $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161.6 MHz): δ 47.9

(s). ^{13}C NMR (CDCl_3 , 100 MHz): δ 21.5 (-Me), 21.7 (2 -Me), 21.8 (-Me), 42.3 (d, -CHPh₂, $^1J_{\text{CP}} = 50.0$ Hz), 56.4 (d, -CH, $^2J_{\text{CP}} = 2.2$ Hz), 67.3 (-CH), 67.4 (-CH), 67.0 (*o*-Cp & 5 Cp), 69.5 (*m*-Cp), 70.1 (*m*-Cp), 70.7 (d, *o*-Cp, $^3J_{\text{CP}} = 1.7$ Hz), 86.2 (*i*-Cp), 127.6 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 12.0$ Hz), 128.3 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 12.0$ Hz), 131.0 (d, *p*-Ar, $^4J_{\text{CP}} = 2.9$ Hz), 131.1 (d, *p*-Ar, $^4J_{\text{CP}} = 2.9$ Hz), 131.1 (d, *i*-Ar, $^1J_{\text{CP}} = 80.9$ Hz), 132.0 (d, 2 *o*-Ar, $^2J_{\text{CP}} = 9.8$ Hz), 133.2 (d, 2 *o*-Ar, $^2J_{\text{CP}} = 9.5$ Hz), 134.6 (d, *i*-Ar, $^1J_{\text{CP}} = 78.5$ Hz), 167.1 (d, C=O, $^3J_{\text{CP}} = 5.6$ Hz), 168.5 (d, C=O, $^3J_{\text{CP}} = 4.9$ Hz). HRMS m/z (+ESI) ($\text{M} + \text{H}$)⁺ calcd for $\text{C}_{32}\text{H}_{36}\text{O}_4\text{P}_1\text{S}_1\text{Fe}_1$: 603.1421, found: 603.1423.

S8: Similar procedure to S7; orange powder; yield: 80%. m.p. 164°C; ^1H NMR (CDCl_3 , 300 MHz): δ 3.36 – 3.42 (m, 1H, Cp), 3.45 (s, 3H, -CH₃), 3.81 (s, 3H, -CH₃), 3.91 – 3.96 (m, 1H, Cp), 4.06 (s, 5H, Cp), 4.09 – 4.15 (m, 1H, Cp), 4.64 (dd, 1H, -CHPh₂, $^2J_{\text{CP}} = 19.8$ Hz, $^3J_{\text{HH}} = 3.54$ Hz), 4.79 (dd, 1H, -CH<, $^2J_{\text{CP}} = 13.5$ Hz, $^3J_{\text{HH}} = 3.5$ Hz), 7.27 – 7.34 (m, 2H, -Ar), 7.35 – 7.51 (m, 4H), 7.52 – 7.63 (m, 2H, Ar), 7.81 – 7.95 (m, 2H, Ar). $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161.6 MHz): δ 47.3 (s). ^{13}C NMR (CDCl_3 , 100 MHz): δ 43.6 (d, -CHPh₂, $^1J_{\text{CP}} = 49.0$ Hz), 52.4 (s, -OMe), 53.2 (s, -OMe), 55.4 (s, -CH), 68.4 (s, *o*-Cp), 68.4 (s, *m*-Cp), 68.5 (s, 5 Cp), 70.0 (*m*-Cp), 70.5 (s, *o*-Cp), 85.6 (*i*-Cp), 127.6 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 12.0$ Hz), 128.3 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 12.0$ Hz), 131.1 (d, *o*-Ar, $^3J_{\text{CP}} = 8.0$ Hz), 131.7 (d, *o*-Ar, $^3J_{\text{CP}} = 10$ Hz), 133.2 (d, *o*-Ar, $^3J_{\text{CP}} = 10$ Hz), 133.9 (s, Ar), 134.7 (s, Ar), 167.9 (s, C=O), 169.1 (s, C=O). HRMS m/z (+ESI) ($\text{M} + \text{H}$)⁺ calcd for $\text{C}_{28}\text{H}_{28}\text{O}_4\text{P}_1\text{S}_1\text{Fe}_1$: 547.0795, found: 547.0792.

