Part I: Synthesis, characterization and reactivity studies on Ir(III) and Ru(IV) complexes with sulfur ligands. Part II: Catalytic applications of Ru and Pd metallacycles in C-C and C-P bond formations

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Part I:
Synthesis, Characterization and Reactivity Studies on Ir(III)
and Ru(IV) Complexes with Sulfur ligands

Part II:
Catalytic Applications of Ru and Pd Metallacycles in C-C
and C-P Bond Formations

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Summary

The thesis is divided into two parts; Part I: Synthesis, Characterization and Reactivity Studies on Ir(III) and Ru(IV) complexes with Sulfur ligands and part II: Catalytic applications of Ru and Pd Metallacycles in C-C and C-P bond formations.

Chapter 1 involves the discussion on the synthesis of $[\text{Cp}^*\text{Ir}(\text{C}_4\text{H}_8\text{S}_3\text{-}\kappa\text{S}, \text{S}', \text{S}'')]$ (**4**) and investigations on its reactivity as metalloligand towards other metal compounds and towards alkylation reaction with MeI. The catalytic potential of the complex in β -alkylation reaction of alcohols and N-alkylation of amines with alcohols have also been investigated. The results show that the complex can effectively catalyze β -alkylation reaction involving both aliphatic and aromatic secondary alcohols and selectively catalyze the N-alkylation of amines with alcohols leading to the formation of imines as the predominant product.

Furthermore, the reaction of $[(\eta^3\text{-C}_{10}\text{H}_{16})\text{Ru}(\mu\text{-Cl})\text{Cl}]_2$ with dithiuram disulfides $[\text{R}_2\text{NC}(\text{S})\text{S-}]_2$ ($\text{R} = \text{Me}, ^i\text{Pr}$) and monosulfide $[\text{Me}_2\text{NC}(\text{S})]_2\text{S}$ is also presented. This study showed that the bis(allyl)ruthenium(IV)-mediated C-S bond cleavage of thiuram monosulfide is much more facile than that of S-S cleavage in dithiuram disulfide.

In the second part, ruthenacycle catalyzed β -alkylation reaction of alcohols were extensively studied and palladacycle-catalyzed domino cyclization/alkylation of *o*-alkynylaniline derivatives to synthesize 2,3-substituted indoles is described. Chiral palladacycles catalyzed hydrophosphination reaction was also demonstrated.

In Chapter 2, a brief introduction about the metallacycles was given. The applications of metallacycle complex in organic synthesis and some recent developments in this region were also presented.

In Chapter 3, an efficient synthesis of 2,3-substituted indoles *via* palladacycle-catalyzed domino cyclization/alkylation reaction of 2-alkynylanilines with allylic alcohols was described. This protocol allows the incorporation of allylic substituents at C-3 position of C-2 substituted indoles. Some mechanistic insight is also provided. A novel ruthenacycle compound was synthesized and some of its congeners were tested for their catalytic potential towards the one-pot β -alkylation of secondary alcohols with primary alcohols. This is the first report of the use of a ruthenacycle in this particular organic synthetic scenario and counts among the few instances in literature when non-iridium-based catalysts have been employed successfully.

In Chapter 4, an efficient protocol for the synthesis of chiral monophosphine ligands bearing substituted methyldene malonate ester and ferrocenyl groups *via* chiral palladacycle catalysts is described. The approach provides a practical direct route towards two new classes of optically pure functionalized tertiary chiral phosphines in high yields and enantio-selectivities.

List of Abbreviations

Ac	acetyl
ACN	acetonitrile
aq.	aqueous
Ar	aryl
BINAP	2,2'-Bis(diphenylphosphine)-1,1'-binaphthyl
BMS	Borane-dimethyl-sulfide
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
br	broad
BSA	N,O-Bis(trimethylsilyl) acetamide
Bu	butyl
Bz	benzoyl
calcd.	calculated
cat.	Catalytic
Cp	η^5 -cyclopentadienyl
Cp*	η^5 -pentamethylcyclopentadienyl
COD	1,5-cyclooctadiene
Conc.	Concentrated
d	doublet
D-A	Diels-Alder
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
dd	doublets of doublet
dt	doublet of a triplet
de	diastereomeric excess
decomp.	Decomposed
deg	degree(s)
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DMPP	3,4-dimethyl-1-phenylphosphole
DTC	dithiocarbamate
<i>ee</i>	enantiomeric excess
EI	electron ionization
eq.	equivalent
<i>et al.</i>	and others (Latin <i>alii</i>)
ESI	electrospray ionization
Et	ethyl
g	gram
h	hour
hex	hexyl
HMB	η^6 -hexamethylbenzene

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
IR	infrared
<i>i</i> Pr	isopropyl
<i>J</i>	coupling constants
<i>M</i>	concentration (mol/L)
<i>M</i> ⁺	parent ion peak (mass spectrum)
<i>m</i>	multiplet
<i>m</i>	meta
Me	methyl
min	minute
mp	melting point
MS	mass spectrum
M.S.	molecular sieves
Ms	methanesulfonyl
NAP	2-naphthylmethyl
NBA	<i>N</i> -bromoacetamide
NBS	<i>N</i> -bromosuccinimide
<i>n</i> Bu	<i>n</i> -butyl
NMR	nuclear magnetic resonance
OTf	trifluoromethanesulfonate
<i>o</i>	ortho
<i>p</i>	para
Ph	phenyl
ppm	parts per million
q	quartet
<i>R</i>	rectus (Latin: right absolute configuration)
Rosy	2D rotating frame Nuclear Overhauser Enhancement
rt	room temperature
s	singlet
<i>S</i>	sinister (Latin: left absolute configuration)
t	triplet
<i>t</i>	tertiary
T	temperature (°C)
TBAF	tetrabutylammonium fluoride
<i>t</i> Bu	<i>tert</i> -butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	tolyl
tpdt	tridentate 3-thiapentane-1,5-dithiolate
v	volume
σ	sigma bonding
η	hapticity in π-bonding ligands

μ	descriptor for bridging
δ	NMR chemical shift in ppm
$\text{\AA}$	angstrom(s)
$[\alpha]_D$	specific rotation measure at sodium D line (589 nm)

Chapter 1. Synthesis, Characterization and Reactivity Studies of some Thioether-Dithiolate Complexes of Cp*Ir and Dithiocarbamato Complexes of Bis(allyl)ruthenium(IV)

1.1. Introduction

There is an increasing interest in the chemistry of transition metal complexes with sulfur-containing ligands because of their biological and industrial significance.¹ For example, out of the twenty naturally occurring amino acids that make up proteins, two have side chains that contain sulfur atoms (Figure 1). One of the important industrial use of sulfur ligand is in vulcanization of rubber, where polysulfides crosslink organic polymers.² In addition, over the last two decades, due to the high coordination ability of the sulfur atom to most transition metals, asymmetric sulfur ligands have also been extensively studied for enantioselective catalysis (Scheme 1).³

Figure 1.

Scheme 1.

It has already been well established that the sulfur atom is considered as a soft atom which can form strong bonds with soft metals.⁴ It is regarded as a poor σ -donor and poor π -acceptor ligand.⁴ The trans-effect of the sulfur ligands, is stronger when compared to those of the nitrogen- and

oxygen-containing ligands but weaker than that of phosphines.⁴ It is also worth pointing out that sulfur-containing compounds usually are easily available and highly stable and do not require special storage and handling. Furthermore, from the point of asymmetric synthesis, sulfur ligands open new possibilities over other chelates because a new stereogenic center is formed at the sulfur by mere coordination to the metal.³

Hitherto, a variety of sulfur ligands have been thoroughly studied. However much less is known of the dianion of the acyclic congener bis(2-mercaptoethyl)sulfide and the dithiocarbamate ligand. This work is concerned with the study of the reactivity of these two ligands towards Cp*Ir and bisallyl Ru(IV) metal centers as well as their subsequent reactivity towards methylation as metalloligands to form bimetallic species. The study also revealed some hitherto unexplored catalytic potential for the Ir-dithiolate-thioether complex.

1.1.1 Metal Chemistry of the Bis(2-mercaptoethyl)sulfide Dianion

The chemistry of transition metals with thiolate ligands has been extensively studied by virtue of their potential applications as models for biological systems and as catalysts in various synthetic processes.⁵ Numerous reports have since been published on such studies involving predominantly coordination compounds containing mono- and bi-dentate thiolate ligands.⁶ Among these reports, surprisingly, literature reports on metal complexes of the tridentate 3-thiapentane-1,5-dithiolate ligand, S(CH₂CH₂S⁻)₂ (*tpdt*), incorporating both thioether and thiolate sulfur atoms are rather limited in comparison. The isolated reports mainly relate to the radio-pharmaceutically significant compounds of Re and Tc,⁷⁻⁸ as well as those of various other metals, such as In,⁹ Sb,¹⁰ Nb, Ta,¹¹ and Sn(IV)¹² (Figure 2). The *tpdt* ligand in a bridging coordination mode has been found in dinuclear complexes of Ni¹³ and In⁹ and in tri-nuclear

compounds of Pd^{13a-b} and Ru^{13c} (Figure 3). Current intense interest in thiolate-bridged dinuclear complexes also stems from their potential to achieve biomimicry of the active sites of [NiFe]hydrogenase,¹⁴ [Fe-only]hydrogenase¹⁵ and the related activity at [Fe(NO)] centers^{14c} (Figure 4). Recently, Nishibayashi and co-workers also reported using ruthenium thiolate complexes as catalyst precursors for a variety of C-C bond formation reactions (Scheme 2).^{5i-k}

Figure 2.

Figure 3.

Figure 4.

Scheme 2

The first non-carbonyl organometallic complexes **1** and **2** of *tpdt* were obtained from the treatment of μ -dichlorido complexes $[(\text{HMB})\text{RuCl}_2]_2$ ¹⁶ ($\text{HMB} = \eta^6\text{-C}_6\text{Me}_6$) and $[\text{Cp}^*\text{RuCl}_2]_2$ ¹⁷

(Cp* = η^5 -C₅Me₅) (Scheme 3) with *tpdt* and have been thoroughly investigated for a comparison of their chemistry with that of the (9S3) analogue [(HMB)Ru(9S3)]²⁺ (9S3 = 1,4,7-trithiacyclononane) (**3**) (Scheme 4).¹⁸

Scheme 3.

Scheme 4.

In complexes **1** and **2**, the *tpdt* ligand is bonded to Ru *via* one thioether S atom and two thiolato S atoms. Further in-depth studies on these *tpdt* ligand motifs revealed interesting reactivity features involving the acyclic S3 dithiolato ligand, eg. (i) ability to undergo ring closure either across the S-Ru-S open ‘jaw’ with α,ω -dibromoalkanes, thus transforming **1** to **3** (Scheme 5),¹⁶ or with metal fragments to produce di- to tetra-nuclear derivatives¹⁹ and (ii) potential to undergo protonation and alkylation.²⁰ It was observed that the inherent subtle electronic differences between **1** and **2** have a profound influence on the manner in which the *tpdt* ligand functions as a dithiolate ligand in these reactions scenarios.²¹

Scheme 5.

As a logical extension of the above studies, we embarked upon an investigation of the reactions of $[\text{Cp}^*\text{IrCl}_2]_2$ with the *tpdt* ligand, and their potential application as catalyst, having noted that firstly reports on Cp^*Ir complexes bearing dithiolate ligands have been scarce in literature, with only a few recent examples involving the sulfur ligands, 1,3- or 1,4-dithiane,²² 1,4,7-trithiacyclononane and 1,4,7-trithiacyclodecane;²³ and secondly Cp^*Ir complexes have proven catalytic potential, being frequently used in organic syntheses.²⁴ Indeed, such complexes bearing carbene, amine or phosphine ligands, have been previously employed as effective catalysts in hydrogenation, C–C bond formation, coupling and cycloaddition reactions.²⁴ A study on the impact of the thiolate moiety on this proven catalytic potential of the Cp^*Ir center in reactions involving hydrogen transfer was thus undertaken.

1.1.2 Dithiocarbamate Complexes of Bis(allyl)ruthenium(IV)

Another important sulfur ligand is the dithiocarbamate (DTC) ligand. The coordination chemistry of the dithiocarbamate ligand indeed has been extensively studied, and quite a number of comprehensive reviews on the ligand's coordination chemistry have been published (Figure 5).²⁵

Figure 5.

In the context of preparation of the DTC ligands, very few free dithiocarbamic acids have been isolated as they are inherently unstable.²⁶ Consequently, the chemistry of the corresponding alkali metal salts of the dithiocarbamates is more developed than the dithioacids (Scheme 6).²⁶ Reactions of the thiuram disulfides with transition metal compounds have often resulted in cleavage of the disulfide bond, leading to the generation of the corresponding DTC complexes. The generation of some DTC complexes of Cp*Ru²⁷ and of CpCr²⁸ have previously been reported. It has been established that by virtue of their delocalization and the high electron density of the sulfur donors (Scheme 7), DTC ligands are capable of stabilizing transition metals in a wide range of oxidation states in coordination compounds, especially those in high formal oxidation states. Such DTC coordination complexes involving Ru(IV) have indeed been known since the late 1970's.²⁹ However, examples of DTC complexes involving organoruthenium (IV) still remains scarce.^{27,30} The compound $[(\eta^3\text{:}\eta^3\text{-C}_{10}\text{H}_{16})\text{RuCl}(\kappa^2\text{-S}_2\text{CNEt}_2)]$, isolated by Toerien from the reaction of $[\{(\eta^3\text{:}\eta^3\text{-C}_{10}\text{H}_{16})\text{Ru}(\mu\text{-Cl})\text{Cl}\}_2]$ with sodium diethyldithiocarbamate, and characterized *via* ¹H and ¹³C NMR spectroscopy, is the first DTC complex of bis(allyl)Ru(IV).³¹

Scheme 6.

Scheme 7.

The chemistry of the μ -dichlorido-complexes $[(\text{HMB})\text{RuCl}_2]_2$, and $[\text{Cp}^*\text{RuCl}_2]_2$ with thioether-thiolato ligands³² and disulfide ligands $[\text{XC}(\text{S})\text{S}]_2$ ($\text{X} = \text{NR}_2$, OR ($\text{R} = \text{alkyl}$)) has previously been extensively investigated.^{27,30b} Since reactions of the thiuram disulfides with transition metal compounds may lead to the generation of dithiocarbamate (DTC) complexes, the analogous reactions of bis(allyl)Ru(IV) with dithiuram disulfides $[\text{R}_2\text{NC}(\text{S})\text{S}]_2$ ($\text{R} = \text{Me}$, $i\text{Pr}$) were explored.

Although S–S bond cleavage in the disulfide is anticipated, C–S bond cleavage of the dithiuram monosulfide (bis(thiocarbamoyl)sulfide) using transition metal compounds is extremely rare. To date, there are only two examples in literature – that of the reaction of $[\text{RhCl}(\text{PPh}_3)_3]$ to yield $[\text{Rh}(\text{SCNMe}_2)(\text{S}_2\text{CNMe}_2)(\text{Cl})(\text{PPh}_3)]$ and the reaction of $[\text{Ru}(\text{CO})_2(\text{PPh}_3)_3]$ to yield $[\text{Ru}(\text{SCNMe}_2)(\text{S}_2\text{CNMe}_2)(\text{CO})(\text{PPh}_3)]$, containing bidentate dithiocarbamate and thiocarbamoyl ligands, arising from C–S cleavage of bis(thiocarbamoyl)sulfide.³³ The reactions of bis(allyl)Ru(IV) with monosulfide $[\text{Me}_2\text{NC}(\text{S})]_2\text{S}$ were also investigated.

In summary, this chapter involves the discussions on the synthesis of a $[\text{Cp}^*\text{IrCl}_2]_2$'s derivative with the *tpdt* dianion ligand and investigations on its reactivity as metalloligand towards other metal compounds and towards the alkylation reaction. The catalytic potential of the complex in β -alkylation reaction of alcohols and N-alkylation of amines with alcohols has also been investigated. Furthermore, the reactions of $[\{(\eta^3\text{:}\eta^3\text{-C}_{10}\text{H}_{16})\text{Ru}(\mu\text{-Cl})\text{Cl}\}_2]$ with dithiuram disulfides $[\text{R}_2\text{NC}(\text{S})\text{S}]_2$ ($\text{R} = \text{Me}$, $i\text{Pr}$) and monosulfide $[\text{Me}_2\text{NC}(\text{S})]_2\text{S}$ were also explored.

1.2. Results and Discussion

1.2.1. Investigations on the Thioether-Dithiolate Complexes of Cp*Ir

1.2.1.1. Synthesis of [Cp*Ir(*tpdt*)] (**4**)

The previously reported literature method for the preparation of *tpdt* complexes of (HMB)Ru(II)¹⁶ and Cp*Ru(III)¹⁷ was adopted to generate the corresponding Ir analogue. When the [Cp*IrCl₂]₂ complex was treated with S(CH₂CH₂S⁻)₂, obtained from the deprotonation of the corresponding dithiol with freshly prepared NaOMe, it yielded orange-red monomeric complex [Cp*Ir(*tpdt*)] (**4**) in 81% yield (Scheme 8). Single crystal X-ray diffraction analysis of **4** confirmed the presence of the expected tridentate bonding mode of the ligand at the iridium center. Analysis of the ORTEP (Figure 6) shows that the coordination geometry of complex **4** is very similar to that of its ruthenium analogue¹⁷ with both dithiolato and thioether sulfur atoms coordinated simultaneously to the metal atom. The ¹H NMR spectrum of **4** showed a characteristic resonance at δ 1.64 for the Cp* moiety and four sets of symmetrical multiplets centered at δ 2.26, 1.97, 1.80 and 1.66, assignable to the SCH₂ groups.

Scheme 8.

Figure 6. Molecular structure of **4** with ellipsoids shown at 50% thermal probability. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and bond angles [deg]: Ir–S(1) 2.3630(14), Ir–S(2) 2.3121(13), Ir–S(3) 2.3602(12), S(2)–Ir(1)–S(1) 85.33(5), S(3)–Ir(1)–S(1) 90.80(6).

1.2.1.2. Synthesis of Bimetallic Complexes

It was observed that complex **4** reacts with $[\text{Cp}^*\text{IrCl}_2]_2$ in 1:0.5 mole ratio and subsequently undergoes an anion metathesis with NH_4PF_6 to yield a binuclear compound $[\text{Cp}^*\text{Ir}(\text{C}_4\text{H}_8\text{S}_3)\text{Cp}^*\text{IrCl}](\text{PF}_6)$ (**5**) in 86% yield (Scheme 9). Single crystal X-ray diffraction studies reveal that the Cp^*IrCl moiety from the dimer coordinates to the $[\text{Cp}^*\text{Ir}(\text{C}_4\text{H}_8\text{S}_3)]$ through the two thiolate sulfur atoms. It needs to be pointed out that this complexation pattern, as shown in Figure 7, is at variance with what had been previously observed in earlier studies.¹⁷ For instance, the reaction between $[\text{Cp}^*\text{Ru}(\text{tpdt})]$ and $[\text{Cp}^*\text{RuCl}_2]_2$ had previously resulted in the formation of a Ru–Ru bonded binuclear complex $[\text{Cp}^*\text{Ru}(\text{tpdt})\text{Cp}^*\text{RuCl}]^+$ (Scheme 10),¹⁷ while the reaction between $[(\text{HMB})\text{Ru}(\text{tpdt})]$ and $[\text{Cp}^*\text{RuCl}_2]_2$, had afforded a Ru-centered tri-nuclear complex $[(\text{HMB})\text{Ru}(\text{tpdt})\text{Ru}^{\text{III}}\text{ClCp}^*\text{Ru}(\text{tpdt})\text{Cl}]^+$ as the major product, in admixture with others, arising from the underlying Ru(II)/Ru(III) redox processes (Scheme 11).^{19d}

Figure 7. Molecular structure of the cation of **5** with ellipsoids shown at 50% thermal probability. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and bond angles [deg]: Ir(1)–S(1) 2.3522(14), Ir(1)–S(2) 2.3687(14), Ir(1)–S(3) 2.2862(15), Ir(2)–S(1) 2.3812(13), Ir(2)–S(2) 2.4173(14), Ir(2)–Cl(1) 2.3868(15), S(1)–Ir(1)–S(2) 81.11(5), S(3)–Ir(1)–S(1) 87.36(5), S(3)–Ir(1)–S(2) 87.29(5), S(1)–Ir(2)–S(2) 79.53(5), Ir(1)–S(1)–Ir(2) 99.17(5), Ir(1)–S(2)–Ir(2) 97.70(5).

Scheme 9.

Scheme 10.

Scheme 11.

Complex **4**, when reacted with $[\text{Cp}^*\text{IrCl}_2]_2$ in 1:1 mole ratio, afforded a tri-metallic complex **6** in 79% yield (Scheme 12). The cation of **6** possesses almost the same coordination environment as

5 with the uni-negative Cp^*IrCl_3 present as the anion. It is obvious that the excess Cp^*IrCl_2 had indeed ligated the chloride ion released in the formation of the cationic **5** species. The solid state structure of **6** was subsequently confirmed by single crystal X-ray diffraction analysis (Figure 8).

Scheme 12.

Figure 8. Molecular structure of **6** with ellipsoids shown at 50% thermal probability. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and bond angles [deg]: Ir(1)–S(1) 2.3705(9), Ir(1)–S(2) 2.2934(8), Ir(1)–S(3) 2.3538(9), Ir(2)–S(1) 2.4086(10), Ir(2)–S(3) 2.3742(8), Ir(2)–Cl(1) 2.4071(10), S(1)–Ir(1)–S(2) 87.82(4), S(3)–Ir(1)–S(1) 80.53(3), S(3)–Ir(1)–S(2) 88.09(3), S(1)–Ir(2)–S(3) 79.34(3), Ir(1)–S(1)–Ir(2) 98.66(3), Ir(1)–S(3)–Ir(2) 100.11(3).

The reactivity of $[\text{Cp}^*\text{Ru}(\text{tpdt})]$ and $[(\text{HMB})\text{Ru}(\text{tpdt})]$ has been extensively studied previously.²¹ Both $[\text{Cp}^*\text{Ru}(\text{tpdt})]$ and $[(\text{HMB})\text{Ru}(\text{tpdt})]$ have a rich chemistry and can undergo the “cross-interaction” reaction to yield a plethora of homo-bimetallic complexes.²¹ Similar reactions with other hetero-metal moieties can also produce interesting hetero-bimetallic complexes when **4** is reacted with a second metal species.

In this present work, complex **4** is reacted with $[(\text{COD})\text{MCl}]_2$ (M= Ir, Rh) in 1:0.5 molar ratio to give high yields of bimetallic complexes **7** and **9** (Scheme 13). The structural analysis of **7** and **9** (Figure 9, 11) showed that reaction with **4** induces the cleavage of the dimer $[(\text{COD})\text{MCl}]_2$ into two equivalent $[(\text{COD})\text{MCl}]$ units and coordinates to the $[(\text{COD})\text{MCl}]$ unit as a mono-dentate

metallo-thiolato ligand, resulting in the formation of new homo- and hetero-bimetallic complexes. This complexation pattern is unexpected and significantly different from what has been previously observed in the analogous reactions of $[\text{Cp}^*\text{Ru}(\text{tpdt})]$ and $[(\text{HMB})\text{Ru}(\text{tpdt})]$ with $[(\text{COD})\text{RuCl}_2]_n$.^{19d} In the first instance the reaction afforded a Ru centered tri-metallic complex $[\text{Cp}^*\text{Ru}(\text{tpdt})\text{Ru}^{\text{II}}\text{Cp}^*\text{Ru}(\text{tpdt})\text{Cl}]^+$ with displacement of the COD and a chloride ligand, while in the second instance, the complex $[(\text{HMB})\text{Ru}(\text{tpdt})]$ acted as a bidentate metallo-dithiolato ligand to the coordinatively-intact $(\text{COD})\text{Ru}$ center (Scheme 14).^{19d}

Scheme 13.

Scheme 14.

Complex **4** also reacts with $[(\text{COD})\text{MCl}]_2$ in 1:1 mole ratio providing quantitative yields of the binuclear compounds **8** and **10** (Scheme 15), containing 16-electron metal centers in both cation and anion.

Scheme 15.

As shown in Figures 10 and 12, in compounds **8** and **10**, the ‘disproportionate’ cleavage of the chloride bridge of $[(\text{COD})\text{MCl}]_2$ produced one cationic moiety, $[(\text{COD})\text{M}]^+$, and an anionic unit, $[(\text{COD})\text{MCl}_2]^-$ unlike the symmetric nature of the Cl bridge cleavage seen earlier. This complexation pattern also contrasts with what was observed in $[\text{Cp}^*\text{Ru}(\text{tpdt})\text{Ru}^{\text{II}}\text{Cp}^*\text{Ru}(\text{tpdt})\text{Cl}]^+$ (Scheme 14).^{19d} One may indeed envisage that the excess $[(\text{COD})\text{MCl}]$ moiety induces the cleavage of the chloride ligand in **7** or **9**, and itself transforms into the anionic $[(\text{COD})\text{MCl}_2]$, thus simultaneously forcing the metal center to coordinate to the second thiolato sulfur of **4** in order to retain its 16e status. However, in practice, **7** and **9** did not further react with $[(\text{COD})\text{MCl}]_2$ to form **8** and **10**, respectively.

Figure 9. Molecular structure of **7** with ellipsoids shown at 50% thermal probability. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and bond angles [deg]: Ir–S(1) 2.4008(19), Ir–S(2) 2.319(2), Ir–S(3) 2.362(2), S(2)–Ir(1)–S(1) 86.36(7), S(3)–Ir(1)–S(1) 96.95(7).

Figure 10. Molecular structure of **8** with ellipsoids shown at 50% thermal probability. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and bond angles [deg]: Ir(1)–S(1) 2.3809(5), Ir(1)–S(3) 2.3776(5), Ir(2)–S(1) 2.3700(5), Ir(2)–S(2) 2.3113(6), Ir(2)–S(3) 2.3642(5), S(3)–Ir(1)–S(1) 84.316(18), S(2)–Ir(2)–S(3) 87.31(2), S(2)–Ir(2)–S(1) 87.47(2), S(3)–Ir(2)–S(1) 84.851(18).

Figure 11. Molecular structure of **9** with ellipsoids shown at 50% thermal probability. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and bond angles [deg]: Ir(1)–S(1) 2.3814(11), Ir(1)–S(2) 2.3177(12), Ir(1)–S(3) 2.3551(11), Rh(1)–S(1) 2.3869(11), S(2)–Ir(1)–S(1) 87.24(4), S(2)–Ir(1)–S(3) 86.43(4), S(3)–Ir(1)–S(1) 95.34(4), Ir(1)–S(1)–Rh(1) 124.89(5).

