

Sequential Processes Using Catalytic C-O Bond Activation

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Abstract

This thesis is centred around sequential C-C bond forming processes using oxygenated electrophiles. A major part of this research focuses on the constructive deoxygenation of 2-methoxyphenol (guaiacol), a major breakdown product of the renewable feedstock, lignin.

1,2-dielectrophiles are known to be challenging substrates for catalysis if both leaving groups are of similar reactivity, however high selectivity was observed in the palladium-catalysed Grignard cross-coupling of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate. The previously untested Grignard cross-coupling catalyst, [PdCl₂(Xylyl-Phanephos)], was found to be highly active.

A 2-benzoxazolyl functionality was shown to be an excellent directing group for the chelation-controlled nucleophilic aromatic substitution of aryl methyl ethers. However, this modified Meyers reaction is limited to aryl ethers containing an *ortho*-chelating group. To expand the ether scope, nickel-catalysed Grignard cross-coupling was studied. [NiCl₂(P^{*n*}Bu₃)₂] showed increased activity in the Grignard cross-coupling of challenging *ortho*-substituted anisoles compared to the well-renowned [NiCl₂(PCy₃)₂] and several Ni⁰-NHC systems, with a ligand steric effect demonstrated. The success of [NiCl₂(P^{*n*}Bu₃)₂] was extended to more activated methoxynaphthalene substrates, in which the lowest reported catalyst loadings (0.1-0.25 mol%) were reported. Induction periods at 0.1 mol% suggested the requirement of inorganic Lewis-acidic magnesium salts to be formed *in situ* before any considerable activity was observed. Further work is required to increase reaction and ether scope, but this work provides a basis for exploiting lignin-derived phenols as a framework in the synthesis of functionalised chemicals of higher value.

The final results chapter concerns an alternative sequential C-C bond forming process using another oxygenated electrophile. [PdCl₂((*S*)-Xylyl-Phanephos)] was used to accomplish a Grignard cross-coupling of vinyl tosylate, with the product then subjected to a highly enantioselective methoxycarbonylation using the same catalyst. This led to a concise synthesis of (*S*)-Flurbiprofen.

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Finally, I thank my partner Lois, who is just incredible, in everything she does. Thanks for always being there and I'm looking forward to the next chapter of our lives together.

Abbreviations and Acronyms

[α]	Specific rotation of a chiral compound
Å	Angstrom
acac	Acetylacetone
Ac	Acetyl
AD	Alzheimer's disease
Am	Amyl
aq	Aqueous
Ar	Aromatic group
ASAP	Atmospheric solids analysis probe
ATR	Attenuated total reflectance
β_n	Natural bite angle
b/l	Branched / linear ratio
br	Broad (NMR)
Bu	Butyl
°C	Degrees Celsius
c	Concentration
C _{Ar}	Aromatic carbon
cat.	Catalyst
CI	Chemical ionisation (mass spectrometry)
cin	Cinnamyl
<i>cis</i>	Two particular atoms or functional groups lie on the same side of a given plane in the molecule
cm ⁻¹	Reciprocal centimeters
cod	1,5-cyclooctadiene
COX	cyclooxygenase
Cy	Cyclohexyl
d	Doublet (NMR)
dba	Dibenzylideneacetone
dcype	1,2- <i>bis</i> (dicyclohexylphosphino)ethane
dd	Doublet of doublets (NMR)
ddd	Doublet of doublet of doublets (NMR)
depe	1,2- <i>bis</i> (diethylphosphino)ethane
DMAc	Dimethylacetamide
dppf	1,1'- <i>bis</i> (diphenylphosphino)ferrocene
dt	Doublet of triplets (NMR)
e.e.	Enantiomeric excess
EI	Electron ionisation (mass spectrometry)
elim.	Elimination
equiv.	Equivalents
ESI	Electrospray ionisation (mass spectrometry)
Et	Ethyl
<i>et al.</i>	And others
FDA	Food and drug administration
g	Gram
GC	Gas chromatography

GCMS	Gas chromatography – mass spectrometry
h	Hours
Hal	Halogen
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
ICy	1,3-dicyclohexylimidazol-2-ylidene
IDM	1,3- <i>bis</i> methylimidazol-2-ylidene
Im	Imidazole
IMes	1,3- <i>bis</i> (2,4,6-trimethylphenyl)imidazol-2-ylidene
<i>in situ</i>	In place
<i>in vacuo</i>	Under reduced pressure
<i>in vivo</i>	Taking place in a living organism
IPr	1,3- <i>bis</i> (2,6-diisopropylphenyl)-imidazol-2-ylidene
IPr*	1,3- <i>bis</i> (2,6- <i>bis</i> (diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene
IR	Infrared
<i>J</i>	Coupling constant (NMR)
L	Ligand
L	Litre
LA	Lewis acid
LG	Leaving group
lit.	Literature value
μ	Micro
m	Medium (IR)
m	Multiplet (NMR)
<i>m-</i>	<i>meta</i> (position)
M	Molarity
Me	Methyl
mg	Milligram
min	Minute
mL	Millilitre
mmol	Millimoles
mol	Moles
mp	Melting point
MS	Molecular sieves
m/z	Mass to charge ratio
<i>n-</i>	Linear/Primary substitution
n.d.	Not determined
NHC	N-heterocyclic carbene
NMDP	Neomenthyl diphenyl phosphine
NMR	Nuclear magnetic resonance
NSAID	Nonsteroidal anti-inflammatory drug
Nuc	Nucleophile
<i>o-</i>	<i>ortho</i> (position)
OAc	Acetoxy
<i>p-</i>	<i>para</i> (position)
Ph	Phenyl
PhMe	Toluene
ppm	Parts per million

Pr	Propyl
PTSA	<i>para</i> -Toluenesulfonic acid
py	Pyridyl
q	Quartet (NMR)
R	Any group where carbon, hydrogen or heteroatom is attached
<i>R</i>	(<i>R</i>)-enantiomer – <i>rectus</i> , priorities of substituent decrease in a clockwise direction according to the Cahn-Ingold-Prelog
<i>rac</i>	Racemic
rt	Room temperature
s	Singlet (NMR)
s	Strong (IR)
<i>S</i>	(<i>S</i>)-enantiomer – <i>sinister</i> , priorities of substituent decrease in a counter-clockwise direction according to the Cahn-Ingold-Prelog
<i>s</i> ⁻/ <i>sec</i> -	Secondary
SIPr	1,3- <i>bis</i> (2,6-diisopropylphenyl)-imidazolidin-2-ylidene
SM	Starting material
S _N Ar	Nucleophilic aromatic substitution
θ	Tolman cone angle
ν	Tolman electronic parameter
t	Triplet (NMR)
T	Temperature
<i>t</i> ⁻/ <i>tert</i> -	Tertiary
td	Triplet of doublets (NMR)
TEM	Transmission electron microscopy
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
t _R	Retention time
<i>trans</i>	Two particular atoms or functional groups lie on the opposite side of a given plane in the molecule
TLC	Thin layer chromatography
Tol	Tolyl
TON	Turnover number
TMEDA	Tetramethylethylenediamine
V _{bur}	Buried volume
<i>vice versa</i>	With the main items in the preceding statement the other way round
% v/v	Volume (of solute) per volume (of solution)
w	Weak (IR)

Contents

Declaration.....	i
Abstract.....	iii
Acknowledgements	iv
Abbreviations and Acronyms	v
I Introduction.....	1
1.1 Transition metal-catalysed cross-coupling	1
1.2 Quantifying ligand parameters in cross-coupling catalysis	7
1.2.1 The Tolman electronic parameter, ν	7
1.2.2 Steric Parameters	8
1.2.2.1 The Tolman cone angle, θ	8
1.2.2.2 % Buried volume, $\%V_{\text{bur}}$	8
1.2.2.3 Natural bite angle, β_n	9
1.3 Grignard cross-coupling	10
1.3.1 Grignard cross-coupling of phenolic electrophiles	12
1.3.1.1 Aryl phosphates	13
1.3.1.2 Aryl esters	16
1.3.1.3 Aryl carbamates	17
1.3.1.4 Aryl phenolates	18
1.4 Cleavage of methyl ethers with C-C bond formation.....	20
1.4.1 Oxazolines – An efficient directing group to enable methyl ether cleavage.....	20
1.4.1.1 Oxazoline-assisted nucleophilic aromatic substitution reactions	21
1.4.2 Nickel-catalysed cross-coupling of aryl methyl ethers	24
1.4.2.1 Nickel-catalysed cross-coupling of aryl methyl ethers with aryl Grignard reagents	24
1.4.2.2 Nickel-catalysed cross-coupling of aryl methyl ethers with alkyl/alkenyl Grignard reagents.....	28
1.4.2.3 Other nucleophiles	31

1.4.2.3.1	Organoborane reagents.....	31
1.4.2.3.2	Organozinc reagents.....	34
1.4.2.3.3	Organolithium reagents.....	35
1.4.2.3.4	Trialkylaluminium reagents.....	37
1.4.2.4	Carbon-Heteroatom formation.....	38
1.4.2.5	Nickel-catalysed reductive cleavage/hydrogenolysis.....	39
1.4.2.6	Mechanistic considerations in the activation of aryl methyl ethers.....	40
1.4.2.6.1	“Classical” cross-coupling mechanism.....	41
1.4.2.6.2	Lewis acid-assisted oxidative addition.....	42
1.4.2.6.3	[Ni-ate] ⁻ mechanism.....	44
1.5	Project aims.....	47
II	Catalytic constructive deoxygenation of lignin-derived phenols: cross-coupling of 2-methoxyphenyl-1<i>H</i>-imidazole-1-sulfonate	49
2.1	Introduction.....	49
2.2	Results and discussion.....	54
2.2.1	Grignard cross-coupling of vicinal dielectrophiles.....	54
2.2.2	Cross-coupling of the activated guaiacol derivative, 2-methoxyphenyl-1 <i>H</i> -imidazole-1-sulfonate.....	56
2.2.2.1	Palladium-catalysed Grignard cross-coupling.....	57
2.2.2.2	Nickel-catalysed Grignard cross-coupling.....	64
2.2.2.3	[PdCl ₂ (Xylyl-Phanephos)]-catalysed cross-coupling of 2-methoxyphenyl-1 <i>H</i> -imidazole-1-sulfonate with other nucleophiles.....	68
2.3	Summary and future work.....	71
III	Constructive deoxygenation of lignin-derived phenols: nucleophilic aromatic substitution of <i>ortho</i>-substituted aryl ethers	73
3.1	Introduction.....	73
3.2	Results and discussion.....	75
3.2.1	Modified Meyers reaction with benzoxazole.....	75

3.2.2	Extension of the modified Meyers reaction to other nucleophiles	79
3.2.3	Modified Meyers – benzoxazole cleavage.....	83
3.2.4	Extension of the modified Meyers reaction to other heterocycles.....	84
3.3	Summary and future work	89
IV	New nickel catalysts for the cross-coupling of aryl methyl ethers with Grignard reagents.....	91
4.1	Introduction.....	91
4.2	Results and discussion	94
4.2.1	Attempted Pd-Phanephos catalysed cross-coupling of 2-methoxybiphenyl	94
4.2.2	Ligand preparation	95
4.2.3	Preparation of nickel complexes.....	97
4.2.4	Catalysis studies.....	99
4.2.4.1	Effect of phosphine cone angle on the nickel-catalysed Grignard cross-coupling of 2-methoxybiphenyl.....	99
4.2.4.2	Effect of Grignard reagent on the nickel-catalysed cross-coupling of 2-methoxybiphenyl.....	111
4.2.4.3	Extending this nickel-catalysed Grignard cross-coupling to other challenging anisoles	114
4.2.4.4	Heterocyclic/chelating effect	118
4.2.4.4.1	Nickel-catalysed cross-coupling of 2-(2-methoxyphenyl)benzo[<i>d</i>]oxazole.....	119
4.2.4.4.2	Nickel-catalysed cross-coupling of 2-(2-methoxyphenyl)pyridine	121
4.2.4.5	Nickel-catalysed cross-coupling of methoxynaphthalenes..	122
4.2.4.6	Time profile analysis	130
4.3	Summary and future work	135
V	Synthesis of (<i>S</i>)-Flurbiprofen utilising a highly enantioselective palladium-catalysed methoxycarbonylation	139
5.1	Introduction.....	139

5.1.1	Flurbiprofen	139
5.1.2	Asymmetric routes to Flurbiprofen.....	141
5.1.3	Asymmetric hydroxy-/methoxycarbonylation of vinyl arenes	144
5.2	Results and discussion	150
5.2.1	Grignard cross-coupling to obtain vinyl arene.....	150
5.2.2	Catalytic carbonylation	158
5.2.2.1	Hydroxycarbonylation	158
5.2.2.2	Methoxycarbonylation	160
5.2.2.3	Attempts at a one-pot, consecutive cross-coupling – carbonylation reaction	163
5.2.3	Hydrolysis of enantioenriched Flurbiprofen methyl ester	168
5.3	Summary and future work	170
VI	Conclusions and future work.....	173
VII	Experimental	177
7.1	General information.....	177
7.2	Preparation of organometallic reagents	180
7.2.1	Preparation of titrating agent, salicylaldehyde phenylhydrazone	180
7.2.2	Preparation of Grignard reagents	180
7.2.3	Preparation of benzofuran-2-yl lithium and benzofuran-2-yl zinc chloride	181
7.3	Transition metal-catalysed Grignard cross-coupling of aryl/vinyl electrophiles	182
7.3.1	Preparation of substrates	182
7.3.1.1	General procedure 1: synthesis of aryl imidazole-sulfonates	182
7.3.2	Preparation of hydroxyphosphine ligand	187
7.3.3	General procedure 2: transition metal-catalysed Grignard cross- coupling of aryl/vinyl electrophiles	188
7.3.4	Product data	188
7.4	Modified Meyers reaction.....	197

7.4.1	Preparation of 2-(2-methoxyphenyl)benzo[<i>d</i>]oxazole.....	197
7.4.2	General procedure 3: modified Meyers reaction	198
7.4.3	Product data	198
7.5	Benzoxazole cleavage.....	209
7.5.1	General procedure 4: aryl benzoxazole cleavage.....	209
7.5.2	Product data	209
7.6	Preparation of nickel complexes.....	212
7.6.1	Preparation of phosphine ligands.....	212
7.6.2	Preparation of nickel complexes.....	214
	7.6.2.1 General procedure 5: Preparation of nickel complexes.....	214
	7.6.2.2 Product data	215
7.7	Nickel-catalysed Grignard cross-coupling of aryl methyl ethers	219
7.7.1	Preparation of 1-phenyl-2-methoxynaphthalene.....	219
7.7.2	General procedures	220
	7.7.2.1 General procedure 6: nickel-catalysed Grignard cross- coupling of aryl methyl ethers	220
	7.7.2.2 General procedure 7: nickel-catalysed Grignard cross- coupling of aryl methyl ethers using NHC salts	220
7.7.3	Time profile analysis of the nickel-catalysed Grignard cross- coupling of 2-methoxynaphthalene with <i>p</i> -TolMgBr	222
7.7.4	Product data	225
7.8	Palladium-catalysed carbonylation of 3-fluoro-4-phenylstyrene	236
7.8.1	Preparation of 3-fluoro-4-phenylstyrene.....	236
7.8.2	Palladium-catalysed hydroxycarbonylation of 3-fluoro-4-phenylstyrene	238
	7.8.2.1 General procedure 8: Palladium-catalysed hydroxycarbonylation	238
	7.8.2.2 Product data	239
7.8.3	Palladium-catalysed methoxycarbonylation of 3-fluoro-4-phenylstyrene	240
	7.8.3.1 General procedure 9: Palladium-catalysed methoxycarbonylation	240

7.8.3.2	Product data	241
7.8.4	Full experimental for tandem Grignard cross-coupling – carbonylation reactions	243
7.8.4.1	Grignard cross-coupling – methoxycarbonylation	243
7.8.4.2	Grignard cross-coupling – hydroxycarbonylation	248
VIII	References.....	251
IX	Appendix.....	xiv
9.1	[PdCl ₂ (Xyllyl-Phanephos)]-catalysed Grignard cross-coupling of vinyl tosylate with 2-fluoro-1,1'-biphenyl magnesium bromide, from which the average yield was obtained	xiv
9.2	Publications.....	xv
 <i>Additional data is found on the attached CD.</i>		
9.3	NMR spectra of novel compounds	xvi
9.4	X-ray data for crystal structures	xxxviii

Chapter I: Introduction

1.1 - Transition metal-catalysed cross-coupling

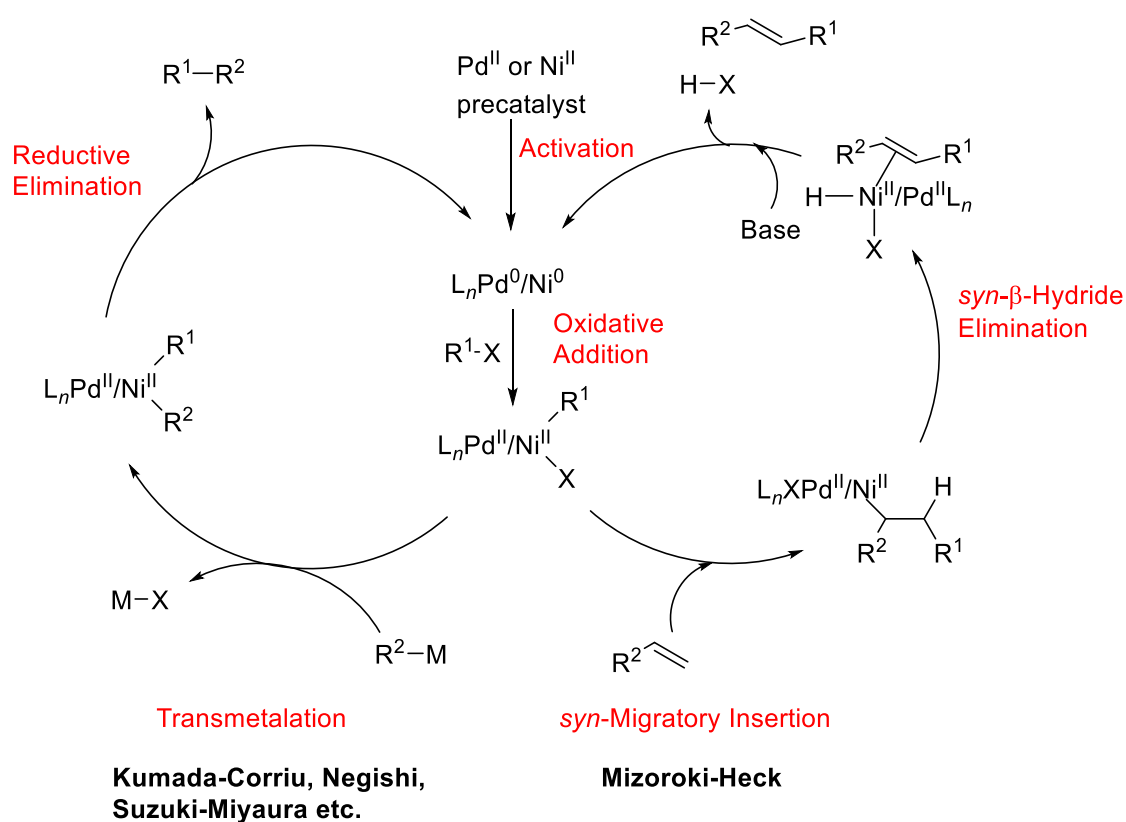
Carbon-carbon bond formations are vital in creating structural complexity and diversity in organic synthesis. Since the discovery of transition metal-catalysed cross-coupling in the early 1970s there has been a huge rise in importance of this reaction; this is exemplified by the awarding of Richard Heck, Ei-ichi Negishi and Akira Suzuki the Nobel Prize in 2010 for “*Palladium-Catalysed Cross-Couplings in Organic Synthesis*”.¹
² Their work capped an outstanding forty years of research in the field of cross-coupling chemistry in homogeneous catalysis.