G1: HP procedure of the respective enone produced orange-yellow precipitates. The reaction solvent was removed *via* cannula and solids washed with cold hexanes. Thereafter, 1 equivalent of ClAu.SMe₂ was added and solids dissolved in 5 mL degassed DCM. The solution was left for 24 h in absence of light. Thereafter, the solvent was removed under reduced pressure and crude purified on SiO₂; silica gel column chromatography (Hexane/E.A); brownish-orange

powder; yield: 90%. m.p. 180°C(decomp.); ^1H NMR (CDCl_3 , 400 MHz): δ 2.42 (s, 3H, - *Me*), 3.39 (s, 1H, Cp), 3.36 - 3.49 (m, 1H, - *CH*), 3.88 - 4.00 (m, 7H, - *CH* & 6 *Cp*), 4.19 (s, 1H, Cp), 4.36 (s, Cp), 4.65 – 4.74 (m, 1H, -*CHPPH*₂), 7.27 - 7.35 (m, 4H, - Ar), 7.35 – 7.50 (m, 6H, - Ar), 7.80 – 7.92 (m, 4H, - Ar). $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161.6 MHz): δ 48.9 (s). ^{13}C NMR (CDCl_3 , 100 MHz): δ 21.9 (-*Me*), 34.6 (d, -*CHPPH*₂, $^1J_{\text{CP}} = 36.2$ Hz), 41.7(d, -*CH*₂, $^2J_{\text{CP}} = 12.0$ Hz), 67.7 (d, *o*-Cp, $^3J_{\text{CP}} = 3.0$ Hz), 67.8 (*m*-Cp), 68.8 (5 Cp), 69.2 (*m*-Cp), 70.4 (d, *o*-Cp), 86.9 (*i*-Cp), 128.1 (d, *i*-Ar, $^1J_{\text{CP}} = 80.1$ Hz), 128.4 (2 *m*-Ar), 128.6 (d, *i*-Ar, $^1J_{\text{CP}} = 86.1$ Hz), 128.7 (d, 2 *o*-Ar, $^2J_{\text{CP}} = 11.6$ Hz), 129.3 (d, 2 *o*-Ar, $^2J_{\text{CP}} = 11.2$ Hz), 129.7 (2 *o*-Ar), 132.0 (d, *p*-Ar, $^4J_{\text{CP}} = 2.5$ Hz), 132.3 (d, *p*-Ar, $^4J_{\text{CP}} = 2.4$ Hz), 132.3 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 11.5$ Hz), 133.7 (*p*-Ar), 134.3 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 13.0$ Hz), 134.6 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 13.0$ Hz), 145.0 (*i*-Ar), 196.0 (d, C=O, $^3J_{\text{CP}} = 9.1$ Hz). HRMS m/z (+ESI) ($\text{M} + \text{H}$)⁺ calcd for $\text{C}_{32}\text{H}_{30}\text{O}_1\text{P}_1^{35}\text{Cl}_1\text{Fe}_1\text{Au}_1$: 749.0738, found: 749.0739.

G2: Similar procedure to G1; brownish-orange powder; yield: 89%. m.p. 178°C(decomp.); ^1H NMR (CDCl_3 , 300 MHz): 3.45 (m, 1H, Cp), 3.53 - 3.92 (m, 2H, -*CH*₂), 4.01 (m, 1H, Cp), 4.12 (m, 5H, Cp), 4.21 (m, 2H, Cp), 4.70 (m, 1H, -*CHPPH*₂), 6.49 (s, 1H, - Ar), 7.34 – 7.69 (m, 8H, - Ar), 7.74 – 7.90 (m, 2H, - Ar), 7.92 – 8.06 (m, 2H, - Ar). $^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 , 282.2 MHz): δ -62.83 (s), -58.25 (s). $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161.6 MHz): δ 52.5 (s). ^{13}C NMR (CDCl_3 , 100 MHz): δ 32.7 (d, -*CHPPH*₂, $^1J_{\text{CP}} = 34.6$ Hz), 47.2(d, -*CH*₂, $^2J_{\text{CP}} = 12.7$ Hz), 67.6 (d, *o*-Cp, $^3J_{\text{CP}} = 4.4$ Hz), 68.1 (*m*-Cp), 68.8 (5Cp), 69.4 (*m*-Cp), 69.8 (d, *o*-Cp, $^3J_{\text{CP}} = 1.9$ Hz), 86.8 (d, *i*-Cp, $^2J_{\text{CP}} = 7.3$ Hz), 122.7 (q, CF_3 , $^1J_{\text{CF}} = 273.4$ Hz), 122.9 (q, CF_3 , $^1J_{\text{CF}} = 274.2$ Hz), 123.9(m, *p*-Ar), 127.5 (d, *i*-Ar, $^1J_{\text{CP}} = 74.3$ Hz), 127.6 (m, *m*-Ar), 127.8 (m, *m*-Ar), 128.1 (d, *i*-Ar, $^1J_{\text{CP}} = 81.4$ Hz), 128.9 (d, 2 *o*-Ar, $^2J_{\text{CP}} = 11.8$ Hz), 129.6 (d, 2 *o*-Ar, $^2J_{\text{CP}} = 11.1$ Hz), 130.2 (q, *m*-Ar, $^2J_{\text{CF}} = 32.8$ Hz), 132.4 (d, *p*-Ar, $^4J_{\text{CP}} = 2.5$ Hz), 133.0 (d, *p*-Ar, $^4J_{\text{CP}} = 2.2$ Hz), 134.4 (q, *m*-Ar, $^2J_{\text{CF}} = 33.0$ Hz), 134.6 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 13.3$ Hz), 135.2 (d, 2 *m*-Ar, $^3J_{\text{CP}} = 13.8$ Hz), 140.3 (s,

