Metal-Catalysed Hydroamination

A thesis submitted in partial fulfilment of the requirements for admission to the degree of

Doctor of Philosophy

by

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Preface

This thesis is a report of original research undertaken by the author and is submitted for admission to the degree of Doctor of Philosophy at the University of Sydney. The work was completed in the School of Chemistry at the University of Sydney during the period March 2003 to November 2006. The work and results presented in this thesis are those of the author, unless otherwise acknowledged.

Sections of this work have been published:

Cyclization of Acetylenic Amides Using a Cationic Rhodium(I) Complex
S. Burling, L. D. Field, H. L. Li, B. A. Messerle, A. Shasha
Australian Journal of Chemistry, **2004**, 57, 677-680.

Sections of this work have been presented at Scientific Conferences:

Catalysed Synthesis of Pyrrolines, Pyrrolidines and Indoles
S. Burling, L. D. Field, B. A. Messerle, A. Shasha, and S. Wren
Southern Highlands Conference on Heterocyclic Chemistry 13, Moss Vale, Australia September **2002**. Poster Presentation.

Synthesis of *N*-Heterocycles Using Cationic Metal Catalysts
S. Burling, L. D. Field, B. A. Messerle, A. Shasha, S. Wren
Cornforth Foundation for Chemistry Symposium, University of Sydney, Sydney, 30th September-1st October **2002**. Poster Presentation.

Metal-Catalysed Hydroamination of Alkynes
L. D. Field, B. A. Messerle, A. Shasha
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Organometallic Catalysts for the Synthesis of Heterocycles

L. D. Field, B. A. Messerle, A. Shasha

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Organometallic Catalysts for the Synthesis of Heterocycles

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Metal-Catalysed Hydroamination of Alkynes

L. D. Field, B. A. Messerle, A. Shasha

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Organometallic Catalysts for the Synthesis of Heterocycles

S. Burling, L. D. Field, H. L. Li, B. A. Messerle, S. Rumble, A. Shasha and H. van Heyden

XXIst International Conference on Organometallic Chemistry, Vancouver, Canada, 25th-30th July **2004**. Poster Presentation, Poster 155.

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Exploring New Metal Catalysts for Hydroamination

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Exploring New Metal Catalysts for Hydroamination

L. D. Field, B. A. Messerle, A. Shasha

12th The Royal Australian Chemical Institute Convention (RACI Connect 2005), Sydney Convention and Exhibition Centre, Darling Harbour, Sydney, 3rd-7th July, **2005**. Oral Presentation, Abstract 125.

Exploring New Metal Catalysts for the Synthesis of Heterocycles via Hydroamination

S. Burling, L. D. Field, H. L. Li, B. A. Messerle, S. Rumble and A. Shasha

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Abstract

This thesis describes the synthesis of terminal and internal amino- and amidoalkynes and their hydroamination (cyclisation) catalysed by the complex (*bis*(*N*-methylimidazol-2-yl)methane)dicarbonylrhodium(I) tetraphenylborate (**1**). A series of analogous palladium complexes were also prepared and investigated for catalytic hydroamination.

The scope of the rhodium(I) complex (**1**) for the intramolecular hydroamination of more complex amino- and amidoalkyne substrates was investigated. This was made possible with the synthesis of aliphatic substrates, namely, 4-pentyn-1-amide (**3**) and 5-hexyn-1-amide (**4**) and a number of aromatic substrates, namely, 1, 4-diamino-2, 5-diethynylbenzene (**5**), 1, 4-diamino-2, 5-*bis*(phenylethynyl)benzene (**6**), 2, 3-diamino-1, 4-diethynylbenzene (**7**), 2, 3-diamino-1, 4-*bis*(phenylethynyl)benzene (**8**), 1, 5-*bis*(acetamido)-2, 4-diethynylbenzene (**9**), *N*-(acetyl)-2-ethynylbenzylamine (**10**) and *N*-(acetyl)-2-(phenylethynyl)benzylamine (**11**).