Cross-coupling chemistry has become an incredibly useful strategy for organic synthesis with strategies and methods completely changed in both academia and industry as a result of this field of work. Instead of lengthy linear total syntheses of a complex molecule, the synthesis can be broken up into fragments and then seamed together by cross-coupling methods, often in a very clean and atom efficient manner. Presently, there are numerous types of cross-coupling reactions, each with their own specific traits (often found in the transmetalation step). Among the most heavily utilised are the: Heck Coupling, Kumada-Corriu Coupling (Grignard cross-coupling), Negishi Coupling, Stille Coupling and Suzuki-Miyaura Coupling. The reactions are transition metal catalysed and the catalytic cycle consists of three main steps:

1. Oxidative Addition
2. Transmetalation/Alkene Insertion
3. Reductive Elimination

Oxidative addition involves the coordination of (often) an organohalide to a low valent transition metal species (often Pd⁰ or Ni⁰) resulting in C-X bond cleavage to give a metal^{II} species. Transmetalation then occurs when an organometallic nucleophile exchanges its organic fragment for the halide on the metal thus beginning the “building” process. Alkene insertion (specific to the Heck Coupling) utilises the π -interaction that can occur

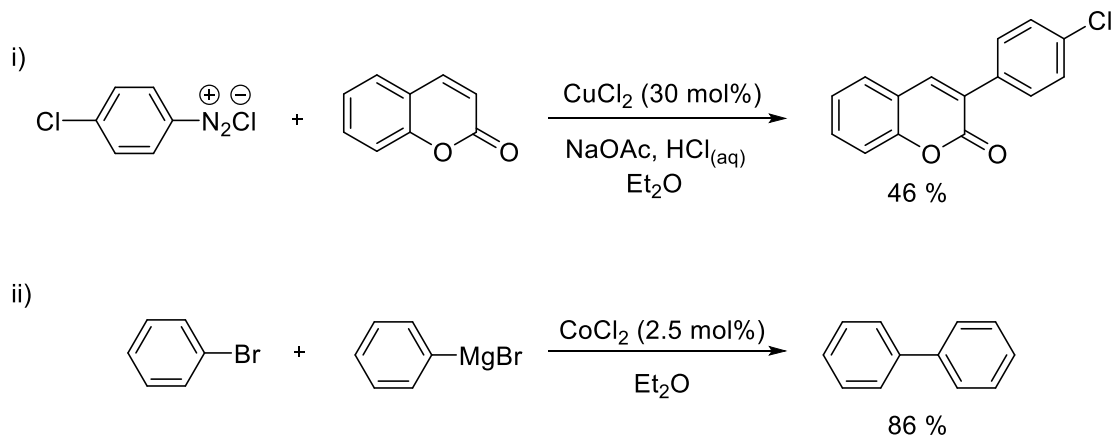
between an alkene and a transition metal to introduce an organic fragment to the framework, thus not requiring an organometallic species. These two organic functionalities, bound to the metal centre, are then “coupled” together in the reductive elimination step, forming a new (often C-C) bond. The active catalyst is then regenerated, proving that the metal simply provides a framework for the reaction to occur smoothly (Scheme 1.1). Each of these steps can be influenced by differing reaction conditions, including steric and electronic properties around the metal centre, that can be fine-tuned by correct ligand choice (see Section 1.2).



Scheme 1.1 – General cross-coupling catalytic cycles.

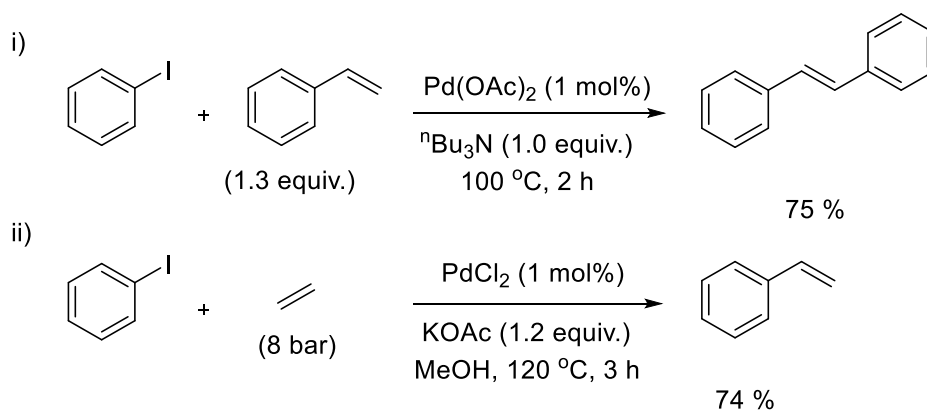
Although a major expansion of this field began in the 1960s and 1970s, the idea and the name of cross-coupling stems back to homocoupling reactions in the late 1800s with the Glaser Coupling, a copper-mediated homocoupling of phenylacetylene.³ This was then extended by Ullmann in 1901, who demonstrated that the homocoupling of 2-halonitrobenzenes could also be possible with copper under forcing conditions.⁴ Key breakthroughs for catalysis didn't occur until the late 1930s and early 1940s, with

Meerwein arylations (1939) (Scheme 1.2 i)⁵ and Grignard-based Kharasch Couplings (1941) (Scheme 1.2 ii).⁶ These two reactions were the first examples of catalytic C-C bond formation using transition metal coupling methods.



Scheme 1.2 – i) Meerwein arylation using catalytic copper(II) chloride. ii) Kharasch Coupling utilising catalytic cobalt(II) chloride and Grignard reagents for C-C bond formation.

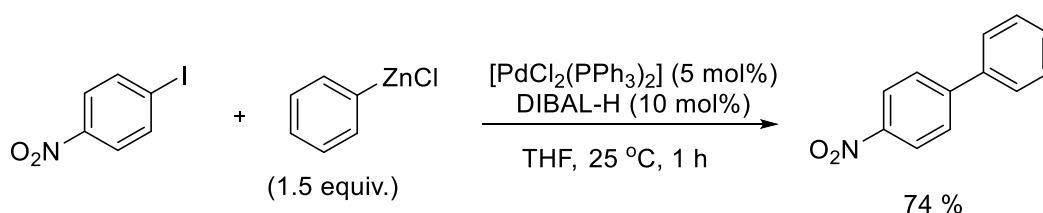
A significant discovery for cross-coupling chemistry occurred in the late 1960s when Richard Heck saw the potential of palladium in coupling chemistry. He^{7,8} and Mizoroki⁹ independently found that this transition metal could be used in catalytic quantities to successfully couple aryl halides with vinylic substrates (Scheme 1.3).



Scheme 1.3 – i) Heck cross-coupling of iodobenzene with styrene. ii) Mizoroki's finding of the reaction of iodobenzene with ethylene.

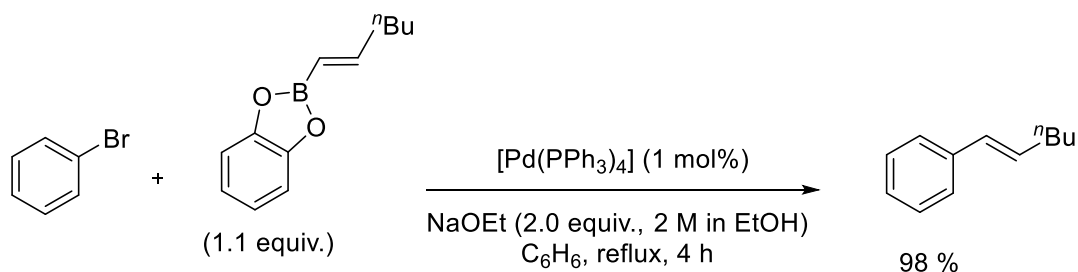
The Grignard cross-coupling reaction was then developed independently in 1972 by Kumada¹⁰ and Corriu,¹¹ in what was the first nickel-catalysed cross-coupling process.

Throughout the 1970s this discovery of transition metal-catalysed cross-coupling was expanded to include functional group tolerance in a number of varying electrophiles, as well as onto new cross-coupling reaction types with new organometallic nucleophiles. In 1977, Negishi demonstrated that cross-coupling processes could be extended to the use of organozincs as coupling partners, forming C-C bonds under palladium-catalysis (Scheme 1.4).¹² These alternative organometallic species showed good reactivity. The use of milder, less electropositive organozinc reagents allowed a relatively general reaction with impressive functional group tolerance to be established.



Scheme 1.4 – The Negishi cross-coupling using an organozinc reagent as the nucleophilic coupling partner.

Arguably the most important, and frequently used, cross-coupling reaction was developed in 1979 using organoboranes as the coupling partner. Suzuki and Miyaura initially found that alkenyl boranes could couple with aryl halides under palladium catalysis (Scheme 1.5).¹³ This was then later advanced to the coupling of arylboronic acids with aryl halides, which could be used to synthesise pharmaceutically interesting biaryls.¹⁴ These organoboranes were found to be air and moisture stable, allowed the use of mild reaction conditions and also yielded more benign by-products, thus making the Suzuki-Miyaura reaction industrially attractive.^{15, 16}



Scheme 1.5 – The first Suzuki-Miyaura cross-coupling reaction.

The high cost of (often) precious metal required for cross-coupling catalysis is compensated by the low catalytic loadings that are now possible in the best cases; often making the reaction cheaper than alternatives. While particularly heavily exploited in lab-scale synthesis, metal-catalysed cross-coupling methods are also used at large scale for the manufacturing of a range of pharmaceutical and fine-chemicals (Figure 1.1).^{15, 17}

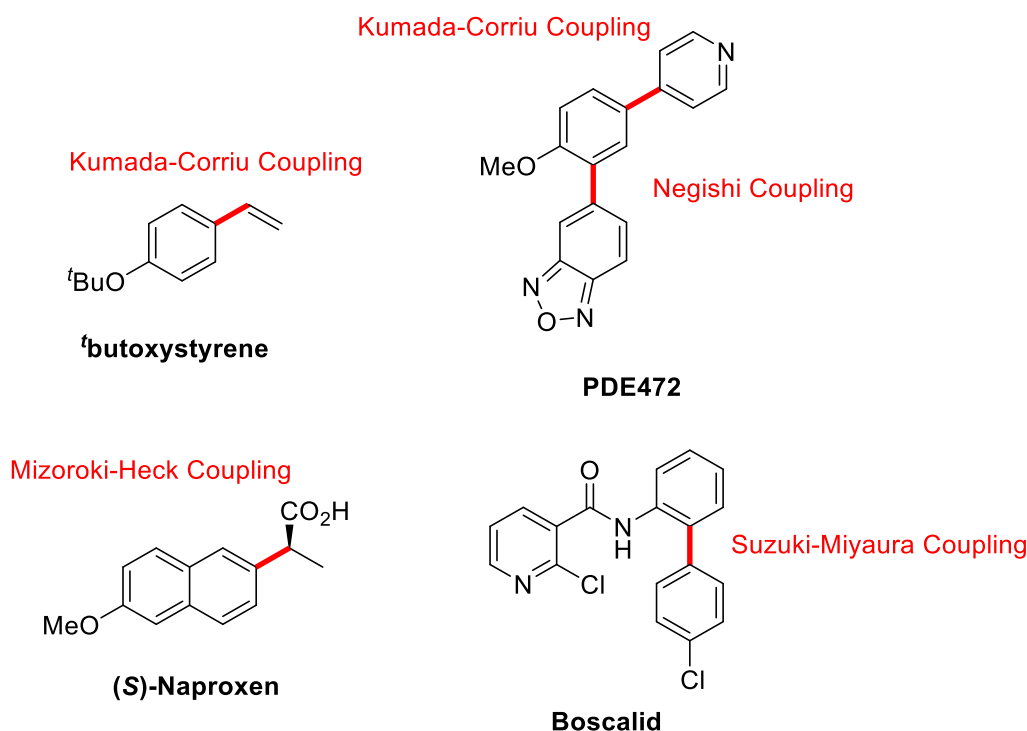


Figure 1.1 – The importance of cross-coupling chemistry in industry.

The four examples above each contain cross-coupling chemistry as a key step in the synthesis. Kumada-Corriu coupling (Grignard cross-coupling) (Section 1.3) was utilised by Hokko Chemical Industry for the production of several key vinylarene intermediates, with *t*-butoxystyrene reported to be produced on a 200 tonnes/year scale.¹⁸ Grignard cross-coupling was also used, alongside Negishi cross-coupling, in the large-scale production of PDE472, a potential drug for the treatment of asthma.¹⁹ The Heck coupling is present in the synthesis of (*S*)-Naproxen, (500 tonnes/year), to obtain a functionalised alkene which is subsequently hydroxycarbonylated and resolved.²⁰⁻²² The fungicide Boscalid is one of the largest products synthesised *via* a Suzuki-Miyaura reaction. Developed by BASF in 2002, it is produced on a scale of > 1000 tonnes/year.^{16, 23, 24}

These select drugs and fine-chemical building blocks exemplify the progress and the now apparent dependence on cross-coupling reactions within the chemical synthesis industry; for which the 2010 Nobel Prize has been suitably awarded.

1.2 - Quantifying ligand parameters in cross-coupling catalysis

Ligands play a critical role in modulating the properties of a catalyst in cross-coupling. Aspects such as product distribution, activity, and regio-, chemo-, and enantio-selectivity can often be altered by the choice of ligand. Key rate-determining steps can be accelerated e.g. increasing the σ -donating ability of the ligand can favour oxidative addition through rendering the metal more electron-rich,²⁵⁻²⁷ whilst bulky (often bidentate) ligands can accelerate reductive elimination processes instead of side reactions such as β -hydride elimination.^{28, 29} Ligand bulk can also accelerate oxidative addition by maximising the proportion of mono-ligated metal(0) species over more saturated di- and tri-ligated species.

1.2.1 - The Tolman electronic parameter, ν

In 1967, the electronic effects of phosphines were demonstrated by Strohmeier and Muller by measuring the change in infra-red (IR) frequency of the distinctive CO stretch for monophosphine-ligated nickel carbonyl complexes, $[\text{Ni}(\text{CO})_3\text{L}]$.³⁰ This concept was then heavily expanded by Tolman into what is now widely known as the Tolman Electronic Parameter (TEP), ν .^{31, 32} This electronic ranking system now applies to various ligand-types, including N-heterocyclic carbenes (NHCs).³³ Coordination of σ -donating ligands results in an increase in electron density at the metal centre. Consequently, the metal-carbonyl bond becomes stronger due to increased π -backbonding into the π^*_{CO} antibonding orbital, resulting in a weakening of the carbon-oxygen triple bond of the metal-bound carbonyl, which is easily detected by IR spectroscopy (Figure 1.2). The opposite effect is also true, with relatively electron-withdrawing ligands strengthening the carbon-oxygen triple bond. Estimations of the TEP, ν , for unsymmetrical phosphine ligands, or phosphines with no previous data, is also possible by using substituent contributions, χ , developed by Tolman, due to the additive relationship of the electronic parameters.

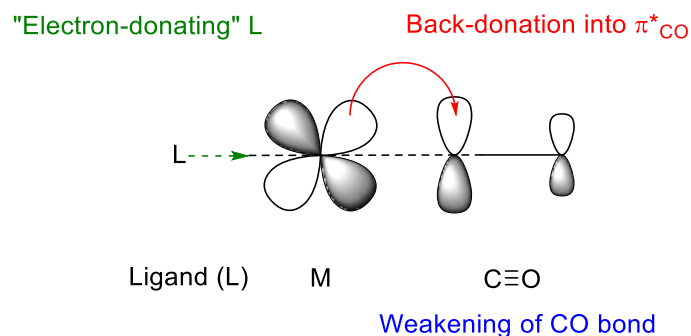


Figure 1.2 – The electronic effect of ligands on CO bonding in metal-carbonyl complexes through π -backbonding.³⁴

1.2.2 - Steric Parameters

1.2.2.1 - The Tolman cone angle, θ

In 1977, Tolman introduced the concept of phosphine cone angle to quantify the steric bulk around the metal, imposed by coordinated phosphines.³⁵ The Tolman cone angle, θ , for symmetrical ligands, is defined as “the apex angle of a cylindrical cone, centred 2.28 Å from the centre of the phosphorus atom, which just touches the van der Waals radii of the outermost atoms of the model” (Figure 1.3).³² A wide range of symmetrical phosphine ligands were measured using Corey-Pauling-Koltun (CPK) space-filling molecular models. An effective cone angle for unsymmetrically substituted phosphines can be calculated from the sum of the half angles for the three substituents.

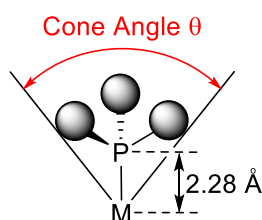


Figure 1.3 – The Tolman cone angle, θ .³⁶

1.2.2.2 - % Buried volume, $\%V_{\text{bur}}$

The percentage buried volume, $\%V_{\text{bur}}$, was introduced in 2003 by Nolan and co-workers.³⁷ It was found that the Tolman cone angle could not be effectively transferred

for use with NHC ligands.^{33, 38} NHC ligands are inherently less symmetrical than phosphines and therefore the steric impact can often be unevenly distributed, and thus challenging to model effectively. The steric impact of NHC ligands was defined (using x-ray crystal structure data and SambVca software³⁸), as the percentage of a sphere (radius 3.5 Å) occupied by the ligand and with the metal centre at the core (metal-carbon bond lengths of 2.00 or 2.28 Å) (Figure 1.4).

