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**NANYANG
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**Cyclometalated Pd(II)-Catalyzed Asymmetric C-C and C-P Bond
Formation Reactions**

Gan Jun Hao Kennard

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Cyclometalated Palladium(II)-Catalyzed Asymmetric C-C and C-P Bond Formations

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fulfillment of the requirement for the degree of Doctor of
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"If you've never failed, you've never succeeded"

Dedicated to my parents and my wife, Jinny Foo.

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Thesis Abstract

This thesis aims to provide a full account of synthetic strategies employed for the asymmetric formation of C-C and C-P bonds catalyzed by cyclometalated palladium(II) complexes.

Chapter 1 presents a general introduction on: i) the common synthetic pathways of ferrocenyl phosphines, ii) their application as ligands in asymmetric catalysis scenarios, iii) palladacycle synthesis and iv) palladacycles as pre-catalyst or catalyst complexes for asymmetric transformations.

Chapter 2 is split into two parts; Part 1: An alternate approach toward a novel ferrocenyl phosphapalladacycle and Part 2: Enantioselective preparation of ferrocenyl monophosphines *via* classical kinetic resolution of planar ferrocenyl racemates. In Part 1, a stepwise approach toward a ferrocenyl phosphapalladacycle bearing central and planar chirality elements utilizing asymmetric hydrophosphination and diastereoselective C-H activation is described. Its catalytic efficiency toward arylboronic acid addition to cycloenones was also examined. In Part 2, a one step strategy toward the generation of ferrocenyl monophosphines bearing central and planar chiralities *via* kinetic resolution of *racemic* ferrocenyl enones is outlined.

Chapter 3 is also split into two parts: Part 1: Phosphapalladacycle-catalyzed arylboronic acid addition onto α , β -unsaturated ketones and Part 2: Phosphapalladacycle-catalyzed arylboronic acid addition onto α , β , γ , δ -unsaturated ketones. In Part 1, a series of metalacycles was examined for the addition of arylboronic acids onto both cyclic and acyclic enones. In Part 2, a series of metalacycles was examined for the addition of arylboronic acids onto α , β , γ , δ -unsaturated ketones. It was realized that the addition proceeded regiospecifically to only yield 1, 4-products.

Chapter 4 describes the efficient kinetic resolution of *racemic* monosubstituted cyclohexenones by arylboronic acids catalyzed by the ferrocenyl phosphapalladacycle synthesized in Chapter

2.1. The major products were found to be of high diastereomeric and enantiomeric purity. To explain the observed balance between catalyst and substrate control, theoretical studies were also conducted to supplement these experimental observations.

List of Abbreviations

Ac	acetyl
ACN	acetonitrile
aq.	aqueous
Ar	aryl
BINAP	2, 2'-bis(diphenylphosphine)-1, 1'-binaphthyl
Bn	benzyl
br	broad
but	butyl
calcd.	calculated
cat.	catalyst
Cp	η^5 -cyclopentadienyl
COD	1, 5-cyclooctadiene
conc.	concentrated
d	doublet
DCE	1, 2-dichloroethane
dd	doublet of a doublet
dt	doublet of a triplet

<i>de</i>	diastereomeric excess
deg	degree(s)
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DMPP	3, 4-dimethyl-1-phenylphosphole
<i>ee</i>	enantiomeric excess
EI	electron ionization
eq.	equivalent(s)
<i>et. al.</i>	and others (Latin <i>alii</i>)
ESI	electrospray ionization
Et	ethyl
g	gram
hrs	hours
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infrared
<i>i</i> -Pr	isopropyl
<i>J</i>	coupling constant(s)

M	molar, concentration (mol / L)
M ⁺	parent ion peak (mass spectrometry)
m	multiplet
<i>m</i>	meta
Me	methyl
mins	minutes
mp	melting point
MS	mass spectrometry
<i>n</i> -But	<i>n</i> -butyl
NMR	nuclear magnetic resonance
<i>o</i>	ortho
<i>p</i>	para
Ph	phenyl
ppm	parts per million
q	quartet
<i>R</i>	rectus (Latin: right absolute configuration)
RT / rt	room temperature
s	singlet

S	sinister (Latin: left absolute configuration)
t	triplet
<i>t</i>	tertiary
T	temperature in degree celsius (°C)
<i>t</i> -But	<i>tert</i> -butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
tol	tolyl
v	volume
α	alpha
β	beta
γ	gamma
δ	delta or NMR chemical shift in ppm
Å	angstrom(s)
$[\alpha]_D$	specific rotation measured at sodium D line (589 nm)

Chapter 1.

General Introduction

1.1.1.

The sandwich mosaic: Ferrocene

The enigma of ferrocene has charmed the imagination of many chemists since its discovery in 1951 by Kealy, Pauson and Miller.¹ In contrast to popular ideologies, particularly the classical Wernerian model of ligand coordination, the serendipitous encounter with ferrocene induced a novel concept of π -bonding between a metal ion and carbocycles.² Furthermore, it displayed unique physical properties, such as its thermal³ and chemical stability, non-polar character⁴ and aromatic nature.⁵

Woodward *et. al.* discovered the striking similarity between the reactivity of ferrocene and benzene. Ferrocene (**1**) undergoes typical electrophilic aromatic substitutions such as Friedel-Crafts acylation, Vilsmeier reaction and Mannich reaction (Scheme 1.1) affording acetylferrocene (**2**), ferrocenecarboxyaldehyde (**3**) and Ugi's amine (**4**) respectively which in turn, are key building blocks for ferrocenyl ligand syntheses. These observations could be explained by a high electronic density present within the cyclopentadienyl ring (Cp) enhanced by π back donation from the Fe d orbital.

Scheme 1.1.

In addition to Woodward's study on the electrophilic aromatic substitution of ferrocene, the groups of Nesmeyanov⁶ and Benkeser⁷ examined the nucleophilic substitution pattern of ferrocene and its monosubstituted analogs. The stepwise lithiation (*n*-BuLi or *t*-BuLi in the presence of TMEDA and *t*-BuOK respectively) followed by electrophile quench grants a complementary pathway for the syntheses of numerous other ferrocenyl derivatives such as ferrocenyl carboxylic acid (**5**) and diphenylphosphinoferrocene (**6**) (Scheme 1.2).

Scheme 1.2.

The ferrocene motif also implicates certain rigidity and bulkiness due to the limited degree of freedom of rotation or tilting and the volume inhabited by the basal cyclopentadienyl (Cp) ring. This steric influence imparted by the bulky basal Cp ring plays a crucial role in achieving high diastereoselectivities and / or enantioselectivities during ligand synthesis (see Chapter 1.3) and asymmetric catalysis⁸ (see Chapter 4.2).

With these synthetic tools in hand, numerous ferrocenyl derivatives were designed and subsequently exploited in the fields of fuel additives, liquid crystals and medicinal studies. To date, arguably the most significant contribution to the chemical society would be their dynamic performances as catalysts / catalyst precursors toward asymmetric transformations.

1.1.2

Planar Chirality

The distinct ferrocene scaffold allows for an exclusive dimension rarely found in other ligand systems: *Planar Chirality*. Planar chirality, defined by IUPAC as the stereoisomerism resulting from the arrangement of out-of-plane groups with respect to a plane, emerges upon the introduction of at least two differing substituents in one cyclopentadienyl ring⁹ (Figure 1.1).

Figure 1.1. Planar Chirality.

The infusion of planar chirality onto ferrocene ligands consequently sparked debate regarding its role in the promotion of diastereoselectivity and / or enantioselectivity during catalytic processes. Initial studies attempting to discern its function when used in tandem with other chirality elements presented mixed conclusions.¹⁰ Latter studies however, described a crucial fundamental attribute necessary for selectivity enhancement: chiral element matching.

Chiral element matching is relevant to ligands when two or more chiral components are present within the metal-ligand complex. A detailed study by Deng *et. al.* discussed the influence of matched / mis-matched chirality pairs for the Pd-catalyzed allylic alkylation¹¹ (Scheme 1.3).

Scheme 1.3. Pd(II)-catalyzed Allylic Alkylation.

Ligand (L)	L Chiral Elements	Yield (%)	ee (%)	Product (9) configuration
L1 	Central	99	91	(S)
L2 	Central and (R) Planar	99	98.6	(S)
L3 	Central and (S) Planar	99	69.7	(R)

Although near quantitative yields (99 %) and excellent selectivities (91 % ee) were obtained with a Pd(II)-L1 catalyst system, the introduction of planar chirality onto the ligand scaffold (L2) resulted in a significant enhancement of ee (L1: 91 % ee vs. L2: 98.6 % ee). Furthermore, it is also apparent that simply switching the planar configuration (L2 vs. L3) results not only in a 29 % difference in enantioselectivity, but also remarkably, a change in product chirality.

These examinations offer concise insights into the influence of planar chirality and the effect of matched / mis-matched chiralities on both the configuration and stereogenic outcome.

1.1.3.

Syntheses of 1, 2-disubstituted Ferrocenyl Phosphines

There are diverse routes to imbue planar chirality onto the ferrocenyl scaffold. These generally gravitate toward 1) diastereoselective *ortho*-directed metalation (DOM) (Chapter 1.1.3.1), 2) enantioselective *ortho*-directed metalation (Chapter 1.1.3.2) and 3) kinetic resolution of ferrocenyl racemates (Chapter 1.1.3.3).

1.1.3.1

Diastereoselective *ortho*-directed metalation (DOM)

Scheme 1.4. General DOM pathway.

DMG = **Chiral** Directed Metalation Group
R = *n*-Bu, *s*-Bu, *t*-Bu

E⁺ = Electrophile

Diastereoselective *ortho*-directed lithiation relies on the presence of an appropriate chiral auxiliary / directing *ortho*-metalation group (DMG*) bearing central chirality which upon coordination to an alkyl lithium source (RLi) is able to effect stereoselective C-H abstraction.^{9a, 12} Subsequent quenching with an electrophile (E*) yields the desired 1, 2-disubstituted ferrocenyl product. DOM is the most common route to access stereogenic ferrocenes due to its DMG* versatility and practicality. The position of C-H abstraction is mainly dependent on steric influences between the basal cyclopentadienyl ring and the coordinated ligand-metal arrangement (Scheme 1.5).

Scheme 1.5. Steric influences during DOM.

DOM generally leads to 1, 2-disubstituted ferrocenyl products containing **both central** (DMG*) and **planar** (E) chirality elements. Chiral DMGs may be divided into four classes: i) methylamines, ii) sulfoxides, iii) acetals, and iv) oxazolines. i) Ugi's amine and other chiral ferrocenylmethylamines.

i) DMG*: Methylamines.

The development of chiral α -substituted ferrocenylmethylamines as a competent DMG* stemmed from the seminal discovery by Ugi in 1970. The lithiation of *N, N*-dimethylethylaminoferrocene (now commonly known as Ugi's amine) with *n*-butyllithium resulted in the preferential formation of $(R_C R_{pl})$ ferrocenyl configurations with 92 % *de*.^{9a} Utilizing this revelation, numerous ferrocenyl ligands derived from Ugi's amine by treatment of ferrocenyllithium species with appropriate electrophiles with subsequent pseudo- S_N1 substitution of the $-NMe_2$ group with retention of configuration were successfully synthesized by Kumada and Hayashi (Scheme 1.6).¹³

Scheme 1.6.

Other Ugi amine derivatives with pyrrolidine¹⁴, piperidine, binaphthyl azepine¹⁵ and ephedrine¹⁶ moieties have also been investigated (Figure 1.2).

Figure 1.2.

ii) DMG*: Sulfoxides.

The pioneering work on sulfoxide assisted direct *ortho*-lithiation by Kagan in 1993 paved an alternate approach toward the construction of valuable ferrocenyl diphosphines. In this instance, the sulfoxide moiety can be readily converted to other functional groups, similar to the psuedo- S_N1 substitution of Ugi's amine (Scheme 1.7).^{17b, 18}

Scheme 1.7.

iii) DMG*: Acetals and other unprotected Hydroxyls.

Once again, efforts to incorporate chiral acetals as a DMG* was led by Kagan in 1993. A three step procedure from commercially available ferrocene carboxyaldehyde afforded the corresponding enantiopure acetal in near quantitative yields. Subsequently, the step-wise lithiation-electrophile quench strategy led to 1, 2-disubstituted ferrocenyl acetals with up to 98 % *de* (Scheme 1.8).¹⁹

Scheme 1.8.

With the consideration that acetals and O-methylephedrine were able to effectively stabilize lithiation transition states, Knochel²⁰ and Ueberbacher²¹ further developed procedures using α -methoxybenzyl and α -carbinols as DMGs* respectively (Scheme 1.9).

Scheme 1.9.

iv) DMG*: Oxazolines.

Although the aforementioned DMGs* all allow facile access to enantiorich 1, 2-disubstituted ferrocenyl compounds, they often need to be remodeled or replaced with suitable P, S or N donor ligands for effective transition metal coordination. However, oxazolines being excellent N-donor ligands for transition metal catalysis negates the need for further modifications.²² Hence, Richards,²³ Sammiaka²⁴ and Uemura²⁵ sought to exploit this unique characteristic by attempting to utilize chiral oxazolines as DMGs*. Hence, treatment of chiral ferrocenyl oxazolines with alkylolithiums resulted in >99 % *de* upon electrophile quenching. In this instance, product selectivity is mainly influenced by sterics between the oxazoline pendant (R) and the alkyl group of the lithium source (Scheme 1.10).

Scheme 1.10.

1.1.3.2.

Enantioselective *ortho*-directed metalation

Scheme 1.11. General enantioselective *ortho*-directed metalation pathway.

Enantioselective *ortho*-directed metalation differs from its diastereoselective counterpart by the *source* of chiral induction. While diastereoselective *ortho*-metalation leans on a stereogenic ferrocene precursor, enantioselective *ortho*-metalation relies on chiral alkyllithium / chiral dialkyl amide bases to effect selective C-H activation.

In contrast to the rapid growth of diastereoselective *ortho*-directed metalation methodologies, enantioselective *ortho*-directed lithiation remained relatively unexplored, probably due to disappointing selectivities obtained by Nozaki in 1970 (3 % ee).²⁶ In 1995, however, Simpkins,²⁷ Snieckus²⁸ and Hoppe²⁹ independently demonstrated the potential for the enantioselective protocol when they achieved impressive results when utilizing α -carbonyl ferrocenyl substrates (Figure 1.12). Furthermore, enantioselective *ortho*-directed lithiation generally affords ferrocenyl derivatives consisting of **only** planar chirality. Commonly exploited external chiral inducers include: i) sparteine and its surrogates and ii) tertiary diamines.

Scheme 1.12.

Enantioselective lithiation of ferrocenecarboxamides.

More recently, sparteine surrogates³⁰ and other chiral tertiary diamines such as (*S*, *S*)-TMCDA,³¹ and (*R*, *R*)-*N*, *N'*-dimethyl-*N*, *N'*-di-(3, 3-dimethylbutyl)cyclohexanediamine³² have also emerged as powerful auxiliaries for the enantioselective *ortho*-directed lithiation (Figure 1.3).

Figure 1.3.

1.1.3.3

Resolution of Ferrocenyl Racemates

Resolution of Ferrocenyl Racemates, either enzymatically or by chiral catalysts offers a third avenue to accessing stereogenic ferrocenyl motifs. This method customarily illustrates a classical kinetic resolution of ferrocenes possessing one or more chiral elements, including planar chirality. While relatively unexplored relative to the predominance of the above lithiation pathways, resolution provides access to ferrocenyl compounds whose parent scaffold is susceptible to competing side reactions with lithium bases.

Both enzymatic and non-enzymatic classical kinetic resolution procedures have been briefly illustrated by Nicolosi,³³ Moyano,³⁴ Ogasawara³⁵ and Kudo³⁶ (Scheme 1.13). These methods generally requires an efficient discrimination between planar chiral ferrocenyl racemates by enzymes / chiral catalysts, and results in both enantioenriched ferrocenyl parent compound and product.

Scheme 1.13. Kinetic resolution of ferrocenyl racemates.

Nicolosi's Lipase-Catalyzed Esterification.

R = -CH₂NMe₂, -SMe, -SPh, -S*t*-Bu, -I

Moyano's Asymmetric Dihydroxylation.

R = -CON(*i*-Pr)₂, -TMS, -I, -4, 4-dimethyl-1, 3-oxazolin-2-yl

Ogasawara's Asymmetric Ring-Closing Metathesis.

Kudo's Asymmetric 1, 4-Michael Addition of Nitromethane.

1.1.4.

Ferrocenyl Ligands in Asymmetric Catalysis

Ferrocenyl phosphines are extensively endorsed as privileged and powerful chiral ligands for a variety of asymmetric syntheses.³⁷ The utility of ferrocenyl phosphine ligands is not only defined within academia or research. Remarkably, these precious motifs have also established their influence in the industrial production of fine chemicals.³⁸ A notable example is the large-scale asymmetric synthesis of herbicide precursors by Ir-Xyliphos / Ir-Josiphos complexes with turnover numbers exceeding two million and turnover frequencies of around half a million per hour at approximately ten thousand tons per annum.³⁹ This process currently constitutes the largest scale enantioselective catalytic process in the chemical industry.

Endogenous to the chemical laboratory, ferrocenyl phosphines are incorporated for a broad range of transformations furnishing desired products with high yields and excellent enantiocontrol. These include and are not limited to, i) Asymmetric Hydrogenation, ii) Conjugate Additions, iii) Coupling Reactions and iv) Pericyclic Additions. This sub-chapter shall attempt to highlight their major contributions to the field of asymmetric catalysis. Figure 1.4 illustrates seven popular 1, 2-disubstituted ferrocenyl bidentate ligands incorporating both central and planar chirality elements which have been employed to date.

Figure 1.4.

i) Asymmetric Hydrogenation.

Asymmetric hydrogenation of C=C bonds have become one of the most studied reactions and is the choice method for the production of optically active products on an industrial scale. Due to the relevance and biological importance of these reduced products, it has also matured into the preferred method for the screening of new stereogenic ligands. An assortment of conjugated C=C functionalities (dehydroamino acids,⁴⁰ itaconate derivatives,⁴¹ enamides,⁴² enamines⁴³ and quinolines⁴⁴) may be selectively reduced by Rh-ferrocene phosphine systems affording high yields and excellent enantioselectivities. A selection of prominent examples are shown in Scheme 1.14.

Scheme 1.14.

R = -H, -Ph
R¹ = -Me, -Ot-Bu,

BoPhoz: >99 % ee
Taniaphos: >99 % ee
Walphos: 95 % ee

BoPhoz: 97 % ee

Rh(I) / Ferrocene Ligand

H₂

Josiphos: 99 % ee

Fc-Phox: 90 % ee

Still within the context of C=C bond reductions, Blaser and co-workers extended this methodology to the manufacture of medicinal accessories. They developed water-soluble ferrocene ligands for the hydrogenation of folic acid (**10**) to L-tertrahydrofolic acid (**11**), which serves as an important co-factor in enzymatic reactions (Scheme 1.15).⁴⁵ Another group at Takeda Chemical Industries studied the Rh-catalyzed asymmetric reduction of a β , β -diaryl-substituted α , β -unsaturated acid (**12**), providing the corresponding propanoic acid derivative (**13**, a key intermediate of a therapeutic drug to cure neurodegenerative diseases) in a 95 % conversion with 93 % ee.⁴⁶ Another case in point would be the successful synthesis of the peroxime proliferator activated receptor (PPAR) (**15**) agonist precursor *via* asymmetric reduction of (Z)-2-ethoxycinnamic acid precursors by Haurez *et. al.* in a 78 % yield and 92 % ee (Scheme 1.15).⁴⁷

Scheme 1.15.

On the contrary, the stereoreduction of imines is relatively less examined. Nonetheless, this particular reduction sequence contributes to a major proportion of chemicals manufactured by companies. The stereoselective hydrogenation of imine **16** produces the synthetic intermediate of the herbicide (*S*)-metolachlor (Syngenta). The endorsed catalyst system (Ir-Xyliphos) provides the metolochlor precursor in 80 % ee, with outstanding reaction rate (Scheme 1.16).³⁹

Scheme 1.16.

ii) Conjugate Additions.

In congruence to the importance of conjugate addition as a powerful tool for asymmetric C-C bond formations, numerous chiral ligand-transition metal systems have been developed in recent years.^{48, 49} It is thus conceivable that ferrocenyl ligands constitutes an integral role to its advancement. Both 1, 2- and 1, 4-conjugate additions have been extensively nursed by ferrocenyl phosphines, furnishing desired products in high yields and selectivities.

Although there are numerous well defined catalyst complexes for the enantioselective 1, 2-additions to aldehydes, studies with its ketone counterpart failed to provide similar results due to its lower steric / electronic dissimilarity. However, on the basis of their previous investigation, Shibasaki and co-workers successfully coached a diastereo- and enantioselective aldol addition of silyl ketene acetals (**19**) to ketones (**18**), catalyzed by a Cu-Taniaphos complex (Scheme 1.17).⁵⁰

Scheme 1.17.

1, 2-additions to imines have also received relatively less scrutiny, again due to the diminished electrophilicity compared to its aldehyde analog. Nonetheless, inspired by Tomioka's work in the addition of diethylzinc to *N*-tosylimines,⁵¹ Wang and co-workers utilized Cu(II)-PPFA to obtain high stereocontrol for the addition of diethylzinc (**22**) to *N*-phosphinoyl imines (**21**) (Scheme 1.18).⁵²

Scheme 1.18.

Ferrocenyl phosphines are additionally well represented in the 1, 4-conjugate Michael addition of Grignard reagents to both cyclic⁵³ (**24**) and acyclic enones⁵⁴ (**25**). Utilizing a Cu-Taniaphos or Cu-Josiphos catalyst combinations, excellent enantioselectives (>90 %) and regioselectivity (1, 4- vs. 1, 2-) was obtained (Scheme 1.19).

Scheme 1.19.

iii) Asymmetric coupling reactions.

Biaryls incorporating axial chirality are vital structural units in biologically active compounds and chiral auxiliaries. Despite the fundamental interest of generating new biaryls, the direct asymmetric formation of the C-C biaryl bond remains a synthetic challenge. Hayashi, Ito and co-workers reported the highly atropoenantioselective cross-coupling of aryl halides (**28**) with aryl Grignard reagents (**29**), yielding chiral binaphthalenes (**30**) with up to 95 % ee when employing a ferrocenyl monophosphine (ppf-OMe) (Scheme 1.20).⁵⁵

Scheme 1.20.

This seminal work triggered consequent advancement in enantioselective biaryl couplings. Cambridge and co-workers expanded on this scope by showcasing an efficient Suzuki cross-coupling of iodonaphthalenes (**31**) with boronic esters (**32**) in the presence of Pd-PPFA catalysts (Scheme 1.21).⁵⁶

Scheme 1.21.

The Heck reaction remains a valuable tool in the realm of organic synthesis, more specifically, natural product synthesis, with both intra- and inter-molecular variants well documented. For the intermolecular Heck reaction of 2, 3-dihydrofuran (**34**) and aryl triflates (**35**), Guiry was able to obtain the kinetic product (**36**) in a 61 % yield with 98 % ee.⁵⁷ This result is significant as the kinetic product may experience double bond isomerization to the thermodynamically stable vinyl ether (**37**) (Scheme 1.22).

Scheme 1.22.

Guiry was also able to obtain excellent results for the intramolecular Heck reaction, synthesizing spiro-lactam (**39**) in a 71 % yield and 82 % ee, and *cis*-decalins (**41**) in a 30 % yield and 85 % ee (Scheme 1.23).⁵⁸

Scheme 1.23.

1.2.

Palladacycles

Organopalladium complexes are firmly established as valuable catalyst precursors for a legion of cross-coupling reactions.⁵⁹ These precious motifs have also found applications in the development of organic light emitting devices⁶⁰ (OLE), liquid crystals,⁶¹ supramolecular structures,⁶² medicinal and biological chemistry. Their rich, diverse chemistry has led to numerous specialized reviews devoted to their synthesis, structural attributes, catalytic and physical properties. Naturally, to engage in thorough discussion of these components would be overwhelming and beyond the scope of this dissertation. Nonetheless, this introduction shall attempt to provide a sizable description of i) their main characteristics, ii) general synthetic pathways and iii) catalytic competency.

1.2.1.

Characteristics

Palladacycles are depicted by at least one palladium carbon bond (Pd-C), with intramolecular stabilization by a neighbouring donor atom (N, P, S, As, etc.) (Figure 1.5), hence the term *cycle*. The metalated bracelet generally consists of 5 / 6 member atoms, inclusive of L, C and Pd.

Figure 1.5.

1.2.2.

General synthetic pathways

There are a host of synthetic pathways available for palladacycle construction, namely i) C-H activation, ii) oxidative addition, iii) transmetalation and iv) nucleophilic addition. The elected method is generally conformed by the functionalities present within the substrate and / or the individuals' desired outcome, for instance; oxidative addition is often the avenue of choice for *in-situ* pre-catalyst formation from *ortho*-halogenated mono-dendates.

i) C-H Bond Activation.

Orthopalladation, described as 'chelation assisted cyclopalladation' offers a direct route toward palladacycle construction from simple monodendates.⁶³ The typical mechanism entails initial ligand-metal coordination followed by C-H activation, with the formation of a thermodynamically stable 5 / 6-membered ring as its main driving force (Scheme 1.24).

Scheme 1.24.

Unlike an oxidative addition mechanism, whereby Pd is inserted into the C-X bond (hence forming a C-Pd-X intermediate), C-H activations are generally considered to abide by an electrophilic aromatic substitution pathway.⁶⁴ There is also evidence to suggest that the C-H bond is only activated when it is in close proximity to the palladium centre (Scheme 1.25).⁶⁵

Scheme 1.25.

Common palladation agents include tetrachloropalladated salts⁶⁶ or palladium acetate due to their accessibility and ease of use. The former requires the presence of a weak base for H abstraction, while the latter (technically already a base due to the coordinating acetate ligands) requires acetic acid or aromatic solvents for efficient palladation. In rare cases, if both reagents fail to provide adequate yield, cyclopalladated ligand exchange (CLE) is employed.⁶⁷ This approach involves the *transfer* of palladium from a parent cyclopalladated complex (**42**) to another ligand (**43**). This method is dependent on relative acid stability of the ligands involved (Scheme 1.26). In this instance, the parent N-C palladacycle releases Pd(II) by acidolysis, and the more acid resistant P-C palladacycle (**44**) is formed.

Scheme 1.26.

Parent Palladacycle

ii) Oxidative Addition.

The oxidative addition of aryl halides and, to a lesser extent alkyl halides containing a neighbouring two electron donor is another convenient scheme for palladacycle construction. Dissimilar to C-H activation, whereby palladation is promoted by palladium(II) sources, oxidative addition utilizes palladium(0) as its metal precursor. These include $\text{Pd}(\text{dba})_2$, $\text{Pd}_2(\text{dba})_3$ or

$\text{Pd}(\text{PPh}_3)_4$, resulting in neutral, dimeric palladacycles, or triphenylphosphine bound monomers (Scheme 1.27).

Scheme 1.27.

This method is commonly used for the *in-situ* preparation of catalyst precursors. A drawback, however would be the accessibility of a halogenated substrate, which may require laborious synthetic protocols for their procurement.

iii) Transmetalation.

An alternative method to synthesize palladacycles utilizes organo-lithium or organo-mercurial reagents. This avenue provides facile access to bis-cyclopalladated compounds by a transmetalation *via* organo-lithium⁶⁸ or mercurial N- or O-containing ligands⁶⁹ with halogenated dimeric palladacycles. It is also a useful method for the generation of planar chiral cyclopalladated complexes containing the $\text{Cr}(\text{CO})_3$ moiety (Scheme 1.28).⁷⁰

Scheme 1.28.

Synthesis of a bis-cyclopalladated complex by organo-lithium mediated transmetalation.

Synthesis of a planar cyclopalladated complex by organo-mercury mediated transmetalation.

1.2.3.

