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MECHANISM AND LIGAND DESIGN IN RUTHENIUM CATALYSIS

By

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ABSTRACT

The known ruthenium pincer complex RuCl(η³-dcpx)(PPh₃) (7) (PCP = η³-2,6-(PCy₂CH₂)₂C₆H₃) was transformed into several different hydride products under standard transfer hydrogenation conditions. In situ ³¹P NMR analysis during thermolysis of 7 in basic isopropanol permitted identification of RuH(η³-dcpx)(PPh₃)(N₂) (8a/b), RuH(η³-dcpx)(PPh₃) (10), and RuH(η³-dcpx)(PPh₃)(H₂) (9a/b). A spectrscopically unobservable species, Ru(H)₂[η²-PC(H)P] (12), is proposed as the active species in transfer hydrogenation catalysis. The novel precatalyst, RuCl(η³-dcpx)(py)₂ (14), which may provide a more active catalyst, was synthesized and characterized.

Routes were explored to chelating monoanionic ligands containing a pyrrole group functionalized with N-heterocyclic carbene donors. The imidazolium salts were synthesized and characterized by NMR, IR, and mass spectrometry. Attempts to make transition metal complexes of these ligands were unsuccessful due to facile isomerization under the basic conditions required to form the free carbenes, and oxidation of the ligands in the presence of ruthenium(II), silver(I), and palladium(II) precursors.

Several primary and secondary phosphine complexes of ruthenium were synthesized and tested for their activity in catalytic transfer hydrogenation. Of these, only the bulky HPCy₂ ligand in RuCl₂(HPCy₂)₄ (18a/b) provided high catalytic activity. Reaction of RuCl₂(PCy₃)₂(=CHPh) (24) with HPCy₂ transforms it cleanly to 18a, potentially opening new opportunities in tandem catalysis.
# TABLE OF CONTENTS

ABSTRACT ........................................................................................................... ii  
LIST OF ABBREVIATIONS .................................................................................. v  
ACKNOWLEDGEMENTS ...................................................................................... viii  
PUBLICATION FROM THESIS WORK ................................................................ iv

CHAPTER 1 ........................................................................................................... 1  
1.1. Homogeneous Catalysis ............................................................................ 1  
1.2. Pincer Complexes ..................................................................................... 2  
1.3. Transfer Hydrogenation ............................................................................ 3  
1.4. Scope of This Thesis ................................................................................ 4  
1.5. References ................................................................................................. 5

CHAPTER 2 ........................................................................................................... 6  
2.1. Materials and Methods ............................................................................ 6  
2.2. Experimental Procedures for Chapter 3 .................................................. 8  
2.3. Experimental Procedures for Chapter 4 .................................................. 13  
2.4. Experimental Procedures for Chapter 5 .................................................. 15  
2.5. References ................................................................................................. 18

CHAPTER 3 ........................................................................................................... 19  
3.1. Introduction ............................................................................................... 20  
3.2. Synthesis of RuCl(η₃-dcpp)(PPh₃) (7) ......................................................... 24  
3.3. Transfer Hydrogenation by RuCl(η₃-dcpp)(PPh₃) (7) ............................... 25  
3.4. In Situ NMR Experiments Under Catalytic Conditions ......................... 29  
3.6. Mechanistic-Based Design of a New Precatalyst (14) ............................... 40  
3.5. Conclusions ............................................................................................... 41  
3.6. References ................................................................................................. 43

CHAPTER 4 ........................................................................................................... 45  
4.1. Introduction ............................................................................................... 46  
4.2. Synthesis of Imidazolium Ligand Precursors .......................................... 50  
4.3. Conclusions ............................................................................................... 55  
4.4. References ................................................................................................. 56

CHAPTER 5 ........................................................................................................... 57  
5.1. Introduction ............................................................................................... 58  
5.2. Synthesis of Primary and Secondary Phosphine Complexes .................. 61  
5.3. Transfer Hydrogenation Catalysis by \textit{18a/b-23} ..................................... 67  
5.4. Conclusions ............................................................................................... 70  
5.5. References ................................................................................................. 71

CHAPTER 6 ........................................................................................................... 72
LIST OF ABBREVIATIONS

atm atmosphere (1 atm = 760 mmHg, 101.3 kPa, 14.696 psi)

br broad

c- cis

\(^{13}\text{C}(^{1}\text{H})\) proton-decoupled carbon-13 (NMR)

Cy cyclohexyl

d doublet

dcpx 1,3-bis[(dicyclohexylyphosphanyl)-methyl]-benzene

dcpyb 1,4-bis(dicyclohexylyphosphino)butane

DEPT Distortionless Enhancement by Polarization Transfer

DMF N,N-dimethylformamide

dmso dimethylsulfoxide

ESI Electro Spray Ionization (mass spectrometry)

HMBC Heteronuclear Multiple Bond Coherence

HMQC Heteronuclear Multiple Quantum Coherence

Hz Hertz, cycles per second

IMes bis(1,3-(2,4,6-trimethylphenyl)imidazol-2-ylidene

IR Infrared

\(J\) coupling constant, in Hz

L ligand

LAH lithium aluminum hydride
\( \lambda \) wavelength

M central metal atom in a complex

m multiplet (NMR)

\( m \) meta

NN' 2-[(2,6-diisopropylphenyl)imino]pyrrolide

NHC N-heterocyclic carbene

NMR Nuclear Magnetic Resonance

\( o \) ortho

\(^{31}\text{P}(^1\text{H})\) proton-decoupled phosphorus-31 (NMR)

PP chelating ditertiary phosphine ligand

py pyridine

pyr pyrrole

q quartet (NMR)

RT room temperature

s singlet (NMR)

t triplet (NMR)

\( \text{tert} , , ^{1} \) tertiary

\( t \) trans

THF tetrahydrofuran

TOF mol substrate x mol catalyst\(^{-1}\) x h\(^{-1}\)

\( T_{1} \) longitudinal relaxation time (NMR)

XRD X-Ray Diffraction
$\delta$ chemical shift (in ppm)

$\nu$ frequency (in cm$^{-1}$)

$\eta$ hapticity

$\mu$ bridging
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PUBLICATION FROM THESIS WORK

1.1. Homogeneous Catalysis.

Homogeneous ruthenium catalysts promote a wide range of transformations\textsuperscript{1} useful in the fine chemicals industry. These successes in various catalytic transformations are partly due to new ligand designs, resulting in increased activity and selectivity in catalysis enough so as to make it more economically viable.\textsuperscript{2-4} Basic phosphines and N-heterocyclic carbenes have been reported to have an activating effect on two important ruthenium catalyzed reactions in the fine chemicals industry, hydrogenation\textsuperscript{5} and metathesis.\textsuperscript{6} Our group and others have reported that the metal center can be switched between the two forms of catalysis by changing the active site from an alkylidene to a hydride, while retaining the same basic phosphine or NHC donors.\textsuperscript{7-9} This has allowed for tandem catalysis applications for these two transformations, such that the ruthenium catalyst may be used in a more economical and convenient fashion.

Insights into the solution chemistry of a catalytic system from in situ observation have proven invaluable in homogeneous catalysis. In the context of hydrogenation chemistry, the work of Halpern\textsuperscript{10} in the mechanism elucidation of rhodium catalyzed hydrogenation of olefins with bidentate phosphines has demonstrated the utility of increasing our understanding of a specific catalytic
system, as it provides a rational working hypothesis to understand and further improve a system.

1.2. Pincer Complexes.

Chelating ligands help define the active site of a metal center, thus allowing greater selectivity while also inhibiting deactivation processes.\textsuperscript{11} The tremendous interest in organometallic complexes containing pincer ligands (Figure 1.1) (a recent search reveals 634 Chemical Abstracts entries for articles containing “pincer” in the title, including 57 entries for both “ruthenium” and “pincer” in the title) has been driven in large part by the potential of such species in catalysis.\textsuperscript{12-17}

![Figure 1.1. PCP pincer class of ligand on metal.](image)

Pincer ligands are bound $\eta^3$ to a transition metal usually in a planar meridional fashion, in which the two neutral donors are located trans to each other and cis to a metal-carbon bond. This bonding motif is thought to stabilize metal complexes, and has been employed extensively in catalysis. Such complexes exhibit versatile catalytic activity in transfer hydrogenation, alkane
dehydrogenation, atom-transfer radical polymerization (ATRP), ring-opening metathesis polymerization (ROMP), and oxidative coupling of arenes with alkenes.\textsuperscript{12-14,17-20}

Most of the PCP systems reported to date have used aryl-phosphine ligands.\textsuperscript{12} Bulky alkyl-phosphine pincers could expand opportunities for tuning activity and selectivity of the metal center, and possibly even incorporating two consecutive mechanistically different tandem processes, such as olefin metathesis followed by transfer hydrogenation. A further more ambitious goal lies in the introduction of chirality into the pincer ligand to provide enantioselectivity for both processes.

1.3. Transfer Hydrogenation.

Transfer hydrogenation\textsuperscript{21} is a very attractive form of catalysis to employ in a reduction when compared to direct hydrogenation, due to the convenient use of ordinary glassware instead of high-pressure bombs and flammable gasses. This is usually carried out in an alcohol solvent as the reducing agent, instead of using H\textsubscript{2} gas (Figure 1.2). The disadvantages of transfer hydrogenation with alcohols are that it requires a large excess of solvent relative to the substrate to drive the reaction to completion, since there is no strong thermodynamic driving force and it is a reversible, equilibrium process. Such a high substrate dilution can lower the rate of catalysis. The major advantage in direct hydrogenation over transfer
hydrogenation is that the reaction is highly exothermic and will therefore go to completion more readily, eliminating the need for excess solvent.

![Chemical structure](image)

**Figure 1.2.** Transfer hydrogenation catalysis.

1.4. The Scope of This Thesis.

This thesis describes three main areas of investigation. Chapter 3 discusses the mechanistic investigation of known ruthenium pincer complexes in transfer hydrogenation, revealing new insights into the underlying transformations under catalytic conditions. Chapter 4 is describes the synthesis of new pincer ligands based on pyrrolide chelated to basic N-heterocyclic carbenes. Finally, Chapter 5 discusses the results of catalytic investigations of ruthenium complexes of secondary phosphines in transfer hydrogenation catalysis, and the underlying inorganic chemistry involved.
References

CHAPTER 2

Experimental Procedures

2.1. Materials and Methods.

2.1.1. Solvents.

Reagent grade toluene, hexanes, diethyl ether and tetrahydrofuran (BDH) were dried and degassed using an Anhydrous Engineering solvent purification system. Other solvents were refluxed over and distilled from an appropriate drying agent under an atmosphere of N\textsubscript{2}; benzene over sodium benzophenone ketyl; pentane over sodium; dichloromethane, isopropanol, and pyridine over calcium hydride; methanol over Mg/l\textsubscript{2}. All solvents (with the exception of methanol and isopropanol) were stored over Linde 4 Å molecular sieves under an atmosphere of N\textsubscript{2}. Deuterated solvents (CDCl\textsubscript{3}, C\textsubscript{6}D\textsubscript{6}, C\textsubscript{7}D\textsubscript{8}, THF-d\textsubscript{8}, and D\textsubscript{2}O) were obtained from Cambridge Isotope Laboratories Ltd. CDCl\textsubscript{3} was refluxed over and distilled from Drierite under an atmosphere of N\textsubscript{2}. C\textsubscript{6}D\textsubscript{6} was deoxygenated by consecutive freeze/pump/thaw cycles and stored over Linde 4 Å molecular sieves. All other deuterated solvents were used as received, in ampoule form.

2.1.2. Gases.

Hydrogen (Praxair UHP grade) and argon (Research Grade) were passed through a Drierite column before use.
2.1.3. Phosphines.