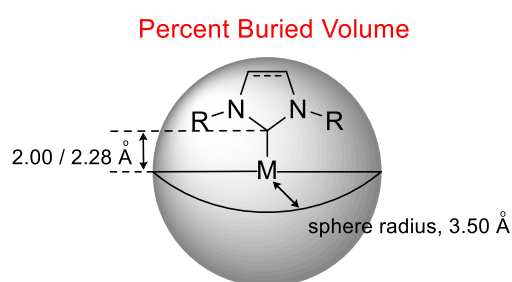


Figure 1.4 – The percentage buried volume, % V_{bur} , of an NHC ligand.³⁶

1.2.2.3 - Natural bite angle, β_n

The natural bite angle, β_n , is defined as the angle at which two donor atoms in a chelating bidentate ligand bind to a transition metal. It was introduced by Casey and Whiteker in 1990 by the use of molecular mechanics.³⁹ No crystal structure was required and thus a certain degree of flexibility was able to be modelled. Values are calculated using a “dummy metal atom” that is placed at a constant distance (depending on metal used) between the phosphorus atoms, to direct their lone pairs of electrons and substituents. This allows the constraints that would be imposed by a metal atom to be simulated (Figure 1.5).⁴⁰

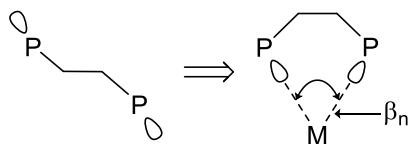
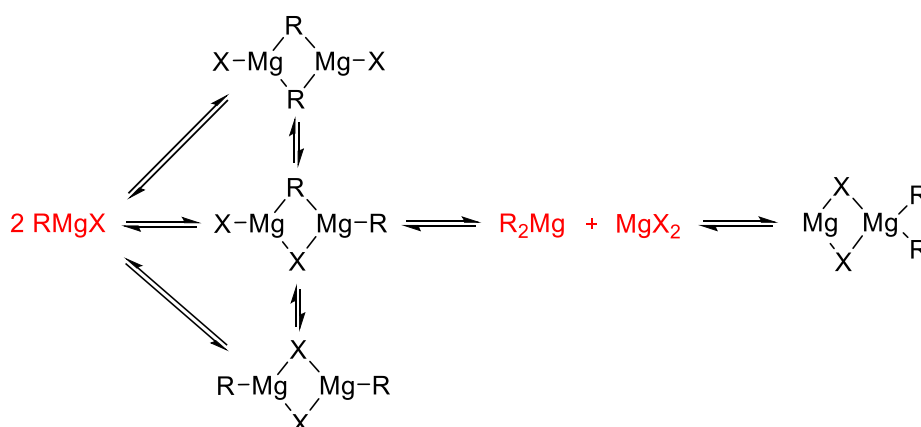


Figure 1.5 – The natural bite angle, β_n , of a bidentate phosphine ligand.⁴⁰

1.3 - Grignard cross-coupling

In 1900, Victor Grignard reacted alkyl halides with magnesium in ethereal solvent and discovered one of the most widely used organometallic reagents in chemistry,⁴¹ earning him the Nobel Prize in 1912 for “*the discovery of the so-called Grignard reagent, which in recent years has greatly advanced the process of organic chemistry*”.⁴² Generally expressed as “RMgX”, the Grignard reagent is known for its high nucleophilicity due to the increased electron density of the “R” group, caused by coordination of a magnesium ion. In 1905 Abegg first speculated the presence of an equilibrium for the composition of a Grignard reagent in an ethereal solvent.^{43,44} Schlenk and Schlenk then extended this to incorporate molecular association and also demonstrated that a dynamic system was present, in what is now known as the “Schlenk equilibrium” (Scheme 1.6).^{44,45}

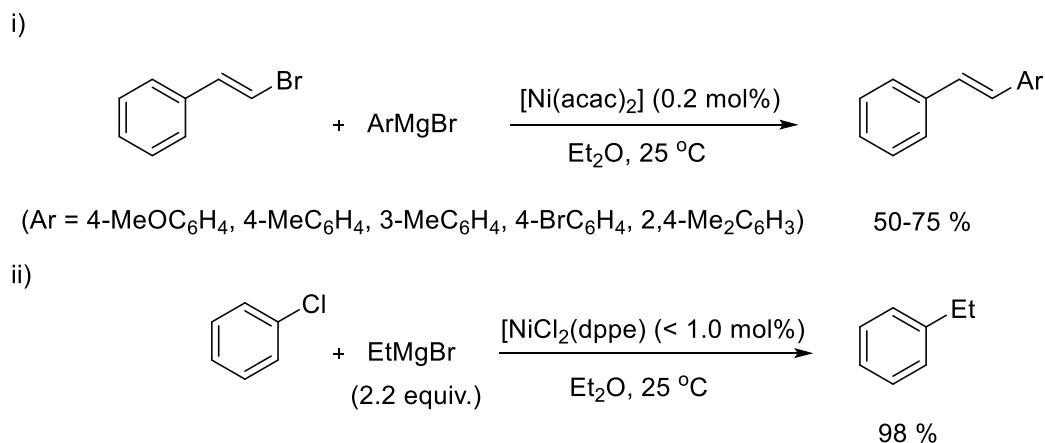


Scheme 1.6 – The Schlenk equilibrium.⁴⁶

Further understanding of this equilibrium has been difficult due to the vast number of factors/interactions that are prominent when in solution, ultimately having an effect on composition. Some of these include: solvent type, concentration, anion, “R” group, temperature.⁴⁴ This was exemplified by Ashby and Walker, who demonstrated that monomeric, dimeric and oligomeric species could exist in solution, depending on these conditions (Scheme 1.6).⁴⁷

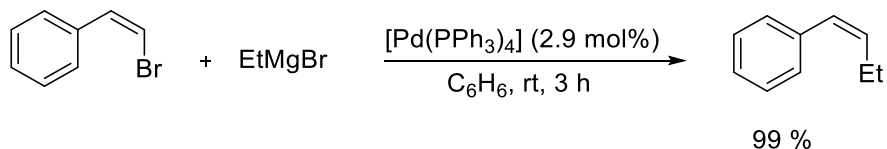
In the beginning of the 1970s Corriu¹¹ and Kumada¹⁰ independently utilised Grignard reagents as organometallic partners in the nickel-catalysed cross-coupling of alkenyl or

aryl halides with alkenyl or aryl magnesium halides (Scheme 1.7). The discovery of this novel C-C bond formation preceded the development of many other cross-coupling processes, namely the Negishi and Suzuki-Miyaura couplings. Kumada also introduced the first use of phosphine ligands in cross-coupling catalysis.



Scheme 1.7 – i) Examples of the Grignard cross-coupling of alkenyl halides developed by Corriu. ii) The nickel-phosphine-catalysed cross-coupling of an aryl halide and Grignard reagent discovered by Kumada.

Research by Murahashi followed in 1975 which resulted in the coupling of Grignard reagents under palladium catalysis (Scheme 1.8).⁴⁸ Palladium showed increased selectivity and broader substrate scope of the organometallic coupling partner, compared to nickel. This however, came at a price. Initially, only reactive substrates such as organobromides could be coupled effectively with palladium, and reactions with unreactive organohalides such as aryl chlorides and pseudohalides were more challenging.²⁹ Nevertheless, continuous ligand improvement in the development of cross-coupling managed to resolve this issue of low reactivity.^{49, 50}



Scheme 1.8 – The first palladium-catalysed Grignard cross-coupling.

The main drawback of Grignard cross-coupling is the relatively poor functional group tolerance, often limiting substrate scope. It is still common practice to use less-reactive

nucleophiles such as organoborane and organozinc reagents to ensure good functional group tolerance. However, there is beginning to be an increase in the number of examples of Grignard cross-couplings with reactive functional groups present, due to better catalytic systems allowing milder reaction conditions.^{51, 52} One key advantage is the low cost of the often commercially available Grignard reagents compared to organoboranes used in the Suzuki-Miyaura coupling. Kumada-Corriu type couplings also have the advantage of shortening the synthetic procedure, as the boronic acids used in Suzuki-Miyaura couplings are often derived from Grignard reagents.⁵³

1.3.1 - Grignard cross-coupling of phenolic electrophiles

Since phenols are widely available, the cross-coupling of phenol-derivatives has been the focus of much research, with the aim to broaden the scope of these reactions. To gain success, often the relatively inert phenolic bond must be activated, due to the high bond dissociation energies caused by p- π conjugation.⁵⁴ Significant progress has been made with the use of leaving groups such as triflates and tosylates, but with these come some significant drawbacks. Aryl triflates have found vast applicability in the field of cross-coupling due to their strong electron-withdrawing nature rendering the C_{aryl}-O bond more susceptible to interaction with the (often) electron-rich metal catalyst.^{55, 56} But, expensive and corrosive triflating agents such as triflic anhydride are required for their synthesis, which are relatively temperature and moisture sensitive, and breakdown products are suggested to be genotoxic.^{57, 58} Therefore, the use of milder activating functionalities such as tosylates grew in popularity. Aryl tosylates are significantly cheaper to synthesise and are often stable, crystalline solids, thus aiding handling. This stability however results in lower reactivity relative to triflates and thus the requirement for more forcing reaction conditions.⁵⁹ Consequently, other activating groups have emerged and although often lower in reactivity, they offer much more in regards to lower cost, toxicity and potential environmental impact, thus significantly increasing their applicability (Figure 1.6).

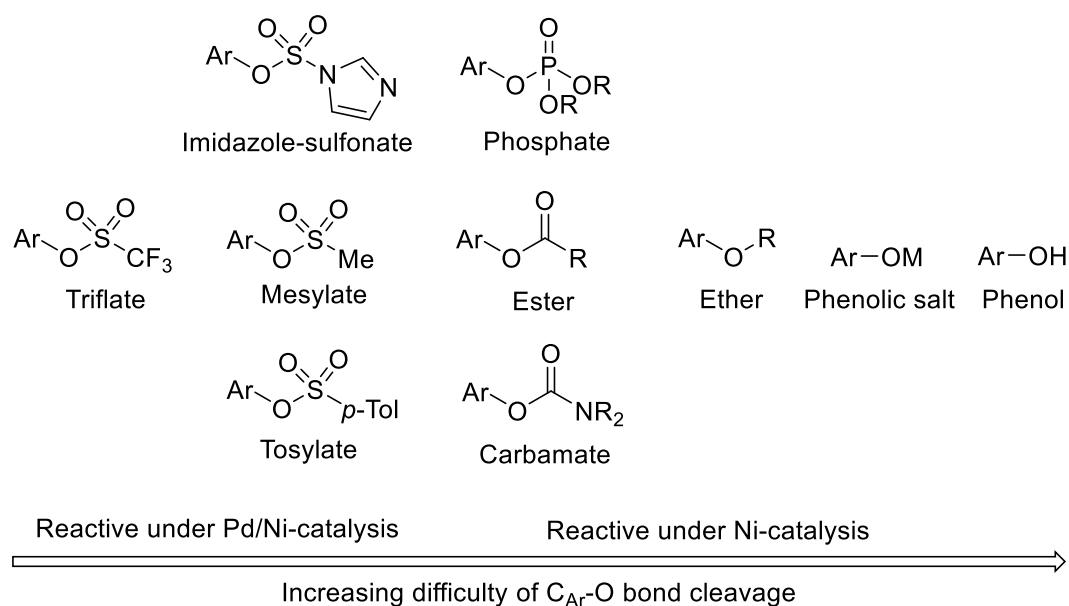
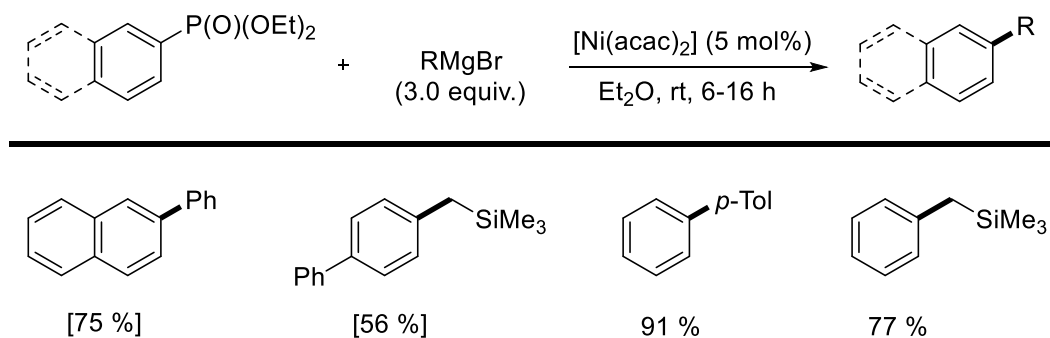


Figure 1.6 – Phenol derivatives used as alternative electrophiles to halogens in cross-coupling catalysis.^{54, 60}

Although the use of triflates and tosylates have allowed several transition metals to catalyse their cross-couplings with relative ease, nickel has shown the best and most general credentials for the cross-coupling of less-activated phenol derivatives. This is particularly evident with Grignard reagents, resulting in the resurgence of the use of nickel.^{61, 62} This group 10, earth abundant (1.8 %)⁶² metal is significantly cheaper than its precious counterparts palladium and platinum (\$1.20 mol⁻¹ vs \$1500 mol⁻¹ vs \$10000 mol⁻¹ respectively),⁶³ resulting in higher catalyst loadings being accepted (from an economic viewpoint). This increased reactivity observed with nickel for the challenging phenolic-based derivatives is thought to be due to the numerous oxidation states, and thus mechanistic flexibility that can be gained, as well as the smaller, more nucleophilic nature of the metal centre.^{59, 63}

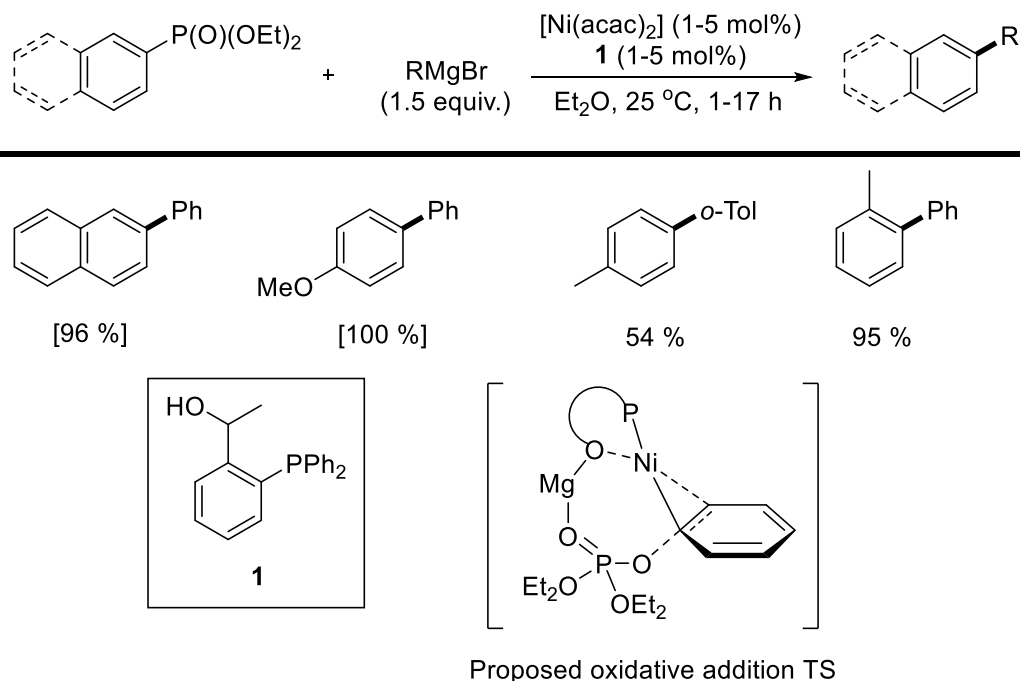
1.3.1.1 - Aryl phosphates

Phosphates were one of the first phenolic electrophiles to be successfully cross-coupled back in 1981 by Kumada and co-workers.⁶⁴ They showed that the reaction of vinyl and aryl phosphates with aryl and alkyl Grignard reagents could be effectively catalysed by nickel catalysts (Scheme 1.9).



Scheme 1.9 – The first nickel-catalysed Grignard cross-coupling of aryl phosphates. *Values in brackets are isolated yields.*

Nakamura and co-workers developed a hydroxyphosphine ligand (**1**) that facilitates a phosphine/magnesium alkoxide bimetallic species when coordinated to nickel.⁶⁵ This aids the troublesome oxidative addition of unreactive aryl electrophiles by bringing the substrate and nickel species into close proximity through mutual interaction with the Lewis-acidic magnesium salt (formed from deprotonation of the hydroxyl functionality of the ligand). This facilitates stronger η^2 -coordination between the nickel and substrate and allows a cooperative push-pull mechanism of the nucleophilic nickel and Lewis-acidic magnesium. The cross-coupling of several challenging electrophiles including phosphates (Scheme 1.10) and carbamates were coupled with Grignard reagents, under relatively mild conditions.



Scheme 1.10 – The Grignard cross-coupling of aryl phosphates with aryl Grignard reagents facilitated by the hydroxyphosphine ligand (**1**).⁶⁵ Values in brackets are isolated yields.

The use of aryl phosphates as electrophiles has found application in natural product synthesis as well as drug discovery, with the cross-coupling reactions yielding precursors for the cdc 25 protein phosphatase inhibitors cryptotanshinone (**2**) and tanshinone IIA (**3**),^{66, 67} as well as the drug candidate **4**, for the inhibition of interleukin-1 cytokine generation (Figure 1.7).⁶⁸

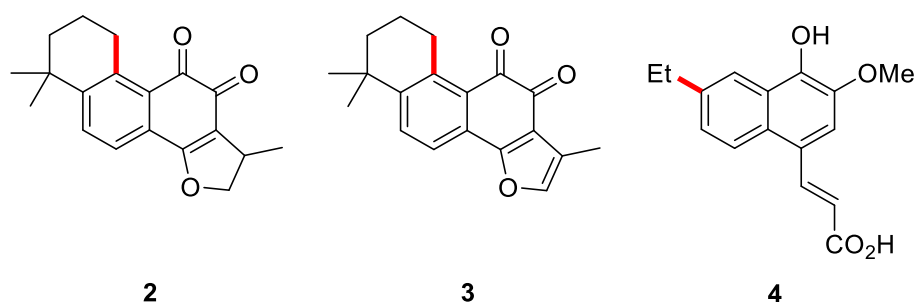
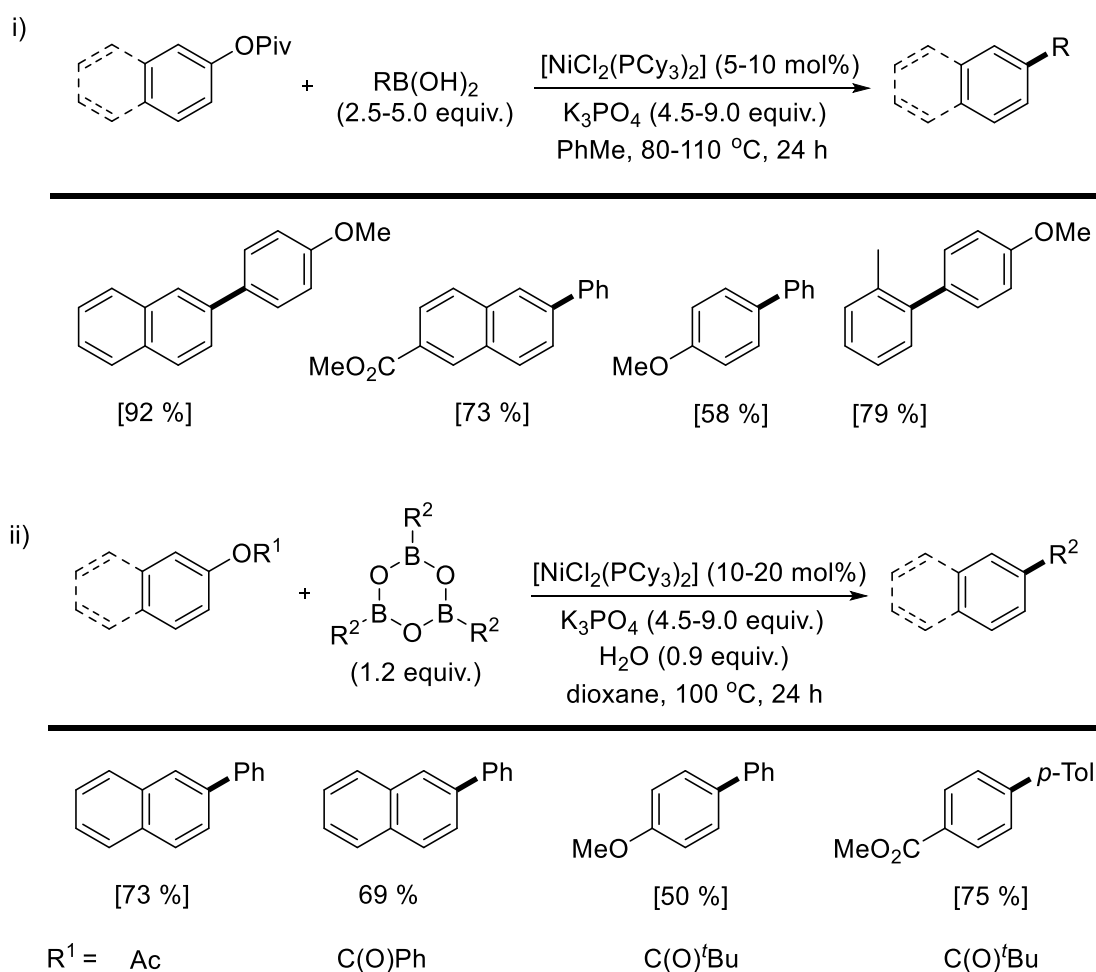


Figure 1.7 – Natural products and drug candidates partly synthesised by Grignard cross-coupling of aryl phosphates.