Palladacycle catalysis

The successful cyclopalladation of tri-*o*-tolylphosphine by Herrmann and co-workers stimulated much excitement about this contemporary class of palladium complexes.⁷¹ Their anchored, well-defined structure was postulated to deliver high enantioselectivities and contribute new insights toward $\text{Pd}(0) / (\text{II})$ and $\text{Pd}(\text{II}) / (\text{IV})$ redox mechanisms. While palladacycles have indeed fulfilled and even surpassed initial expectations in the aspect of catalyst turnover and substrate / reaction condition tolerance, there are other areas in which their performance has been found to be lacking. For instance, Cheprakov *et. al.* hypothesized that palladacycles are routinely dismantled during pre-catalyst activation, releasing $\text{Pd}(0)$.⁷² Their hypothesis has since been backed by computational studies and experimental evidence. Hence, initial conclusions portrayed palladacycles as 'dormant species' and a source of ' $\text{Pd}(0)\text{L}_2$ ' (where L = *o*-tolylphosphine). This conclusion was further met with approval when the attempt to perform an enantioselective Heck reaction with a chiral palladacycle only resulted in racemic products.⁷³

Nonetheless, early palladacycles have displayed higher catalytic activity relative to classical phosphine-based catalysts. For instance, the Suzuki coupling of bromoarenes with styrene proceeded with a turnover number (TON) of seven thousand. Similar TON was observed for the same catalyst system when employing activated chloroarenes.⁷⁴

Despite the disappointing revelation, many chemists maintained their interest in developing conditions and pathways in which the palladacycle skeleton is preserved and as such, operates as the 'active catalyst'. Their pursuits finally disclosed the competency of palladacycles as active catalysts for various asymmetric transformations, notably rearrangements and P-H addition reactions.

1.2.3.1.

The allylic imidate rearrangement

The allylic imidate rearrangement, which is the key mechanism in the conversion of allylic alcohols to their corresponding allylic amines was initially reported by Overman *et. al.* in 1974.⁷⁵ This concerted [3, 3]-sigmatropic rearrangement was first investigated by cationic palladium(II)-complexes containing chiral bidentate N, N or N, P ligands.⁷⁶ However, these attempts only led to moderate yield and enantioselectivity. In contrast, neutral palladium(II)-complexes were found to result in near quantitative conversion within minutes without heat or mercury(II) additives. Subsequent developments hinged on planar ferrocenyl complexes for the efficient chirality projection perpendicular to the palladium(II) square planar coordination plane (Scheme 1.29).⁷⁷

Scheme 1.29.

From (*E*): Up to 91 % yield and 92 % ee
 From (*Z*): Up to 96 % yield and 96 % ee

From (*E*): Up to 99 % yield and 98 % ee
 From (*Z*): Up to 97 % yield and 99 % ee

Up to 94 % yield and 99.6 % ee

1.2.3.2

Asymmetric Hydrophosphination

Asymmetric hydrophosphination has emerged as a powerful, atom economical protocol for the synthesis of valuable phosphine ligands. Seminal endeavors by Leung and co-workers identified palladacycles as efficient catalytic promoters for the asymmetric synthesis of enantiorich, or in some cases, enantiopure tertiary monophosphines. The addition of diphenylphosphine to activated, electron-deficient alkenes in the presence of either a C-N based palladacycle or its C-P analogue affords enantioenriched, tertiary monophosphines in quantitative yields (generally >90 % yields and >90 % ee) (Scheme 1.30).⁷⁸

Scheme 1.30. General AHP pathway.

R: -Alkyl, -Aryl

EWGs include:

Ketones

Malonates

Imines

2-nitro-alkenylisoxazoles

Ketoesters

N-enoyl phthalimides

This protocol has also been extended to the synthesis of diphosphines⁷⁹ and *P*-heterocycles⁸⁰ (Scheme 1.31).

Scheme 1.31.

R: -Alkyl / -Aryl

Although this protocol requires inert gas protection due to the air-sensitive nature of diphenylphosphine (**58**), the phospha-Michael addition generally proceeds to completion within twenty four hours at low temperatures (-40 °C to -60 °C). From a mechanistic standpoint, the catalytic cycle proceeds by three steps: i) phosphine substitution, ii) substrate coordination and iii) phosphide addition (Scheme 1.32).^{78a}

Scheme 1.32.

The addition is initiated by diphenylphosphine substitution of an acetonitrile ligand, forming intermediate **A**. Through this coordination, diphenylphosphine is significantly acidified and is easily deprotonated by triethylamine (NEt_3) and can be observed by a colour change from light yellow to dark yellow or light red upon basification. Coordination of substrate *via* substitution of the second acetonitrile ligand gives intermediate **C**. Subsequent phospho-Michael addition of diphenylphosphide to the activated substrate and protonation yields intermediate **D**. Here, the newly generated labile tertiary phosphine is substituted by another acetonitrile ligand, thus regenerating the active Pd(II)-catalyst complex.

An exclusive stereochemical feature of palladacycles **C5** and **C6** is that the five-membered organopalladium ring is locked in either a δ or λ conformation. For (*R*)-**C5** / **6**, the ring is locked in a δ configuration, while (*S*)-**C5** / **6** is locked in a λ configuration. Due to steric influences

between the methyl spacer at the stereogenic carbon and the promixal naphthalene proton H(8), the ring is non-interconvertible in both solid and solution (Figure 1.6).

Figure 1.6.

From figure 1.35, it is observed that the methyl substituent at the stereogenic carbon adopts an axial position, and the R_2 groups on the donor N / P are fixated into non-interchangeable axial and equatorial positions. Furthermore, the electronic differences between the sigma donating L and pi-accepting naphthalene carbon coerces the incoming phosphine nucleophile to adopt a position *trans* to L, and thus conceding the substrate to assume the final coordination site *trans* to C.

Studies conducted by Leung *et. al.* also determined that the methyl pendant presents the incoming phosphine nucleophile with the main steric influence, as compared to the axial R group on L (Figure 1.7).

Figure 1.7.

1.3.

Objectives

Due to dynamism and efficacious performances of ferrocenyl phosphines in asymmetric catalysis scenarios, a large volume of research is catered toward developing new methods to incorporate central and planar chirality into the ferrocenyl scaffold. These explorations have mainly revolve around the diastereomeric and enantiomeric *ortho*-directed metalation protocols. However, the major drawback with these 2 methods is the requirement of stoichiometric amounts of chiral directing group (whether internal or external). Furthermore, the ferrocenyl scaffold must also be tolerant toward strongly basic conditions, such as lithium addition. Hence, there is a need to develop an alternate method to generate ferrocenyl phosphines which negates the need for expensive and / or specific substrates and inert atmosphere.

Taking into consideration the numerous advantages afforded by the asymmetric hydrophosphination protocol (good atom economy, high yields and selectivities, low catalyst loading), alternate protocols to develop a novel set of ferrocenyl phosphines are attempted.

As a result of this motivation, a step-wise protocol for the formation of a novel ferrocenyl phosphapalladacycle is reported, followed closely by a one-step formation of ferrocenyl tertiary monophosphines incorporating central and planar chirality through the kinetic resolution of racemic 1, 2-disubstituted ferrocenyl enones *via* asymmetric hydrophosphination.

Another objective is to develop new strategies for the efficient C-C bond formation reaction *via* arylboronic acid addition to both cyclic and acyclic enones utilizing cyclometalated Pd(II) catalysts. Although this field has been dominated by Rh and Cu catalysis, recent advancements have found that Pd catalysts are also able to effect high yields and selectivities. Deriving motivation from these developments, new strategies for the selective formation of C-C bonds and regioselective 1, 4-formation of C-C bonds from arylboronic acids and α , β - / α , β , γ , δ -

unsaturated ketones are reported. This addition protocol is also extended to the efficient formation of multi-substituted cycloalkanones from its parent racemic mono-substituted cycloalkenones. This significant result is due to the synergistic control by both catalyst and substrate, which is uncommon within Rh and Cu systems.

1.4.

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Chapter 2.1

An alternate approach toward a ferrocenyl phosphapalladacycle bearing central and planar chirality elements

2.1.1.

Introduction

Enantiomerically pure cyclopalladated complexes have emerged as powerful auxiliaries for asymmetric catalysis, leading to extensive efforts toward its development.¹ These pursuits led to the generation of ferrocenyl CN-palladacycles incorporating both central and planar chirality elements, which administered remarkable results (up to >99 % ee) for C-N² and C-O³ bond formation reactions.

It is of interest to elucidate the catalytic potential of analogous ferrocenyl CP-palladacycles. To the best of our knowledge, catalytic trials of ferrocenyl phosphapalladacycles have revolved around the Hayashi-Miyaura reaction (Scheme 2.1.1).⁴

Scheme 2.1.1

Ferrocene CP catalyst (**C7**):

The attempted 1, 4-addition of arylboronic acids (**60**) to cyclohexenone (**24**) afforded 3-arylcyclohexanones (**61**) with high yields (up to 92 %) and moderate enantioselectivities (79 %), however, although the analogous 1, 2-addition to aromatic aldehydes (**62**) proceeded with near quantitative yield (up to >99 %), poor enantioselectivities were obtained (up to 11 %).

The synthesis of ferrocenyl phosphapalladacycles generally comprises of two steps, i) the formation of a C-chiral monophosphine and ii) subsequent cyclopalladation. The former may be achieved through either diastereo-⁵ / enantio-selective lithiation⁶ or phosphine substitution⁷ of a Ugi amine derivative. Both these methods however, require *stoichiometric* quantities of an

appropriate *enantiopure* reagent. The desired ferrocenyl CP complex may then be secured by either diastereoselective C-H activation,⁸ or oxidative addition of Pd(0) (Scheme 2.1.2).⁴

Scheme 2.1.2.

A hitherto unexplored route to the enantioselective formation of mono-ferrocenyl phosphines is the palladium(II)-catalyzed asymmetric hydrophosphination reaction (AHP). As described in Chapter 1.2.3, the AHP protocol affords enantioenriched tertiary mono-phosphines in high yields and short reaction times.⁹

In the first part of Chapter 2, we discuss the first AHP based enantioselective synthesis of a series of *C*-chiral tertiary ferrocenyl phosphines, subsequent diastereoselective cyclopalladation of one such AHP product and a catalytic demonstration of the resultant Pd(II)-complex in the Hayashi-Miyaura reaction.

2.1.2.

Results and Discussion

Scheme 2.1.3.

Table 2.1.1.

Entry	Cat.	Solvent	t (hrs)	Yield (%)	ee (%)
1	C5	DCM	12	99	60
2	C5	MeOH	2	99	60
3	C5	THF	168	Nil	Nil
4	C5	Acetone	168	50	n.d
5	C5	MeCN	168	Nil	Nil
6	C5	Dry MeOH	2	99	>99
7	C6	Dry MeOH	168	49	n.d

^a Catalyst (**C5** / **C6**) (0.05 mmol, 10 mol %) was added to a solution of diphenylphosphine (**58**) (0.5 mmol, 1 eq.) at room temperature and stirred for 5 minutes. Substrate (**64a**) (0.5 mmol, 1 eq.) and NEt₃ (0.5 mmol, 1 eq.) were subsequently added and the dark purplish solution left to stir for the stipulated time.

The synthetic approach was initiated by screening an array of conditions for the addition of diphenylphosphine (**58**) to ferrocenyl enone (**64a**) at room temperature. The phosphination was monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR by the disappearance of the diphenylphosphine signal at δ -40 and the formation of the tertiary phosphine adduct signal at δ 0 - 10. The phospho-Michael addition was found to proceed smoothly in DCM and MeOH, affording the desired ferrocenyl tertiary phosphine (**65a**) in near quantitative yields, however, poor conversions were obtained with THF, Acetone and MeCN (Table 2.1.1, Entries 1-5). Subsequent examination with dried MeOH revealed a significant increase in selectivity (up from 60 % to >99 %) without any decline in reactivity and product yield (Table 2.1.1, Entry 5 vs. Entry 6). These preliminary results also show a remarkable difference between the performances of the 2 chosen catalysts. While the N-C palladacycle (**C5**) catalyzed the addition within 2 hours, the P-C analogue (**C6**) failed to deliver full conversion after 1 week. Furthermore, when the AHP was conducted in MeOH, the tertiary phosphine adduct was seen to precipitate upon formation, enabling a facile procedure in which the enantio-rich product can be isolated by mere cannula filtration under N_2 protection.

Scheme 2.1.4.

^a Catalyst **C5** (0.05 mmol, 10 mol %) was added to a methanolic solution of diphenylphosphine (**58**) (0.5 mmol, 1 eq.) and left to stir at room temperature for 5 minutes. Substrate (**64a - e**) (0.5 mmol, 1 eq.) was subsequently added and the flask was cooled to $-80\text{ }^\circ\text{C}$. Following which, NEt_3 (0.5 mmol, 1 eq.) was added dropwise and the resulting solution left to stir for the stipulated time.

Having determined the optimized conditions, a series of tertiary ferrocenyl phosphine analogues were generated through the variation of the ketone substituent. Although good yields were achieved with all substrates (**65a - e**), poor selectivities (30 - 49 %) were attained when the AHP was conducted at room temperature. Hence, in an effort to obtain enhanced results, these ensuing examinations were conducted at $-80\text{ }^\circ\text{C}$ and improved ee values (42 - >99 %) were observed (Scheme 2.1.4).

With these enantio-rich tertiary phosphines in hand, the possibility for the integration of planar chirality onto the ferrocenyl scaffold through cyclopalladation was examined (Scheme 2.1.5). Adopting prior methodologies by Dunina *et. al.*,¹⁰ initial cyclopalladation endeavors utilized Pd(OAc)₂ as the palladium source. However the targeted palladium(II) complex was obtained with a poor yield of 20 % after heating in toluene at 60 °C for 3 hours (Table 2.1.2, Entry 1). Attempted variation of solvent, temperature and palladium sources also failed to stimulate effective C-H activation (Table 2.1.2)

Scheme 2.1.5.

Table 2.1.2.

Entry	Pd source	Additives	Solvent	T (°C)	t (hrs)	Yield (%)
1	Pd(OAc) ₂	Nil	Toluene	RT	5	20
2	Pd(OAc) ₂	Nil	Toluene	60	3	20
3	Pd(OAc) ₂	Nil	MeOH	60	> 24	Nil
4	PdCl ₂	1 eq. NEt ₃	Toluene	60	3	Nil
5	Na ₂ PdCl ₄	1 eq. NEt ₃	Toluene	40	> 24	Nil
6	PdCl ₂ (NCMe) ₂	Nil	Toluene	40	> 24	Nil

These disappointing results could be attributed to insufficient steric promotion of the C-H bond by the -PPh₂ moiety, resulting in the formation of only coordination compounds.¹⁰

A 2 step process involving the coordination of (**65a**) to dimer (**66**) followed by cleavage of the N-C chelate with HCl under acetone reflux was next attempted.¹¹ Subsequent purification *via* silica gel column chromatography afforded the desired ferrocenyl phosphapalladacycle (**67**) as an orange powder with an overall yield of 98 % (Scheme 2.1.6).

Scheme 2.1.6.

The attempted resolution of **67** with Sodium Prolinate displayed 2 singlets at δ 68.1 and δ 68.8 with a ratio of 1 : 5.3 (crude $^{31}\text{P}\{^1\text{H}\}$ NMR), indicating an efficient cyclopalladation *de* of ca. 66 % (Scheme 2.1.7).

Scheme 2.1.7.

Slow recrystallization from DCM : Diethyl Ether afforded $(R_c S_{pl} S_{pro})\text{-68}$ as yellowish-orange blocks in an overall yield of 65 % (Figure 2.1.1). Selected bond lengths (Å) and angles (°) are displayed in Table 2.1.3.

Column chromatography of the enriched mother liquor with 5 Acetone : 1 DCM : 1 *n* - hexanes allowed the acquisition of $(S_c S_{pl} S_{pro})\text{-68}$ in an overall yield of 10 %.

Separate treatment of both $(S_c S_{pl} S_{pro})\text{-68}$ and $(R_c S_{pl} S_{pro})\text{-68}$ with LiCl and AcOH in MeOH regenerated $(S_c S_{pl})\text{-67}$ and $(R_c S_{pl})\text{-67}$ respectively in quantitative yield with full chirality transfer (Scheme 2.1.8).

Scheme 2.1.8.

Figure 2.1.1.

Table 2.1.3.

Bond	Length	Bond	Angle
Pd (1)-P (1)	2.2185 (14)	P (1)-Pd (1)-O (1)	97.01 (11)
Pd (1)-C (1)	1.979 (5)	P (1)-Pd (1)-C (1)	82.01 (15)
Pd (1)-O (1)	2.099 (4)	C (1)-Pd (1)-N (1)	100.4 (2)
Pd (1)-N (1)	2.145 (4)	N (1)-Pd (1)-O (1)	81.81 (17)
P (1)-C (18)	1.812 (5)	Pd (1)-O (1)-C (34)	115.0 (4)
P (1)-C (24)	1.824 (5)	O (1)-C (34)-C (33)	118.4 (5)
P (1)-C (11)	1.877 (6)	C (34)-C (33)-N (1)	113.0 (5)
C (2)-C (11)	1.534 (7)	C (33)-N (1)-Pd (1)	107.3 (3)
C (1)-C (2)	1.444 (7)	Pd (1)-C (1)-C (2)	124.1 (4)
N (1)-C (33)	1.507 (8)	C (1)-C (2)-C (11)	121.0 (5)
C (33)-C (34)	1.523 (8)	C (2)-C (11)-P (1)	102.9 (4)
C (34)-O (1)	1.286 (7)	Pd (1)-P (1)-C (11)	109.96 (17)
		Pd (1)-P (1)-C (24)	110.54 (18)
		C (24)-P (1)-C (18)	106.7 (2)
		C (18)-P (1)-C (11)	107.5 (2)
		N (1)-Pd (1)-P(1)	171.41 (14)
		O (1)-Pd (1)-C (1)	171.78 (19)
		C (24)-P (1)-C (11)	109.7 (2)
		C (18)-P (1)-Pd (1)	112.38 (17)

The rationale for the observed selectivity may be explained by steric influences between the basal cyclopentadienyl ring and the coordinated ligand-metal arrangement as discussed in Chapter 1.1.3.1.

Scheme 2.1.9.

With reference to Scheme 2.1.9, if the prochiral S_{pl} ferrocenyl proton is activated, an $(R_c S_{pl})$ -phosphapalladacycle arrangement will be generated. However, if the prochiral R_{pl} ferrocenyl proton is activated, an $(R_c R_{pl})$ -phosphapalladacycle arrangement will be generated instead. The preference of prochiral S_{pl} activation is due to sterics between the basal ferrocenyl ring and the side alkyl chain of the tertiary phosphine.

This protocol thus provides a viable alternative for accessing ferrocenyl palladacycles from achiral activated alkenes *via* an atom-economical, efficient hydrophosphination followed by a diastereoselective *orthopalladation*.

With this newly synthesized ferrocenyl phosphapalladacycle in hand, a succinct demonstration of its efficacy as a catalyst in C-C bond formation scenarios was demonstrated. The Hayashi-

Miyaura reaction is a dynamic and powerful mechanism for the alkylation / arylation of activated alkenes.¹² Phosphapalladacycles, on the other hand, have only recently received attention as a feasible surrogate for the 1, 4-addition of arylboronic acids to conjugated enones as mentioned previously in Chapter 2.1.1.⁴

Thus, the investigation commenced with the catalytic application of (*R_c* *S_{pl}*)-**67** for the arylboronic acid addition to 2-cyclohexenone (Scheme 2.1.10).

Scheme 2.1.10.^a

^a Reaction conditions: **24** (0.1 mmol), **60a - e** (0.2 mmol), (*R_c S_{pl}*)-**67** (2.5×10^{-3} mmol, 2.5 mol % **24**), K₃PO₄ (0.1 mmol) in 1 mL of Toluene at room temperature for 3 hours. Isolated yields. ee determined by HPLC using a chiral column.

Adopting un-optimized conditions, high yields of 82 - 90 % and moderate ee values of 61 - 71 % were realized when the addition was proceeded in Toluene and K₃PO₄ base. Lowering of the reaction temperature and utilizing an aqueous solution of K₃PO₄ (5M) revealed a significant increase in ee values obtained for the addition of (*p*-OMe)PhB(OH)₂ (**60d**) onto 2-cyclohexenone (**24**), albeit with an 8 fold increase in reaction duration. These unfledged results compare favorably with results previously obtained from analogous additions catalyzed by phosphapalladacycles.

A separate examination was conducted with (*R_c R_{pl}*)-**67** under the same conditions as per Scheme 2.110 to analyze the influence and importance of chiral element matching (Scheme 2.1.11).

Scheme 2.1.11.

A comparison of results obtained with (*R_c S_{pl}*)-**67** and (*R_c R_{pl}*)-**67** revealed the relevance of chiral element matching for the 1, 4-addition of phenylboronic acid to cyclohexenone. Although yields obtained with both catalysts are similar, ee values exhibit significant disparity (67 % ee with (*R_c S_{pl}*)-**67** vs. 55 % ee with (*R_c R_{pl}*)-**67**). Furthermore, it can also be seen that the switch of planar chirality results in an alteration of product configuration, with (*R*)-**61a** obtained when (*R_c S_{pl}*)-**67** was used while its diastereomer (*R_c R_{pl}*)-**67** afforded (*S*)-**61a**. Hence, it is apparent from this correlation that chiral element matching plays a crucial role in the optimization of product attributes.

2.1.3

Conclusion

In conclusion, a highly enantioselective AHP based protocol for accessing ferrocenyl tertiary phosphine motifs from achiral substrates as well as a viable alternate protocol for achieving their diastereospecific C-Pd bond formation with the aim of generating novel cyclopalladated systems incorporating both central and planar chirality elements was developed. A preliminary catalytic evaluation indicated their relevance in asymmetric C-C bond formation which will be thoroughly examined in Chapter 4.

2.1.4.

Experimental Section

All air-sensitive manipulations were proceeded under dry nitrogen by means of conventional Schlenk techniques unless stated. Solvents were de-gassed / distilled prior to use whenever necessary. A low temperature pairstirrer PSL-1800 machine was used for low temperature experiments (0 °C / -80 °C). Thin layer chromatography was performed on Merck silica gel 60 F254 aluminium backed plates. NMR spectra were recorded on 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, $^{19}\text{F}\{^1\text{H}\}$ at 282 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 161 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 are referenced to an internal SiMe_4 standard at δ 0 or to the chosen residual solvent signal (CD_2Cl_2 at δ 5.32, CDCl_3 at δ 7.26). Optical rotations were measure on the specified solution in a 0.1 dm cell at 20 °C with a Perkin-Elmer 341 polarimeter. Melting points were documented on a SRS Optimelt MPA 100 point system.

Asymmetric Hydrophosphination Procedure:

A flask was charged with HPPH_2 (50.0 mg, 0.27 mmol) and solvent (2 ml). Subsequently, catalyst (S) - **5** (13.1 mg, 0.027 mmol) was added and the yellow solution was stirred at the stipulated temperature for 5 mins. Following that, ferrocenyl enone (**64a - e**) (0.27 mmol) and NEt_3 (27.3 mg, 37.6 μL , 0.27 mmol) diluted with solvent (2 ml) were added. The resulting purple mixture was allowed to stir at the stated temperature and monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR. For reactions conducted in MeOH: Upon reaction completion, the mother liquor was transferred out via cannula and the residue was washed with minimal cold MeOH and *n* - hexanes to yield the orange enantiopure tertiary phosphine. For reactions conducted in other solvents: Upon reaction completion, the solvent was removed via vacuum and the residue re - dissolved in DCM. The DCM solution was passed through a silica gel pipette column to obtain the enantio - enriched tertiary phosphine.

Determination of ee: Coordination to (S)-**69**:

(S)-**69** (0.51 equiv.) was added to a DCM solution (5 ml) of the purified tertiary ferrocenyl phosphine (**65a - e**). The orange solution was then left to stir at RT for one hour. $^{31}\text{P}\{^1\text{H}\}$ NMR was then conducted on the crude solution to determine ee.

65a

Orange solid. ^1H NMR (CD_2Cl_2 , 400 MHz): δ 3.15 - 3.22 (m, 1H, $-\text{CH}_2$), 3.41 - 3.50 (m, 1H, $-\text{CH}_2$), 3.67 (s, 1H, Cp), 3.83 (s, 1H, Cp), 3.94 (s, 1H, Cp), 4.00 (s, 6H, Cp), 4.19 (m, 1H, $-\text{CHPPh}_2$), 6.54 (m, 1H, -Ar), 7.15 (d, 1H, Ar), 7.25 - 7.34 (m, 8H, Ar), 7.45 - 7.46 (m, 2H, Ar), 7.61 (m, 1H, Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 100 MHz): δ 32.3, 41.4 ($-\text{CH}_2\text{PPh}_2$, $J = 19.8$ Hz), 66.8, 67.0, 67.2, 68.5, 68.8, 90.6, 112.2, 117.0, 127.9, 128.0, 128.1, 128.2, 128.6, 129.0, 133.3, 133.5, 134.4, 134.6, 152.8, 187.3 ($-\text{C=O}$). $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 162 MHz): δ 6.0. $[\alpha]_{\text{D}} = -126$ (c 0.3, DCM).

65b

Orange solid. ^1H NMR (CD_2Cl_2 , 400 MHz): δ 3.21 - 3.30 (m, 1H, $-\text{CH}_2$), 3.51 - 3.60 (m, 1H, $-\text{CH}_2$), 3.68 (s, 1H, Cp), 3.84 (s, 1H, Cp), 3.94 (s, 1H, Cp), 4.01 (s, 5H, Cp), 4.20 - 4.24 (m, 1H, $-\text{CHPPh}_2$), 7.15 (t, 1H, Ar), 7.26 - 7.34 (m, 8H, Ar), 7.47 - 7.50 (m, 2H, Ar), 7.67 (d, 1H, Ar), 7.70 (s, 1H, Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 100 MHz): δ 32.5, 42.4 ($-\text{CH}_2\text{PPh}_2$, $J = 20$ Hz), 66.8, 67.0, 67.2, 68.6, 68.9, 90.7, 127.9, 128.0, 128.1, 128.2, 128.2, 128.6, 129.1, 131.8, 133.3, 133.5, 133.8, 134.4, 134.6, 136.1, 137.0, 144.5, 191.1 ($-\text{C}=\text{O}$). $^{31}\text{P}\{^1\text{H}\}$ (CD_2Cl_2 , 162 MHz): δ 5.87. $[\alpha]_{\text{D}} = -110$ (c 0.5, DCM).

65c

Orange solid. ^1H NMR (CD_2Cl_2 , 400 MHz): δ 3.33 - 3.39 (m, 1H, $-\text{CH}_2$), 3.61 - 3.69 (m, 1H, $-\text{CH}_2$), 3.70 (s, 1H, Cp), 3.85 (s, 1H, Cp), 3.94 (s, 1H, Cp), 4.00 (s, 5H, Cp), 4.01 (s, 1H, Cp), 4.29 (m, 1H, $-\text{CHPPh}_2$), 7.25 - 7.33 (m, 8H, Ar), 7.45 - 7.50 (m, 4H, Ar), 7.56 - 7.60 (m, 1H, Ar), 7.93 (s, 1H, Ar), 7.95 (s, 1H, Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 100 MHz): δ 31.9, 41.9 ($-\text{CHPPh}_2$, $J = 20.2$ Hz), 66.8, 67.0, 67.3, 68.5, 69.0, 91.0, 127.9, 128.0, 128.2, 128.2, 128.6, 129.0, 133.0, 133.3, 133.5, 134.4, 134.6, 197.97 ($-\text{C}=\text{O}$). $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 162 MHz): δ 6.1. $[\alpha]_{\text{D}} = -100.9$ (c 1.7, DCM).