Figure 12. Molecular structure of **10** with ellipsoids shown at 50% thermal probability. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and bond angles [deg]: Ir(1)–S(1) 2.3100(10), Ir(1)–S(2) 2.3633(9), Ir(1)–S(3) 2.3603(10), Rh(1)–S(2) 2.3831(10), Rh(1)–S(3) 2.3770(10), S(1)–Ir(1)–S(2) 87.30(4), S(1)–Ir(1)–S(3) 87.27(4), S(3)–Ir(1)–S(2) 85.26(3), S(3)–Rh(1)–S(2) 84.45(3), Ir(1)–S(2)–Rh(1) 87.57(3), Ir(1)–S(3)–Rh(1) 87.78(3).

The proton NMR spectra of **7–10** show a strong singlet resonance signal for Cp* and multiplets for the SCH₂ groups and the COD, with corresponding ¹³C resonances also being observed.

However, in the case of **8** and **10**, because of the extensive overlap of the multiplets for COD and SCH₂ groups, it is not possible to give a conclusive assignment of signals for these two groups.

Coordinated thiolate complexes have distinguished themselves by their ability to readily undergo facile S-alkylation reactions. The two thiolate sulfur atoms in [(HMB)Ru(*tpdt*)] and [Cp*Ru(*tpdt*)] could also be consecutively methylated with MeI (Scheme 16). Likewise, complex **4** could also undergo alkylation reaction with MeI. With four equivalent excess MeI in toluene at -30 °C for 2 h, mono-methylated product [Cp*Ir(C₅H₁₁S₃)]I **11** (Figure 13), was formed in high yield (Scheme 17). However, further reaction with 20 mole equivalents of MeI overnight in methanol (in which **11** is more soluble) did not yield the expected di-methylated species unlike previously seen with [Cp*Ru(*tpdt*)] and [(HMB)Ru(*tpdt*)]. In the case of [Cp*Ru^{III}(*tpdt*)], the formation of the S-alkylated product could be rationalized based on an initial electrophilic attack of the Me⁺ on one of the thiolato sulfur atoms and the subsequent electron transfer processes yielding thiyl radicals, which couple to form the observed disulfide-bridged dinuclear complex.²¹ However, the alkylation of [(HMB)Ru^{II}(*tpdt*)] to form mono- and di-methylated derivatives is the result of electrophilic attack at the thiolato sulfur atoms. Taking into perspective the resemblances of the electronic structures of Ru^{II} and Ir^{III} and their relatively higher stabilities when compared to Ru^{III}, it is therefore appropriate to conclude that the alkylation of complex **4** may not be an alkylation-initiated radical reaction and the di-methylated reaction is not so facile as [(HMB)Ru(*tpdt*)].

Scheme 16.

Scheme 17.

Figure 13. Molecular structure of the cation of **11** with ellipsoids shown at 50% thermal probability. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and bond angles [deg]: Ir–S(1) 2.338(4), Ir–S(2) 2.309(3), Ir–S(3) 2.376(3), S(2)–Ir(1)–S(1) 87.41(13), S(2)–Ir(1)–S(3) 86.59(12), S(3)–Ir(1)–S(1) 85.98(13).

1.2.1.3. Crystallographic Studies

The molecular structure of **4** is shown in Figure 6 and selected distances as well as bond angles are also listed. The iridium atom is surrounded in the usual piano-stool arrangement of the planar Cp* ring together with one thioether sulfur atom and two thiolate sulfur atoms of the C₄H₈S₃ dianion.

The structures of complexes **5** and **6** are illustrated in Figures 7 and 8. The Cp*IrCl unit from the dimer coordinates to [Cp*Ir(C₄H₈S₃)] through the two thiolate sulfur atoms. The structural data of **5** showed that the Ir–S bond lengths fell within a range of 2.363–2.403 Å and the S(thiolate)–Ir1–S(thiolate) angle is 81.11(5)° which is much smaller than that in **4** (90.80(6)°). A Cl ligand (Ir–Cl, 2.3868(15) Å) occupies the same face as the bridging tpd ligand. The cation of **6** is the same as **5** and the anion is the Cp*IrCl₃ unit.

The molecular structures of **7** and **9** are shown in Figures 9 and 11. Because of the presence of a Cl ligand on Ir2, one of the thiolate sulfur atom (S3) does not coordinate to the second metal center. Although the Ir1–S3 bond distances remain similar to that observed in **4**, the Ir1–S2 bond distances (2.319(2) and 2.3177(12) Å, respectively) are slightly longer than in **4** (2.3121(13) Å) while the Ir1–S1 (2.4008(19) and 2.3814(11) Å, respectively) bond distance is much longer than in complex **4** (2.3630(14) Å). Furthermore, the S1–Ir1–S3 angles (96.95(7)° and 95.34(4)°, respectively), are significantly larger than that of **4** (90.80(6)°).

The ORTEP diagram of complexes **8** and **10** are shown in Figures 10 and 12. The cationic unit [(COD)M] (M = Ir, Rh) coordinates to **4** through the two thiolate sulfur atoms, which is distinctly different from the coordination mode seen in complexes **7** and **9**. A close scrutiny of the relevant bond length and angle parameters revealed that the [Cp*Ir(*tpdt*)] entity as a whole is now more symmetrically disposed. The bond length subtended at the metal atoms remain similar as that in **1** while the S(thiolate)–Ir–S(thiolate) bond angles (84.316(18)° and 85.26(3)°, respectively) became much smaller than that in **4** (90.80(6)°).

The structure of the cation of **11** is shown in Figure 13. The cation of **11** possesses the same coordination environment as **4**, except for the fact that one thiolate sulfur atom (S1) is also

coordinated to a methyl group. The crystallographic data for the complexes **4-11** are summarized in Table 1.

Table 1. Single crystal X-ray crystallographic data for complexes **4-11**.

	4	5	6	7	8	9	10	11
Empirical formula	C ₁₄ H ₂₃ IrS ₃	C ₂₄ H ₃₈ ClF ₆	C ₃₄ H ₃₃ Cl ₄	C ₂₂ H ₃₅ ClIr ₂	C ₂₂ H ₃₅ Ir ₂ S ₃	C ₂₂ H ₃₅ ClIr	C ₃₀ H ₄₇ Cl ₂	C _{16.33} H ₂₈ Ir
formula weight	571.84	987.54	1276.34	815.53	1151.36	726.24	972.78	649.01
crystal system	Monoclinic	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Triclinic	Monoclinic	Monoclinic
space group	<i>P2(1)</i>	<i>Pbca</i>	<i>P2(1)</i>	<i>P2(1)/c</i>	<i>P2(1)/n</i>	<i>P-1</i>	<i>P2(1)/n</i>	<i>P2(1)/n</i>
<i>a</i> (Å)	9.4461(9)	14.9777(4)	8.5045(2)	16.6681(4)	12.0393(3)	8.0250(3)	12.0115(7)	17.7762(4)
<i>b</i> (Å)	9.3981(10)	16.1975(4)	24.4829(6)	15.0354(4)	12.3730(3)	9.3138(3)	12.3442(7)	11.8918(3)
<i>c</i> (Å)	12.2601(14)	24.7586(5)	9.1949(2)	20.4483(5)	21.5371(6)	17.0470(7)	21.5711(12)	31.1793(7)
α (deg)	90	90	90	90	90.00	104.403(3)	90	90
β (deg)	100.887(4)	90	92.6330	109.7210(10)	95.090(2)	97.249(3)	95.006(3)	104.0970(10)
γ (deg)	90	90	90	90	90.00	102.661(2)	90	90
<i>V</i> (Å ³)	1068.8(2)	6006.5(2)	1912.49(8)	4824.0(2)	3195.56(14)	1181.88(8)	3186.2(3)	6392.5(3)
<i>Z</i>	2	8	2	8	4	2	4	12
<i>d</i> _{calcd} (g/cm ³)	1.777	2.184	2.216	2.246	2.393	2.041	2.028	2.023
μ (mm ⁻¹)	6.541	9.256	10.879	11.401	12.846	6.708	5.575	8.005
crystal size (mm)	0.30 x 0.20 x 0.20	0.34 x 0.32 x 0.30	0.32 x 0.24 x 0.10	0.24 x 0.14 x 0.04	0.26 x 0.14 x 0.06	0.20 x 0.12 x 0.04	0.44 x 0.38 x 0.24	0.30 x 0.20 x 0.04
total, unique no. of rflns	21995, 9758	50797, 9600	79183, 23373	43916, 10536	121479, 18360	43906, 7543	60156, 11530	100867, 16489
<i>R</i> (int)	0.0348	0.0737	0.0341	0.0582	0.0385	0.0404	0.0512	0.0849
data, restraints, parameters	9758, 1, 232	9600, 0, 343	23373, 123, 450	10536, 0, 514	18360, 0, 348	7543, 0, 258	11530, 0, 348	16489, 58, 622
Final <i>R</i> indices[I>2sigma(I)]	<i>RI</i> = 0.0352, <i>wR2</i> = 0.0790	<i>RI</i> = 0.0365, <i>wR2</i> = 0.0762	<i>RI</i> = 0.0244, <i>wR2</i> = 0.0508	<i>RI</i> = 0.0354, <i>wR2</i> = 0.0788	<i>RI</i> = 0.0228, <i>wR2</i> = 0.0435	<i>RI</i> = 0.0339, <i>wR2</i> = 0.0773	<i>RI</i> = 0.0288, <i>wR2</i> = 0.0680	<i>RI</i> = 0.0658, <i>wR2</i> = 0.1789
<i>R</i> indices (all data)	<i>RI</i> = 0.089, <i>wR2</i> = 0.0950	<i>RI</i> = 0.0623, <i>wR2</i> = 0.0870	<i>RI</i> = 0.0299, <i>wR2</i> = 0.0703	<i>RI</i> = 0.0578, <i>wR2</i> = 0.0901	<i>RI</i> = 0.0347, <i>wR2</i> = 0.0469	<i>RI</i> = 0.0473, <i>wR2</i> = 0.0825	<i>RI</i> = 0.0448, <i>wR2</i> = 0.0863	<i>RI</i> = 0.1121, <i>wR2</i> = 0.1970
Absolute structure parameter	0.022(8)		0.015(4)					
GOF	1.073	1.046	1.088	1.050	1.023	1.098	1.222	1.268

1.2.1.4. Catalytic Studies

Catalytic β -alkylation of secondary alcohols with primary alcohols

The alkylation of secondary alcohols with primary alcohols is a multi-step tandem reaction protocol that typically involves the dehydrogenation of alcohols to the corresponding aldehyde or ketone, aldol coupling, loss of water and subsequent hydrogenation of the resulting enone species to the coupled alcohol product (Scheme 18).³⁴

Scheme 18.

A literature survey of the reaction revealed that the first attempt to employ a catalyst to achieve this multistep reaction was in 2003 by Cho and coworkers using RuCl₂(PPh₃)₂ as catalyst.³⁵ Subsequently several other transition metal complexes have been reported to catalyze this reaction, including the extremely active Ru and Ir catalyst systems with N-heterocyclic carbenes (NHCs)³⁶ and terpyridine ligands.³⁷ Dimeric transition metal complexes devoid of such functionalized moieties, e.g. [Cp*IrCl₂]₂,³⁴ [RuCl₂(DMSO)₄],³⁸ have also been found to be efficient catalysts for this reaction. For instance, it has been reported recently by Fujita *et al.* that [Cp*IrCl₂]₂ possesses extremely high catalytic activity in the direct β -alkylation of secondary alcohols with primary alcohols in the absence of any hydrogen acceptors or hydrogen donors.³⁴ Taking into consideration that [Cp*IrCl₂]₂ is the precursor of **4** and with an aim of understanding the structural and electronic impact of the *tpdt* ligand in catalysis, [Cp*Ir(C₄H₈S₃)] as a catalyst was tested under

similar conditions. This was done in spite of the possibility that poisoning and concomitant decrease in activity frequently occur in the presence of sulfur-bearing catalysts. Unexpectedly, the investigations revealed that some of the new Ir dithiolato thioether derivatives described herein possess an appreciably higher catalytic activity than the parent $[\text{Cp}^*\text{IrCl}_2]_2$ complex.

Based on a preliminary screening of the synthesized complexes **4-10**, complexes **4** and **9** were further tested for catalysis in this reaction and they proved to be highly efficient at extremely low catalyst loadings (the lowest reported so far in literature for a metal catalyst in this reaction scenario). The results from the reaction condition optimization studies are summarized in Table 2.

Table 2. β -Alkylation of phenylethanol (**I**) with phenylmethanol (**II**) under various conditions.^a

$\text{R-C}_6\text{H}_4\text{-CH(OH)CH}_3$ (**I**) + $\text{C}_6\text{H}_5\text{-CH}_2\text{OH}$ (**II**) $\xrightarrow{[\text{cat.}]}$ $\text{R-C}_6\text{H}_4\text{-CH(OH)CH}_2\text{CH}_2\text{Ph}$ (**III**) or / + $\text{R-C}_6\text{H}_4\text{-C(=O)CH}_2\text{CH}_2\text{Ph}$ (**IV**)

Entry	Catalyst (mol%)	R	Base (mol%)	Conversion ^b	Yield ^c III+IV	Product (%)	
						III	IV
1	4 (1.0)	H	NaO ^t Bu(100)	97	92	95	5
2	4 (0.1)	H	NaO ^t Bu(100)	96	90	93	7
3	4 (0.1)	H	NaO ^t Bu(50)	93	68	94	6
4	4 (0.1)	H	NaOH(100)	87	80	75	25
5	9 (0.1)	H	NaO ^t Bu(100)	89	68	96	4
6	9 (0.1)	H	NaO ^t Bu(50)	89	35	58	42
7	9 (0.1)	H	NaOH(100)	96	54	91	9
8	4 (0.1)	4-OMe	NaO ^t Bu(100)	88	82	81	19
9	4 (0.1)	4-Cl	NaO ^t Bu(100)	98	85	95	5
10 ^d	4 (0.1)	H	NaO ^t Bu(100)	99	88	77	23
11 ^e	$[\text{IrCp}^*\text{Cl}_2]_2$ (1.0)	H	NaO ^t Bu(100)			75	

^a The reaction was carried out with secondary alcohol (1 mmol), primary alcohol (1 mmol), catalyst and base in toluene (0.3 mL) at 110 °C for 17 h. ^b Conversions (based on the secondary alcohol) are determined by the consumption of alcohol. ^c Yields of **III** (based on the secondary alcohol, **I**) were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. ^d The reaction was carried for 48 h. ^e Reported value from literature.³⁴

When compared with the previously reported work using Cp^*IrCl_2 as catalyst (Entry 11), under exactly the same conditions, in this instance 1,3-diphenyl-1-propanol (**III**) was formed in a substantially higher yield using **4** as catalyst (Entry 1). More significantly, it was seen that the desired product **III** could also be achieved within the same reaction time and conditions with a significantly reduced catalyst loading (0.1 mol% vs 1.0 mol%) in good yield (Entry 2). A survey of related literatures revealed that this is the lowest catalyst loading which has been reported for the β -alkylation of 1-phenylethanol (**I**) with phenylmethanol (**II**) in literature using any metal based catalyst. Subsequently complex **9** was also screened for catalytic activity under the same conditions and it was noted that **4** provides higher yields and selectivity than **9** (Entry 2 vs Entry 5). The presence of substituents on the secondary alcohol (Entry 8 and Entry 9) did not produce any concomitant drastic reduction in either yield or selectivity. Replacement of the base (NaO^tBu with NaOH) also did not affect the catalytic potential (Entry 2 vs Entry 4, Entry 5 vs Entry 7) while the use of Na_2CO_3 as a base gave no product yields. It was also noted that when the amount of base was reduced by 50% the yields substantially reduced but the product selectivity (**III** vs **IV**) did not show any noticeable change for **4** (Entry 2 vs Entry 3). As seen in previous reports,^{36a} a longer reaction time did not improve yields since it led to the dehydrogenation of the coupled alcohol product to form the ketone (Entry 2 vs Entry 10).

It is indeed worthwhile to mention that aliphatic secondary alcohols upon reaction with aliphatic primary alcohols have been found to give very low chemical yields (< 5 mol%) in such coupling reactions.³⁴⁻³⁷ Using the present catalyst, the β -alkylation of isopropyl alcohol with both *n*-pentanol and *n*-hexyl alcohol could still proceed to an appreciable extent albeit with low yields of 41% and 50%, respectively (Table 3, Entry 2, 3). These results indicate that **4** can effectively

catalyze the coupling of both aliphatic and aromatic alcohols, thus widening the substrate scope.³⁴⁻³⁸ However, the attempted β -alkylation reaction of isopropyl alcohol with benzeneethanol did not yield the expected products. The favorable results aforementioned are of consequence in the context that incorporation of the *tpdt* moiety into the IrCp* unit led to a substantial increase in yield at a drastically reduced catalytic loading.

Table 3. β -alkylation of aliphatic secondary alcohol with primary alcohol or second alcohol with aliphatic primary alcohol.

$$\text{R}-\text{CH}(\text{OH})-\text{CH}_3 + \text{R}'-\text{CH}_2\text{OH} \xrightarrow{[\text{cat. } \mathbf{4}]} \text{R}-\text{CH}(\text{OH})-\text{CH}_2\text{CH}_2\text{R}'$$

Entry	Secondary alcohol	Primary alcohol	Product	Yield (%)
1				67
2				41
3				50
4				85
5				58

^a The reaction was carried out with secondary alcohol (1 mmol), primary alcohol (1 mmol), catalyst **4** (0.1 mol%) and NaO^tBu (100 mol%) in toluene (0.3 mL) at 110 °C for 17 h. ^b Yields (based on the secondary alcohol) were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

The mechanistic investigations undertaken previously for [Cp*IrCl₂]₂ as catalyst had revealed multiple steps in a tandem process (Scheme 18),³⁴ involving oxidation of alcohols to aldehyde and ketone, generation of a hydrido iridium species, base-mediated cross aldol condensation, and

successive transfer hydrogenation of C=C and C=O bonds, yielding the coupled alcohol product. It was therefore pertinent in our protocol to confirm whether the catalytic activity observed using **4** can also be attributed to such a mechanism. We investigated these individual steps in our protocol using the same methodology adopted by Fujita *et al.* in their mechanistic investigation on the parent complex (Scheme 19).³⁴ The results obtained after the catalytic oxidation of 1-phenylethanol into acetophenone using acetone as hydrogen acceptor (< 5% yield), alkylation of acetophenone with benzyl alcohol (55% yield), and transfer hydrogenation of benzylideneacetophenone using 2-propanol as hydrogen donor (50% yield) prompted us to investigate the low yield for the Oppenauer-type oxidation step for the secondary alcohol. It was noted that upon completion the oxidation if 1 equiv. of benzyl alcohol was added into the crude reaction mixture and the reaction allowed to proceed further, the same yield of coupled alcohol products as from the original one-pot single step sequence was obtained.

Scheme 19.

The aforementioned results indicate that the low yield for the Oppenauer-type oxidation of secondary alcohol may be attributed to the fact that the acetophenone formed after the initial hydrogen transfer to the acetone/iridium may revert back to the secondary alcohol. Previous studies have also shown that with hemilabile ligands on Ir this transfer may occur predominantly through a direct hydrogen transfer between the coordinated ketone and the alcohol.^{24b} However

when conducted as a single step; one-pot protocol, the presence of the primary alcohol allows the β -alkylation reaction to proceed thus precluding the opportunity for the ketone to form the parent alcohol.

Based on these mechanistic results, a possible mechanism was proposed as shown in Scheme 20. The first step of the reaction would involve the oxidation of primary and secondary alcohols to aldehyde and ketone accompanied by the generation of a hydrido iridium species. Then, base-mediated cross-aldol condensation between aldehyde and ketone would occur to give an α , β -unsaturated ketone. Successive transfer hydrogenation of C-C and C-O double bonds of the α , β -unsaturated ketone by the hydrido iridium species would occur to give the final products.

Scheme 20.

In summary, the potential of Ir-thiolate complexes as catalyst for the β -alkylation of alcohols in low catalyst loading and in the absence of any sacrificial hydrogen acceptor or an additional hydrogen donor with only water as the co-product has been explored. This makes the current protocol an attractive alternative that is environmentally benign and provides excellent atom

economy. It also reveals that the electronic factors brought into play by the incorporation of the *tpdt* ligand on the iridium center have a profound impact on their catalytic potential in the current synthetic scenario.

Catalytic N-alkylation of amines with alcohols

The N-alkylation reaction of amines with alcohols is of current interest since it is an efficient methodology for the synthesis of novel amines which in turn can be incorporated as a crucial step in the atom-economical synthesis of pharmaceutically significant molecules.^{36a-c} In such reactions, imines are often transient intermediates that are often detected but usually not isolated due to their rapid reduction during the return of the borrowed hydrogen as part of the hydrogen auto-transfer process mediated by the metal catalyst.³⁹ For instance recent reports have focused on an efficient methodology for the direct alkylation of amines with alcohols at 115 °C for 10 h using 1 mol% [Cp*IrI₂]₂ in water with no added base giving high yields of the amine products.⁴⁰

Investigations revealed that complex **4** is also active for this N-alkylation reaction (Table 4). Surprisingly the main product from the reaction was the imine and not the amine as is usually expected from protocols involving organometallic catalysts. A survey of literature revealed that only few other catalysts are known for selective imine synthesis.^{36a,41} In this case, the results are comparable to or better than those obtained for most of the previously reported catalysts except for the recent work by Milstein *et al.* where impressive yields were obtained using a Ru PNP pincer complex under neutral conditions.^{41d}

It is also worthwhile to mention that imines are versatile synthetic intermediates for manufacture of pharmaceuticals, dyes and other commercially important compounds.⁴²

Traditionally, oxidation protocols that employ stoichiometric amounts of oxidants have been used for the synthesis of imines and these make them unattractive from an atom economy and environmental point of view.

The reaction of aniline and its derivatives with benzyl alcohol was initially undertaken in order to explore the catalytic potential (Table 4, Entry 11, 12).⁴² Although amines were formed as expected, the yields observed was lower when compared to previous reports. While exploring ways to improve the catalytic activity and widen the range of substrates, the reaction of benzyl amine with benzyl alcohol under similar conditions was also carried out. Surprisingly, in contrast to the corresponding reaction with aniline, imine was obtained as major product in moderate yields that compared favorably with literature values.⁴¹ The results are summarized in Table 4.

Although reducing the reaction time did not adversely affect the product selectivity (Entry 1 vs Entry 2), it led to lower yields. Presence of a strong base KOH played a critical role in determining the selectivity of product. Bases such as K_2CO_3 and KO^tBu showed poor selectivity (Entry 3 and Entry 4). The conversion to the desired imine could be achieved using substituted benzyl amines or benzyl alcohols (Entry 5, 6, 7, 10) and therefore did not indicate any clear preference for electronic-withdrawing and electron-donating substituents. Aliphatic 1-pentanol when treated with benzyl amine also gave appreciable yield (Entry 8) while the use of aliphatic 2-propanamine was detrimental (Entry 9). The reactions of secondary benzyl alcohol with benzyl amine and with secondary benzyl amine were also carried out, and in both instances the desired imine products were not obtained. A brief exploration of several parameters including temperature, concentration and catalyst loading yielded no significant improvement to yields or selectivities. It was therefore clear from these studies that the presence of the thiolato moiety

Table 4. N-alkylation of Amines with Alcohols.^a

$$\text{R}-\text{CH}_2\text{OH} + \text{R}'\text{-NH}_2 \xrightarrow[110\text{ }^\circ\text{C, 45 h}]{\text{Cat. 4 1\%, KOH 100\%}} \text{R}-\text{CH}=\text{N}-\text{R}' + \text{R}-\text{CH}_2\text{NH}-\text{R}'$$

Entry	R	R'	Base	Reaction Time (h)	Yield ^b	Product (%)	
						%imine	%amine
1	Ph	PhCH ₂	KOH	45	61	100	0
2	Ph	PhCH ₂	KOH	17	41	100	0
3	Ph	PhCH ₂	K ₂ CO ₃	45	50	50	50
4	Ph	PhCH ₂	KO ^t Bu	45	26	46	54
5	Ph	4-ClC ₆ H ₄ CH ₂	KOH	45	68	94	6
6	Ph	4-OMeC ₆ H ₄ CH ₂	KOH	45	40	86	14
7	4-OMeC ₆ H ₄	PhCH ₂	KOH	45	36	100	0
8	ⁿ Pr	PhCH ₂	KOH	45	85	96	4
9	Ph	ⁱ Pr	KOH	45	4	100	0
10	4-OMeC ₆ H ₄	ⁱ Pr	KOH	45	1	100	0
11	Ph	Ph	KOH	45	63	9	91
12	Ph	Ph	KOH	17	46	1	99

^aThe reaction was carried out with amine (1 mmol), primary alcohol (1 mmol), catalyst **4** (1 mol%) and KOH (100 mol%) in toluene (0.3 mL) at 110 °C for 45 h. ^bYields (based on the primary alcohol) were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

hinder the second stage of the returning “borrowing hydrogen” process which has been reported previously for selective imine formation protocols.

1.2.2. Dithiocarbamate Complexes of Bis(allyl)ruthenium(IV)

1.2.2.1. Synthesis

The bis(allyl)ruthenium(IV) complex **12** was obtained from the direct treatment of RuCl₃ with

isoprene (Scheme 21).⁴³⁻⁴⁵

Scheme 21.

The subsequent reaction of complex **12** with 2 equivalents of tetraalkyl dithiuram disulfide (alkyl = methyl, isopropyl) yielded the complexes **13a** and **13b** in yields of 95% and 73%, respectively (Scheme 22).

Scheme 22.

Evidently complex **12** had initiated an S–S bond cleavage process in the disulfide with the resultant dithiocarbamate group undergoing subsequent coordination to the mono-nuclear fragment of complex **12**, with concomitant displacement of a chlorido ligand. This is indeed different from what is referred to as Toerien's reaction (Scheme 23) which was envisaged to involve dimer cleavage followed immediately by a ring closure and loss of NaCl.^{43b} The reaction as represented in Scheme 22 is reminiscent of that seen in the case of [Cp*RuCl₂]₂ with similar dithiolato ligands in which cases all chlorido ligands remained intact (Scheme 24)²⁷ or with metallodithiolato ligands with dissociation of a chlorido ligand (Scheme 25).²⁹

Scheme 23.

As previously observed with chloride ligands at dithiolato Ru(II) and Ru(III) complexes,⁴⁶ the chlorido ligand at Ru(IV) in **13a** can be extracted with KPF_6 in MeCN, yielding the corresponding solvento derivative **14** (Scheme 26). Such a reactivity feature had been previously observed with the benzothiazole-2-thiolato complex when treated with AgBF_4 (Scheme 27).^{43b}

Scheme 24.