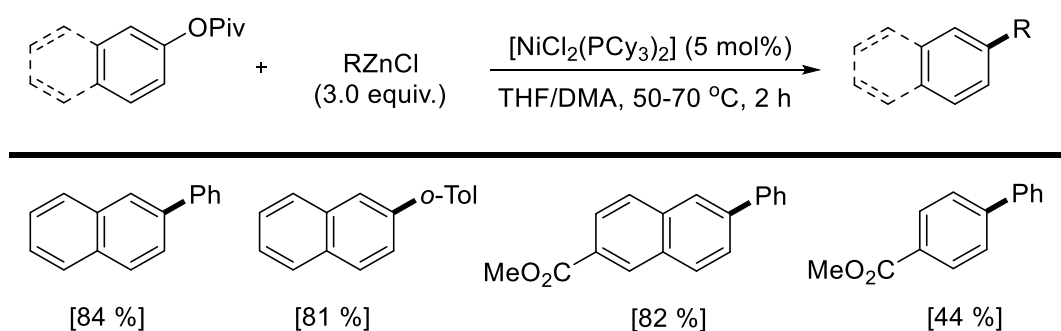
1.3.1.2 - Aryl esters

Aryl esters are another attractive electrophile, due to their ready availability and stability, however, issues surrounding chemoselectivity have had to be overcome. The use of strongly nucleophilic Grignard reagents has been restricted due to direct attack on the carbonyl C=O functionality rather than facilitating cross-coupling *via* cleavage of the phenolic C_{aryl}-O bond. Therefore, Garg⁶⁹ and Shi⁷⁰ independently found that Suzuki-Miyaura reactions, using less-reactive organoborane reagents could successfully cross-couple this class of phenol derivative (Scheme 1.11). Whilst Garg exclusively studied aryl pivalates, Shi demonstrated a wider range of aryl esters, with varying success. A drawback was that relatively forcing conditions were often required, due to the lower reactivity of the nucleophile.



Scheme 1.11 – i) Reactions of aryl pivalates with aryl boronic acids, demonstrated by Garg.⁶⁹
 ii) The enhanced reaction scope using aryl boroxines, developed by Shi.⁷⁰ Values in brackets are isolated yields.

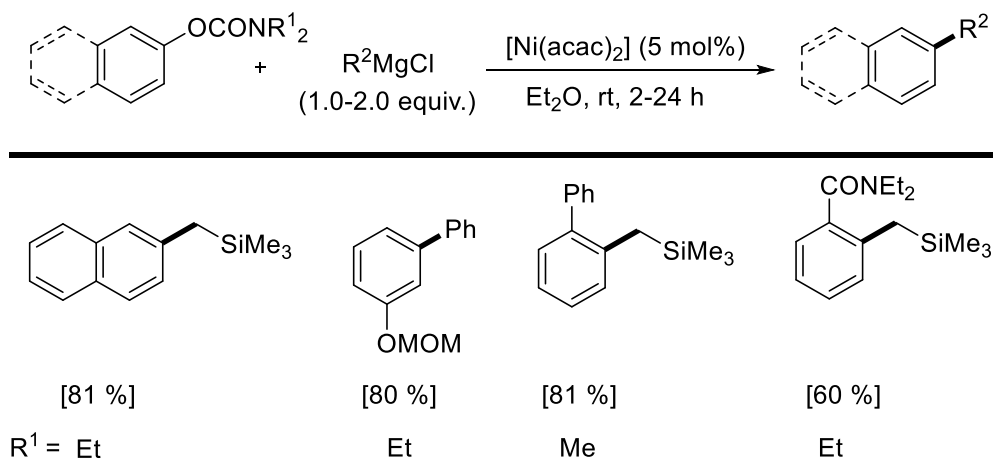
Shi and co-workers then demonstrated that milder conditions could be used with organozinc reagents as the nucleophilic agent.⁷¹ Successful nickel-catalysed Negishi cross-couplings of aryl pivalates with aryl organozinc reagents were reported (Scheme 1.12). In order to avoid hydrolysis to the phenol, increased steric bulk around the carbonyl functionality was required to suppress direct C=O attack. Therefore, only aryl pivalates were successfully coupled, with other esters such as naphthyl acetate being hydrolysed. Non-activated anisole substrates were low yielding. The authors proposed a “classical” mechanism involving oxidative addition, transmetalation and reductive elimination.



Scheme 1.12 – Nickel-catalysed Negishi cross-couplings of naphthyl pivalates with arylzinc reagents. *Values in brackets are isolated yields.*

1.3.1.3 - Aryl carbamates

Snieckus and co-workers were the first to report the nickel-catalysed Grignard cross-coupling of aryl carbamates in 1992 (Scheme 1.13).⁷² Compared to aryl esters, there were no issues regarding chemoselectivity. *ortho*-substituted aryl carbamates were also coupled, allowing a strategy for phenols to be transformed into 1,2-disubstituted arenes through the prior use of directed *ortho*-metallation.

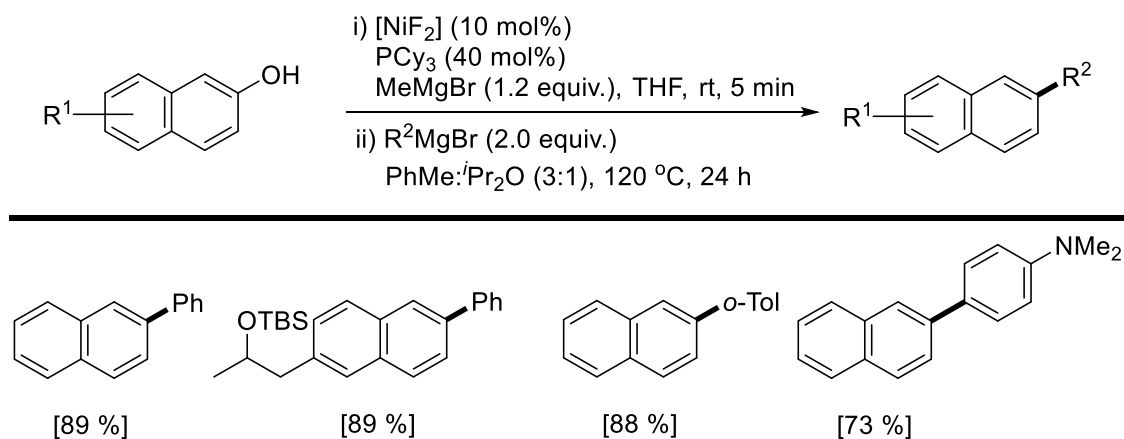


Scheme 1.13 – The initial nickel-catalysed Grignard cross-coupling of aryl carbamates under mild reaction conditions. *Values in brackets are isolated yields.*

Similar to with aryl phosphates (Scheme 1.10), Nakamura and co-workers reported an improved procedure for the cross-coupling of aryl carbamates using the hydroxyphosphine ligand **1**. Again, a broad substrate and Grignard reagent scope was apparent and yields were comparable with those of aryl phosphates, although slightly higher catalyst loadings were often required.

1.3.1.4 - Aryl phenolates

Apart from directly coupling phenol, (or methyl ethers), these activated phenolic salts provide the most direct route of functionalisation. The large bond dissociation energy of the C_{aryl}-OH bond and the fact that phenolates can act as relatively strong σ -donating ligands were envisaged to severely hinder this possibility. Shi and co-workers have recently shown an impressive nickel-catalysed Grignard cross-coupling of 2-naphthol salts.⁷³ The reaction was limited to 2-naphthol substrates although a wide range of functionalisation within the substrate and Grignard reagent could be tolerated (Scheme 1.14).



Scheme 1.14 – The impressive nickel-catalysed Grignard cross-coupling of naphtholates generated *in situ*. Values in brackets are isolated yields.

2-naphthol was initially deprotonated by MeMgBr and the subsequent magnesium salt was shown to efficiently react with aryl Grignard reagents. An X-ray crystal structure of the activated naphthol showed a dimeric species, [(2-naphthyl)OMgBr(THF)₂]₂, containing a four-membered-ring core, incorporating bridging magnesium ions. C_{aryl}-O bond lengths were the same value as the initial 2-naphthol, indicating no considerable change to the bond strength. This magnesium interaction was shown to enhance the cleavage of the C_{aryl}-O bond in what was predicted to be by a Lewis acid-assisted oxidative addition mechanism.

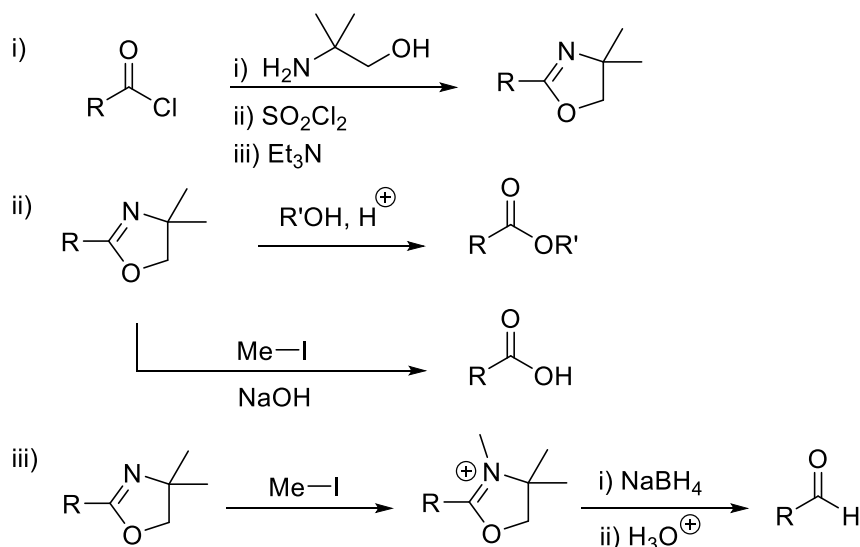
1.4– Cleavage of methyl ethers with C-C bond formation

Aryl methyl ethers have been shown to be stubbornly unreactive to a wide range of cross-coupling conditions. Although low in reactivity, this functionality has many attractive features that has driven the increased research on them in the last decade. Methyl ethers show considerably lower costs than other phenolic electrophiles such as triflates and tosylates, and are widely available. They are also present in a range of pharmaceutical and biologically active compounds, and their lower reactivity enables the possibility for late-stage functionalisation of these.

1.4.1 - Oxazolines – An efficient directing group to enable methyl ether cleavage

First prepared in 1884,⁷⁴ the oxazoline functionality lay relatively dormant for almost a century, becoming more utilised in the 1970s. Initially used as a protecting group for carboxylic acids and esters,⁷⁵ it has grown to become a versatile heterocycle that can enable several different reactions including *ortho*-metalation, nucleophilic addition, as well as the now heavily used, directed nucleophilic aromatic substitution (S_NAr). Aryl oxazolines have become a powerful chemo-, regio- and stereoselective directing/protecting group that can build complexity in compounds with speed and efficiency. Chiral variants have also been established which have found use in a range of syntheses from optically active biaryls and naphthyls, to chiral ligands for asymmetric catalysis.⁷⁶

Usually prepared by the reaction of an aryl acid chloride with a desired amino alcohol, followed by cyclisation with thionyl chloride,⁷⁷ aryl oxazolines can be deprotected (after desired reaction) to give the related carboxylic acid or ester by acidic hydrolysis (Scheme 1.15 i).⁷⁸ When acid-sensitive functionalities are present, alkaline hydrolysis can be successfully performed *via* conversion to the oxazolium salt, to yield the carboxylic acid (Scheme 1.15 ii).^{79, 80} Nordin demonstrated that aldehydes can be efficiently formed by the reduction of the oxazolium salt with $NaBH_4$ (Scheme 1.15 iii).⁸¹

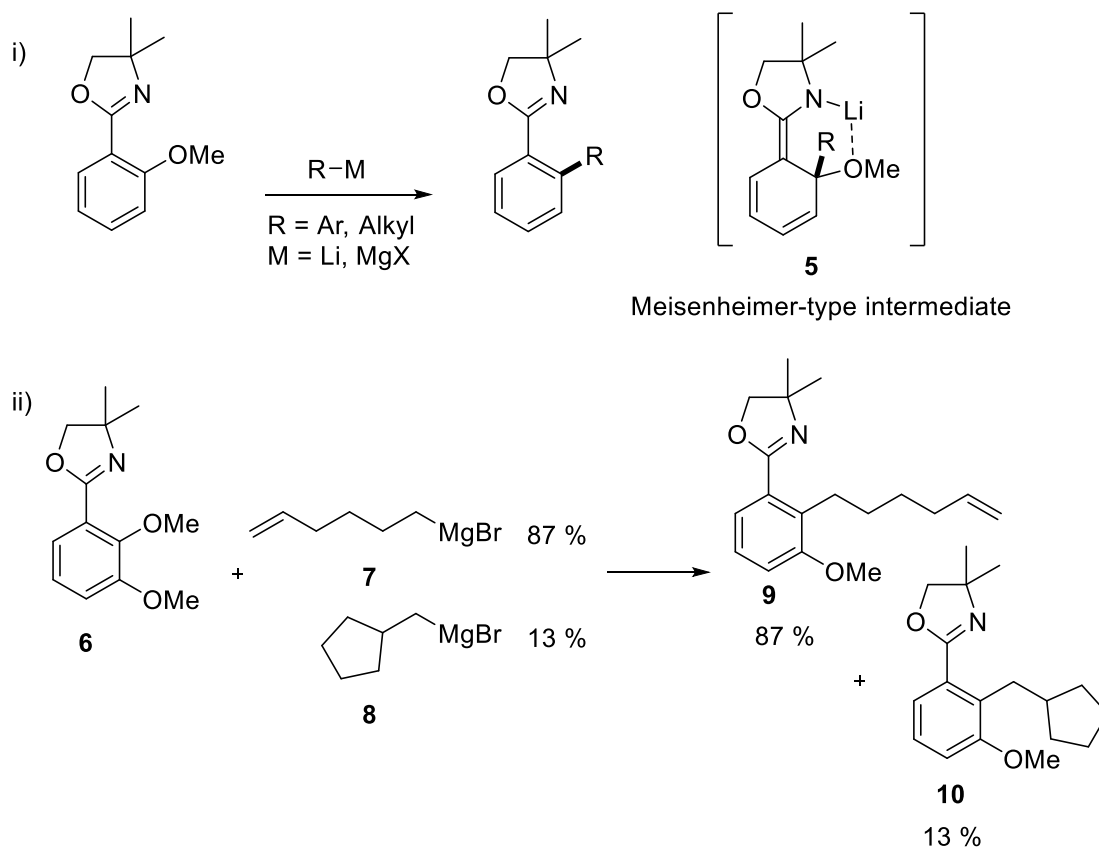


Scheme 1.15 – i) Synthesis of oxazolines. ii) Acid and alkaline hydrolysis of oxazolines. iii) Synthesis of aldehydes by oxazoline reduction.

1.4.1.1 - Oxazoline-assisted nucleophilic aromatic substitution reactions

Meyers and Mihelich were the first to exploit the directing characteristics of oxazolines in a nucleophilic aromatic substitution ($\text{S}_{\text{N}}\text{Ar}$) sense.⁷⁹ *Ortho*-(methoxy)aryloxazolines can successfully react with a range of nucleophiles to replace the relatively inert aryl methyl ether. This reaction was initially surprising as oxazolines are not particularly electron-withdrawing, which is usually an important prerequisite for $\text{S}_{\text{N}}\text{Ar}$ reactions. The success of this reaction relies on the chelating capability of the nitrogen lone pair of electrons to interact with the metal cation of the nucleophile, and consequently it is limited to *ortho*-substituted substrates. This chelation is such a driving force that *ortho*-lithiation does not occur when *ortho*-methyl ethers are present.⁸² The substitution is proposed to be following an addition-elimination mechanism, where the chelation-assisted addition of the nucleophile gives the stabilised metalated enamine (or Meisenheimer-type complex) intermediate (**5**), which can then eliminate the methoxide giving the desired *ortho*-substituted aryloxazoline (Scheme 1.16 i). After speculation regarding the likelihood of the reaction following a free-radical pathway, Meyers and co-workers studied the $\text{S}_{\text{N}}\text{Ar}$ reaction of aryloxazoline **6**, with hexenylmagnesium bromide (**7**) (Scheme 1.16 ii).⁸² The authors predicted that if an electron-transfer mechanism was apparent, a large quantity of the methylcyclopentane-substituted aryl oxazoline, **10**, should result, due to the large rate of rearrangement of the straight chain Grignard reagent to cyclopentylmethylmagnesium

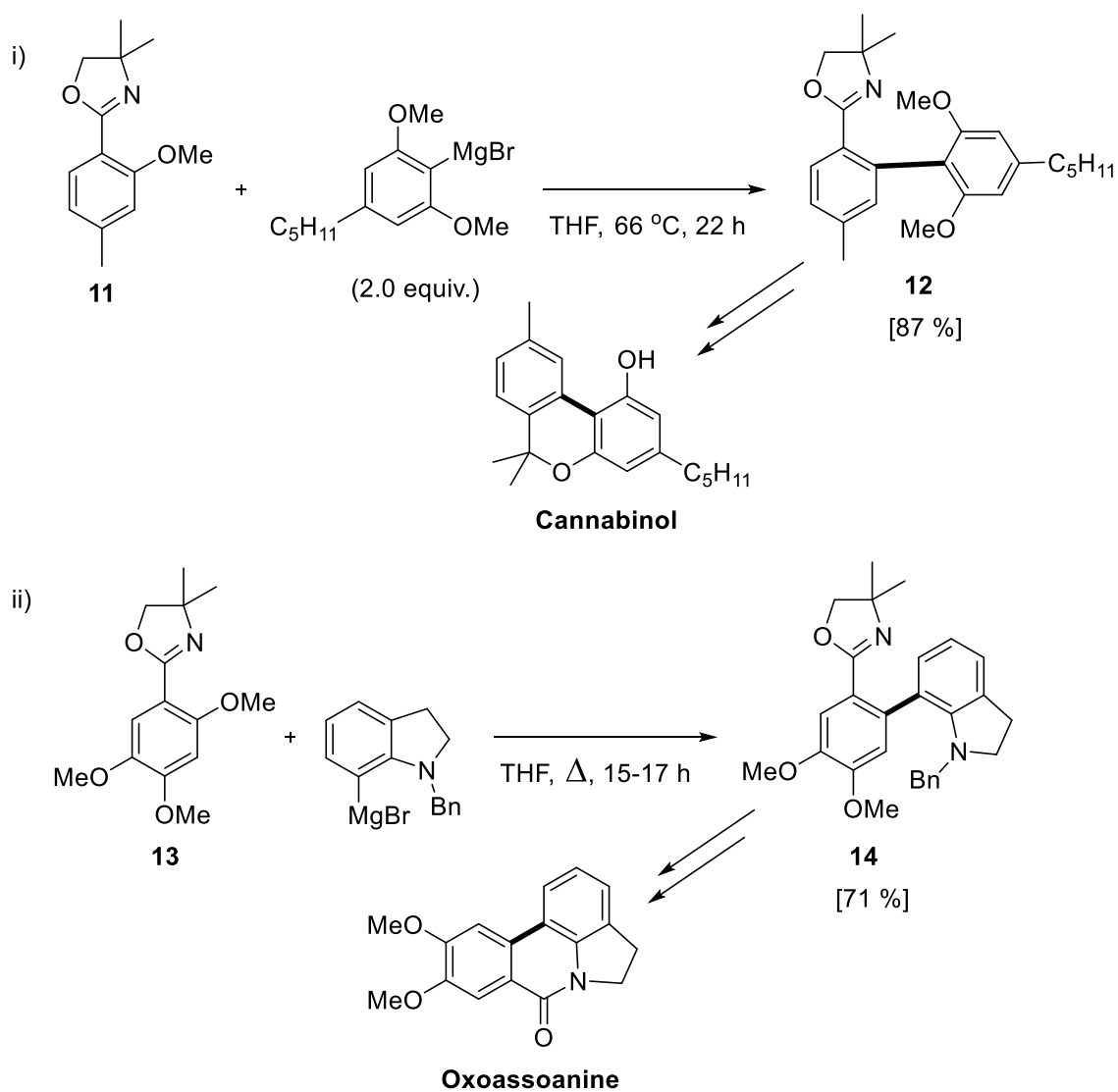
bromide (**8**), under radical conditions.⁸³ The initial relative ratio of the two Grignard species was measured prior to the attempted S_NAr reaction, and pleasingly this ratio was again apparent in the product distribution, therefore implying that the reaction was not following an electron-transfer mechanism.