65d

Orange solid. ^1H NMR (CD_2Cl_2 , 400 MHz): δ 2.50 (s, 3H, -OMe), 3.27 - 3.39 (m, 1H, -CH₂), 3.52 - 3.61 (m, 1H, -CH₂), 3.67 (s, 1H, Cp), 3.83 (s, 1H, Cp), 3.92 (s, 1H, Cp), 3.97 (s, 5H, Cp), 4.00 (s, 1H, Cp), 4.27 (m, 1H, -CHPPh₂), 7.26 - 7.33 (m, 10H, Ar), 7.48 (m, 2H, Ar), 7.84 (s, 1H, Ar), 7.85 (s, 1H, Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 100 MHz): δ 21.3 (-OMe), 32.0, 41.6 (-CHPPh₂, J = 20.1 Hz), 66.8, 66.8, 66.9, 67.2, 68.4, 69.0, 69.0, 91.0, 127.9, 127.9, 128.0, 128.2, 128.2, 128.5, 128.9, 129.2, 133.2, 133.4, 134.4, 134.6, 197.68 (-C=O). $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 162 MHz): δ 6.1. $[\alpha]_{\text{D}} = -92.3$ (c 1.4, DCM).

65e

Orange solid. ^1H NMR (CD_2Cl_2 , 500 MHz): δ 2.03 (s, 3H, -Me), 2.83 - 2.88 (m, 1H, -CH₂), 3.06 - 3.14 (m, 1H, -CH₂), 3.70 (s, 1H, Cp), 3.77 (s, 1H, Cp), 3.96 (s, 1H, Cp), 4.02 (s, 1H, Cp), 4.08 (s, 5H, Cp), 4.19 (m, 1H, -CHPPh₂), 7.28 - 7.35 (m, 8H, Ar), 7.42 - 7.50 (m, 2H, Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 125 MHz): δ 30.3 (-Me), 31.9, 46.9 (-CHPPh₂, J = 19.6 Hz), 66.8, 67.3, 68.5, 68.8, 128.0, 128.0, 128.2, 128.3, 128.7, 129.1, 133.5, 133.6, 134.5, 134.7, 206.3 (-C=O). $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 202 MHz): δ 6.2. $[\alpha]_{\text{D}} = +72.3$ (c 1.0, DCM).

Cyclopalladation and Prolinate resolution:

Dimer **66**² (54.9 mg, 0.1 mmol) was added to an acetone solution (10 ml) of (*R_c*) - **65a** (25.1 mg, 0.05 mmol) and left to stir for 20 mins. 37 % HCl (82.0 μ L) was subsequently added dropwise to the orange solution and heated to reflux for 90 mins. The reaction mixture was then cooled to RT and water (20 ml) was added with rapid stirring. Upon standing, the orange product was filtered, washed with water and dried under vacuum. The analytically pure cyclopalladated complex **67** was purified via chromatography on silica gel (DCM).

A slight excess of Sodium Prolinate (50.0 mg, 0.36 mmol) was added to a suspension of **67** (216.9 mg, 0.17 mmol) in MeOH (10 ml). The mixture was left to stir at RT overnight to give a homogenous solution which was evaporated to dryness, re - dissolved in DCM (10 ml), washed with water (3 x 10 ml) and dried to afford **68** in a yield of 98 % as a light orange amorphous powder.

(*R_c* *S_{pl}* *S_{pro}*)-**68**

Light orange solid. ¹H NMR (CDCl₃, 500 MHz): δ 1.82 (m, 1H), 2.14 - 2.22 (m, 2H), 2.51 - 2.52 (m, 1H), 2.63 - 2.71 (m, 1H), 3.00 - 3.04 (m, 1H), 3.49 (m, 1H), 3.60 (m, 1H), 3.78 (m, 5H), 3.89 (m, 1H), 4.14 - 4.19 (m, 3H), 4.56 - 4.58 (m, 1H, -CHPPh₂), 6.29 (m, 1H, Ar), 6.71 (m, 1H, Ar), 7.01 - 7.02 (m, 3H, Ar), 7.37 (m, 1H, Ar), 7.54 - 7.65 (m, 5H, Ar), 8.56 - 8.60 (m, 2H, Ar). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 15.3, 25.7, 30.2, 35.8, 36.1, 44.9, 51.6, 63.7, 64.9, 65.1, 67.6, 68.9, 69.0, 70.0, 90.9, 91.0, 101.2, 101.5, 127.7, 128.0, 128.1, 128., 128.8, 129.1, 129.2, 129.7,

130.1, 130.9, 131.6, 133.1, 134.6, 134.8, 134.9, 135.0, 135.7, 181.7, 197.6. ^{31}P $\{^1\text{H}\}$ NMR (CDCl_3 , 161 MHz): δ 68.8. LC - MS (M/Z) 711.23. Decomposition T 190 - 191 $^\circ\text{C}$. $[\alpha]_{\text{D}} = +43$ (c 0.09 DCM).

($R_c S_p$)-**67**

Orange solid. ^1H NMR (CDCl_3 , 400 MHz): δ 2.65 - 2.76 (m, 1H), 3.05 - 3.15 (m, 1H), 3.87 - 3.91 (m, 5H, Cp), 4.01 - 4.15 (m, 2H, Cp), 4.41 - 4.68 (m, 2H, Cp & $-\text{CHPPh}_2$), 6.30 - 6.31 (m, 1H, Ar), 6.66 - 6.67 (m, 1H, Ar), 7.07 - 7.13 (m, 3H, Ar), 7.38 (s, 1H, Ar), 7.52 - 7.84 (m, 6H, Ar), 8.56 - 8.61 (m, 1H, Ar), 8.88 - 8.93 (m, 1H, Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 44.5, 53.4, 64.1, 66.6, 69.3, 69.5, 71.1, 111.9, 117.5, 127.7, 127.8, 129.1, 129.2, 130.9, 131.8, 134.9, 135.0, 135.5, 135.7, 146.4, 151.4, 186.2. ^{31}P $\{^1\text{H}\}$ NMR (CDCl_3 , 161 MHz): δ 70.7, 72.0. LC - MS (M/Z) 1265.76. Decomposition T 176 - 177 $^\circ\text{C}$. $[\alpha]_{\text{D}} = -285$ (c 0.4, DCM).

Boronic acid addition procedure:

To a 10 ml flask were placed arylboronic acid (2.0 mmol), catalyst ($R_c S_p$)-**67** (63.25 mg, 0.05 mmol), 2 - cyclohexen - 1 - one (**24**) (96.0 mg, 1.0 mmol), K_3PO_4 (5 M) and toluene (2 ml). The resulting solution was stirred at 0 $^\circ\text{C}$ for 6 hours. The addition product was purified via chromatography on silica gel (n - hexanes to 5 n - hexanes : 1 Ethyl Acetate).

3 - Phenylcyclohexanone (**61a**)

Colourless oil. ^1H NMR (CDCl_3 , 400 MHz): δ 1.79 - 1.88 (m, 2H), 2.07 - 2.18 (m, 2H), 2.38 - 2.59 (m, 4H), 3.00 - 3.02 (m, 1H, $-\text{CHPh}$), 7.21 - 7.26 (m, 3H, Ar), 7.31 - 7.35 (m, 2H, Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 25.6, 32.8, 41.2, 44.8, 49.0, 126.6, 126.7, 128.7, 144.4, 211.0. LC - MS (M/Z) 174.98. The enantiomeric ratio was determined via HPLC using a chiral column (Daicel Chiralpak AD - H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 254 nm, 18.3 mins (minor), 21.9 mins (major).

3-(4 -methylphenyl) cyclohexanone (**61b**)

Colourless oil. ^1H NMR (CDCl_3 , 400 MHz): δ 1.75 - 1.86 (m, 2H), 2.05 - 2.17 (m, 2H), 2.33 (s, 3H, $-\text{CHPh}(\text{Me})$), 2.37 - 2.61 (m, 4H), 2.95 - 3.01 (m, 1H, $-\text{CHPh}(\text{Me})$), 7.01 - 7.16 (m, 4H, Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 21.0, 25.6, 32.9, 41.2, 44.4, 49.1, 126.5, 129.4, 136.3, 141.4, 211.2. LC - MS (M/Z) 188.97. The enantiomeric ratio was determined via HPLC using a chiral column (Daicel Chiralpak AD - H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 270 nm, 16.4 mins (minor), 18.2 mins (major).

3-(1-naphthyl) cyclohexanone (**61c**)

Colourless oil. ^1H NMR (CDCl_3 , 400 MHz): δ 1.94 - 2.03 (m, 2H), 2.19 - 2.27 (m, 2H), 2.46 - 2.79 (m, 4H), 3.86 - 3.67 (m, 1H, $-\text{CHAr}$), 7.39 - 7.56 (m, 4H, Ar), 7.75 - 7.77 (d, 1H, Ar, $J = 8.0$ Hz), 7.87 - 7.89 (d, 1H, Ar, $J = 8.0$ Hz), 8.03 - 8.05 (d, 1H, Ar, $J = 8.0$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 25.6, 32.3, 39.4, 41.5, 48.6, 122.4, 122.7, 125.5, 125.6, 126.2, 127.3, 129.1, 130.9, 134.0, 140.0, 211.2. LC - MS (M/Z) 225.11. The enantiomeric ratio was determined via HPLC using a chiral column (Daicel Chiralpak AD - H), *n* - hexanes : IPA = 99 : 1, 0.5 ml / min, 270 nm, 42.7 mins (minor), 47.5 mins (major).

3-(4-methoxyphenyl) cyclohexanone (**61d**)

Light yellow oil. ^1H NMR (CDCl_3 , 400 MHz): δ 1.73 - 1.83 (m, 2H), 2.04 - 2.16 (m, 2H), 2.36 - 2.60 (m, 4H), 2.94 - 3.00 (m, 1H, $-\text{CHPh}(\text{OMe})$), 3.80 (s, 3H, $-\text{CHPh}(\text{OMe})$), 6.86 - 6.88 (m, 2H, Ar), 7.13 - 7.15 (m, 2H, Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 25.5, 33.0, 41.2, 44.0, 49.3, 55.3, 114.0, 127.5, 136.6, 158.3, 211.2. LC - MS (*M / Z*) 204.96. The enantiomeric ratio was determined via HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 90 : 10, 0.5 ml / min, 270 nm, 35.0 mins (major), 38.8 mins (minor).

3-(4-fluorophenyl) cyclohexanone (**61e**)

Colourless oil. ^1H NMR (CDCl_3 , 400 MHz): δ 1.74 - 1.87 (m, 2H), 2.04 - 2.17 (m, 2H), 2.35 - 2.61 (m, 4H), 2.98 - 3.03 (m, 1H, $-\text{CHPh}(\text{F})$), 6.99 - 7.03 (m, 2H, - Ar), 7.16 - 7.20 (m, 2H, -Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 25.4, 32.9, 41.1, 44.0, 49.1, 115.4, 115.6, 128.0, 140.0, 140.1, 210.7. $^{19}\text{F}\{^1\text{H}\}$ (CDCl_3 , 282 MHz): δ 116.3. LC - MS (*M / Z*) 192.98. The enantiomeric ratio was determined via HPLC using a chiral column (Daicel Chiralpak AD - H), *n* - hexanes : IPA = 99 : 1, 0.5 ml / min, 210 nm, 35.2 mins (minor), 46.7 mins (major).

2.1.5.

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Chapter 2.2.

Enantioselective Preparation of Ferrocenyl Monophosphines *via* Classical Kinetic Resolution of Planar Ferrocenyl Racemates

2.2.1.

Introduction

Planar chiral 1, 2-disubstituted ferrocenyl mono- and diphosphines have gained significant interest as dynamic ligands for an array of asymmetric catalysis scenarios.¹ Current protocols to access these precious motifs revolve around diastereoselective² or enantioselective³ *ortho*-directed lithiation of ferrocenyl precursors. Although synthetically relevant and practical, these methods require suitable directing groups or expensive chiral promoters. An efficient catalytic methodology which utilizes racemic substrates whilst affording direct access to 1, 2-substituted ferrocenyl phosphines containing both central and planar chirality elements in a single step is currently lacking in the synthetic library.

Non-enzymatic kinetic resolution of planar ferrocenyl racemates has been briefly utilized by Kudo, Takahashi and Moyano for the synthesis of ferrocenyl frameworks (See Chapter 1.1.3.3).⁴ However, to date, kinetic resolution has not yet been diluted to the synthesis of 1, 2-disubstituted ferrocenyl monophosphines.

Encouraged by the efficacy of palladacycle-catalyzed P-H addition to activated ferrocenyl enones described in Chapter 2.1, an extension of this protocol to the generation of enantio-enriched ferrocenyl monophosphines incorporating *both* central and planar chirality was of significant interest.

The fusion of the above concepts could grant an alternate avenue to the synthesis of enantio-enriched 1, 2-disubstituted ferrocenyl monophosphines *via* the balance between inner-sphere stereinduction and catalyst-substrate recognition.

2.2.2.

Results and Discussion

We begun our initial investigation by electing *rac*-(**70a**) and diphenylphosphine (**58**) as our model substrates. The addition of 1.2 equivalents of diphenylphosphine (**58**) to *rac*-(**70a**) in the presence of 10 mol % catalyst (S)-**C5** and 1.2 equivalents NEt₃ in dried MeOH over 24 hours at RT proceeded with exclusive regioselectivity, affording (S_c S_{pl})-**71a** as the sole product in a 60 % isolated yield, 68 % *de* and 55 % *ee* (Scheme 2.2.1). Interestingly, the yields did not improve significantly after extended reaction times: 48 hours (62 %), or 72 hours (64 %). Subsequent attempts with 20 mol % catalyst (S)-**C5** over a period of 24 hours failed to provide satisfactory yields (64 %) either.

Efficient phosphine substitution of an unprotected hydroxyl moiety has been previously reported under protic environments, however, under current conditions, neither the substitution product (**72a**) nor diphosphine (**73a**) was observed in spite of excess diphenylphosphine in MeOH. This allows us to rule out a plausible parallel kinetic resolution (PKR).

Scheme 2.2.1.

Concerned by the poor conversions (heightened by the significant retardation of reaction rate after 50 % conversion), and in conjunction with poor selectivity values, we sought out classical kinetic resolution as an alternate means to obtain enantioenriched **71a**. Both enzymatic and non-enzymatic kinetic resolution of ferrocenyl racemates have been employed as a method to obtain optically active 1, 2-disubstituted ferrocenes as discussed previously at the start of the chapter.

Hence, the addition of 0.5 equivalents of diphenylphosphine (**58**) to *rac*-**70a** in the presence of 10 mol % catalyst *(S)*-**C5** and 0.5 equivalents NEt₃ in dried MeOH over 24 hours afforded (*S_c*, *S_{pl}*)-**71a** in a 48 % isolated yield, 71 % *de* and 60 % *ee*. Attempts to enhance selectivity values *via* solvent variation only led to further setbacks, with DCM, THF, MeCN and acetone failing to administer adequate conversions (<30 %), *de* (<70 %) or *ee* (<60 %) when the phosphamichael addition was proceeded at RT. The switch of catalyst to its phosphapalladacycle analog *(S)*-**C6** did not furnish appreciable selectivities either (Table 2.2.1, Entry 2). Gratifyingly, heightened selectivity values were achieved during low temperature experiments. We were able to acquire a balance between reactivity and selectivity at -60 °C over 24 hours, with 46 % yield, 91 % *de* and 87 % *ee* obtained (Table 2.2.1, Entry 5). Although near perfect *de* was attained at -80 °C, incomplete conversion was also observed (Table 2.2.1, Entry 6).

Table 2.2.1.^a

Entry	Cat.	T (°C)	Yield ^b (%)	de ^c (%)	ee ^d (%)
1	C5	RT	48	71	60
2	C6	RT	45	45	58
3	C5	-20	48	79	70
4	C5	-40	47	82	79
5	C5	-60	46	91	87
6	C5	-80	15	>99	n.d

^a Reaction conditions: Diphenylphosphine (**58**) (10 mg, 9.34 μ L, 0.054 mmol, 0.50 eq.), Catalyst (**C5** / **C6**) (10 mol % of *rac*-**70a**), *rac*-**70a** (37 mg, 0.11 mmol, 1 eq.) and NEt₃ (5.4 mg, 7.48 μ L, 0.054 mmol, 0.50 eq.) was stirred in 5 ml of dry MeOH at the stipulated temperature for 24 hours after which S₈ (0.22 mg, 6.75 $\times 10^{-3}$ mmol, 0.50 eq.) in 1 ml of DCM was added and the mixture raised to RT for 1 hour. ^b Isolated yield of (S_c S_{pl})-**71aa**. ^c de of (S_c S_{pl})-**71aa**. Determined by ³¹P{¹H} NMR integration of the crude reaction mixture. ^d ee of (S_c S_{pl})-**71aa**. Determined by HPLC using a chiral column.

Heartened by these initial results, we proceeded to ascertain the tolerance of this methodology by variation of the ferrocenyl ring substituent (R_1), terminal aryl moiety (R_2) and secondary phosphines (Ar) (Table 2.2.2).

Table 2.2.2.^a

Entry	Substrate	Phosphine	Yield ^b (%) (70 : 71)	ee ^c (%) (70)	de ^d (%) (71)	ee ^e (%) (71)
1	70a	58a	52 : 46	74	91	87
2	70b	58a	84 : 10	n.d	>99	86
3	70c	58a	50 : 46	n.d	>99	82
4	70d	58a	56 : 42	53	87	88
5	70e	58a	42 : 50	85	90	92
6	70f	58a	46 : 48	n.d	95	88
7	70g	58a	46 : 50	n.d	94	>99
8	70h	58a	42 : 50	n.d	84	86
9	70i	58a	52 : 46	82	>99	>99
10	70i	58b	54 : 44	37	84	80
11	70i	58c	52 : 46	37	93	82
12	70i	58d	50 : 46	57	>99	90

^a Reaction conditions: Diphenylphosphine (**58**) (10 mg, 9.34 μ L, 0.054 mmol, 0.50 eq.), Catalyst (**C5**) (10 mol % of *rac*-**70**), *rac*-**70** (37 mg, 0.11 mmol, 1 eq.) and NEt₃ (5.4 mg, 7.48 μ L, 0.054 mmol, 0.50 eq.) was stirred in 5 ml of dry MeOH at the stipulated temperature for 24 hours after which S₈ (0.22 mg, 6.75 x 10⁻³ mmol, 0.50 eq.) in 1 ml of DCM was added and the mixture raised to RT for 1 hour. ^b Isolated yield. ^c ee of (*R*_{pl})-**70**. Determined by HPLC using a chiral column. ^d de of (S_c S_{pl})-**71**. Determined by ³¹P{¹H} NMR integration of the crude reaction mixture. ^e ee of (S_c S_{pl})-**71**. Determined by HPLC using a chiral column.

In general, homologous results were obtained, with yields of (S_c S_{pl})-**71** comparative to the theoretical maximum of 50 %, good to excellent *de* (84 - >99 %) and *ee* (80 - >99%) with selectivity factors ranging from 15 - >500. Enantioenriched (S_{pl})-**70** was isolated in good yields with up to 85 % *ee*. Notably, the addition of diphenylphosphine (**58**) to *rac*-(**70g**) and (**70i**) afforded (S_c S_{pl})-(**71g**) and (**71i**) in >99 % *ee*.

To our disappointment, the P-H addition of a trimethylsilyl derivative (*rac*-**70b**) only afforded 10 % yield, with excellent *de* (>99 %) and appreciable *ee* (86 %) (Table 2.2.2, Entry 2). In contrast, the addition proceeded smoothly when an iodo-substituted substrate (*rac*-**70c**) was used, with 46 % yield, >99 % *de* and 82 % *ee* obtained (Table 2.2.2, Entry 3). This result is momentous in that it allows for the construction of MOPF or 5-membered diphosphine ligands upon consequent cross-couplings reactions (Scheme 2.2.2).

Scheme 2.2.2.

A deflation of *ee* was observed when the aryl moieties on the phosphine nucleophile was varied, with both *meta*- and *para*-tolyl phosphines affording their corresponding adducts in 80 and 82 % *ee* respectively, while *para*-methoxyphenyl phosphine provided 90 % *ee* (Table 2.2.2, Entries 10 - 12).

The selectivity factor (*s* factor) is a term commonly associated with classical kinetic resolution. Due to a large number of statistical information related to a classical kinetic resolution (conversion of starting material to product, *ee* of the starting material, *ee* of the product), Kagan and Fiaud derived *s* factor as a singular expression to simplify the resolution efficiency. However, their derivation assumes a simple first order kinetic dependence on substrates and the absence of non-linear effects involving the catalyst. Hence, to validate the relevance of *s* factor calculations in this instance, a series of controlled experiments were carried out (Scheme 2.2.3).

Scheme 2.2.3.^a

^a Reaction conditions: NEt₃ (5.4mg, 7.48μL, 0.054 mmol, 0.50 eq.) was added to a dried methanolic solution of diphenylphosphine (**58**) (10 mg, 9.34 μL, 0.054 mmol, 0.50 eq.), **C5** (10 mol % of *rac-70i*) and *rac-70i* (37 mg, 0.11 mmol, 1 eq.) at RT. The purple solution was stirred for 1 minute before 0.50 mL was extracted and injected into a N₂ protected NMR tube.

The first rate determining experiment was carried out by the addition of 0.5 eq. HPPH₂ (**58**) to *rac-70i* in the presence of 10 mol % (S)-**C5**, 1 eq. NEt₃ in dried methanol at room temperature. 5 minute intervals were taken between each collected conversion data point. Although the aforementioned phospho-Michael resolution procedures were conducted at -60 °C, the inability to maintain a lowered temperature during the transition between NEt₃ addition and the first

conversion data point at 5 minutes compelled this experiment to be carried out at room temperature instead. Table 2.2.3 tabulates the conversion and ln conversion values at 5 minutes.

Table 2.2.3.

Time (mins)	Conv. (%)	ln Conv.
0	0	0
5	23	3.14
10	34	3.526
15	38.5	3.6506
20	42.5	3.7495
25	43.5	3.7727
30	46	3.8286
35	48	3.8712
40	49	3.8918

The calculation of conversions are taken from crude $^{31}\text{P}\{^1\text{H}\}$ NMR and are as follows:

$$([\text{Integration of product (S}_c \text{ S}_{pl})\text{-7ia signal} - \text{Integration of diphenylphosphine } \mathbf{58} \text{ signal}] / 2)$$

The plot of ln Conv. (y-axis) vs. time (x-axis) is displayed in Plot 2.2.1.

Plot 2.2.1. In Conv. vs. time (mins) (best fit line).

Plot 2.2.2. In Conv. vs. time (mins) (best fit logarithmic curve)

The best fit line for this data set has an R^2 value of -0.425 (plot 2.2.1), however, the best fit logarithmic curve for the same data set presented in Table 2.2.3 was found to have an R^2 value of 0.9568 (Plot 2.2.2).

For a first order kinetic dependence, the best fit line should be linear and hence have a R^2 value close to 1. It can thus be initially concluded that the kinetic resolution of 1, 2-disubstituted enones *via* asymmetric hydrophosphination does not proceed as first order kinetics due to the poor R^2 value of the best fit line shown in Plot 2.2.1.

A second experiment was conducted utilizing *rac*-**70g** as the model and an interval of 3 minutes, with all other variables kept constant (Scheme 2.2.3).

Scheme 2.2.4.

^a Reaction conditions: NEt_3 (5.4 mg, 7.48 μL , 0.054 mmol, 0.50 eq.) was added to a dried methanolic solution of diphenylphosphine (**58**) (10 mg, 9.34 μL , 0.054 mmol, 0.50 eq.), **C5** (10 mol % of *rac*-**70g**) and *rac*-**70g** (37 mg, 0.11 mmol, 1 eq.) at RT. The purple solution was stirred for 1 minute before 0.50 mL was extracted and injected into a N_2 protected NMR tube.

Table 2.2.4 displays the data obtained at 3 minute intervals.

Table 2.2.4.

Time (mins)	Conv.	ln Conv.
0	0	0
4	15	2.71
7	20	3
10	28	3.35
13	28.5	3.35
16	29.3	3.38
19	30.7	3.43
22	29.9	3.4
25	35.9	3.58
28	40.4	3.7
31	35.2	3.56
34	29.8	3.39
37	42.6	3.75
40	35.8	3.58
43	37.7	3.63
46	30.9	3.43
49	46	3.83
52	41.7	3.73
55	40.6	3.7
58	38.5	3.65
61	42	3.74
64	38.6	3.65
67	35.3	3.56
70	40.2	3.69

The plot of ln Conv. vs. time is displayed in Plot 2.2.3.

Plot 2.2.3. In Conv. vs. time (mins) (best fit line).

Plot 2.2.4 In Conv. vs. time (mins) (best fit logarithmic curve).

Once again, the R^2 value of the logarithmic curve in plot 2.2.4 has a R^2 value closer to 1 as compared to the R^2 value of the best fit line in plot 2.2.3 (0.7685 vs. -2.967). As these 2 independent experiments have shown, it is unlikely that the phospho-Michael resolution

proceeds by a first order kinetic dependence and hence s factor calculations are irrelevant in this instance.

We further attempted to procure ($R_c R_{pl}$)-**71a** via the addition of fresh **58** to the residual enantioenriched (S_{pl})-**70a** (Table 2.2.2, Entry 1, 74 % ee) employing (R)-**C5** under the same conditions. Thus, ($R_c R_{pl}$)-**71a** was indeed obtained in an 80 % yield (with respect to (R_{pl})-**70a**) with near perfect selectivities (Scheme 2.2.5).

Scheme 2.2.5.

As discussed earlier in the introduction, the presence of the hydroxyl functionality serves as a versatile functional handle. Hence, the addition of diphenylphosphine to ($R_c R_{pl}$)-**71a** afforded the corresponding diphosphine ($R_c R_{pl}$)-**73a** in a 95 % yield (with respect to ($R_c R_{pl}$)-**71a**) with imperceptible loss of ee (Scheme 2.2.6).

Scheme 2.2.6.

Enthused by these results achieved from the first instance of a kinetic resolution based AHP protocol, the basis of the observed catalyst-substrate selectivity control was further investigated. The mechanism of Pd(II)-catalyzed phospho-Michael addition of diphenylphosphines to enones has been previously examined (see Chapter 1).⁵ An analogous catalytic cycle is postulated to be abided by this system. Further consultation of the single crystal X-ray diffraction data of (*S*_c *S*_{pl})-**71i** reveal both chiral elements to bear the *S* configuration (Figure 2.2.1).

Figure 2.2.1.

Selected Bond Lengths (Å)

Selected Bond Angles (°)

P1-S1	1.9584(9)	C10-C11	1.500(7)	O1-C11-C10	112.8(7)	O1A-C11A-C10	101.9(9)
C12-P1	1.853(3)	C10-C11A	1.547(12)	C9-C12-C13	112.53(19)	C9-C12-P1	107.92(17)
C19-P1	1.815(3)	C11-O1	1.451(12)	C13-C12-P1	109.79(17)	C14-C13-C12	114.6(2)
C25-P1	1.809(3)	C11A-O1A	1.463(15)	O2-C14-C13	124.3(2)	C24-C19-P1	123.0(2)
C9-C12	1.503(3)	C14-O2	1.214(3)	C20-C19-P1	117.7(2)	C26-C25-P1	121.6(2)
C12-C13	1.546(3)	C13-C14	1.503(4)	C30-C25-P1	118.6(2)	C25-P1-C19	106.17(11)
C14-C15	1.473(8)			C25-P1-C12	104.22(11)	C19-P1-C12	107.33(12)
				C25-P1-S1	114.19(9)	C19-P1-S1	111.69(9)
				C12-P1-S1	112.65(8)		

An analysis based on Drieding models suggest that the C=C bond of the enone side arm would experience larger steric hindrance when partially eclipsed with the substituent (Cp-R₁) at the *ortho* position on the Cp ring as compared to the adjacent unsubstituted site (Cp-H) (Figure 2.2.3, Conformation 1). Furthermore, the rigid structure of the basal Cp ring restricts phosphide nucleophilic attack to only the top face due to sterics (Figure 2.2.2, Conformation 2).

Figure 2.2.2.