Scheme 25.

Scheme 26.

Scheme 27.

Complex **13a** could also be obtained in high yield from the reaction of **12** with dithiuram monosulfide (Scheme 28, path (a)). Clearly the reaction also involves a C–S bond cleavage in the monosulfide. A qualitative comparison of completion time of this reaction ($-15^{\circ}\text{C}/1\text{h}$) versus that of the disulfide ($\text{RT}/48\text{h}$) is consistent with a much lower activation energy for C–S bond scission than the S–S bond cleavage in the disulfide. This is surprising as in the context that the reported S–S bond energy (ca. 213 kJ/Mol) is much lower than the C–S bond energy (ca. 260 kJ/Mol).⁴⁷ The scission process in the monosulfide would generate a negatively charged dithiocarbamate fragment and simultaneously an accompanying carbonium ion, $(\text{Me}_2\text{N})\text{C}(\text{S})^+$. This fragment has been previously observed in the synthetic route to aliphatic and aromatic thioamides *via* the reaction of dithiuram monosulfide with organolithium derivatives.⁴⁸ The other reported instances of this fragment are as the bidentate thiocarbamoyl ligand in the complex $[\text{Rh}(\text{SCNMe}_2)(\text{S}_2\text{CNMe}_2)(\text{Cl})(\text{PPh}_3)]$, obtained from the reaction of $[\text{RhCl}(\text{PPh}_3)_3]$ with $[\text{Me}_2\text{NC}(\text{S})]_2\text{S}$ and in the structurally uncharacterized complex $[\text{Ru}(\text{SCNMe}_2)(\text{S}_2\text{CNMe}_2)(\text{CO})(\text{PPh}_3)]$ obtained from the reaction of $[\text{Ru}(\text{CO})_2(\text{PPh}_3)_3]$ with $[\text{Me}_2\text{NC}(\text{S})]_2\text{S}$.³³ In the present case, since no Ru-containing product other than **13a** was detected

in the reaction mixture, the byproduct must be an organic species, which would therefore remain in the methanol solvent after the completion of the reaction. Careful removal of the solvent at liquid nitrogen temperature left behind a colourless low-melting residue, the ^1H NMR spectrum of which showed a methyl singlet at 1.71 ppm in CD_3OD . A GC-MS investigation showed the presence of a single species, which possessed mass fragments, m/z 119 $[(\text{Me}_2\text{N})\text{C}(\text{S})\text{OMe}]^+$, 104 $[(\text{Me}_2\text{N})\text{C}(\text{S})\text{O}]^+$ and 88 $[(\text{Me}_2\text{N})\text{C}(\text{S})]^+$, indicating an efficient capture of $(\text{Me}_2\text{N})\text{C}(\text{S})^+$ by MeOH, the solvent medium, thus precluding any subsequent reaction of the species with the organometallic substrates present.

Prior treatment of **12** with KPF_6 in acetonitrile followed by reaction with the monosulfide $[\text{Me}_2\text{NC}(\text{S})]_2\text{S}$, yielded complex **14** in good yield (Scheme 28, path (b)).

Scheme 28.

1.2.2.2 Spectral Characteristics

The NMR spectra of the complexes **13–14**, recorded at 298 K, are consistent with the molecular structures predicted. Both the ^1H and ^{13}C NMR resonances indicate non-equivalent halves of the octadienediyl ligand. Thus the proton spectra display one set of four terminal allylic, two internal allylic and two methyl resonances, as expected of a single diastereoisomer, as was observed for the EtDTC analogue,^{43b} and other similar mononuclear $(\eta^3:\eta^3\text{-C}_{10}\text{H}_{16})\text{Ru}(\text{IV})$ compounds

previously.^{43c} Geometric isomers have been found in such compounds containing hydroxypyridine, pyridine thiolate or quinoline thiolate ligands.^{43c} The presence of separate proton and carbon resonances for the two methyl groups in the DTC ligands of **13a** and **14**, indicate that they are in different environments, as a consequence of restricted rotation of the C–N bond; this is further supported by single crystal X-ray diffraction data. In the ¹H NMR spectrum of **13b**, the broad unresolved nature of the resonances pertaining to the CH's and the CH₃'s of the ^tPr group can be rationalized on the basis of fluxional behavior in solution.

Figure 14.

1.2.2.3. Single Crystal X-ray Diffraction Analyses

in the orthorhombic lattice, but with different space groups. As shown in Figure 15, the Ru atom exhibited a distorted trigonal bipyramidal coordination geometry. The three basal sites being occupied by two allyl groups and one sulfur atom S(1) from the bidentate DTC ligand. The apical positions were occupied by the chlorido ligand Cl(1) and the sulfur atom S(2) of DTC. Compound **14** crystallizes in a triclinic lattice with a $P\bar{1}$ space group. The coordination environment at Ru is similar to that of compound **13a**, with the chlorido ligand being replaced by MeCN in this instance.

Figure 15. Molecular structure of compound **13a**, **13b** with ellipsoids shown at 50% thermal probability. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and bond angles [deg] for **13a**: Ru(1)-Cl(1) 2.4622(4); Ru(1)-S(1) 2.426(4); Ru(1)-S(2) 2.388(3); C(11)-N(1) 1.323(2); C(11)-S(1) 1.704(15); C(11)-S(2) 1.716(16); N(1)-C(12) 1.452(2); N(1)-C(13) 1.458(2); Cl(1)-Ru(1)-S(1) 83.414(15); Cl(1)-Ru(1)-S(2) 154.917(14); S(2)-Ru(1)-S(1) 71.623(13); S(1)-C(11)-S(2) 110.90(9); C(12)-N(1)-C(13) 117.76(15). For **13b**: Ru(1)-Cl(1) 2.4622(13); Ru(1)-S(1) 2.416(14); Ru(1)-S(2) 2.382(14); C(11)-N(1) 1.341(7); C(11)-S(1) 1.707(5); C(11)-S(2) 1.732(5); N(1)-C(12) 1.490(13); N(1)-C(13) 1.460(8); Cl(1)-Ru(1)-S(1) 83.44(5); Cl(1)-Ru(1)-S(2) 154.43(5); S(2)-Ru(1)-S(1) 71.14(5); S(1)-C(11)-S(2) 108.5(3); C(12)-N(1)-C(13) 118.2(10).

Figure 16. Molecular structure of compound **14** with ellipsoids shown at 50% thermal probability. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and bond angles [deg]: Ru(1)–N(2) 2.097(6); Ru(1)–S(1) 2.419(2); Ru(1)–S(2) 2.377(2); C(11)–N(1) 1.336(12); C(11)–S(1) 1.711(8); C(11)–S(2) 1.687(10); N(1)–C(12) 1.435(13); N(1)–C(13) 1.460(12); S(2)–Ru(1)–S(1) 71.73(8); S(1)–C(11)–S(2) 111.6(5); C(12)–N(1)–C(13) 118.3(8); N(2)–Ru(1)–S(1) 87.4(2); N(2)–Ru(1)–S(2) 159.1(2).

Selected crystallographic data derived from the structure determinations of **13–14** are listed in Table 5. The Ru–C(octadienediyl) bond lengths fall within a range (2.192(16)–2.250(8) Å), which is similar to that observed for other reported ($\eta^3\text{:}\eta^3\text{-C}_{10}\text{H}_{16}$)Ru(IV) compounds (2.169(9)–2.269(11) Å).^{43–45} The Ru–Cl bond lengths in **13a** and **13b** (2.4622 Å) are longer than the analogous non-bridging Ru–Cl bond (2.39(7) Å) found in **12**.⁵² In fact, they are longer than those of all other previously reported mononuclear ($\eta^3\text{:}\eta^3\text{-C}_{10}\text{H}_{16}$)Ru(IV) compounds (2.368–2.459 Å).^{43,53,54} Notably, it is very close to that in [$(\eta^3\text{:}\eta^3\text{-C}_{10}\text{H}_{16})\text{Ru}(\text{SC}_9\text{H}_6\text{N})\text{Cl}$] (2.461(2) Å).^{43c} The longer Ru–Cl bond in these can be attributed to the trans effect of the sulfur donor atoms, though the Cl–Ru–S deviates substantially from linearity, the angle being only about 154° in **13a** and **13b**. The Ru–N(acetonitrile) distance in **14** (2.097(6) Å) is comparable with those in [$(\eta^3\text{:}\eta^3\text{-C}_{10}\text{H}_{16})\text{RuCl}(\text{MeCN})_2$] (2.084(5) and 2.064(5) Å),⁵⁵ and in [$(\eta^3\text{:}\eta^3\text{-C}_{10}\text{H}_{16})\text{RuCl}(\text{MeCN})(\kappa^1P\text{-LH})^+$, where LH is a phosphane ligand (2.031(7) Å).⁵⁴ All C–S bond lengths [1.687(1)–1.732(5) Å] fall intermediate between those for the C–S single bond (1.81

Å) and the C=S double bond (1.61 Å),⁵⁶ consistent with extensive electron delocalization in the S₂CNR₂ ligand. The C–N bond distances [1.323(2)–1.341(7) Å] also fall intermediate between those for a C–N single bond (1.47 Å) and a C=N double bond (1.28 Å)⁵⁶ as is typical of dithiocarbamate ligands and this is in turn attributed to the presence of the thioureide resonance forms. The bond angles subtended at the metal atoms in **13a**, **13b** and **14** fall within a narrow range [71.14(5)–71.73(8) Å] which falls within the range previously observed in similar ruthenium DTC complexes, namely in the Cp*Ru(IV)²⁷ and (Indenyl)Ru(II)⁵⁷ systems [70.70(3)–72.22(3) Å]. The Ru–S bond distances found in these complexes [2.377(2)–2.426(4) Å] also compare well with those observed in the above-mentioned studies [2.3644(7)–2.4068(1) Å].

1.3. Conclusion

The complex [Cp*Ir(*tpdt*)] **4** is easily obtained in high yield from the reaction of [Cp*IrCl₂]₂ with the sodium salt of *tpdt* dianion. The subsequent use of **4** as metallothiolato ligand towards its parent complex [Cp*IrCl₂]₂, as well as [(COD)MCl]₂ (M = Ir, Rh), had generated several new homo- and hetero-bimetallic complexes, wherein **4** assumed both unidentate and bidentate bridging roles. Sulfur-alkylation reaction of **4** yielded mono-alkylated derivative. Complex **4** and its mixed metal derivative Cp*Ir(*tpdt*)(COD)RhCl (**9**) have also been found to be more effective than [Cp*IrCl₂]₂ in the catalysis of the β -alkylation reaction involving both aliphatic and aromatic secondary alcohols in extremely low catalyst loading. This is the first report on the use of thiolato metal complexes as catalysts in alcohol synthesis. Interestingly, **4** can also effectively catalyze the N-alkylation of amines with alcohols with an interesting reversal in product selectivity leading to the formation of imines as the predominant product in moderate yields.

Table 5. X-ray crystallographic data for complexes **13-14**.

	13a	13b	14
Empirical formula	C ₁₃ H ₂₂ ClNRuS ₂	C ₁₇ H ₃₀ ClNRuS ₂	C ₁₅ H ₂₅ F ₆ N ₂ PRuS ₂
formula weight	392.96	449.06	543.53
crystal system	orthorhombic	Orthorhombic	triclinic
space group	<i>P2₁2₁2₁</i>	<i>Pbca</i>	<i>P$\bar{1}$</i>
<i>a</i> (Å)	10.6266(3)	12.3228(4)	7.8081(3)
<i>b</i> (Å)	10.6360(2)	15.4954(6)	11.1080(4)
<i>c</i> (Å)	13.9339(3)	21.0632(8)	12.4822(4)
α (deg)	90	90	95.397(2)
β (deg)	90	90	90.910(2)
γ (deg)	90	90	102.808(2)
<i>V</i> (Å ³)	1574.87(6)	4021.9(3)	1050.24(6)
<i>Z</i>	4	8	2
<i>d</i> _{calcd} (g/cm ³)	1.657	1.483	1.719
μ (mm ⁻¹)	1.413	1.117	1.076
crystal size (mm)	0.30 x 0.20 x 0.20	0.34 x 0.32 x 0.30	0.32 x 0.24 x 0.10
total, unique no. of rflns	39 613, 10 823	47 677, 6100	21 135 , 4511
<i>R</i> (int)	0.0297	0.0578	0.0466
data, restraints, parameters	9758, 1, 232	9600,0,343	23373 ,123, 450
Final <i>R</i> indices[I>2sigma(I)]	<i>RI</i> =0.0288, <i>wR2</i> = 0.0604	<i>RI</i> = 0.0761, <i>wR2</i> = 0.2198	<i>RI</i> = 0.0679, <i>wR2</i> = 0.1859
<i>R</i> indices (all data)	<i>RI</i> = 0.0382, <i>wR2</i> = 0.0648	<i>RI</i> = 0.0933, <i>wR2</i> = 0.2605	<i>RI</i> = 0.0925, <i>wR2</i> = 0.2355
GOF	1.023	1.146	1.171

The reactivity studies also showed that the bis(allyl)ruthenium(IV)-mediated C–S bond cleavage of thiuram monosulfide is much more facile than that of S–S cleavage in dithiuram disulfide. Indeed, such facile transition-metal mediated carbon–sulphur cleavage is of much interest, on account of its relevance in biological,⁵⁸ industrial, environmentally benign processes⁵⁹ and synthetic organic processes.⁶⁰ In view of current interest in the potential of complex

[Cp*Ir(C₄H₈S₃)] **4** as catalyst or catalyst precursor in a variety of reactions, e.g. polymerization, alkyne cyclotrimerization, de-protection, isomerization of allylamines and allylic alcohols, transfer hydrogenation and others,⁶¹ the obtained results are significant in understanding the chemistry of these compounds.

1.4. Experimental Section

General Procedures. All reactions and manipulations were carried out under dry, oxygen-free argon using the standard Schlenk technique or in an atmosphere of Argon in a M. Braun UNIlab glovebox.

NMR spectra were recorded on a Bruker AV 300 spectrometer (¹H at 300 MHz, ¹³C at 75 MHz) or a Bruker AV 400 (¹H at 400 MHz, ¹³C at 100 MHz) or a Bruker AV 500 (¹H at 500 MHz, ¹³C at 125 MHz). For ¹H and ¹³C NMR spectra, chemical shifts are referenced to residual solvent peak in the respective deuterio-solvents. LC-MS spectra were obtained in ESI mode on a Thermo Finnigan LCQ Deca XP MAX system, [M]⁺ was specified as the cation parts of ionic compounds. X-ray crystallographic analyses were performed on a Bruker X8 Kappa CCD diffractometer. Elemental analyses were performed in-house. Methanol was distilled from magnesium methoxide and THF distilled from sodium benzophenone ketyl. All other solvents used were purified, using the M. Braun MB SPS-800 solvent purification system. Silica gel (40–63 μm, Silicycle), aluminum oxide (activated, neutral, Alfa Aesar) and celite (Fluka AG) were dried at 140 °C overnight before use.

*Preparation of compound [Cp*Ir(C₄H₈S₃)] (**4**)*

To a white suspension of sodium methoxide (freshly generated from sodium (46 mg, 2.00 mmol, in methanol)) in toluene (5 mL) was injected 2-mercaptoethyl sulfide (135 μl, 1.00 mmol). The

mixture was stirred overnight, resulting in a milky solution and then $[\text{Cp}^*\text{IrCl}_2]_2$ (400 mg, 0.50 mmol) was added into the solution. The milky solution which turned orange-red immediately was stirred at room temperature for another 4 h and then filtered *via* a cannula to remove solid NaCl. The orange-red filtrate was evacuated to dryness to remove trace remnants of 2-mercaptoethyl sulfide. The residue was subsequently re-dissolved in toluene (2 mL) and then loaded on a neutral Al_2O_3 column (20 cm x 1 cm) packed in hexane. A red band was eluted out using hexane/THF = 1:2 (386 mg, 0.81 mmol, 81% yield). Anal. Calcd for $\text{C}_{14}\text{H}_{23}\text{IrS}_3$: C, 35.05; H, 4.83; S, 20.05. Found: C, 35.22; H, 4.87; S, 20.20. ^1H NMR (300 MHz, C_6D_6) δ : 2.30–2.22 (m, 2H, CH_2), 2.00–1.93 (m, 2H, CH_2), 1.85–1.76 (m, 2H, CH_2), 1.70–1.62 (m, 2H, CH_2), 1.64 (s, 15H, C_5Me_5); $^{13}\text{C}\{\text{H}\}$ NMR (75 MHz, C_6D_6) δ : 91.5 (C_5Me_5), 45.26(CH_2), 27.79 (CH_2), 8.17 (C_5Me_5). ESI^+ -MS: m/z 480 $[\text{M}+\text{H}]^+$.

Preparation of $[\text{Cp}^\text{Ir}(\text{C}_4\text{H}_8\text{S}_3)\text{Cp}^*\text{IrCl}](\text{PF}_6)$ (5)*

The complex $[\text{Cp}^*\text{IrCl}_2]_2$ (17 mg, 0.02 mmol) was added to a solution of compound **4** (20 mg, 0.04 mmol) in acetone (4 mL) and the mixture was stirred for 2 h, resulting in a yellow solution. Subsequently NH_4PF_6 (33 mg, 0.20 mmol) was added to the resultant solution. After stirring for another 1 h, the solution was filtered through celite giving a clear orange solution. The solution was concentrated to 2 mL and toluene (10 mL) added dropwise with swashing. Yellow solids precipitated out from the solution and were collected (34 mg, 0.03 mmol, 86%) using sintered glass filter (Porosity 4). Anal. Calcd for $\text{C}_{24}\text{H}_{38}\text{Ir}_2\text{S}_3\text{ClPF}_6$: C, 29.19; H, 3.88; S, 9.74. Found: C, 29.15; H, 4.06; S, 9.15. ^1H NMR (300MHz, $(\text{CD}_3)_2\text{CO}$) δ : 3.84–3.77 (m, 2H, CH_2), 3.19–3.05 (m, 4H, CH_2), 1.96 (s, 15H, C_5Me_5), 1.81–1.73 (m, 2H, CH_2), 1.64 (s, 15H, C_5Me_5); $^{13}\text{C}\{\text{H}\}$ NMR

(75MHz, (CD₃)₂CO) δ : 96.27 (C₅Me₅), 91.67 (C₅Me₅), 43.09 (CH₂), 30.48 (CH₂), 8.15 (C₅Me₅), 7.65 (C₅Me₅); ESI⁺-MS: m/z 843 [[M]⁺-Cl+MeCN]⁺, 802 [[M]⁺-Cl]⁺.

*Preparation of [Cp*Ir(C₄H₈S₃)Cp*IrCl][Cp*IrCl₃] (6)*

The complex [IrCp*Cl₂]₂ (100 mg, 0.12 mmol) was added to a solution of compound **4** (60 mg, 0.12 mmol) in acetone (5 mL) and the mixture was stirred for 2 h, resulting in a yellow solution and a yellow precipitate which was collected (37 mg, 0.03 mmol, 24%) using a sintered glass filter (Por. 4). The yellow filtrate was concentrated to 2 mL and toluene (8 mL) added dropwise with swashing. Yellow solids precipitated out from the solution and were similarly collected (84 mg, 0.07 mmol, 55%). ¹H NMR analysis confirmed that the two crops are the same compound **6** (121 mg, 0.10 mmol, 79%). Anal. Calcd for C₃₄H₅₃Ir₃S₃Cl₄: C, 31.99; H, 4.19; S, 7.54. Found: C, 31.96; H, 4.07; S, 8.17. ¹H NMR (300 MHz, CD₂Cl₂) δ : 3.83–3.73 (m, 2H, CH₂), 3.18–3.11 (m, 2H, CH₂), 3.03–2.95 (m, 2H, CH₂), 1.89 (s, 15H, C₅Me₅), 1.69–1.65 (m, 2H, CH₂), 1.58 (s, 15H, C₅Me₅), 1.54 (s, 15H, C₅Me₅); ¹³C{H} NMR (75 MHz, CD₂Cl₂) δ : 96.27 (C₅Me₅), 91.80 (C₅Me₅), 43.92 (CH₂), 31.18 (CH₂), 8.95 (C₅Me₅), 8.84 (C₅Me₅), 8.23 (C₅Me₅); ESI⁺-MS: m/z 843[[M]⁺+MeCN]⁺, 802 [M]⁺.

*Preparation of compound Cp*Ir(C₄H₈S₃)(COD)IrCl (7)*

The complex [(COD)IrCl]₂ (14 mg, 0.02 mmol) was added with stirring to a reddish solution of compound **4** (20 mg, 0.04 mmol) in THF (4 mL). The mixture was allowed to stir overnight at room temperature yielding an orange-red solution. The resultant solution was concentrated to dryness and triturated with diethyl ether (5 mL $\times$ 3). The orange-red solid residue is the compound

(C₅Me₅), 71.79 (CH, COD), 58.96 (CH, COD), 46.05 (SCH₂), 34.93 (SCH₂), 32.01 (CH₂, COD), 31.96 (CH₂, COD), 8.89 (C₅Me₅). ESI⁺-MS: *m/z* 813 [[M]⁺ + MeOH]⁺.

*Preparation of Cp*Ir(C₄H₈S₃)(COD)RhCl (9)*

The complex [(COD)RhCl]₂ (11 mg, 0.02 mmol) was added to a stirred reddish solution of compound **4** (20 mg, 0.04 mmol) in THF (4 mL). The mixture was stirred overnight at room temperature to give a clear yellow solution. The resultant solution was then concentrated to dryness and triturated with diethyl ether (5 mL). Orange-red solid residue obtained is the compound Cp*Ir(C₄H₈S₃)Rh(COD)Cl (30 mg, 0.04 mmol, 92%). Anal. Calcd for C₂₂H₃₅IrRhS₃Cl: C, 36.38; H, 4.86; S, 13.24. Found: C, 36.18; H, 5.09; S, 13.61. ¹H NMR (300 MHz, C₆D₆) δ: 4.58 (br, 4H, COD), 3.21–3.05 (m, 2H, SCH₂), 2.74–2.64 (m, 2H, SCH₂), 2.64–2.53 (m, 4H, 2CH₂, COD), 2.00–1.86 (m, 2H, SCH₂), 1.76–1.64 (q, 4H, 2CH₂, *J*(C-H) 7.68 Hz, COD), 1.62–1.55 (m, 2H, SCH₂), 1.43 (s, 15H, C₅Me₅). ¹³C{H} NMR (75 MHz, C₆D₆) δ: 92.60 (C₅Me₅), 80.53 (d, *J*(cod-Rh) 9.80 Hz, CH, COD), 44.09 (SCH₂), 30.99 (CH₂, COD), 29.88 (SCH₂), 8.00 (C₅Me₅); ESI⁺-MS: *m/z* 722 [M-Cl+MeOH]⁺.

*Preparation of [Cp*Ir(C₄H₈S₃)(COD)Rh][COD)RhCl₂] (10)*

The complex [(COD)RhCl]₂ (62 mg, 0.12 mmol) was added into the orange solution of compound **4** (60 mg, 0.12 mmol) in THF (6 mL) with stirring. An instantaneous color change from orange to yellow occurred and orange solid started to precipitate out after 15 mins. The mixture was stirred for 1 h. Then the supernatant was removed using pipette and the residue was washed with diethyl ether to give an orange solid of the title compound (109 mg, 0.11 mmol, 93%). Anal. Calcd for

$C_{30}H_{47}IrRh_2S_3Cl_2$: C, 37.04; H, 4.87; S, 9.89. Found: C, 37.12; H, 5.04; S, 10.15. 1H NMR (400 MHz, CD_2Cl_2) δ : 4.33 (s, 4H, 4CH, COD^+), 4.16 (s, 4H, 4CH, COD^-), 3.84–3.78 (m, 2H, SCH_2), 2.57–2.28 (m, 14H, SCH_2 , COD^+ , COD^-), 2.11–1.92 (m, 4H, COD^-), 2.03 (s, 15H, C_5Me_5), 1.77–1.65 (br, 4H, CH_2 , COD^+); $^{13}C\{H\}$ NMR (75 MHz, CD_2Cl_2) δ : 95.23 (C_5Me_5), 85.11 (d, $J(cod-Rh)$ 11.36 Hz, CH, COD), 45.13 (SCH_2), 31.80 (SCH_2), 31.08 (d, $J(cod-Rh)$ 6.82 Hz, CH_2 , COD), 8.87 (C_5Me_5); ESI $^+$ -MS: m/z 691 $[M]^+$.

Preparation of $[Cp^*Ir(C_5H_4S_3)]I$ (II)

To a stirred orange solution of compound **4** (20 mg, 0.04 mmol) in toluene (3 mL) at $-30^\circ C$ was injected methyl iodide (13 μl , 0.20 mmol). Immediately there was yellow precipitate came out. The mixture was stirred for another 2 h and then the solvent was removed via a cannula. The residue obtained was washed with diethyl ether (3 mL x 2) to give light yellow solid (23 mg, 0.04 mmol, 93%). Anal. Calcd for $C_{15}H_{26}IrS_3I$: C, 28.98; H, 4.22; S, 15.47. Found: C, 28.51; H, 4.56; S, 15.09. 1H NMR (300 MHz, $(CD_3)_2CO$) δ : 3.17–3.03 (m, 3H, CH_2), 2.97–2.93 (m, H, CH_2), 2.81–2.74 (m, 3H, CH_2), 2.56 (s, 3H, CH_3), 2.30–2.28 (m, 1H, CH_2), 2.02 (s, 15H, C_5Me_5); $^{13}C\{H\}$ NMR (75 MHz, $(CD_3)_2CO$) δ : 96.55 (C_5Me_5), 45.78 (CH_2), 38.82 (CH_2), 36.29 (CH_2), 16.04 (CH_2), 8.39 (CH_3), 7.77 (C_5Me_5); ESI $^+$ -MS: m/z 495 $[M]^+$.

β -Alkylation of Secondary Alcohols with Primary Alcohols: Typical Procedure.

The reaction was carried out with secondary alcohol (1.00 mmol), primary alcohol (1.00 mmol), catalyst (1.00 μmol), and Na t OBu (1 mmol) in toluene (0.3 mL) at $110^\circ C$ for 17 h. The reaction mixture was then cooled, diluted with 1 mL CH_2Cl_2 and filtered through a plug of celite. The

filtrate was evacuated to dryness and the resulting residue was dissolved in deuterated solvents and analyzed by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene added as an internal standard. The confirmation of the nature of the products was performed by comparison with literature data.³⁶

N-Alkylation of Amines with Alcohols: Typical Procedure.