The nucleophiles that can undertake this reaction include organolithiums, Grignard reagents, lithium amides,⁸⁴ alkoxides as well as silyllithiums.^{79, 82} However, limitations include “softer”, more delocalised anions such as benzyl Grignard reagents, enamines, thiolates and enolates, often resulting in demethylation.

This methodology has been successfully utilised in many areas of research including the synthesis of biaryls (often containing heterocycles of biological interest) and chiral ligands for asymmetric catalysis. Unsymmetrical biaryls can be readily formed using these S_NAr processes with oxazolines, often providing a more reliable method than

classical options such as transition metal-catalysed Ullman and Grignard cross-couplings. The high-yielding synthesis of the tetrahydrocannabinol (THP) metabolite, cannabiniol, involving the chelation-assisted displacement of the *ortho*-methyl ether in **11**, to form the hindered biphenyl oxazoline **12**, was reported by Novak and Saleminik (Scheme 1.17 i).⁸⁵ Oxoassoanine, part of the pyrrolophenanthridone class of alkaloids, was synthesised in high yield by reacting (1-benzylindolin-7-yl)magnesium bromide with 2-(2,4,5-trimethoxyphenyl)-4,4-dimethyloxazoline (**13**), to give biaryl **14**, which was subjected to partial hydrolysis, transesterification and benzyl deprotection, followed by cyclisation (Scheme 1.17 ii).⁸⁶



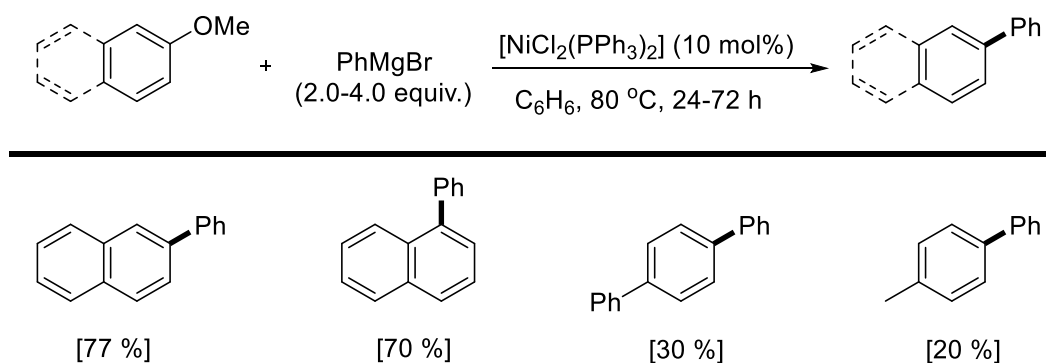
Scheme 1.17 – i) Synthesis of cannabiniol utilising a high-yielding oxazoline-directed S_NAr reaction. ii) Unsymmetrical biaryl formation using a S_NAr of an *ortho*-(methoxy)aryloxazoline in the total synthesis of oxoassoanine.

S_NAr of *ortho*-(methoxy)aryloxazolines provides a complimentary approach to the aforementioned *ortho*-lithiation reactions, as both ultimately result in *ortho*-substituted benzoic acids, once hydrolysed. Oxazolines have shown to be a remarkably efficient director that provides unprecedented generality, predictability and high yields, that is often not observed in C-C bond formation.⁸⁷

1.4.2 - Nickel-catalysed cross-coupling of aryl methyl ethers

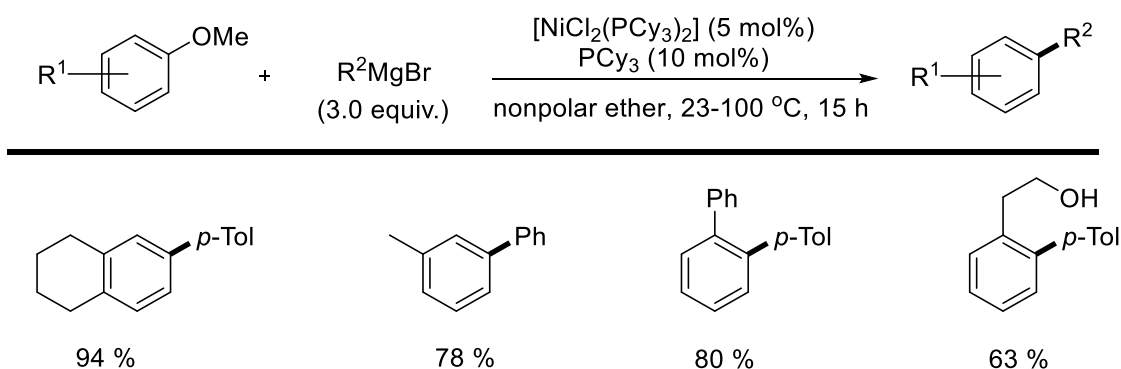
1.4.2.1 - Nickel-catalysed cross-coupling of aryl methyl ethers with aryl Grignard reagents

The Meyers reaction discussed in Section 1.4.1 is limited to compounds with oxazoline directing groups. Nickel catalysis has been found to expand the scope of aryl methyl ether cleavage. The major breakthrough, albeit under-utilised at the time, was when Wenkert and co-workers reported the first Grignard cross-coupling of aryl methyl ethers in 1979.⁸⁸ $[NiCl_2(PPh_3)_2]$ was shown to facilitate the cross-coupling of phenylmagnesium bromide (PhMgBr) with a range of naphthyl ethers (Scheme 1.18). Interestingly, there were problems regarding low reactivity of anisole derivatives (compared to naphthyl ethers), a recurring issue throughout the expanding literature. It was also reported that the alkyl Grignard reagent methylmagnesium bromide (MeMgBr) was completely unreactive, therefore giving an indication of poor nucleophilic scope, which has again plagued this area of research for some time.



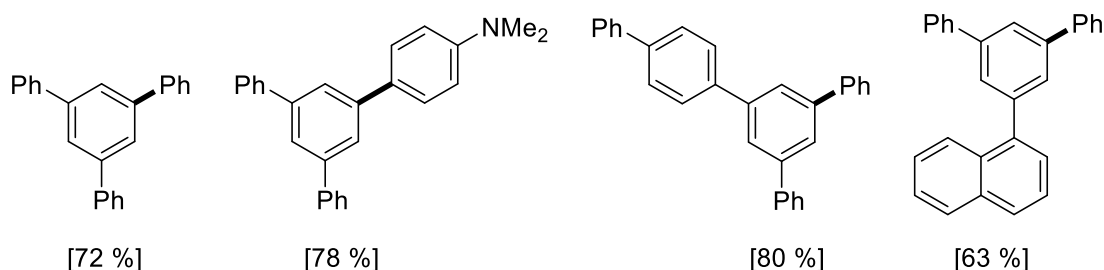
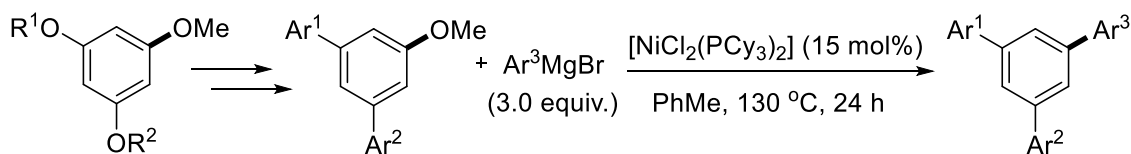
Scheme 1.18 – Seminal work by Wenkert and co-workers in the nickel-catalysed Grignard cross-coupling of aryl methyl ethers to form biaryls. *Values in brackets are isolated yields.*

This discovery was under-exploited for twenty five years until Dankwardt re-visited the Grignard cross-coupling of aryl ethers in 2004.⁸⁹ This lack of expansion throughout the 1980s and 1990s was likely due to the large success of palladium-catalysed cross-coupling processes, such as the Negishi (1977) and Suzuki-Miyaura (1979) reactions, that were heavily developed during this period. Dankwardt expanded the scope of this reaction to the more challenging non-activated aryl ethers, with the use of nickel(II) complexes containing strongly σ -donating alkyl phosphines with relatively large cone angles, such as $[\text{NiCl}_2(\text{PCy}_3)_2]$ and $[\text{NiCl}_2(\text{PCy}_2\text{Ph})_2]$. Biaryls were obtained in high yields by reacting large excesses of aryl Grignard reagents with various anisole derivatives (Scheme 1.19).



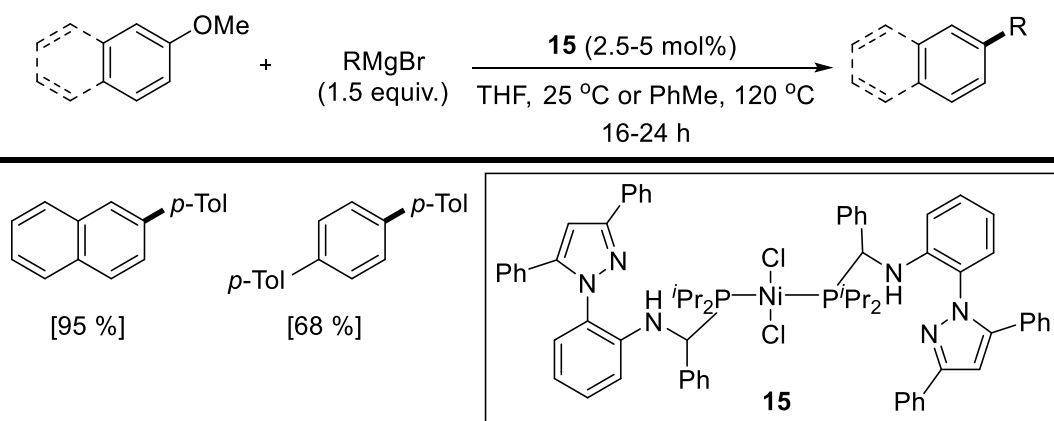
Scheme 1.19 – Research by Dankwardt that extended the substrate scope to include challenging anisole derivatives. Values in brackets are isolated yields and substrates containing an acidic functionality required an additional equivalent of Grignard reagent.

With the finding that $[\text{NiCl}_2(\text{PCy}_3)_2]$ was capable of facilitating the cross-coupling of the challenging, “inert”, $\text{C}_{\text{aryl}}\text{-OMe}$ bond, Shi and co-workers exploited the reactivity differences between other phenolic electrophiles and methyl ethers.⁹⁰ Sequential cross-coupling processes were performed in high selectivity to obtain a range of multiarylated benzenes (Scheme 1.20). Understandably, the methyl ether functionalisation was conducted at the final stages of the synthesis and the presence of electron-withdrawing aryl groups appeared to aid the cross-coupling reaction, with anisole derivatives lacking phenyl substituents giving poor yields. Increased sterics, due to prior naphthyl functionalisation, also resulted in more challenging ether substitution.



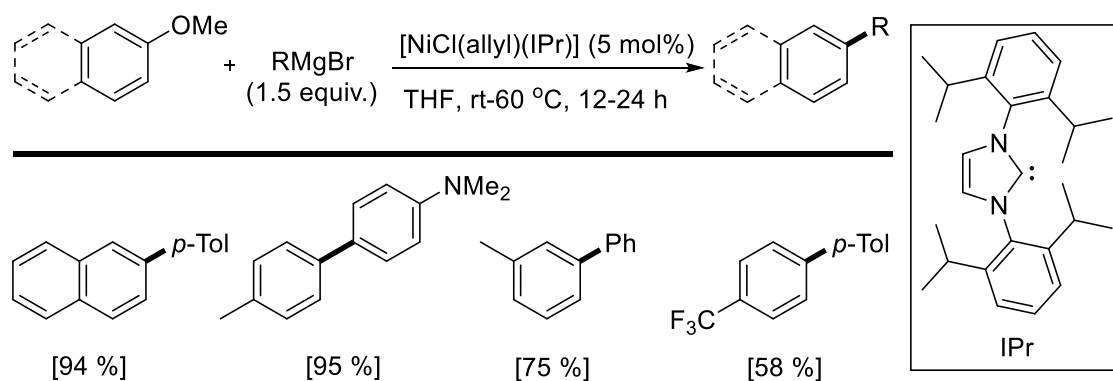
Scheme 1.20 – Sequential C(sp²)-O bond activation using the reactivity differences between phenolic electrophiles, including the nickel-catalysed Grignard cross-coupling of aryl Grignard reagents with [NiCl₂(PCy₃)₂]. Values in brackets are isolated yields.

With Dankwardt suggesting the requirement of monodentate, strong σ -donating phosphines containing a significant amount of steric bulk, Xie and Wang designed nickel(II) catalysts containing pyrazolyl amino phosphines such as **15** (Scheme 1.21).⁹¹ These were able to successfully cross-couple a range of naphthyl and aryl ethers with aryl Grignards. Again, naphthyl ethers were significantly more active and could be substituted under mild conditions. Complexes containing phenyl phosphines, were found to be less-reactive than **15**, reiterating the requirement for σ -donating alkyl phosphine ligands. Although a wide reaction scope was apparent, there were no *ortho*-substituted anisoles reported, which are another step-up in difficulty.



Scheme 1.21 – Catalyst **15**, containing a bulky, electron-rich trialkylphosphine, developed by Xie and Wang, as a successful alternative for the nickel-catalysed Grignard cross-coupling of aryl methyl ethers with aryl Grignard reagents. Values in brackets are isolated yields.

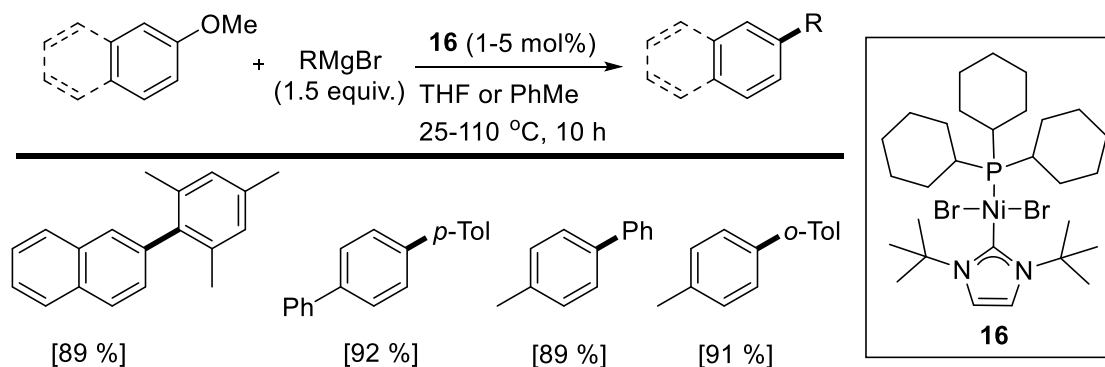
Although the use of strongly σ -donating alkyl phosphines like PCy_3 appear to be required in this area of research, N-heterocyclic carbenes (NHCs) have also been extensively used in cross-coupling reactions since their first isolation in 1991.⁹² NHCs have been shown to deliver very electron-rich metal centres.³⁷ Nicasio and co-workers trialled their use in the nickel-catalysed aryl ether cross-coupling, using aryl Grignard reagents.⁹³ Naphthyl methyl ethers were able to be transformed at room temperature using 5 mol% of $[\text{NiCl}(\text{allyl})(\text{IPr})]$, containing the bulky NHC 1,3-*bis*(2,6-diisopropylphenyl)-imidazol-2-ylidene (IPr) (Scheme 1.22). Anisole derivatives were also successfully reacted at the relatively low temperature of 60 °C and with only a small excess of Grignard reagent. However, no *ortho*-substituted anisoles were successfully coupled. Increased sterics within the Grignard reagent gave negligible reactions, resulting in only three Grignard reagents being reported (PhMgBr , *p*- TolMgBr and *p*- $\text{N}(\text{Me})_2\text{PhMgBr}$).



Scheme 1.22– The first use of an NHC ligand in aryl methyl ether cross-coupling. Values in brackets are isolated yields.

Finally, in 2015 Zhang and co-workers combined the previous successes of alkyl phosphines and NHCs to create mixed NHC/phosphine nickel(II) complexes.⁹⁴ It was envisaged that a synergic effect could be apparent. This effect in nickel catalysis was first reported by Shibata and co-workers in the Grignard cross-coupling of aryl halides, where the mixed complex $[\text{NiCl}_2(\text{PPh}_3)(\text{IPr})]$ was shown to have higher activity than its relative *bis*-phosphine and *bis*-carbene complexes.⁹⁵ It was suggested that this superior activity was due to the hemilability of the phosphine to create a vacant site, and the stability of this active species was enabled by the coordinated bulky NHC. Zhang and co-workers therefore extended this methodology to aryl ethers by utilising the renowned

tricyclohexylphosphine (PCy₃) with 1,3-ditertbutylimidazol-2-ylidene (tBu), in the complex [NiBr₂(PCy₃)(tBu)] (**16**) (Scheme 1.23).



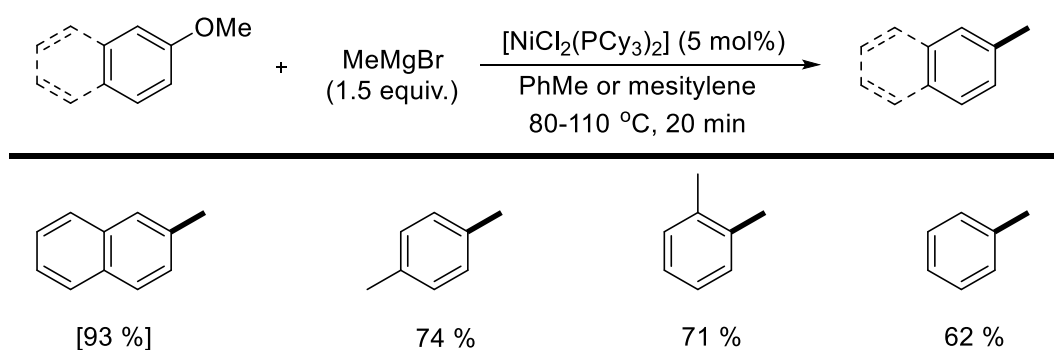
Scheme 1.23 – The cross-coupling of aryl methyl ethers catalysed by **16**. Values in brackets are isolated yields.

This system allowed significant improvements to previous literature in regards to catalyst loadings, with only 1 mol% required for the active naphthyl ethers and loadings as low as 2 mol% for anisole derivatives. It was also the first to show extended diversity in terms of the Grignard reagent, with a range of aryl Grignard reagents with varying electronic and steric properties being successfully coupled with methoxynaphthalenes, albeit with increased catalyst loadings or temperatures. Unsurprisingly, the scope of the more challenging anisole derivatives was lower and elevated temperatures of 110 °C were required to gain activity. Again, no *ortho*-substituted anisoles were reported.

1.4.2.2 - Nickel-catalysed cross-coupling of aryl methyl ethers with alkyl/alkenyl Grignard reagents

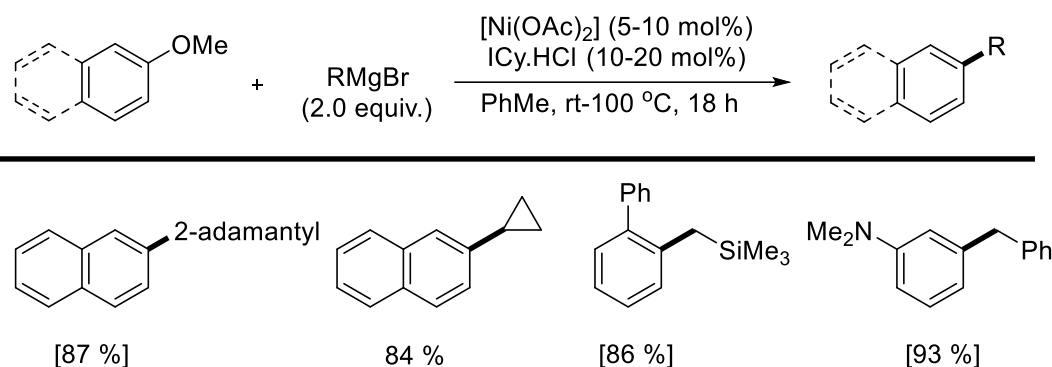
Although work had expanded the scope of the nickel-catalysed Grignard cross-coupling of aryl methyl ethers since the early discoveries, there was still a void in regards to coupling C(sp³)- and C(sp)-based Grignard reagents. The majority of the initial success had come from utilising aryl Grignard reagents of limited steric bulk. A major complication of attempting to couple alkyl nucleophiles is the inherent β -hydride elimination that can occur when coordinated to the metal centre.