i-Ar), 141.2 (*i*-Ar), 199.2 (d, C=O, $^3J_{CP} = 4.6$ Hz). HRMS m/z (+ESI) (M + H)⁺ calcd for C₃₃H₂₆O₁P₁³⁵Cl₁Fe₁Au₁F₆: 871.0329, found: 871.0333.

G3: Similar procedure to G1; brownish-orange powder; yield: 95%. m.p. 119°C(decomp.); ¹H NMR (CDCl₃, 400 MHz): δ 3.30 - 3.48 (m, 2H, Cp & CH), 3.74 - 3.88 (m, 1H, -CH), 3.95 (m, 1H, Cp), 3.98 (s, 5H, Cp), 4.21 (s, 1H, Cp), 4.36 (s, 1H, Cp), 4.53 – 4.64 (m, 1H, -CHPh₂), 6.56 (m, 1H, -thienyl CH), 7.25 (m, 1H, -thienyl CH), 7.30 – 7.54 (m, 8H, -Ar), 7.46 – 7.56 (m, 2H, -Ar), 7.63 (m, 1H, -thienyl CH), 7.83 – 7.92 (m, 2H, -Ar). ³¹P{¹H} NMR (CDCl₃, 161.6 MHz): δ 49.0 (s). ¹³C NMR (CDCl₃, 100 MHz): δ 32.9 (d, -CHPh₂, $^1J_{CP} = 35.6$ Hz), 41.3 (d, -CH₂, $^2J_{CP} = 11.9$ Hz), 67.6 (d, *o*-Cp, $^3J_{CP} = 4.4$ Hz), 67.8 (*m*-Cp), 68.3 (5Cp), 69.2 (*m*-Cp), 70.1 (d, *o*-Cp, $^3J_{CP} = 1.9$ Hz), 86.6 (d, *i*-Cp, $^2J_{CP} = 6.9$ Hz), 112.8 (furyl Ar), 118.1 (furyl Ar), 127.8 (d, *i*-Ar, $^1J_{CP} = 72.5$ Hz), 128.4 (d, *i*-Ar, $^1J_{CP} = 78.6$ Hz), 128.7 (d, 2 *o*-Ar, $^3J_{CP} = 11.6$ Hz), 129.2 (d, 2 *o*-Ar, $^3J_{CP} = 11.2$ Hz), 132.1 (d, *p*-Ar, $^4J_{CP} = 2.7$ Hz), 132.3 (d, *p*-Ar, $^4J_{CP} = 2.6$ Hz), 134.4 (d, 2 *m*-Ar, $^2J_{CP} = 13.1$ Hz), 134.6 (d, 2 *m*-Ar, $^2J_{CP} = 13.2$ Hz), 147.1 (furyl Ar), 152.1 (furyl Ar), 185.6 (d, C=O, $^3J_{CP} = 8.9$ Hz). HRMS m/z (+ESI) (M + H)⁺ calcd for C₂₉H₂₆O₂P₁³⁵Cl₁Fe₁Au₁: 725.0374, found: 725.0370.