The reaction was carried out with amine (1 mmol), primary alcohol (1 mmol), catalyst **4** (0.01 mmol) and KOH (1 mmol) in toluene (0.3 mL) at 110 °C for 45 h. The reaction mixture was then cooled, diluted with 1 mL toluene and filtered through a plug of celite. The filtrate was evacuated to dryness and the resulting residue was dissolved in deuterated solvents and analyzed by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene added as an internal standard. The confirmation of the nature of the products was performed by comparison with literature.⁴¹

*Preparation of $[\text{Ru}(\eta^3\text{:}\eta^3\text{-C}_{10}\text{H}_{16})\text{Cl}(\text{S}_2\text{CNMe}_2)]$ (**13a**)*

*Method A. Reaction of **12** with $[\text{Me}_2\text{NC}(\text{S})\text{S}]_2$*

$[\text{Me}_2\text{NC}(\text{S})\text{S}]_2$ (81 mg, 0.32 mmol) was added to a purple-colored suspension of **12** (100 mg, 0.16 mmol) in MeOH (4 mL) and the mixture was stirred for 48 h at room temperature, resulting in a suspension of yellow solids in a brown solution. The yellow solid of **13a** (89 mg, 0.23 mmol, 71%) were collected on a sintered glass filter (Por. 4). The brown-yellow mother liquid was concentrated in vacuo to ca. 1 mL and loaded onto the top of a neutral Al_2O_3 column (20 cm x 1 cm). Elution with 15 mL toluene gave a light yellow band consisting of the excess ligand (38 mg, as indicated by NMR). Further elution with ether (8 mL) gave a yellow band which afforded more

of the *title compound* (30 mg, 0.08 mmol, 24%). The two crops of the title compound (119 mg, 0.03 mmol, 95%) were combined. Yellow block single crystals of X-ray diffraction quality were obtained by slow diffusion of hexane into the toluene solution of the *title compound* after 2 d at -30 °C. (Found: C 39.98, H 5.58, N 3.63, S 16.16. C₁₃H₂₂RuS₂NCl requires C 39.73, H 5.64, N 3.56, S 16.32%). IR (ν cm⁻¹, KBr, just shown below 2800 cm⁻¹): 1531vs (NCSS, observed range 1450–1550 cm⁻¹),²⁸ 1400vs, 1255m, 1157m (NC₂, observed range 1138–1152 cm⁻¹),^{28a} 1029m and 995m (SCS, observed range 950–1050 cm⁻¹),^{28a,d} 943m. ¹H NMR (300 MHz, C₆D₆) δ : 4.99, 4.34, 3.97 and 2.73 (each s, 1H, H^a), 4.62 (dd, 1H, J(H^c-CH₂) 7.8 and 2.7 Hz, respectively, H^c), 3.08 (t, 1H, J(H^c-CH₂) 4.7 Hz, H^c), 2.53 and 1.98 (each s, 3H, Me), 2.45–2.34 (m, 1H, CH₂), 2.40 and 2.26 (each s, 3H, NMe), 2.13–2.08 (m, 2H, CH₂), 2.02–1.94 (m, 1H, CH₂). ¹³C{¹H} NMR (75 MHz, C₆D₆) δ : 206.3 (C_{quaternary}, S₂C), 113.6 and 108.1 (C^b's), 98.3 and 87.3 (C^c's), 76.5 and 73.8 (C^a's), 36.3 and 36.02 (NMe's), 34.7 and 31.1 (CH₂'s), 18.7 and 18.5 (Me's). HRMS-ESI⁺ Calc. for C₁₃H₂₂RuNS₂[M⁺]: 358.0218. Found: 358.0237.

Method B. Reaction of 12 with [Me₂NC(S)]₂S

A suspension of purple solid of **12** (100 mg, 0.16 mmol) in a MeOH solution (5 mL) of [Me₂NC(S)]₂S (68 mg, 0.32 mmol) was stirred at -15 °C for 1 h, resulting in a clear yellow solution. The resultant solution was concentrated under vacuo at liquid nitrogen temperature. Trituration with diethyl ether (5 mL, pre-cooled to -15 °C) followed by filtration gave an orange solid of the *title compound* (115 mg, 0.29 mmol, 91%). ¹H, ¹³C and HRMS-ESI⁺ data were identical to those mentioned in the alternate synthetic protocol described above.

In a repeat reaction, an extremely volatile colorless product was trapped in the second of two

consecutive liquid nitrogen cold traps for the solvent removal step. Its weight (24 mg) was estimated by the weight balance between total reactants and products. Although colorless block crystals were obtained for this compound at $-31\text{ }^{\circ}\text{C}$, these were found to be extremely low-melting, thus obviating a single crystal diffraction analysis. The presence of the species $[(\text{Me}_2\text{N})\text{C}(\text{S})\text{OMe}]^+$ was inferred from the proton NMR spectrum and the GC-MS: ^1H NMR: δ_{H} (300 MHz, CD_3OD): 1.71 (NMe). GC-MS: the single peak in the GC showed mass fragments, m/z : 119 $[(\text{Me}_2\text{N})\text{C}(\text{S})\text{OMe}]^+$, 104 $[(\text{Me}_2\text{N})\text{C}(\text{S})\text{O}]^+$ and 88 $[(\text{Me}_2\text{N})\text{C}(\text{S})]^+$.

*Preparation of compound $[\text{C}_{10}\text{H}_{16}\text{RuCl}(\text{S}_2\text{CN}^i\text{Pr}_2)]$ (**13b**)*

Compound **12** (100 mg, 0.16 mmol) was stirred with $[\text{Pr}_2\text{NC}(\text{S})\text{S}]_2$ (115 mg, 0.32 mmol) in MeOH (5 mL) for 9 h, resulting a clear brown solution. The solvent was removed under vacuo and the residue extracted using toluene ($3 \times 3\text{ mL}$). The extract was concentrated in vacuo to ca. 2 mL and loaded on a silica gel column (20 cm x 1 cm). Elution gave four fractions: (i) a light yellow eluant in hexane/ether (1:1, ca. 5 mL), which gave excess ligand (46 mg, 40% recovery); (ii) a yellow eluant in hexane/ether (1:3, 15 mL), which gave the *title compound* (105 mg, 73% yield); (iii) a brown-yellow eluant in MeCN (ca. 2 mL) which gave a trace of unidentifiable solid (3 mg), and (iv) a brown-black eluant in MeCN/MeOH (10:1, ca. 2 mL), which afforded also an unidentifiable species (8 mg). Orange block single crystals of X-ray diffraction quality for the *title compound* were obtained by slow diffusion of hexane into toluene solution at $-30\text{ }^{\circ}\text{C}$ after 2 d. (Found: C 45.68, H 6.57, N 2.32. $\text{C}_{17}\text{H}_{30}\text{RuS}_2\text{NCl}$ requires C 45.47, H 6.73, N 3.12). IR ($\nu\text{ cm}^{-1}$, KBr, just shown below 2800 cm^{-1}): 1487vs (NCSS, observed range $1470\text{--}1498\text{ cm}^{-1}$),²⁸ 1453m, 1446m, 1381m, 1371m, 1337vs, 1196m, 1148m (NC_2),^{28a} 1047m and 1020w (SCS),^{28a,d} 845w,

827w. ^1H NMR (300 MHz, C_6D_6) δ : 5.00, 4.35, 3.99 and 2.83 (each s, 1H, H^{a}), 4.62 (dd, 1H, $J(\text{H}^{\text{c}}\text{-CH}_2)$ 7.9 and 2.6 Hz, respectively, H^{c}), 4.33, 4.04 (each br, 1H, $\nu_{1/2}$ ca. 57 and 54 Hz, respectively, $\text{CH}(\textit{i}\text{Pr})$'s), 3.01 (t, 1H, $J(\text{H}^{\text{c}}\text{-CH}_2)$ 4.6 Hz, H^{c}), 2.55, 1.98 (each s, 3H, Me), 2.47–2.33 (m, 1H, CH_2), 2.15–2.09 (m, 2H, CH_2), 2.02–1.94 (m, 1H, CH_2), 1.05, 0.97 (each br, 6H, $\text{Me}(\textit{Pr})$). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, C_6D_6) δ : 205.8 ($\text{C}_{\text{quaternary}}$, S_2C), 113.6 and 107.3 (C^{b} 's), 98.0 and 87.5 (C^{c} 's), 76.4 and 73.3 (C^{a} 's), 49.2 and 49.1 ($\text{CH}(\textit{Pr}_2)$'s), 34.8 and 31.0 (CH_2 's), 19.4 and 19.2 ($\text{Me}(\textit{Pr})$'s), 18.7 and 18.4 (Me's). HRMS-ESI $^+$ Calc. for $\text{C}_{17}\text{H}_{30}\text{RuNS}_2[\text{M}^+]$: 414.0847. Found: 414.0863.

*Preparation of compound $[\text{C}_{10}\text{H}_{16}\text{RuCl}(\text{CH}_3\text{CN})(\text{S}_2\text{CNMe}_2)](\text{PF}_6)$ (**14**)*

*Method A. Reaction of **12** with $[\text{Me}_2\text{NC}(\text{S})]_2\text{S}$*

Compound **12** (80 mg, 0.13 mmol) and KPF_6 (192 mg, 1.04 mmol) were stirred in MeCN (4 mL) for 1 h. The solution was filtered through celite giving a clear yellow solution. Tetramethylthium monosulfide (54 mg, 0.26 mmol) was added to this solution and the mixture was stirred for 24 h. After the reaction was completed, the yellow crude reaction mixture was extracted with toluene to remove excess monosulfide ligand and trace amount of **13a**. The yellow residue was redissolved in MeCN, and chromatographed on silica gel (20 cm x 1 cm) column. Elution gave two fractions: (i) an unidentified yellow compound in hexane/ether (10:1, ca. 1 mL, 10 mg); (ii) the *title compound* in 15 mL THF (108 mg, 0.20 mmol, 76%). Single yellow crystals of X-ray diffraction quality were obtained by diffusion of hexane into its CH_2Cl_2 solution at -30°C after 3 d. (Found: C 32.88, H 3.53, N 2.06, S 11.72. $\text{C}_{15}\text{H}_{25}\text{RuS}_2\text{N}_2\text{PF}_6$ requires C 33.15, H 4.64, N 5.15, S 11.72%). IR ($\nu\text{ cm}^{-1}$, KBr, just shown below 2800 cm^{-1}): 2317w ($\text{C}\equiv\text{N}$), 2288w ($\text{C}\equiv\text{N}$),

1541vs (NCSS),³⁷ 1462m, 1400s, 1350w, 1258m, 1159m (NC₂),^{37a} 1026m and 997m (SCS),^{37a,d} 837vs and 557s (PF₆). ¹H NMR (500 MHz, CD₂Cl₂) δ: 4.62, 3.80, 3.47 and 2.68 (each s, 1H, H^a), 4.38–4.35 (t, 1H, *J*(H^c-CH₂) 5.7 Hz, H^c), 3.89 (dd, 1H, *J*(H^c-CH₂) 7.0 and 3.5 Hz, respectively, H^c), 3.31 and 3.15 (each s, 3H, Me), 2.95–2.78 (m, 4H, CH₂), 2.47, 2.33 (each s, 3H, NMe), 2.41 (s, 3H, MeCN). ¹³C{¹H} NMR (75 MHz, CD₂Cl₂) δ: 205.1 (C_{quaternary}, S₂C), 126.4 (MeCN), 118.1 and 113.4 (C^b's), 97.9 and 97.2 (C^c's), 73.5 and 71.8 (C^a's), 38.3 and 37.5 (NMe's), 35.2 and 33.9 (CH₂'s), 19.3 and 18.9 (Me's), 3.95 (MeCN). δ_P (CD₃CN) –144.0 (septet, *J*_{PF} 703 Hz, PF₆). HRMS-ESI⁺ - Calc. for C₁₅H₂₅RuN₂S₂ [M⁺]: 399.0523. Found: 399.0503

Method B. Reaction of 13a with KPF₆

Compound **13a** (20 mg, 0.05 mmol) and KPF₆ (12 mg, 0.06 mmol) were stirred in MeCN (3 mL) for 1 h. The resultant solution was filtered through celite giving a clear yellow solution. The solution was evacuated to dryness in vacuo, and the residue triturated with diethyl ether; filtration then gave a yellow solid of **14** (26 mg, 0.05 mmol, 96% yield). ¹H, ¹³C and HRMS-ESI⁺ data were identical to those observed above.

X-ray Crystallography. X-ray-quality single crystals of compounds **4-11**, **13-14** were obtained by the slow diffusion method at –30 °C. Red diffraction-quality crystals of **4** were obtained by slow diffusion of hexane into its toluene solution after 2 d; crystals of **5** and **6** were obtained by the slow diffusion of diethyl ether into MeCN solution after three days; compound **7** were obtained by the slow diffusion of diethyl ether into its benzene solution after 2 d. Red diffraction-quality single crystals of **5** were obtained by the slow diffusion of diethyl ether into its

MeCN solution after 3 d. The orange x-ray-quality single crystals of **9** and **10** were obtained by the slow diffusion of diethyl ether into its MeCN solution after 2 d. Crystals of **11** were obtained by the slow diffusion of diethyl ether into MeCN solution after three days. Crystals of **13** were obtained by the slow diffusion of diethyl ether into MeCN solution after overnight. Crystals of **14** were obtained by the slow diffusion of diethyl ether into MeCN solution after three days. Crystallographic data were collected on a Bruker X8 Kappa CCD diffractometer at 173 K using graphite-monochromated Mo K α radiation ($\lambda = 0.71063$ Å). The APEX2 software suite was used for data acquisition, structure solution and refinement. Absorption corrections were applied using SAD-ABS.⁶² The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using SHELXTL-97.⁶³

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Chapter 2. Cyclometalation Reaction and Metallacycles' applications in Organic Synthesis

2.1. General Introduction

Since the discovery in the 1960s of a cyclometallated Nickel (II) complex (Figure 17),¹ cyclometalation has been recognized to be the easiest way for formation of a transition-metal complex with a carbon-metal bond. By definition, it refers to metal-mediated activation of a C-R bond that transforms a molecule of type RC-Y to a CY-metallacycle which contains a new metal-carbon σ bond (Scheme 29).²

Figure 17.

Scheme 29.

Considerable amount of cyclometallation reactions have been subsequently done not only with transition metals but also with main group metals. So far, the most widely used cyclometalation reaction protocol proceeds *via* C-H bond activation but examples involving C-C, C-O, and C-Si bond activation have also been reported in literature.² The formed metallacycles in which the metal is bound by a chelating carbo-ligand, or *via* aryl M-C σ -bonds, are referred to as '*ortho*-metallated complexes'.³ The latter kind of chelation mode strengthens the generally highly susceptible M-C bond and thus stabilizes the metallacycle. As a process that has attracted enormous interest from a synthetic and industrial point of view, it has been used widely as part of

the quest for efficient methods of functionalizing hydrocarbon sources into value-added products. Cyclometalated compounds are usually classified according to the metal,⁴ the heteroatom donor,^{3,5} or the atom number of constituents in the chelate ring.⁶ An enormous number of cyclometalated compounds containing nitrogen, phosphorus, arsenic, oxygen and sulfur as the donor atoms with almost all the transition metals have now been reported. As to the ring sizes of these metallacycles, five-membered rings are the most common due to the minimal ring strain it imparts on the cyclometallated system.⁶

Although a comprehensive review of metallacycles is not possible due to the tremendous progress achieved in cyclometalation chemistry, a brief review of relevant Ru and Pd based metallacycles is undertaken in this section.

2.2. General Considerations

2.2.1 General Mechanism

Cyclometalation reactions can be mainly categorized as follows: electrophilic C-H bond activation (EA), oxidative addition (OA), and σ -bond metathesis (SBM). The dividing line amongst the three classes is rather blurred and further studies are needed to strengthen one or the other.^{2,7} In a pioneering review, Cámpora and co-workers used one general scheme to explain these three major processes (Scheme 30).⁸

Generally, the electronic configuration at the metal center together with the nature of the C-H bond determines which mechanism may be most probable during a cyclometalation procedure. Concerning this, Ackermann annotated these three pathways as: electrophilic activation with electron-deficient late transition metals, oxidative addition with electron-rich late transition metals,

and σ -bond metathesis with early transition metals.⁹ It should be emphasized here also that the exact mechanism is far from being well understood and compelling experimental data is not enough to provide a converging picture. Any subtle changes of factors concerning all/or part of the cyclometalation process may transform one pathway to the other.

Scheme 30.

With the three broad classes of the C-H activation identified, further insight can often be obtained from the results of computational methods which can even put forward new activation mechanisms, such as Goddard's recent suggestion of "oxidative hydrogen migration".¹⁰ There are also some new names to differentiate the pathways which have been recognized, such as "CMD" (concerted metalation-deprotonation), "IES" (internal electrophilic substitution), or "AMLA" (ambiphilic metal ligand activation) and so on.⁹ All these novel insights into the nature of cyclometalation reactions have stimulated the development of novel transformations and broadened the scope of C-H bond functionalization in recent years.

2.2.2. Influence of Donor on Cyclometalation Reaction

Apart from the genuine interest in the mechanism and scope of this fundamental bond-activation process, the cyclometalation reaction can be divided into two consecutive steps: bonding of metal center by the hetero atom Y and then the intramolecular C-R bond activation. This sequence can be regarded as a typical tandem process.² First, bonding of metal center by the

hetero atom effect the electron density at the metal center, and it also provides steric constraints which is helpful for the bond-activation step. This is decisive, because it reduces the entropic and enthalpic costs of the subsequent bond-activation step and the metallacycle ring closure step.² Second, because of the ease of intramolecular bond activation compared to the intermolecular activation, the subsequent intramolecular C-R bond activation occurs and the ring closure is completed.^{2,11}

In the actual cyclometalation reaction, there are quite a number of factors which will effect the reaction. For example, the metal precursor, the donor ligand Y, and the C-R bond which will be activated. However, compared with the difficulty of understanding the exact mechanism, the influencing factors in the cyclometalation reactions are well understood. Herein, our goal is to discuss the donor effect.

As mentioned above, the first step of cyclometalation, the pre-coordination of metal with the donor Y will impact the electron density at the metal center. This may be in charge of the thermodynamically controlled substitution or a dimer cleavage process, especially when the intramolecular coordination site is a strong neutral donor such as phosphine, imine, or amine.

The influence of the donor group Y in cyclometalation reactions may generally abide by the hard-soft acid-base (HSAB) principles as described by Pearson.¹² Specifically, cyclometalation with “hard” high-valent early transition metals will be much easier when the donor atoms are hard, such as in alkoxides, aryloxides, and so on. On the other hand, “soft” low-valent late transition metals, e.g., the platinum group metals, much more likely to bond with soft Lewis bases, such as phosphines and sulfides and so on. The hard-soft principle provides only a general guideline and is not applicable to all cases. A large number of examples have been reported where relatively soft

donor atoms have indeed been used in cyclometalations with hard metals (Scheme 31)¹³ and likewise, hard donors have been used in combination with soft transition metals (Scheme 32).¹⁴ However, the hard-soft mismatches may generate some problems in regioselectivity of metalation. For example, the more effective delocalization of the positive charge in the Wheland intermediate, formed by the attack at C(1) of a naphthalene system, usually outweighs the unfavorable steric interaction of the electrophilic with H(8), thereby directing the reaction kinetically to the 1-position. Nevertheless, in the palladation of 2-[(dimethylamino)methyl]naphthalene, only the 3-metalated complex is formed (Scheme 33).¹⁵

Scheme 31.

Scheme 32.

Scheme 33.

After pre-coordination, for the second step, donor group Y still plays an important role. Arising from the experimental and computational studies, the formation of the intermediate is essential and delicate and in some extent depends on the M-Y bond strength. Too strong a bonding restraints ligand dissociation from the coordination metal precursor, while too weak bonding may revert the reaction to the starting materials, not to mention the formation of the intermediate.² Both steric and electronic factors of the substituent on the donor group Y can effect the strength of the M-Y bond, so except considering the nature of the donor group Y, other factors also need to be considered at the same time.

For example, Y = NMe₂ has proven to give particularly stable compounds when it coordinates to the palladium atom in a palladacycle and it has been widely used as a catalyst in asymmetric Diels-Alder reactions.¹⁶ This synthetic methodology can be extended to the synthesis of diphosphine motifs *via* asymmetric hydrophosphination of vinylic and other unsaturated phosphine-functionalized substrates.¹⁶ However when the Me group is changed to ⁱPr group, it has been found that it can not form the metallacycle any more due to the excessive shielding of the nitrogen atom (Scheme 34).¹⁷

Scheme 34.

There is a fundamental rule in the chemistry of orthopalladated compounds: direct activation of C-H bonds by palladium(II) to afford corresponding palladacycles is the most feasible in the case of tertiary amines, whereas primary and secondary amines are usually inert toward such activation. The unique properties of tertiary amines were first accounted for in terms of stronger binding to the metal of primary and secondary amines compared with tertiary ones, thus preventing effective electrophilic attack of palladium(II) on the aromatic ring. Although recent findings of Dunina, who developed a procedure to orthopalladate secondary amines *via* C-H bond cleavage,¹⁸ and Avshu and Clark, who showed a way to access palladacycles with primary amines,¹⁹ has altered this view, the general situation has not changed.

For another example, phosphines and sulfides as softer donors can easily coordinate to metal even when bulky substituents are present in the metalacycle ring motif. Steric effects, especially large cone angle phosphine ligands, ensure that the M-P bond does not become too strong. So it will not deteriorate ligand dissociation from the metal precursors and coordination of ligands in the *cis* position is restricted.² Shaw has first disclosed and demonstrated the beneficial effect of steric bulk at phosphorus (Scheme 35).²⁰ In the paper, Shaw pointed out that if R^1 , R^2 are small, metallation would sometimes not occur, but if the R^1 , R^2 are bulky, e. g. $t\text{Bu}$, then the metallation often occurs readily and rapidly.²⁰ So from their view, it is clearly steric effects that are dominant over electronic effects. With sterically demanding phosphines, cyclometalation is favored.

Scheme 35.

2.3. Cyclometalation products in organic synthesis

There are three advantages when using the cyclometalated products in organic syntheses.^{4a,4c,6b}

First, the cyclometalation reaction can easily proceed yielding the potential catalysts. Second, the cyclometallated systems allow considerable electronic and steric tuning. Third, the application of many kinds of catalytic reactions is possible because the cyclo-metalation proceeds with a variety of metal compounds.

The most popular domain of cyclometalation is the cyclometalation using the platinum group metals. A vast number of metallacycles of the platinum group have been prepared by heteroatom-assisted C-H bond activation. Nearly all the platinum group metals Ru, Os, Rh, Ir, Pd, and Pt have received attention, with palladium being the transition metal that has been studied in greatest detail.

This section aims at summarizing the most general aspects of cyclometalation using palladium and ruthenium reported in literature relevant to the preceding discussion.

2.3.1. Palladacycles in organic synthesis

Since the discovery of the cyclometalation reaction, many transition metals have been successfully used to lead to this type of organometallic compounds. However, palladium is without any doubt the transition metal that has been the most studied, as cyclopalladated compounds are known for nearly all classes of ligands to date.

Palladacycles were first discovered by the cyclopalladation of azobenzene derivatives in the middle 1960s.²¹ It is one of the most popular classes of metallacycles. It can be mainly divided into two types: anionic four-electron donor or six-electron donor, abbreviated as CY and YCY, respectively (Scheme 36).^{4c} For CY type, the metalated carbon is usually an aromatic sp^2 carbon (see examples, Scheme 37). Some examples in which the metalated carbon is an sp^3 carbon²² or an sp^2 vinylic carbon²³ have also been reported (see examples, Scheme 38). The most common of CY palladacycles are obtained from the tertiary amines and imines and usually incorporate five- or six-membered rings. It is worth pointing out that cyclopalladated complexes derived from primary amines are very rare. Noteworthy is that the three- and four-membered rings are not usually stable, although there are some examples that prove their existence (see examples, Scheme 39).²⁴ Chirality also has been incorporated into CY type palladacycle compounds, especially, planar chirality (see examples, Scheme 40).²⁵ In addition, CY type usually exist as halogen or acetate bridged dimers, as two geometric isomers (*cisoid* and *transoid* conformations).

Scheme 36.

Scheme 37.

Scheme 38.

Scheme 39.

Scheme 40.

YCY type palladacycles, so-called palladium “pincer” complexes, are usually symmetrical (two equivalent five- and less commonly, six-membered rings) or are unsymmetrical (mixed, five- and six-membered rings). In common, pincer ligands, have a general formula $[2,6-(YCH_2)_2C_6H_3]$ (YCY) and comprise a potentially Y,C,Y terdentate coordinating, mono-anionic array, where Y is a neutral two-electron donor such as NR_2 , PR_2 and so on.²⁶ A large variety of binding modes have been found when a transition metal cyclometalated to a pincer ligand, such as: monodentate, Y,C,Y tridentate and so on.²⁷ By far, YCY coordination mode is the most popular one for platinum group metals (Scheme 41). This terdentate coordination mode, consisting two metallacycles which share one M-C bond, forces the aryl ring of the pincer ligand into a conformation which is approximately coplanar with the coordination plane of metal centers. So far, PCP, NCN, PCN, SCS-type pincer complexes have been extensively investigated. When compared with others, NCN-type seems more diverse and versatile. van Koten and co-workers pointed out that “Modification of various ligand parameters of NCN-type pincer allows for a refined adjustment of

the steric and electronic properties of the metal center without changing its bonding pattern significantly".²⁶ Detailed studies of a large variety of palladium pincers have provided direct access to a variety of reactions in organic synthesis (Scheme 42).²⁸

Scheme 41.

Scheme 42.

Palladacycles have also been identified as powerful catalysts for the formation of C-C (Scheme 43) or C-Y bonds (Scheme 44) and proximally (ortho or peri) directed arylation reactions since unprecedented TON or TOF numbers were obtained.^{4c} In addition, palladacycles can tolerate a variety of functional groups, so they offer the opportunity to form several different types of bonds in one pot (Scheme 45).²⁹ Chiral palladacycles have also been prepared for asymmetric catalysis (Scheme 46, 47).³⁰

Scheme 43.

Scheme 44.

Scheme 45.

Scheme 46.

Scheme 47.

Chiral CY type palladacycle complexes have proven to be effective in asymmetric C-C bond forming reactions and this body of work has been reviewed previously with extensive amount of data added subsequently.¹⁶ For instance, Leung *et al.* have shown that asymmetric Diels-Alder reaction has been considered to be one of the most efficient and elegant methods for construction of chiral six-membered rings; 3,4-dimethyl-1-phenylphosphole (DMPP) is a rather poor cyclic diene due to its aromaticity, without the help from outside environment the reaction between DMPP and vinyl phosphine can not proceed. However in the presence of palladacycles, upon coordination to palladium complex, the phosphole is activated and thus capable of reacting with a variety of dienophiles, such as α,β -unsaturated ketone, ester, aldehyde, amide, thioester, thioamide, and sulfoxide compounds. The asymmetric Diels-Alder reactions can proceed *via* controlled *exo*- and *endo*-pathways to afford a large group of functionalized P-chiral mono- and bis-phosphine ligands (Scheme 48).^{16,31}

Scheme 48.