The rhodium(I) complex (**1**) catalytically cyclised the aliphatic 4-pentyn-1-amide (**3**) regioselectively to the 6-membered ring, 3, 4-dihydro-2-pyridone (**64**) as the sole product. Attempts to cyclise 5-hexyn-1-amide (**4**) to produce either the 6- or 7-membered ring were unsuccessful. Compounds **5**, **6**, **7** and **8** were doubly cyclised to 1, 5-dihydro-pyrrolo[2, 3-*f*]indole (**71**), 1, 5-dihydro-2, 6-diphenyl-pyrrolo[2, 3-*f*]indole (**73**), 1, 8-dihydro-pyrrolo[2, 3-*g*]indole (**74**) and 1, 8-dihydro-2, 7-diphenyl-pyrrolo[2, 3-*g*]indole (**75**) respectively.

The aromatic amides with terminal acetylenes **9** and **10** cyclised to give 1, 7-diacetyl-pyrrolo[3, 2-*f*]indole (**76**) and *N*-(acetyl)-1, 2-dihydroisoquinoline (**77**) respectively. However, attempts to cyclise **11** were unsuccessful. Thus the

rhodium(I) complex (**1**) successfully catalysed *via* hydroamination both terminal and internal acetylenic amine and amide substrates, to give pyridones, indoles and isoquinolines.

Cationic and neutral palladium complexes incorporating the bidentate heterocyclic nitrogen donor ligand *bis*(*N*-methylimidazol-2-yl)methane (bim; **2**) were synthesised: $[Pd(bim)Cl_2]$ (**15**), $[Pd(bim)_2][BF_4]_2$ (**17**) $[Pd(bim)(Cl)(CH_3)]$ (**14**), $[Pd(bim)(CH_3)(NCCH_3)][BF_4]$ (**16**). All of the complexes were active as catalysts for the intramolecular hydroamination reaction, using the cyclisation of 4-pentyn-1-amine (**21**) to 2-methyl-1-pyrroline (**22**) as the model test reaction. Percentage conversions, turnover numbers and reaction profiles for each complex were compared to the rhodium(I) complex (**1**). These studies have shown that the catalytic activity was not significantly dependent on the bim donor ligand or the choice of metal. Substitution of the bim (**2**) ligand with the COD ligand and the use of methanol as the solvent did impact significantly on the efficiency of the hydroamination reactions.

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List of Abbreviations

Ac	Acetate
app	apparent
aq	aqueous
Ar	aromatic
ATI	aminotroponiminate
$(B(Ar^F)_4)^-$	$(B(3, 5\text{-}C_6H_3(CF_3)_2)_4)^-$
bik	*bis*(*N*-methylimidazol-2-yl)ketone
bim	*bis*(*N*-methylimidazol-2-yl)methane
bpm	*bis*(1-pyrazolyl)methane
bs	broad singet (NMR)
Bu	Butyl
COD	η^4-1, 5-cyclooctadiene
COT	1, 3, 5, 7-cyclooctatetraene
Cp	η^5-cyclopentadienyl
Cp*	η^5-pentamethylcyclopentadienyl
Cy	cyclohexyl
δ	chemical shift (ppm)
d	deutero
d	doublet (NMR)
dec.	decomposed
DIPAMP	1, 2-*bis*[(*o*-methylphenyl)(phenyl)phosphino]ethane
DMF	*N*, *N*-dimethylformamide
EI	Electron Impact Ionisation
ESI	Electrospray Ionisation
Et	Ethyl
Et_2NH	diethylamine

Et_3N	triethylamine
EtOH	ethanol
h	hours
HRMS	High Resolution Mass Spectrometry
Hz	hertz (s^{-1})
Im	*N*-methylimidazol-2-yl
IR	Infrared
J	scalar coupling constant (NMR)
L	Ligand
m	multiplet (NMR)
m	meta
m.p.	melting point
m/z	mass to charge ratio
Me	Methyl
min	minutes
Morpho-CDI	*N*-Cyclohexyl-*N*′-(2-morpholinoethyl)carbodiimide methyl-*p*-toluenesulfonate
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
N-N	bidentate nitrogen donor ligand
N_t (h^{-1})	turnover number (moles of product produced per mole of catalyst used per hour)
o	ortho
OTf	trifluoromethanesulfonate
p	pentet (NMR)
p	para
Ph	Phenyl
ppm	parts per million
py	pyridine
pz	1-pyrazolyl
q	quartet (NMR)
R_f	thin layer chromatography retention factor

s	singlet (NMR)
t	triplet (NMR)
t-Bu	*t*-Butyl (-C(CH_3)$_3$)
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	trimethylsilyl
Tos	tosyl (*p*-toluenesulfonyl)
Triphos	*bis*(diphenylphosphinoethyl)phenylphosphine

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