DS1: A Schlenk tube was charged with racemic catalyst (1.95 mg, 4 x 10⁻³ mmol), diarylphosphine (0.02 mmol) and anhydrous MeOH (1 ml). The clear yellow solution was further stirred at -60 °C for 10 minutes before the racemic ferrocenyl enone (0.04 mmol) in 1 ml of anhydrous MeOH was added. The resulting dark purple solution was stirred for 10 minutes followed by dropwise addition of NEt₃ (2.03 mg, 2.79 μL, 0.02 mmol) in anhydrous MeOH (0.5 ml). The resulting solution was stirred for 24 hours. Following that, sulphur (1.92 mg, 0.06 mmol) in degassed DCM (1 ml) was administered. The reaction mixture was then warmed to RT and stirred for another hour. The crude was then concentrated and purified via silica gel column chromatography (DCM: EA; 10: 1); Yellow oil; yield: 50%. ¹H NMR (CDCl₃,

500 MHz): δ 1.31 (m, 1H, -CH₂OH), 2.39 (s, 3H, -ArCH₃), 3.55 - 3.90 (m, 4H, -CH₂OH and -CH(PPh₂)CH₂), 3.91 (s, 5H, -Cp), 4.06 (m, 1H, -Cp), 4.25 (m, 1H, -Cp), 4.71 (m, 1H, -Cp), 4.93 (m, 1H, -CHPPh₂), 7.17 - 7.50 (m, 10H, -Ar), 7.92 (d, 2H, ³J = 8.5 Hz, -Ar), 8.06 - 8.10 (m, 2H, -Ar). ¹³C NMR (CDCl₃, 100 MHz): δ 21.7 (*p*-tol Ph -CH₃), 32.5 (d, -CHPPh₂, ¹J_{CP} = 53.0 Hz), 41.9 (d, -CH(PPh₂)CH₂C=O, ³J_{CP} = 5.0 Hz), 58.8 (-CH₂OH), 67.7 (*m*-Cp), 67.8 (*o*-Cp), 68.4 (*m*-Cp), 68.8 (5-Cp), 85.6 (*i*-Cp), 88.8 (*i*-Cp), 127.9 (Ar), 128.0 (Ar), 128.3 (Ar), 128.7 (Ar), 128.8 (Ar), 129.2 (Ar), 129.4 (Ar), 129.5 (Ar), 129.9 (Ar), 131.3 (Ar), 131.4 (Ar), 131.8 (Ar), 131.9 (Ar), 132.0 (Ar), 132.5 (Ar), 132.6 (Ar), 132.7 (Ar), 133.6 (Ar), 144.6 (Ar-*p*-tol), 196.9 (C=O). ³¹P{¹H} NMR (CDCl₃, 161.6 MHz): δ 54.4 (major diastereomer), 52.5 (minor diastereomer). d.r (95:5). HRMS (+ESI) calcd for C₃₃H₃₂O₂P₁S₁Fe₁ [M + H]⁺ 579.1210, found 579.1200.

DS3: Similar procedure to DS1; yellow oil; yield: 50%. Bright yellow oil. ¹H NMR (CDCl₃, 500 MHz): 1.22 (m, 1H, -CH₂OH), 3.46 - 3.80 (m, 4H, -CH₂OH and -CH(PPh₂)CH₂), 3.96 (s, 5H, -Cp), 4.08 (m, 1H, -Cp), 4.26 (m, 1H, -Cp), 4.66 (m, 1H, -Cp), 4.84 (m, 1H, -CHPPh₂), 6.52 - 6.52 (m, 1H, -Ar), 7.20 - 8.10 (m, 12H, -Ar). ¹³C NMR (CDCl₃, 125): δ 32.5 (d, -CHPPh₂, ¹J_{CP} = 52.5 Hz), 41.5 (d, -CH₂, ²J_{CP} = 7.5 Hz), 58.7 (-CH₂OH), 60.4 (*m*-Cp), 67.1 (*o*-Cp), 67.7 (*m*-Cp), 69.0 (5-Cp), 85.5 (*i*-Cp), 88.5 (d, *i*-Cp, ²J_{CP} = 1.3 Hz), 112.5 (furyl-CH), 117.9 (furyl-CH), 127.9 (Ar), 128.0 (Ar), 128.1 (Ar), 128.3 (Ar), 128.4 (Ar), 128.6 (Ar), 128.7 (Ar), 128.9 (Ar), 129.5 (Ar), 131.4 (Ar), 131.42 (Ar), 131.8 (Ar), 131.9 (Ar), 132.0 (Ar), 132.1 (Ar), 132.2, 132.5 (Ar), 132.6 (Ar), 132.7 (Ar), 146.8 (furyl-Ar), 152.1 (furyl-Ar), 186.3 (d, C=O, ³J_{CP} = 8.9 Hz). ³¹P{¹H} NMR (CDCl₃, 161.6 MHz): δ 54.1 (major diastereomer). HRMS (+ESI) calcd for C₃₀H₂₈O₃P₁S₁Fe₁ [M + H]⁺ 555.0846, found 555.0848.