In view of the efficacy of that methodology in the activation and subsequent stereo-controlled C-C bond formation (of what in most cases were essentially two phosphine moieties), it seemed logical to explore the possibility of using a similar protocol for P-C bond formations. The addition of secondary phosphines to carbon-carbon multiple bond, known as hydrophosphination, is the most valuable and convenient process for synthesis of functionalized tertiary phosphine ligands.³² In general, when the phosphorus functionalized olefins were employed, the hydrophosphination reactions can produce a class of useful bis-phosphine ligands. For example, as shown in Scheme 49, upon activation by coordination to palladium complex, the hydrophosphination reaction proceeded smoothly with high regio- and stereo-selectivity under mild conditions to generate the chiral 1,2-bis-phosphine (*R*)-PROPHOS, which indicated that the orthometallated amine complexes can also serve as efficient template for the asymmetric hydrophosphination reaction in stereo-controlled C-P bond formations.³³

Scheme 49.

The flexibility and potential of this chiral auxiliary continues to show scope for expansion and recently they have proven to be extremely efficient in certain catalytic versions of the asymmetric H-P addition process.³⁴ Apart from being air-sensitive, the generally stable M-P coordination renders technical difficulties in the elimination of the tertiary phosphine product in catalytic process involving transition metal ions as catalysts. However, the asymmetric hydrophosphination of aromatic enones could be catalyzed by the same organopalladium(II) complex **16** with high yields and stereoselectivity (Scheme 50).^{34a} From the mechanistic standpoint, the catalytic cycle is carried forward due to the labile nature of the products in the presence of excess secondary phosphine. This is consistent with the observation in which the generally inert P-Pd coordination in the *trans* N-Pd-P moiety becomes kinetically labile when it is treated with even slight excess of tertiary phosphine ligand. Following this concept, a new phosphapalladacycle-based C-P catalyst **17** is found to be superior to its C-N analogue, as the substrate-Pd coordination is weaker in the *trans* P-Pd-P coordination moiety and the P-Ph groups in the catalyst are able to control the stereochemistry of the addition reactions better than the N-Me counterparts. Selected examples of hydrophosphination reactions catalyzed by this phosphapalladacycle catalyst are given in Scheme 51.^{34b}

Scheme 50.

Scheme 51.

2.3.2. Ruthenacycles in organic synthesis

In the years 1968 and 1969, the first instances of cycloruthenation reaction with [(PPh₃)₃RuHCl] were disclosed independently by Levison and Robinson and by Parshall, Knoth and Schunn.³⁵ Ruthenacycles have since been found to be highly useful due to their unique photophysical and electrochemical properties.³⁶ Thus they have been used for solar cells and other electron-transfer systems.³⁷ In addition, ruthenacycles are among the most active catalysts known to date for transfer hydrogenation reactions.³⁸

The cycloruthenation by C-H bond activation is a major route for the formation of cycloruthenated compounds.³⁶ Cycloruthenation reaction is extremely versatile and of very broad scope. It can activate, including, for example, C(sp²)-H bonds in chromium arenes and ferrocenes.³⁸ However, in contrast with the palladium counterpart, a large library of ligands which can lead to successful cycloruthenation through C-H activation has not been built up yet. The versatility of cycloruthenation originates last but not least from the great diversity of available ruthenium precursors (Scheme 52).^{38,39}

Scheme 52.

Unlike for palladacycles, a whole mechanistic picture of the cycloruthenation process is far from being complete.^{2,36} Currently, no compelling evidence is available for certain reaction pathways. However, steric and electric factors can influence the fate and rate of the cyclometallation in many ways. The presence of a formal external or internal base and the existence of free coordination sites is a condition for the feasibility of the cyclometallation itself. For example, in the presence of Na_2CO_3 , Bennett and Latten discovered a cycloruthenation reaction involving C-H bond activation at the *ortho*-methyl substituent of the Ru-bound phosphane ligand (Scheme 53).⁴⁰ In this case, a hydridoruthenium intermediate, which formed upon hydrogen atom transfer from 2-propanol, was propositioned.

Scheme 53.

Although the mechanism of the cycloruthenation is not clear yet, the cycloruthenated products have been comprehensively used. For example, a few examples of cycloruthenated complexes

have shown excellent activities in the ortho-deuteration (Scheme 54),⁴¹ C-C bond formation (Scheme 55)⁴² and hydrogenation reactions (Scheme 56).⁴³ It is worth pointing out that hydrogenation reactions have been extensively investigated, especially the reduction of ketones and aldehydes by transfer hydrogenation. This reaction was usually accomplished by using 2-propanol as a hydrogen source that reduces the ketone, leading to the corresponding alcohol, as illustrated in Scheme 56. Endeavors to improve the promising results involved modifying the electronic properties of the substituents on the chelated ligand, incorporating chiral centers on the arm of the ligand and so on, to improve the yield and the ee value (Scheme 56).⁴⁴

Furthermore, Arends and coworkers have demonstrated the possibility of using those ruthenacycle complexes as hydrogen transfer catalysts to achieve the dynamic kinetic resolution of secondary alcohols.⁴⁵ It was shown that ruthenacycle was fully compatible with the enzyme and the acyl residue, leading to the conversion of rac-1-phenylethanol into pure (*R*)-1-phenylethyl acetate in 86% yield and 99% ee (Scheme 57).

Scheme 54.

Scheme 55.

Scheme 56.

Scheme 57.

2.4. Aims of the present project

As aforementioned, the metallacycles of the platinum group have been successfully employed in a variety of organic reaction scenarios. With the aim of extending the scope further, we tested the palladacycle catalyzed one-pot cyclization-alkylation reaction for the synthesis of 2,3-functionalized indoles and the ruthenacycle catalyzed β -alkylation of secondary alcohols with primary alcohols.

In conjunction with this, we also tested the palladacycle catalyzed asymmetric hydrophosphination reaction involving substrates bearing diester and ferrocene backbones to generate chiral monophosphine ligands.

The work reported in the Chapter 3 and Chapter 4 is part of our efforts in the development of

new catalytic reactions using metallacycles as catalysts for C-C bond formation scenarios and for the formation of chiral monophosphine ligands by means of asymmetric hydrophosphination reaction involving P-C bond formations.

Chapter 3 overview

Chapter 4 overview

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Chapter 3. Palladacycle catalyzed Domino Cyclization/Alkylation reaction and Ruthenacycle catalyzed one pot β -Alkylation reaction

3.1. Introduction

3.1.1. Palladacycles

Within the family of organotransition metal catalysts, metallacycles have been under intensive scrutiny due to their promising catalytic ability in a wide array of organic synthesis protocols.¹ Undoubtedly, palladacycles which were initially isolated and characterized from the cyclopalladation of azobenzene derivatives in the middle 1960s have been the most studied owing to their wide and proven applications in not only catalysis but also in biological chemistry and materials science.² Moreover, palladacycle skeletons are also often encountered as intermediate species in many reactions promoted by palladium complexes.³ For example, on the basis of the mechanistic studies, Fango and co-workers proposed a catalytic cycle for the intramolecular alkane arylation of amide which involved palladacycle as an intermediate (Scheme 58).⁴

Scheme 58.

Thus far, palladacycles have been used as catalyst in a variety of reactions, including Heck, Suzuki, Sonogashira and Buchwald-Hartwig reactions.⁵ In particular, nitrogen-based CN-palladacycles, which are readily accessible and air/moisture stable have attracted continuing

interest in organic synthesis, homogeneous catalysis, drug design, asymmetric synthesis, resolution of racemic ligands and in development of luminescent organic materials because of their unique physical and chemical properties.⁶ For example, CN-palladacycle (*R/S*)-**15** and its derivatives have been widely used as efficient promoters in the synthesis of a wide range of functionalized tertiary mono-, di- and tri-phosphine ligand motifs including those carrying alcohol, aldehyde and keto functionalities.⁷ It was found that this palladacycle and its derivatives can be utilized as excellent catalyst for the asymmetric Claisen rearrangement, hydroamination, hydrophosphination and tandem allylic amination/allylation reactions with good yields and enantioselectivities.⁸ Further investigations into the potential of this complex in catalytic C-C and C-X bond formation scenarios is therefore of great interest.

The indole structural motif and its derivatives are abundant and important in many biologically active compounds and natural products. Consequently, development of efficient, economical and environmentally friendly synthetic methods targeting the generation of the indole nucleus has attracted continued research interest (Scheme 59).⁹ Development of synthetic methods for the alkylation of 2-substituted indoles to yield 2,3-disubstituted indoles has also continued to attract much attention.¹⁰ Recent literature reports indicate substantial effort being directed at developing methodologies that allow for one-pot/sequential/domino formation of 2,3-disubstituted indoles. Notable amongst these include the PdCl₂ catalyzed domino-cyclization-Heck of 2-ethynylphenylcarbamates in the presence of reoxidant and excess Bu₄NF,¹¹ one pot three component Sonogashira-Cacchi domino sequence consisting of 2-iodo-N-trifluoroacetylanilides, alkynes and aryl bromides using Pd(OAc)₂ and in the presence of PPh₃,¹² a

$\text{PdBr}_2(\text{BINAP})$ -complex catalyzed reaction of arylamines with α -diketones under reductive conditions¹³ and the N-arylation and Fischer cyclization of N-tosylhydrazones with benzyne.¹⁴

Scheme 59.

A protocol involving a domino catalytic sequence for the cyclization of unprotected *o*-alkynylanilines (attractive starting material by virtue of the fact that they are readily available *via* Sonogashira-type reactions) to yield C-2 substituted indoles and their subsequent regio-selective alkylation at C-3 using allylic alcohols has not been attempted hitherto. The development of such a single catalyst promoted reaction protocol which allows for low catalyst loading, avoids use of protecting agents on N (at the risk of N-alkylated products) and tolerates the use of benign alcohols (as opposed to conventional Lewis acids) as alkylating agents (in spite of their acidic nature and poor leaving group behavior) is highly challenging, yet desirable in the synthesis of these compounds.

In the subsequent section (section 3.2.1), studies on the use of palladacycles to achieve the aforementioned domino sequence towards 2,3-substituted indoles under mild conditions in one-pot without the need for any additive or protecting agent will be described. The reaction not only proceeds in an efficient manner but also yields hitherto inaccessible indole derivatives *via* a

“green” protocol without the need for additives or protecting groups and with water being the only side product during the alkylation step.

3.1.2. Ruthenacycles

Like Palladacycles, ruthenacycles have also attracted recent attention in the synthesis of a wide array of valuable catalysts, anti-cancer drugs and electron shuttles.¹⁵ However the most extensively studied organic transformations catalyzed by ruthenacycles are typically limited to C-C or C-X (X = heteroatom) bond formation, hydrogenation, dehydrogenation, hydrogen transfer and racemisation reactions (see section 2.3.2).^{15a, 16} In spite of their reputation in promoting these reactions and their inherent unique redox characteristics exhibited in the context of their application as electron shuttles in redox-catalyzed processes, the potential of ruthenacycles acting as both an oxidant and reductant in a one-pot multi-step β -alkylation reaction has remained surprisingly unexplored.

By virtue of the fact that it is an efficient tandem protocol giving β -alkylated secondary alcohols as product with only water as by-product, catalytic one-pot β -alkylation has attracted interest in recent years.¹⁷ In comparison to traditional protocols used to attain such alcohols, catalytic one-pot β -alkylation has positioned itself as a “green” process in terms of atom economy, avoidance of protecting groups and waste minimization.^{17,18} Typically traditional protocols of alkylation of secondary alcohols with primary alcohols involves dehydrogenation of the alcohols to aldehyde or ketone, aldol coupling, loss of water and subsequent hydrogenation of the resulting enone to yield the coupled alcohol (Scheme 18).^{17g} A possible side product of this procedure which is usually observed is the alkylated ketone.

A survey of literature reveals very clearly that iridium-based catalysts dominate the scene in one-pot, multi-step β -alkylation reactions.¹⁷ Recently, several ruthenium-based catalysts which incorporate N-heterocyclic carbenes (NHCs),¹⁹ phosphines or terpyridine ligands²⁰ have also been developed for the β -alkylation reaction. However, until now, there are no literature reports on the application of ruthenacycles to allow discriminatory formation of alkylated secondary alcohols in a one-pot process. The evaluation of a series of ruthenacycles bearing C-N chelate ligands that show potential as excellent catalysts for the β -alkylation protocol will be demonstrated in section 3.2.2. Careful selection and design of these palladacycles also revealed a possible key factor that determines the reactivity in such metallacycle mediated hydrogen transfer scenarios.

3.2 Results and Discussion

3.2.1 Investigations on the palladacycle-catalyzed domino reaction for synthesis of substituted indoles

Catalytic cyclization of 2-alkynylaniline derivatives to 2-substituted indoles has proven to be an efficient approach for the synthesis of indole derivatives.²¹ Unfortunately, only a few such methods can deal with nitrogen unprotected primary 2-alkynylaniline.²² With the palladacycle **16** (Figure 18) in hand, the cyclization of unprotected 2-(phenylethynyl)aniline (**22a**) was first attempted. After some investigations, excellent yields (up to 99%) of free NH 2-substituted indoles (**23a**) were achieved (Table 6).

Figure 18.

Table 6: Optimization of reaction conditions for the formation of **23a**.^a

Entry	Catalyst (mol%)	Temperature (°C)	Time (h)	Solvent	Yield ^b (%)
1	10	110	24	Tol	91
2	20	110	24	Tol	78
3	5	110	24	Tol	93
4	10	110	9	Tol	91
5	10	90	24	ACN	97
6	10	80	24	DCE	91
7	10	80	9	DCE	99
8	10	70	9	DCE	98
9	10	60	9	DCE	90

^a The reaction was carried out with 2-alkynylaniline (0.1 mmol, 1 equiv.), catalyst **16** (10 mol%) in 2 mL of specified solvent. ^b Yields were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

Subsequently the allylic alkylation of **23a** with 1,3-diphenyl-2-propenol (**24a**) was also attempted. The alkylation of indoles with allylic alcohols to give C3- or N-substituted indoles, have hitherto been achieved using Lewis acids, Brønsted acids, and iodine as catalysts via the Friedel-Crafts pathway²³ as well as by transition metal catalyzed allylic alkylations.²⁴ Recently, Hirashita *et al.* have reported that allylic alcohols when reacted with indoles in the absence of catalyst in iron-exchanged water at 220°C could yield the desired alkylation product.²⁵ Using **16** as

catalyst, the alkylation in low-coordinating solvents (toluene, dichloroethane) gave clean conversion to **25a** at only 70 °C. No trace of N-allylic substituted indole was observed (Table 7).

Table 7. Optimization of reaction conditions for the formation of **25a**.^a

Reaction scheme: 2-phenylindole (**23a**) + 1-phenyl-2-propen-1-ol (**24a**) $\xrightarrow{16}$ 2-allyl-3-phenylindole (**25a**)

Entry	Catalyst (mol%)	Temperature (°C)	Time (h)	Solvent	Yield ^b (%)
1	20	110	24	Tol	71
2	10	110	24	Tol	97
3	10	90	24	ACN	NR
4	10	80	24	THF	80
5	10	80	24	DCE	84
6	10	70	9	Tol	91
7	10	70	9	DCE	91
8	10	60	9	DCE	NR

^a The reaction was carried out with 2-alkynylaniline (0.1 mmol, 1 equiv.), catalyst **16** (10 mol%) in 2 mL of specified solvent. ^b Yields were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

In order to test whether it is possible to integrate the two steps involved into one single operative synthetic procedure, **22a**, **24a** and 10% catalyst **16** were treated in dichloroethane at 70 °C for 9h. Upon completion of the reaction, 2,3-substituted indole **25a** was formed in up to 98% yield (Table 8, entry 1). In order to render some information on the mechanism, Pd(OAc)₂ as catalysts was also employed to test the reaction. The results shows that Pd(OAc)₂ could catalyze the cyclization of unprotected *o*-alkynylanilines, but it could not catalyze the allylic alkylation with allylic alcohol to yield the alkylation product. The other three palladacycles **19**, **20** and **21** (Figure 18) were also investigated under the same conditions and the summarized results are shown in Table 8. The results showed that catalyst **16** and **19** were much more effective than their benzyl amine analogues **20** and **21**, which indicates that the difference in electronic influence of the C_{naphthyl}-Pd bond and C_{phenyl}-Pd bond has an effect on the catalytic cycle. From the results, **16**

and **19** are comparable, indicating that the anion effect does not play an important role. Thus, the stable and well-characterized **16** was chosen as catalyst.

Table 8: Optimization of reaction conditions for the formation of **25a**.^a

Entry	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield ^b (%)
1	16 (10)	70	9	98
2	19 (10)	70	9	98
3	20 (10)	70	9	NR ^c
4	21 (10)	70	9	18
5	16 (10)	60	9	NR ^c
6	16 (10)	70	3	75
7	16 (10)	70	6	91
8	16 (5)	70	9	64

^a The reaction was carried out with 2-alkynylaniline (0.1 mmol, 1 equiv.), 1,3-diphenyl-2-propenol (0.1 mmol, 1 equiv.), catalyst, 2 mL of dichloroethane. ^b Yields were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. ^c Almost quantitative amount of **23a** was obtained together with un-reacted allylic alcohol.

To further probe the general feasibility of this synthetic protocol, various 2-alkynylanilines bearing different functional groups on the aromatic ring were subject to the reaction with 1,3-diphenyl-2-propenol and substituted 1,3-diphenyl-2-propenol respectively (Table 9). The results from these test reactions showed that all these 2-alkynylanilines could react with 1,3-diphenyl-2-propenol very efficiently to afford the desired 2,3-substituted indoles exclusively with excellent yields and regio-selectivities (Table 9, entries 1-5). The reactions of 2-alkynylanilines with unsymmetrical allylic alcohol **24b** were also studied. The results showed that the reactions between 2-alkynylanilines and unsymmetrical **24b** can also afford the 2,3-substituted indole exclusively and in excellent yields. However, the product is a mixture of the isomers **25** and **25'**. This lack of regioselectivity for the alkylation step is in line with literature

precedent²⁶ and indicated that the alkylation step may be proceeding via the Tsuji-Trost pathway rather than the Friedel-Crafts pathway. It should be mentioned that, upon completion of the reaction, the formation of Pd black was also observed, which is also consistent with the Tsuji-Trost mechanism. The reactions of 2-alkynylanilines with 4-phenyl-3-buten-2-ol and cinnamyl alcohol, unfortunately, yielded only cyclized products.

Although a detailed mechanism deserves further investigations, based on the previously reported mechanistic studies dealing with the cyclization and alkylation step, a reaction mechanism as described in Scheme 60 is proposed to rationalize the formation of 2,3-substituted indoles. Firstly, intramolecular nucleophilic attack of the amino group towards the Pd-activated C-C triple bond (**26**) leads to the formation of the palladium intermediate (**27**). This palladium intermediate then undergoes a rapid proton-palladium exchange followed by regeneration of the palladium catalyst with the formation of indole. Secondly, indole as a nucleophile attacks the π -allylpalladium intermediate (**28**), leading to the 2,3-substituted indole that underwent the protonation to form the final product.

Table 9: Palladacycle catalyzed domino cyclization-alkylation with *o*-alkynylanilines and allylic alcohols. ^a

Entry	R ¹	R ²	Allylic alcohol	Product	Overall Yield ^b (%)
1	H	Ph	24a	25a	98
2	Cl	Ph	24a	25b	95
3	CN	Ph	24a	25c	90
4	H	4-MePh	24a	25d	94
5	Cl	4-MePh	24a	25e	90
6	H	Ph	24b	25f/f'	91
7	Cl	Ph	24b	25g/g'	98

^a The reaction was carried out with 2-alkynylaniline (0.1 mmol, 1 equiv.), allylic alcohol (0.1 mmol, 1 equiv.), catalyst **16** (10 mol%) in 2 mL of dichloroethane at 70 °C for 9 h. ^b Overall yields (combined yields of two isomers for entries 6-10) were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

Scheme 60.

3.2.2. Ruthenacycle-Catalyzed One-pot β -alkylation reaction.

3.2.2.1. Synthesis and Characterisation of the Ruthenacycle Complexes

Treatment of phenylmethanamine, *N*-methyl-1-phenylmethanamine and *N,N*-dimethyl-1-phenylmethanamine with 0.5 equiv of $[(\eta^6\text{-C}_6\text{H}_6)\text{RuCl}_2]_2$ in the presence of 1 equiv of NaOH and

1 equiv of KPF_6 led to the formation of ruthenacycles **18**, **29** and **30** (Scheme 61) in high yields as per reported procedures.²⁷ Solid state structures of **18** and **29** have not been reported previously in literature and therefore crystals suitable for single crystal X-ray diffraction studies were obtained by the slow diffusion of diethyl ether into acetonitrile.

Scheme 61.

The molecular characteristics of **18** and **29** (shown in Figure 19 and 20) were in accordance with those previously reported for **30**²⁸ and other ruthenacycles.²⁹ The presence of methyl substituents on the nitrogen (in **29** and **30**) resulted in extended Ru-N bond lengths (2.139(2), 2.1600(13), 2.170(2) Å,²⁸ respectively). Although from an electronic viewpoint, the presence of a methyl substituent on the nitrogen should increase its nucleophilicity resulting in stronger Ru-N bonds, the steric effect overshadows the electronic effect especially in the context of the constricted environment surrounding the ruthenium metal center.

Figure 19: ORTEP representation of the cation of **18** with ellipsoids shown at 50% thermal probability. Selected hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Ru(1)-N(2) 2.055(2), Ru(1)-C(1) 2.067(2), Ru(1)-N(1) 2.139(2), N(2)-Ru(1)-C(1) 86.14(8), N(2)-Ru(1)-N(1) 87.57(8), C(1)-Ru(1)-N(1) 77.16(9).

Figure 20: ORTEP representation of the cation of **29** with ellipsoids shown at 50% thermal probability. Selected hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and bond angles [deg]: Ru(1)-N(2) 2.0436(14), Ru(1)-C(1) 2.0598(14), Ru(1)-N(1) 2.1600(13), N(2)-Ru(1)-C(1) 86.09(6), N(2)-Ru(1)-N(1) 84.19(5), C(1)-Ru(1)-N(1) 78.06(5).

It is indeed very well established and expected that besides tuning the substituents on the N donor, altering the organic ligand attached to the metal atom can also modify drastically the activity, selectivity and stability of transition metal catalysts.³⁰ Therefore, the synthesis of complex **31** was conducted with the aim of evaluating a series of complexes which could provide further insights into catalyst design. The reaction of naphthalen-1-ylmethanamine with $[(\eta^6\text{-C}_6\text{H}_6)\text{RuCl}_2]_2$ led to the formation of ruthenacycle **31** in high yield (Scheme 62).

Scheme 62.

The characteristic downfield chemical signal ($\delta = 8.04$) of the aromatic proton *ortho* to the Ru-C bond as well as the presence of a downfield chemical shift ($\delta = 164.20$) attributed to the highly de-shielded Ru bound carbon indicated that the desired complex **31** had been synthesized successfully. With the four ruthenacycles **18**, **29-31** in hand, their catalytic potential for the β -alkylation reaction was studied.

The most accepted mechanism for the one-pot β -alkylation of secondary alcohols with primary alcohols involves dehydrogenation of the alcohols to an aldehyde or ketone, aldol coupling, loss of water and subsequent hydrogenation of the resulting enone to yield the coupled alcohol (Scheme 63).^{17g}

Scheme 63.

Ruthenacycles have been previously employed as catalysts for the transfer hydrogenation of carbonyl compounds.¹⁵ Among these, particular attention has been devoted to catalysts which incorporate an amine in the metallacycle ring.^{30,31} In the absence of acidic NH protons, it is generally assumed that Ru-catalyzed transfer hydrogenation occurs *via* metal hydride and alkoxide species through an inner-sphere mechanism.^{31b} An outer-sphere mechanism, involving a Ru-H hydride and N-H proton has also been proposed by various groups.^{31b,32} Both mechanisms have a common factor in that they involve two parallel reactions that can transfer hydrogen between the carbonyl compounds and alcohols. It was therefore rational to test the catalytic potential of the ruthenacycles synthesized in the current study since the one-pot β -alkylation protocol also involves a similar transfer hydrogenation scenario.

The catalytic screening was initiated with equimolecular amount of benzyl alcohol and 1-phenylethanol with the aim of evaluating the feasibility of the catalytic system and to ascertain the optimized conditions required for the same (Table 10). In a typical reaction run, a mixture of 1-phenylethanol (1.0 mmol) and benzyl alcohol (1.0 mmol) was dissolved in toluene (0.3 mL) in

the presence of NaO^tBu (1.0 mmol) and catalyst (1.0 mol%) and allowed to react at 110 °C for 17 h. The highest yield for the alcohol was obtained using **18** as the catalyst (entries 1, 6 and 7, Table 10). When the amount of base was reduced to half (entries 2, 9, 11 and 13, Table 10) the selectivity for the alcohol product was lowered. Likewise, lowering the catalyst loading also had a detrimental impact on the selectivity, but not on the reactivity (entry 3, Table 10). The reaction time had a considerable influence on the selectivity of the process. It was consistently observed for the four catalysts that allowing the reaction to proceed for an extended period of time (48 h) favored the formation of the ketone co-product *via* dehydrogenation of the alcohol. A similar decrease in alcohol formation was also evident at higher temperatures. With shorter reaction times, higher selectivity in favor of the alcohol product was observed, but the overall product conversion deteriorated (entry 7, Table 10). Lowering the temperature from 110 °C to 90 °C resulted in an appreciable decrease in the product conversion with catalyst **18** (entry 6, Table 10). The use of a less basic additive, NaOH also resulted in a lower conversion and selectivity (entry 4, Table 10) while the use of Na₂CO₃ gave no product (entry 5, Table 10). Overall under the various conditions tested, ruthenacycles **29**, **30** and **31** exhibited lower activity selectivity when compared to **18**.