With $[\text{NiCl}_2(\text{PCy}_3)_2]$ shown to be an active catalyst for this difficult transformation, Shi and co-workers reported the first examples of methylation in 2008.⁹⁶ Although simpler in the sense that no β -hydride elimination could occur, this was still an important discovery, especially since Dankwardt and Wenkert had previously been unable to promote this reaction. MeMgBr was successfully reacted with naphthyl and aryl ethers in as little as 20 minutes, to give high yields of the desired products (Scheme 1.24).



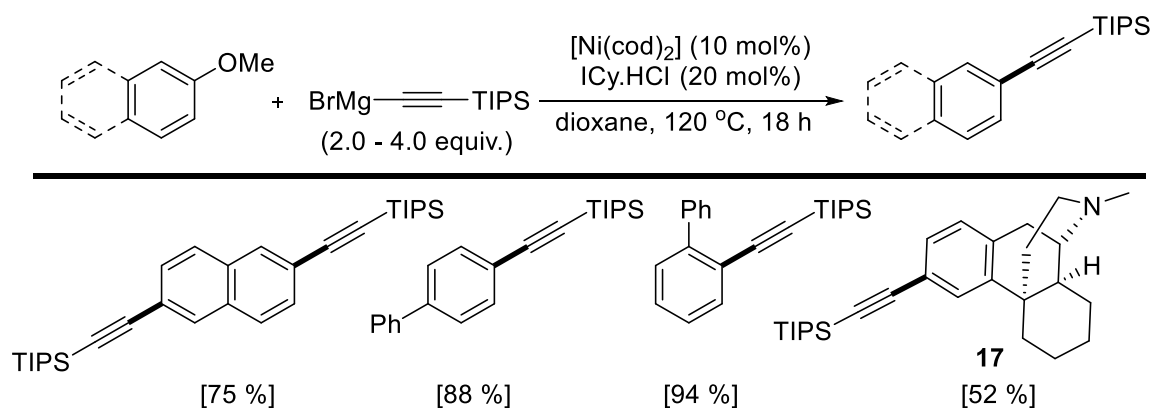
Scheme 1.24 – First examples of methylation of aryl methyl ethers by nickel-catalysed cross-coupling. Values in brackets are isolated yields. For further comments on this protocol, see page 116.

Chatani and co-workers found a combination of $[\text{Ni}(\text{OAc})_2]$ and 1,3-dicyclohexylimidazolium chloride ($\text{ICy}\cdot\text{HCl}$) to be effective in the cross-coupling of challenging anisole derivatives and methoxynaphthalenes with $\text{Me}_3\text{SiCH}_2\text{MgCl}$, where PCy_3 was unsuccessful.⁹⁷ After failed attempts with alkyl Grignard reagents containing β -hydrogen atoms, such as ${}^n\text{C}_5\text{H}_{11}\text{MgBr}$ and ${}^i\text{PrMgBr}$, gave undesired reduction instead of alkylation, the authors demonstrated reactivity with a range of alkyl Grignard reagents that either lacked β -hydrogen atoms, or were able to severely hinder the competing elimination. These included the first introduction of ArCH_2 , adamantyl and cyclopropyl groups to aryl methyl ethers (Scheme 1.25).



Scheme 1.25 – Ni/ICy-catalysed alkylation of aryl methyl ethers including the *ortho*-substituted 2-methoxybiphenyl. Values in brackets are isolated yields.

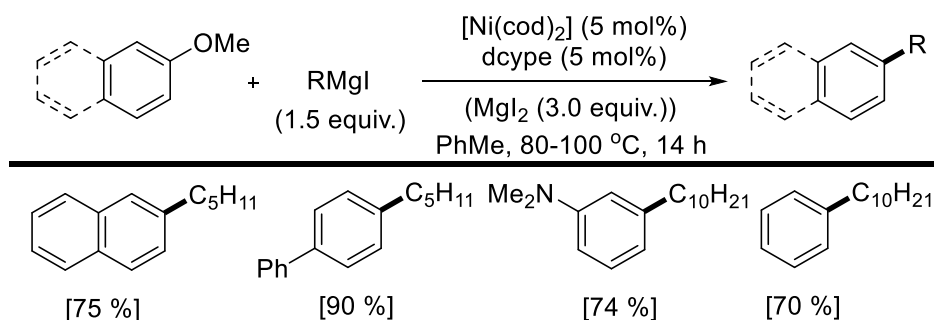
Previous to this, Chatani and co-workers also demonstrated the first nickel-catalysed alkylation of anisoles earlier in 2015.⁹⁸ [Ni(cod)₂] in combination with ICy·HCl was able to cross-couple anisoles, including the *ortho*-substituted 2-methoxybiphenyl, with a triisopropylsilyl (TIPS)-protected alkyne, in good to excellent yields (Scheme 1.26). The use of this bulky, protected alkyne was essential to the success of the reaction, most likely due to the suppression of the alkyne interacting with the nickel centre. Interestingly, this reaction was the first to show no significant bias towards naphthyl methyl ethers.⁹⁸



Scheme 1.26 – Examples of the first nickel-catalysed alkylation of aryl methyl ethers. Values in brackets are isolated yields.

This coupling was shown to be of great synthetic value in late stage derivatisation of substances relevant to pharmaceuticals: such as the antitussive drug Dextromethorphan to give **17**; or even organic materials: such as derivatisation of the organic semiconductor 3,10-dimethoxypicene, which can be further functionalised.⁹⁹

The same authors recently demonstrated the only methodology that fully overcomes the problem of β -hydride elimination when subjecting aryl methyl ethers to nickel-catalysed cross-coupling with alkyl Grignard reagents.¹⁰⁰ 1,2-*bis*(dicyclohexylphosphino)ethane (dcype) was found to be far superior to other common C_{aryl}-OMe activating ligands such as PCy₃ and NHCs, which returned starting material along with small quantities of reduced product. This ligand effect was due to the bidentate nature of dcype being able to prevent undesired β -hydride elimination from an alkylnickel intermediate. Interestingly, the halide of the Grignard reagent had a large effect on the success of the reaction. A simple change from alkylMgBr to alkylMgI facilitated the cross-coupling of a range of methoxynaphthalenes, whilst more challenging anisoles could be successfully reacted with the addition of a large excess of MgI₂ (Scheme 1.27).



Scheme 1.27 – Alkylation of aryl methyl ethers with Grignard reagents containing β -hydrogens. Values in brackets are isolated yields.

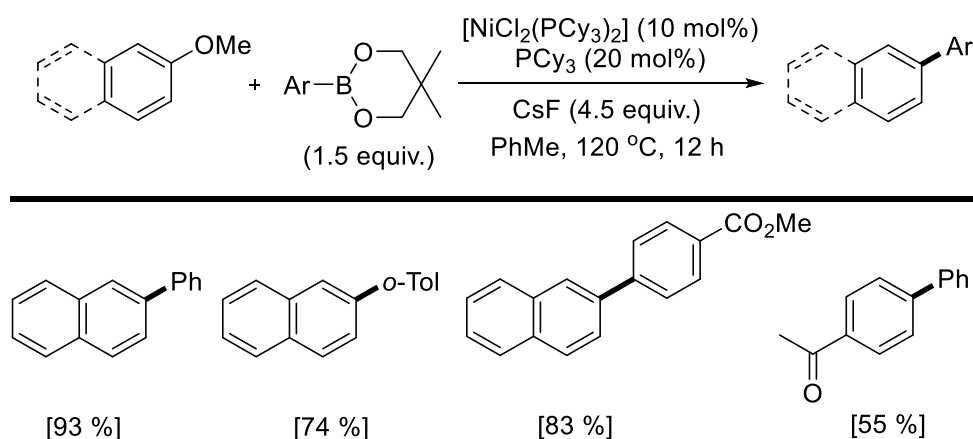
The only limitation of this alkylation was that steric effects appeared to severely hinder the reaction. Therefore, no *ortho*-substituted aryl ethers were successfully alkylated, regardless of the extent of substitution e.g. 1-methoxy-2-methylbenzene was completely unreactive.

1.4.2.3 - Other nucleophiles

1.4.2.3.1 - Organoboron reagents

In attempts to overcome the limited functional group tolerance that was apparent with Grignard reagents, Chatani and co-workers investigated the nickel-catalysed Suzuki-Miyaura reaction of aryl methyl ethers back in 2008.¹⁰¹ A [Ni(cod)₂]/PCy₃ catalytic

system was used, and similar to that observed with the Grignard cross-coupling reactions, methoxy groups connected to a fused aromatic ring showed enhanced activity. 2-methoxynaphthalene was reacted in high yield with a range of boronic esters, varying in steric and electronic properties (Scheme 1.28). As the relatively milder organoboron reagents were used, functional groups such as ketones and esters were untouched during the reaction. The only anisole derivative to yield any considerable product was 4-acetylanisole, albeit in a lower yield of 55 %, thought to be due to the increased activation of the methyl ether by the electron-withdrawing nature of the acetyl group. Consequently, substrate scope was considerably lower than when more reactive nucleophiles such as Grignard reagents were used, and this reactivity difference was also represented in the requirement for forcing reaction conditions.

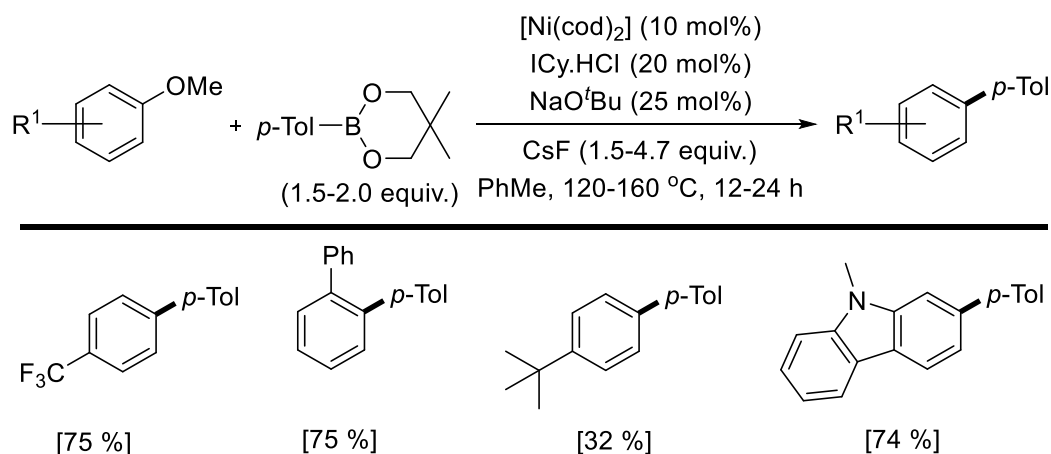


Scheme 1.28 – The first use of boronic acid derivatives in the cross-coupling of aryl methyl ethers. Values in brackets are isolated yields.

Percec and co-workers also studied this methodology using aryl neopentylglycolboronates. However, substrate scope was again limited, this time with no anisole derivatives successfully reacted, even with extended phenyl substitution present.¹⁰²

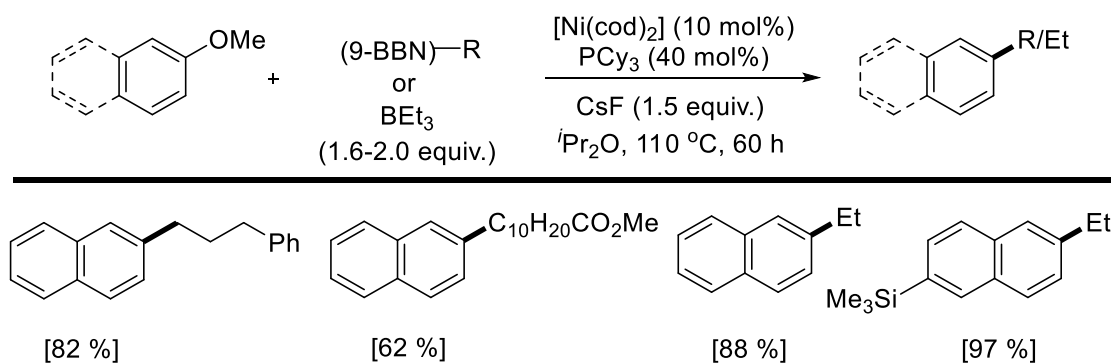
In 2014, Chatani and co-workers found ICy to be a superior ligand for the nickel-catalysed cross-coupling of aryl methyl ethers with organoboron reagents.^{103, 104} This ligand outperformed a wide range of other NHCs as well as the heavily utilised PCy₃, and broadened the substrate scope to include non-activated anisole derivatives such as the sterically encumbered 2-methoxybiphenyl (Scheme 1.29). Electron-rich anisoles such as

4-tertbutylanisole gave lower yields, even with more forcing conditions. Heteroaromatics could also be successfully coupled, showing no signs of catalyst poisoning by the heteroatom, opening up the possibility for this methodology to be used in natural product modifications (due to the functional group tolerance of organoborane reagents).



Scheme 1.29 – The use of Ni/ICy allowed challenging non-fused anisole derivatives to be cross-coupled with aryl organoborane derivatives. *Values in brackets are isolated yields.*

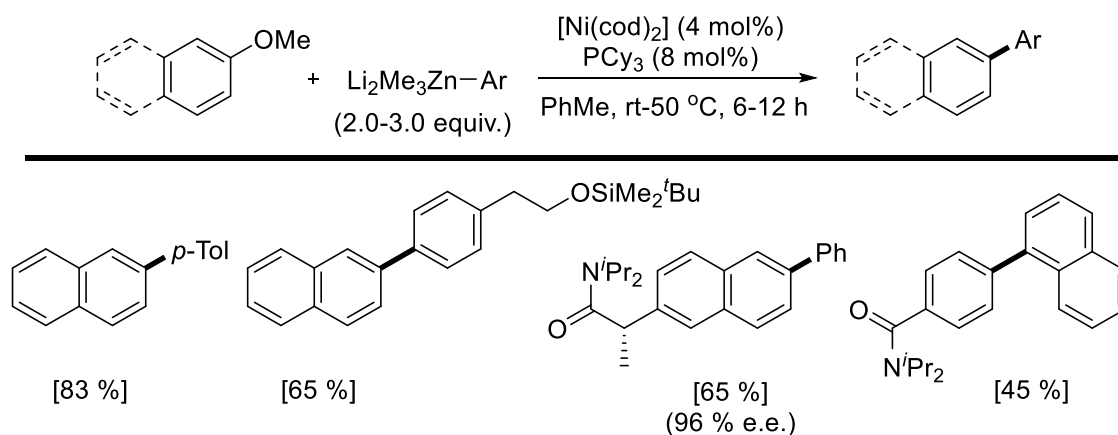
In 2016, as part of their efforts for a more general catalytic system (something that the field of aryl ether cross-coupling is severely lacking), Rueping and co-workers envisaged alkylboranes to be mild, yet effective nucleophiles for the nickel-catalysed cross-coupling of aryl methyl ethers. They also predicted that the Lewis-acidic nature of the alkylborane could aid the methyl ether cleavage, similar to a Grignard reagent (see mechanistic considerations, Section 1.4.2.6).¹⁰⁵ Many different *B*-alkyl-9-borabicyclo[3.3.1]nonanes (*B*-alkyl-9-BBNs), as well as triethylborane were successfully reacted with a wide range of substituted polycyclic aromatic methyl ethers in high yields, with no β -hydride elimination occurring, using a Ni(0)/PCy₃ catalytic system (Scheme 1.30) Anisole derivatives showed no significant reactivity, even after extensive testing.



Scheme 1.30 – Examples of the first nickel-catalysed cross-coupling of aryl methyl ethers with alkylboron reagents with no competing β -hydride elimination. *Values in brackets are isolated yields.*

1.4.2.3.2 - Organozinc reagents

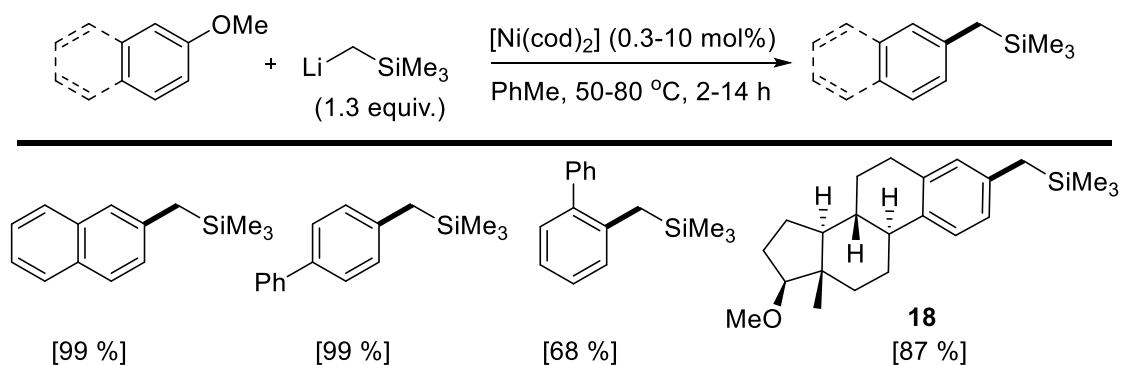
Uchiyama and co-workers have developed the only nickel-catalysed Negishi cross-coupling of aryl methyl ethers in the literature to date.¹⁰⁶ The Ni(0)/PCy₃-catalysed process enabled several different classes of naphthyl methyl ethers to be functionalised with varying aryl zincates (Scheme 1.31). The nickel(II) precatalyst [NiCl₂(PCy₃)₂] was found to have the same catalytic activity as [Ni(cod)₂]/2PCy₃. The high nucleophilicity and low basicity of the dianion zincates used was crucial to reaction success. This facilitated room temperature coupling and thus good functional group tolerance of e.g. amino, silyloxy and amide functionalities, in the electrophile or nucleophile, unlike in the vast majority of Grignard cross-coupling reactions. Issues regarding low reactivity of anisole derivatives, even with an electron-withdrawing amide at 50 °C, were unable to be solved with this methodology.



Scheme 1.31 – The first Negishi cross-coupling of aryl methyl ethers using aryl zincates as nucleophilic coupling partners. *Values in brackets are isolated yields.*

1.4.2.3.3 - Organolithium reagents

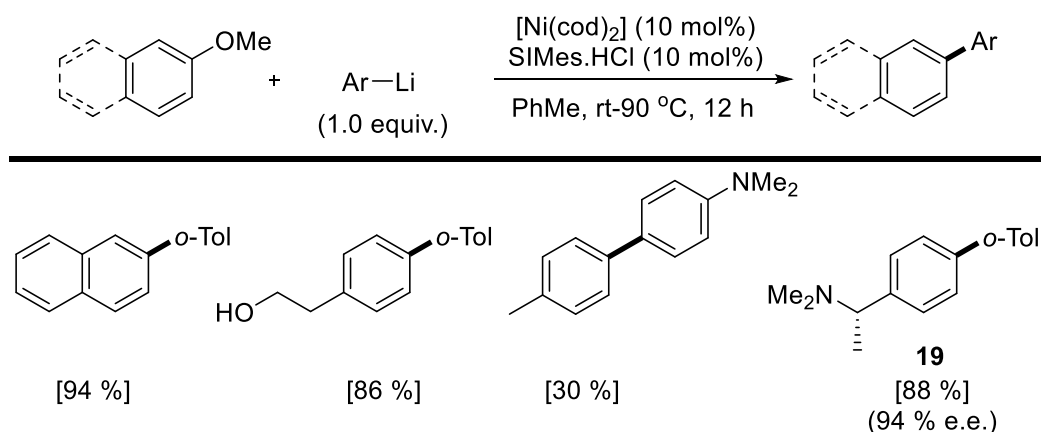
In 2014, Rueping and co-workers developed the first nickel-catalysed cross-coupling of aryl methyl ethers with an organolithium reagent.¹⁰⁷ Highly reactive organolithium reagents previously struggled to find application in nickel-catalysed cross-coupling reactions of aryl ethers, due to their high reactivity, dehalogenation capabilities and instability under common coupling reaction conditions.¹⁰⁸ Despite this, the bifunctional nucleophile (trimethylsilyl)methyl lithium ($\text{LiCH}_2\text{SiMe}_3$) was successfully reacted with several methoxynaphthalenes and anisoles in the first example of a ligandless system (Scheme 1.32). Catalyst loadings of $[\text{Ni}(\text{cod})_2]$ were generally quite low, ranging from 1 mol% for 2-methoxynaphthalene, to 2.5 mol% for phenyl-substituted anisoles, however more complex ethers such as dimethoxy- β -estradiol (product **18**), required up to 10 mol% of catalyst. A scaled-up reaction with 2-methoxynaphthalene was carried out with just 0.3 mol% of $[\text{Ni}(\text{cod})_2]$, although time and temperature had to be increased slightly (14 hours and 80 °C respectively). The challenge of sterically encumbered *ortho*-substituted anisoles was yet again evident from only the one example: 2-methoxybiphenyl was coupled in significantly lower yield than its *meta*- and *para*- counterparts (68 % vs 93 % vs 99 % respectively).