Phenylphosphine, diphenylphosphine, triphenylphosphine, and dicyclohexylphosphine (Strem) were used as received. All phosphines, with the exception of PPh₃, were stored under N₂.

2.1.4. Other Materials.

Benzophenone, potassium hydride, copper(I) chloride, HCl (2.0 M in Et₂O), and potassium tri(sec-butyl)borohydride (1.0 M in Et₂O) were purchased from Aldrich and used as received. Triethylamine (Aldrich) was distilled from CaSO₄ and stored under N₂. Hydrated RuCl₃ (38-43% Ru) and the Grubbs catalyst, RuCl₂(PCy₃)₂(=CHPh) (24), were obtained from Strem Chemicals and used as received. RuCl₂(PPh₃)₃ (1),¹ RuHCl(PPh₃)₃ (2),² 1,3-(Cy₂PCH₂)₂C₆H₄ (dcpx),³ RuCl(η²-dcpx)(PPh₃) (7),⁴ RuH(η²-dcpx)(PPh₃)(N₂) (8a/b),⁵ RuH(η²-dcpx)(PPh₃)(H₂) (9a/b),⁵ RuCl₂(HPCy₂)₄ (18a/b),⁶ RuCl₂(HPPh₂)₄ (19a/b),⁶ RuCl₂(H₂PPh)₄ (20a/b),⁶ and pyrrole ligand precursors⁷ were prepared as previously described.

2.1.5. Instrumentation.

Infrared spectra were recorded on a Bomem MB100 IR spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 300 (300 MHz for ¹H, 121 MHz for ³¹P, 75 MHz for ¹³C, 282 MHz for ¹⁹F) or a Bruker AMX-500 (500 MHz for ¹H, 202 MHz for ³¹P, 125 MHz for ¹³C) FT-NMR
spectrometer. For $^1$H and $^{13}$C NMR spectra, the residual proton and carbon signals of the deuterated solvent were used as internal standards. $^{31}$P NMR spectra were referenced externally against PPh$_3$ ($\delta_p -5.06$, C$_6$D$_6$: -5.46, CDCl$_3$: -4.80, 2:1 isopropanol:C$_2$D$_6$): shifts are reported relative to 85% H$_3$PO$_4$. Downfield shifts are taken as positive for all nuclei. Variable temperature NMR spectra and 2D experiments (HMQC, HMBC, EXSY) were carried out on the Bruker Avance 300 or the Bruker AMX-500 instrument. Mass spectrometric analyses were performed by the Ottawa-Carleton Mass Spectrometry Centre. Gas chromatography data were obtained with an Agilent GC (6890N) instrument.

2.1.6. Laboratory Techniques.

Unless otherwise stated, all inorganic reactions containing ruthenium were carried out at room temperature (RT, $\sim$22 °C) under N$_2$, using standard Schlenk or drybox techniques. Organic manipulations, other than those involving phosphine reagents, were carried out in air. All pyrrole compounds were stored cold (-19 °C) and protected from light.

2.2. Experimental Procedures for Chapter 3.

2.2.1. RuCl($\eta^3$-dcpx)(PPh$_3$)$_3$ (7): NMR-Scale.

(a) In the original report,$^4$ 7 was prepared by reaction of RuCl$_2$(PPh$_3$)$_3$ (1) with dcpx in toluene, in the presence of one equivalent of NEt$_3$. In this modification, no base was added. A mixture of RuCl$_2$(PPh$_3$)$_3$ (20 mg, 0.021 mmol)
and dcpx (10 mg, 0.021 mmol) in 1 mL toluene was stirred for 1 h, over which
time it turned dark green. Quantitative conversion to 7 was confirmed by $^{31}$P($^1$H)
NMR analysis.\(^4\text{,}^5\)

(b) In a further modification, RuHCl(PPh$_3$)$_3$ (2) was used as precursor in
place of 1. A mixture of 2 (20 mg, 0.022 mmol) and dcpx (10 mg, 0.022 mmol) in
1 mL C$_6$D$_6$ was stirred for 1 h. The solution turned dark green immediately.
Quantitative conversion to 7 was confirmed by NMR analysis. $^{31}$P($^1$H) NMR
(C$_6$D$_6$): \(\delta\) 80.9 (t, Ru-PPPh$_3$, $^2$J$_{pp} = 32$ Hz), 37.5 (d, Ru-PCy$_2$, $^2$J$_{pp} = 32$ Hz), –5.06
(s, PPh$_3$).\(^4\text{,}^5\)

2.2.2. Conditions for in situ NMR experiment under catalytic conditions.

A solution of 7·PPh$_3$ (7 mg, 0.006 mmol) in 0.3 mL C$_7$D$_6$ was mixed with a
solution of KO'Bu (13 mg, 0.012 mmol) in 0.6 mL isopropanol and heated at 82
°C under N$_2$. The solution was monitored by $^{31}$P NMR spectroscopy over three
days. Species present: (a) Before addition of base, RT: 7. (b) 10 minutes after
addition of base, RT: 8a/b. (c) After 10 minutes pretreatment; spectrum at 80 °C:
6. (d) After 1 h pretreatment; spectrum at RT: 8a/b and 9a/b (ratio of 8:9 = 99:1).
(e) After 3 days at 80 °C; spectrum at RT: 8a/b. $^{31}$P($^1$H) NMR (2:1 C$_7$D$_6$:
isopropanol). For 7: \(\delta\) 81.2 (t, Ru-PPPh$_3$, $^2$J$_{pp} = 32$ Hz), 37.0 (d, Ru-PCy$_2$, $^2$J$_{pp} = 32$
Hz). For 8a: \(\delta\) 60.5 (br, Ru-PCy$_2$), 45.6 (t, Ru-PPPh$_3$, $^2$J$_{pp} = 17$ Hz). For 8b: 55.5
(br, Ru-PCy$_2$) 29.4 (t, Ru-PPPh$_3$, $^2$J$_{pp} = 14$ Hz). For 9a: \(\delta\) 68.9 (d, Ru-PCy$_2$, $^2$J$_{pp} =
16 Hz), 57.0 (br, Ru-PPh₃). For 9b: δ 71.8 (d, Ru-PC₂, ²J.pp = 15 Hz), 37.8 (br, Ru-PPh₃). For 10 (at 80 °C): δ 63-65 (br, Ru-PC₂), 45.5 (br, Ru-PPh₃).

2.2.3. RuH(η³-dcpx)(PPh₃) (10): NMR-scale.

A pale red solution of 8a/b (10 mg, 0.01 mmol) in 1 mL C₆D₆ was frozen and placed under vacuum, then allowed to thaw under argon. The solution immediately turned deep red, and the spectrum was run within 10 minutes. ³¹P NMR analysis showed 8b and 10 (ratio 1:2). ³¹P{¹H} NMR for 10 (C₆D₆): δ 63-65 (br, Ru-PC₂), 45.3 (t, Ru-PPh₃, ²J.pp = 17 Hz).


A dark green solution of 7•PPh₃ (10 mg, 0.009 mmol) in 1 mL of C₆D₆ was placed under 1 atm of H₂ for 24 h. No colour change was observed, but ³¹P NMR analysis (under H₂) revealed minor signals for 11 in addition to those for 7 (7% 11). ³¹P{¹H} for 11 (C₆D₆): δ 53.6 (d, PC₂, ²J.pp = 16.3 Hz), 23.2 (t, PPh₃, ²J.pp = 16.3 Hz).

2.2.5. K[Ru(H)₄(η³-dcpx)(PPh₃)] (13).

To a pale red solution of 8a/b (25 mg, 0.028 mmol) in C₆D₆ (1 mL) was added KH₆Bu₆ (28 μL of a 1.0 M solution in Et₂O, 0.028 mmol). The solution was stirred at 80 °C for 1 h, over which time a yellow suspension deposited. This was filtered off and dried under vacuum, leaving a colourless supernatant. Yield:
22 mg (90 %). Analysis of the latter showed no signal other than PPh₃. $^{31}P(^1H)$
NMR (protio-THF, unlocked): δ 74.6 (br, $PCy_2$), 67.3 (br, $PPh_3$).

2.2.6. Thermal Displacement of dcpx from 7 with PPh₃ and Base.

Solid 7•PPh₃ (30 mg, 0.031 mmol) dissolved immediately upon addition to
a solution of KO$^t$Bu (70 mg, 0.62 mmol) and PPh₃ (65 mg, 0.248 mmol) in 15 mL
of isopropanol. A colour change to red occurred within minutes. The solution was
heated at 80 °C for 1 h, which resulted in the precipitation of a yellow solid. This
was filtered off and washed with 5 mL hexanes. $^1H$ NMR analysis reveals
complete disappearance of the cyclohexyl signals for dcpx. Three different,
unknown Ru-hydride species are present. $^1H$ NMR ($C_6D_6$): δ 7.5-6.5 (br, ArH, 40
H), -8.52 (m, RuH, 1 H), -10.23 (m, RuH, 1H), -12.76 (br, RuH, 1H). $^{31}P(^1H)$ NMR:
d 57.25 (d, PPh₃, $^2J_{PP} = 16$ Hz, 2P), 50.15 (br, PPh₃, 1P), 44.67 (d, PPh₃, $^2J_{PP} =
16$ Hz, 2P), 42.00 (br, PPh₃, 1P).

2.2.7. RuCl($\eta^3$-dcpx)(py)$_2$ (14).

Solid 7 (100 mg, 0.087 mmol) was stirred in 2 mL of pyridine for 3 h, over
which time the solution changed colour from green to bright orange. The solution
was removed under vacuum to afford an orange oil. Addition of 5 mL of cold
pentane precipitated a bright orange powder, which was then filtered and dried
under vacuum. Yield 54 mg (80%). $^1H$ NMR ($C_6D_6$): δ 11.24 (m, py, o-CH, 2H),
7.92 (m, py, CH, 2H), 7.35 (d, dcpx o-CH, $^2J_{HH} = 7$ Hz, 2H), 7.05 (t, dcpx p-CH,
$^{2}J_{HH} = 7$ Hz, 1H), 6.55 (m, py, CH, 2H), 6.36 (m, py, CH, 2H), 5.87 (m, py, o-CH, 2H), 3.09 (s, PCH$_2$, 4H), 2.80 (br, Cy, 4H), 1.93-0.67 (br, Cy, 40H). $^{31}$P{$^1$H} NMR: δ 42.36 (s, PCy$_3$).

2.2.8. Representative procedure for transfer hydrogenation with 7•PPh$_3$. A catalyst solution of standard concentration was prepared by dissolving 7•PPh$_3$ (234 mg, 0.200 mmol) in 10.0 mL toluene. Likewise, a KOH solution of standard concentration was prepared by dissolving solid KOH (213 mg, 3.80 mmol) in 19.0 mL isopropanol, and a substrate solution of standard concentration by dissolving acetophenone (7.200 g, 0.060 mol) in 51 mL isopropanol. In a routine pretreatment procedure, 100 μL of the catalyst solution was mixed with 200 μL of the base solution, and the mixture was refluxed under N$_2$ for 1.0 hours. A colour change from dark green to red occurred within five minutes. After the pretreatment period, 1.70 mL (0.002 mmol) of the substrate solution was added by syringe. The reaction was monitored for 4 h, with sampling every ten minutes for the first hour, and every 30 minutes thereafter. Conversions were determined by gas chromatography.

2.2.8.1. Effect of Additives. Transfer hydrogenations with 7•PPh$_3$ were carried out as above, adding the freshly prepared catalyst solution to either one equivalent of CuCl (0.2 mg, 0.002 mmol), 8 equivalents of PPh$_3$ (4.2 mg, 0.016 mmol), or 20 equivalents of
N\textsuperscript{4}Bu\textsubscript{4}Cl (6.62 mg, 0.08 mmol). This was followed by pretreatment and addition of substrate solution as above.

2.3. Experimental Procedures for Chapter 4.

2.3.1. 2,5-Bis[(imidazolum)methyl]-pyrrole (15).