These results indicated that complex **30**, without the NH moiety could still generate the product in high yields. However when compared with **29** and **30**, complexes **18** and **31** (with the NH₂ group on the metallacycle) gave better results thus indicating the possibility that the NH functionality plays a role in enhancing the reaction yield. Noyori had previously reported a similar enhancement of reactivity by N-H moieties in transfer hydrogenations.³²

Table 10: Screening of Catalysts and Optimization of reaction conditions.^a

Entry	Catalyst (mol%)	Base (mol%)	Conversion (%)	Alcohol:Ketone
1	18 (1.0)	NaO ^t Bu (100)	96	97:3
2	18 (1.0)	NaO ^t Bu (50)	75	78:22
3	18 (0.5)	NaO ^t Bu (100)	97	58:42
4	18 (1.0)	NaOH (100)	99	66:34
5	18 (1.0)	Na ₂ CO ₃ (100)	0	0
6 ^b	18 (1.0)	NaO ^t Bu (100)	82	93:7
7 ^c	18 (1.0)	NaO ^t Bu (100)	60	99:1
8	29 (1.0)	NaO ^t Bu (100)	96	76:24
9	29 (1.0)	NaO ^t Bu (50)	99	63:37
10	30 (1.0)	NaO ^t Bu (100)	84	96:4
11	30 (1.0)	NaO ^t Bu (50)	96	76:24
12	31 (1.0)	NaO ^t Bu (100)	99	50:50
13	31 (1.0)	NaO ^t Bu (50)	99	67:33

^a Reaction conditions: 1 mmol of 1-phenylethanol, 1 mmol of benzyl alcohol, catalyst, base, 0.3 mL of toluene, 110 °C, 17 h.

Conversions (based on the secondary alcohol) and ratios were determined by ¹H NMR. ^b Reaction conducted at 90 °C.

^c Reaction time shortened to 9 h.

In view of the results from the catalyst screening studies, the scope of the substrates and limitations of catalyst **18** using a wide assortment of secondary alcohols and primary alcohols under the optimized conditions (Table 11) were also investigated. Generally, catalyst **18** was able to activate the efficient transformations of many primary and secondary alcohols into the targeted alkylated alcohols. The reactions of 1-phenylethanol or 1-(4-methoxyphenyl)ethanol with various benzyl alcohols containing an electron-donating or an electron-withdrawing group proceeded with excellent conversion (90-98%) and good to excellent selectivity for the alcohol products (entries 1a-1d and 2a-2d, Table 11). These values are comparable with those obtained for the reported iridium-based catalyst systems.^{17,18}

A closer examination revealed that varying the substituent on 1-phenylethanol did not have any impact on the product conversion and selectivity on reaction with benzyl alcohol (entries 1a, 2a

and 3a, Table 11). Interestingly, unsaturated primary alcohols and aromatic secondary alcohols (entries 1e-1f and 2e, Table 11) also gave moderate yields of alkylated alcohols and ketones. The results from the alkylation of such unsaturated alcohol substrates are conspicuously rare in literature reports involving both Ir and Ru catalysts. Aromatic primary alcohols and aromatic secondary alcohols gave better conversions compared to aliphatic primary alcohols with aromatic secondary alcohols (entries 4 and 5, Table 11) and aliphatic primary alcohols with aromatic secondary alcohols (entries 1g, 2f and 3b, Table 11). It is seen from literature reports that aliphatic alcohols do not usually result in good conversions for this coupling reaction.¹⁷

Table 11: β -Alkylation of Secondary Alcohols with Primary Alcohols.^a

Entry		$R^2\text{-CH}_2\text{-OH}$	Conversion (%) ^b	Alcohol: Ketone
1a	Ph	Ph	96	97:3
1b	Ph	3-ClC ₆ H ₄	90	75:25
1c	Ph	4-ClC ₆ H ₄	94	96:4
1d	Ph	4-MeOC ₆ H ₄	98	62:38
1e	Ph	C ₆ H ₅ CH=CH	67	70:30
1f	Ph	CH ₂ =CH	44	38:62
1g	Ph	<i>n</i> -Bu	40	80:20
2a	4-MeOC ₆ H ₄	Ph	93	90:10
2b	4-MeOC ₆ H ₄	3-ClC ₆ H ₄	94	60:40
2c	4-MeOC ₆ H ₄	4-ClC ₆ H ₄	92	85:15
2d	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	95	55:45
2e	4-MeOC ₆ H ₄	CH ₂ =CH	44	34:66
2f	4-MeOC ₆ H ₄	<i>n</i> -Bu	51	75:25
3a	4-ClC ₆ H ₄	Ph	92	98:2
3b	4-ClC ₆ H ₄	<i>n</i> -Bu	70	96:4
4	CH ₃	Ph	85	36:64
5		Ph	90	40:60

^a Reaction conditions: 1 mmol of 1-phenylethanol, 1 mmol of benzyl alcohol, 1 mmol of NaO^tBu, 1 mol% **18**, 0.3 mL of toluene, 110 °C, 17 h. ^b Conversions (based on the secondary alcohol) and ratios were determined by ¹H NMR spectroscopy.

When considering the catalytic cycle for the β -alkylation reaction involving “hydrogen borrowing”, an important intermediate is the metal hydride species.¹⁷ In the present context, the Ru-H species is already an 18 electron entity and this precludes the coordination of the substrate to the Ru center. Thus the enhanced conversions seen for aromatic alcohols could be rationalized by two explanations. Firstly, CH/ π attractions based on both electrostatic and charge-transfer interactions exist between the η^6 -benzene ligand of the catalyst and the phenyl moiety of the substrate resulting in enhanced interaction when both are brought together in closer proximity during the catalytic cycle. Thereby it is postulated that with such improved interaction it will be more efficient in assisting the hydrogen transfer during the catalytic cycle resulting in excellent conversions. Secondly, alkyl alcohols will form less electrophilic aldehyde species when undergoing the catalytic process rendering them less susceptible to attack by the nucleophile thus resulting in diminished conversions. Additionally, alkyl alcohols lack the postulated CH/ π attractions for improved interaction. Evidently, complex **18** is an efficient catalyst for this coupling reaction giving excellent conversions for most substrates.

The formation of the Ru-H species is also facilitated by the tendency of the intermediate ruthenium alkoxides to undergo thermal decomposition to metal hydrides.^{31b} Simultaneously, both alcohols are subjected to the dynamic ruthenium-catalyzed redox shuttle to form the carbonyl precursors for the aldol condensation reaction to form the β -unsaturated ketone (Scheme 64). Together with successful formation of an 18-electron metal hydride species, the last steps are reduction of the C-C double bond through a Michael-type addition to yield the coupled ketone and subsequent reduction of the carbonyl group to give the coupled alcohol product. To confirm this proposed two-stage reduction pathway, the transfer hydrogenation of 1,3-diphenyl-2-propenone

under similar conditions, but with refluxing in t PrOH. Once the reaction was complete, the saturated ketone was obtained in 50% yield along with the presence of the starting material. On the basis of the above-mentioned experiment, it is obvious that the catalyst is very selective for C-C double bond hydrogenation over C-O double bond. The high yields of coupled alcohols obtained when the β -alkylation reaction was conducted, proves the two-stage nature of the ketone reduction step whereby a saturated ketone leads to the subsequent formation of the saturated alcohol product. The same experiment also proves that possible steric issues (due to presence of Ph groups) that may exist in the aforementioned CH/ π attractions do not affect the catalytic cycle.

The catalytic studies employing various ruthenacycles has therefore provided preliminary insights as to why complex **18** has overall superior reactivity for the β -alkylation process over the other analogues tested in this study. For the catalysis scenario (Scheme 64), taking into consideration the fact that catalyst **30** possesses no proton on the amino nitrogen and in light of the experimental evidence of Baratta and co-workers that the coordinated primary amine in ruthenacycles displays relatively weak acidity,^{31b} an alternate mechanism was proposed as shown in Scheme 64.

The presence of a hydrogen bond greatly assists the hydrogen transfer process to generate a ruthenacycle-hydride species as shown in Scheme 64, thus enhancing the reactivity of complex **18** and **31** as compared to **29** and **30**.

Scheme 64.

3.3 Conclusion

In conclusion, a very simple, clean and atom-efficient protocol for the synthesis of 2,3-substituted indoles from 2-alkynylanilines and allylic alcohols via the palladacycle catalyzed domino cyclization/alkylation has been developed. This protocol more importantly allows the incorporation of previously unavailable substituents at C-3 position of C-2 substituted indole motifs which have potential for further functionalization via the C=C bond. The attractiveness of the procedure is further enhanced by the fact that it requires no additives, no protection on the nitrogen and can proceed with the use of alcohols thereby yielding only water as a side product during the alkylation step.

Ruthenacycles, prepared easily in a single step from benzyl amines, have also demonstrated good potential as catalysts in the one-pot β -alkylation of secondary alcohols with primary alcohols. This is the first report of the use of a ruthenacycle in this particular organic synthetic scenario and counts among the few instances in literature when non-iridium- based catalysts have been

employed successfully. The catalyst and substrate screening studies, besides expanding the reaction scope to unsaturated primary alcohols, also revealed the importance of the amino hydrogen in controlling the catalytic activity of the ruthenacycles in such hydrogen transfer processes.

3.4 Experimental Section

General Procedures. All reactions and manipulations were carried out under dry, oxygen-free environment using the standard Schlenk technique or in an atmosphere of Argon in a M. Braun UNIlab glovebox. NMR spectra were recorded on a Bruker AV 500 (^1H at 500 MHz, ^{13}C at 125 MHz). For ^1H and ^{13}C NMR spectra, chemical shifts are referenced to residual solvent peak in the respective deuterio-solvents. HR-MS spectra were obtained in ESI mode on a Waters Q-Tof Premier MS system. LC-MS spectra were obtained in ESI mode on a Thermo Finnigan LCQ Deca XP MAX system. X-ray crystallographic analyses were performed on a Bruker X8 Kappa CCD diffractometer. All solvents used were purified, using the M. Braun MB SPS-800 solvent purification system. Celite (Fluka AG) were dried at 140 °C overnight before use.

The four palladacycles catalysts **16**, **19-21** were prepared by treating the corresponding chloro-bridged dimeric palladium compounds³³ with silver perchlorate / silver triflate in acetonitrile *via* a procedure reported previously.³⁴ *o*-Alkynylanilines were prepared according to the published procedure.³⁵ All the other reactants and reagents were used as supplied.

Typical procedure for the palladacycle catalyzed cyclization of 22a:

22a (19.3 mg, 0.1 mmol), catalyst **16** (4.9 mg, 10 mol%), and 2 mL of varying solvent were placed in a 25 mL argon-filled sealed Schlenk tube and allowed to reflux at the given temperature for

given time. Upon the reaction time finished, internal standard, 1,3,5-trimethoxybenzene, was added and dissolved in the mixture. The reaction mixture was then filtered through celite. The filtrate was evacuated to dryness and the resulting residue was dissolved in deuterated solvents and analyzed by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. The signals due to the product **23a** were confirmed by comparisons with values obtained from literature.³⁶

Typical procedure for the palladacycle catalyzed allylic alkylation of 23a with 24a:

23a (19.3 mg, 0.1 mmol), **24a** (21.0 mg, 0.1 mmol), catalyst **16** (4.9 mg, 10 mol%), and 2 mL of varying solvent were placed in a 25 mL argon-filled sealed Schlenk tube and allowed to reflux at the given temperature for given time. Upon the reaction time finished, internal standard, 1,3,5-trimethoxybenzene, was added and dissolved in the mixture. The reaction mixture was then filtered through celite. The filtrate was evacuated to dryness and the resulting residue was dissolved in deuterated solvents and analyzed by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. The signals due to the product **25a** were confirmed by comparisons with values obtained from literature.³⁷

Typical procedure for the palladacycle catalyzed domino cyclization/alkylation of 22a with 24a:

22a (19.3 mg, 0.1 mmol), **24a** (21.0 mg, 0.1 mmol), specified catalyst and amount, and 2 mL of dichloroethane were placed in a 25 mL argon-filled sealed Schlenk tube and allowed to reflux at the given temperature for given time. Upon the reaction time finished, internal standard, 1,3,5-trimethoxybenzene, was added and dissolved in the mixture. The reaction mixture was then filtered through celite. The filtrate was evacuated to dryness and the resulting residue was

dissolved in deuterated solvents and analyzed by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. The signals due to the product **25a** were confirmed by comparisons with values obtained from literature.³⁷

Typical procedure for the palladacycle catalyzed domino cyclization/alkylation of o-alkynylanilines with allylic alcohols:

o-alkynylaniline (0.1 mmol, 1 equiv.), allylic alcohol (0.1 mmol, 1 equiv.), catalyst **16** (10 mol%), and 2 mL of dichloroethane were placed in a 25 mL argon-filled sealed Schlenk tube and allowed to reflux at 70 °C for 9 h. Upon the reaction time finished, internal standard, 1,3,5-trimethoxybenzene, was added and dissolved in the mixture. The reaction mixture was then filtered through celite. The filtrate was evacuated to dryness and the resulting residue was dissolved in deuterated solvents and analyzed by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. The analytically pure products were obtained by flash chromatography in Hexane/DCM.

25b: pale yellow solid (25.9 mg, 62%). ^1H NMR (CDCl_3 , 300 MHz): δ 8.14 (s, 1H, *NH*), 7.53-7.11 (m, 18H, Ar), 6.83 (dd, 1H, $J = 15.9, 7.5$ Hz, $\text{CH}=\text{CHPh}$), 6.41 (d, 1H, $J = 15.8$ Hz, $\text{CH}=\text{CHPh}$), 5.25 (d, 1H, $J = 7.2$ Hz, $\text{CHCH}=\text{CH}$); ^{13}C NMR (CDCl_3 , 75 MHz): δ 143.0, 137.3, 137.0, 134.6, 132.5, 131.6, 131.5, 128.9, 128.6, 128.5, 128.4, 128.2, 127.3, 126.4, 125.3, 122.5, 120.4, 113.7, 111.9, 44.9. HRMS (ESI): calcd for $\text{C}_{29}\text{H}_{23}\text{NCl}$ $[\text{M}+\text{H}]^+$: 420.1519; found: 420.1527.

25c: yellow solid (21.7 mg, 53%). ^1H NMR (CDCl_3 , 300 MHz): δ 8.45 (s, 1H, *NH*), 7.72-7.26 (m, 18H, Ar), 6.82 (dd, 1H, $J = 15.9, 7.2$ Hz, $\text{CH}=\text{CHPh}$), 6.40 (d, 1H, $J = 15.9$ Hz, $\text{CH}=\text{CHPh}$), 5.29

(d, 1H, $J = 7.2$ Hz, $CHCH=CH$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.7, 137.9, 137.8, 137.0, 131.8, 131.8, 131.1, 129.1, 128.9, 128.6, 128.6, 128.5, 128.0, 127.6, 127.5, 126.6, 126.5, 126.4, 125.2, 120.8, 114.8, 111.8, 102.9, 44.7. HRMS (ESI): calcd for $C_{30}H_{23}N_2$ $[M+H]^+$: 411.1861; found: 411.1859.

25d: pale yellow solid (22.7 mg, 57%). 1H NMR ($CDCl_3$, 300 MHz): δ 8.04 (s, 1H, NH), 7.43-6.96 (m, 18H, Ar), 6.88 (dd, 1H, $J = 15.9, 7.2$ Hz, $CH=CHPh$), 6.40 (d, 1H, $J = 15.9$ Hz, $CH=CHPh$), 5.27 (d, 1H, $J = 7.2$ Hz, $CHCH=CH$), 2.40 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.6, 138.0, 137.6, 136.2, 135.7, 132.4, 131.0, 130.1, 129.6, 128.5, 128.5, 128.3, 128.3, 127.1, 126.3, 126.1, 122.0, 121.2, 119.7, 113.6, 110.9, 45.2, 21.3. HRMS (ESI): calcd for $C_{30}H_{26}N$ $[M+H]^+$: 400.2065; found: 400.2067.

25e: pale yellow solid (23.4 mg, 54%). 1H NMR ($CDCl_3$, 400 MHz): δ 8.09 (s, 1H, NH), 7.42-7.09 (m, 18H, Ar), 6.82 (dd, 1H, $J = 15.6, 7.2$ Hz, $CH=CHPh$), 6.39 (d, 1H, $J = 15.6$ Hz, $CH=CHPh$), 5.23 (d, 1H, $J = 7.2$ Hz, $CHCH=CH$), 2.41 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.1, 138.4, 137.4, 137.2, 134.5, 131.7, 131.4, 129.6, 129.6, 129.0, 128.5, 128.5, 128.4, 128.2, 127.2, 126.4, 126.3, 125.2, 122.3, 120.3, 113.4, 111.9, 45.0, 21.3. HRMS (ESI): calcd for $C_{30}H_{25}NCl$ $[M+H]^+$: 434.1676; found: 434.1679.

25f/f': pale yellow solid (20.0 mg, 50%). 1H NMR ($CDCl_3$, 300 MHz): δ 8.10 (s, 1H, NH), 7.55-6.92 (m, 18H, Ar), 6.89-6.79 (m, 1H, $CH=CHPh$), 6.42-6.35 (m, 1H, $CH=CHPh$), 5.28-5.23 (m, 1H, $CHCH=CH$), 2.30 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.6, 140.4, 137.6, 136.9, 136.3, 135.6, 134.7, 133.0, 132.5, 131.3, 131.0, 130.9, 129.1, 129.0, 128.8, 128.6, 128.4, 128.3,

128.2, 128.2, 128.0, 128.0, 127.1, 126.3, 126.2, 126.1, 122.1, 121.3, 121.3, 120.0, 114.1, 110.9, 45.1, 44.8, 21.1, 21.0. HRMS (ESI): calcd for $C_{30}H_{26}N$ $[M+H]^+$: 400.2065; found: 400.2073.

25g/g': pale yellow solid (20.8 mg, 48%). 1H NMR ($CDCl_3$, 400 MHz): δ 8.13 (s, 1H, *NH*), 7.54-7.08 (m, 18H, Ar), 6.84-6.74 (m, 1H, *CH=CHPh*), 6.41-6.35 (m, 1H, *CH=CHPh*), 5.24-5.20 (m, 1H, *CHCH=CH*), 2.32-2.32 (m, 3H, Me); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.2, 139.9, 137.4, 137.1, 137.0, 137.0, 135.8, 134.6, 134.6, 132.5, 131.9, 127.2, 126.4, 126.3, 125.2, 122.5, 120.5, 120.4, 113.9, 111.9, 44.9, 44.6, 21.2, 21.0. HRMS (ESI): calcd for $C_{30}H_{25}NCl$ $[M+H]^+$: 434.1676; found: 434.1688.

25h/h': yellow solid (17.8 mg, 42%). 1H NMR ($CDCl_3$, 400 MHz): δ 8.43 (s, 1H, *NH*), 7.73-7.09 (m, 18H, Ar), 6.83-6.73 (m, 1H, *CH=CHPh*), 6.41-6.35 (m, 1H, *CH=CHPh*), 5.28-5.23 (m, 1H, *CHCH=CH*), 2.33-2.32 (m, 3H, Me); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.8, 139.5, 137.9, 137.7, 137.7, 137.3, 137.1, 136.1, 134.3, 131.8, 131.7, 131.6, 131.4, 130.1, 129.3, 129.3, 129.1, 128.8, 128.6, 128.6, 128.5, 128.3, 128.1, 127.9, 127.7, 127.4, 126.6, 126.6, 126.4, 126.3, 126.0, 125.1, 120.8, 120.8, 115.0, 111.8, 102.8, 102.8, 44.7, 44.4, 21.2, 21.0. HRMS (ESI): calcd for $C_{31}H_{25}N_2$ $[M+H]^+$: 425.2018; found: 425.2030.

25i/i': pale yellow solid (21.5 mg, 52%). 1H NMR ($CDCl_3$, 300 MHz): δ 8.11 (s, 1H, *NH*), 7.49-7.02 (m, 18H, Ar), 6.90-6.84 (m, 1H, *CH=CHPh*), 6.43-6.39 (m, 1H, *CH=CHPh*), 5.30-5.26 (m, 1H, *CHCH=CH*), 2.45 (s, 3H, Me), 2.35 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.7, 140.5, 138.0, 137.7, 136.8, 136.2, 135.7, 135.6, 135.5, 134.8, 132.6, 131.4, 130.9, 130.8, 130.1, 129.5, 129.1, 129.0, 128.5, 128.4, 128.3, 128.2, 128.2, 128.0, 127.0, 126.3, 126.2, 126.0, 121.9,

121.2, 121.2, 119.6, 113.7, 110.8, 45.2, 44.9, 21.3, 21.2, 21.0. HRMS (ESI): calcd for $C_{31}H_{28}N$ $[M+H]^+$: 414.2222; found: 414.2222.

25j/j': pale yellow solid (22.4 mg, 50%). 1H NMR ($CDCl_3$, 300 MHz): δ 8.09 (s, 1H, *NH*), 7.41-7.10 (m, 18H, Ar), 6.80-6.73 (m, 1H, *CH=CHPh*), 6.41-6.34 (m, 1H, *CH=CHPh*), 5.23-5.18 (m, 1H, *CHCH=CH*), 2.41 (s, 3H, Me), 2.32 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.2, 140.0, 138.3, 137.1, 137.1, 137.0, 135.7, 134.6, 134.5, 132.0, 131.3, 131.2, 130.7, 129.6, 129.2, 129.1, 129.0, 128.5, 128.3, 128.2, 128.0, 127.2, 126.3, 126.2, 125.1, 122.3, 120.3, 113.5, 111.8, 44.9, 44.6, 21.3, 21.2, 21.0. HRMS (ESI): calcd for $C_{31}H_{27}NCl$ $[M+H]^+$: 448.1832; found: 448.1835.

*Procedure for the preparation of $[(\eta^6-C_6H_6)Ru(C_{10}H_6-2-CH_2NH_2)CH_3CN]^+PF_6^-$ (**31**):*

Naphthalen-1-ylmethanamine (157 mg, 1.0 mmol) was dissolved in MeCN (5 mL) and benzene ruthenium(II) chloride dimer (276 mg, 0.5 mmol) was added. Next, NaOH (40 mg, 1.0 mmol) and excess KPF_6 (386 mg, 2.1 mmol) was added to the mixture. The mixture was left to stir for 4 h at 45 °C. The resulting suspension was filtered, washed with hexane and dried under vacuum to afford yellowish brown solid. This solid was redissolved in MeCN, filtered over neutral Al_2O_3 , using MeCN as eluent. A yellow fraction was collected and concentrated in vacuo. The resulting yellow residue was dissolved in minimum of CH_2Cl_2 and upon adding few drops of hexene, a yellow precipitate was obtained (209 mg, 40% yield). Anal. Calcd for $C_{19}H_{19}N_2RuPF_6$: C, 43.7; H, 3.7; N, 5.4. Found: C, 43.2; H, 3.7; N, 5.3. 1H NMR (500 MHz, CD_3CN): δ 8.04 (d, 1H, $^3J_{H-H} = 8.15$ Hz, *H2*), 7.80 (d, 1H, $^3J_{H-H} = 7.20$ Hz, Ar), 7.56 (m, 2H, Ar), 7.39 (m, 1H, Ar), 7.32 (m, 1H, Ar), 5.63 (s, 6H, $\eta^6-C_6H_6$), 5.22 (br s, 1H, *N-H*), 4.55 (m, 1H, *C-H*), 4.09 (m, 1H, *C-H*), 3.84 (br s,

1H, N-H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CD_3CN): δ 164.2 (C1), 141.5, 137.9, 131.3, 128.7, 128.2, 125.6, 125.1, 123.4, 123.2, 86.7 ($\eta^6\text{-C}_6\text{H}_6$), 52.7 (CH_2). ESI $^+$ -MS: m/z 376.79 $[\text{M} - \text{PF}_6]^+$.

Typical Procedure for the Ruthenacycle-Catalyzed β -alkylation of Secondary Alcohols with Primary Alcohols :

The primary alcohol (1.0 mmol), secondary alcohol (1.0 mmol), NaO^tBu (1.0 mmol), ruthenium catalyst (1.0 mol%) and toluene (0.3 mL) were placed in a 10 mL argon-filled, sealed Schlenk tube and allowed to reflux at 110 $^\circ\text{C}$ for 17 h. The internal standard, 1,3,5-trimethoxybenzene, was added and dissolved in the mixture. The reaction mixture was then filtered through celite. The solvent was removed on a rotary evaporator to give the respective alcohol. The conversion was determined by ^1H NMR spectroscopy.

Procedure for the Ruthenacycle-Catalyzed β -alkylation of Secondary Alcohols with Primary Alcohols:

1,3-diphenyl-2-propenone (1.0 mmol), NaO^tBu (1.0 mmol), ruthenium catalyst **18** (1.0 mol%) and $^i\text{PrOH}$ (2.0 mL) were placed in a 10 mL argon-filled sealed Schlenk tube and allowed to reflux at 82 $^\circ\text{C}$ for 17 h. The internal standard, 1,3,5-trimethoxybenzene, was added and dissolved in the mixture. The mixture was then filtered through celite. The solvent was removed on a rotary evaporator to give the respective alcohol. The conversion was determined by ^1H NMR spectroscopy.

X-ray Diffraction Studies. X-ray-quality single crystals of compounds **18** and **29** were obtained by the slow diffusion method at $-30\text{ }^\circ\text{C}$. Yellow diffraction-quality crystals of **18** and **29** were obtained by slow diffusion of diethyl ether into MeCN solution after three days. Crystallographic data were collected on a Bruker X8 Kappa CCD diffractometer at 173 K using

graphite-monochromated Mo K α radiation ($\lambda = 0.71063$ Å). The APEX2 software suite was used for data acquisition, structure solution and refinement. Absorption corrections were applied using SAD-ABS.³⁸ The structures were solved by direct methods and refined by full-matrix least-squares on F^2 using SHELXTL-97.³⁹

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Chapter 4. Enantioselective P-H Additions to Substituted Methyldene Malonate esters and Ferrocenyl enones

4.1 Introduction

Development of methodologies to synthesize enantiomerically pure phosphines have continued to attract considerable interest by virtue of the fact that they have contributed greatly to the development of asymmetric catalysis.¹ Progress in the development of new transition-metal catalysts for enantioselective reactions, especially asymmetric hydrogenations, hydrosilylations, allylic substitutions and other C-C bond formations depends to a very large extent on the availability of new chiral phosphine ligands.² Among these phosphine ligands, optically pure tertiary phosphines have emerged as extremely versatile due to their proven ability to form highly active and selective complexes with late-transition metals. For example, during the development of optically pure phosphines for asymmetric transformations, several ligands such as CHIRAPHOS,³ BICP,⁴ BINAP,⁵ DIPAMP,⁶ JOSIPHOS,⁷ have been proven to be highly enantioselective in organic synthetic scenarios (Figure 21).