These considerations thus advocates a staggered configuration between the C=C bond and Cp-R₁ substituent and a top faced phosphide attack, which gives rise to conformation 3 (Figure 2.2.3, Conformation 3).

Figure 2.2.3.

The intramolecular phosphide addition involves a square planar transition state reinforced by the palladacyclic ring adopting either the λ or δ conformation.^{5e-g} (S)-**C5** adopts an absolute λ in both solid state and in solution as discussed previously in Chapter 1. Here, it is noteworthy to

mention that the chiral methyl pendant on (S)-**C5** does not engage in severe steric interactions with either the substrate nor the phosphine, but rather, it locks the 5-membered ring into a conformationally rigid assignment and coerces one of the aromatic groups on the phosphine nucleophile to take up an axial position above the top of the square plane. On this basis, two Dreiding models which describes the possible transition states may be hypothesized (Figure 2.2.4).

Figure 2.2.4.

The discrimination between planar chiral (S_{pl}) or (R_{pl})-ferrocenyl substrate is due to sterics between the axial aryl fragment of the phosphine and the ferrocenyl pendant (R_1), thus affording (S_c , S_{pl}) configurations in the major isomer.

2.2.3

Conclusion

In conclusion, we have devised a protocol which provides direct access to enantio-enriched ferrocenyl monophosphines incorporating *both* central and planar chirality elements from their parent racemates. This methodology is tolerant to a range of biaryl-secondary phosphines and ring substituents, affording precious scaffolds which have potential synthetic value as chiral ligands and biologicals. We have further demonstrated a facile substitution procedure which yields diphosphines with negligible loss in stereoselectivity.

2.2.4.

Experimental

All air-sensitive manipulations were carried out under dry N₂ by means of Schlenk techniques unless otherwise stated. Solvents were degassed and / or distilled and stored over 4 Å molecular sieves prior to use. Glassware were oven-dried and placed under vacuum for 30 minutes prior to use. A low temperature pairstirrer PSL-1800 machine was used for low temperature experiments. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F254 aluminium backed plates and visualized under UV light or I₂. Flash column chromatography was conducted using Merck silica gel 60. NMR spectra were obtained using a Bruker AV 300 spectrometer (¹H at 300 MHz, ¹³C{¹H} at 75 MHz, ³¹P{¹H} at 121 MHz), Bruker AV 400 spectrometer (¹H at 400 MHz, ¹³C{¹H} at 100 MHz, ³¹P{¹H} at 161 MHz) or Bruker AV 500 spectrometer (¹H at 500 MHz, ¹³C{¹H} 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. Optical rotations were measured on the specified solution in a 0.1 dm cell at 20 °C with a Perkin-Elmer 341 polarimeter. Melting points were documented on a SRS Optimelt MPA 100 point system. Mass spectrometry was obtained in ESI mode on a Thermo Finnigan LCQ Deca XP MAX system.

General procedures:

Preparation of **70a, d - i**:

Racemic-1-formyl-2-hydroxymethyl ferrocene

Under an atmosphere of N₂, hydroxymethyl ferrocene (0.188 g, 0.87 mmol) was dissolved in anhydrous Et₂O (10 ml) and cooled to 0 °C *via* an ice bath. *n*-BuLi (1.20 ml, 1.91 mmol, 1.6 M in *n* - hexanes) was subsequently added dropwise and the yellow mixture warmed to RT. After 16 hours, the temperature was brought down to 0 °C *via* an ice bath and anhydrous DMF (0.14 ml, 1.74 mmol) was added dropwise. The orange mixture was allowed to warm to RT and stirred for an additional 2 hours before H₂O (20 ml) was added dropwise. The organic layer was separated and the resultant aqueous layer extracted with DCM (3 x 20 ml). The organic layers were then combined, dried and concentrated *via* rotary evaporation in vacuo. The crude oil was purified over silica gel (DCM to 10 DCM : 1 Et₂O) to afford *racemic*-1-formyl-2-hydroxymethyl ferrocene (60 % yield) as a deep orange oil. ¹H NMR (CDCl₃, 300 MHz): δ 3.90 (s, 1H, -CH₂OH), 4.28 (s, 5H, Cp), 4.43 - 4.61 (m, 3H, -CH₂OH and Cp), 4.61 - 4.76 (m, 2H, Cp), 9.93 (s, 1H, -CHO).

70a, d - i

Racemic-1-formyl-2-hydroxymethyl ferrocene (0.98 g, 4 mmol) was dissolved in 5 ml of absolute EtOH and the respective aromatic methyl ketone (4 mmol) and 40 % KOH (1 ml) was added respectively. The dark orange reaction mixture was then left to stir at RT for 3 hours. Thereafter, H₂O (0.5 ml) was added. Solvents were removed *via* rotary evaporation in vacuo and the aqueous layer extracted with DCM. The organic layer was then dried and concentrated to yield a dark purple oil. The crude adduct was then chromatographed on silica gel (DCM to 5 DCM : 1 EA) to afford **70a, d - i**.

(*rac*)-70a

80 % yield. ¹H NMR (CDCl₃, 400 MHz): δ 1.90 (t, 1H, ³J = 5.2 Hz, -CH₂OH), 4.15 (s, 5H, -Cp), 4.47 - 4.56 (m, 3H, -CH₂ and -Cp), 4.61 - 4.69 (m, 3H, -CH₂OH and -Cp), 7.27 (d, 1H, ³J = 15.6 Hz, -HC=CHCO), 7.45 - 7.55 (m, 3H, -Ar), 7.86 (d, 1H, ³J = 15.6 Hz, -HC=CHCO), 7.97 - 7.99 (m, 2H, -Ar). ¹³C{¹H} NMR (CDCl₃, 400 MHz): δ 59.3, 68.3, 70.1, 70.3, 72.5, 78.7, 88.5, 120.1, 128.4, 128.6, 132.6, 138.5, 144.4, 189.7.

(rac)-70d

82 % yield. ¹H NMR (CDCl₃, 400 MHz): δ 2.19 (broad s, 1H, -CH₂OH), 2.40 (s, 3H, -ArCH₃), 4.13 (s, 5H, -Cp), 4.44 - 4.54 (m, 3H, -CH₂OH and -Cp), 4.61 - 4.68 (m, 2H, -CH₂OH and -Cp), 7.24 (d, 1H, ³J = 15.2 Hz, -HC=CHCO), 7.27 (d, 2H, ³J = 8.0 Hz, -Ar), 7.84 (d, 1H, ³J = 15.2 Hz, -HC=CHCO), 7.90 (d, 2H, ³J = 8.0 Hz, -Ar). ¹³C{¹H} NMR (CDCl₃, 500 MHz): δ 21.7, 29.7, 59.2, 68.2, 70.1, 70.2, 70.3, 72.5, 78.8, 88.5, 120.1, 128.6, 129.3, 135.9, 143.3, 143.9, 189.3.

(rac)-70e

90 % yield. ¹H NMR (CDCl₃, 400 MHz): δ 1.26 (broad s, 1H, -CH₂OH), 3.86 (s, 3H, -ArOCH₃), 4.14 (s, 5H, Cp), 4.44 - 4.67 (m, 5H, -CH₂OH and -Cp), 6.95 (d, 2H, ³J = 8.8 Hz, -Ar), 7.27 (d, 1H, ³J = 15.6 Hz, -HC=CHCO), 7.82 (d, 1H, ³J = 15.2 Hz, -HC=CHCO), 7.99 (d, 2H, ³J = 8.8 Hz, -Ar). ¹³C{¹H} NMR (CDCl₃, 400 MHz): δ 29.7, 55.5, 59.3, 68.2, 70.1, 72.4, 79.0, 88.3, 113.8, 119.9, 130.7, 131.3, 143.4, 163.2, 188.1.

(rac)-70f

92 % yield. ¹H NMR (CDCl₃, 500 MHz): δ 1.78 (m, 1H, -CH₂OH), 4.22 (s, 5H, -Cp), 4.36 - 4.74 (m, 5H, -CH₂OH and -Cp), 7.27 (d, 1H, ³J = 15.3 Hz, -HC=CHCO), 7.50 (d, 2H, ³J = 7.50 Hz, -Ar), 7.92 (d, 1H, ³J = 15.3 Hz, -HC=CHCO), 7.97 (d, 2H, ³J = 7.50 Hz, -Ar). ¹³C{¹H} NMR (CDCl₃, 400 MHz): δ 59.3, 68.4, 70.2, 70.5, 72.7, 78.6, 88.5, 119.5, 128.9, 129.8, 136.8, 138.9, 145.0, 188.3.

(rac)-70g

90 % yield. ¹H NMR (CDCl₃, 500 MHz): δ 1.88 (broad m, 1H, -CH₂OH), 4.19 (s, 5H, -Cp), 4.50 - 4.76 (m, 5H, -CH₂OH and -Cp), 7.43 (d, 1H, ³J = 15.0 Hz, -HC=CHCO), 7.54 - 7.61 (m, 2H, -Ar), 7.88 - 8.09 (m, 5H, -HC=CHCO and -Ar), 8.50 (s, 1H, -Ar). ¹³C{¹H} NMR (CDCl₃, 400 MHz): δ 59.2, 68.1, 70.2, 70.3, 70.4, 72.7, 78.8, 88.7, 120.0, 124.6, 126.7, 127.8, 128.3, 128.5, 129.6, 129.8, 132.6, 135.4, 135.8, 144.6, 189.6.

(rac)-70h

84 % yield. ¹H NMR (CDCl₃, 500 MHz): δ 1.85 (m, 1H, -CH₂OH), 4.20 (s, 5H, -Cp), 4.51 - 4.72 (m, 5H, -CH₂OH and -Cp), 7.18 - 7.21 (m, 2H, -HC=CHCO and -Ar), 7.68 (m, 1H, -Ar), 7.84 (m, 1H, -Ar), 7.90 (d, 1H, ³J = 15.5 Hz, -HC=CHCO). ¹³C{¹H} NMR (CDCl₃, 400 MHz): δ 59.3, 68.4, 70.1, 70.3, 72.6, 78.6, 88.4, 119.9, 128.2, 131.4, 133.4, 143.6, 145.8, 181.5.

(rac)-70i

66 % yield. ¹H NMR (CDCl₃, 500 MHz): δ 1.65 - 1.67 (m, 1H, -CH₂OH), 4.11 (s, 5H, -Cp), 4.42 - 4.52 (m, 3H, -CH₂OH and Cp), 4.56 - 4.66 (m, 2H, -CH₂OH and -Cp), 6.50 - 6.52 (m, 1H, -Ar), 7.09 (d, 1H, ³J = 15.5 Hz, -HC=CHCO), 7.21 - 7.23 (m, 1H, -Ar), 7.57 (m, 1H, -Ar), 7.84 (d, 1H, ³J = 15.5 Hz, -HC=CHCO). ¹³C{¹H} NMR (CDCl₃, 400 MHz): δ 59.2, 68.2, 70.2, 70.4, 72.5, 78.5, 88.7, 112.5, 117.1, 119.4, 143.6, 146.2, 153.9, 177.5.

Preparation of **70b** and **c**:

Synthesis of **70b**:

75a was synthesized according to a reported procedure.⁷

75a was dissolved in 5 ml of absolute EtOH and acetophenone (1 equiv.) and 40 % KOH was added respectively. The dark orange reaction mixture was then left to stir at RT for 3 hours. Thereafter, H₂O (0.5 ml) was added. Solvents were removed *via* rotary evaporation in vacuo and the aqueous layer extracted with DCM. The organic layer was then dried and concentrated to yield a dark purple oil. The crude adduct was then chromatographed on silica gel (DCM to 5 DCM : 1 EA) to afford **70b**.

(rac)-70b

70 % yield. ^1H NMR (CDCl_3 , 500 MHz): δ 0.33 (s, 9H, $-\text{SiMe}_3$), 4.17 (s, 5H, $-\text{Cp}$), 4.40 (s, 1H, $-\text{Cp}$), 4.64 (s, 1H, $-\text{Cp}$), 4.87 (s, 1H, Cp), 7.11 (d, 1H, $^3J = 15.0$ Hz, $-\text{HC}=\text{CHCO}$), 7.47 - 7.56 (m, 3H, $-\text{Ar}$), 7.85 (d, 1H, $^3J = 15.5$ Hz, $-\text{HC}=\text{CHCO}$), 7.95 - 7.96 (m, 2H, $-\text{Ar}$). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 500 MHz): δ 0.6, 69.1, 69.9, 73.3, 76.2, 77.7, 83.9, 120.0, 128.4, 128.5, 132.3, 147.6, 190.0.

Synthesis of **1c**:

75b was synthesized according to a reported procedure.⁸

75b was dissolved in 5 ml of absolute EtOH and acetophenone (1 equiv.) and 40 % KOH was added respectively. The dark orange reaction mixture was then left to stir at RT for 3 hours. Thereafter, H_2O (0.5 ml) was added. Solvents were removed *via* rotary evaporation in vacuo and the aqueous layer extracted with DCM. The organic layer was then dried and concentrated to yield a dark purple oil. The crude adduct was then chromatographed on silica gel (DCM to 5 DCM : 1 EA) to afford **70c**.

(rac)-70c

90 % yield. ^1H NMR (CDCl_3 , 500 MHz): δ 4.16 (s, 5H, -Cp), 4.55 (m, 1H, -Cp), 4.71 (m, 1H, -Cp), 4.28 (m, 1H, -Cp), 7.28 (d, 1H, $^3J = 15.0$ Hz, -HC=CHCO), 7.48 - 7.57 (m, 3H, -Ar), 7.81 (d, 1H, $^3J = 15.5$ Hz, -HC=CHCO), 7.99 (m, 2H, -Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 500 MHz): δ 46.3, 65.6, 71.9, 72.8, 78.0, 80.2, 120.8, 128.5, 128.6, 132.6, 138.4, 145.7, 189.6.

Kinetic resolution procedure:

A 2-neck Schlenk tube was charged with **C5** (1.95 mg, 4×10^{-3} mmol), diarylphosphine (0.02 mmol) and anhydrous MeOH (1 ml). The bright yellow solution was allowed to stir at -60°C for 10 minutes before **70** (0.04 mmol) in 1 ml of anhydrous MeOH was added. The purple solution was then stirred for a further 10 minutes before NEt_3 (2.03 mg, 2.79 μL , 0.02 mmol) in anhydrous MeOH (0.5 ml) was added dropwise. The resulting solution was stirred for 24 hours before sulphur (1.92 mg, 0.06 mmol) in degassed DCM (1 ml) was administered. The reaction mixture was then raised to RT and stirred for another 1 hour.

Determination of *de*:

The sulphurized crude solution was concentrated *via* rotary evaporation and re-dissolved in CDCl_3 for $^{31}\text{P}\{^1\text{H}\}$ NMR analysis. The relevant pair of diastereomeric resonance signals centred at δ 52 and 54 were integrated for calculation of *de*.

(S_c S_{pl})-71a

Bright yellow oil. ¹H NMR (CDCl₃, 500 MHz): δ 0.87 (m, 1H, -CH₂OH), 3.57 - 3.88 (m, 4H, -CH₂OH and -CH(PPh₂)CH₂), 3.91 (s, 5H, -Cp), 4.07 (m, 1H, -Cp), 4.26 (m, 1H, -Cp), 4.71 (s, 1H, -Cp), 4.95 (m, 1H, -CHPPh₂), 7.20 - 7.56 (m, 11H, -Ar), 8.01 - 8.11 (m, 4H, -Ar). ¹³C{¹H} NMR Spectrum (CDCl₃, 400 MHz): δ 32.3, 32.9, 42.0, 42.1, 58.7, 67.7, 67.8, 68.4, 68.8, 68.9, 85.6, 88.6, 127.8, 128.0, 128.2, 128.6, 128.8, 131.4, 131.9, 132.0, 132.1, 132.5, 132.6, 133.7, 197.2. ³¹P{¹H} NMR (CDCl₃, 400 MHz): δ 52.3 (minor diastereomer), 54.4 (major diastereomer) for 91 % *de*. [α]_D = +21.0 (0.5 c in DCM). MS (*m/z*) = 564.49. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IF), *n* - hexanes : IPA = 90 : 10, 0.75 ml / min, 280 nm, 44.0 mins (major), 65.9 mins (minor) for 87 % *ee*.

(S_c S_{pl})-71b

Bright yellow oil. ¹H NMR (CDCl₃, 400 MHz): δ 0.00 (s, 9H, -SiMe₃), 3.95 - 4.07 (m, 8H, -CH(PPh₂)CH₂ and -Cp), 4.54 (m, 1H, -Cp), 4.65 (m, 1H, -CHPPh₂), 5.25 (m, 1H, -Cp), 6.87 - 8.09 (m, 15H, -Ar). ¹³C{¹H} NMR (CDCl₃, 500 MHz): δ 0.1, 15.3, 34.6, 35.0, 44.9, 45.0, 53.4, 65.9, 68.8, 71.1, 71.3, 73.1, 73.5, 76.8, 94.1, 123.1, 124.7, 127.9, 128.0, 128.1, 128.3, 128.5, 128.6, 128.7, 128.9, 129.1, 131.2, 132.0, 132.2, 132.4, 132.8, 133.1, 133.2, 133.3, 133.5, 136.2,

196.3, 196.4. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 400 MHz): δ 55.4 for >99 % *de*. $[\alpha]_{\text{D}} = -24.0$ (0.02 *c* in DCM).

MS (*m/z*) = 660.50. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 99 : 1, 1.00 ml / min, 240 nm, 18.9 mins (major), 37.5 mins (minor) for 86 % *ee*.

(*S_c* *S_{pl}*)-**71c**

Bright yellow oil. ^1H NMR (CDCl_3 , 500 MHz): δ 3.79 - 3.89 (m, 7H, $-\text{CH}(\text{PPh}_2)\text{CH}_2$ and $-\text{Cp}$), 4.27 (m, 1H, $-\text{Cp}$), 4.34 (m, 1H, $-\text{Cp}$), 4.34 (m, 1H, $-\text{Cp}$), 4.79 (m, 1H, $-\text{CHPPh}_2$), 7.11 - 7.56 (m, 11H, $-\text{Ar}$), 8.01 - 8.19 (m, 4H, $-\text{Ar}$). $^{13}\text{C}\{^1\text{H}\}$ NMR Spectrum (CDCl_3 , 400 MHz): δ 25.4, 34.0, 34.5, 42.3, 47.5, 66.8, 68.5, 69.4, 71.5, 73.6, 89.1, 127.6, 127.7, 128.2, 128.4, 128.5, 128.6, 128.7, 128.8, 131.3, 132.0, 132.1, 132.2, 132.4, 210.4, 132.8, 133.5, 136.2, 196.6. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 400 MHz): δ 55.1 for >99 % *de*. $[\alpha]_{\text{D}} = +13.9$ (0.4 *c* in DCM). MS (*m/z*) = 606.80. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IF), *n* - hexanes : IPA = 99 : 1, 1.00 ml / min, 270 nm, 36.7 mins (major), 48.5 mins (minor) for 82 % *ee*.

(*S_c* *S_{pl}*)-**71d**

Bright yellow oil. ^1H NMR (CDCl_3 , 500 MHz): δ 1.31 (m, 1H, $-\text{CH}_2\text{OH}$), 2.39 (s, 3H, $-\text{ArCH}_3$), 3.55 - 3.90 (m, 4H, $-\text{CH}_2\text{OH}$ and $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.91 (s, 5H, -Cp), 4.06 (m, 1H, -Cp), 4.25 (m, 1H, -Cp), 4.71 (m, 1H, -Cp), 4.93 (m, 1H, $-\text{CHPPH}_2$), 7.17 - 7.50 (m, 10H, -Ar), 7.92 (d, 2H, $^3J = 8.5$ Hz, -Ar), 8.06 - 8.10 (m, 2H, -Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 400 MHz): δ 21.7, 25.4, 32.2, 32.7, 41.9, 42.0, 58.8, 67.7, 67.8, 68.4, 68.8, 85.6, 88.6, 127.9, 128.0, 128.3, 128.7, 128.8, 129.2, 129.4, 129.5, 129.9, 131.3, 131.4, 131.8, 131.9, 132.0, 132.5, 132.6, 132.7, 133.6, 144.6, 196.9. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 400 MHz): δ 52.4 (minor diastereomer), 54.4 (major diastereomer) for 87 % *de*. $[\alpha]_{\text{D}} = +28.6$ (0.8 c in DCM). MS (*m/z*) = 577.05. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 90 : 10, 1.00 ml / min, 280 nm, 23.0 mins (major), 25.2 mins (minor) for 88 % *ee*.

(*S_c* *S_{pl}*)-**71e**

Bright yellow oil. ¹H NMR (CDCl₃, 500 MHz): δ 0.80 - 0.90 (m, 1H, -CH₂OH), 3.53 - 3.69 (m, 3H, -CH₂OH and -CH(PPh₂)CH₂), 3.85 (m, 4H, -ArOCH₃ and -CH₂OH or -CH(PPh₂)CH₂), 3.92 (s, 5H, -Cp), 4.06 (m, 1H, -Cp), 4.26 (m, 1H, -Cp), 4.72 (m, 1H, -Cp), 4.93 (m, 1H, -CHPPh₂), 6.92 (d, 2H, ³J = 8.5 Hz, -Ar), 7.18 - 7.49 (m, 8H, -Ar), 8.02 (d, 1H, ³J = 8.0 Hz, -Ar), 8.07 - 8.11 (m, 2H, -Ar). ¹³C{¹H} NMR (CDCl₃, 400 MHz): δ 24.7, 32.3, 32.8, 36.7, 41.3, 41.6, 55.5, 58.7, 67.6, 67.8, 68.4, 68.8, 85.7, 88.6, 114.0, 127.8, 128.0, 128.7, 128.8, 129.2, 130.5, 131.3, 131.4, 131.8, 131.9, 132.0, 132.5, 132.6, 163.9, 195.5. ³¹P{¹H} NMR (CDCl₃, 400 MHz): δ 54.4 for >99 % *de*. [α]_D = +34.7 (0.6 c in DCM). MS (*m/z*) = 592.28. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 90 : 10, 270 nm, 36.4 mins (major), 41.5 mins (minor) for 92 % *ee*.

(*S_c* *S_{pl}*)-**71f**

Bright yellow oil. ¹H NMR (CDCl₃, 500 MHz): δ 1.18 (m, 1H, -CH₂OH), 3.53 - 3.84 (m, 4H, -CH₂OH and -CH(PPh₂)CH₂), 3.91 (s, 5H, -Cp), 4.06 (m, 1H, -Cp), 4.69 (m, 1H, -Cp), 4.90 (s,

^1H , $-\text{CHPPh}_2$), 7.19 - 4.48 (m, 10H, -Ar), 7.94 (d, 2H, $^3J = 8.5$ Hz, -Ar), 8.04 - 8.08 (m, 2H, -Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 400 MHz): δ 25.4, 32.5, 33.1, 42.0, 42.1, 58.8, 64.4, 67.8, 67.9, 68.4, 68.5, 68.8, 69.0, 85.6, 88.6, 127.9, 128.0, 128.1, 128.4, 128.5, 128.7, 128.8, 128.9, 129.0, 129.1, 129.6, 131.4, 131.5, 131.6, 131.9, 132.0, 132.1, 132.4, 132.5, 132.6, 134.3, 140.2, 195.9, 196.0. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 500 MHz): δ 52.2 (minor diastereomer), 54.3 (major diastereomer) for 95 % *de*. $[\alpha]_{\text{D}} = +34.4$ (0.2 c in DCM). MS (m/z) = 596.82. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IF), *n* - hexanes : IPA = 80 : 20, 1.00 ml / min, 280 nm, 15.7 mins (major), 21.8 mins (minor) for 88 % *ee*.

(S_{c} S_{pl})-71g

Bright yellow oil. ^1H NMR (CDCl_3 , 500 MHz): δ 1.30 (s, 1H, $-\text{CH}_2\text{OH}$), 3.57 - 3.82 (m, 3H, $-\text{CH}_2\text{OH}$ and $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.92 - 4.08 (m, 7H, -Cp and $-\text{CH}_2\text{OH}$ or $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 4.28 (m, 1H, -Cp), 4.78 (m, 1H, -Cp), 5.01 (m, 1H, $-\text{CHPPh}_2$), 7.19 - 7.62 (m, 10H, -Ar), 7.85 - 8.13 (m, 6H, -Ar), 8.55 (s, 1H, -Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 500 MHz): δ 14.2, 21.1, 32.4, 32.8, 42.1, 58.8, 60.4, 67.7, 67.9, 68.5, 68.8, 85.5, 88.7, 123.7, 127.0, 127.8, 127.9, 128.0, 128.7, 128.8, 129.2, 129.7, 130.0, 131.4, 131.9, 132.0, 132.1, 132.5, 132.6, 133.4, 135.8, 196.9, 197.0. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 500 MHz): δ 52.4 (minor diastereomer), 54.5 (major diastereomer) for 94 % *de*. $[\alpha]_{\text{D}} = +24.8$ (0.1 c in DCM). MS (m/z) = 614.19. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IF), *n* - hexanes : IPA = 80 : 20, 250 nm, 28.0 mins (major), 40.6 mins (minor) for >99 % *ee*.

(*S_c* *S_{pl}*)-**71h**

Bright yellow oil. ^1H NMR (CDCl_3 , 500 MHz): 1.19 (m, 1H, $-\text{CH}_2\text{OH}$), 3.50 - 3.82 (m, 4H, $-\text{CH}_2\text{OH}$ and $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 4.00 (s, 5H, -Cp), 4.06 (m, 1H, -Cp), 4.26 (m, 1H, -Cp), 4.68 (m, 1H, -Cp), 4.87 (m, 1H, $-\text{CHPPH}_2$), 7.09 - 8.09 (m, 13H, -Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 300 MHz): δ 14.2, 21.1, 32.7, 33.3, 42.3, 42.4, 58.8, 60.4, 67.7, 67.8, 68.4, 68.5, 68.9, 69.0, 85.5, 88.6, 127.8, 128.0, 128.3, 128.6, 128.7, 128.8, 129.7, 131.4, 131.6, 131.9, 132.0, 132.1, 132.5, 132.6, 132.7, 134.4, 143.3, 190.1. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 400 MHz): δ 52.0 (minor diastereomer), 54.1 (major diastereomer) for 94 % *de*. $[\alpha]_{\text{D}} = +20.0$ (0.6 c in DCM). MS (*m/z*) = 570.97. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IF), *n* - hexanes : IPA = 80 : 20, 280 nm, 20.0 mins (major), 37.8 mins (minor) for 86 % *ee*.

(*S_c* *S_{pl}*)-**71i**

Bright yellow oil. ^1H NMR (CDCl_3 , 500 MHz): 1.22 (m, 1H, $-\text{CH}_2\text{OH}$), 3.46 - 3.80 (m, 4H, $-\text{CH}_2\text{OH}$ and $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.96 (s, 5H, -Cp), 4.08 (m, 1H, -Cp), 4.26 (m, 1H, -Cp), 4.66 (m, 1H, -Cp), 4.84 (m, 1H, $-\text{CHPPH}_2$), 6.52 - 6.52 (m, 1H, -Ar), 7.20 - 8.10 (m, 12H, -Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 ,): δ $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 400 MHz): δ 54.1 for >99 % *de*. $[\alpha]_{\text{D}} = +12.7$ (0.1 c in DCM). MS (*m/z*) = 554.93. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IE), *n* - hexanes : IPA = 80 : 20, 280 nm, 34.3 mins (major), 78.1 mins (minor) for >99 % *ee*.