2-Iodopropane (2.04 g, 12 mmol) was added to 2,5-bis[(imidazol)methyl]-pyrrole\textsuperscript{8} (1.00 g, 4.09 mmol) in 25 mL of DMF. The mixture was heated for 30 minutes at 70 °C, which resulted in complete conversion to 15 (confirmed by TLC). The solvent was then removed under reduced pressure, and the resulting brown solid was dissolved in 100 mL of distilled water, then filtered through Celite to remove insoluble purple byproducts, leaving a clear, colourless solution. This was added dropwise to a solution of NH\textsubscript{4}PF\textsubscript{6} (1.36 g, 8.4 mmol) in 200 mL of dH\textsubscript{2}O to yield a white precipitate, which was filtered off and washed with dH\textsubscript{2}O (20 mL), then THF (2 x 20 mL). Yield after drying under vacuum 1.8 g (73%). \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}) \(\delta\) 11.32 (t, pyrr-NH, \(J_{\text{HH}}\) = 2.5 Hz, 1H), 9.15 (pseudo-t, imid-H1, \(J_{\text{HH}}\) = 2.5 Hz, 2H), 7.88 (pseudo-t, imid-H3, \(J_{\text{HH}}\) = 2.5 Hz, 2H), 7.65 (pseudo-t, imid-H4, \(J_{\text{HH}}\) = 2.5 Hz, 2H), 6.20 (d, pyrr-H3, \(J_{\text{HH}}\) = 2.5 Hz, 2H), 5.30 (s, CH\textsubscript{2}, 4H), 4.63 (septet, (CH\textsubscript{3})\textsubscript{2}CH, \(J_{\text{HH}}\) = 7 Hz, 2H), 1.45 (d, (CH\textsubscript{3})\textsubscript{2}CH, \(J_{\text{HH}}\) = 7 Hz, 12H). \textsuperscript{13}C\textsuperscript{1}(\textsuperscript{1}H) NMR: \(\delta\) 135.3 (s, imid-C1), 126.5 (s, pyrr-C2), 123.1 (s, imid-C3), 121.5 (s, imid-C4), 110.5 (s, pyrr-C3), 53.2 (s, (CH\textsubscript{3})\textsubscript{2}CH), 46.2 (s, CH\textsubscript{2}), 23.1 (s, CH\textsubscript{3}). IR (Nujol): v(NH) 3389. ESI-MS: \textit{m/z} Calcd for C\textsubscript{18}H\textsubscript{27}F\textsubscript{6}N\textsubscript{6}P (M\textsuperscript{+}) 458; Found 458.
2.3.2. 2,5-Bis[(imidazolium)methyl]-pyrrole (16).

Methyl iodide (1.80 g, 13.0 mmol) was added to a solution of 2,5-bis[(imidazol)methyl]-pyrrole (1.00 g, 4.09 mmol) in 50 mL of THF. The solution was heated to reflux for 3 h, after which conversion to 16 was complete, as judged by TLC analysis. A white precipitate deposited, which was filtered off, washed with THF (2 x 20 mL), and dried under vacuum. Yield 1.9 g (85%). $^1$H NMR (DMSO-d$_6$): $\delta$ 11.33 (t, pyrr-NH, $J_{NH}$ = 2.5 Hz, 1H), 9.07 (pseudo-t, imid-H1, $J_{NH}$ = 3 Hz, 2H), 7.71 (pseudo-t, imid-H4, $J_{NH}$ = 3 Hz, 2H), 7.68 (pseudo-t, imid-H3, $J_{NH}$ = 3 Hz, 2H), 6.20 (d, pyrr-H3, $J_{NH}$ = 2.5 Hz, 2H), 5.34 (s, CH$_2$, 4H), 3.85 (s, CH$_3$, 6H). $^{13}$C($^1$H) NMR: $\delta$ 137.0 (s, imid-C1), 126.5 (s, pyrr-C2), 124.7 (s, imid-C3), 122.9 (s, imid-C4), 110.7 (s, pyrr-C3), 46.1 (s, CH$_2$), 36.9 (s, CH$_3$). IR (Nujol): $\nu$(NH) 3391 cm$^{-1}$. ESI-MS: m/z Calcd for C$_{14}$H$_{21}$N$_5$I (M$^+$) 384; Found 384.

2.3.3. 2-[(Imidazolium)methyl]-pyrrole (17).

2-Iodopropane (1.00 g, 6.00 mmol) was added to a solution of 2[(imidazol)methyl]-pyrrole (0.600 g, 4.00 mmol) in 25 mL DMF. Conversion was complete after heating to 70 °C for 15 min (TLC). The solvent was removed under reduced pressure to afford a brown solid. This was dissolved in 100 mL of distilled water, then filtered through Celite to remove insoluble purple byproducts. Dropwise addition of the filtrate to a solution of sodium tetraphenylborate (1.36 g, 8.4 mmol) in 200 mL dH$_2$O caused a white precipitate to deposit. This precipitate was filtered off and washed with 20 mL of dH$_2$O, then 2 x 20 mL of hexanes. Yield
1.5 g (83%). \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}): \(\delta\) 11.05 (m, pyrr-NH, 1H), 8.97 (pseudo-t, imid-H1, \(J_{\text{HH}}=\) 3 Hz, 1H), 7.17 (m, 7.64 (pseudo-t, imid-H5, \(J_{\text{HH}}=\) 3 Hz, 1H), 7.65 (pseudo-t, imid-H4, \(J_{\text{HH}}=\) 3 Hz, \(J_{\text{HH}}=\) 3 Hz, 1H), 6.20 (d, pyrr-H3, \(J_{\text{HH}}=\) 2.5 Hz, 2H), 5.30 (s, \(CH_2\), 4H), 4.63 (septet, \(CH\), \(J_{\text{HH}}=\) 7 Hz, 1H), 1.45 (d, \(CH_3\), \(J_{\text{HH}}=\) 7 Hz, 6H). \textsuperscript{13}C\textsuperscript{1}(H) NMR: \(\delta\) 135.3 (s, imid), 126.5 (s, pyrr), 123.1 (s, imid), 121.5 (s, pyrr), 53.2 (s, CHMe\textsubscript{2}), 46.2 (s, \(CH_2\)), 23.1 (s, \(CH_3\)). IR (Nujol): v(NH) 3407. ESI-MS: \textit{m/z} Calcd for \(C_{35}H_{38}BN_3\) (M\textsuperscript{+}) 411; Found 411.

2.4. Experimental Procedures for Chapter 5.

2.4.1. RuCl\textsubscript{2}(HPCy\textsubscript{2})\textsubscript{4} (18a or 18b): NMR Scale.

(a) Cis isomer, 18a: In the literature route,\textsuperscript{6} a mixture of the cis and trans isomers (18a and 18b, respectively) was obtained by thermolysis of RuCl\textsubscript{3} and HPCy\textsubscript{2} in methanol. In the present route, the cis isomer was selectively prepared by use of well-defined precursors. Thus, addition of HPCy\textsubscript{2} (13 mg, 0.065 mmol) to a brown suspension of RuCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{3} (15 mg, 0.0156 mmol) in 1 mL C\textsubscript{6}D\textsubscript{6} afforded a clear solution within minutes at room temperature. In situ \textsuperscript{31}P\textsuperscript{1}(H) NMR analysis reveals the characteristic signals for 18a.\textsuperscript{6} \textsuperscript{31}P\textsuperscript{1}(H) NMR (C\textsubscript{6}D\textsubscript{6}): \(\delta\) 51.54 (t, \(\textsuperscript{2}J_{pp} = 27\) Hz), 24.39 (t, \(\textsuperscript{2}J_{pp} = 27\) Hz).

(b) Trans isomer, 18b: In a second modification, 18b was prepared by displacing the ligands from the Grubbs catalyst. Thus, HPCy\textsubscript{2} (22 mg, 0.1 mmol) was added to a purple solution of Grubbs catalyst (15 mg, 0.018 mmol) in 1 mL C\textsubscript{6}D\textsubscript{6} at room temperature. Within 10 minutes, the solution turned clear yellow. In
situ NMR analysis reveals 18b,6 accompanied by singlets for free PCy₃ (11.03 ppm) and P(CH₂Ph)Cy₂ (3.10 ppm), as well as free (excess) HPCy₂ (-26.51 ppm). ³¹P{¹H} NMR (C₆D₆) for 18b: δ 14.56 (s).

2.4.2. RuHCl(HPCy₂)₄ (21).

HPCy₂ (60 mg, 0.3 mmol) was added to a purple suspension of RuHCl(PPh₃)₃ (30 mg, 0.06 mmol) in 1 mL of C₆D₆ to afford a clear, colourless solution within 15 minutes at room temperature. In situ ³¹P{¹H} NMR analysis shows complete reaction. Addition of hexanes precipitated a microcrystalline white powder. Yield 53 mg (95%). ¹H NMR (C₆D₆): δ 4.46 (m, PH, 4H), 3.2-0.8 (br, CyH, 88H), -19.92 (pentet, RuH, ²J_HH = 14 Hz, 1H). ³¹P{¹H} NMR (C₆D₆): δ 35.66 (s, HPCy₂).

2.4.3. RuH₂(HPCy₂)₄ (22).

To a yellow solution of RuCl₂(HPCy₂)₄ 18a/b (30 mg, 0.03 mmol) in THF was added KHBD₅Bu₃ (64 uL of 1M solution in diethyl ether, 0.064 mmol) at room temperature. The solution decolourized within minutes, and in situ ³¹P{¹H} NMR analysis shows complete reaction. Addition of hexanes precipitated a microcrystalline white powder. Yield 25 mg (80%). ³¹P{¹H} NMR (protio-THF, unlocked): δ 50.70 (t, HPCy₂, ²J_pp = 22 Hz), 38.80 (t, HPCy₂, ²J_pp = 22 Hz).
2.4.4. RuCl(η²-dcpx)(H₂PPh₂) (23).

H₂PPh (40 mg, 0.36 mmol) was added to a dark green solution of RuCl(η³-dcpx)(PPh₃) 3 (200 mg, 0.17 mmol) in 3 mL toluene. The solution turned clear yellow within few minutes at room temperature. In situ ³¹P{¹H} NMR analysis shows solely the A₂BC splitting pattern due to 23. Addition of hexanes precipitated a microcrystalline yellow powder. Yield 210 mg (92%). ³¹P{¹H} NMR (C₇H₈, unlocked): δ 52.25 (dd, PCy₂, ²Jₚₚ = 34 Hz, ²Jₚₚ = 20), -15.55 (dt, H₂PPh, ²Jₚₚ = 34 Hz, ²Jₚₚ = 19 Hz), -45.23 (td, H₂PPh, ²Jₚₚ = 19 Hz, ²Jₚₚ = 20 Hz).
References


CHAPTER 3

Mechanistic Insights Into Transfer Hydrogenation involving a Ruthenium-Pincer Ligand Complex

![Chemical Structures and Reactions]

Figure 3.1. Pictorial summary of Chapter 3.

Part of this Chapter has been published:
3.1. Introduction.

The general importance of transition metal-catalyzed transfer hydrogenation was discussed in Chapter 1. Of particular interest is the effect of base. For example, the rate of hydrogen transfer from secondary alcohols to ketones in the presence of transition metal complexes such as RuCl$_2$(PPh$_3$)$_3$ (1) is enhanced if a small quantity of KOH is added to the system.$^1$ In a seminal contribution, Bäckvall and co-workers reported that the monohydride species RuHCl(PPh$_3$)$_3$ (2) is initially formed on heating 1 in basic isopropanol, but that this is then converted into the dihydride species RuH$_2$(PPh$_3$)$_3$ (3).$^2$ They identified 3 as the catalytically active species in transfer hydrogenation of acetophenone, as 3 was able to effect reduction in the absence of added base. The hydrogenation most likely occurs by a conventional, inner-sphere mechanism, which requires coordinative unsaturation for high activity (Figure 3.2).