Scheme 1.32 – Examples of the first nickel-catalysed reaction of aryl methyl ethers with organolithium reagents, namely the bifunctional (trimethylsilyl)methyl lithium. *Values in brackets are isolated yields.*

$\text{LiCH}_2\text{SiMe}_3$ was especially attractive as it then provided scope for a variety of further transformations such as oxidation to acyl silanes (and then subsequent functionalisation), or Peterson olefination.

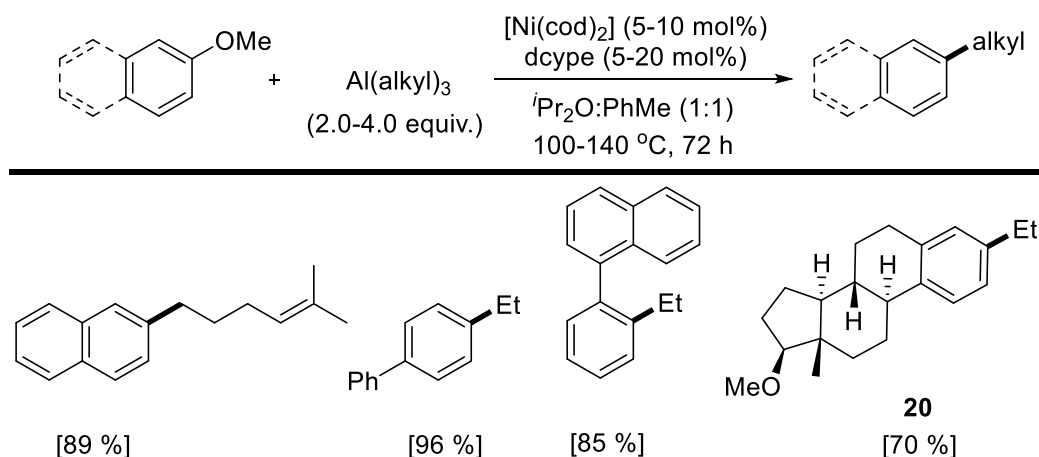
Uchiyama and co-workers extended the reaction scope of aryl ethers with organolithiums.¹⁰⁸ Using a $\text{Ni}(0)/\text{SiMe}_3\cdot\text{HCl}$ system, ($\text{SiMe}_3\cdot\text{HCl} = 1,3\text{-bis}(2,4,6\text{-trimethylphenyl})\text{imidazolinium chloride}$), a wide range of aryl methyl ethers were reacted with aryl lithium reagents varying in steric and electronic properties (Scheme 1.33). Higher temperatures were required for anisole derivatives, with moderate to good yields often obtained, depending on complexity. Substrate scope was still low in terms of anisole-based derivatives, with only five reported and giving a wide range of yields. Reactions were shown to proceed without racemisation when enantioenriched 1-(4-methoxyphenyl)-*N,N*-dimethylethan-1-amine (94 % e.e.) was coupled with (2-methylphenyl) lithium to give **19**, even at 70 °C, highlighting the applicability of this reaction.



Scheme 1.33 – Selected examples of the Ni(0)/NHC-catalysed cross-coupling of aryl methyl ethers with various organolithium reagents. *Values in brackets are isolated yields and substrates containing an alcohol moiety required 1.0 equivalent of methyl lithium to be added.*

1.4.2.3.4 - Trialkylaluminium reagents

Rueping and co-workers utilised trialkylaluminium reagents to incorporate alkyl groups without any competing β -hydride elimination occurring.¹⁰⁹ These were the first examples, regardless of nucleophile, to successfully install alkyl groups in place of aryl methyl ethers in a nickel-catalysed manner. These were accomplished with the use of $[\text{Ni(cod)}_2]$ and the bidentate phosphine 1,2-*bis*(dicyclohexylphosphino)ethane (dcype) (Scheme 1.34). All other ligands tested failed, similar to that observed by Chatani and co-workers, using alkyl Grignards, in Scheme 1.27. 2-methoxynaphthalene was reacted with a range of trialkylaluminiums, varying in chain length, under relatively forcing conditions. Biphenyl anisoles gave high yields but required increased temperatures, with the only *ortho*-substituted anisole, 2-(naphthyl)anisole, giving 85 % yield with 10 mol% of catalyst at 140 °C. Again, the derivative of the hormone estradiol, dimethoxy- β -estradiol could be successfully functionalised to give **20** in 70 % yield.

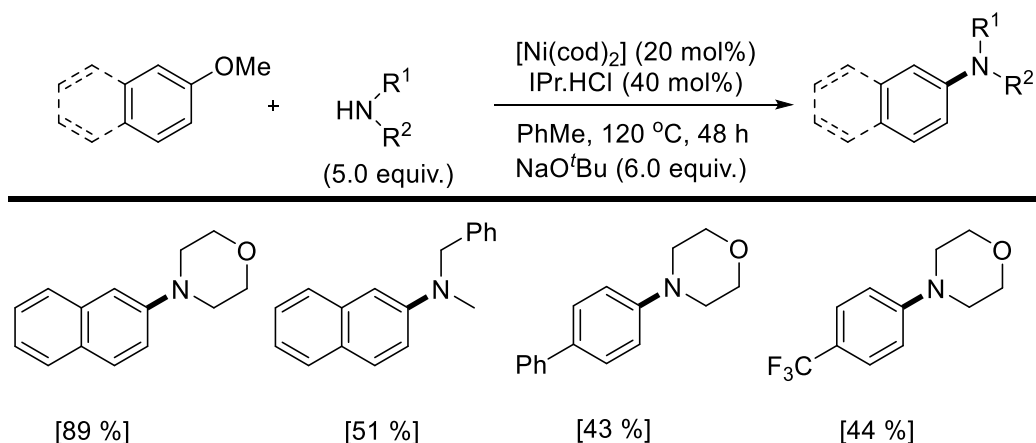


Scheme 1.34 – Successful alkylations with alkylaluminiums without the limiting β -hydride elimination. *Values in brackets are isolated yields.*

The authors demonstrated that the key to the observed success was the Lewis-acidic ability of the trialkylaluminium to activate the $\text{C}_{\text{aryl}}\text{-OMe}$ to oxidative addition, efficient transmetalation due to the stability of dialkylaluminium methoxide formed, and suppressed β -hydride elimination as a result of blocked vacant sites by the bidentate dcype (see mechanistic considerations, Section 1.4.2.6).

1.4.2.4 - Carbon-Heteroatom formation

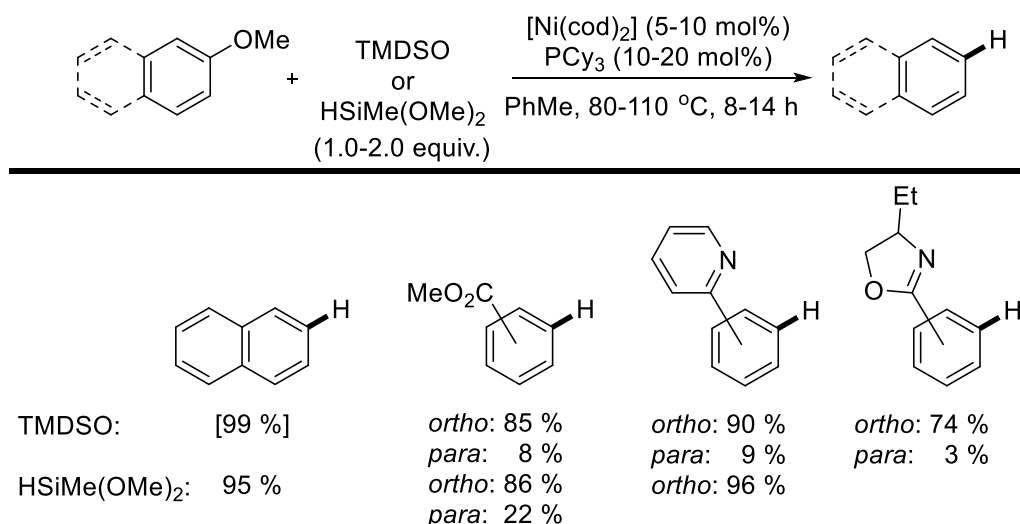
As well as carbon-carbon bond formation, aryl methyl ethers can be cross-coupled to give a range of carbon-heteroatom products. This area of research has not expanded as quickly as the carbon-carbon bond forming cross-coupling using nucleophiles such as the reactive Grignard reagents or organoboranes. Heteroatom formation would be beneficial as it increases the possibility of further functionalisation if so desired, as well as generating products relating to the pharmaceutical industry. For example, Ni^0/IPr -catalysed amination has been reported for less sterically hindered aryl ethers (Scheme 1.35).^{110, 111} There have also been borylations¹¹² and silylations¹¹³ reported.



Scheme 1.35 – Nickel-catalysed amination of aryl methyl ethers. Values in brackets are isolated yields.

1.4.2.5 - Nickel-catalysed reductive cleavage/hydrogenolysis

As well as nickel-catalysed functionalisation reactions, the deoxygenative reduction of aryl ethers has also expanded greatly since the initial discovery in 2010, when Martin and co-workers demonstrated that a combination of $[\text{Ni}(\text{cod})_2]/\text{PCy}_3$ and tetramethyldisiloxane (TMDSO) could reduce a range of aryl methyl ethers.¹¹⁴ Chatani and co-workers utilised the same catalytic system but this time using dimethoxy(methyl)silane ($\text{HSiMe}(\text{OMe})_2$) as the reducing agent.¹¹⁵ In both cases, substrates containing extended π -conjugation were readily reduced, but anisoles required the use of an *ortho*-chelating group to gain any considerable activity (Scheme 1.36). Nickel-catalysed hydrogenolysis of ethers (including lignin model compounds) have also been demonstrated,^{116, 117} while reductive cleavage without the requirement of an external reductant has recently been developed, increasing functional group tolerance.¹¹⁸



Scheme 1.36 – Initial nickel-catalysed reduction of aryl methyl ethers using external reducing agents, showing a clear *ortho*-directing effect for challenging anisole-based substrates. *Values in brackets are isolated yields.*

1.4.2.6 - Mechanistic considerations in the activation of aryl methyl ethers

Although significant progress has occurred, there is still a lack of a general catalytic process for the cross-coupling of aryl methyl ethers, especially regarding the nucleophile and catalyst/ligand of choice. Nickel has offered the most promise and its application continues to grow. However, previous sections have displayed one of the major pitfalls: the recurring issue of the “naphthalene effect”. Naphthyl methyl ethers, containing extended π -conjugation, have consistently produced higher reaction rates, yields and scope, compared to the more challenging anisole-based substrates.

This reactivity difference is likely due to the increased ability of naphthyl ethers to coordinate to the nickel centre in an η^2 -manner, as well as the increased aromaticity, and electron-withdrawing nature of the substrate rendering the C_{aryl}-OMe bond weaker. A reactivity difference of this scale and consistency is not found in other cross-coupling processes involving other transition metals. Consequently, great lengths have been taken to obtain a greater understanding of the mechanism of the cross-coupling of aryl methyl ethers, particularly C_{aryl}-OMe bond activation, in order to solve some of these recurring problems.

1.4.2.6.1 - “Classical” cross-coupling mechanism

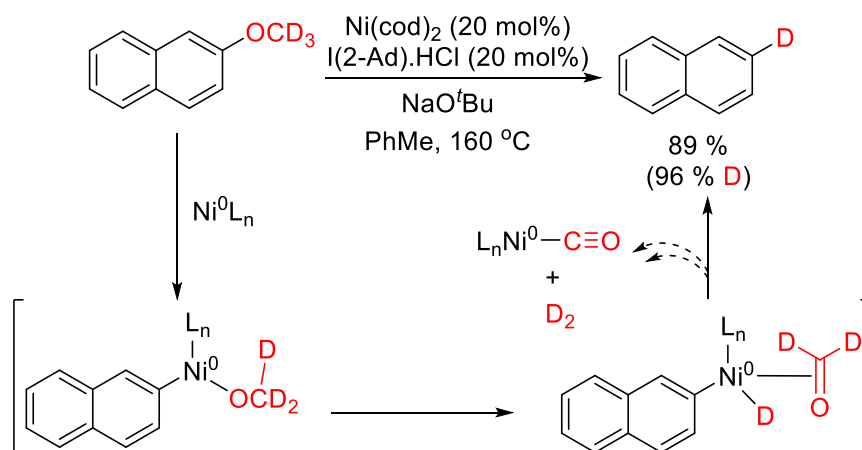
It is not outwith the realms of possibility that the mechanism of nickel-catalysed cross-coupling of aryl methyl ethers could conform to the “classical” oxidative addition *via* a three-centred transition state, transmetalation, and reductive elimination pathway (Scheme 1.1), that is generally accepted for many other electrophiles and transition metals.

Chatani and co-workers suggested this pathway to exist in the nickel-catalysed cross-coupling of aryl methyl ethers with boronic esters.¹⁰¹ It was shown that the electronic nature of the boronic ester did not affect reaction success, therefore implying that this Ni⁰ to Ni^{II} oxidative addition step was rate-limiting. The lack of successful examples with (non-activated) anisoles (Scheme 1.28) reinforced this mechanism, in the sense that they proposed that the oxidative addition may involve initial η^2 -coordination to the nickel centre, resulting in partial loss of aromaticity. The same authors also reinforced this mechanism with the discovery that the strongly σ -donating NHC ligand ICy facilitated the Suzuki-Miyaura cross-coupling of aryl methyl ethers, when many other ligands failed, through increased electron density at the nickel centre (often a prerequisite for the Ni⁰ to Ni^{II} process), (Scheme 1.29).¹⁰³

Rueping and co-workers assumed that the functionalisation of aryl methyl ethers with LiCH₂SiMe₃ (Scheme 1.32) occurred *via* this “classical” process, similar to that observed in similar reactions with cobalt. However, it was stressed that exact mechanistic investigations were required.¹⁰⁷ Since the reactions involved a ligandless system, and 2-methoxynaphthalene was coupled using just 0.3 mol% of catalyst, this possibly suggests the formation of a heterogeneous catalytic system.

Chatani and co-workers also demonstrated that a “classical” oxidative addition must be occurring in the reductive cleavage of aryl methyl ethers in the absence of external reductant.¹¹⁸ The subsequent β -hydride elimination (confirmed by labelling studies, Scheme 1.37) leads to the formation of the reduced product, in agreement with the stoichiometric mechanistic studies by Agapie and co-workers using (diphosphino)aryl

methyl ethers.¹¹⁹ Further confirmation of the β -hydride elimination was apparent by the higher yields obtained with aryl ethyl ethers, due to the lower tendency of the acetaldehyde complex to decompose to give inactive Ni(CO) species *via* decarbonylation.



Scheme 1.37 – Deuterium labelling experiment showing that the methyl ether is the source of hydrogen for the reduction in the absence of reducing agents. This suggests “classical” oxidative addition is likely to be occurring, followed by β -hydride elimination.¹²⁰

Forcing conditions are often required for aryl methyl ether cross-coupling reactions. However, more recent applications utilising lower temperatures have put this mechanism into doubt; due to the high bond dissociation energy of a C_{aryl}-OMe bond that would need to be surpassed. Also, the reasons for large discrepancies between results obtained with different classes of nucleophiles is not satisfactorily solved by the use of this mechanism, as “classical” oxidative addition is unlikely to be altered by the type of nucleophile.

1.4.2.6.2 – Lewis acid-assisted oxidative addition

With the fact that the vast majority of successful reactions involve the use of Grignard cross-coupling, Cornella and Martin hypothesised a Lewis acid-assisted oxidative addition.¹²¹ Preliminary experiments involving very low temperature (-30 °C) cleavage of 2,3-dihydrofurans suggested that the C_{aryl}-OMe bond may be electrophilically activated by coordination to the Lewis-acidic magnesium ion of a Grignard reagent (**21**, Figure 1.8). A stoichiometric ¹H NMR spectroscopy study revealed that oxidative addition only occurred in the presence of a Grignard reagent. It also became apparent that the counterion

on the Grignard reagent had a large influence on reaction success, again suggesting a deviation from the “classical” oxidative addition mechanism.

Similarly, Rueping and co-workers showed that significant coordination between the aryl methyl ether and the trialkylaluminium reagent strongly favoured the oxidative addition process (Scheme 1.34, and **22** Figure 1.8).¹⁰⁹ Coordination was confirmed by ²⁷Al and ¹H NMR spectroscopy studies, and computational analysis showed that the Lewis acid interaction drastically reduced the energy barrier for oxidative addition ($\Delta G^\ddagger_{\text{OA}} = 18.6 \text{ kcal mol}^{-1}$ vs $40.0 \text{ kcal mol}^{-1}$).

Rueping and co-workers again suggested this pathway, this time in the nickel-catalysed reaction of aryl methyl ethers with alkylborane reagents (Scheme 1.30).¹⁰⁵ It was envisaged that methyl ether coordination with the Lewis-acidic alkylboranes should aid oxidative addition processes (**23**, Figure 1.8). But, the lack of any successful anisole derivatives, even when several Lewis acid additives were present, does suggest that other mechanisms may be operating; although the authors argue that the reactivity difference between naphthyl ethers and anisoles was due to aromaticity values and a generally lower ability to undergo C_{aryl}-OMe bond cleavage. This Lewis acid effect being restricted to naphthyl methyl ethers was also briefly demonstrated by Sergeev and Hartwig in nickel-catalysed hydrogenolysis reactions, with AlMe₃ only significantly improving activity for the reduction of 2-methoxynaphthalene but having little effect with 4-methoxybiphenyl.¹¹⁶

Agapie and co-workers reported a dramatic acceleration in the activation of aryl methyl ethers using AlMe₃.¹²² The rate of oxidative addition was shown to be several orders of magnitude greater with the use of AlMe₃ in the stoichiometric system involving nickel complexes containing *meta*-terphenyl diphosphine ligands with an aryl ether functionality (**24**_{trans} and **24**_{cis} Figure 1.8). DFT calculations were also carried out and showed a lowering of the oxidative addition activation barrier by $\sim 5 \text{ kcal mol}^{-1}$ with the use of the Lewis acid, which made the methoxide a better leaving group. Kinetic studies showed a concentration dependence of AlMe₃, therefore suggesting two competing mechanisms. The major pathway was found to involve a single equivalent of AlMe₃ facilitating Al-ether

interaction in a *trans*-facial manner (**24_{trans}**). It was proposed that excess Lewis acid allowed the slow conversion of the initial associative *trans*-facial AlMe₃ adduct to the *cis* adduct, which then underwent aryl methyl ether cleavage *via* **24_{cis}**, in a faster, lower energy process, through a methyl group of AlMe₃ bridging to the nickel centre. Interestingly, the use of alkyl boranes did not result in increased reactivity.