(*S_c* *S_{pl}*)-**71j**

Bright yellow oil. ^1H NMR (CDCl_3 , 500 MHz): 1.14 (m, 1H, $-\text{CH}_2\text{OH}$), 2.19 (s, 3H, $-\text{ArCH}_3$), 2.38 (s, 3H, $-\text{ArCH}_3$), 3.45 - 3.88 (m, 4H, $-\text{CH}_2\text{OH}$ and $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.95 (s, 5H, -Cp), 4.10 (m, 1H, -Cp), 4.28 (m, 1H, -Cp), 4.68 (m, 1H, -Cp), 4.77 (m, 1H, $-\text{CHPPH}_2$), 6.51 - 6.52 (m, 1H, -Ar), 7.02 - 7.93 (m, 12H, -Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 400 MHz): δ 21.2, 21.5, 25.4, 32.3, 32.8, 41.5, 41.5, 58.7, 67.7, 68.5, 68.8, 69.0, 85.8, 88.5, 112.4, 117.8, 127.7, 127.8, 128.3, 128.4, 128.5, 128.6, 129.2, 129.3, 131.5, 132.2, 132.3, 132.9, 133.0, 133.5, 133.6, 137.8, 137.9, 138.7, 138.8, 146.8, 152.1, 186.3, 186.4. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 400 MHz): δ 51.9 (minor diastereomer), 54.1 (major

diastereomer) for 84 % *de*. $[\alpha]_D = +34.6$ (1.1 c in DCM). MS (*m/z*) = 584.15. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IE), *n* - hexanes : IPA = 80 : 20, 280 nm, 26.0 mins (major), 50.9 mins (minor) for 80 % *ee*.

(*S_c* *S_{pl}*)-71k

Bright yellow oil. ^1H NMR (CDCl_3 , 500 MHz): 0.88 (m, 1H, $-\text{CH}_2\text{OH}$), 2.26 (s, 3H, $-\text{ArCH}_3$), 2.37 (s, 3H, $-\text{ArCH}_3$), 3.43 - 3.86 (m, 4H, $-\text{CH}_2\text{OH}$ and $-\text{CH}(\text{PPh}_2)\text{CH}_2$), 3.93 (s, 5H, $-\text{Cp}$), 4.10 (m, 1H, $-\text{Cp}$), 4.26 (m, 1H, $-\text{Cp}$), 4.63 (m, 1H, $-\text{Cp}$), 4.76 (m, 1H, $-\text{CHPPh}_2$), 6.50 - 6.51 (m, 1H, $-\text{Ar}$), 6.98 - 7.95 (m, 12H, $-\text{Ar}$). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 400 MHz): δ 14.2, 21.4, 21.5, 32.5, 33.0, 41.6, 41.6, 58.8, 60.4, 67.7, 67.9, 68.5, 68.8, 69.0, 85.8, 88.4, 112.4, 117.8, 128.6, 128.8, 129.3, 129.5, 131.9, 132.0, 132.6, 132.7, 142.6, 146.7, 152.2, 186.4. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 400 MHz): δ 51.3 (minor diastereomer, 53.5 (major diastereomer) for 93 % *de*. $[\alpha]_D = +32.1$ (0.7 c in DCM). MS (*m/z*) = 584.19. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IE), *n* - hexanes : IPA = 80 : 20, 280 nm, 34.5 mins (major), 122.2 mins (minor) for 84 % *ee*.

(S_c S_{pl})-**71I**

Bright yellow oil. ¹H NMR (CDCl₃, 500 MHz): 1.31 (m, 1H, -CH₂OH), 3.43 - 3.72 (m, 7H, -CH₂OH, -CH(PPh₂)CH₂ and -ArOCH₃), 3.81 (s, 3H, -ArOCH₃), 3.94 (s, 5H, -Cp), 4.08 (m, 1H, -Cp), 4.24 (m, 1H, -Cp), 4.61 (m, 1H, -Cp), 4.73 (m, 1H, -CHPPh₂), 6.49 (m, 1H, -Ar), 6.67 - 6.69 (m, 2H, -Ar), 6.95 - 6.96 (m, 2H, -Ar), 7.17 - 7.19 (m, 2H, -Ar), 7.56 (m, 1H, -Ar), 7.95 - 7.99 (m, 2H, -Ar). ¹³C{¹H} NMR (CDCl₃, 400 MHz): δ 32.8, 33.3, 41.6, 53.4, 55.3, 55.4, 58.8, 67.6, 67.8, 68.8, 69.0, 70.2, 70.3, 85.8, 88.6, 112.4, 113.4, 113.5, 114.1, 114.2, 117.8, 119.8, 120.6, 123.2, 124.1, 133.7, 133.8, 134.4, 134.5, 146.8, 152.2, 162.0, 162.5, 186.4. ³¹P{¹H} NMR (CDCl₃, 400 MHz): δ 54.4 for >99 % *de*. [α]_D = +45.3 (0.1 c in DCM). MS (*m/z*) = 616.87. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IE), *n* - hexanes : IPA = 65 : 35, 210 nm, 29.1 mins (major), 74.6 mins (minor) for 90 % *ee*.

2.2.5.

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Chapter 3.1.

Phosphapalladacycle-Catalyzed Arylboronic Acid Addition onto α , β -Unsaturated Ketones

3.1.1.

Introduction

The conjugate addition (CA) of boronic acids to activated alkenes (also acknowledged as the Hayashi-Miyaura reaction) is widely regarded as a powerful synthetic tool for C-C bond construction furnishing β -substituted functionalized compounds which serve as versatile synthons for subsequent organic manipulations (Scheme 3.1.1).¹

Numerous β -activating functionalities / electron-withdrawing groups have been examined and found to encompass: ketones,² aldehydes,³ esters,⁴ nitroalkenes,⁵ sulfones,⁶ phosphonates,⁷ strained alkenes⁸ and borylalkenes.⁹

The past decade have spawned an array of catalyst systems for their efficient formation, with extensive focus fixated on the *asymmetric* propagation of these β -substituted variants. Excellent conversions and stereoselectivities have thus been realized for the 1, 4-addition of organoboron nucleophiles to diverse cyclic / linear C=C unsaturated moieties with Rhodium (Rh) (Figure 3.1.1) and copper (Cu) (Figure 3.1.2) complexes.

Scheme 3.1.1.

General CA of boronic acids to activated alkenes.

EWG: Electron-withdrawing group

R: -alkyl, -aryl

Ketones

Aldehydes

Esters

Nitroalkenes

Sulfones

Phosphonates

Strained Alkenes

Borylalkenes

X = C, O, N
n = 0 - 2

Figure 3.1.1.

Common Rh catalyst / ligand systems for the Hayashi-Miyaura reaction.

Rh(I) salt precursors: i) $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$, ii) $[\text{Rh}(\text{Cl})(\text{C}_2\text{H}_4)_2]_2$, iii) $[\text{Rh}(\text{COD})_2]\text{BF}_4$.

BINAP and BINAP based ligands:

R = -H, -I, -CH=C(H)TMS

C_2 symmetric bidendate phosphorous ligands:

Non C_2 symmetrical bidendate phosphorous ligands:

Chiral diene ligands:

R = -Ph, -Bn

Chiral bis-sulfoxide ligands:

Figure 3.1.2.

Common Cu catalyst / ligand systems for the Hayashi-Miyaura reaction.

Cu salt precursors: i) $\text{Cu}(\text{MeCN})_4\text{BF}_4$, ii) $\text{Cu}(\text{OTf})_2$

Ligand Systems:

Chiral amidophosphane ligands:

Chiral phosphoramidite ligands:

Despite the dominance of Rh and Cu catalyst systems for the Hayashi-Miyaura addition methodology, palladium systems have recently received considerable attention as an efficacious alternative, highlighted by the formation of all-C quarternary centres (Scheme 3.1.2).¹⁰

Scheme 3.1.2.

However, the addition of boronic acids to acyclic enones *via* palladium-catalysis is hitherto relatively unexplored.¹¹ In lieu of this compelling absence and as part of a continuing interest in palladacycle-catalyzed C-C, C-N and C-P bond formation strategies, the competency of palladacycles for the asymmetric 1, 4-addition of arylboronic acids to both cyclic and linear enones was explored.

3.1.2.

Results and Discussion

Using 2-cyclohexenone (**24**) and phenylboronic acid (**60a**) as representative substrates, the catalytic competency of a cluster of metalacycles was examined. Disconcertingly, the addition of 2 equivalents of **60a** to 1 equivalent of **24** in the presence of 2.5 mol % catalyst (with respect to **24**) in toluene and 1 equivalent K_3PO_4 base yielded Pd black in all catalytic vessels before reaction completion (monitored by TLC). In an attempt to improve yields with the rational of increasing the rate of addition relative to the rate of Pd decomposition, an additional survey was conducted by the increase of phenylboronic acid loading (2 equivalents vs. 5 equivalents). However, no significant improvement in yields was observed (43 % with 2 equivalents **60a** to 47 % with 5 equivalents **60a**).

A survey of literature prompted an inclusion of catalytic amounts of triphenylphosphine (PPh_3) as a decomposition inhibitor. Thus, the addition of 6 mol % PPh_3 additive under the same conditions (5 equivalents of **60a**, 1 equivalent of **24**, 2.5 mol % catalyst, 1 equivalent of K_3PO_4 in toluene) allowed the addition to reach full conversion within 3 - 24 hours, without copious formation of Pd black (Table 3.1.1).

Scheme 3.1.3.

Table 3.1.1.^a

Entry	Cat.	t (hrs)	Yield ^b (%)	ee ^c (%)
1	C7	24	nil	n.d
2	C8	24	39	9
3	C9	10	89	92
4	C10	10	87	75
5	C11	10	62	54
6	C12	24	23	75
7	(<i>R_c</i> <i>S_{pl}</i>)- 67	3	90	76
8	C6	24	45	67

^a Reaction conditions: **24** (0.10 mmol), **60a** (0.5 mmol), catalyst (2.5 mol %, 5 mol % of Pd), PPh₃ (6 mol %) and K₃PO₄ (0.1 mmol) in 1 ml of Toluene at room temperature for the stipulated time. ^b Isolated yields. ^c ee was determined by HPLC using a chiral column.

From Table 3.1.1, it was observed that the amine-appended platinacycle **C7** failed to effect any product generation (Entry 1), with starting materials quantitatively recovered after 24 hours. Its palladium analog **C8** did not provoke significant upgrade, with only a poor yield of 39 % and inferior ee of 9 % gathered (Entry 2). The introduction of a diphenylphosphino ligand moiety on the naphthyl skeleton drastically improved both the reactivity and selectivity, affording the 1, 4-adduct in a 89 % yield and 91 % ee (Entry 3), which supersedes the results obtained with the ferrocenyl phosphapalladacycle (*R_c* *S_{pl}*)-**67** as acquainted in Chapter 2.1 (Table 3.1.1, Entry 7) or with other phosphapalladacycle derivatives (Table 3.1.1, Entry 4 - 6, 8).

Having now appraised the catalyst influence, development of other reaction specifications such as solvent medium, base and phosphine additive were motioned (Table 3.1.2). Firstly, a range of solvents was screened to determine the appropriate medium, with non-polar, aprotic solvents yielding the best balance between yield and selectivity. In the presence of toluene (Table 3.1.2, Entry 1), a yield of 89 % and 92 % ee was attained, while *p*-xylene (Table 3.1.2, Entry 2) accorded a yield of 79 % and 79 % ee. Retardation of yield to 22 % was observed when 1, 4-dioxane was serviced, although near perfect ee was surprisingly obtained (Table 3.1.2, Entry 3). DMF was found to be an unsuitable environment, with no product generation (Table 3.1.2, Entry 6). Chlorinated solvents, DCM and DCE administered similar yields and ee values (Table 3.1.2, Entries 4 and 5). Both MeCN and MeOH also failed to deliver high conversions and ee (Table 3.1.2, Entries 7 and 8).

Modification of the base to cesium carbonate (Table 3.1.2, Entry 9), triethylamine (Table 3.1.2, Entry 10) or potassium fluoride (Table 3.1.2, Entry 11) did not further enhance yields and selectivities.

As a final resort, tri-*o*-tolylphosphine (Table 3.1.2, Entry 13) and 3, 4-dimethyl-1-phenylphosphole (DMPP, Table 3.1.2, Entry 14) were introduced as alternatives to triphenylphosphine as the decomposition inhibitor, but once again, either low yields were obtained or no product formation was realized.

Table 3.1.2.^a

Entry	Solvent	Base	Additive	Yield ^b (%)	ee ^c (%)
1	Toluene	K ₃ PO ₄	PPh ₃	89	92
2	<i>p</i> -xylene	K ₃ PO ₄	PPh ₃	79	79
3	1, 4-dioxane	K ₃ PO ₄	PPh ₃	22	>99
4	DCM	K ₃ PO ₄	PPh ₃	79	85
5	1, 2-DCE	K ₃ PO ₄	PPh ₃	82	85
6	DMF	K ₃ PO ₄	PPh ₃	nil	n.d
7	MeCN	K ₃ PO ₄	PPh ₃	23	34
8	MeOH	K ₃ PO ₄	PPh ₃	38	53
9	Toluene	Cs ₂ CO ₃	PPh ₃	21	79
10	Toluene	NEt ₃	PPh ₃	23	76
11	Toluene	KF	PPh ₃	62	85
12	Toluene	nil	PPh ₃	11	63
13	Toluene	K ₃ PO ₄	P(<i>o</i> -tol) ₃	20	73
14	Toluene	K ₃ PO ₄	DMPP	nil	n.d

^a Reaction conditions: **24** (0.10 mmol), **60a** (0.5 mmol), **C9** (2.5 mol %, 5 mol % of Pd), phosphine additive (6 mol %) and base (0.1 mmol) in 1 ml of solvent at room temperature until reaction completion or for 24 hours. ^b

Isolated yields. ^c ee was determined by HPLC using a chiral column.

Scheme 3.1.4.^a

^a Reaction conditions: **76** - **78** (0.10 mmol), **60a** (0.5 mmol), **C9** (2.5 mol %, 5 mol % of Pd), phosphine additive (6 mol %) and base (0.1 mmol) in 1 ml of solvent at room temperature until reaction completion. Isolated yields. ee was determined by HPLC using a chiral column.

With all reaction variables optimized, the functional group tolerance was tested amongst a range of cyclic and acyclic α , β -unsaturated ketones (Scheme 3.1.4).

Amongst the cyclic conjugated enones, while both 2-cyclohexenone (**60**) and 2-cycloheptenone (**77**) were prime substrates, offering good yields (89 and 72 % respectively) and selectivities (92 and 87 % respectively) upon phenylation. However, 2-cyclopentenone (**76**) advertised an aberration with only 64 % yield and 50 % ee obtained (Scheme 3.1.4, **79**).

Interestingly, the reaction proceeded homogeneously with halogenated substrates, facilitating the adduct in high yields and selectivities (Scheme 3.1.4, **81b - d**). Also, no coupling product was observed, suggesting Pd(0) was not generated unlike previous cases mentioned in Chapter 1.2.3. Both electron-donating (Scheme 3.1.4, **81f**) and electron-withdrawing (Scheme 3.1.4, **81g**) moieties provided high yields, albeit with a significant difference in ee values obtained (81 % for **81f** and 69 % for **81g**).

The influence of the aryl source was next investigated through the addition of a selection of arylboronic acids with *trans*-chalcone (**82**) (Scheme 3.1.5).

Scheme 3.1.5.^a

^a Reaction conditions: **82** (0.10 mmol), **60b, d - i** (0.5 mmol), **C9** (2.5 mol %, 5 mol % of Pd), phosphine additive (6 mol %) and base (0.1 mmol) in 1 ml of solvent at room temperature until reaction completion. Isolated yields. ee was determined by HPLC using a chiral column.

In general, good yields and ee values were obtained with the alteration of the aryl source. The addition proceeded smoothly when bulky or electron rich boronic acids were used (Scheme 3.1.5, **83a**, **e** and **f**). On the other hand, the yield dropped significantly when an electron poor aryl boronic acid (**60i**) was used, with only 47 % yield of the desired addition product **83g** obtained. In addition, interesting results were obtained with *para*-halogenated phenylboronic acids. While *para*-fluoro phenyl boronic acid (**60e**) proceeded smoothly affording the desired product **83b** in 92 % yield and 79 % ee, poor yield (56 % yield) was obtained with its chloro-counterpart (**83c**) while poor ee (56 % ee) was observed for its bromo-counterpart (**83d**).

The 1, 4-Michael addition of acyclic substrates poses an additional consideration. The relative orientation between the carbonyl C=O and vinyl C=C bond of the substrate may exist in either the *s*-cis or *s*-trans configurations (Figure 3.1.3). There has been prior discussions in analogous conjugate addition and Diels-Alder scenarios whereby the *s*-cis configuration is disfavoured when coordinated to catalysts due to sterics present in the reaction transition state, thus increasing its activation energy (Scheme 3.1.6).¹² However, these reported arylboronic acid additions onto acyclic substrates proceeded with appreciable selectivities.

Figure 3.1.3.

Scheme 3.1.6.

Free Substrate

Metal Coordinated Substrate

The influence of these 2 configurations is highlighted from the attempted addition of phenylboronic acid (**60a**) to *s*-cis locked (*E*)-2-benzylidenecyclohexanone (Scheme 3.1.7).

Scheme 3.1.7.

Under similar conditions as reported in Scheme 3.1.3, no desired product or side product was observed even at elevated temperatures, thus accentuating the requirement for these enone substrates to adopt a *s*-trans configuration for efficient arylation.

The rationale of the observed stereochemistry might be explained by sterics between the axial methyl pendant of the catalyst and the alkene chain of the substrate (Figure 3.1.4 and 3.1.5).

Figure 3.1.4.

Figure 3.1.5.

The *S* catalyst **C5** / **C6** adopts a λ configuration as discussed in Chapter 1.3.1.2. Using phenylboronic acid as the model, the phenyl ring will adopt a position *trans* to the donor atom (L).¹³ The substrate will hence coordinate *via* the ketone oxygen and the alkenyl chain may take

up a position above the palladium pluckered square planar plane (highlighted by dashes), leading to *R* face attack. It may also take up a position below the coordination plane thus leading to *S* face attack. However, due to sterics between the alkenyl chain and the axial methyl pendant of the catalyst, this conformation is not preferred, leading to the observed stereochemistry. This catalyst-aryl-substrate configuration may also explain the observed stereochemistry in Chapter 3.2.

3.1.3.

Conclusion

In conclusion, a phosphapalladacycle catalyzed asymmetric 1, 4-conjugate addition of arylboronic acids to a series linear and cyclic enones is examined. The protocol generally proceeds smoothly at room temperature affording the 1, 4-products in good yields and selectivities. Furthermore, this methodology tolerates a wide range of functional groups, both on the enone substrate or on the boronic acid.

3.1.4.

Experimental

3-phenylcyclohexanone (**61a**)

Colourless oil. 89 % yield. ^1H NMR (CDCl_3 , 300 MHz): δ 1.82 - 1.93 (m, 2H), 2.11 - 2.18 (m, 2H), 2.32 - 2.64 (m, 4H), 2.96 - 3.05 (m, 1H), 7.21 - 7.36 (m, 5H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 25.5, 32.8, 41.2, 44.7, 48.9, 126.6, 126.7, 128.7, 144.3, 211.0. $[\alpha]_{\text{D}} = +4.8$ (c 0.467 in DCM). HRMS (ESI): Calcd for $\text{C}_{12}\text{H}_{15}\text{O}$ ($\text{M}^+ + \text{H}$): 175.1123 Found: 175.1110. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak AD-H), *n* - hexanes : IPA = 98 : 2, 1.0 ml / min, 270 nm, 10.2 mins (minor), 12.0 mins (major) for 92 % ee.

3-phenylcyclopentanone (**79**)

Colourless oil. 64 % yield. ^1H NMR (CDCl_3 , 300 MHz): δ 1.96 - 2.07 (m, 1H), 2.24 - 2.51 (m, 4H), 2.63 - 2.71 (m, 1H), 3.37 - 3.49 (m, 1H), 7.22 - 7.37 (m, 5H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 31.2, 38.8, 42.2, 45.8, 126.70, 126.71, 128.6, 143.0, 218.3. $[\alpha]_{\text{D}} = -36.4$ (c 0.385 in DCM). HRMS (ESI): Calcd for $\text{C}_{11}\text{H}_{13}\text{O}$ ($\text{M}^+ + \text{H}$): 161.0966 Found: 161.0973. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak OB-H), *n* - hexanes : IPA = 98 : 2, 0.8 ml / min, 230 nm, 55.3 mins (major), 64.6 mins (minor) for 50 % ee.

3-phenylcycloheptanone (**80**)

Yield 72%, colourless oil, $[\alpha]_{\text{D}} +38.3$ (0.500, CH_2Cl_2), 87% ee

Colourless oil. 72 % yield. ^1H NMR (CDCl_3 , 300 MHz): δ 1.44 - 1.51 (m, 1H), 1.64 - 1.81 (m, 2H), 1.95 - 2.11 (m, 3H), 2.57 - 2.67 (m, 3H), 2.85 - 2.98 (m, 2H), 7.16 - 7.33 (m, 5H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 24.2, 29.2, 39.2, 42.7, 43.9, 51.2, 126.3, 126.4, 128.6, 146.9, 213.4. $[\alpha]_{\text{D}} = +38.3$ (c 0.500 in DCM). HRMS (ESI): Calcd for $\text{C}_{17}\text{H}_{17}\text{O}$ ($\text{M}^+ + \text{H}$): 189.1279 Found: 189.1273. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak AD-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 254 nm, 19.1 mins (minor), 21.5 mins (major) for 87 % ee

4-phenylpentan-2-one (**81a**)

Yellow oil. 56 % yield. ^1H NMR (CDCl_3 , 300 MHz): δ 1.27 (d, 3H, $^3J = 7.2$ Hz), 2.06 (s, 3H), 2.71 (m, 2H), 3.30 (m, 1H), 7.16 - 7.32 (m, 5H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 22.0, 30.5, 35.5, 126.3, 127.8, 128.5, 146.2, 207.8. $[\alpha]_{\text{D}} = -23.4$ (c 0.392 in DCM). HRMS (ESI): Calcd for $\text{C}_{11}\text{H}_{15}\text{O}$ ($\text{M}^+ + \text{H}$): 163.1123 Found: 163.1121. The enantiomeric ratio was determined *via*

HPLC using a chiral column (Daicel Chiralpak AS-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 200 nm, 13.3 mins (minor), 14.5 mins (major) for 93 % *ee*.

3-(4-fluorophenyl)-1, 3-diphenylpropan-1-one (**81b**)

White solid. 88 % yield. ^1H NMR (CDCl_3 , 300 MHz): δ 3.71 (d, 2H, $^3J = 7.2$ Hz), 4.81 (t, 1H, $^3J = 7.2$ Hz), 6.90 - 6.98 (m, 2H), 7.15 - 7.30 (m, 7H), 7.40 - 7.57 (m, 3H), 7.91 (d, 2H, $^3J = 1.5$). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 44.8, 45.2, 115.3, 126.5, 127.7, 128.0, 128.6, 129.27, 133.1, 137.0, 139.3, 161.4, 197.8. $^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 , 282 MHz): δ -116.8. $[\alpha]_{\text{D}} = -4.2$ (c 0.59 in DCM). HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{18}\text{FO}$ ($\text{M}^+ + \text{H}$): 305.1342 Found: 305.1335. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak AD-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 280 nm, 38.9 mins (minor), 42.1 mins (major) for 81 % *ee*.

3-(4-chlorophenyl)-1, 3-diphenylpropan-1-one (**81c**)

White solid. 92 % yield. ^1H NMR (CDCl_3 , 300 MHz): δ 3.70 (dd, 2H, $^3J = 7.3$ Hz, $^3J = 0.9$ Hz), 4.786 (t, 1H, $^3J = 7.3$ Hz), 7.16 - 7.30 (m, 9H), 7.41 - 7.46 (m, 2H), 7.52 - 7.58 (m, 1H), 7.91 - 7.94 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 44.6, 45.3, 126.6, 127.7, 128.0, 128.6 - 128.7, 129.2, 132.1, 133.2, 136.9, 142.6, 143.7, 197.7. $[\alpha]_{\text{D}} = +7.6$ (c 0.634 in DCM). HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{18}\text{ClO}$ ($\text{M}^+ + \text{H}$): 321.1046 Found: 321.1060. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak AD-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 280 nm, 40.2 mins (minor), 49.2 mins (major) for 78 % *ee*.

3-(4-bromophenyl)-1, 3-diphenylpropan-1-one (**81d**)

White solid. 88 % yield. ^1H NMR (CDCl_3 , 300 MHz): δ 3.71 (dd, 2H, $^3J = 7.2$ Hz, $^3J = 0.9$ Hz), 4.79 (t, 1H, $^3J = 7.2$ Hz), 7.12 - 7.58 (m, 13H), 7.90 - 7.91 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 44.5, 45.3, 120.2, 126.6, 127.7, 128.0, 128.6, 128.7, 129.6, 131.6, 133.2, 136.9, 143.1, 143.6, 197.6. $[\alpha]_{\text{D}} = +10.4$ (c 0.660 in DCM). HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{18}\text{BrO}$ ($\text{M}^+ + \text{H}$):

365.0541 Found: 365.0554. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak AD-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 240 nm, 43.1 mins (minor), 53.5 mins (major) for 78 % ee.

1, 3-diphenyl-3-(*p*-tolyl)propan-1-one (**81e**)

White solid. 97 % yield. ¹H NMR (CDCl₃, 300 MHz): δ 2.30 (s, 3H), 3.74 (d, 2H, ³J = 7.2 Hz), 4.82 (t, 1H, ³J = 7.2 Hz), 7.08 - 7.11 (m, 2H), 7.15 - 7.22 (m, 3H), 7.25 - 7.63 (m, 8H), 7.94 - 7.96 (m, 2H). ¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 20.9, 44.8, 45.6, 126.3, 127.7, 127.8, 128.0, 128.5, 129.3, 133.0, 135.9, 137.1, 141.1, 144.4, 198.1. [α]_D = +11.7 (c 0.420 in DCM). HRMS (ESI): Calcd for C₂₂H₂₁O (M⁺ + H): 301.1592 Found: 301.1587. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak AD-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 270 nm, 32.0 mins (minor), 39.3 mins (major) for 81 % ee.

3-(4-methoxyphenyl)-1, 3-diphenylpropan-1-one (**81f**)

White solid. 95 % yield . ¹H NMR (CDCl₃, 300 MHz): δ 3.71 (d, 2H, ³J = 7.4 Hz), 3.87 (s, 3H), 4.79 (t, 1H, ³J = 7.5 Hz), 6.80 - 6.83 (m, 2H), 7.14 - 7.20 (m, 3H), 7.27 - 7.31 (m, 4H), 7.41 - 7.47 (m, 2H), 7.50 - 7.60 (m, 1H), 7.92 - 7.95 (m, 2H). ¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 44.9, 45.2, 55.2, 113.9, 126.3, 127.3, 128.1, 128.5, 128.6, 128.8, 133.0, 136.3, 137.1, 144.5, 158.1, 198.2. [α]_D = +5.2 (c 0.605 in DCM). HRMS (ESI): Calcd for C₂₂H₂₁O₂ (M⁺ + H): 317.1542 Found: 317.1540. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak AD-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 270 nm, 66.4 mins (minor), 71.0 mins (major) for 81 % ee.

1, 3-diphenyl-3-(4-(trifluoromethyl)phenyl)propan-1-one (**81g**)

White solid. 92 % yield. ¹H NMR (CDCl₃, 300 MHz): δ 3.75 (dd, 2H, ³J = 7.3 Hz, ³J = 2.1 Hz), 4.89 (t, 1H, ³J = 7.2 Hz), 7.17 - 7.58 (m, 12H), 7.92 - 7.95 (m, 2H). ¹³C{¹H} NMR (CDCl₃, 75

MHz): δ 44.4, 45.7, 124.2, 125.5, 126.8, 127.8, 128.0, 128.2, 128.7, 128.8, 133.3, 136.8, 143.3, 148.2, 197.4. $^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 , 282 MHz): δ -62.4. $[\alpha]_{\text{D}} = +4.9$ (c 1.12 in DCM). HRMS (ESI): Calcd for $\text{C}_{22}\text{H}_{18}\text{F}_3\text{O}$ ($\text{M}^+ + \text{H}$): 355.1310 Found: 355.1318. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak AD-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 240 nm, 30.3 mins (minor), 34.4 mins (major) for 69 % *ee*.