![Figure 3.2. A generic catalytic cycle for transfer hydrogenation via an inner-sphere mechanism.](image-url)
Research by van Koten and coworkers has shown that Ru(II) complexes of the dppx pincer ligand, RuX(η³-dppx)(PPh₃) (Figure 3.3; dppx = 1,3-bis[(diphenylphosphanyl)-methyl]-benzene), have high activity in transfer hydrogenation of ketones. For example, in hydrogenation of acetophenone, complex 4a achieved a good turnover frequency (TOF = (mol substrate converted)/(mol catalyst))⁻¹h⁻¹ of 2,300 h⁻¹ at 50% conversion (in comparison to the poor TOF of 100 h⁻¹ for the reduction of the more challenging substrate, benzophenone under the same conditions). Base was required for this transformation; the ratio of base to catalyst was 20:1, which is the standard ratio used.³⁵ Higher activity was found for 4b, which contains a weakly bound triflate ligand. In comparison, Samantha Drouin of this research group reported extremely high turnover frequencies (9,600 h⁻¹ at 50% conversion) for transfer hydrogenation of benzophenone using RuH(CO)[(OC(Ph)(C₆H₄)](dcypb) (6) (dcypb = 1,4-bis(dicyclohexyl)phosphinobutane).⁶,⁷ No data were collected for acetophenone reduction. The highly active “Noyori-class” catalyst RuCl₂(dppe)(en), which utilizes an outer-sphere mechanism, achieves a TOF of 6,700 at 50% conversion for reduction of acetophenone under conditions similar to those used for 4a.⁸
Figure 3.3. Ruthenium complexes containing an arylphosphine “PCP-pincer” ligand, 4a and 4b.

Transfer hydrogenations involving 4a/b were carried out in the presence of base and isopropanol, conditions which were proposed to effect formation of the anionic mono-hydride species, [RuH(O’Pr)(η²-PCP)(PPh₃)]⁻ (5).⁵ Notable in 5 is retention of the η³-PCP “pincer” ligand, the stability of which is often cited as an advantage of such ligands in catalysis, in that it contributes to greater catalyst robustness.⁹ The stability of the ligand architecture is also viewed as critical to asymmetric catalysis via chiral pincer ligands. In contrast to the Noyori catalyst RuCl₂(binap)(en*),⁸ (en* = a chiral diamine) however, chiral Ru-pincer complexes have not yet enabled high enantioselectivities in transfer hydrogenation.⁹

While Group 9 and 10 metal complexes with aryl- and alkyl-PCP ligands have received much attention, the PCP-pincer chemistry of Group 8 metals has focused principally on the important family of arylphosphine derivatives, as indeed exemplified by 4a. Examples of alkylphosphine-pincer complexes in Group 8 chemistry are confined to tert-butyl¹⁰-¹³ and isopropyl¹⁴ PCP ligands, but these have not been explored in catalysis. In view of the profound influence of pincer ligand properties and chelate bite angles on structure and reactivity,⁹ and motivated by the high transfer-hydrogenation activity of the cyclohexylphosphine complex 6 noted above,⁶,⁷ our group was interested in the possibility of improving
the activity of the Ru-pincer systems by incorporating cyclohexylphosphine donors. Group 9 and 10 complexes of the dcpx ligand (dcpx = 1,3-bis[(dicyclohexylphosphanyl)-methyl]-benzene) have been studied by the Cross\textsuperscript{15-18} and Park\textsuperscript{19-22} groups, but this ligand was not used in ruthenium chemistry prior to our efforts.

With the intention of examining the effect of increased ligand basicity on catalyst activity in transfer hydrogenation, Dr. Dino Amoroso of this research group synthesized and characterized the dcpx complex analogue of 4a. Thus, high-yield routes were established to RuCl(η\textsuperscript{3}-dcpx)(PPh\textsubscript{3}) (7), as well as its hydride derivatives RuH(η\textsuperscript{3}-dcpx)(PPh\textsubscript{3})(N\textsubscript{2}) (8a/b) and RuH(η\textsuperscript{3}-dcpx)(PPh\textsubscript{3})(H\textsubscript{2}) (9a/b), Figure 3.4.\textsuperscript{23,24} These complexes are close structural analogues to the earlier-reported phenyl, isopropyl, and tert-butyl PCP-pincer complexes.\textsuperscript{14-16,25} Preliminary catalytic studies of 7 and 8a/b were carried out.\textsuperscript{23,24} In the present work, a detailed mechanistic investigation was undertaken. A key, unexpected finding in this work is indirect evidence for an active catalyst containing an η\textsuperscript{2}-bound pincer ligand, which may limit catalyst lifetime and/or selectivity.
Figure 3.4. Cyclohexylphosphine pincer complexes 7, 8a/b and 9a/b.


In our original synthesis of 7·PPh₃, RuCl₂(PPh₃)₃ (1) was reacted with one equivalent of dcpx in the presence of NEt₃. The product was isolated as the PPh₃ solvate. In keeping with suggestions from other groups, we initially assumed that the reaction proceeded via deprotonation of the RuCl₂(η^3-PC(H)P-arene)(PPh₃) intermediate by NEt₃.¹¹,²⁶-²⁸ In the present work, however, reaction of RuCl₂(PPh₃)₃ (1) with dcpx was found to effect complete formation of 7 at room temperature, even in the absence of NEt₃ (Figure 3.5a). This implies that the RuCl₂(η^3-PC(H)P-arene) intermediate is sufficiently acidic to be deprotonated by PPh₃. The pKₐ of PPh₃·HCl is 2.73, as compared to 10.75 for NEt₃·HCl.²⁹

In an alternative synthetic route, 7 was prepared by reaction of RuHCl(PPh₃)₃ (2) with dcpx. The stoichiometry of the reaction requires loss of H₂, and indeed evolution of gas is noted in the reaction (Figure 3.4b). This reactivity
suggests that formation of 7 with loss of H₂ gas is energetically favored over an η²-bound RuHCl(η²-PC(H)P-arene) intermediate.

Figure 3.5. Synthesis of 7 from (a) RuCl₂PPh₃ (1) or (b) RuHCl(PPh₃)₃ (2) without added base.

3.3. Transfer hydrogenation by RuCl(η³-dcpx)(PPh₃)(7).

Previous work by Dino Amoroso demonstrated that 7·PPh₃ was an effective catalyst for hydrogenation of benzophenone in the presence of base co-catalyst. As noted above, however, reduction of benzophenone is more challenging than reduction of acetophenone. With the intention of expanding our mechanistic understanding of this reaction using an experimentally convenient substrate, we undertook a detailed study of the transfer hydrogenation of acetophenone. Reactions were monitored by gas chromatography. Turnover
frequencies (TOF) were cited at 20% conversion, in order to minimize the influence on the rate of decreases in substrate concentration (Table 3.1).

Table 3.1. Transfer hydrogenation of acetophenone using precatalyst 7·PPh₃.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pretreatment</th>
<th>Additive</th>
<th>TOF c (h⁻¹)</th>
<th>time b (min)</th>
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<tr>
<td>1</td>
<td>0</td>
<td>KOH</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>KOH</td>
<td>450</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>KOH</td>
<td>1300</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>KO'Bu</td>
<td>1300</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>KOH + N°Bu₄Cl d</td>
<td>320</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>KOH + PPh₃ e</td>
<td>480</td>
<td></td>
</tr>
<tr>
<td>7f</td>
<td>60</td>
<td>KO'Bu / H₂</td>
<td>2500</td>
<td></td>
</tr>
</tbody>
</table>

a Conditions: 2.0 mmol acetophenone, [Ru] = 0.1 mol %, additives 2.0 mol %, 2.0 mL 'PrOH, reflux (82 °C), N₂ atmosphere, unless otherwise noted. b Precatalyst heated in presence of base before addition of substrate. c Mol substrate converted per mol Ru per h at 20% conversion d 2 mol % N°Bu₄Cl. e 0.8 mol % PPh₃. f Reaction and pretreatment under H₂ (1 atm).

At high concentrations, strong base (including alkali metal hydroxides) can effect hydrogen transfer of isopropanol to ketones, via a process related to the classical Meerwin-Ponndorf-Verley (MPV) reduction using aluminum alkoxides.31-33 While forcing conditions are typical (temperatures up to 150 °C),
rates can be significant even at 82 °C. LePage and James, for example, report 60% conversion of acetophenone to 1-phenylethanol within 4 h, for reactions in refluxing isopropanol with 34 mol % NaOH, relative to substrate. While this might suggest that base catalysis is preferable to transition-metal catalysis, the disadvantages of high base concentrations (such as the self-condensation of enolisable ketone-containing substrates) limits the usefulness of MPV catalysis to non-enolisable ketones such as benzophenone.

In some cases, MPV chemistry may go unrecognized. For example, Le Floch and coworkers recently reported extraordinary activity (TON >18 x 10⁶) for transfer hydrogenation of acetophenone by RuCl(η⁶-p-cymene)((1,2-methylpyridine)phosphole). While the “catalyst” concentration was extremely low (5 x 10⁻⁶ mol % Ru relative to acetophenone), the base concentration was 34 mol %. A parallel with the base-catalyzed reaction conditions reported by LePage and James is obvious: the true TON, assuming that NaOH is the catalyst, is a more realistic value of 2.

In order to rule out the possibility that MPV chemistry contributes to the reduction of acetophenone under our standard conditions (2 mol % KOH, 82 °C), we carried out a control experiment involving incubation of substrate with base in the absence of the ruthenium catalyst 7. This results in only 2% reduction of acetophenone after 4 h, indicating that MPV reduction does not contribute significantly. Catalyst activity is very sensitive to the duration of pretreatment (heating of the precatalyst in basic isopropanol before addition of the substrate).
After only 10 minutes of pretreatment, the activity increases by 50% relative to the reactions carried out in the absence of this initial heating step. The activity increases four-fold after 1 h of pretreatment (Entries 1-3). Approximately identical activity was found using KOH or KO\textsuperscript{t}Bu, although the base strength varies by three orders of magnitude (pK\textsubscript{a} KOH = 16; pK\textsubscript{a} KO\textsuperscript{t}Bu = 19; Entries 3, 4). This suggests that the base is not involved in the rate-determining step, but rather promotes formation of the catalytically active species, most probably in a rapid pre-equilibrium involving formation of the isopropoxide ion.\textsuperscript{40,41} More than 1 h of pretreatment did not measurably enhance the catalysis any further, which suggests after the 1 h pretreatment, no more catalytically active species forms.

Finally, we note that under a hydrogen atmosphere the catalyst activity at 20% conversion (Entry 7) is double than that observed under a nitrogen atmosphere (as found previously\textsuperscript{23,24} for benzophenone reduction). This higher activity may imply that both direct H\textsubscript{2} hydrogenation and transfer-hydrogenation pathways are involved. Alternatively, coordination of N\textsubscript{2} may be responsible. Dino Amoroso earlier described the efficacy of N\textsubscript{2} in binding to other Ru-dicyclohexylphosphine complexes.\textsuperscript{42}

Addition of the soluble chloride donor N\textsuperscript{t}Bu\textsubscript{4}Cl (20 equiv per Ru) reduces the activity of the catalyst to the level observed without pretreatment (Entries 1, 5). Excess chloride is presumed to compete with the substrate for coordination to the metal center. Its inhibiting effect is consistent with van Koten’s report that complex 4b, containing the weakly coordinating triflate ion, is much more active
than its chloride analogue 4a. Addition of PPh₃ to the system also diminishes the activity; this suggests that an equilibrium involving loss of PPh₃ precedes the rate-determining step, and that excess PPh₃ can compete with the substrate for vacant sites. Both the bound and the solvating PPh₃ present in the precatalyst 7•PPh₃ will thus diminish the overall activity of the system. Attempts to generate a more active catalytic species by addition of CuCl as a phosphine scavenger also resulted in decreased activity. This suggests that unwanted deactivating interactions of the CuCl with the ruthenium catalyst occurs.