Figure 21

In the area of organophosphorus chemistry, specifically in the field of new phosphine moieties, the addition of P-H bond to unsaturated substrates assumes enormous significance in terms of synthetic value as well as atom economy. However, due to the lack of a natural chiral pool, lack of efficient chiral resolution methods and the inherent configurational instability of phosphorus stereocenters (especially at the elevated temperatures often required in their synthetic protocols), the direct synthesis of chiral tertiary phosphines have posed considerable challenges to scientists working in this area. Asymmetric addition of the P-H moiety across a double bond have therefore become a potentially effective, albeit enormously challenging, synthetic strategy for the preparation of chiral phosphines for potential applications in asymmetric synthesis and biological studies.⁸ However, compared with the wide application of chiral phosphines, the synthesis methodology of asymmetric hydrophosphination is rather rare, especially techniques that can directly generate tertiary phosphines and not their borane or sulfur adducts which require further manipulation prior to metal chelation.⁹ Therefore, more efforts in developing new methodologies and catalysts for catalytic asymmetric synthesis of chiral tertiary phosphines is highly desirable.

Leung *et al.* had previously disclosed the extensive utilization of stoichiometric amounts of a chiral palladacycle (*R/S*)-**15** and its derivatives towards the synthesis of a wide range of chiral tertiary phosphine ligand motifs *via* cycloaddition, hydroamination, hydrophosphination, and hydroarsination reactions.¹⁰ Recently, their use has also been extended to the catalytic asymmetric hydrophosphination of aromatic enones thus directly generating chiral keto functionalized tertiary phosphines in good yields and enantioselectivities (Scheme 50, 51).¹¹ Notable work by other research groups in this field also includes: Pt⁰-(Me-Duphos) and Pt⁰-(diphos) catalyzed hydrophosphination of activated olefins (Scheme 65);^{9a-b,12} organocatalyst catalyzed

hydrophosphination of nitroalkenes (Scheme 66)¹³ and α,β -unsaturated aldehydes¹⁴ and chiral P,C,P and P,C,N pincer complex catalyzed hydrophosphination of enones and α,β -*N*-acylpyrroles generating phosphine oxides (Scheme 47, 67).¹⁵

Scheme 65.

Scheme 66.

Scheme 67.

As seen from the aforementioned, asymmetric P-H addition leading to the direct enantioselective/diastereoselective formation of optically active tertiary phosphines is a field that is still in a developmental stage and has enormous scope for improvement. It is thus imperative that in the near future even more types of enantiomerically pure tertiary phosphines incorporating a wide range of functionality will be accessed *via* the asymmetric hydrophosphination reaction.

4.2. The investigation of P-H addition to Substituted Methylidenemalonate Esters.

4.2.1. Introduction

As aforementioned, functionalized stereogenic phosphines are widely utilized as efficacious ligands towards a range of metal catalyzed industrially relevant asymmetric transformations such as hydrogenations, cross coupling reactions and hydroformylations. However the synthetic protocol adopted often relied on the use of stoichiometric amounts of promoters or resolving agents. Metal-catalyzed asymmetric hydrophosphination of unsaturated functionalized substrates offers an alternative atom-efficient protocol for accessing these compounds. However, catalytic asymmetric hydrophosphination of substrates other than those carrying cyano, keto, nitro, aldehyde and pyrrole functionalities has been absent in literature except for the few instances wherein ester functionalized phosphine products were obtained in very low ee's.^{9a-b, 12} This is indeed a drawback when considering the vast range of functionalities tolerated in traditional methods and the critical role functionalities play in the potential use of these targetted compounds in catalysis and biological applications.

In this section, the palladacycle promoted asymmetric P-H addition of ester functionalized unsaturated moieties and the results from studies which involve the first instance in literature of a catalytic addition of secondary phosphines to esters leading to the efficient generation of the corresponding chiral tertiary phosphines in good yields and high enantioselectivities will be presented.

4.2.2. Results and Discussion

The three palladacycles chosen for this study (Figure 22) were prepared by treating their corresponding chloro-bridged dimeric palladium compounds¹⁶ with silver perchlorate in acetonitrile *via* a reported procedure for (*R*)-**16**¹⁷ and (*R*)-**17** and by following a similar protocol to

obtain (*S*)-**32**.^{11a} Over the past decades, these complexes and their derivatives have repeatedly proven their efficacy in asymmetric C-C, C-N, C-P and C-As bond formation scenarios.^{10,18}

Figure 22.

The key structural design feature in these palladacycles from the point of view of asymmetric catalysis is that the organometallic ring is locked into the static δ conformation in solution (for the *R* isomer).¹⁹ This in turn fixes the position of the prochiral NMe/PPh groups into non-equivalent axial and equatorial positions whereby they can control the stereochemistry at the neighbouring coordination sites where reactions occur during catalysis. The different electronic influence of the N and P heteroatoms and the comparatively stronger π -accepting aromatic carbon of the organopalladium ring allows the complex to possess unique molecular recognition ability with respect to incoming substrates.²⁰

The three chosen palladacycles thus provided an opportunity to investigate the effect of variation in key electronic factors (N vs P), steric tuning of substituents on the heteroatom (Me₂ vs Ph₂) and the effect of different moieties at the site adjacent to the Pd-C bond on the aromatic ring (H vs Me) while retaining the key structural features that have made this class of compounds highly effective chiral auxiliaries. With these catalysts in hand, their efficacy in the asymmetric P-H addition to unsaturated esters was explored.

The investigation initially started with the addition of diphenylphosphine to ethyl cinnamate. The reactions were performed under the conditions which have been established from previous studies¹¹ on enones: HPPH₂ (1 equiv.), ethyl cinnamate (1 equiv.), NEt₃ (1 equiv.) and with the

presence of 5 mol% of (*R*)-**16**, (*R*)-**17** and (*S*)-**32**, respectively. Unfortunately, all three complexes failed to generate any monophosphine product even after 2 weeks at room temperature. The reaction of diethyl allylmalonate with diphenylphosphine also did not proceed under similar conditions.

The adequate activation of the C=C bond by adjacent electron withdrawing moieties has been established to be a key factor which aids such P-H addition protocols using metal complexes. It was evident from initial results that the activation in these two instances does not meet the requirements for a metal catalyzed P-H addition across the C=C bond. Leung *et al.* have previously reported that this class of cyclopalladated complexes can indeed recognize the subtle electronic differences between the keto and ester functional groups. For instance, they activate the C=C bonds in vinyl ketones efficiently towards cycloaddition reactions²¹ but provide only poor activation to the C=C bonds in acrylates (Scheme 68).²² Therefore, the addition of diphenylphosphine to diethyl benzylidenemalonate (**33a**) was next examined. With this diester substituted substrate, the hydrophosphination proceeded in a facile manner requiring only 1.5 hours for full product conversion at room temperature (Table 12, entry 1). The ³¹P{¹H} NMR spectrum of the product in CDCl₃ displayed a singlet at δ 2.7 indicating a highly regioselective addition.

Scheme 68.

An efficient procedure for the analysis of ee of tertiary phosphines has been previously reported^{11a} and this protocol (Scheme 69) was adopted to determine the ee of 63% for the asymmetric P-H bond addition to diethyl phenylmethylene malonate (Table 12, entry 1). It needs to be noted that the use of this procedure also offered a chance to obtain single crystals of the adducts of the tertiary phosphines on the palladacycle thus allowing the assignment of absolute stereochemistry from x-ray diffraction data (Figure 23). In current case, the absolute configuration of the major product is determined to be *S*.

Scheme 69.

Figure 23. Molecular structure and absolute stereochemistry of the tertiary phosphine **34a** (major isomer) coordinated to the palladacycle complex (Scheme 69) with 50% probability thermal ellipsoids shown (Cl atom on Pd replaced with I to aid in crystallization).

Table 12. Screening of reaction conditions.^a

Entry	Cat	Solvent	Base	Temp(°C)	Reactivity (hrs)	Conversion ^b (%)	ee ^c (%)
1	(<i>R</i>)- 17	DCM	NEt ₃	RT	1.5	99	63
2	(<i>R</i>)- 17	DCM	NEt ₃	-80	3.5	99	96
3	(<i>S</i>)- 32	DCM	NEt ₃	-80	24	99	65
4	(<i>R</i>)- 16	DCM	NEt ₃	-80	7	99	86
5	(<i>S</i>)- 17	DCM	NEt ₃	-80	3.5	99	96
6	(<i>R</i>)- 17	DCM	NEt ₃	-40	2.5	99	93
7	(<i>R</i>)- 17	Acetone	NEt ₃	-80	> 6	99	95
8	(<i>R</i>)- 17	MeCN	NEt ₃	-40	4	99	81
9	(<i>R</i>)- 17	Chloroform	NEt ₃	-40	24	99	85
10	(<i>R</i>)- 17	THF	NEt ₃	-80	NIL	NIL	NIL
11	(<i>R</i>)- 17	1, 4-dioxane : Water = 10 : 1	NEt ₃	RT	10	83	18
12	(<i>R</i>)- 17	Toluene	NEt ₃	-80	> 24	NIL	NIL
13	(<i>R</i>)- 17	DCM	DBU	-80	24	35	--
14	(<i>R</i>)- 17	DCM	<i>t</i> -BuONa ^d	-40	5.5	99	36

^a Conditions: HPPH₂ (50.0 mg, 2.69 x 10⁻⁴ mol), 5 mol % Cat, 1.2 equiv diethyl benzylidenemalonate (80.2 mg, 3.23 x 10⁻⁴ mol), 1 equiv Base (2.69 x 10⁻⁴ mol), 6 mL of specified solvent were reacted at indicated temperature. ^b Conversion was calculated from ³¹P{¹H} NMR. ^c ee was determined from ³¹P{¹H} NMR integration of the respective signals *via* the use of a chiral derivatizing agent. ^d Solid *t*-BuONa was used.

The asymmetric hydrophosphination reaction of diethyl benzylidenemalonate was then screened as a model reaction in order to examine the effect of the palladacycles as catalysts. The results showed that the palladacycle complex (*R*)-**17** was the most effective among the three

(Table 12, entries 2 to 5) and was thus selected as the catalyst. The reaction when performed in the presence of 5 mol% **17** generated the desired product in 99% yield with 96% ee (Table 12, entries 2 and 5) within 3.5 hrs at -80 °C. It was seen that the change of catalyst from (*R*)-**17** to its equally accessible enantiomeric counterpart (*S*)-**17** resulted in the generation of the opposite enantiomeric form of the tertiary phosphine product in exactly the same ee (Table 12, entries 2 and 5). Besides providing definitive evidence of the influence of the chiral catalyst in stereocontrol, this experiment also provides access to both enantiomers of the product in high optical purity.

Under the optimum conditions mentioned above, with (*R*)-**17** as the catalyst, effect of varying solvents, temperatures and bases were also subsequently examined (Table 12, entries 6-14). Dichloromethane uniformly gave the highest conversions (99%) and ee values (36-96%) (Table 12, entries 1-2 and 5-6). Although similar selectivity was observed with acetone as solvent (Table 12, entry 7), it was accompanied by a concomitant decrease of reactivity. Appreciable selectivities were also recorded with acetonitrile and chloroform but these were not comparable with those obtained using dichloromethane as solvent (Table 12, entries 8-9). No desired phosphine product was obtained when the hydrophosphination was carried out in THF (Table 12, entry 10) and extremely poor reactivity was observed with toluene (Table 12, entry 12) and poor selectivity was attained with 1, 4-dioxane : water = 10 : 1 (Table 12, entry 11). The results of screening of bases showed that Et₃N offered the most appropriate basicity, compared with ^tBuONa which was associated with a low ee (36%) and DBU which caused lowering of reactivity (Table 12, entries 13-14). Noticeably, in the absence of base, no product formation was observed even after 1 week at room temperature. A variety of temperatures were also examined using dichloromethane as solvent. The analysis (Table 12, entries 1-2 and 6) revealed a general trend: an increase in

temperature leads to an increase in reactivity, coinciding with a decrease in enantioselectivity. When the temperature was increased from -80 to -40 °C, the reaction time decreased by 1 hour with an slight decrease of ee (3%). When the temperature was raised from -40 °C to room temperature, the reaction time again decreased by 1 hour, but a marked 30% drop in ee was observed.

With the optimized conditions established i.e., (*R*)-**17** as the catalyst, dichloromethane as solvent and with NEt₃ as base at -80 °C, various substituted methylenemalonate esters were subsequently screened and the results are summarized in Table 13. The catalyst is highly efficient for the P-H addition process (99% conversion; Table 13, entries a–f) allowing the transformation of substrates to the corresponding C-chiral monophosphine adducts (ee value 66–99%; Table 13, entries e–f). The substituents at the β -position of the substituted methylenemalonate esters also had a large influence on the ee value of the products. Substrates bearing aromatic phenyl group and with substituted phenyl group showed higher stereoselectivities (ee: 96, 99%; Table 13, entries a and e) than their aliphatic counterparts (ee: 74, 66% ; Table 13, entries b and c).

Interestingly, the asymmetric hydrophosphination of diethyl cinnamylidenemalonate (Table 13, entry f) also proceeded with excellent regio- and enantio-selectivities. Diphenylphosphide addition occurred exclusively at the more electron deficient C=C bond yielding a vinyl phosphine adduct with an ee value of > 99%. Addition of 2 equivalents of diphenylphosphine to the substrate under similar conditions also resulted in the generation of the same monophosphine product with no trace of diphosphines observed in the crude ³¹P{¹H} NMR spectrum. Substrates bearing furan-2-yl heterocyclic beta-substituent also showed a rather high reactivity and stereoselectivity (ee, 94%, Table 13, entry d). The lack of reactivity seen in the case of diethyl 2-(aminomethylene)malonate

(Table 13, entry g) is attributed to the potential chelation impeding the availability of catalyst vacant sites in the catalyst (*vide infra*).

Table 13. Substrate scope for the phosphapalladacycle catalyzed P-H addition of diphenylphosphine to substituted methylidenemalonate esters.^a

Entry	R	Conversion ^b (%)	ee ^c (%)
a	Ph	99	96
b	OEt	99	74
c	Me	99	ca. 66
d	2-furyl	99	94
e	4-MeOC ₆ H ₄	99	ca. 99
f	(<i>E</i> -)PhCH=CH	99	>99
g	NH ₂	NIL	NIL

^a Conditions: HPPH₂ (50.0 mg, 2.69 x 10⁻⁴ mol), 5 mol % Cat (*R*)-**17** (8.4 mg, 1.34 x 10⁻⁵ mol, 5 mol% of HPPH₂), 1.2 equiv malonate ester (3.23 x 10⁻⁴ mol), 1 equiv NEt₃ (27.1 mg, 2.69 x 10⁻⁴ mol), 6 mL of degassed DCM were reacted at -80 °C. ^b Conversion was calculated from ³¹P{¹H} NMR. ^c ee was determined from ³¹P{¹H} NMR integration of the respective signals *via* the use of a chiral derivatizing agent.

The possible mechanism in place for such metal catalyzed hydrophosphination scenarios using palladacycles has been discussed previously.¹¹ A similar mechanism is proposed for this particular synthetic scenario (Scheme 70). However the screening of the three palladacycles in this study provided further insights into the key catalyst design features which are of consequence in the catalytic cycle. For instance, the hindered reactivity of (*S*)-**32** when compared to (*R/S*)-**17** (Table 12, entries 2, 3 and 5) is a clear indication that the presence of the Me group at the site adjacent to the Pd-C bond on the aromatic ring in (*S*)-**32** prevents the easy accessibility of the bulky

phosphine moieties involved to the electronically preferred coordination site (*trans* to the P of the palladacycle).²⁰ It needs to be noted that the coordination of diphenylphosphine to palladium and the subsequent P-H activation is crucial in generating the nucleophile prior to the P-C bond formation as shown in Scheme 70.

Scheme 70.

The enhanced reactivity observed for the phosphapalladacycle (*R*)-**17** when compared to the naphthylamine based palladacycle (*R*)-**16** (Table 12, entries 2, 4 and 5) can also be attributed to the fact that the phosphorus of the metallacycle ring (by virtue of its ability to accommodate extensive back donation from the metal centre) makes the activation of the diphenylphosphine moiety and its subsequent nucleophilic attack on the diester more facile. The relatively slower reactivity of the C,N complex (*R*)-**16** can also be attributed to the fact that *trans* N-Pd-P bonds are more stable than the *trans* P-Pd-P bonds. Thus the product elimination process will be appreciably slower when (*R*)-**16** is employed. The enhanced stereoselectivity exhibited by (*R*)-**17** and (*S*)-**32**

can also be attributed to the fact that the conformational rigidity of the palladacycle fixes the positions of the phenyl groups on P (as compared to Me on (*R*)-**16**) into axial and equatorial positions from wherein they can project their greater stereochemical influence on the adjacent reaction site where the hydrophosphination occurs.

Based on the same mechanism, it is also easy to understand why diethyl 2-(aminomethylene)malonate failed to undergo the P-H addition (Table 13, entry g). The product from the initial hydrophosphination reaction in this instance will be a P,N (N from the amino moiety) chelate on palladium which can then potentially block the access of both catalytic sites on the metal to incoming substrates by chelation thus effectively terminating the reaction once the 5% of catalyst is rendered inactive via chelation.

4.3. Investigation on the Asymmetric P-H Additions to Ferrocenyl enones – Direct Synthesis of Monophosphino ferrocenes (MOPF`s)

4.3.1. Introduction

The most significant feature of the sandwich complex, ferrocene, is the planar chirality. Associated with this special design other chiralities such as central and axial could be incorporated in a catalyst derived from a ferrocenyl ligand. In this regard, multifunctional derivatives of this metallocene are particularly valuable for the asymmetric catalysis.

Chiral phosphines attract increasing interest as ligands in transition metal complexes used in enantioselective synthesis and catalysis. The syntheses of chiral phosphines usually involve expensive procedures, including the use of chiral auxiliaries or resolution from racemic mixtures.

In the past decade, the asymmetric hydrophosphination process emerged as another effective approach.⁸

However, as for the synthesis of chiral ferrocenyl phosphine ligands, they are mainly depended on the chiral auxiliary: Ugi's amine.²³ For example, starting with Ugi's chiral amine, Hayashi *et al.* prepared a series of chiral (aminoalkylferrocenyl)phosphine ligands, which have been used successfully for the asymmetric hydrosilylation, hydrogenation, and Grignard cross-coupling reactions (Scheme 71).²⁴ Recently, Manoury *et al.* reported a set of chiral ferrocenyl phosphine ligands which can be used in asymmetric allylic substitution reaction (Scheme 72).²⁵ Cheung *et al.* also applied Ugi's amine as starting material to synthesize a series of ligands which was successfully used in the allylic alkylation of indole (Scheme 73).²⁶ In the 90s, a new method produced by Kagan *et al.* came out as an alternative approach (Scheme 74).²⁷ They started with ferrocene and were able to prepare a new family of aryl-monophosphino ferrocene ligands (aryl-MOPF) which have been used by Johannsen *et al.* in the palladium catalyzed asymmetric hydrosilylation and Suzuki-Miyaura reactions.²⁸ Other novel methods have also shown their abilities, including in solid supported asymmetric catalysis by grafting onto silica supports and attaching to dendrimer.²⁹ Although successful results were achieved in these catalytic studies of the new ferrocenyl phosphine ligands, the synthesis of such chiral ferrocenyl phosphine ligands is still very challenging.

Scheme 71.

Scheme 72.

Scheme 73.

Scheme 74.

Research is continuing in the hope of finding more efficient and facile methods to synthesize from achiral sources these useful chiral ferrocenyl phosphine ligands. The following section involves investigations into the palladacycle promoted asymmetric P-H addition of ferrocene functionalized unsaturated moieties in the absence of an pre-existing chiral centers. The results from primary studies which involves the first instance in literature of catalytic addition of secondary phosphines to α,β -unsaturated ferrocene leading to the efficient generation of the chiral ferrocenyl tertiary phosphines in good yields and high enantioselectivities will be shown.

4.3.2. Results and Discussion

Having established a protocol for the hydrophosphination as seen from the previous section, synthesis of MOPF ligands from achiral substrates was attempted. Such a direct generation of MOPF has not been attempted before.

Initially, the P-H addition of diphenylphosphine to **35a** was investigated. The reactions were performed in the presence of 5 mol% of (*S*)-**16** and 1 equiv. of NEt₃ and monitored by ³¹P{¹H} NMR spectroscopy. After some investigations, when the reaction was performed in DCM at room temperature, ee values up to 60% were obtained with the full conversion of HPPH₂ (Table 14, entry 1). Subsequently the conditions for the asymmetric hydrophosphination of furan ferrocenyl chalcones were screened as a model reaction and the results are given in Table 14. During the process of examination of solvent and temperature effect, interestingly, it was found that the solubility of the phosphine product was very poor in MeOH and it would precipitate out of the reaction solution after its formation. This is a key point which would enhance the reactivity and improve ee value drastically when the reactions were conducted in MeOH (Table 14, entries 1, 4, 7-9). Furthermore this allows an excellent procedure by which the enantiopure product could be harvested directly from the reaction pot. The ee increased slightly from 70% at room temperature to 75% at -80 °C (Table 14, entries 3 and 4). The catalyst loading had little effect on reactivity, but impacts the selectivity (Table 14, entries 4 and 6). Complex **17** as catalyst was also attempted to conduct the asymmetric synthesis of ferrocene derivatives. However, the stereoselectivity of product was very poor.

With optimum conditions established, a range of ferrocenyl chalcones were screened for the asymmetric hydrophosphination reaction. The results are presented in Table 15, which indicates

that the substituents on the substrates influence the reactivity and selectivity. Substrates bearing aromatic moiety show higher selectivities than the non-aromatic substrates (Table 15, entries 1-5

Table 14. Screening of reaction conditions.^a

Entry	Cat. loading(%)	Solvent	Temp (°C)	Reactivity	Conversion ^b (%)	ee ^c (%)
1	5	DCM	RT	12h	>99	60
2	5	DCM	-40	1d	>99	71
3	10	DCM	-80	5d	>99	84
4	5	MeOH	RT	3h	>99	70(58) ^d
5	5	MeOH	-80	4d	>99	75(63) ^d
6	10	MeOH	RT	2h	>99	99(65) ^d
7	5	THF	RT	7d	NIL	--
8	5	Acetone	RT	7d	50	--
9	5	Acetonitrile	RT	7d	Trace	--

^a Conditions: HPPH₂ (50.0 mg, 2.69 x 10⁻⁴ mol), Cat (*R*)-**16**, **35a** (82.3mg, 2.69 x 10⁻⁴ mol), NEt₃ (27.1 mg, 2.69 x 10⁻⁴ mol), 4 mL of specified solvent were reacted at given temperature. ^b Conversion was calculated from ³¹P{¹H} NMR. ^c ee was determined from ³¹P{¹H} NMR integration of the respective signals *via* the use of a chiral derivatizing agent. ^d In parentheses are the ee's of all products.

vs 6). In particular, substrate bearing furan ring shows ee value up to 99% even at RT (Table 15,

entry 1). This room temperature reaction is thus in stark contrast to the hydrophosphination of diesters discussed previously wherein low temperature conditions are required in order to maintain enantioselectivity. As expected, when the reaction is performed at lower temperature the enantioselectivity increased (Table 15, entry 2 vs 3) and with substrates bearing electron donating groups the selectivity decreased (Table 15, entry 2 vs 4). Substrate bearing NO₂ group is not stable under the reaction condition and no hydrophosphination reaction was observed (entry 5).

Table 15. Substrate scope for the palladacycle catalyzed P-H addition of diphenylphosphine to α, β -unsaturated ferrocenyl chalcones.^a

Entry	R	Temperature	Conversion ^b (%)	ee ^c (%)
1		RT	>99	99
2	Ph	RT	>99	60
3	Ph	-40	>99	71
4	<i>p</i> -(OMe)C ₆ H ₄	RT	>99	49
5	<i>p</i> -(NO ₂)C ₆ H ₄	RT	NIL	--
6	Me	RT	>99	30

^a Conditions: HPPH₂ (50.0 mg, 2.69 x 10⁻⁴ mol), Cat (*R*)-**16** (10 mol%), **35** (2.69 x 10⁻⁴ mol, 1 equiv. of HPPH₂), NEt₃ (27.1 mg, 2.69 x 10⁻⁴ mol), 4 mL of MeOH were reacted at room temperature. ^b Conversion was calculated from ³¹P{¹H} NMR. ^c ee after a crystallization and was determined from ³¹P{¹H} NMR integration of the respective signals *via* the use of a chiral derivatizing agent.

The mechanism in place for this particular hydrophosphination is expected to follow the same mechanism discussed for the malonate esters in the previous section. It was however surprising that the enantioselectivity of the nucleophilic addition process could be maintained even at room temperature unlike in the case of the malonate diester. The steric and conformational rigidity of the ferrocenyl system is expected to play a critical role in this. At the point of writing of this dissertation work is progressing on the development of more variants and their screening for various catalytic processes of interest. It is expected that this protocol could provide a new methodology for the synthesis of not only monophosphino ferrocenes but also could be expanded in the future to bis-phosphines. Coordination of such species to metal centers could lead to the generation of not only diphosphine metal complexes of interest but also to cyclometallated systems (*via* cyclometallation of the synthesised MOPF's) which could have potential as catalysts.

4.4 Conclusion

In summary, an efficient protocol for the palladacycle catalyzed asymmetric P-H additions to substituted methyldene malonate esters and ferrocenyl chalcones was demonstrated. This approach thus provides a practical direct route towards two new classes of optical pure functionalised tertiary chiral phosphines in high yields and enantioselectivities, circumventing the need for elaborate protection and deprotection protocols as well as avoiding the need to deal with phosphine oxides which can in some instances lead to complications.¹⁸ This body of work has also provided insights into the factors which need to be considered when designing catalysts for such asymmetric P-H additions.

4.5. Experimental Detail

General information

All reactions and manipulations were carried out under dry, oxygen-free nitrogen using the standard Schlenk technique. NMR spectra were recorded on a Bruker AV 300 spectrometer (^1H at 300 MHz, ^{13}C at 75 MHz, ^{31}P at 121 MHz) or a Bruker AV 400 (^1H at 400 MHz, ^{13}C at 100 MHz, ^{31}P at 162 MHz) or a Bruker AV 500 (^1H at 500 MHz, ^{13}C at 125 MHz, ^{31}P at 202 MHz). Chemical shift are given in ppm and are referenced to residual solvent peak in the respective deuterio-solvents. (^1H NMR and ^{13}C NMR) or to an 85% H_3PO_4 in D_2O externally (^{31}P NMR). Solvents were degassed prior to use when necessary. DCM, toluene, THF and acetone were purchased from TEDIA COMPANY (AR) and used as supplied. Low Temp PAIRSTIRRER PSL-1800 machine was used for controlling low temperatures for reactions. Column chromatography was conducted on Silica gel 60 (Merck). Optical rotations of the free phosphine products were measured as soon as possible without inert gas protection on the specified solution in a 0.1 dm cell at 20 °C with a Perkin-Elmer 341 polarimeter.