3-(naphthalen-2-yl)-1, 3-diphenylpropan-1-one (**81h**)

Yellow solid. 88 % yield. ^1H NMR (CDCl_3 , 300 MHz): δ 3.86 (dd, 2H, $^3J = 7.5$ Hz, $^3J = 2.7$ Hz), 5.02 (t, 1H, $^3J = 7.2$ Hz), 7.17 - 7.58 (m, 11H), 7.74 - 7.79 (m, 4H), 7.93 - 7.96 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 44.6, 46.0, 125.5, 125.8, 126.0, 126.4, 126.7, 127.6, 127.8, 128.0, 128.1, 128.3, 128.58, 128.59, 132.2, 133.1, 133.5, 137.1, 141.5, 144.0, 198.0. $[\alpha]_{\text{D}} = +36.4$ (c 0.594 in DCM). HRMS (ESI): Calcd for $\text{C}_{25}\text{H}_{21}\text{O}$ ($\text{M}^+ + \text{H}$): 337.1592 Found: 337.1583. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak AD-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 270 nm, 58.7 mins (minor), 62.8 mins (major) for 85 % *ee*.

3-([1, 1'-biphenyl]-4-yl)-1, 3-diphenylpropan-1-one (**81j**)

Yellow solid. 85 % yield. ^1H NMR (CDCl_3 , 300 MHz): δ 3.77 (dd, 2H, $^3J = 7.4$ Hz, $^3J = 0.9$ Hz), 4.87 (t, 1H, $^3J = 7.5$ Hz), 7.16 - 7.57 (m, 17H), 7.93 - 7.96 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 44.7, 45.6, 126.4, 127.0, 127.1, 127.3, 127.8, 128.1, 128.2, 128.6, 128.7, 133.1, 137.0, 139.3, 140.8, 143.2, 144.1, 197.9. $[\alpha]_{\text{D}} = +22.4$ (c 0.580 in DCM). HRMS (ESI): Calcd for $\text{C}_{27}\text{H}_{23}\text{O}$ ($\text{M}^+ + \text{H}$): 363.1749 Found: 363.1785. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralcel AD-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 230 nm, 57.3 mins (minor), 68.6 mins (major) for 79 % *ee*.

3-(benzo[d][1, 3]dioxol-5-yl)-1, 3-diphenylpropan-1-one (**81i**)

Yellow oil. 95 % yield. ^1H NMR (CDCl_3 , 300 MHz): δ 3.77 (d, 2H, $^3J = 7.2$ Hz), 4.74 (t, 1H, $^3J = 6.9$ Hz), 5.87 (s, 2H), 6.68 - 6.75 (m, 3H), 7.15 - 7.19 (m, 1H), 7.23 - 7.29 (m, 4H), 7.41 - 7.45 (m, 2H), 7.51 - 7.57 (m, 1H), 7.91 - 7.94 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 44.8, 45.6, 100.9, 108.2, 108.4, 120.7, 127.4, 127.6, 128.0, 128.56, 128.58, 133.1, 138.1, 133.2, 146.0, 147.7, 198.0. $[\alpha]_{\text{D}} = +4.0$ (c 0.622 in DCM). HRMS (ESI): Calcd for $\text{C}_{22}\text{H}_{19}\text{O}_3$ ($\text{M}^+ + \text{H}$): 331.1334 Found: 311.1337. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak AD-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 230 nm, 77.7 mins (minor), 83.8 mins (major) for 81 % ee.

3-(naphthalen-2-yl)-1, 3-diphenylpropan-1-one (**83a**)

Yellow solid. 97 % yield. ^1H NMR (CDCl_3 , 300 MHz): δ 3.86 (dd, 2 H, $^3J = 7.5$ Hz, $^3J = 2.7$ Hz), 5.02 (t, 1H, $^3J = 7.2$ Hz), 7.17 - 7.58 (m, 11H), 7.74 - 7.79 (m, 4H), 7.93 - 7.96 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 44.6, 46.0, 125.5, 125.8, 126.0, 126.4, 126.7, 127.6, 127.8, 128.0, 128.1, 128.3, 128.58, 128.59, 132.2, 133.1, 133.5, 137.1, 141.5, 144.0, 198.0. $[\alpha]_{\text{D}} = -16.8$ (c 0.900 in DCM). HRMS (ESI): Calcd for $\text{C}_{25}\text{H}_{21}\text{O}$ ($\text{M}^+ + \text{H}$): 337.1592 Found: 337.1586. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak AD-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 210 nm, 58.8 mins (major), 63.0 mins (minor) for 77 % ee.

3-(4-fluorophenyl)-1, 3-diphenylpropan-1-one (**83b**)

White solid. 92 % yield. ^1H NMR (CDCl_3 , 300 MHz): δ 3.71 (d, 2H, $^3J = 7.2$ Hz), 4.81 (t, 1H, $^3J = 7.2$ Hz), 6.90 - 6.98 (m, 2H), 7.15 - 7.30 (m, 7H), 7.40 - 7.57 (m, 3H), 7.91 (d, 2H, $^3J = 1.5$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ = 44.8, 45.2, 115.3, 126.5, 127.7, 128.0, 128.6, 129.27, 133.1, 137.0, 139.3, 161.4, 197.8. $^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 , 282 MHz): δ -116.8. $[\alpha]_{\text{D}} = +9.7$ (c 0.532 in DCM). HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{18}\text{FO}$ ($\text{M}^+ + \text{H}$): 305.1342 Found: 305.1345. The

enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak AD-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 280 nm, 38.3 mins (major), 40.5 mins (minor) for 79 % *ee*.

3-(4-chlorophenyl)-1, 3-diphenylpropan-1-one (**83c**)

White solid. 56 % yield. ^1H NMR (CDCl_3 , 300 MHz): δ 3.70 (dd, 2H, $^3J = 7.3$ Hz, $^3J = 0.9$), 4.79 (t, 1H, $^3J = 7.3$ Hz), 7.16 - 7.30 (m, 9H), 7.41 - 7.46 (m, 2H), 7.52 - 7.58 (m, 1H), 7.91 - 7.94 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 44.6, 45.3, 126.6, 127.7, 128.0, 128.6 - 128.7, 129.2, 132.1, 133.2, 136.9, 142.6, 143.7, 197.7. $[\alpha]_{\text{D}} = -8.2$ (*c* 0.490 in DCM). HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{18}\text{ClO}$ ($\text{M}^+ + \text{H}$): 321.1046 Found: 321.1032. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak AD-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 280 nm, 37.7 mins (major), 45.4 mins (minor) for 82 % *ee*.

3-(4-bromophenyl)-1, 3-diphenylpropan-1-one (**83d**)

White solid. 88 % yield. ^1H NMR (CDCl_3 , 300 MHz): δ 3.71 (dd, 2H, $^3J = 7.2$ Hz, $^3J = 0.9$), 4.79 (t, 1H, $^3J = 7.2$ Hz), 7.12 - 7.58 (m, 13H), 7.90 - 7.91 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 44.5, 45.3, 120.2, 126.6, 127.7, 128.0, 128.6, 128.7, 129.6, 131.6, 133.2, 136.9, 143.1, 143.6, 197.6. $[\alpha]_{\text{D}} = -8.5$ (*c* 0.474 in DCM). HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{18}\text{BrO}$ ($\text{M}^+ + \text{H}$): 365.0541 Found: 365.0531. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak AD-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 254 nm, 41.6 mins (major), 51.6 mins (minor) for 56 % *ee*.

1, 3-diphenyl-3-(*p*-tolyl)propan-1-one (**83e**)

White solid. 89 % yield. ^1H NMR (CDCl_3 , 300 MHz): δ 2.30 (s, 3H), 3.74 (d, 2H, $^3J = 7.2$ Hz), 4.82 (t, 1H, $^3J = 7.2$ Hz), 7.08 - 7.11 (m, 2H), 7.15 - 7.22 (m, 3H), 7.25 - 7.63 (m, 8H), 7.94 - 7.96 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 20.9, 44.8, 45.6, 126.3, 127.7, 127.8, 128.0, 128.5, 129.3, 133.0, 135.9, 137.1, 141.1, 144.4, 198.1. $[\alpha]_{\text{D}} = +4.8$ (*c* 0.550 in DCM). HRMS (ESI):

Calcd for $C_{22}H_{21}O$ ($M^+ + H$): 301.1592 Found: 301.1593. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak AD-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 254 nm, 30.3 mins (major), 39.3 mins (minor) for 69 % *ee*.

3-(4-methoxyphenyl)-1, 3-diphenylpropan-1-one (**83f**)

White solid. 83 % yield. 1H NMR ($CDCl_3$, 300 MHz): δ 3.71 (d, 2H, $^3J = 7.4$ Hz), 3.87 (s, 3H), 4.79 (t, 1H, $^3J = 7.5$ Hz), 6.80 - 6.83 (m, 2H), 7.14 - 7.20 (m, 3H), 7.27 - 7.31 (m, 4H), 7.41 - 7.47 (m, 2H), 7.50 - 7.60 (m, 1H), 7.92 - 7.95 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 44.9, 45.2, 55.2, 113.9, 126.3, 127.3, 128.1, 128.5, 128.6, 128.8, 133.0, 136.3, 137.1, 144.5, 158.1, 198.2. $[\alpha]_D = -8.7$ (c 0.514 in DCM). HRMS (ESI): Calcd for $C_{22}H_{21}O_2$ ($M^+ + H$): 317.1542 Found: 317.1546. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak AD-H), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 270 nm, 68.4 mins (major), 71.6 mins (minor) for 85 % *ee*.

1, 3-diphenyl-3-(4-(trifluoromethyl)phenyl)propan-1-one (**83g**)

White solid. 47 % yield. 1H NMR ($CDCl_3$, 300 MHz): δ 3.75 (dd, 2H, $^3J = 7.3$ Hz, $^3J = 2.1$ Hz), 4.89 (t, 1H, $^3J = 7.2$ Hz), 7.17 - 7.58 (m, 12H), 7.92 - 7.95 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 44.4, 45.7, 124.2, 125.5, 126.8, 127.8, 128.0, 128.2, 128.66, 128.67, 128.8, 133.3, 136.8, 143.3, 148.2, 197.4. $^{19}F\{^1H\}$ NMR ($CDCl_3$, 282 MHz): δ -62.4. $[\alpha]_D = -2.9$ (c 0.417 in DCM). HRMS (ESI): Calcd for $C_{22}H_{18}F_3O$ ($M^+ + H$): 355.1310 Found: 355.1340. The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 254 nm, 12.9 mins (major), 13.6 mins (minor) for 93 % *ee*.

3.1.5.

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Chapter 3.2.

Phosphapalladacycle-Catalyzed Arylboronic Acid Addition onto α , β , γ , δ -Unsaturated Ketones

3.2.1.

Introduction

Although the transition metal-catalyzed enantioselective 1, 4-conjugate addition of carbon nucleophiles to α , β -unsaturations have witnessed tremendous advancement over the past decade,¹ the analogous addition to polyconjugated systems (in particular α , β , γ , δ -unsaturated enones) have been relatively scarce due to the challenge of synchronous regio- (1, 2 vs. 1, 4- vs. 1, 6-addition, Scheme 3.2.1) and enantio-control.

Scheme 3.2.1.

Recent reports by Hayashi *et. al.* have introduced an Iridium-chiral diene-catalyzed protocol that affords 1, 6-products exclusively with high yields (up to 99 %) and enantioselectivities (up to 99 % ee) (Scheme 3.2.2).²

Scheme 3.2.2.

Other notable examples of regio- and enantioselective 1, 6-addition of organometallic reagents to α , β , γ , δ -unsaturated enones however, involve moisture-sensitive Grignard / trialkylaluminium / organozinc reagents.³

A remarkable methodology for the regio-selective 1, 4-addition of alkyl or aryl substituents to α , β , γ , δ -unsaturated enones utilizes a Cu-Fc-Phox system.⁴ However, the attempted introduction of a benzyl moiety led to poor yields and enantioselectivities (Scheme 3.2.3).

Scheme 3.2.3.

Encouraged by the results obtained in the palladacycle catalyzed 1, 4-addition of arylboronic acids to cyclic and linear enones described in Chapter 3.1, it is of interest to develop a

methodology for a regioselective addition protocol which allows the simultaneous control of both 1, 4-regio and enantioselectivity. Furthermore, of particular intrigue would be the regioselectivity pattern exhibited by these catalysts.

3.2.2.

Results and Discussion

The study was commenced establishing the reaction of (2*E*, 4*E*)-1, 5-diphenylpenta-2, 4-dien-1-one (**84a**) with 2 equivalents of phenylboronic acid (**60a**) as the model (Scheme 3.2.1). Subsequently, a range of palladacycles (**C8** - **11** and (*R_c S_{pl}*)-**67**) were screened to assess their catalytic efficacy in toluene at room temperature for 24 hours with 6 mol % PPh₃ additive and 1 equivalent of K₃PO₄ as a base. The C-N type palladacycle (**C8**) was inert toward the addition reaction (Table 3.2.1, Entry 1) as per previous observations in Chapter 3.1. Their phosphapalladacycle analogues **C9** - **11** and (*R_c S_{pl}*)-**67** on the other hand, afforded the desired 1, 4-product in poor yields and moderate selectivities (Table 3.2.1, Entries 2 - 4).

Scheme 3.2.4.

Table 3.2.1.^a

Entry	Cat. (mol %)	PhB(OH) ₂ (eq.)	T (°C)	t (hrs)	Yield ^b (%)	ee ^c (%)
1	C8 (2.5)	2	RT	48	0	n.d
2	C11 (2.5)	2	RT	48	<10	19
3	(<i>R_c S_{pl}</i>)- 67 (2.5)	2	RT	48	30	44
4	C9 (2.5)	2	RT	48	40	53
5	C9 (3)	5	RT	48	87	76
6	C9 (3)	5	0	48	60	79

^a Reaction conditions: **84a** (0.1 mmol), **60a** (0.2 mmol or 0.5 mmol), catalyst (2.5 or 3 mol %), PPh₃ (6 or 8 mol %) K₃PO₄ (1 eq.) were stirred in 1 ml of Toluene at RT for 48 hours. ^b Isolated yield. ^c ee determined by HPLC using a chiral column.

An analysis of the results described in Table 3.2.1 suggests that phosphapalladacycle **C9** has the most potential amongst all the cyclopalladated catalysts tested, offering **85a** in an unoptimized 40 % yield and 53 % ee (Table 3.2.1, Entry 4).

The effect of the aryl source was also investigated. The use of both phenylboroxine (PhBO)₃ and phenyl potassium trifluoroborate salt (K⁺PhBF₃⁻) however, did not lead to any product formation (Scheme 3.2.5).

Scheme 3.2.5.

Thus, the impact of the tandem increase in both boronic acid concentration and catalyst loading (5 eq. and 3 mol % vs. 2 eq. and 2.5 mol %) was studied. These modifications led to an

appreciable increase in yield to 87 % (from 40 %) and selectivity to 76 % (from 53 %) (Table 3.2.1, Entry 4 vs. 5). Lowering the reaction temperature to 0 °C only provided incremental improvement in selectivity from 76 to 79 % ee, but deteriorated the reactivity significantly (Table 3.2.1, Entry 5 vs. 6).

Due to the traditional efficacy of rhodium(I)-diphosphine systems, a series of rhodium(I)-diphosphine catalyst complexes, where rhodium(I) = $[\text{Rh}(\text{COD})\text{Cl}]_2$ / $[\text{Rh}(\text{COD})\text{OH}]_2$ and diphosphine = (S)-BINAP / (R_c , S_{pl})-Josiphos (Scheme 3.2.3) was also screened. Although **85a** was indeed obtained at elevated temperatures (40 or 70 °C) over 48 hours, either impoverished yields (< 20 %) or ee values (5 %) were obtained.

Scheme 3.2.6.

Using the chosen phosphapalladacycle **C9** and adopting the optimized conditions as in Table 3.2.1, Entry 6), the addition of phenylboronic acid **60a** to various derivatives of dienone **84a - k** obtained by the variation of the aryl moiety at the carbonyl carbon (Scheme 3.2.7) was proceeded.

Scheme 3.2.7.^a

^a Reaction conditions: **84a - k** (0.1 mmol), **60a** (0.5 mmol), **C9** (3 mol %), PPh_3 (8 mol %), K_3PO_4 (1 eq.) were stirred in 1 ml of Toluene at RT for 48 hours. ^b Isolated yield. ^c ee determined by HPLC using a chiral column.

Generally, this addition provided the 1, 4-adducts exclusively, with satisfactory yields and moderate *ee* values. Interestingly, although the phenylation of 2-furyl and 2-thiophene appended ketones **84b** and **c** proceeded smoothly yielding **85b** and **c** respectively, no adduct was observed when 2-pyridyl functionalized conjugated ketone was employed (Scheme 3.2.8). This could be due to competitive coordination between the carbonyl oxygen and the pyridyl nitrogen. Thus, if the coordination equilibrium is shifted toward the nitrogen, the catalytic cycle would break down due to diminished activation at the β -position (Scheme 3.2.9).

Scheme 3.2.8.

Scheme 3.2.9.

The addition proved robust when relatively bulky naphthyl and substituted benzyl substrates were applied (**84d** to **f**) yielding their corresponding 1, 4-products in good yields (80 - 86 %) and moderate selectivities (70 - 80 % ee). Furthermore, the electronic influence of the *para*-substituent on reactivity was clearly evident when results obtained with **85g** and **85h** were compared. With an electron donating group (*p*-OMe, **85g**), moderate yield of 60 % with 66 % ee was obtained. In contrast, when an electron withdrawing group (*p*-CF₃, **85h**) was applied, high yield of 86 % and 77 % ee was achieved.

This addition procedure can also be extended to *para*-halogenated aromatic substrates (**84i** to **k**). In these cases, yields obtained were consistently high (90 %), with fluorinated and brominated appended products (**85i** and **85k**) providing 72 % ee while the chlorinated derivative (**85j**) yielded 76 % ee.

Subsequently, the tolerance of this protocol to the use of other arylboronic acids when used in conjunction with various linear dienones (Scheme 3.2.10) was studied.

Scheme 3.2.10.

^a Reaction conditions: **84a, f, j** (0.1 mmol), **60** (0.5 mmol), **C9** (3 mol %), PPh₃ (8 mol %), K₃PO₄ (1 eq.) were stirred in 1 ml of Toluene at RT for 48 hours. ^b Isolated yield. ^c ee determined by HPLC using a chiral column.

Tolylboronic acids (**85l**, **m** and **n**) in general gave comparatively low yields (60 - 66 %) when compared to an unsubstituted phenyl nucleophile (**85a**, 85 % yield). When the methyl substituent is aligned closer to B (-*o*-tolyl vs. -*m*-tolyl vs. -*p*-tolyl boronic acids), lower yields were obtained (66 vs. 74 vs. 78 % yield respectively).

Selectivities, on the other hand, showed an opposite trend with high ee values obtained (94 - >99 %) when substituents on the aryl boronic acid moiety was in the *ortho* position (**85l**, **q** and **r**), while those with substituents in the *meta* and *para* positions gave lower enantioselectivity values (60 % ee for meta substituted **85m** and 66 % for para substituted **85n**).

In this instance, the degree of electronic influence did not alter the yields and selectivities of the obtained 1, 4-products, with an electron donating *p*-methoxyphenylboronic acid (**60d**) and electron withdrawing *p*-fluorophenylboronic acid (**60e**) both providing the same yields (80 %) and ee (76 %).

The 1, 4-regioselectivity of the phenylated products **85** was unambiguously determined via comparison of ¹H NMR spectra of previous literature (Spectra 3.2.1 - 3.2.3).

Spectrum 3.2.1. ^1H NMR Spectrum of 1, 6-product

Spectrum 3.2.2. ^1H NMR Spectrum of 1, 4-product (**85n**)

Spectra 3.2.1 and 3.2.1 show the ^1H NMR spectra of 1, 6- and 1, 4- regioisomers of **85n** respectively. A comparison between the two spectra display 3 major differences: a) the chemical shift of the methylene CH_2 protons, δ 3.05 for the 1, 6- and δ 3.47 for the 1, 4-, b) the chemical shift of the methine CH proton at the chiral centre, δ 4.14 (triplet) for the 1, 6- and δ 4.26 (doublet of a doublet of a triplet) for the 1, 4-, furthermore, the splitting patterns of these two signals differ, and lastly, c) the pattern of the aromatic regions, for the 1, 6-, the vinylic protons on the adjacent vinyl functionality can be clearly seen at δ 6.77 and 6.92, however, this pattern is not observed for the 1, 4-spectrum.

Spectrum 3.2.3. 2D COSY NMR of **85b**.

1, 4-product

1, 6-product

Spectrum 3.2.3 shows the COSY NMR of 1, 4-product **85b**. The splitting pattern and coupling partners of the methine proton (a and a1) of the above 1, 4-product and 1, 6-product would differ considerably, since a would be able to have 2 strong coupling partners, with the right methylene protons and vinylic proton b, whereas a1 would be able to couple to the methylene protons and would not be able to couple strongly to vinylic proton b1. An analysis of coupling partners of proton a in Spectrum 3.2.3 suggests 2 strong coupling partners, thus evidencing the formation of the 1, 4-products.

3.2.3

Conclusion

In conclusion a protocol for the regiospecific 1, 4-addition of aryl groups to linear α , β , γ , δ -unsaturated ketones catalyzed by a phosphapalladacycle is developed. This facile methodology proceeds smoothly at room temperature using easily accessible and stable boronic acids. It has to be noted that preceding literature required the use of moisture sensitive Grignard reagents at $-70\text{ }^{\circ}\text{C}$. The ability of this current protocol to tolerate a wide range of substituted enone substrates as well as arylboronic acid variants makes it a versatile method which fills the lacunae that currently exists.

3.2.4.

Experimental

Thin layer chromatography was performed on Merck silica gel 60 F254 aluminum backed plates and visualized under UV. Flash chromatography was performed using Merck silica gel 60. NMR spectra were recorded on a Bruker AV 300 spectrometer (^1H at 300 MHz, $^{13}\text{C}\{^1\text{H}\}$ at 75 MHz), Bruker AV 400 spectrometer (^1H at 400 MHz, $^{13}\text{C}\{^1\text{H}\}$ at 100 MHz) or Bruker AV 500 spectrometer (^1H at 500 MHz, $^{13}\text{C}\{^1\text{H}\}$ at 125 MHz). ^1H spectra are referenced to an internal SiMe_4 standard at δ 0 ppm or to CDCl_3 at δ 7.26 ppm. Optical rotations were measured on the specified solution in a 0.1 dm cell at 20 °C with a Perkin - Elmer 341 polarimeter. Mass spectrometry was obtained in ESI mode on a Thermo Finnigan LCQ Deca XP MAX system.

Synthesis of α , β , γ , δ -unsaturated ketones:

The appropriate ketone (1 eq.) was added dropwise to a solution of diluted *trans*-Cinnamaldehyde (1 eq.) was in absolute EtOH and cooled to 0°C. NaOH (2.75 M, 1.3 eq.) was subsequently added dropwise. The mixture was gently stirred at 0°C for 1 hour before it was raised to RT for a further 3 hours. The yellow precipitate was then filtered off and air-dried before direct usage.

Procedure for Pd(II)-catalyzed arylboronic acid addition to α , β , γ , δ -unsaturated ketones:

Arylboronic acid (0.5 mmol, 5 eq.) and α , β , γ , δ -unsaturated ketone (0.1 mmol, 1 eq.) was added to a solution of catalyst (0.015 mmol, 3 mol %) in toluene (0.5 ml). K_3PO_4 (0.1 mmol, 1 eq.) was subsequently added and the solution left to stir for 48 hours. The crude product was then purified via silica gel chromatography (10 *n* - hexanes : 1 EA or 1 *n* - hexanes : 1 DCM)

85a (+)-1, 3, 5-triphenylpent-4-en-1-one

Light yellow oil. ^1H NMR (CDCl_3 , 300 MHz): δ 3.51 (m, 2H, $-\text{CH}_2$), 4.31 (m, 1H, $-\text{CHAr}$), 6.40 (m, 2H), 7.18 - 7.56 (m, 13H), 7.94 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 44.0, 44.6, 126.3, 126.7, 127.3, 127.8, 128.1, 128.5, 128.7, 128.7, 130.1, 132.7, 133.1, 137.2, 137.2, 143.4, 198.2. MS (*M* / *Z*): 312.91. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{21}\text{O}$ [*M* + *H*] $^+$ 313.1592, found 313.1591. $[\alpha]_D = +3.01$ (c 0.7 in CHCl_3). The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 254 nm, 22.1 mins (major), 25.3 mins (minor).

85b (-)-1-(furan-2-yl)-3, 5-diphenylpent-4-en-1-one

Light yellow oil. ^1H NMR (CDCl_3 , 400 MHz): δ 3.33 (m, 2H, $-\text{CH}_2$), 4.27 (m, 1H, $-\text{CHAr}$), 6.38 (m, 2H), 6.84 (m, 1H), 7.14 - 7.30 (m, 11H), 7.54 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 44.0, 44.3, 112.3, 117.2, 126.3, 126.7, 127.3, 127.8, 128.5, 128.7, 130.2, 132.3, 137.2, 143.0, 146.4, 153.0, 187.4. MS (*M* / *Z*): 303.21. HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{19}\text{O}_2$ [*M* + *H*] $^+$ 303.1385, found 303.1382. $[\alpha]_D = -1.9$ (c 0.2 in DCM). The enantiomeric ratio was determined *via* HPLC using a

chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 254 nm, 35.2 mins (major), 38.5 mins (minor).

85c (+)-3, 5-diphenyl-1-(thiophen-2-yl)pent-4-en-1-one

Light yellow oil. ^1H NMR (CDCl_3 , 400 MHz): δ 3.41 (m, 2H, $-\text{CH}_2$), 4.28 (m, 1H, $-\text{CHAr}$), 6.40 (m, 2H), 7.09 - 7.32 (m, 11H), 7.60 (m, 1H), 7.70 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 44.3, 45.4, 126.3, 126.7, 127.3, 127.8, 127.9, 128.1, 128.5, 128.6, 128.7, 130.3, 131.9, 132.3, 133.7, 137.2, 143.1, 144.5, 191.0. MS (*M* / *Z*): 318.16. HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{19}\text{OS}$ [*M* + *H*] $^+$ 319.1157, found 319.1167. $[\alpha]_{\text{D}} = +1.3$ (*c* 0.8 in DCM). The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 254 nm, 19.9 mins (major), 21.5 mins (minor).

85d (-)-1-(naphthalen-2-yl)-3, 5-diphenylpent-4-en-1-one

Light yellow oil. ^1H NMR (CDCl_3 , 300 MHz): δ 3.62 (m, 2H, $-\text{CH}_2$), 4.35 (m, 1H, $-\text{CHAr}$), 6.43 (m, 2H), 7.13 - 8.01 (m, 16H), 8.44 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 44.1, 44.6, 123.9, 126.3, 126.7, 126.8, 127.3, 127.8, 127.8, 128.4, 128.5, 128.7, 129.6, 129.7, 130.1, 132.5, 132.6, 134.5, 135.6, 137.2, 143.4, 198.1. MS (*M* / *Z*): 362.38. HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{23}\text{O}$ [*M* + *H*] $^+$ 363.1749, found 363.1756. $[\alpha]_{\text{D}} = -2.7$ (*c* 0.5 in DCM). The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 95 : 5, 0.5 ml / min, 280 nm, 17.5 mins (major), 18.6 mins (minor).