3.4. In situ NMR experiments under catalytic conditions.

In view of the marked dependence of catalytic activity on pretreatment time, in situ NMR analysis of the precatalyst 7 under the conditions of catalysis was undertaken in order to gain insight into the nature of the active species (Figure 3.6). In these experiments, KO'Bu was used in preference to KOH, in order to ensure that the base dissolves fully.
Figure 3.6. In situ $^{31}\text{P}(^1\text{H})$ NMR spectra of precursor 7 under transfer hydrogenation conditions (2:1 isopropanol: $\text{C}_7\text{D}_6$, $\text{N}_2$ atmosphere, 20 equiv KO'Bu). (a) Before addition of base; 22 °C. (b) 10 min after adding base; 22 °C. (c) After 10 minutes at 80 °C (spectrum measured at 80 °C). (d) After 1 h at 80 °C (spectrum measured at 22 °C). (e) After 3 days at 80 °C (spectrum measured at 22 °C).

After 10 minutes in the presence of base and isopropanol at ambient temperature under $\text{N}_2$, the signals for 7 (Figure 3.6a) have disappeared completely, being replaced by two new $\text{A}_2\text{B}$ patterns assigned to $8\text{a/b}$ (Figure 3.6b and Table 5.2; ratio 1:1). The latter assignments were confirmed by $^{31}\text{P}(^1\text{H})$ NMR analysis of authentic samples of $8\text{a/b}$ in 2:1 isopropanol: $\text{C}_7\text{D}_6$. 
Table 5.2. Summary of $^{31}$P($'\text{H}$) NMR data for complexes 7–10 under catalytic conditions.\(^a\)

<table>
<thead>
<tr>
<th>Cpd</th>
<th>$\delta_{P(\text{A})}$</th>
<th>$\delta_{P(\text{B})}$</th>
<th>$^{2}J_{PP}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCP</td>
<td>PPh$_{3}$</td>
<td></td>
</tr>
<tr>
<td>RuCl($\eta^{2}$-dcpx)(PPh$_{3}$) (7)</td>
<td>37.0</td>
<td>81.2</td>
<td>31</td>
</tr>
<tr>
<td>RuH($\eta^{3}$-dcpx)(PPh$<em>{3}$)(N$</em>{2}$) (8a)$^{b}$</td>
<td>60.5</td>
<td>45.6</td>
<td>17</td>
</tr>
<tr>
<td>(8b)</td>
<td>55.5</td>
<td>29.4</td>
<td>14</td>
</tr>
<tr>
<td>RuH($\eta^{3}$-dcpx)(PPh$_{3}$) (10)$^{c}$</td>
<td>63-65 (br)</td>
<td>45.5</td>
<td></td>
</tr>
<tr>
<td>(9b)</td>
<td>63-65 (br s)</td>
<td>45.3</td>
<td>17</td>
</tr>
<tr>
<td>RuH($\eta^{3}$-dcpx)(PPh$<em>{3}$)(H$</em>{2}$) (9a)</td>
<td>68.9</td>
<td>57.0</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>63-65 (br s)</td>
<td>37.8</td>
<td>15</td>
</tr>
</tbody>
</table>

\(^a\) 300 MHz ($'\text{H}$); 121 MHz ($^{31}$P); 295K, $J$ in Hz. All spectra recorded in 2:1 PrOH: C$_{7}$D$_{8}$, unless otherwise noted. All PCP signals doublets; all PPh$_{3}$ signals triplets, unless otherwise noted. $^{b}$ Spectra at 253K; unresolved at 295K. $^{c}$ Spectra at 295K under N$_{2}$. $^{d}$ Spectra at 355K under Ar in C$_{6}$D$_{6}$.

Although N$_{2}$ remains bound to 8a/b at room temperature, on warming the NMR probe, the signals due to dinitrogen-bound 8a and 8b progressively diminish until, at 82 °C, they disappear (Figure 3.6c and Table 3.2). The new spectrum is attributed to coordinatively unsaturated 10 ($^{31}$P, br 63-65 and 45 ppm; Table 3.2). The assignment of 10 was supported by exchanging the N$_{2}$ atmosphere of an NMR sample of 8a/b with Ar at room temperature, instantly generating 10. This result suggests that in electron-rich pincer complex 8a/b, the bound dinitrogen can be thermally removed.
Figure 3.7. Synthesis of dinitrogen-bound monohydrides \(8a/b\) and dinitrogen-free monohydrde \(10\).

After the typical pretreatment period used in catalysis of 1 h at 82 °C, the spectrum is essentially unchanged: resonances for \(10\) still dominate the spectrum, accompanied by a new \(A_2B\) pattern (X; 1% integrated intensity) at \(\delta\) 57.3 (triplet), and 45.0 (doublet, \(^2J_{pp} = 23\) Hz), and emerging signals corresponding to RuH(\(\eta^3\)-dcpx)(PPh\(_3\))(H\(_2\)) (\(9a/b\)) (<1% by \(^{31}\)P('H) analysis, Figure 3.6c). The complexes \(9a/b\) exist as a mixture of two conformational isomers, with the hydride trans (9a) or cis (9b) to dihydrogen: the cis isomer predominates by a ratio of 3:1. The high stability of hydride cis to H\(_2\) has been noted\(^{44}\) and may provide a driving force for exchange in the case of \(8a/b\). The \(T_1\)(min) relaxation times for the dihydrogen ligand in \(9a/b\) were measured and found to be longer in \(9b\) than in \(9a\), as expected for a dihydrogen ligand perturbed by a favorable interaction with a cis-hydride\(^{44}\) (\(9a\): 20 msec; \(9b\), 24 msec; both at 265K, 500 MHz).
Figure 3.8. Formation of $9a/b$ by thermolysis of $8a/b$ in basic isopropanol. $H_2$ in $9a$ is postulated to form from a dihydride intermediate as discussed below.

Our group reported previously that $8a/b$ react readily with $H_2$ to form $9a/b^{23,24}$ but the analogous reaction with chloride complex 7 gave only 7% by integration of a new $A_2B$ system in the $^{31}P$ NMR spectrum (53.6 (d), 23.2 (t), $^2J_{pp} = 16.3$ Hz) under 1 atm $H_2$ for 24 h. The multiplicity indicates retention of $PPh_3$ and the pincer ligand within the coordination sphere, and the structure is tentatively assigned as $\text{RuCl(}\eta^3\text{-dcpx})(PPh_3)(H_2)$ 11.

As the probe is cooled back to room temperature after the 1 h pretreatment, the signals for $8a$ and $8b$ reappear (Figure 3.6c) and a 1:1 integration is re-established, but the new signals (X) and the signals for $8a/b$ still remain as well. Further heating of the NMR sample for three days at 82 °C resulted in a colour change from red to pale yellow, with the $^{31}P$ NMR spectrum revealing clean conversion to the hydride complexes $9a$ and $9b$ (>98% by
integration). These results from the in situ NMR spectrum shown in Figure 3.6, when combined with the kinetic data discussed above (Table 3.1), give mechanistic insights into pincer complexes 7, 8a/b, 9a/b and 10 in transfer hydrogenation catalysis.

In situ NMR analysis reveals no N₂-bound Ru species at the higher temperatures used in catalytic conditions. From the kinetic data, maximum activity requires a “pretreatment” period as long as 1 h, which was at first assumed to be necessary to convert all the ruthenium bulk species into the active species. However, the in situ NMR experiments surprisingly show complete conversion of 7 to monohydrides 8a/b in <10 minutes even at room temperature, and no further spectroscopically observable change was observed after the 1 h pretreatment, despite a large change in activity. Thus, the monohydride complexes 8a/b are probably not the catalytically most active species, but merely a resting state that delivers this species. Furthermore, the emergence of dihydrogen-bound monohydride species 9a/b under nitrogen atmosphere strongly suggests the intermediacy in the catalysis of a dihydride species, and our observations provide strong circumstantial support for the accessibility of such an entity. The complexes 9a/b are also concluded to be resting states, since we only observe a small rate increase when the reaction is run under H₂, whereas we would expect a very large increase in activity due to facile formation of 9a/b under H₂. The absence of spectroscopic evidence for either a PPh₃-free or a dihydride species after the 1 h of pretreatment points towards the operation
of a highly active catalyst present in low concentration. A favored candidate is Ru(H)$_2$[η$^5$-PC(H)P](L) (12, L = solvent or substrate), formed by elimination of the activated pincer carbon. In favor of 12 are its coordinative unsaturation and enhanced flexibility.$^{45-47}$ One other possible candidate is anionic K[Ru(H)$_2$(η$^3$-dcpx)(PPh$_3$)] 13. This species would be less likely to be catalytically active due to its coordinative saturation. Attempted synthesis of 12 was unsuccessful due to the instability of this entity with respect to 9a/b, the thermodynamic resting state of our system. To access 13, one equivalent of KH$_2$Bu$_3$ was added to monohydride 8a/b in benzene at 80 °C. A yellow solid precipitated out of solution within minutes (Figure 3.9). This yellow precipitate is only soluble in polar solvents such as THF, and appears to be fluxional in solution with two broad peaks in the $^{31}$P NMR spectrum (74.6 and 67.3 in a 2:1 ratio). Initial catalytic trials show no catalytic activity for 13 under the standard transfer hydrogenation conditions. This result suggests that dihydride 13 is not the catalytically active species.
Based on indirect evidence of dihydride formation and the evidence that a \( \eta^3 \)-bound dihydride 13 is not the catalytically active species, we can postulate a transient \( \eta^2 \)-bound PC(H)P Ru dihydride 12 as the active species (Figure 3.10). Since the activity under an H\(_2\) atmosphere is approximately twice than that seen under a N\(_2\) atmosphere, the barrier to formation of the active species is possibly lower when the catalysis is performed under the H\(_2\) atmosphere.
Figure 3.10. Two pathways leading to the proposed active catalyst, 12.

One way that the dihydrogen-bound monohydrides 9a/b could give rise to 12 more easily than the non-dihydrogen coordinated complex 8a/b is through the lower energy route (compare path a and b, Figure 3.10) to 12 via heterolytic cleavage of H₂. This is the reverse of the process shown in Figure 3.4, where the synthesis of 7 results from the loss of an H₂ molecule from RuHCl(PPh₃)₃ and dcpx. Thus, even though the ruthenium-carbon bond is stable in catalytically inactive PCP pincer complexes in transfer hydrogenation, these results show that the ruthenium-carbon bond is possibly cleaved to form a catalytically active transient η²-dcpx-bound 12.

In addition, the ease with which the η³-dcpx structure could be regenerated would give access to a stable resting state, accounting for the
thermal stability and robustness of the catalyst (supported by the observation that no decomposition occurs even after 3 days at 82 °C), as well as the spectroscopic invisibility of the η²-species. However, an η²-bound dcpx ligand in 12 would be more labile, suggesting it could be possible to displace the dcpx ligand in the presence of excess PPh₃. Addition of 8 equivalents of PPh₃ to a solution of 7·PPh₃ in basic isopropanol, followed by heating results in the rapid precipitation of a yellow solid. ¹H NMR analysis of the solid shows only aryl peaks, with the absence of aliphatic peaks representative of the cyclohexyl groups on dcpx (Figure 3.11). This results suggests under catalytic conditions the dcpx ligand can be displaced from the metal center by PPh₃.