DS4: Similar procedure to DS1; yellow oil; yield: 50%. ¹H NMR (CDCl₃, 500 MHz): δ 1.19 (m, 1H, -CH₂OH), 3.50 - 3.82 (m, 4H, -CH₂OH and -CH(PPh₂)CH₂), 4.00 (s, 5H, -Cp), 4.06

(m, 1H, -Cp), 4.26 (m, 1H, -Cp), 4.68 (m, 1H, -Cp), 4.87 (m, 1H, -CHPPh₂), 7.09 - 8.09 (m, 13H, -Ar). ¹³C NMR (CDCl₃, 100 MHz): δ 33.0 (d, -CHPPh₂, ¹J_{CP} = 69.0 Hz), 42.3 (d, -CH₂, ²J_{CP} = 7.5 Hz), 60.4 (*m*-Cp), 67.7 (*o*-Cp), 68.4 (*m*-Cp), 69.0 (5-Cp), 85.5 (*i*-Cp), 88.6 (d, *i*-Cp, ²J_{CP} = 2.0 Hz), 128.0 (thienyl Ar), 128.3 (thienyl Ar), 128.6 (Ar), 128.7 (Ar), 128.8 (Ar), 129.7 (Ar), 131.4 (Ar), 131.6 (Ar), 131.9 (Ar), 132.0 (Ar), 132.1 (Ar), 132.5 (Ar), 132.6 (Ar), 132.7 (Ar), 134.4 (thienyl Ar), 143.3 (thienyl Ar), 190.1 (d, C=O, ³J_{CP} = 14.0 Hz). ³¹P{¹H} NMR (CDCl₃, 161.6 MHz): δ 54.1 (major diastereomer), δ 52.0 (minor diastereomer). (Diastereomeric ratio 96:4). HRMS (+ESI) calcd for C₃₀H₂₈O₂P₁S₂Fe₁ [M + H]⁺ 571.0618, found 571.0607.

5.5.1 Materials & Methods for Anti-tumour Studies:

Patient-derived hematolymphoid cell lines and culture. We used four different types of CTCL cell lines – 1) HuT78, derived from the peripheral blood of a 53 years old Caucasian male suffering from Sézary syndrome; 2) MyLa, derived from a patient suffering from non-Hodgkin CTCL; 3) MJ, derived from a plaque biopsy of a 50 years old Caucasian male suffering from mycosis fungoides; 4) HH, derived from a tumour nodule of a 61 years old Caucasian male suffering from aggressive mycosis fungoides. HuT78 and HH cells were cultured in Gibco® RPMI-1640 supplemented with 10% fetal bovine serum. MJ cells were cultured in Gibco® IMDM supplemented with 20% fetal bovine serum. MyLa cells were cultured in Gibco® RPMI-1640 supplemented with 10% human serum and 4 ng.mL⁻¹ each of IL-2 and IL-4. Gibco® Penicillin-Streptomycin (100 U.mL⁻¹) was added to all the culture media.

MTS-based cell viability assay. The cytotoxic effect of compounds on hematolymphoid cells was determined using CellTiter 96® AQueous One Solution Cell Proliferation Assay kit according to manufacturer's instructions (Promega Corporation, Madison, WI, USA). Compounds were diluted in dimethyl sulfoxide to obtain 20 mM stock solutions. Appropriate aliquots of these stock solutions were further diluted in the cell culture medium to obtain final working concentrations. CTCL cells (HuT78, MyLa, MJ and HH) were seeded at 5×10⁴ cells/well in 96-well tissue culture plates (Nunc). Cells were treated with the various compounds at concentrations ranging from 1 to 100 µM for 24 h in triplicates. After the treatment period, cells were incubated with 20 µL MTS reagent (provided with the assay kit) for 2 h at 37°C. Absorbance was recorded at 490 nm using a microplate reader (BioTek) and IC₅₀ values for each compound were determined using GraphPad Prism (GraphPad Software Inc., La Jolla, CA, USA).