85e (+)-3, 5-diphenyl-1-(*p*-tolyl)pent-4-en-1-one

Light yellow oil. ^1H NMR (CDCl_3 , 500 MHz): δ 2.39 (s, 3H, $-\text{ArMe}$), 3.46 (m, 2H, $-\text{CH}_2$), 4.29 (m, 1H, $-\text{CHAr}$), 6.39 (m, 2H), 7.16 - 7.31 (m, 12H), 7.84 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 21.7, 44.0, 44.4, 126.3, 126.6, 127.2, 127.8, 127.9, 128.3, 128.5, 128.5, 128.7, 129.3, 130.0, 132.7, 134.7, 137.3, 143.4, 143.9, 197.8. MS (*M* / *Z*): 326.72. HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{23}\text{O}$ [*M*

+ H]⁺ 327.1749, found 327.1744. [α]_D = +0.8 (c 0.4 in DCM). The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 280 nm, 21.4 mins (major), 23.2 mins (minor).

85f (-)-1-(2, 5-dimethylphenyl)-3, 5-diphenylpent-4-en-1-one

Light yellow oil. ¹H NMR (CDCl₃, 400 MHz): δ 2.27 (s, 3H, -ArMe), 2.33 (s, 3H, -ArMe), 3.39 (m, 2H, -CH₂), 4.23 (s, 1H, -CHAr), 6.37 (m, 2H), 7.07 - 7.33 (m, 13H). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 20.3, 20.9, 44.5, 47.6, 126.2, 126.7, 127.3, 127.8, 128.5, 128.6, 128.6, 128.7, 130.1, 131.8, 131.9, 132.5, 134.7, 135.1, 137.2, 138.5, 143.2, 202.9. MS (*M* / *Z*): 341.07. HRMS (ESI) calcd for C₂₅H₂₅O [*M* + H]⁺ 341.1905, found 341.1906. [α]_D = -28.4 (c 0.2 in DCM). The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 280 nm, 15.3 mins (major), 16.0 mins (minor).

85g (-)-1-(4-methoxyphenyl)-3, 5-diphenylpent-4-en-1-one

Light yellow oil. ¹H NMR: δ 3.42 (m, 2H, -CH₂), 3.90 (s, 3H, -OMe), 4.32 (m, 1H, -CHAr), 6.42 (m, 1H), 6.91 - 7.97 (m, 15H). ¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 29.7, 44.1, 44.2, 113.8, 126.2, 126.6, 127.2, 127.8, 128.3, 128.4, 128.7, 130.0, 130.3, 130.4, 132.3, 132.8, 137.3, 143.5, 163.5, 196.7. MS (*M* / *Z*): 342.16. HRMS (ESI) calcd for C₂₄H₂₃O₂ [*M* + H]⁺ 343.1698, found 343.1699. [α]_D = -3.1 (c 0.3 in DCM). The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 95 : 5, 0.5 ml / min, 254 nm, 26.6 mins (major), 28.7 mins (minor).

85h (+)-3, 5-diphenyl-1-(4-(trifluoromethyl)phenyl)pent-4-en-1-one

Light yellow oil. ^1H NMR (CDCl_3 , 400 MHz): δ 3.53 (m, 2H, $-\text{CH}_2$), 4.29 (m, 1H, $-\text{CHAr}$), 6.40 (m, 2H), 7.19 - 7.33 (m, 10H), 7.71 (d, 2H), 8.03 (d, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 28.0, 29.7, 36.7, 44.0, 44.9, 125.7, 126.3, 126.8, 127.4, 128.4, 128.5, 128.8, 130.4, 132.2, 134.4, 137.0, 143.1, 197.4. ^{19}F NMR (CDCl_3 , 282 MHz): δ -63.1. MS (M/Z): 381.03. HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{20}\text{OF}_3$ [$M + \text{H}$] $^+$ 381.1466, found 381.1464. $[\alpha]_{\text{D}} = +9.1$ (c 0.3 in DCM). The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 254 nm, 10.0 mins (major), 10.5 mins (minor).

85i (+)-1-(4-fluorophenyl)-3, 5-diphenylpent-4-en-1-one

Light yellow oil. ^1H NMR (CDCl_3 , 400 MHz): δ 3.47 (m, 2H, $-\text{CH}_2$), 4.28 (m, 1H, $-\text{CHAr}$), 6.39 (m, 2H), 7.08 - 7.31 (m, 12H), 7.95 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 29.7, 44.0, 44.4, 115.6, 115.9, 126.2, 126.7, 127.3, 127.7, 128.5, 128.7, 130.2, 130.7, 132.4, 137.1, 143.2, 164.1, 167.4, 196.6. ^{19}F (CDCl_3 , 282 MHz): δ -105.2. MS (M/Z): 330.85. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{OF}$ 331.1498, found 331.1494. $[\alpha]_{\text{D}} = +0.28$ (c 0.5 in DCM). The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 280 nm, 13.1 mins (major), 13.7 mins (minor).

85j (+)-1-(4-chlorophenyl)-3, 5-diphenylpent-4-en-1-one

Light yellow oil. ^1H NMR (CDCl_3 , 400 MHz): δ 3.41 (m, 2H, $-\text{CH}_2$), 4.23 (m, 1H, $-\text{CHAr}$), 6.35 (m, 2H), 7.19 - 7.27 (m, 10H), 7.37 (d, 2H), 7.82 (d, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 44.0, 44.5, 126.3, 126.7, 127.3, 127.7, 128.5, 128.7, 129.0, 129.5, 130.2, 132.4, 135.5, 137.1, 139.6, 143.1, 197.0. MS (M/Z): 346.18. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{OCl}$ [$M + \text{H}$] $^+$ 347.1203, found 347.1190. $[\alpha]_{\text{D}} = +26.6$ (c 0.1 in DCM). The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 280 nm, 14.2 mins (major), 15.3 mins (minor).

85k (+)-1-(4-bromophenyl)-3, 5-diphenylpent-4-en-1-one

Light yellow oil. ^1H NMR (CDCl_3 , 400 MHz): δ 3.41 (m, 2H, $-\text{CH}_2$), 4.23 (m, 1H, $-\text{CHAr}$), 6.34 (m, 2H), 7.14 - 7.27 (m, 10H), 7.54 (d, 2H), 7.75 (d, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 44.0, 44.5, 126.3, 126.8, 127.3, 127.7, 128.3, 128.5, 128.7, 129.6, 130.2, 131.9, 132.3, 135.9, 137.1, 143.1, 197.2. MS (M/Z): 390.50. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{OBr}$ $[\text{M} + \text{H}]^+$ 391.0698, found 391.0692. $[\alpha]_{\text{D}} = +8.8$ (c 0.2 in DCM). The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 280 nm, 13.2 mins (major), 13.9 mins (minor).

85l (+)-1, 5-diphenyl-3-(*o*-tolyl)pent-4-en-1-one

Light yellow oil. ^1H NMR (CDCl_3 , 400 MHz): δ 2.44 (s, 3H, $-\text{ArMe}$) 3.51 (m, 2H, $-\text{CH}_2$), 4.55 (m, 1H, $-\text{CHAr}$), 6.35 (m, 2H), 7.13 - 7.97 (m, 14H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 19.7, 39.3, 44.0, 125.5, 126.2, 126.3, 126.4, 126.5, 127.0, 127.2, 127.3, 128.1, 128.4, 128.6, 128.6, 128.9, 129.2, 129.9, 130.7, 132.4, 132.7, 133.1, 136.2, 137.2, 137.3, 141.3, 141.9, 144.9, 198.2. MS (M/Z): 326.09. HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{23}\text{O}$ $[\text{M} + \text{H}]^+$ 327.1749, found 327.1740. $[\alpha]_{\text{D}} = +6.5$ (c 0.6 in CHCl_3). The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 99 : 1, 0.5 ml / min, 210 nm, 21.4 mins (major), 24.0 mins (minor).

85m (+)-1, 5-diphenyl-3-(*m*-tolyl)pent-4-en-1-one

Light yellow oil. ^1H NMR (CDCl_3 , 400 MHz): δ 2.33 (s, 3H, $-\text{ArMe}$), 3.48 (m, 2H, $-\text{CH}_2$), 4.26 (m, 1H, $-\text{CHAr}$), 6.38 (m, 2H), 7.01 - 7.56 (m, 12H), 7.93 (m, 2H, $-\text{Ar}$). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 21.5, 43.9, 44.6, 124.7, 126.3, 127.2, 127.4, 128.1, 128.4, 128.6, 128.6, 130.0, 132.7, 133.1, 137.2, 137.3, 138.3, 143.3, 198.3. MS (M/Z): 326.09. HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{23}\text{O}$ $[\text{M} + \text{H}]^+$ 327.1749, found 327.1742. $[\alpha]_{\text{D}} = +19.9$ (c 0.2 in DCM). The enantiomeric ratio was

determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 99 : 1, 0.5 ml / min, 280 nm, 25.7 mins (major), 28.0 mins (minor).

85n (+)-1, 5-diphenyl-3-(*p*-tolyl)pent-4-en-1-one

Light yellow oil. ^1H NMR (CDCl_3 , 400 MHz): 2.31 (s, 3H, -ArMe), 3.47 (m, 2H, -CH₂), 4.26 (m, 1H, -CHAr), 6.38 (m, 2H), 7.10 - 7.56 (m, -12H), 7.94 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): δ 21.2, 43.7, 44.7, 126.2, 127.6, 128.1, 128.4, 128.6, 129.4, 132.8, 133.0, 136.2, 137.3, 140.3, 198.4. MS (*M* / *Z*): 326.09. HRMS (ESI) calcd for C₂₄H₂₃O [*M* + *H*]⁺ 327.1749, found 327.1750. [α]_D = +5.2 (c 0.2 in DCM). The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 99 : 1, 0.5 ml / min, 210 nm, 26.5 mins (major), 29.9 mins (minor).

85o (+)-3-(4-methoxyphenyl)-1, 5-diphenylpent-4-en-1-one

Light yellow oil. ^1H NMR (CDCl_3 , 400 MHz): δ 3.47 (m, 2H, -CH₂), 3.79 (s, 3H, -ArOMe), 4.26 (m, 1H, -CHAr), 6.38 (m, 2H), 6.86 (d, 2H), 7.18 - 7.55 (m, 10H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 29.7, 43.2, 44.7, 114.1, 126.2, 127.2, 128.1, 128.5, 128.6, 128.7, 129.8, 133.0, 133.1, 135.3, 137.2, 137.3, 158.3, 198.3. MS (*M* / *Z*): 342.00. HRMS (ESI) calcd for C₂₄H₂₃O₂ [*M* + *H*]⁺ 343.1710, found 343.1710. [α]_D = +19.6 (c 0.1 in DCM). The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 95 : 5, 0.5 ml / min, 254 nm, 19.5 mins (major), 20.6 mins (minor).

85p (+)-3-(4-fluorophenyl)-1, 5-diphenylpent-4-en-1-one

Light yellow oil. ^1H NMR (CDCl_3 , 400 MHz): δ 3.47 (m, 2H, -CH₂), 4.30 (m, 1H, -CHAr), 6.376 (m, 2H), 6.971 - 7.55 (m, 12H), 7.93 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 43.2, 44.5, 115.4, 115.6, 127.4, 129.2, 129.3, 130.2, 132.5, 133.2, 137.1, 137.1, 138.9, 138.9, 160.4, 162.8, 198.0. ^{19}F NMR (CDCl_3 , 282 MHz): δ -116.4. MS (*M* / *Z*): 330.20. HRMS (ESI) calcd for

$C_{23}H_{20}O$ $[M + H]^+$ 331.1498, found 331.1496. $[\alpha]_D = +26.4$ (*c* 0.1 in DCM). The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 99.5 : 0.5, 0.5 ml / min, 230 nm, 30.0 mins (major), 33.3 mins (minor).

85q (+)-1-(2, 5-dimethylphenyl)-5-phenyl-3-(*o*-tolyl)pent-4-en-1-one

Light yellow oil. 1H NMR ($CDCl_3$, 400 MHz): δ 2.24 (s, 3H, -ArMe), 2.33 (s, 3H, -ArMe), 2.36 (s, 3H, -ArMe), 3.38 (m, 2H, -CH₂), 4.45 (m, 1H, -CHAr), 6.30 (m, 2H), 7.07 - 7.35 (m, 12H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 19.6, 20.2, 20.9, 40.0, 47.1, 126.2, 126.3, 126.4, 126.7, 127.2, 128.5, 128.6, 129.9, 130.7, 131.7, 131.8, 132.2, 134.7, 135.1, 136.2, 137.2, 138.5, 141.0, 203.0. MS (*M / Z*): 354.48. HRMS (ESI) calcd for $C_{26}H_{27}O$ $[M + H]^+$ 355.2062, found 355.2070. $[\alpha]_D = +15.7$ (*c* 0.3 in DCM). The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 99 : 1, 0.5 ml / min, 254 nm, 13.8 mins (major), no minor enantiomer detected.

85r (+)-1-(4-chlorophenyl)-5-phenyl-3-(*o*-tolyl)pent-4-en-1-one

Light yellow oil. 1H NMR ($CDCl_3$, 400 MHz): δ 2.42 (s, 3H, -ArMe), 3.46 (m, 2H, -CH₂), 4.51 (m, 1H, -CHAr), 6.30 (m, 2H), 7.10 - 7.28 (m, 9H), 7.41 (d, 2H), 7.88 (d, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 19.7, 29.7, 39.3, 44.0, 126.2, 126.3, 126.4, 126.5, 127.3, 128.5, 129.0, 129.5, 130.1, 130.8, 132.2, 135.4, 136.2, 137.1, 139.6, 141.1, 197.0. MS (*M / Z*): 360.36. HRMS (ESI) calcd for $C_{24}H_{22}OCl$ $[M + H]^+$ 361.1359, found 361.1358. $[\alpha]_D = +195.5$ (*c* 0.01 in DCM) The enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 97 : 3, 0.5 ml / min, 280 nm, 10.6 mins (major), 11.2 mins (minor).

3.2.4.

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Chapter 4.

Kinetic resolution of racemic monosubstituted cyclohexenones *via* C-C bond formation

4.1.

Introduction

Stereogenic multi-substituted cyclic ketones are valuable intermediates for a myriad of synthetic building blocks and biologically relevant compounds such as spirooxindole alkaloids (Scheme 4.1).¹ These optically active cycloalkanones are usually obtained from enantiomerically pure cycloenones,² which in turn, lack an extensive natural library and thus require laborious synthetic procedures.³ Therefore, the preparation of these valuable motifs converges upon the kinetic resolution of readily available racemic monosubstituted cycloalkenones *via* catalyzed 1,4-additions.⁴

Scheme 4.1.

Seminal endeavors by Tomioka and Feringa *et. al.* have established remarkably efficient resolution of 5-substituted cyclohexenones utilizing Cu(I) / (II) phosphoramidite complexes with *alkyl*zinc C nucleophiles (Scheme 4.2).^{4a, b}

Scheme 4.2.

Consequent advances engaging Rh(I) systems on similar substrates (*alkyl*₂Zn and 5-substituted cyclohexenones) are plagued with low diastereoselectivity in spite of excellent enantio-control due to the predominance of catalyst influence.^{4a, c} Simultaneous examinations with Cu on the other hand, suffer from moderate enantioselectivities due to the dominance of substrate control.^{4b, e} These protocols are also limited by the synergistic reliance on either thermal activation and / or the administration of moisture sensitive Zn *alkyl* nucleophiles.

It is thus prudent to develop a methodology which allows facile access to optically active 3, 5-disubstituted cycloalkanones, specifically 3-alkyl-5-aryl cycloalkanones utilizing moisture / air stable reagents.

von Zezschwitz and co-workers recently reported the conjugate addition of arylboronic acids to racemic 5-methyl cyclohexenone mediated by Rh(I) / (S)-BINAP.^{4c} Their attempts proceeded with high enantiocontrol (>99 %) but with poor *de* (0%) (Scheme 4.3).

Scheme 4.3.

The propensity of 3, 6-disubstituted cycloalkanones to undergo epimerization yielding thermodynamically stable *trans* products consents the practicality of the aforementioned Rh(I) / Cu protocols.^{4g-j} Thus, the kinetic resolution of 6-monosubstituted cyclohexenones yields *trans*-3, 6-disubstituted cycloalkanones almost exclusively upon nucleophile addition and subsequent treatment with bases (Scheme 4.4).

Scheme 4.4.

As part of a continuing interest in the development and application of palladacycles in C-C⁵ and C-X⁶ (X = N, P) bond formation reactions, we have recently showcased their efficiency for the addition of arylboronic acids to acyclic enones⁷ (Chapter 3) as well as conducting a preliminary study on the catalytic potential of a novel ferrocenyl phosphapalladacycle for the addition of arylboronic acids to 2-cyclohexenone (Chapter 2).⁸ Heartened by these results, we sought to evaluate a series of palladacycles for the kinetic resolution of racemic 5-alkylcyclohexenones

via arylboronic acid addition, with the concomitant generation of enantioenriched *trans* 3-alkyl-5-aryl cycloalkanones of interest.

4.2.

Results and Discussion

Adapting prior optimized reaction conditions discussed in Chapter 2 and 3, we commenced our study by treating racemic 5-methylcyclohexenone (**86a**) with 0.6 eq. phenylboronic acid (**60a**), 2.5 mol % palladacycle catalysts (**C8** and (*R_c S_{pl}*)-**67**) and 0.6 eq. 5M K₃PO₄ in toluene at room temperature for 18 hours (Scheme 4.5).

Scheme 4.5.

The resolution proceeded smoothly when the ferrocenyl phosphapalladacycle (*R_c S_{pl}*-**67**) was employed, furnishing *trans*-(3*R*, 5*R*)-3-methyl-5-phenylcyclohexanone (3*R*, 5*R*)-**87a** as the major product in 48 % isolated yield, 95 : 5 *dr* and 70 % *ee* (Table 4.1, Entry 1). Although **C9** was the choice catalyst for both the 1, 4-conjugate addition of arylboronic acids to linear and cyclic enones (Chapter 3.1) and α, β, γ, δ-unsaturated enones (Chapter 3.2), it only afforded

(3*R*, 5*R*)-**87a** in a 19 % conversion. Hence, subsequent focus was placed on optimizing reaction conditions with (*R_c* *S_{pl}*)-**67** as the catalyst.

Further examination revealed 5M K₃PO₄ to be the base of choice. In an attempt to enhance both *dr* and *ee* values, a sequence of low temperature resolutions were conducted (Table 4.1, Entries 7-9), and *trans*-(3*R*, 5*R*)-(**87a**) was attained in a 45 % yield, with accompanying 97 : 3 *dr* and 81 % *ee* when the addition was conducted at 0 °C over 24 hrs (Table 4.1, Entry 7).

Table 4.1.^a

Entry	Base (5M)	T (°C)	t (hrs)	Yield ^b (%)	<i>dr</i> ^c	<i>trans ee</i> ^d (%)
1	K ₃ PO ₄	RT	18	47	95 : 5	70
2	KOH	RT	18	32	99 : 1	66
3	KF	RT	18	32	95 : 5	73
4	K ₂ CO ₃	RT	18	35	97 : 3	70
5	NEt ₃	RT	18	10	>99 : 1	73
6	<i>t</i> -BuOK	RT	18	15	95 : 5	55
7	K₃PO₄	0	24	45	97 : 3	82
8	K ₃ PO ₄	-25	48	34	>99 : 1	83
9	K ₃ PO ₄	-40	72	28	>99 : 1	84

^a Reaction conditions: **60a** (12.2 mg, 0.1 mmol), **86a** (16.3 mg, 0.17 mmol), (*R_c* *S_{pl}*)-**67** (5.4 mg, 4.25 x 10⁻³ mmol, 2.5 mol % of **86a**) and 5M base (20.0 μL, 0.1 mmol) in 0.1 mL of toluene at the stated temperature. ^b Isolated yields. ^c *de* of (3*R*, 5*R*)-**87a** determined by integration of crude ¹H NMR in toluene-*d*₈. ^d *ee* of (3*R*, 5*R*)-**87a** determined by HPLC using a chiral column. Chirality determined *via* comparison of HPLC elution times and optical rotation values with known dossiers.

Having determined the optimized conditions for the kinetic resolution of racemic 5-methylcyclohexenone (**86a**) with phenylboronic acid (**60a**), efforts were directed toward the addition of various functionalized arylboronic acid derivatives onto **86a** (Scheme 4.6).

Scheme 4.6.^a

^a Reaction conditions: **60** (12.2 mg, 0.1 mmol), **86a** (16.3 mg, 0.17 mmol), (*R_c*, *S_{Pl}*)-**67** (5.4 mg, 4.25 × 10⁻³ mmol, 2.5 mol % of **86a**) and 5M base (20.0 μL, 0.1 mmol) in 0.1 mL of toluene at 0 °C for 24 hours. Isolated yields.

de of (3*R*, 5*R*)-**87** determined by integration of crude ¹H NMR in toluene-d₈. ^d *ee* of (3*R*, 5*R*)-**87** determined by HPLC using a chiral column. Chirality determined *via* comparison of HPLC elution times and optical rotation values with known dossiers.

In general, satisfactory conversions were achieved with excellent *dr* and moderate to good *trans ee* values. The influence of the aryl fragment on yields and selectivities are typically homogenous, with aberrations observed due to increased sterics (*o*-tolylboronic acid with 5-methylcyclohexenone, **87b**) and when *p*-hydroxyphenylboronic acid (**60m**) were serviced. This could be attributed to its poor solubility in toluene, thus requiring MeOH as a co-solvent and the resolution to be conducted at RT (**87j**). Interestingly, both the electron-withdrawing *para*-fluorophenyl (**60e**) and electron donating *para*-methoxyphenyl (**60d**) boronic acid groups are well tolerated in this protocol and yield similar results (**87h**: 50 % yield, 98 : 2 *dr*, 86 % *ee* and **87i**: 51 % yield, 99 : 1 *dr*, 82 % *ee*).

The addition of both phenylboronic acid and *p*-methoxyphenylboronic acid onto additional monosubstituted cyclohexenone derivatives was examined next (Scheme 4.7).

Scheme 4.7.

^a Reaction conditions: **60a, d** (12.2 mg, 0.1 mmol), **86b - e** (16.3 mg, 0.17 mmol), (*R_c S_{pl}*)-**67** (5.4 mg, 4.25 × 10⁻³ mmol, 2.5 mol % of **86**) and 5M base (20.0 μL, 0.1 mmol) in 0.1 mL of toluene at 0 °C for 24 hours. Isolated yields.

³ *de* of (3*R*, 5*R*)-**87** determined by integration of crude ¹H NMR in toluene-*d*₈. ^d *ee* of (3*R*, 5*R*)-**87** determined by HPLC using a chiral column. Chirality determined *via* comparison of HPLC elution times and optical rotation values with known dossiers.

Reiteratively, relatively poor results were obtained once sterically hindered cyclohexenones were applied. When the methyl spacer is placed closer to the electrophilic β -carbon, the *dr* is seen to improve till a single diastereomer (**87k**). While the yield generally decreases as the steric bulk is increased, *dr* ratios and *ee* values by and large remain consistent.

The selectivity factor (*s*-factor) is a term commonly associated with classical kinetic resolution procedures. In this instance, it is assumed that the addition protocol follows a first order dependence on substrate and calculations are based on the following equation:

$$s = \ln[1 - C(1 + ee)] / \ln[1 - C(1 - ee)],$$

where C = conversion,

ee = *ee* of (3*R*, 5*R*)-cycloalkanone product **87**.

It is also possible to rule out a possible simultaneous parallel kinetic resolution after analysis of all the crude ¹H NMR spectra as only the leftover enantioenriched (*S*)-**86** and arylated (3*R*, 5*R*)-**87** may be observed. These considerations allow the exclusion of a possible parallel kinetic resolution. An example is illustrated in Spectra 4.1 - 4.3.

Spectrum 4.1. *rac*-**86a**

Spectrum 4.2. (3*R*, 5*R*)-**87h**

Spectrum 4.3.

The ^1H spectra (CDCl_3) of *rac*-**86a** and (3*R*, 5*R*)-**87h** are displayed in Spectra 4.1 and 4.2 respectively, while Spectrum 4.3 shows a crude ^1H spectrum of the kinetic resolution of *rac*-**86a** by the addition of *p*-methoxyphenyl boronic acid (**60d**) after work-up in CDCl_3 . A comparison of all 3 spectra suggest that only *rac*-**86a** and (3*R*, 5*R*)-**87h** are the only species present in Spectrum 4.3, hence lending support that no parallel kinetic resolution process is transpired.

Intrigued by the efficacy of the current protocol, we decided to further probe the basis of the observed synergistic catalyst-substrate selectivity control with supplementation by computational studies.

The mechanism of Pd-catalyzed conjugate addition of arylboronic acids to 2-cyclohexenone has been comprehensively examined, and is widely acknowledged to involve transmetalation, carbopalladation (β -insertion) and protonation steps.⁹ Although no report concerning Pd(II)-appended phosphapalladacycles has been established, we postulate an analogous catalytic cycle is abided by our system (Scheme 4.8).

Scheme 4.8.

We hereby base our supposition on the following:

- i) The hypotheses that the aryl moiety attunes to the position *cis* to the carbon ligand after transmetalation is substantiated by Fairlamb *et. al.* (Scheme 4.9).^{9b}

Scheme 4.9.

- ii) The β -insertion step involves a square-planar 4-membered cyclic transition state.

With these fundamental requirements, there are 4 possible isomeric alkene insertion transition states. The 3D structures of these reaction intermediates and transition states are shown in Figure 4.1.

Figure 4.1.

Table 4.2.

Transition State	Activation Barrier (kcal / mol)	Product
1	9.10	3 <i>R</i> , 5 <i>R</i>
2	9.35	3 <i>R</i> , 5 <i>S</i>
3	11.29	3 <i>S</i> , 5 <i>S</i>
4	11.04	3 <i>S</i> , 5 <i>R</i>

In all the transition states, the aryl group is situated *cis* to the carbon ligand. The discrimination of substrate by the catalyst is due to the steric hindrance between the alkyl pendant at C5 and the ferrocene sandwich (TS 2 and 4) or between the cyclic alkyl backbone of the cyclohexenone

ring and the ferrocene scaffold (TS 3). The merger of these 2 steric effects thus favors the addition to preferentially proceed *via* TS 1, with the lowest computed activation barrier of 9.10 kcal / mol, leading to a cyclohexanone product with 3*R*, 5*R* configuration as seen in our experimental studies.

4.3.

Conclusion

In summary, we have analyzed the scope of a convenient methodology toward the kinetic resolution of racemic monosubstituted cycloenones affording synthetically relevant cycloalkanone adducts with excellent diastereomeric ratios and good enantiocontrol. It is also the first instance in literature that a desirable balance between catalyst and substrate control has been achieved using a Pd(II)-catalyst system at ambient temperatures. Subsequent examination of all possible transition states revealed the source of diastereo- / enantioselectivity control, which is in agreement with experimental observations.

4.4.

Experimental

Thin layer chromatography was performed on Merck silica gel 60 F254 aluminium backed plates and visualized under UV. Flash chromatography was performed using Merck silica gel 60. NMR spectra were recorded on a Bruker AV 300 spectrometer (^1H at 300 MHz, $^{13}\text{C}\{^1\text{H}\}$ at 75 MHz, ^{31}P at 121 MHz, $^{19}\text{F}\{^1\text{H}\}$ at 282 MHz), Bruker AV 400 spectrometer (^1H at 400 MHz, $^{13}\text{C}\{^1\text{H}\}$ at 100 MHz, ^{31}P at 162 MHz) or Bruker AV 500 spectrometer (^1H at 500 MHz, $^{13}\text{C}\{^1\text{H}\}$ at 125 MHz, ^{31}P at 202 MHz). ^1H spectra are referenced to an internal SiMe_4 standard at δ 0 ppm or to CDCl_3 at δ 7.26 ppm. Optical rotations were measured on the specified solution in a 0.1 dm cell at 20 °C with a Perkin - Elmer 341 polarimeter. Melting points were documented on a SRS Optimelt

MPA 100 point system. Mass spectrometry was obtained in ESI mode on a Thermo Finnigan LCQ Deca XP MAX system. HRMS (ESI) were recorded on a time-of-flight (TOF) LC/MS instrument.