![Figure 3.11. Loss of dcpx ligand under pretreatment conditions with added PPh₃.](image)

The proposed active species 12 bears a resemblance to the highly active transfer hydrogenation catalyst synthesized by our group- cyclohexylphosphine complex K[RuH₃(dcypb)(CO)] 6,⁷ in that they both contain a bidentate dicyclohexyl phosphine ligand with a flexible backbone (Figure 3.12). The activity of 6 is higher by several orders of magnitude (TOF 9,600 h⁻¹ for reduction of benzophenone) than precatalyst 7, possibly due to the flexible backbone.
Figure 3.12. Proposed active species 12, which is similar to highly active literature species, K[RuH₃(dcyph)(CO)] 6.

One reproducible observation during the course of this work is that aged catalyst solutions (those dissolved in toluene in a Schlenk tube outside of the glove box for more than one week) were clearly more active in transfer hydrogenation catalysis than fresh catalyst solutions, with the absence of pretreatment steps in both cases (TOF at 50% conversion was 400 and 200 for the aged and fresh catalyst solution, respectively). Also, while freshly made catalyst solutions increased activity with pretreatment, the aged solutions showed no such enhancement. $^{31}$P NMR analysis of a month old aged solution of catalyst shows 12% by integration of new peaks at δ 52.5, 45.0, and 25.21 ppm that could be attributed to phosphate oxide formation. The recent review by Grushin suggests that the formation of coordinatively unsaturated transition metal species via the oxidation of one bound phosphine (in chelating diphosphine systems) to a weakly bound hemi-labile phosphine-phosphine oxide chelate is common in catalysis. In other homogeneous systems in the literature, aged batches of catalyst behave very differently than freshly made ones - sometimes completely switching the product selectivity - and this difference has been suggested to occur by in situ phosphate oxidation. If phosphate oxidation can create a
coordinatively unsaturated active species, then it could potentially activate precatalyst 7 for catalysis by creating coordinative unsaturation.

3.5. Mechanistic-based design of a new precatalyst (14).

Increasing the lability of the PPh₃ donor of precatalyst 7 could enhance transfer hydrogenation activity. Pyridine is thought to be more labile than PPh₃ on ruthenium,⁵⁰ and therefore could enhance the catalytic activity by increasing the coordinative unsaturation during catalysis by disassociating more readily from ruthenium than PPh₃. It was found that pyridine will replace PPh₃ as a ligand when 7 is stirred in neat pyridine for 3 h, accompanied by the gradual colour change from green to bright orange. A bright orange microcrystalline powder was isolated upon precipitation with cold pentane and was attributed to the bis-pyridine complex RuCl(η³-dcpx)Py₂ (14) (Figure 3.14).

![Figure 3.13. Formation of complex 14.](image)

The ³¹P NMR spectrum of the material assigned as 14 showed the clean formation of a singlet at 42.36 ppm attributed to the two equivalent dcpx phosphines. The ¹H NMR spectrum displayed an uncharacteristic signal at δ 11.24 ppm attributed to ortho pyridine hydrogens above and below the benzene
ring in 14 (Figure 3.14), which are strongly deshielded when compared to the normal range for pyridine which is between 6 and 9 ppm, even in a related Ru-PCP(tpy) (tpy = terpyridine) complex [Ru(η^3-dppx)(terpy)]Cl. This difference could be due to the high steric congestion of 14. This strongly deshielded proton, as well as the sharp features of the ^1H NMR spectrum of the pyridine rings in 14 suggests that they are fixed in one position by the bulky cyclohexyl groups of the dcpx ligand, and that the diamagnetic anisotropy of the benzene ring deshields the hydrogens on the locked pyridine rings. Although 14 is coordinatively saturated, it is predicted that upon activation it will be converted into a coordinatively unsaturated species more easily than 7.

3.6. Conclusions.

A detailed mechanistic study of 7 was carried out in transfer hydrogenation catalysis. Interpretation of kinetics and in situ NMR data links 7, 8a/b, 9a/b, 10, and 12 in catalysis. One surprising conclusion of this work is that the active species is not an η^3-bound dcpx complex, but rather an η^2-PC(H)P-bound transient species 12, in which the ruthenium-carbon bond has been thermally cleaved. We suggest the low enantioselectivity of chiral PCP complexes that have been reported^9 is due to the active species being a η^2-PC(H)P-bound entity, which would not have a rigid chiral pocket. Finally, 4a and 7 show similar activity in transfer hydrogenation catalysis, which is not consistent with our initial hypothesis that the basic phosphine containing 7 would be more active for
transfer hydrogenation than 4a. A possible explanation for this result is that both systems operate by a similar mechanism of catalysis, in which the formation of the active species through PCP carbon-ruthenium bond thermolysis has a stronger influence on activity than the phosphine donor basicity.
References

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Chapter 4

Synthesis of chelating ligands containing pyrrole and highly basic donors.

\[ \text{Figure 4.1. Pictorial summary of chapter 4.} \]
4.1. Introduction.

Chapter 1 discusses the importance of ligands in homogeneous catalysis. In the case of homogeneous ruthenium catalysts for olefin metathesis\cite{1,2} and hydrogenation,\cite{3} highly basic, bulky, chelating ligands have been reported to enhance activity and selectivity. This enhancement could be due to stabilization of coordinatively unsaturated catalytic intermediates.\cite{4,6}

Olefin metathesis is a very important catalytic transformation which has become more practical with the development of the air and moisture resistant Grubbs catalyst, RuCl\(_2\)(PCy\(_3\))\(_2\)(=CHPh) (Figure 4.2 a).\cite{7} Following this discovery, an intense research effort in the past few years has focused on enhancements of this first generation catalyst, including the use of a highly basic N-heterocyclic carbene (NHC) ligand “second generation” Grubbs catalyst (Figure 4.2 b).\cite{2,8,9} A chiral chelating NHC ligand has also been used (Figure 4.2 c).\cite{10}

![Chemical Structures](image)

**Figure 4.2.** Progression of ligand systems applied to olefin metathesis (a) Grubbs catalyst (b) Second generation Grubbs catalyst (c) chiral bidentate system. (Mes = Mesityl)

Further improvements could be possible with mechanistic understanding of this catalyst system. For example, our group reported that ruthenium alkylidenes deactivate by formation of a face-bridged dimer (Figure 4.3),\cite{11,12}
which led us to explore the possibility that incorporation of “pseudohalide” anionic donors could prevent this deactivation pathway. The replacement of the chloride ligands of Grubbs catalyst by us$^{13,14}$ and others$^{15}$ with a pseudohalide ligand to generate RuX$_2$(PCy$_3$)$_2$(=CHPh) ($X =$ perfluorophenoxide, carboxylate) results in increased catalyst lifetime.

\[
\begin{align*}
\text{2} & \quad \begin{array}{c}
\text{Ru} \\
\text{Cl} & \text{Cl}
\end{array} \\
\text{L} & \quad \begin{array}{c}
\text{Ru} \\
\text{Cl} & \text{Cl}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{L} & = \text{PPh}_3, \text{dcypb}
\end{align*}
\]

**Figure 4.3.** Bimolecular deactivation of ruthenium alkylidenes through formation of a stable face-bridged chloride dimer.

Future improvements in catalytic performance could be made by incorporation of a pseudohalide into a highly basic chelating ligand framework. In addition, such a chelating system could provide a robust scaffold to explore potentially useful tandem catalysis transformations,$^{16}$ such as tandem olefin metathesis-hydrogenation, developed by our group$^{17}$ and others.$^{18}$ Toward this goal, Dino Amoroso of our group discovered that the reaction of dcpx with the ruthenium alkylidene RuCl$_2$(PPh$_3$)$_2$(=CHR) generated the agostic complex RuCl$_2$(\(\eta^2\)-dcpx)(=CHR) (Figure 4.4a).$^{19}$ The aryl C-H bond of this complex is not activated to form an \(\eta^3\)-bound ligand, even in the presence of a strong base. In
related work, the research group of Jia\textsuperscript{20,21} has reported the reactivity of an 
alkylidene ligand on ruthenium pincer complexes, and found that the aryl 
carbanion of dppx inserts into the ruthenium alkylidene bond (Figure 4.4 b), 
suggesting the PCP ligand carbanion is too basic, and possibly inserts into the 
ruthenium alkylidene.

![Chemical Structures](image)

**Figure 4.4.** (a) Fogg’s PCP alkylidene (b) Jia’s $\eta^4$ bound pincer (c) Fogg’s 
pyrrolide alkylidene.

An improved ligand would incorporate a less basic anionic donor, which 
would therefore be less likely to insert into the ruthenium alkylidene. An anionic 
donor with the correct geometry to incorporate into a tridentate motif would be 
the pyrrolide anion, in which the pyrrole N-H proton has an acidity (pKa = 16) 
similar to alcohols.\textsuperscript{22} It was discovered by Samantha Drouin\textsuperscript{23,24} of our group that 
a known imino-pyrrolato ligand can successfully be installed as a chelating 
anionic donor on a ruthenium alkylidene to form Ru(NN)Cl(PC\textsubscript{2})\textsubscript{3}(=CHPh) (NN = 
iminopyrrolato) (Figure 4.4 c). This supports the suggestion that a less basic 
anionic donor would be more compatible with the ruthenium alkylidene 
functionality. Furthermore, this catalyst system is similar to those incorporating
Schiff-base ligands, with the same advantage of high air and moisture stability, and the disadvantage of a lower activity than even the first generation Grubbs catalyst. Our group reported that the imino-pyrrolato catalyst system requires oxygen for activation, which was suggested to open an active site by oxidation of the bound PCy\textsubscript{3}. This requirement for phosphine oxidation for activity is possibly due to the strong affinity of PCy\textsubscript{3} to the ruthenium center. A more strongly donating ligand than the imine nitrogen of Ru(NN)Cl(PCy\textsubscript{3})(=CHPh) would make the ruthenium center more electron rich, thus activating it towards metathesis. A novel bidentate or tridentate ligand utilizing pyrrole and a stronger donor such as a NHC or basic phosphine could provide such a highly reactive catalyst system.

Discussed in this chapter is the synthesis and characterization of ligand precursors in which strongly donating NHC donors are incorporated into a chelating framework. The new design is a bidentate carbene-pyrrole (Figure 4.5 a) or tridentate carbene-pyrrole-carbene (Figure 4.5 b) ligand in which the geometry is meridionally coordinating to the metal center, similar to chelating carbene-alcohol ligands that have been reported,\textsuperscript{10,25} and the porphyrin class of ligands.\textsuperscript{26}

![Figure 4.5. Designs for CN type ligand (a) and CNC (b).](image_url)
4.2. Synthesis of Imidazolium Ligand Precursors.

Tridentate CNC ligand precursors 15 and 16 were obtained in 70 % and 80 % overall yield respectively, in a synthesis starting from pyrrole (Figure 4.6). The selective Mannich dimethylamino-methylation of pyrrole in water with formaldehyde and dimethylammonium chloride yields 2,5-bis[[(dimethylamino)methyl]-pyrrole with high selectivity. Subsequent quaternization of the dimethylamino groups with methyl iodide forms 2,5-bis[(trimethylammonium)methyl]-pyrrole diiodide. This strategy is based on work reported by the research group of Elsenbaumer, which demonstrated that this ammonium derivative is particularly suited to further functionalization by nucleophilic displacement of trimethylamine with phenylthiolate. Accordingly, displacement of trimethylamine with imidazole forms 2,5-bis[(imidazol)methyl]-pyrrole.

![Chemical equations](attachment:image)

**Figure 4.6.** Synthesis of CNC ligand precursors 15 and 16.
Treatment of a DMF solution of 2,5-bis[(imidazole)methyl]-pyrrole with 3 equivalents of 2-iodopropane at 70 °C for 1 hr yields 2,5-bis[(isopropylimidazolium)methyl]-pyrrole diiodide (as judged by TLC and NMR analysis of an aliquot of the crude reaction mixture). The solution turns light brown over the course of the reaction, probably due to some decomposition of the thermally sensitive pyrrole ring. A water-insoluble purple byproduct (probably a poly(pyrrole) species) can be removed by filtration through Celite. The remaining clear solution was added drop-wise to an aqueous solution containing 2 equivalents of NH₄PF₆, upon which a fine white solid forms, which was filtered off and dried to yield the white solid 15. Thermally sensitive 15 is soluble only in polar organic solvents such as DMSO and DMF.