Flow-cytometric analysis for cell cycle and apoptosis. For cell cycle analysis, hematolymphoid cells after treatment (as indicated in the corresponding figure legends) were fixed with 70% ethanol and then stained with 50 $\mu\text{g.mL}^{-1}$ propidium iodide (PI) containing 0.25 mg.mL^{-1} RNaseA at room temperature for 30 min. For apoptosis analysis, treated cells were washed with ice-cold phosphate-buffered saline and incubated with a combination of 5 μL each of FITC-Annexin-V and PI (Apoptosis detection kit, Thermo Fisher Scientific, USA) at room temperature in the dark for 15 min. Flow-cytometry analysis was performed to determine cell cycle distribution and apoptosis using a BD FACSCalibreTM flow-cytometer (BD Biosciences).

– **Figure 7.**

Figure 7. G3 Induces apoptosis in human hematolymphoid cells. Flow-cytometry analysis of HuT78 (A), MJ (B), and MyLa (C) cells treated with **G3** IC₅₀ for 24 hr. Representative figures showing population of viable (Q3, Annexin V⁻/PI⁻), early apoptotic (Q4, Annexin V⁺/PI⁻), late apoptotic (Q2, Annexin V⁺/PI⁺) and necrotic (Q1, Annexin V⁻/PI⁺) cells. Bar chart showing increased proportion of early and late apoptotic cells due to **G3** treatment (mean $\pm$ SEM of three independent experiments, *P<0.05, **P<0.01).

Western-immunoblot analysis. Following treatment as described in '*Flow-cytometric analysis for cell cycle and apoptosis*', cells were washed with ice-cold phosphate-buffered saline and lysed in the lysis buffer as described.³⁴ Equal amounts of cell lysates (20 µg each, as determined by Bio-Rad protein estimation kit) were resolved on SDS-PAGE gel and subsequently transferred onto the polyvinylidene difluoride (PVDF) membrane. After blocking in 5% bovine serum albumin for 1 h at room temperature, membranes were washed three times in tris-buffered saline containing Tween 20. The membranes were then incubated overnight at 4°C with primary antibodies (diluted in 5% bovine serum albumin in tris-buffered saline-Tween 20 buffer) with gentle rocking. After three washes in tris-buffered saline-Tween 20, membranes were incubated with horseradish peroxidase-conjugated secondary antibodies for 2 h at room temperature. Primary antibodies: cleaved PARP, cleaved caspase-3 (Cell Signaling Technology) and β -actin (Santa Cruz). Secondary antibodies: horseradish peroxidase-conjugated anti-rabbit and anti-mouse IgG (Cell Signaling Technology). The immunoreactive bands on PVDF membrane were reacted to the ECL detection reagents and visualised by exposure to X-ray films (Kodak, Rochester, NY, USA). Densitometric analysis of the blots was performed by ImageJ software. – **Figure 8.**

Figure 8. G3 induces apoptosis through intrinsic caspase-3/PARP-1 pathway. Western immunoblots showing the expression levels of cleaved PARP-1 and cleaved caspase-3 in HuT78 (A), MyLa (B) and MJ (C) cells treated with DMSO (control) or G3 IC₅₀ for 24 h. Cells were treated with SAHA as a positive control. β -actin served as a loading control. Graph shows densitometry values of cleaved PARP-1 and caspase-3. Data represents at least three independent experiments; *P<0.05.

Cell cycle distribution analysis. G3-treated CTCL cells were stained with PI and percentages of G0/G1, S, G2/M cell population analyzed using flow-cytometry. – **Figure 9.**

Figure 9. G3 inhibits STAT3 expression and phosphorylation in human hematolymphoid cells. Western immunoblots showing the expression levels of Y705 phosphorylated STAT3 (pSTAT3) and total STAT3 protein in HuT78 (A, B), MyLa (C) and MJ (D) cells treated with DMSO (control) or G3 IC₅₀ for 24 h. Cells were treated with SAHA as a positive control. Blots were re-probed with GAPDH as a loading control. Graph shows densitometry values of pSTAT3 and STAT3. Data represents at least three independent experiments; *P<0.05.

Statistical analysis. Where applicable, all the data were expressed as mean $\pm$ SEM. GraphPad prism 4.0 software (GraphPad software) was used for statistical analysis. Student's t-test was performed and used to compare the difference between variables and $p < 0.05$ was considered statistically significant.