Computational Details

DFT calculations were performed with the Gaussian 09 package.¹⁰ Both intermediates and transition state structures involved in the rate-determining step are fully optimized by BP86¹¹ method using general basis set: 6-31G(d)¹² for H, C, O and P, SDD¹³ for Fe and Pd. The SDD ECP is used for Fe and Pd as well. Also, harmonic vibrational frequencies are calculated on the optimized geometries to validate whether they are local minimum or transition state.

Procedure for the Kinetic Resolution of Racemic 5-alkylcyclohexenones *via* arylboronic acid addition:

To a 5 ml vial were placed boronic acid (0.1 mmol, 0.6 eq.) and catalyst (4.17×10^{-3} mmol, 2.5 mol %). The orange solution was allowed to stir for 10 mins at 0 °C before racemic cyclohexenone (0.17 mmol, 1 eq.) and 5M K₃PO₄ (0.1 mmol, 0.6 eq.) was sequentially added. Upon stirring for 18 or 24 hrs, the resulting solution was passed through a short plug of silica gel (5 *n* - hexanes : 1 EA) to yield both 3-aryl, 5-alkyl cyclohexanone (*R_f* : 0.40) and 5-alkyl cyclohexenone (*R_f* : 0.45) as colourless oils.

3-methyl-5-phenyl cyclohexanone (3*R*, 5*R*)-**87a**:

Colourless oil. ¹H NMR (CDCl₃, 400 MHz): δ 1.03 (d, 3H, -CH₃, ³*J* = 5.6 Hz), 1.84 - 1.89 (m, 1H), 2.05 - 2.10 (m, 1H), 2.15 - 2.19 (m, 1H), 2.26 - 2.29 (m, 1H), 2.54 - 2.64 (m, 3H), 3.36 - 3.40 (m, 1H, -CHPh), 7.20 - 7.24 (m, 3H, -CHPh), 7.30 - 7.33 (m, 2H, -CHPh). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 20.3, 29.3, 39.4, 39.6, 47.2, 48.5, 126.5, 127.0, 128.6, 144.4, 211.6. MS (*M*/*Z*) 189.07. HRMS (ESI) calcd for C₁₃H₁₇O [*M* + H]⁺ 189.1279, found 189.1282. [α]_D = -22.32 (c 0.50, DCM). The diastereomeric and enantiomeric ratio was determined *via* HPLC using a chiral column

(Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 210 nm, 28.9 mins (major), 32.2 (minor), 33.3 (minor), 35.4 (minor).

For **86a**:

$[\alpha]_D = 66.2$ (c 0.50, CHCl₃) for 71 % *ee*.

3-methyl-5-(*o*-tolyl)cyclohexanone (3*R*, 5*R*)-**87b**:

Colourless oil. ¹H NMR (CDCl₃, 400 MHz): δ 1.05 (d, 3H, -CH₃, ³*J* = 6.8 Hz), 1.76 - 1.82 (m, 1H), 1.95 - 2.02 (m, 1H), 2.18 - 2.22 (m, 1H), 2.34 (s, 3H, -ArMe), 2.47 - 2.63 (m, 3H), 3.53 - 3.60 (m, 1H, -CHAr), 7.11 - 7.21 (m, 4H, -Ar). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 19.3, 20.1, 29.4, 35.2, 38.1, 47.0, 48.4, 125.7, 126.3, 126.4, 130.7, 135.2, 142.4, 211.9. MS (*M* / *Z*) 203.05. HRMS (ESI) calcd for C₁₄H₁₉O [M + H]⁺ 203.1436, found 203.1433. $[\alpha]_D = -25.99$ (c 0.4, DCM). The diastereomeric and enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 210 nm, 0.5 ml / min, 23.1 mins (major), 26.4 mins (minor).

For **86a**:

$[\alpha]_D = 47.6$ (c 0.50, CHCl₃) for 51 % *ee*.

3-methyl-5-(*m*-tolyl)cyclohexanone (3*R*, 5*R*)-**87c**:

Colourless oil. ¹H NMR (CDCl₃, 400 MHz): δ 1.01 (d, 3H, -CH₃, *J* = 7.2 Hz), 1.81 - 1.86 (m, 1H), 2.02 - 2.09 (m, 1H), 2.12 - 2.17 (m, 1H), 2.25 - 2.31 (m, 1H), 2.33 (s, 3H, -ArMe), 2.52 - 2.62 (m, 3H), 3.29 - 3.36 (m, 1H, -CHAr), 6.99 - 7.03 (m, 3H, -Ar), 7.17 - 7.21 (m, 1H, -Ar). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 20.3, 21.5, 29.3, 39.5, 47.3, 48.4, 124.0, 127.3, 127.8, 128.5, 138.2, 144.4, 211.7. MS (*M* / *Z*) 203.03. HRMS (ESI) calcd for C₁₄H₁₉O [M + H]⁺ 203.1436, found 203.1437. $[\alpha]_D = -20.04$ (c 0.3, DCM). The diastereomeric and enantiomeric ratio was determined *via*

HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 210 nm, 21.5 mins (major), 22.8 mins (minor), 24.4 mins (minor), 24.8 mins (minor).

For **86a**:

$[\alpha]_D = 59.7$ (c 0.50, CHCl₃) for 64 % *ee*.

3-methyl-5-(*p*-tolyl)cyclohexanone (3*R*, 5*R*)-**87d**:

Colourless oil. ¹H NMR (CDCl₃, 400 MHz): δ 1.02 (d, 3H, -CH₃, *J* = 6.92 Hz), 1.85 - 1.87 (m, 1H), 2.02 - 2.09 (m, 1H), 2.13 - 2.18 (m, 1H), 2.23 - 2.29 (m, 1H), 2.33 (s, 3H, -ArMe), 2.52 - 2.60 (m, 3H), 3.31 - 3.38 (m, 1H, -CHAr), 7.09 - 7.14 (m, 4H, -Ar). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 20.3, 21.0, 29.3, 39.2, 39.5, 47.3, 48.5, 76.7, 77.0, 77.4, 126.8, 129.3, 136.1, 141.4, 211.7. MS (*M* / *Z*) 203.03. HRMS (ESI) calcd for C₁₄H₁₉O [*M* + *H*]⁺ 203.1436, found 203.1443. $[\alpha]_D = -16.65$ (c 0.4, DCM). The diastereomeric and enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 210 nm, 24.5 mins (major), 27.2 mins (minor), 28.5 mins (minor), 31.1 mins (minor).

For **86a**:

$[\alpha]_D = 70.9$ (c 0.50, CHCl₃) for 76 % *ee*.

3-methyl-5-(1-naphthalene)cyclohexanone (3*R*, 5*R*)-**87e**:

Colourless oil. ¹H NMR (CDCl₃, 400 MHz): δ 1.04 (d, 1H, -CH₃, *J* = 6.4 Hz), 1.94 - 2.00 (m, 1H), 2.13 - 2.23 (m, 3H), 2.56 - 2.62 (m, 1H), 2.74 (d, 2H, *J* = 6.8 Hz), 4.19 - 4.52 (m, 1H, -CHAr), 7.28 (d, 1H, -Ar, *J* = 7.2 Hz), 7.41 (t, 1H, -Ar, *J* = 7.8 Hz), 7.46 - 7.54 (m, 2H, -Ar), 7.72 (d, 1H, -Ar, *J* = 8.0 Hz), 7.85 (d, 1H, -Ar, *J* = 8.0 Hz), 8.04 (d, 1H, -Ar, *J* = 8.4 Hz). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 20.6, 29.2, 34.9, 38.6, 46.7, 48.9, 122.9, 123.5, 125.4, 125.6, 126.2, 127.3, 129.2, 131.0, 134.0, 140.1, 212.0. MS (*M* / *Z*) 237.21. HRMS (ESI) calcd for C₁₇H₁₉O [*M* + *H*]⁺

239.1436, found 239.1443. $[\alpha]_D = -19.74$ (c 1.0, DCM). The diastereomeric and enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 254 nm, 34.1 mins (major), 37.0 mins (minor), 40.7 mins (minor), 42.9 mins (minor).

For **86a**:

$[\alpha]_D = 78.3$ (c 0.50, CHCl_3) for 84 % ee.

3-methyl-5-(2-naphthalene)cyclohexanone (3*R*, 5*R*)-**87f**:

Colourless oil. ^1H NMR (CDCl_3 , 400 MHz): δ 1.05 (d, 3H, $-\text{CH}_3$, $J = 6.8$ Hz), 1.91 - 1.97 (m, 1H), 2.15 - 2.31 (m, 3H), 2.56 - 2.78 (m, 3H), 3.52 - 3.59 (m, $-\text{CHAr}$), 7.36 (dd, 1H, $J = 1.6$ Hz, 8.4 Hz, $-\text{Ar}$), 7.43 - 7.49 (m, 2H, $-\text{Ar}$), 7.63 (s, 1H, $-\text{Ar}$), 7.81 (d, 3H, $J = 6.8$ Hz, $-\text{Ar}$). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 20.4, 29.2, 39.3, 39.7, 47.0, 48.6, 125.2, 125.6, 125.7, 126.2, 127.6, 127.8, 128.3, 132.2, 133.5, 141.8, 211.5. MS (M / Z) 239.04. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{19}\text{O}$ $[\text{M} + \text{H}]^+$ 239.1436, found 239.1441. $[\alpha]_D = -5.42$ (c 0.7, DCM). The diastereomeric and enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 0.5 ml / min, 254 nm, 37.9 mins (major), 39.8 mins (minor), 45.7 mins (minor), 48.6 mins (minor).

For **86a**:

$[\alpha]_D = 73.7$ (c 0.50, CHCl_3) for 79 % ee.

3-methyl-5-(Biphenyl-4)cyclohexanone (3*R*, 5*R*)-**87g**:

White solid. ^1H NMR (CDCl_3 , 400 MHz): δ 1.04 (d, 3H, $-\text{CH}_3$, $J = 6.8$ Hz), 1.87 - 1.93 (m, 1H), 2.08 - 2.21 (m, 2H), 2.28 - 2.32 (m, 1H), 2.55 - 2.65 (m, 3H), 3.39 - 3.46 (m, 1H, $-\text{CHAr}$), 7.25 - 7.35 (m, 3H, $-\text{Ar}$), 7.41 - 7.45 (m, 2H, $-\text{Ar}$), 7.53 - 7.58 (m, 4H, $-\text{Ar}$). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125

MHz): δ 20.4, 29.3, 39.3, 39.4, 47.2, 48.5, 127.0, 127.2, 127.3, 127.4, 128.8, 139.5, 140.8, 143.4, 211.5. MS (*M / Z*) 265.11. HRMS (ESI) calcd for $C_{19}H_{21}O$ [*M* + *H*]⁺ 265.1592, found 254.1581. $[\alpha]_D = -10.99$ (*c* 0.9, DCM). The diastereomeric and enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 95 : 5, 270 nm, 0.5 ml / min, 30.6 mins (major), 31.5 mins (minor), 33.5 mins (minor), 34.1 mins (minor).

For **86a**:

$[\alpha]_D = 46.6$ (*c* 0.50, $CHCl_3$) for 50 % *ee*.

3-methyl-5-*p*-methoxyphenylcyclohexanone (3*R*, 5*R*)-**87h**:

Colourless oil. ¹H NMR ($CDCl_3$, 400 MHz): δ 1.01 (d, 3H, -*CH*₃, *J* = 6.8 Hz), 1.80 - 1.86 (m, 1H), 2.00 - 2.06 (m, 1H), 2.12 - 2.17 (m, 1H), 2.22 - 2.29 (m, 1H), 2.51 - 2.57 (m, 3H), 3.30 - 3.36 (m, 1H, -*CHAr*), 3.78 (s, 3H, -*ArOMe*), 6.85 (d, 2H, -*Ar*, *J* = 8.4 Hz), 7.12 (d, 2H, -*Ar*, *J* = 8.8 Hz). ¹³C{¹H} NMR ($CDCl_3$, 100 MHz): δ 20.3, 29.2, 38.8, 39.6, 47.5, 48.5, 55.3, 113.9, 127.9, 136.5, 158.2, 211.7. MS (*M / Z*) 218.90. HRMS (ESI) calcd for $C_{14}H_{19}O_2$ [*M* + *H*]⁺ 219.1385, found 219.1395. $[\alpha]_D = -20.00$ (*c* 0.3, DCM). The diastereomeric and enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 90 : 10, 280 nm, 0.5 ml / min, 24.7 mins (major), 27.1 mins (minor), 28.8 mins (minor), 29.9 mins (minor).

For **86a**:

$[\alpha]_D = 78.4$ (*c* 0.50, $CHCl_3$) for 84 % *ee*.

3-methyl-5- *p*-fluorophenylcyclohexanone (3*R*, 5*R*)-**87i**:

Colourless oil. ^1H NMR (CDCl_3 , 400 MHz): δ 1.00 (d, 3H, $-\text{CH}_3$, $J = 6.9$ Hz), 1.83 - 1.86 (m, 1H), 1.98 - 2.05 (m, 1H), 2.12 - 2.17 (m, 1H), 2.20 - 2.26 (m, 1H), 2.50 - 2.56 (m, 3H), 3.31 - 3.38 (m, 1H, $-\text{CHAr}$), 6.96 - 6.70 (m, 2H, $-\text{Ar}$), 7.13 - 7.17 (m, 2H, $-\text{Ar}$). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 20.3, 29.2, 38.9, 39.5, 47.3, 48.4, 115.2, 115.5, 128.3, 128.4, 140.0, 140.0, 160.3, 162.7, 211.3. ^{19}F NMR (CDCl_3 , 282 MHz): δ - 116.6. MS (M/Z) 207.08. HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{16}\text{OF}$ [$M + \text{H}$] $^+$ 207.1185, found 207.1188. $[\alpha]_{\text{D}} = -18.04$ (c 0.5, DCM). The diastereomeric and enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 99 : 1, 280 nm, 0.5 ml / mins, 40.9 mins (major), 47.5 mins (minor), 49.3 mins (minor).

For **86a**:

$[\alpha]_{\text{D}} = 37.3$ (c 0.50, CHCl_3) for 40 % *ee*.

3-methyl-5-*p*-hydroxylphenylcyclohexanone (3*R*, 5*R*)-**87j**:

Colourless oil. ^1H NMR (CDCl_3 , 400 MHz): δ 1.00 (d, 3H, $-\text{CH}_3$, $J = 6.8$ Hz), 1.79 - 1.85 (m, 1H), 1.98 - 2.05 (m, 1H), 2.12 - 2.25 (m, 2H), 2.51 - 2.58 (m, 3H), 3.29 - 3.36 (m, 1H, $-\text{CHAr}$), 5.46 (s, 1H, $-\text{OH}$), 6.78 (d, $-\text{Ar}$, $J = 8.4$ Hz), 7.05 (d, $-\text{Ar}$, $J = 8.4$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 20.4, 29.2, 38.8, 39.5, 47.4, 48.5, 115.4, 128.1, 136.3, 154.3, 212.6. MS (M/Z) 203.00. HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{17}\text{O}_2$ [$M + \text{H}$] $^+$ 205.1229, found 205.1239. $[\alpha]_{\text{D}} = -12.19$ (c 0.4, DCM). The diastereomeric and enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 90 : 10, 280 nm, 0.5 ml / min, 33.6 (major), 35.6 mins (minor), 40.1 mins (minor), 45.4 mins (minor).

For **86a**:

$[\alpha]_{\text{D}} = 35.4$ (c 0.50, CHCl_3) for 38 % *ee*.

4-methyl-3-phenylcyclohexanone (3*R*, 4*R*)-**87k**:

Colourless oil. ^1H NMR (CDCl_3 , 500 MHz): δ 0.78 (d, 3H, $-\text{CH}_3$, 6.5 Hz), 1.50 - 1.59 (m, 2H), 2.09 (m, 1H), 2.13 - 2.18 (m, 1H), 2.45 - 2.58 (m, 5H), 7.17 - 7.27 (m, 3H, $-\text{Ar}$), 7.32 - 7.35 (m, 2H, $-\text{Ar}$). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 19.3, 34.6, 36.8, 14.4, 49.2, 52.1, 126.7, 127.2, 129.8, 143.6, 211.0. MS (M/Z) 189.03. HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{17}\text{O}$ $[\text{M} + \text{H}]^+$ 189.1279, found 189.1282. $[\alpha]_{\text{D}} = +36.76$ (c 0.1, DCM). The diastereomeric and enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 95 : 5, 210 nm, 0.5 ml / min, 25.5 (major), 27.0 (minor).

For **86b**:

$[\alpha]_{\text{D}} = 54.9$ (c 0.60, CHCl_3) for 44 % *ee*.

3-ethyl-5-phenylcyclohexanone (3*R*, 5*R*)-**87l**:

Colourless oil. ^1H NMR (CDCl_3 , 400 MHz): δ 0.88 - 0.91 (m, 3H), 1.36 - 1.40 (m, 2H), 1.93 - 2.08 (m, 3H), 2.21 - 2.26 (m, 1H), 2.53 - 2.62 (m, 3H), 3.31 - 3.33 (m, 1H, $-\text{CHAr}$), 7.20 - 7.24 (m, 3H, $-\text{Ar}$), 7.30 - 7.34 (m, 2H, $-\text{Ar}$). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 11.6, 27.0, 36.1, 37.0, 39.5, 46.5, 47.4, 126.5, 126.9, 128.6, 144.4, 211.7. MS (M/Z) 203.07. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{19}\text{O}$ $[\text{M} + \text{H}]^+$ 203.1436, found 203.1433. $[\alpha]_{\text{D}} = -19.39$ (c 0.1, DCM). The diastereomeric and enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 210 nm, 0.5 ml / min, 25.3 mins (major), 28.2 mins (minor), 29.4 mins (minor), 30.8 mins (minor).

For **86c**:

$[\alpha]_{\text{D}} = 28.4$ (c 0.50, CHCl_3) for 62 % *ee*.

3-propyl-5-phenylcyclohexanone (3*R*, 5*R*)-**87n**:

Colourless oil. ¹H NMR (CDCl₃, 400 MHz): δ 0.85 - 0.88 (m, 3H), 1.30 - 1.31 (m, 4H), 1.88 - 1.94 (m, 1H), 2.00 - 2.10 (m, 2H), 2.19 - 2.24 (m, 1H), 2.51 - 2.60 (m, 3H), 3.27 - 3.34 (m, 1H, -CHAr), 7.19 - 7.25 (m, 3H, -Ar), 7.29 - 7.33 (m, 2H, -Ar). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 14.0, 20.2, 34.1, 36.3, 37.3, 39.5, 46.7, 47.5, 126.5, 126.9, 128.6, 144.4, 211.7. MS (*M* / *Z*) 217.07. HRMS (ESI) calcd for C₁₅H₂₁O [*M* + *H*]⁺ 217.1592, found 217.1600. [α]_D = +2.04 (c 0.1, DCM). The diastereomeric and enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 210 nm, 0.5 ml / min, 21.4 mins (major), 24.4 mins (minor), 26.3 mins (minor), 28.4 mins (minor).

3-butyl-5-phenylcyclohexanone (3*R*, 5*R*)-**87p**:

Colourless oil. ¹H NMR 0.86 - 0.89 (m, 3H), 1.26 - 1.34 (m, 6H), 1.92 - 1.96 (m, 1H), 2.02 - 2.08 (m, 2H), 2.21 - 2.26 (m, 1H), 2.53 - 2.61 (m, 3H), 3.28 - 3.35 (m, 1H, -CHAr), 7.20 - 7.24 (m, 3H, -Ar), 7.30 - 7.34 (m, 2H, -Ar). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 14.0, 14.1, 22.7, 22.7, 29.3, 31.6, 33.8, 34.4, 37.3, 39.5, 46.8, 47.5, 126.5, 126.9, 128.6, 144.4, 211.7. MS (*M* / *Z*) 231.09. HRMS (ESI) calcd for C₁₆H₂₃O [*M* + *H*]⁺ 231.1749, found 231.1756. [α]_D = -1.60 (c 0.5, DCM). The diastereomeric and enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 98 : 2, 210 nm, 0.5 ml / min, 20.0 mins (major), 22.7 mins (minor), 25.0 mins (minor), 27.1 mins (minor).

For **86e**:

[α]_D = 24.4 (c 0.50, CHCl₃) for 50 % ee.

3-ethyl-5-*p*-methoxyphenylcyclohexanone (3*R*, 5*R*)-**87m**:

Colourless oil. ¹H NMR (CDCl₃, 400 MHz): δ 0.89 (t, 3H, *J* = 7.4 Hz), 1.33 - 1.40 (m, 2H), 1.89 - 2.04 (m, 3H), 2.19 - 2.24 (m, 1H), 2.51 - 2.58 (m, 3H), 3.24 - 3.31 (m, 1H, -CHAr), 3.789 (s, 3H,

-ArOMe), 6.84 - 6.86 (m, 2H, -Ar), 7.11 - 7.14 (m, 2H, -Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 11.6, 27.1, 36.0, 37.2, 38.7, 46.5, 47.7, 55.3, 114.0, 127.8, 136.5, 158.2, 211.8. MS (M / Z) 233.02. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{21}\text{O}_2$ $[\text{M} + \text{H}]^+$ 233.1542, found 233.1545. $[\alpha]_{\text{D}} = -13.15$ (c 0.5, DCM). The diastereomeric and enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 95 : 5, 280 nm, 0.5 ml / min, 30.0 mins (major), 33.5 mins (minor), 36.6 (minor), 37.9 (minor).

For **86c**:

$[\alpha]_{\text{D}} = 28.5$ (c 0.50, CHCl_3) for 62 % ee.

3-propyl-5-*p*-methoxyphenylcyclohexanone (3*R*, 5*R*)-**87o**:

Colourless oil. ^1H NMR (CDCl_3 , 500 MHz): δ 0.88 (m, 3H), 1.31 (m, 4H), 1.87 - 1.92 (m, 1H), 1.98 - 2.04 (m, 1H), 2.07 - 2.08 (m, 1H), 2.18 - 2.23 (m, 1H), 2.51 - 2.58 (m, 3H), 3.25 - 3.30 (m, 1H, -CHAr), 3.79 (s, 3H, -ArOMe), 6.85 - 6.86 (m, 2H, -Ar), 7.12 - 7.14 (m, 2H, -Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR: (CDCl_3 , 100 MHz): δ 14.0, 20.2, 34.1, 36.4, 37.5, 38.8, 46.7, 47.8, 55.3, 114.0, 127.8, 136.5, 158.2, 211.8. MS (M / Z) 247.01. HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{23}\text{O}_2$ $[\text{M} + \text{H}]^+$ 247.1698, found 247.1694. $[\alpha]_{\text{D}} = -5.80$ (c 0.3, DCM). The diastereomeric and enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 95 : 5, 280 nm, 0.5 ml / min, 26.8 mins (major), 30.7 mins (minor), 34.7 mins (minor), 35.6 mins (minor).

3-butyl-5-*p*-methoxyphenylcyclohexanone (3*R*, 5*R*)-**87q**:

Colourless oil. ^1H NMR (CDCl_3 , 500 MHz): δ 0.86 - 0.89 (m, 3H), 1.27 - 1.33 (m, 6H), 1.89 - 1.92 (m, 1H), 1.98 - 2.06 (m, 2H), 2.19 - 2.24 (m, 1H), 2.51 - 2.57 (m, 3H), 3.28 - 3.29 (m, 1H, -CHAr), 3.79 (s, 3H, -ArOMe), 6.85 - 6.86 (m, 2H, -Ar), 7.12 - 7.14 (m, 2H, -Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 14.0, 22.7, 29.3, 33.9, 34.4, 37.5, 38.8, 46.8, 47.8, 55.3, 114.0, 127.8,

136.5, 158.2, 211.8. MS (*M* / *Z*) 261.01. HRMS (ESI) calcd for C₁₇H₂₅O₂ [*M* + *H*]⁺ 261.1855, found 261.1849. [α]_D = -1.00 (*c* 0.5, DCM). The diastereomeric and enantiomeric ratio was determined *via* HPLC using a chiral column (Daicel Chiralpak IC), *n* - hexanes : IPA = 95 : 5, 280 nm, 0.5 ml / min, 24.0 mins (major), 27.1 mins (minor), 33.8 mins (minor), 34.4 mins (minor).

For **86e**:

[α]_D = 22.9 (*c* 0.50, CHCl₃) for 47 % ee.

4.5.

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List of Publications and Manuscripts:

Published Manuscripts:

- 1) "Chiral Phosphapalladacycles as Efficient Catalysts for the Asymmetric Hydrophosphination of Substituted Methylidenemalonate Esters: Direct Access to Functionalized Tertiary Chiral Phosphines"

Chang Xu, Kennard Gan, Felix Hennersdorf, Yongxin Li, Sumod A. Pullarkat, Pak-Hing Leung, *Organometallics*, **2012**, 31, 3022.
- 2) "Evaluation of Palladacycles as a Non-Rhodium Based Alternative for the Asymmetric Conjugate 1, 4-Addition of Arylboronic Acids to α , β -Unsaturated Enones"

Jonathan Wong, Kennard Gan, Houguang Jeremy Chen, Sumod A. Pullarkat, *Advanced Synthesis and Catalysis*, **2014**, 16, 3391.
- 3) "Asymmetric Construction of a Ferrocenyl Phosphapalladacycle from Achiral Enones and a Demonstration of its Catalytic Potential"

Kennard Gan, Abdul Sadeer, Chang Xu, Yongxin Li, Sumod A. Pullarkat, *Organometallics*, **2014**, 33, 5074.
- 4) "Palladium catalyzed asymmetric hydrophosphination of α , β - and α , β , γ , δ -unsaturated malonate esters - efficient control of reactivity, stereo- and regio-selectivity"

Xiang-Yuan Yang, Kennard Gan, Yongxin Li, Sumod A. Pullarkat, Pak-Hing Leung, *Dalton Transactions*, **2015**, 44, 1258.
- 5) "Kinetic Resolution of Racemic 5-Alkylcyclohexenones via Pd(II)-Catalyzed 1, 4-Additions of Arylboronic Acids - Access to 3-Alkyl-5-Arylcyclohexanones"

Kennard Gan, Abdul Sadeer, Jia Sheng Ng, Yunpeng Lu, Sumod A. Pullarkat, *Organic Chemistry Frontiers*, **2015**, 2, 1059.
- 6) "Palladium(II)-Catalyzed Selective 1, 4-Addition of Arylboronic Acids to α , β , γ , δ -Unsaturated Ketones"

Kennard Gan, Jia Sheng Ng, Abdul Sadeer, Sumod A. Pullarkat, *Synlett*, **2015**, ASAP article.

Manuscripts currently under review:

- 7) "Kinetic Resolution of Racemic Ferrocenyl Enones *via* Pd(II)-Catalyzed Hydrophosphination "

Kennard Gan, Abdul Sadeer, Yongxin Li, Sumod A. Pullarkat.

Crystal data and structure refinement for (R_c S_{pl} S_{pro})-**68**.

Empirical formula	C ₃₄ H ₃₂ Fe N O ₄ P Pd	
Formula weight	711.83	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 10.0500(3) Å	a = 90°.
	b = 11.2253(3) Å	b = 90°.
	c = 25.4689(8) Å	g = 90°.
Volume	2873.26(15) Å ³	
Z	4	
Density (calculated)	1.646 Mg/m ³	
Absorption coefficient	1.228 mm ⁻¹	
F(000)	1448	
Crystal size	0.20 x 0.16 x 0.10 mm ³	
Theta range for data collection	1.98 to 26.52°.	
Index ranges	-12 ≤ h ≤ 11, -12 ≤ k ≤ 14, -31 ≤ l ≤ 31	
Reflections collected	30716	
Independent reflections	5886 [R(int) = 0.0527]	
Completeness to theta = 26.52°	98.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8871 and 0.7913	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	5886 / 299 / 444	

Goodness-of-fit on F^2	1.144
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0355$, $wR_2 = 0.0925$
R indices (all data)	$R_1 = 0.0484$, $wR_2 = 0.1113$
Absolute structure parameter	-0.03(3)
Largest diff. peak and hole	0.741 and -0.992 e.Å ⁻³