¹H NMR analysis of 15 (figure 4.7) reveals a triplet (J_{HH}= 2.5 Hz) integrating to one proton at δ 11.32 ppm a location characteristic of the pyrrole N-H proton.²⁹ Disappearance of this signal on addition of D₂O to the NMR sample further confirms this assignment, as does the absence of an HMQC correlation with any carbon signal. HMBC experiments reveal two and three-bond correlations to pyrrole ring C2 and C3, respectively. The remaining pyrrole ring protons, H3, appear as a doublet at δ 6.20 ppm (J_{HH}= 2.5 Hz, 2H). The quaternary carbons (C2) on the pyrrole ring provide a signal in the ¹³C(¹H) NMR spectrum at δ 126.5 ppm, confirmed by the absence of only this signal in the DEPT-130 spectrum. The singlet at 5.30 ppm is assigned to the methylene protons, which was confirmed by direct coupling (by HMQC) to the only carbon
that had an even number of protons (signal down in the DEPT 130). The signal at 9.15 ppm (pseudo-t, imid-\textit{H1}, \textit{J_{HH}}= 2.5 Hz, 2H), is characteristic of imidazolium, which correlates to the two other chemically distinct protons the imidazolium ring by COSY (with the same coupling constant for both). The remaining imidazolium protons provide signals at \(\delta\) 7.65 ppm (pseudo-t, imid-\textit{H4}, \textit{J_{HH}}= 2.5 Hz, 2H) and \(\delta\) 7.88 ppm (pseudo-t, imid-\textit{H3}, \textit{J_{HH}}= 2.5 Hz, 2H), assigned by long-distance coupling (HMBC) to the isopropyl and methylene carbon, respectively. The A\(_2\)B system of the isopropyl group reveals the characteristic doublet at 1.45 ppm ((\textit{CH\textsubscript{3}}\textsubscript{2}CH, \textit{J_{HH}}= 7 Hz, 12H) and septet at 4.63 ppm ((\textit{CH\textsubscript{3}}\textsubscript{2}CH, \textit{J_{HH}}= 7 Hz, 2H). IR analysis reveals a characteristic N-H stretching band at 3389 cm\(^{-1}\). The ESI mass spectrum shows the largest mass peak at 458 m/z corresponding to the loss of one PF\(_6\)\(^{-}\) anion from 15. Elemental analysis were not collected due to lack of time.

\[\begin{array}{c}
1 & 2 & 3 \\
\text{N} & \text{N} & \text{N} \\
1 & 4 & \text{15} \\
\end{array}\]

\[\begin{array}{c|c|c}
\text{H} & \text{C} \\
1 & 110.5 & 6.20 \\
 & 126.5 & 5.30 \\
 & 11.32 & 7.65 \\
 & 121.5 & 9.15 \\
 & 135.3 & 7.88 \\
 & 123.1 & 4.63 \\
 & 53.2 & 1.45 \\
 & 23.1 & \\
\end{array}\]

\textbf{Figure 4.7.} NMR analysis of 15.
Less sterically demanding precursor 16 is synthesized by the same route as 15 (Figure 4.6). The structure of 16 was confirmed by $^1$H and $^{13}$C NMR analysis (Figure 4.8). The IR spectrum of 16 also reveals a characteristic NH stretch at 3390 cm$^{-1}$, and the ESI mass spectrum shows the highest mass peak at 384 m/z corresponding to loss of the iodide counter ion from 16.

![Figure 4.8. NMR analysis of 16.](image)

The bidentate ligand precursor 2-[(isopropylimidazolium)methyl]-pyrrole tetraphenylborate 17 was also synthesized by the same method used to synthesize 15, with the only difference in the counterion being B(Ph)$_4^-$ in the case of 17 (Figure 4.9). The structure of 17 was confirmed by $^1$H and $^{13}$C NMR analysis (Figure 4.9). IR analysis shows a characteristic N-H stretching band at 3389 cm$^{-1}$. ESI mass spectrum shows the largest mass peak at m/z corresponding to loss of one B(Ph)$_4^-$ anion from 17.
Figure 4.9. Synthesis and NMR analysis of 17.

The attempts to generate free carbenes from the imidazolium salts 15-17 by deprotonation with the strong bases KH, KO'Bu, or KN(SiMe₃)₂ failed. Addition of base to a suspension of the ligand precursor in dry, degassed THF resulted in the immediate formation of a deep red solution, possibly indicating double bond isomerization to form a conjugated, porphyrinogen-like chromophore.³⁰ The formation of a conjugated porphyrinogen-type product is supported by the observed loss of the characteristic methylene, imidazolium and pyrrole signals of 15 upon addition of base. Attempts at direct metalation of 15-17 with ruthenium(II), silver(I), and palladium(II) precursors always resulted in the
formation of dark red solutions of the ligand byproducts and sometimes ruthenium, silver or palladium black.

4.3. Conclusions.

In conclusion, chelating mono- and di-imidazolium pyrrole complexes were synthesized and characterized. Unfortunately, the free carbenes could not be obtained by deprotonation (possibly due to double-bond isomerization), nor could the metal complexes be obtained via direct metalation. However, substitution at the methylene positions of the proligand (see Figure 4.10) may circumvent isomerization, and permit isolation of stable free carbenes.

![Figure 4.10. A possible improved version of carbene-pyrrole-carbene ligand with R= alkyl or aryl in the methylene position.](image)

References


CHAPTER 5

Transfer Hydrogenation Involving Ruthenium Secondary Phosphine Complexes

\[
\begin{align*}
\text{RuCl}_2(\text{PPh}_3)_3 & \quad \text{18a} \\
& \quad \text{HPCy}_2 \\
& \quad \text{Cy}_2\text{HP} \quad \text{Ru} \quad \text{Cl} \quad \text{PHCy}_2 \\
& \quad \text{Cl} \quad \text{Cl} \\
& \quad \text{18b} \\
& \quad \text{KHB}^{(\text{Bu})}_3 \\
& \quad \text{or KO}^{\text{Pr}} \\
& \quad \text{Cy}_2\text{HP} \quad \text{Ru} \quad \text{Cl} \quad \text{PHCy}_2 \\
& \quad \text{Cl} \quad \text{Cl} \\
& \quad \text{21} \\
& \quad \text{HPCy}_2 \\
& \quad \text{22} \\
& \quad \text{RuHCl}(\text{PPh}_3)_3 \\
& \quad \text{2} \\
\end{align*}
\]

Transfer hydrogenation activity for RuCl_2L_4:
\[L = \text{HPCy}_2(18\text{a/b}) > \text{HPPh}_2(19\text{a/b}) >> \text{H}_2\text{PPh}(20\text{a/b})\]

Figure 5.1. Pictorial Summary of Chapter 5.
5.1. Introduction.

The importance of new ligand design in catalysis was discussed in Chapter 1. Biological enzymes are extremely active in catalysis.¹ Many highly efficient metallo-enzymes utilize cooperative interactions between one or more acidic/basic sites in the outer coordination sphere of the transition metal center to activate substrates and enhance selectivity (Figure 5.2).

![Figure 5.2](image)

**Figure 5.2.** Enzyme's active site, utilizing cooperative interactions with acidic and basic sites to activate a substrate.

One way in which to develop and improve synthetic homogeneous catalysts would be to incorporate acidic and/or basic sites in the outer sphere, akin to natural metallo-enzymes. One famous example of research in this direction is Noyori's highly active ketone hydrogenation catalyst, RuH₂(dppe)(en), which contains a diamine ligand providing acidic sites in the outer sphere of the metal center.²,³ Mechanistic studies revealed that the enhancement of catalysis
occurs via an outer-sphere activation of the ketone oxygen through hydrogen bonding with the amine (Figure 5.3).\textsuperscript{4,7}

![Diagram of the Noyori system mechanism](image)

**Figure 5.3.** Mechanism of the Noyori system which operates through hydrogen bonding.\textsuperscript{4,7}

As phosphine ligands (soft donor, pi back-bonding) play a larger role in catalysis with late transition metals than nitrogen-based ligands (hard donor, no pi back-bonding),\textsuperscript{8} it would be interesting to consider the potential of utilizing primary and secondary phosphine donors in analogy to the nitrogen donors in the Noyori catalyst system. In addition to catalytic applications, the investigation of the nature of potential protic-hydridic interactions between ruthenium hydrides and acidic phosphine protons is of fundamental importance.

Such chemistry has not been intensively investigated in the past, as these ligands are thought to be unstable towards deprotonation and oligomerization.
This is surprising considering a quantitative study has reported a stronger phosphine-ruthenium bond strength (an important characteristic in preventing deactivation of catalytic species) in secondary phosphines than the corresponding tertiary phosphines.\textsuperscript{5} Traditionally, phosphines have been evaluated on their basicity and steric bulk alone, as a transition metal’s electron-richness is well known to be directly linked to phosphine basicity and cone angle,\textsuperscript{9} but consideration of other important properties such as acidic sites could increase the versatility of phosphine ligands in catalysis.

One systematic study has reported that pendent hydrogen atoms, when attached directly to the phosphorus atoms, have a pronounced and unique positive effect on the rates of CO dissociation from Ru(CO)\textsubscript{4}L (L = secondary/primary phosphine) complexes, compared to the complexes of corresponding tertiary phosphines. Significant kinetic isotope effects on CO dissociation by the pendant hydrogen atom were reported,\textsuperscript{10} which is associated with occurrence of direct Ru–H or Ru–P–H agostic bond making as the CO ligand departs from the ruthenium.

Recently, secondary phosphines have been highlighted for their enhanced activities over even bulky tri-alkyl phosphines for palladium catalyzed coupling reactions, in which activity is greatly enhanced by strongly bound ligands.\textsuperscript{11} One reported catalytic study of ruthenium-secondary phosphine complexes was in atom transfer radical polymerization (ATRP), in which the ligand HPC\textsubscript{2}\textsubscript{y} generates a much less active catalyst than PC\textsubscript{y}\textsubscript{z}. This was suggested to be due
to a smaller cone angle (143°) and weaker basicity (pKa H₂PCy₂⁺ = 4.55) compared to the highly basic PCy₃ (170°, pKa HPCy₃⁺ = 9.70).¹²

The P-H bond is a major benefit in elucidating the nature of ruthenium-secondary phosphine interactions by NMR and IR analysis. Both the phosphorus and hydrogen nuclei are close to 100% abundant spin 1/2 nuclei with large sensitivities, and ruthenium complexes of primary and secondary phosphines exhibit many characteristic NMR chemical shifts (³¹P{¹H} RuPH = δₚ 50 to -50 ppm; ¹H RuPH = δₕ 4-6 ppm, ¹JₚH = 300 Hz), and IR signals (ν P-H = 2300-2400 cm⁻¹).¹³

In this chapter is reported the synthesis and catalytic studies of ruthenium primary/secondary phosphine complexes in transfer hydrogenation.