5.5.2 Material & Methods for Antimalarial studies :

Blood collection and parasite culture. To remove the buffy coat, the blood was transferred to EDTA tubes followed by centrifugation at 600 g for 10 minutes thrice. Blood is always stored at 50% hematocrit in Malaria Culture Medium (MCM), which is prepared by supplementing RPMI-1640 (Sigma-Aldrich) with AlbuMAX (ThermoFisher Scientific), sodium bicarbonate (Sigma-Aldrich), hypoxanthine (Sigma-Aldrich) and gentamycin (Gibco).³⁵

3D7 strain of *P. falciparum* parasites were used for all experiments, unless stated otherwise and were cultured in O⁺ erythrocytes at 2.5% hematocrit in MCM under standard conditions as stated previously.³⁶ Chloroquine resistant K1 strain parasites were obtained from MR4. Tight synchronization of parasites (window of 3 h) was achieved by enriching late stage schizonts (46-48 hpi) through magnetic-activated cell sorting (MACS, miltenyi Biotec), incubating them with fresh RBCs and followed by sorbitol (Sigma-Aldrich) treatment (3 hours later) to obtain healthy rings population parasites (0 -3 hpi).³⁷

Intracellular growth inhibition assays. Tightly synchronized trophozoite stage parasites (24 -26 hpi) at 1% parasitemia were incubated with 1 in 2 serial diluted panel of drugs for 52 hours until mid-stage trophozoites (28-30 hpi) appear in the DMSO treated parasites. Samples were fixed with 0.1% glutaraldehyde (Sigma-Aldrich) overnight followed by flow cytometry analysis using an Accuri C6 flow cytometer (BD biosciences, Singapore). Antimalarials such as chloroquine were used as positive controls while 0.03% DMSO - treated parasites (vehicle alone) served as negative controls.

Samples fixed in 0.1 glutaraldehyde were washed with PBS, permeabilized with 0.25% triton X 100 in PBS for 10 minutes at room temperature and washed with PBS. Samples were then stained with Hoechst 33342 (ThermoFisher Scientific) for 30 minutes in dark. All flow

cytometry analyses were done in Becton Dickinson Accuri C6 flow cytometer in a 96 well format, wherein a minimum of 100,000 events was recorded for each sample. The half-maximal inhibitory concentration (IC₅₀) was determined for each drug with GraphPad Prism (version 7, GraphPad software) using the recommended nonlinear regression of a log(inhibitor)-versus-response curve.³⁵

Cytotoxicity Assay. To document the cytotoxic effect of ferrocenyl molecules, a colorimetric MTS based cell viability assay was performed. Human umbilical vein endothelial cells were plated in a 96 well flat bottom plate at 3×10^4 cells per well in endothelial cell growth medium (PromoCell) at 37°C incubator providing 5% CO₂. Cells were treated with either ferrocenyl molecules (10 and 3 μM) or positive control (diamide). DMSO treated cells were used as negative control. The plate was left undisturbed for 20 hours followed by the addition of 20 μl of MTS reagent (CellTiter96® AQueous One Solution Cell Proliferation Assay kit – Promega corporation USA) for 2 hours at 37°C. The absorbance intensity was measured using a microplate reader Tecan's Sunrise absorbance microplate reader) at 495 nm. The experiments were performed in duplicates and the cell viability was expressed as a percentage relative to the vehicle alone treated DMSO cells. A flow cytometry-based assay to determine the hemolysis of human RBCs was performed as described in a prior study.³⁷

Examination of inhibitory effect of hits on DV physiology. Trophozoite-stage parasites (26–28 hpi) were treated with 25 μM of each molecule for 10 hours until early schizonts appeared in DMSO (vehicle-alone) treated samples. – **Figure 12.**

Figure 12. Trophozoite stage parasites were treated with the compounds G3, O2, S1 and DS1 at 25 μ M and Giemsa-stained thin smears were examined 10 hours post treatment. All chemical classes induced phenotypes indicating compromised DV similar to chloroquine.

Malaria stage-transition inhibition assays. For ring to trophozoite stage transition, young ring stage parasites (<5 hpi) at 4% parasitemia were treated with panel of drugs at 1 in 2 serial dilutions for 24 hours until early trophozoites (24-26 hpi) appeared in non-inhibitor treated DMSO controls. For trophozoite to schizont transition, parasites (24-26 hpi) at 4% parasitemia were treated with panel of drugs at 1 in 2 serial dilutions for 12 hours until early schizonts (36-38 hpi) appeared in non-inhibitor treated (DMSO) controls. For schizont to ring stage transition, schizonts (40-42 hpi) at 1% parasitemia were treated with panel of drugs at 1 in 2 serial dilutions for 20 hours until ring stage parasites (12-14 hpi) appeared in non-inhibitor treated (DMSO) controls. All samples were fixed with 0.1% glutaraldehyde overnight and then analyzed using flow cytometer - **Figure 13 & Table 4.**