The three palladacycles catalysts (*R/S*)-**16**, (*R*)-**17**, and (*S*)-**32** were prepared by treating the corresponding chloro-bridged dimeric palladium compounds³⁰ with silver perchlorate in acetonitrile *via* a procedure reported previously for (*R*)-**16**³¹ and (*R*)-**17**.^{11a} The ferrocenyl enones were prepared according to the literature.³² All the other reactants and reagents were used as supplied.

Typical procedure for synthesis of monophosphines via hydrophosphination of substituted methyldene malonate esters:

Catalyst (*R*)-**17** (8.4 mg, 1.34×10^{-5} mol, 5 mol % of HPPH_2) was added to a degassed DCM solution (2 mL) of HPPH_2 (50.0 mg, 2.69×10^{-4} mol). The light yellow mixture was stirred at room

temperature for 10 mins and then cooled to -80 °C. Subsequently, substrate (3.22×10^{-4} mol, 1.2 equivalents of HPPPh₂) and NEt₃ (27.1 mg, 2.69×10^{-4} mol, 1 equivalent of HPPPh₂) were each dissolved in 2 mL of degassed solvent and added dropwise. The hydrophosphination reaction was monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR. Upon completion, the reaction mixture was warmed to room temperature and solvent evaporated by vacuum. The yellowish–orange monophosphine product was re-dissolved in degassed DCM (5 mL) and filtered through a short silica gel column (packed with degassed *n*–hexane) on a two-neck Schlenk flask protected by N₂. The solvent was removed by vacuum pump to give the enantio-enriched phosphine product ($\pm$)**34**.

Determination of ee:

Enantiomeric excess (ee %) were measured by $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the corresponding compounds. The obtained phosphine product ($\pm$)**34** was dissolved in DCM (3 mL) and added 0.51 equiv (a little excess) of enantio-pure (*R*)-**15**. After stirring for 30 min at RT, the solvent was evaporated and the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum recorded. ee value was evaluated by integration of the corresponding products.

Compound **33a** was reacted with HPPPh₂ at -80 °C for 3.5 h according to the general procedure to provide ($\pm$)**34a** (99% conversion, 96% ee) (air-sensitive): $[\alpha]_{\text{D}} = -82.8$ (*c* 1.3, DCM). ^{31}P NMR (CDCl₃, 121 MHz): δ 2.7; ^1H NMR (CDCl₃, 400 MHz): δ 7.64-7.59 (m, 2H, Ar), 7.35-7.31 (m, 3H, Ar), 7.23-7.11 (m, 5H, Ar), 7.05-7.03 (m, 3H, Ar), 6.99-6.96 (m, 2H, Ar), 4.40 (dd, 1H, *J* = 10.76, 3.42 Hz, CH(COOEt)₂), 3.94 (dd, 1H, *J* = 10.76, 7.10 Hz, Ph₂PCH), 3.91-3.84 (m, 3H, COOCH₂CH₃), 3.78-3.70 (m, 1H, COOCH₂CH₃), 1.15 (t, 3H, *J* = 7.24 Hz, CH₂CH₃), 0.92 (t, 3H,

$J = 7.24$ Hz, CH_2CH_3); ^{13}C NMR (CDCl_3 , 75 MHz): δ 167.9 (1C, COOEt), 167.5 (1C, COOEt), 134.7-126.5 (18 C, Ar), 61.5 (1C, CH_2CH_3), 61.3 (1C, CH_2CH_3), 56.2 (d, 1C, $J_{\text{PC}} = 27.03$ Hz, PPh_2CH), 44.2 (d, 1C, $J_{\text{PC}} = 19.57$ Hz, $\text{CH}(\text{CO}_2\text{Et})_2$), 13.8 (1C, CH_2CH_3), 13.7 (1C, CH_2CH_3).

Compound **33b** was reacted with HPPH_2 at -80 °C for 8h according to the general procedure to provide ($\pm$)-**34b** (99% conversion, 74% ee) (air-sensitive): $[\alpha]_{\text{D}} = -90.7$ (c 0.4, DCM). ^{31}P NMR (CDCl_3 , 121 MHz): δ -2.6; ^1H NMR (CDCl_3 , 300 MHz): δ 7.83-7.78 (m, 2H, Ar), 7.52-7.48 (m, 2H, Ar), 7.43-7.41 (m, 3H, Ar), 7.34-7.32 (m, 3H, Ar), 4.87 (dd, 1H, $J = 9.6, 6.9$ Hz, PPh_2CH), 4.19 (q, 2H, $J = 6.9$ Hz, $\text{COOCH}_2\text{CH}_3$), 4.10 (qd, 2H, $J = 7.2, 2.1$ Hz, $\text{COOCH}_2\text{CH}_3$), 3.66 (dd, 1H, $J = 9.9, 6.6$ Hz, $\text{CH}(\text{COOEt})_2$), 3.47 (m, 1H, OCH_2CH_3), 3.03 (m, 1H, OCH_2CH_3), 1.30-1.21 (m, 6H, $\text{COOCH}_2\text{CH}_3$), 0.90 (t, 3H, OCH_2CH_3); ^{13}C NMR (CDCl_3 , 75 MHz): δ 167.5 (1C, $\text{COOCH}_2\text{CH}_3$), 167.0 (1C, $\text{COOCH}_2\text{CH}_3$), 135.6-128.2 (12C, Ar), 80.4 (d, 1C, $J_{\text{PC}} = 20.3$ Hz, PPh_2CH), 69.3 (1C, OCH_2CH_3), 61.5 (2C, $\text{COOCH}_2\text{CH}_3$), 56.9 (d, 1C, $J_{\text{PC}} = 22.5$ Hz, $\text{CH}(\text{CO}_2\text{Et})_2$), 15.1 (1C, OCH_2CH_3), 14.0 (1C, $\text{COOCH}_2\text{CH}_3$), 13.9 (1C, $\text{COOCH}_2\text{CH}_3$).

Compound **33c** was reacted with HPPH_2 at -80 °C for 4h according to the general procedure to provide ($\pm$)-**34c** (99% conversion, 66% ee) (air-sensitive): $[\alpha]_{\text{D}} = -50.2$ (c 0.3, DCM). ^{31}P NMR (CDCl_3 , 202 MHz): δ -3.8; ^1H NMR (CDCl_3 , 500 MHz): δ 7.55-7.49 (m, 4H, Ar), 7.37-7.32 (m, 6H, Ar), 4.20 (qd, 2H, $J = 7.4, 1.0$ Hz $\text{COOCH}_2\text{CH}_3$), 4.14-4.06 (m, 2H, $\text{COOCH}_2\text{CH}_3$), 3.32 (t, 1H, $J = 7.0$ Hz, $\text{CH}(\text{OEt})_2$), 3.20-3.14 (m, 1H, PPh_2CH), 1.27 (t, 3H, $J = 7.2$ Hz, $\text{COOCH}_2\text{CH}_3$), 1.24 (t, 3H, $J = 7.2$ Hz, $\text{COOCH}_2\text{CH}_3$), 1.10 (dd, 3H, $J = 7.0$ Hz, $\text{PPh}_2\text{CHCH}_3$); ^{13}C NMR (CDCl_3 , 125 MHz): δ 168.7 (d, 1C, $J_{\text{PC}} = 7.4$ Hz, COOEt), 168.2 (d, 1C, $J_{\text{PC}} = 9.1$ Hz, COOEt),

134.4-128.4 (m, 12C, Ar), 61.5 (1C, CH₂CH₃), 61.3 (1C, CH₂CH₃), 54.5 (d, 1C, J_{PC} = 21.1 Hz, CH(COOEt)₂), 30.5 (d, 1C, J_{PC} = 14.8 Hz, PPh₂CH), 14.1 (1C, CH₃), 14.0 (1C, CH₃), 13.9 (1C, CH₃).

Compound **33d** was reacted with HPPH₂ at -80 °C for 4h according to the general procedure to provide (±)**34d** (99% conversion, 94% ee) (air-sensitive): [α]_D = -120.7 (*c* 0.6, DCM). ³¹P NMR (CDCl₃, 202 MHz): δ 1.5; ¹H NMR (CDCl₃, 500 MHz): δ 7.57-7.54 (m, 2H, Ar), 7.38-7.32 (m, 3H, Ar), 7.32-7.28 (m, 1H, Ar), 7.23-7.16 (m, 4H, Ar), 7.07 (d, 1H, J = 1.0 Hz, C₅H), 6.08 (q, 1H, C₄H), 5.76 (d, 1H, J = 3.2 Hz C₃H), 4.51 (d, 1H, J = 10.6 Hz, CH(OEt)₂), 4.09-4.02 (m, 4H, COOCH₂CH₃), 3.80 (dd, 1H, J = 10.6, 6.3 Hz, PPh₂CH), 1.24 (t, 3H, J = 7.3 Hz, COOCH₂CH₃), 1.08 (t, 3H, J = 7.5 Hz, COOCH₂CH₃); ¹³C NMR (CDCl₃, 125 MHz): δ 167.7 (1C, COOEt), 167.4 (1C, COOEt), 151.2 (1C, C₂), 140.8 (1C, C₅), 134.6-128.0 (m, 12C, Ar), 110.3 (1C, C₄), 107.4 (d, 1C, J = 2.5 Hz, C₃), 61.8 (1C, CH₂CH₃), 61.5 (1C, CH₂CH₃), 54.5 (d, 1C, J_{PC} = 27.5 Hz, PPh₂CH), 38.3 (d, 1C, J_{PC} = 22.0 Hz, CH(COOEt)₂), 14.0 (1C, COOCH₂CH₃), 13.9 (1C, COOCH₂CH₃).

Compound **33e** was reacted with HPPH₂ at -80 °C for 8h according to the general procedure to provide (±)**34e** (99% conversion, >99% ee) (air-sensitive): [α]_D = -92.9 (*c* 0.7, DCM). ³¹P NMR (CDCl₃, 202 MHz): δ 1.2; ¹H NMR (CDCl₃, 500 MHz): δ 7.61-7.58 (m, 2H, Ar), 7.34-7.31 (m, 3H, Ar), 7.20-7.15 (m, 5H, Ar), 6.92 (d, 2H, J = 8.5 Hz, C₁H), 6.61 (d, 2H, J = 8.5 Hz, C₂H), 4.29 (q, 1H, CH(OEt)₂), 3.89-3.85 (m, 4H, COOCH₂CH₃), 3.76-3.71 (m, 1H, PPh₂CH), 1.24 (t, 3H, J = 7.3 Hz, COOCH₂CH₃), 1.08 (t, 3H, J = 7.5 Hz, COOCH₂CH₃); ¹³C NMR (CDCl₃, 125 MHz): δ 168.0 (1C, COOEt), 167.5 (1C, COOEt), 158.0 (1C, C₃), 134.6-128.0 (m, 15C, Ar), 113.2 (2C,

C₂), 61.6 (1C, CH₂CH₃), 61.3 (1C, CH₂CH₃), 56.3 (d, 1C, J_{PC} = 26.9 Hz, PPh₂CH), 55.1 (1C, OCH₃), 43.3 (d, 1C, J_{PC} = 19.0 Hz, CH(COOEt)₂), 13.9 (1C, COOCH₂CH₃), 13.8 (1C, COOCH₂CH₃).

Compound **33f** was reacted with HPPPh₂ at -80 °C for 4h according to the general procedure to provide (±)**34f** (99% conversion, >99% ee) (air-sensitive): $[\alpha]_D = -160.9$ (c 1.7, DCM). ³¹P NMR (CDCl₃, 121 MHz): δ 0.2; ¹H NMR (CDCl₃, 300 MHz): δ 7.60-7.51 (m, 4H, Ar), 7.40-7.32 (m, 6H, Ar), 7.28-7.12 (m, 5H, Ar), 6.23 (d, 1H, J = 8.5 Hz, PhCH), 6.02-5.92 (m, 1H, PhCH=CH), 4.24-4.10 (m, 4H, COOCH₂CH₃), 3.91 (t, 1H, J = 9.7 Hz, CH(OEt)₂), 3.61-3.55 (dd, 1H, J = 6.7, 2.9 Hz, PPh₂CH), 1.30 (t, 3H, J = 7.1 Hz, COOCH₂CH₃), 1.18 (t, 3H, J = 7.1 Hz, COOCH₂CH₃); ¹³C NMR (CDCl₃, 75 MHz): δ 168.0 (d, 1C, J = 4.2 Hz, COOEt), 167.7 (d, 1C, J = 13.2 Hz, COOEt), 137.0-1226.1 (m, 20C, Ar, CH=CH), 61.7 (1C, CH₂CH₃), 61.4 (1C, CH₂CH₃), 54.5 (d, 1C, J_{PC} = 24.9 Hz, PPh₂CH), 42.0 (d, 1C, J_{PC} = 19.3 Hz, CH(COOEt)₂), 14.1 (2C, CH₃).

General procedure for synthesis of monophosphines via hydrophosphination of ferrocenyl enones:

Catalyst (*S*)-**16** (13.1 mg, 2.69 x 10⁻⁵ mol, 10 mol % of HPPPh₂) was added to a degassed MeOH solution (2 mL) of HPPPh₂ (50.0 mg, 2.69 x 10⁻⁴ mol). The light yellow mixture was stirred at room temperature for 10 mins. Subsequently, substrate (2.69 x 10⁻⁴ mol, 1 equivalent of HPPPh₂) was added and then NEt₃ (27.1 mg, 2.69 x 10⁻⁴ mol, 1 equivalent of HPPPh₂) which was dissolved in 2 mL of MeOH was added drop-wise. The resulting mixture was allowed to stir at room temperature and monitored by ³¹P{¹H} NMR. Upon the reaction finished, the solution was syphoned out *via* a

cannula and the residue was washed with minimum MeOH to give reddish solids of the enantio-enriched phosphine product ($\pm$)**36**.

36a: Compound **35a** was reacted with HPPH₂ at RT for 2.5 h according to the general procedure to provide ($\pm$)**36a** (99% conversion, >99% ee, 38% isolated yield) (air-sensitive): [α]_D = -126 (*c* 0.3, DCM). ³¹P NMR (CD₂Cl₂, 162 MHz): δ 6.0; ¹H NMR (CD₂Cl₂, 400 MHz): δ 7.61 (s, 1H, *H*1), 7.46-7.45 (m, 2H, Ar), 7.34-7.25 (m, 8H, Ar), 7.15 (d, 1H, *J* = 3.36 Hz, *H*3), 6.54 (m, 1H, *H*2), 4.19 (m, 1H, *CH*PPH₂), 4.00 (s, 6H, Cp), 3.94 (s, 1H, Cp), 3.83 (s, 1H, Cp), 3.67 (s, 1H, Cp), 3.50-3.41 (m, 1H, *CH*₂), 3.22-3.15 (m, 1H, *CH*₂); ¹³C NMR (CD₂Cl₂, 100 MHz): δ 187.3 (d, 1C, *J* = 5.3 Hz, CO), 152.8 (1C, C1), 134.6 (Ar), 134.4 (Ar), 133.5 (Ar), 133.3 (Ar), 129.0 (Ar), 128.6 (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 127.9 (Ar), 117.0 (1C, C3), 112.2 (1C, C2), 90.6 (d, 1C, *J* = 12.6 Hz, C4), 68.8 (d, 1C, *J* = 3.2 Hz, Cp), 68.5 (5C, Cp), 67.2 (1C, Cp), 67.0 (1C, Cp), 66.8 (1C, Cp), 41.4 (d, 1C, *J* = 19.8 Hz, PPh₂CH), 32.3 (d, 1C, *J* = 15.9 Hz, *CH*₂).

36b: Compound **35b** was reacted with HPPH₂ at RT for 3h according to the general procedure to provide ($\pm$)**36b** (99% conversion, 60% ee, 52% isolated yield) (air-sensitive): [α]_D = 100.9 (*c* 1.7, DCM). ³¹P NMR (CD₂Cl₂, 162 MHz): δ 6.1; ¹H NMR (CD₂Cl₂, 400 MHz): δ 7.95 (s, 1H, *H*1), 7.93 (s, 1H, *H*1), 7.60-7.56 (m, 1H, *H*3), 7.50-7.45 (m, 4H, Ar), 7.33-7.25 (m, 8H, Ar), 4.29 (m, 1H, *CH*PPH₂), 4.01 (s, 1H, Cp), 4.00 (s, 5H, Cp), 3.94 (s, 1H, Cp), 3.85 (s, 1H, Cp), 3.70 (s, 1H, Cp), 3.69-3.61 (m, 1H, *CH*₂), 3.39-3.33 (m, 1H, *CH*₂); ¹³C NMR (CD₂Cl₂, 100 MHz): δ 197.97 (d, 1C, *J* = 5.2 Hz, CO), 134.6 (Ar), 134.4 (Ar), 133.5 (Ar), 133.3 (Ar), 133.0 (Ar), 129.0 (Ar), 128.6 (Ar), 128.6 (Ar), 128.2 (Ar), 128.2 (Ar), 128.0 (Ar), 127.9 (Ar), 127.9 (Ar), 91.0 (d, 1C, *J* = 12.4

Hz, C4), 69.0 (d, 1C, $J = 2.8$ Hz, Cp), 68.5 (5C, Cp), 67.3 (1C, Cp), 67.0 (1C, Cp), 66.8 (1C, Cp), 41.9 (d, 1C, $J = 20.2$ Hz, PPh₂CH), 31.9 (d, 1C, $J = 15.3$ Hz, CH₂).

36c: Compound **35c** was reacted with HPPH₂ at RT for 3h according to the general procedure to provide (±)**36c** (99% conversion, 60% ee, 45% isolated yield) (air-sensitive): $[\alpha]_D = 92.3$ (c 1.4, DCM). ³¹P NMR (CD₂Cl₂, 162 MHz): δ 6.1; ¹H NMR (CD₂Cl₂, 400 MHz): δ 7.85 (s, 1H, *H*1), 7.84 (s, 1H, *H*1), 7.48 (m, 2H, *H*2), 7.33-7.26 (m, 10H, Ar), 4.27 (m, 1H, CHPPH₂), 4.00 (s, 1H, Cp), 3.97 (s, 5H, Cp), 3.92 (s, 1H, Cp), 3.83 (s, 1H, Cp), 3.67 (s, 1H, Cp), 3.61-3.52 (m, 1H, CH₂), 3.39-3.27 (m, 1H, CH₂); ¹³C NMR (CD₂Cl₂, 100 MHz): δ 197.97 (d, 1C, $J = 5.2$ Hz, CO), 134.6 (Ar), 134.4 (Ar), 133.5 (Ar), 133.3 (Ar), 133.0 (Ar), 129.0 (Ar), 128.6 (Ar), 128.6 (Ar), 128.2 (Ar), 128.2 (Ar), 128.0 (Ar), 127.9 (Ar), 127.9 (Ar), 91.0 (d, 1C, $J = 12.4$ Hz, C4), 69.0 (d, 1C, $J = 2.8$ Hz, Cp), 68.5 (5C, Cp), 67.3 (1C, Cp), 67.0 (1C, Cp), 66.8 (1C, Cp), 41.9 (d, 1C, $J = 20.2$ Hz, PPh₂CH), 31.9 (d, 1C, $J = 15.3$ Hz, CH₂).

36d: Compound **35d** was reacted with HPPH₂ at RT for 3h according to the general procedure. However, there was no precipitate formed during the reaction. Upon completion, the solvent was evaporated by vacuum. The reddish monophosphine product residue was re-dissolved in degassed DCM (5 mL) and filtered through a short silica gel column (packed with degassed *n*-hexane) on a two-neck Schlenk flask protected by N₂. The solvent of the filtrate was removed by vacuum pump to give the enantio-enriched phosphine product (±)**36d** (99% conversion, 30% ee) (air-sensitive): $[\alpha]_D = 72.3$ (c 1.0, DCM). ³¹P NMR (CD₂Cl₂, 202 MHz): δ 6.2; ¹H NMR (CD₂Cl₂, 500 MHz): δ 7.49-7.42 (m, 2H, Ar), 7.35-7.28 (m, 8H, Ar), 4.19 (m, 1H, CHPPH₂), 4.08 (s, 5H, Cp), 4.02 (s, 1H, Cp), 3.96 (s, 1H, Cp), 3.77 (s, 1H, Cp), 3.70 (s, 1H, Cp), 3.14-3.06 (m, 1H, CH₂), 2.88-2.83 (m,

^1H , CH_2); ^{13}C NMR (CD_2Cl_2 , 125 MHz): δ 206.3 (d, 1C, $J = 4.5$ Hz, CO), 134.7 (Ar), 134.5 (Ar), 133.6 (Ar), 133.5 (Ar), 129.1 (Ar), 128.7 (Ar), 128.3 (Ar), 128.2 (Ar), 128.0 (Ar), 128.0 (Ar), 68.8 (d, 1C, $J = 2.8$ Hz, Cp), 68.5 (5C, Cp), 67.3 (1C, Cp), 67.1 (1C, Cp), 66.8 (d, 1C, Cp), 46.9 (d, 1C, $J = 19.6$ Hz, CHPhPh_2), 31.9 (d, 1C, $J = 15.6$ Hz, CH_2), 30.3 (Me).

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List of Publications

1. Chiral Phosphapalladacycles as Efficient Catalysts for the Asymmetric Hydrophosphination of Substituted Methylidenemalonate Esters: Direct Access to Functionalized Tertiary Chiral Phosphines
C. Xu, G. J. H. Kennard, F. Hennersdorf, S. A. Pullarkat*, and P. H. Leung*, *Organometallics*, **2012**, *31*, 3022-3026.
2. Domino Cyclization-Alkylation Protocol for the Synthesis of 2,3-functionalized Indoles from o-alkynylanilines and Allylic Alcohols
C. Xu, V. Kumar and S. A. Pullarkat* *Org. Biomol. Chem.*, **2012**, *10*, 3875-3881.
3. Ruthenacycles as efficient catalysts for the beta-alkylation of secondary alcohols with primary alcohols,
C. Xu, W. C. Low, Y. Li and S. A. Pullarkat* *Tet. Lett.*, **2012**, 1450-1455.
4. New Thioether-dithiolate Complexes of Cp*Ir and some reactivity features
C. Xu, L. Y. Goh* and S. A. Pullarkat* *J. Organomet. Chem.*, **2012**, *26*, 4207-4214.
5. An Ir-thioether-dithiolate Catalyst for low catalyst loading Beta-alkylation and selective imine formation via N-Alkylations Reactions.
C. Xu, Y. Li, L. Y. Goh* and S. A. Pullarkat* *Organometallics*, **2011**, *30*, 6499-6502.
6. Bis(allyl)ruthenium(IV)-initiated S-S and C-S Bond Cleavages in Tetraalkylthiuram Sulfides: Formation and X-ray Crystal structures of Dithiocarbamate Complexes,
C. Xu, S. A. Pullarkat* and L. Y. Goh* *Aus. J. Chem.*, **2009**, *62*, 1537-1543.

Appendices

Table A1. Crystal data and structure refinement for **18**.

Empirical formula	C ₁₅ H ₁₇ F ₆ N ₂ P Ru
Formula weight	471.35
Temperature	103(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 9.4228(3) Å α = 90°. b = 11.2805(3) Å β = 90°. c = 16.3228(4) Å γ = 90°.
Volume	1735.01(8) Å ³
Z	4
Density (calculated)	1.804 Mg/m ³
Absorption coefficient	1.056 mm ⁻¹
F(000)	936
Crystal size	0.20 x 0.20 x 0.10 mm ³
Theta range for data collection	2.19 to 39.05°.
Index ranges	-16<=h<=16, -19<=k<=20, -22<=l<=28
Reflections collected	39486
Independent reflections	9777 [R(int) = 0.0535]
Completeness to theta = 39.05°	99.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9017 and 0.8165
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	9777 / 0 / 227
Goodness-of-fit on F ²	1.047
Final R indices [I>2sigma(I)]	R1 = 0.0387, wR2 = 0.0808
R indices (all data)	R1 = 0.0505, wR2 = 0.0890
Largest diff. peak and hole	1.401 and -0.530 e.Å ⁻³

Table A2. Crystal data and structure refinement for **29**.

Empirical formula	C ₁₆ H ₁₉ F ₆ N ₂ P Ru	
Formula weight	485.37	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 12.0517(3) Å	$\alpha = 90^\circ$.
	b = 8.9742(2) Å	$\beta = 90^\circ$.
	c = 16.3595(4) Å	$\gamma = 90^\circ$.
Volume	1769.35(7) Å ³	
Z	4	
Density (calculated)	1.822 Mg/m ³	
Absorption coefficient	1.039 mm ⁻¹	
F(000)	968	
Crystal size	0.42 x 0.40 x 0.40 mm ³	
Theta range for data collection	2.59 to 40.11°.	
Index ranges	-21 ≤ h ≤ 20, -16 ≤ k ≤ 11, -20 ≤ l ≤ 29	
Reflections collected	23664	
Independent reflections	9211 [R(int) = 0.0200]	
Completeness to theta = 40.11°	98.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.6814 and 0.6695	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	9211 / 1 / 241	
Goodness-of-fit on F ²	1.037	
Final R indices [I > 2σ(I)]	R1 = 0.0245, wR2 = 0.0617	
R indices (all data)	R1 = 0.0280, wR2 = 0.0637	
Absolute structure parameter	0.045(16)	
Largest diff. peak and hole	1.269 and -1.574 e.Å ⁻³	

Table A3. Crystal data and structure refinement for **34a** palladacycle adduct.

Empirical formula	C ₄₀ H ₄₃ I N O ₄ P Pd	
Formula weight	866.02	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.6549(7) Å	α = 90°.
	b = 13.8040(10) Å	β = 90°.
	c = 28.1935(19) Å	γ = 90°.
Volume	3757.5(5) Å ³	
Z	4	
Density (calculated)	1.531 Mg/m ³	
Absorption coefficient	1.398 mm ⁻¹	
F(000)	1744	
Crystal size	0.40 x 0.04 x 0.04 mm ³	
Theta range for data collection	1.64 to 29.62°.	
Index ranges	-12 ≤ h ≤ 13, -18 ≤ k ≤ 14, -31 ≤ l ≤ 37	
Reflections collected	21296	
Independent reflections	8971 [R(int) = 0.0781]	
Completeness to theta = 25.00°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9462 and 0.6047	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	8971 / 0 / 438	
Goodness-of-fit on F ²	1.006	
Final R indices [I > 2σ(I)]	R1 = 0.0557, wR2 = 0.1120	
R indices (all data)	R1 = 0.1074, wR2 = 0.1495	
Absolute structure parameter	-0.03(3)	
Largest diff. peak and hole	0.937 and -1.806 e.Å ⁻³	