5.2. Synthesis of primary and secondary phosphine complexes.

The previously reported RuCl₂L₄ complexes¹³ of the phosphine ligands HPCy₂, HPPPh₂, and H₂PPh were synthesized to study the effect of phosphine acidity and cone angle on catalytic activity. This was accomplished by reaction of RuCl₃ and six equivalents of the phosphine ligand in refluxing methanol for several hours. All the complexes, RuCl₂L₄ (L = HPCy₂ 18a/b, HPPPh₂ 19a/b, and H₂PPh 20a/b) exist as both the cis (18a-20a) and trans (18b-20b) isomers in solution, with greater amounts (~90% by NMR analysis) of the trans isomers,¹³ indicating that these are the thermodynamically most stable isomers (Figure 5.4).
Isomerization between the cis and trans isomers of 18a/b, 19a/b, or 20a/b in solution to yield equilibrium mixtures is very slow at room temperature, on the order of days. This suggests that the barrier to isomerization from cis to trans (possibly occurring through a disassociative mechanism) is relatively large. Reaction of RuCl₂(PPh₃)₃ 1, with four equivalents of HPCy₂ yields predominantly the cis isomer 18a (>95% by in situ ³¹P{¹H} NMR analysis minutes after addition of HPCy₂). This indicates that the trans isomer 18b is more stable, and cis 18a is the kinetic product. This is of interest because the cis and trans isomers may exhibit differing reactivity.

As ruthenium hydrides are probably the active species in transfer hydrogenation, as discussed in Chapter 3, synthesis of the monohydride and dihydride derivatives of 18a/b was undertaken. Addition of four equivalents of HPCy₂ to RuHCl(PPh₃)₃ (2) in benzene results in the decolourization of the initially purple solution, accompanied by the formation of the monohydride RuHCl(HPCy₂)₃ 21 (Figure 5.5a). This is confirmed by ¹H NMR analysis. A single, characteristic pentet integrating one proton appears at δₚ = 19.94 ppm (JₚH = 14
Hz). The multiplicity confirms coupling to four equivalent phosphine ligands (which appear as a singlet at δp 35.66 ppm in the 31P{1H} NMR spectrum). 31P-decoupling causes the hydride pentet to collapse to a singlet.

(a) RuHCl(PPh3)3 2

(b) RuCl2(HPCy2)4 18a/b

\[ \text{Toluene} \]

Figure 5.5. (a) Synthesis of monohydride 21, and (b) dihydride 22.

The cis isomer of dihydride 22 was also prepared. Addition of two equivalents of KHB(âBu)3 to 18a/b in benzene decolourizes the initially yellow solution within minutes. 31P NMR analysis reveals two sets of triplets at δp 50.70 and 38.8 ppm (2Jpp = 22 Hz) in a 1:1 ratio. This \( A_2B_2 \) system is consistent with the formulation of the product as cis dihydride 22 (Figure 5.5b). This complex was isolated by precipitation with hexanes to give a white microcrystalline powder, which is awaiting further characterization.

In an attempt to synthesize a dihydride of a ruthenium phenylphosphine containing complex, KHB(âBu)3 was added to a solution of 20a/b in benzene (Figure 5.6), and a color change from yellow to red is observed, along with moderate bubbling indicating the loss of \( \text{H}_2 \) gas. The 31P{1H} NMR analysis
reveals the appearance of very broad (~20 ppm) signals centered at $\delta_p \approx 140$ ppm, which may indicate a heterogeneous mixture of paramagnetic bridging phosphido species. This result is possibly due to protic-hydridic interactions between a transient ruthenium hydride species and the protons on $\text{H}_2\text{PPh}$, favoring the loss of $\text{H}_2$ gas (Figure 5.6).

![Proposed intermediate](image)

**Figure 5.6. Reaction of KHB($^{\circ}$Bu)$_3$ with 20a/b.**

To further the fundamental understanding of the nature of the interactions of primary phosphines and ruthenium hydrides, use of the well-defined, highly basic dcpx ligand would provide a useful platform to build the chemistry of primary and secondary phosphines on ruthenium. Upon addition of two equivalents of $\text{H}_2\text{PPh}$ to $\text{RuCl}(\eta^3\text{-PCP})\text{PPh}_3$ (3) in toluene, the initially dark green solution went instantly light yellow. We identify the product $\text{RuCl}(\eta^3\text{-PCP})(\text{PH}_2\text{Ph})_2$ 23 on the basis of NMR studies (Figure 5.7).
The in situ $^{31}$P NMR spectrum of 23, shows a characteristic $A_2BC$ system for the three chemically distinct phosphine nuclei. They are assigned as the two equivalent PCP phosphines centered at $\delta_p$ 52.25 ppm (2P, dd $^2J_{pp} = 34$ Hz, $^2J_{pp} = 20$ Hz, PCP), the less shielded PH$_2$Ph trans to chloride anion at $\delta_p$ -15.55 ppm (1P, dt, $^2J_{pp} = 34$ Hz, $^2J_{pp} = 19$ Hz, $^1J_{ph} = 319$ Hz, PH$_2$Ph), and the more shielded PH$_2$Ph trans to the strongly donating aryl carbanion $\delta_p$ -45.23 ppm (1P, dt, $^2J_{pp} = 20$Hz, $^2J_{pp} = 19$ Hz, $^1J_{ph} = 304$ Hz, PH$_2$Ph). The proton-coupled $^{31}$P NMR spectrum reveals no coupled protons for the signal due to the PCP ligand, while the two peaks assigned to the PH$_2$Ph groups were coupled to protons, leading to a complex splitting pattern (broad triplets result from the large P-H coupling constant of 300 Hz). The way is open for future mechanistic studies on hydride derivatives of 23. One result of mechanistic interest is that the highly basic aryl carbanion in the PCP ligand of 23 is stable against deprotonation of a nearby PH$_2$Ph ligand at room temperature.

Hydrophosphinilation involves formation of a carbon-phosphorus bond. An opportunity to study secondary phosphines in tandem catalyst transformations arose due to the high activity of 18a/b in transfer hydrogenation (see later).
products of reaction of the Grubbs Catalyst RuCl₂(PCy₂)(=CHPh) (24) with HPCy₂ may give insight into what opportunities lay in tandem metathesis-hydrogenation for this ligand. Addition of five equivalents of HPCy₂ to 24 in benzene caused the initially purple solution to turn to clear yellow over 20 minutes at room temperature forming 18b (Figure 5.8).

![Diagram](image)

**Figure 5.8.** Synthesis of 18b from Grubbs catalyst.

In situ ³¹P NMR analysis reveals a singlet assigned to trans isomer 18b at δ 14.56, free PCy₃ ligand at δ 3.22 ppm, and P(CH₂Ph)Cy₂ at δ 11.24 ppm (ratio 4:2:1). Formation of P(CH₂Ph)Cy₂ can be rationalized as the hydrophosphination product of the benzylidene ligand and one HPCy₂. The assignments of 18b, PCy₃, and P(CH₂Ph)Cy₂ (synthesized separately by reaction of benzyl bromide with HPCy₂) were confirmed with the NMR spectra of the authentic compounds.
Of note, mostly the trans product 18b (>95%) forms in this reaction, which contrasts with the formation of predominantly cis 18a from the reaction of HPCy₂ with RuCl₂(PPh₃)₃ (Figure 5.3). The clean transformation from Grubbs catalyst to 18a could lead to new and improved tandem catalytic protocols, such as highly selective tandem metathesis/ketone transfer hydrogenation.

5.3 Transfer hydrogenation catalysis by 18a/b-23.

The complexes 18a/b-23 were tested for catalytic activity in transfer hydrogenation of acetophenone (Substrate:Base:Catalyst = 1000:20:1). Only HPCy₂ complexes 18a/b, 21, and 22 were highly active. Furthermore, catalysis under H₂ atm prevents catalyst deactivation (Figure 5.9).

![Transfer Hydrogenation](image)

**Figure 5.9.** Plot of transfer hydrogenation activity for 18a/b under H₂ and N₂ atmosphere, and 19a/b under N₂ atmosphere.
Complexes 20a/b, based on the PH$_2$Ph ligand, show no catalytic activity. The complex may deactivate rapidly under the highly basic conditions used. PHPh$_2$ based complex 19a/b initially shows the same high activity as PHCy$_2$ complex 18a/b (Figure 5.9), but deactivates more readily at moderate conversions. Deactivation could be due to low stabilization of phosphido intermediates by the the weakly-donating HPPh$_2$ ligand. Deactivation for 19a/b was observed under both N$_2$ and H$_2$ atmospheres. Pincer complex 23 showed no catalytic activity, probably due to the constrained geometry.

The catalytic activities observed for the most active complexes, 18a/b, 21, and 22, were virtually identical, suggesting that the dichloride complex 18a/b forms monohydride 21 rapidly, and that 21 goes on to form cis dihydride 22 (Figure 5.10). Deactivation occurs under N$_2$ atmosphere for all three. Hydrogen appears to play a role in the stabilization of the catalytic system, as less deactivation occurred under one atmosphere of hydrogen.

![Figure 5.10. Transformation of the catalytic precursors 18a/b and 21 to dihydride 22 in basic isopropyl alcohol.](image)

By analogy to the Noyori and Bäckvall systems, dihydride 22 may function as the active species in this system. A critical function of H$_2$ may be
regeneration of a Ru(H)(PHR₂) species by addition to the Ru-PR₂ intermediate. An outer sphere mechanism (Figure 5.3) would render more hindered substrates more easily reducible, as the substrates are further from the metal center than in an inner sphere mechanism. Benzophenone, known to be a difficult substrate for inner sphere catalysts due mainly to steric bulk (see Chapter 3), was used as a substrate for 18a/b catalyzed transfer hydrogenation. An initial experiment using precatalyst 18a/b (without pre-treatment), led to very high conversions in 2 hours (80% conversion, S:B:C = 1000:20:1), which is an order of magnitude higher than that for pincer complex 3. The activity of 18a/b is virtually identical when comparing for benzophenone and acetophenone reduction, while the activity of the pincer catalyst 7 and RuH₂(PPh₃)₃ is strongly substrate dependant. The Noyori catalyst, likewise, showed little discrimination between acetophenone and benzophenone. This may be a common characteristic of catalysts operating by outer-sphere coordination of substrate.¹⁴

5.4. Conclusions.

This chapter described the study of RX₂(PHR₂) complexes in catalysis. HPCy₂ complex 18a/b was highly active in transfer hydrogenation catalysis, presumably due to the higher basicity of HPCy₂ compared to the primary and secondary aryl phosphines in 19a/b and 20a/b. The high affinity of HPCy₂ for ruthenium also enabled clean transformation of Grubbs catalyst to 18b,
potentially opening the way to tandem metathesis-hydrogenation catalysis with HPCy₂ as a ligand.
References

CHAPTER 6

Conclusions and Future Considerations

This thesis discussed work in the related themes of mechanistic studies and new ligand design in homogeneous ruthenium catalysis. Mechanistic understanding of ruthenium pincer catalyzed transfer hydrogenation is described in Chapter 3. During the pretreatment of RuCl(η^3-dcpx)PPh_3 (7), several different hydride products were observed. The formation of a catalytically active coordinatively unsaturated η^2-bound PC(H)P intermediate was proposed on the basis of the kinetics and in situ NMR analysis. This highlights the value of understanding the possible formation of a catalytically active η^2-bound PC(H)P species in other ruthenium pincer catalyzed reactions.

In order to utilize the potential of Ru(II) complexes in homogeneous catalysis, it is desirable to minimize the formation of trichloride-bridged dinuclear structures. Use of alternative anionic ligands in place of the chloride donors can possibly inhibit such bimolecular deactivation. Novel ligands incorporating pyrrole derivatives bearing two imidazolium groups were designed and synthesized for potential catalytic applications, but no metal complexes could be generated. Related ligands have been proposed which may enable synthesis of metal complexes of pyrrole-NHC chelates.

Our interest in new ligands useful for catalytic applications led us to test secondary phosphine complexes of ruthenium in transfer hydrogenation catalysis. The bulky secondary phosphine ligand in RuCl_2(HPCy_2)_2 (19),
conferred high activity in transfer hydrogenation. Of interest, this complex could also be generated from the Grubbs catalyst, suggesting potential tandem metathesis-hydrogenation applications. Future work could focus on understanding the mechanism of transfer hydrogenation catalysis by ruthenium-HPCy₂ complexes.