Figure 13. Effect of the selected hits on distinct stages of parasite development. (A) To document the stage-specific effects of the top hits, experiments were carried out during, (3A, left panel) ring–trophozoite transition, (3A, middle panel) trophozoite–schizont transition and (3A, right panel) schizont–ring transition at a range of concentrations and corresponding IC₅₀ values were calculated (Table 2). All of the compounds primarily inhibited maturation/development of trophozoites and beyond with minimal inhibition of ring stage parasites. (B) Flow cytometry plots and Giemsa-stained microscopic images demonstrate that parasites were arrested at trophozoite stage (population represented in black) with an apparent decrease in schizont formation (population indicated in yellow) when treated with G3 compared to DMSO treated controls. Representative thin Giemsa smears were shown inside the flow plots, which indicate the stage of the parasites when the samples were fixed with glutaraldehyde for flow cytometry analysis. (C) Treatment of trophozoites with G3 halts schizont maturation preventing them from establishing ring-stage infections, while rings appear in DMSO treated controls.

Table 4. Malaria stage transition inhibition assay summary of selected hits. Effects of the short-listed compounds on distinct stages of *P. falciparum*. Growth inhibition assays were carried out during ring–trophozoite transition, trophozoite–schizont transition and schizont–ring transition.

Compound ID	IC ₅₀ [R→T]		IC ₅₀ [T→S]		IC ₅₀ [S→R]	
	Mean	SD	Mean	SD	Mean	SD
O2	102.9	0.1872	4.226	0.1699	5.322	0.1955
S1	155.2	0.2351	4.456	0.1531	6.025	0.1545
S4	163.3	0.1879	6.082	0.1392	6.398	0.1656
S7	113.1	0.1908	6.24	0.208	4.221	0.1724
G3	31.96	0.2292	4.082	0.3585	3.511	0.3904
S2	156.1	0.1532	7.785	0.131	8.146	0.1468
S3	147.3	0.7538	6.934	0.2955	6.842	0.1611
S5	136.1	0.4645	16.25	0.3642	12.26	0.3029
DS1	184.4	2.199	7.875	0.242	7.302	0.1439

Evaluation of ROS levels in *P. falciparum*. Magnet-purified trophozoite stage (~30-32 hpi) and late schizont stage parasites (~46–48 hpi) were stained with 5µM of CellROX Green (Invitrogen – ThermoFisher scientific) for 30 minutes and Hoechst 33342 for last 5 minutes of incubation in MCM at 37°C in dark. In addition, parasites were treated with either selected ferrocenyl compounds at 10 µM or DMSO (0.03%) ³⁸ as negative control. As positive control, hydrogen peroxide was used under similar experimental conditions. After 30 minutes, samples were washed in 200µl of 1x PBS thrice, followed by mounting on a cover slip and visualized under a fluorescent microscope (Olympus CKX53 inverted microscope). Images were captured using Olympus DP73 high performance digital color camera.- **Figure 14.**

Figure 14. Treatment with ferrocenyl compounds released reactive oxygen species (ROS) as measured by staining with CellROX green.

Determination of β hematin inhibition. The assay for β hematin inhibition was adapted from Ncokazi and Egan *et al.* with minor modifications.³⁹ The inhibitor concentration corresponded to 0–10 equivalents relative to hematin concentration in the final solution. Each well containing 2.02 μ l of the inhibitor solution was added with 20.2 μ l of hematin stock solution (1.680 mM in 0.1 M NaOH). Then, 11.74 μ l of acetate solution (12.9 M, pH 5.0 - stirred at 60°C) was added and the plate was incubated for 60 minutes at 60°C. Thereafter, 250 μ l of 12% (v/v) pyridine solution in 20 mM Hepes, pH 7.5, was added at room temperature. Plate was centrifuged for the solids to settle down. Then 200 μ l of supernatant was carefully transferred to another flat bottomed 96 well plate. Data were collected using a microplate reader (Tecan's Sunrise absorbance microplate reader) and absorbance was measured at 405nm. The experiment was done in triplicates with chloroquine as a positive control and DMSO (0.03%) as a negative control for β hematin inhibition.

Figure 15. β -hematin assay was performed to study the inhibitory effect of compounds on hemozoin formation. G3 showed 30% inhibition compared to the CQ treated positive control (15 mM) (100%).

5.6 References

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