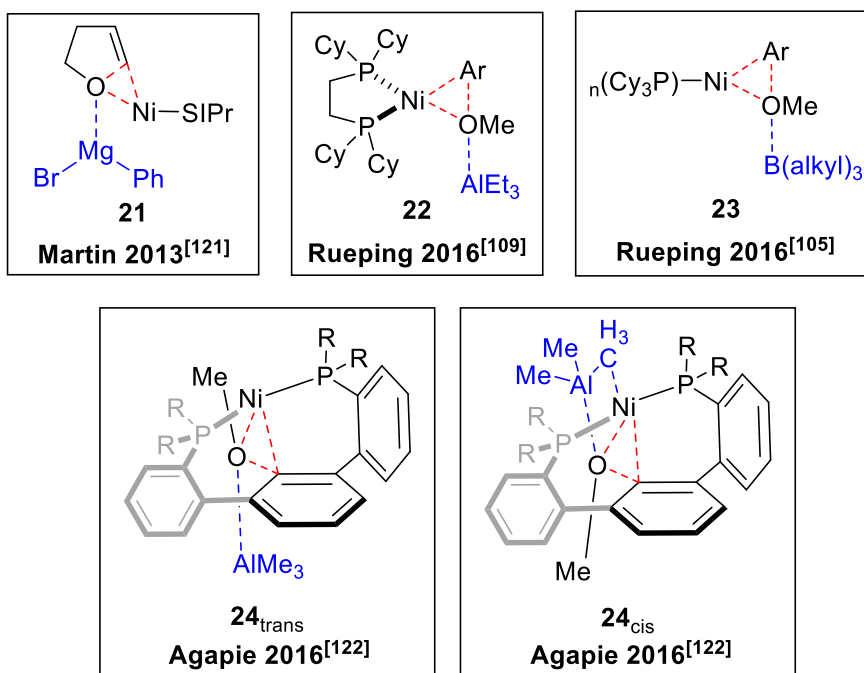


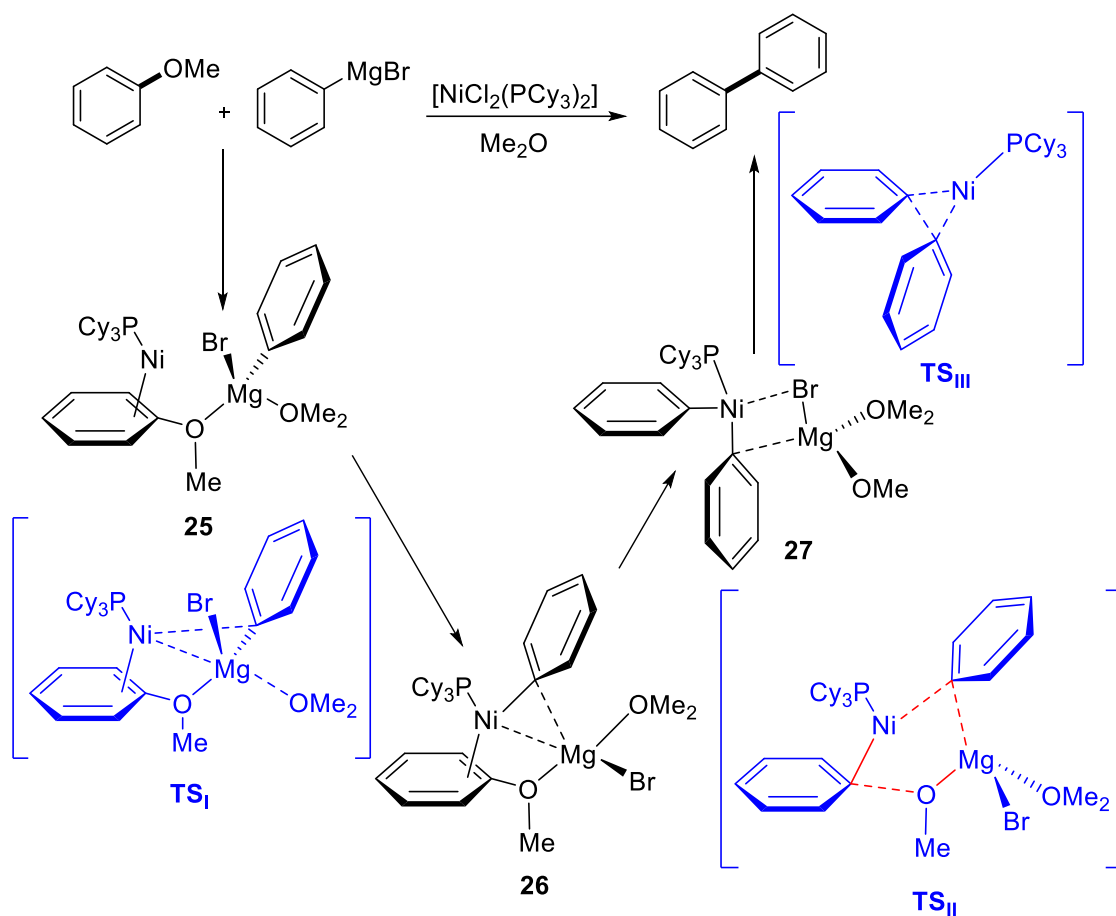
Figure 1.8– Proposed Lewis acid-assisted oxidative addition mechanisms.

This Lewis acid-assisted oxidative addition mechanism does explain the wider scope of aryl methyl ether cross-coupling available when using Grignard reagents. However, it does not account for the lower substrate scope with other nucleophiles. For example, Chatani and co-workers reported no improvement in reactivity with the addition of MgBr₂, LiCl or BPh₃, in the nickel-catalysed Suzuki-Miyaura cross-coupling of aryl methyl ethers with boronic esters.¹⁰¹

1.4.2.6.3 - [Ni⁰-ate]⁻ mechanism

Another plausible mechanism, which addresses the issue of wider reaction scope when Grignard reagents are used, involves the generation of an anionic [Ni⁰-ate]⁻ species which readily facilitates C_{aryl}-OMe bond cleavage. Previously only speculated,^{120, 123, 124}

Uchiyama and co-workers carried out a DFT study into the mechanism between anisole and phenylmagnesium bromide (PhMgBr) in dimethyl ether (Me₂O), whilst taking into consideration reported experimental findings (Scheme 1.38).¹²⁵ Initially, anisole forms an associative complex with the nickel centre, with the Grignard reagent forming a Lewis acid-base interaction with the methyl ether (**25**). This then provides the framework for [Ni⁰-ate]⁻ formation, allowing the transfer of the nucleophilic aryl group of the Grignard reagent prior to the C_{aryl}-OMe bond breaking (**TS_I**). This is important as it is in contrast to the heavily accepted Grignard cross-coupling catalytic cycle, which consists of oxidative addition followed by transmetalation, thus eliminating any possibility of undesired β-hydride elimination from the Ar-Ni^{II}-OCH₃ oxidative addition species, which has been previously suggested by Chatani¹¹⁸ and Agapie.¹¹⁹ It was calculated that this resulting [Ni⁰-ate]⁻ species (**26**) allowed C_{aryl}-OMe bond cleavage to occur with a significantly lower activation energy requirement compared to conventional routes, including the Lewis acid-assisted oxidative addition mechanism, therefore explaining the wide scope and often mild conditions observed. Cleavage occurred *via* a five-membered cyclic transition state (**TS_{II}**), facilitated by a “push-pull” interaction resulting in the Ni^{II} intermediate **27**, which can readily reductively eliminate the functionalised product *via* **TS_{III}**.



Scheme 1.38 – Calculated mechanism for the nickel-catalysed cross-coupling of anisole with phenylmagnesium bromide involving the key $[\text{Ni}^0\text{-ate}]$ species (**26**).¹²⁵

Although very plausible, not every nucleophile can facilitate this anionic mechanism and therefore the difference in scope when varying the nucleophile could be due to a switch between the “classical”, Lewis acid-assisted, and anionic mechanisms.

Various mechanistic proposals have been suggested, with the ones highlighted in this section seeming to be the most probable. However, radical mechanisms involving nickel(I) species or heterogeneous pathways could still play a role in some of these reactions. It is clear that depending on reaction type, the mechanism may change, and consequently, generic reaction conditions in relation to key parameters such as the nucleophile, catalyst, ligand etc. are very difficult to predict, although great progress has been made in the overall understanding of these individual processes.

1.5 - Project aims

The overall aim of this thesis was to investigate the development of selective, sequential C-C coupling reactions, particularly for the functionalisation of lignin-derived 2-methoxyphenol (guaiacol). Lignin is a rich source of phenolic compounds. While important research needs to be carried out on forming or isolating these phenolic compounds in higher yield, it is perhaps time to consider pathways to a fine chemical value chain from some of the compounds available from lignin. This is based on the fact that most existing research has focused on (destructive) hydro-deoxygenation to produce simple aromatics and cycloalkanes (e.g. fuels).

The key aim of this project was to convert key components of the lignin-derived bio-oil into fine chemicals of real value, allowing considerably more economic value to be gained. In the research published to date, guaiacol appears to be a very common major component in lignin-derived bio-oils. Since there are relatively few items of commerce that have two or more phenolic C_{Ar}-O(H) groups, catalytic chemistry to replace C_{Ar}-O bonds with other linkages such as C-C bonds needs to be developed. This project aims to address this challenge by the use of metal-catalysed cross-coupling, as well as nucleophilic aromatic substitution, to selectively functionalise activated guaiacol derivatives, potentially in a tandem or one-pot manner. Within this, focus will be given to find processes to remove the challenging aryl methyl ether functionality, particularly in nickel-catalysed Grignard cross-coupling reactions. Although significant progress has been made in the field of aryl methyl ether cross-coupling, there are still limited successful reactions involving anisole-derivatives, with *ortho*-substituted substrates appearing to be another step-up in difficulty. Therefore, new nickel catalysts to tackle this problem will be developed and tested against the existing state-of-the-art catalytic systems.

The final chapter of this thesis aims to make use of an oxygenated electrophile and sequential C-C coupling, but in this case, utilising some reactivity observed in Chapter II, along with previous results within the Clarke group.

Chapter II: Catalytic constructive deoxygenation of lignin-derived phenols: cross-coupling of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate

2.1 - Introduction

Cleaner catalysis for sustainable development has become an important research topic. Organic chemists are now working towards the utilisation of new sources of carbon to enable a switch to a bio-renewables based economy. If bio-renewables are utilised for fuels and platform chemicals, there will be substantial quantities of the by-product lignin, and thus 2-methoxyphenol (guaiacol) (**28**).¹²⁶ Accounting for 25-35 % of the organic matrix of wood, lignin is the most abundant natural aromatic polymer on earth and the phenolic-rich compound constitutes 30 % of non-fossil organic carbon.¹²⁷ Guaiacol appears to be a major component in lignin-derived bio-oils, and thus using guaiacol as a chemical feedstock could deliver added value from renewable feedstocks.

Currently, the conversion of lignin to aromatics and alkanes is attracting a large amount of research.^{128, 129} Several different depolymerisation methods exist including ionic liquid pre-treatment¹²⁶, thermal cleavage¹³⁰, acid/alkali extraction¹³¹ and catalytic^{117, 132} (Figure 2.1).

Depolymerisation Method

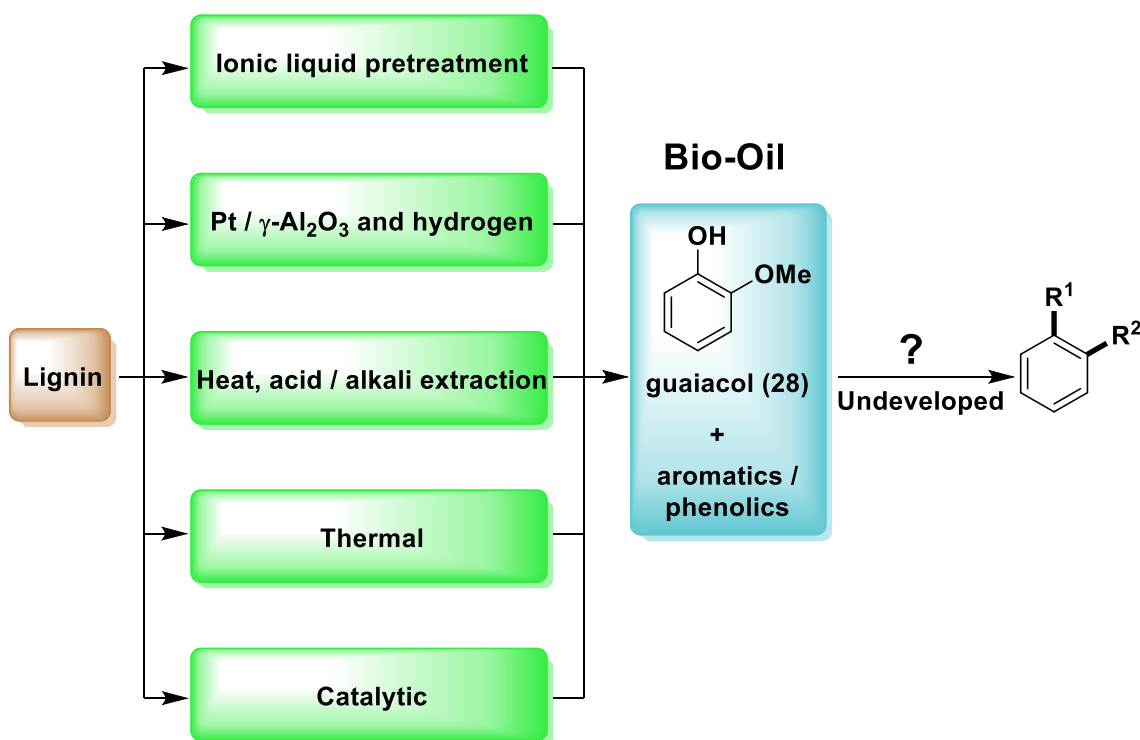
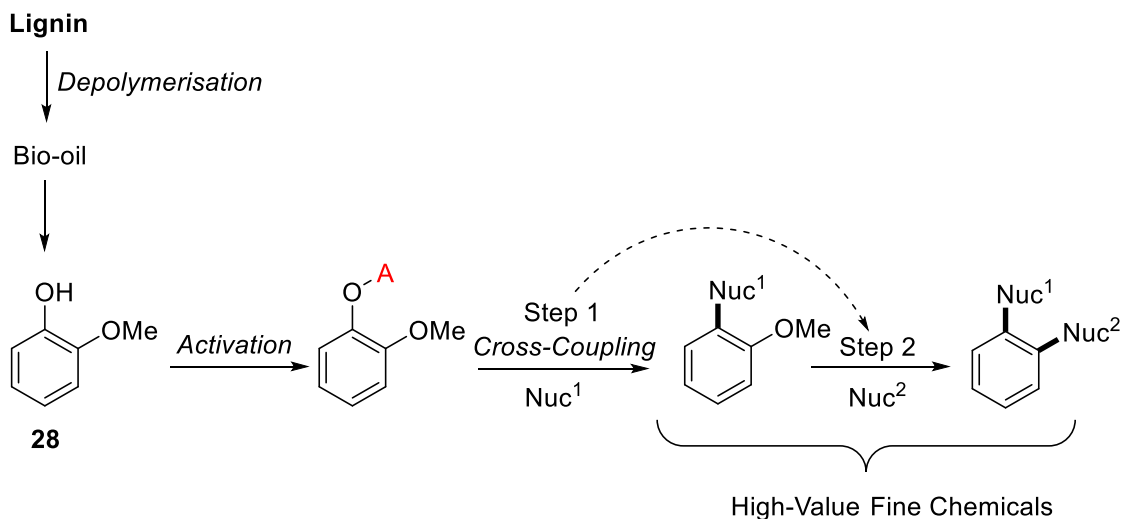


Figure 2.1 – Methods for the depolymerisation of lignin to give promising aromatic building blocks.

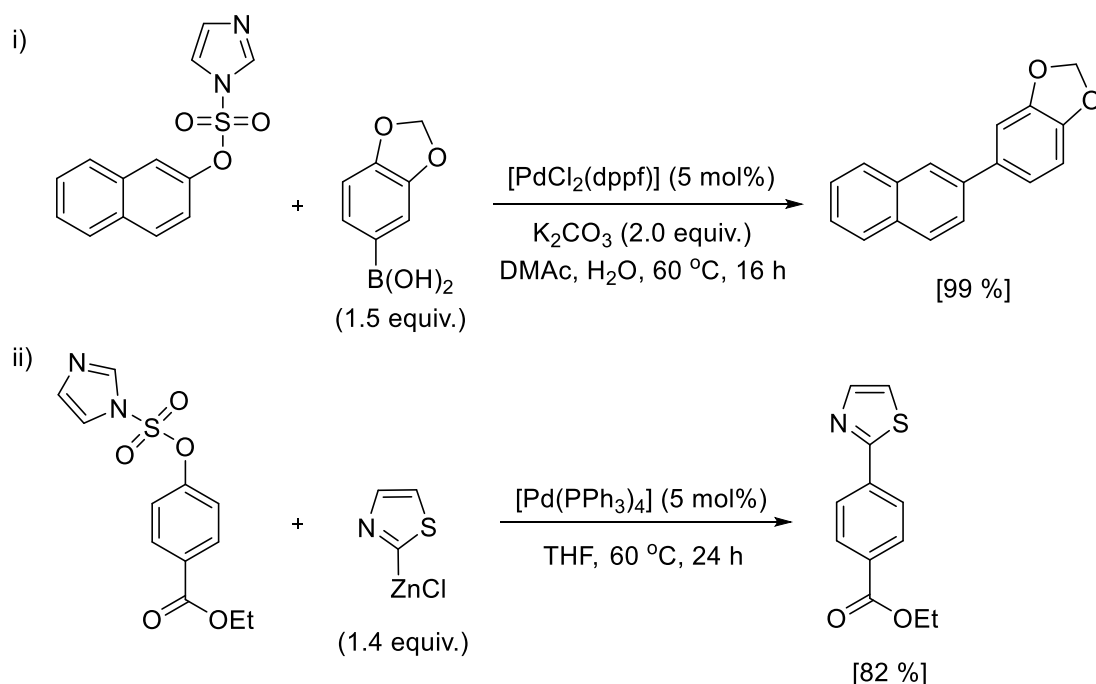
The fate of the phenolic-rich bio-oils obtained is still being debated, with a general focus on hydro-deoxygenation reactions, i.e. the removal of functionality in the C-O bond and replacing these with inert C-H bonds (“destructive deoxygenation”), to give fuels and bulk or commodity chemicals.^{128, 133} However, this project considered converting guaiacol into fine chemicals of higher value. In order to expand the variety of possible fine chemicals available from lignin, guaiacol must be converted into less oxygenated, but still functionalised aromatic compounds, i.e. the challenge of catalytic “constructive deoxygenation” (Scheme 2.1).



Scheme 2.1 – Proposed constructive deoxygenation of lignin-derived guaiacol (**28**).

In order to ensure the cost-effective production of fine chemicals, relatively economic nucleophiles such as Grignard reagents, cyanide and nitromethane were chosen for step 1. Certain activating groups such as triflates were ruled-out due to concerns over the high cost of triflic anhydride, as well as the toxicity and thus waste management implications of triflic acid.⁵⁷ Imidazole-sulfonates were selected as a reasonably economic and greener alternative to other activating groups. Originally utilised as a reactive and versatile leaving group in carbohydrate chemistry by Hanessain and Vatele in 1981,¹³⁴ the use of imidazole-sulfonates has extended to a variety of reactions; particularly metal-catalysed cross-couplings. Imidazole-sulfonates exhibit markedly improved reactivity over tosylates and improved stability and cost over triflates.^{57, 58} They also decompose to give relatively harmless side products (imidazole and sulfate salts/sulfuric acid) unlike other sulfonates, such as triflates and tosylates. Thus, savings can be made in the waste streams and overall disposal after the reaction.

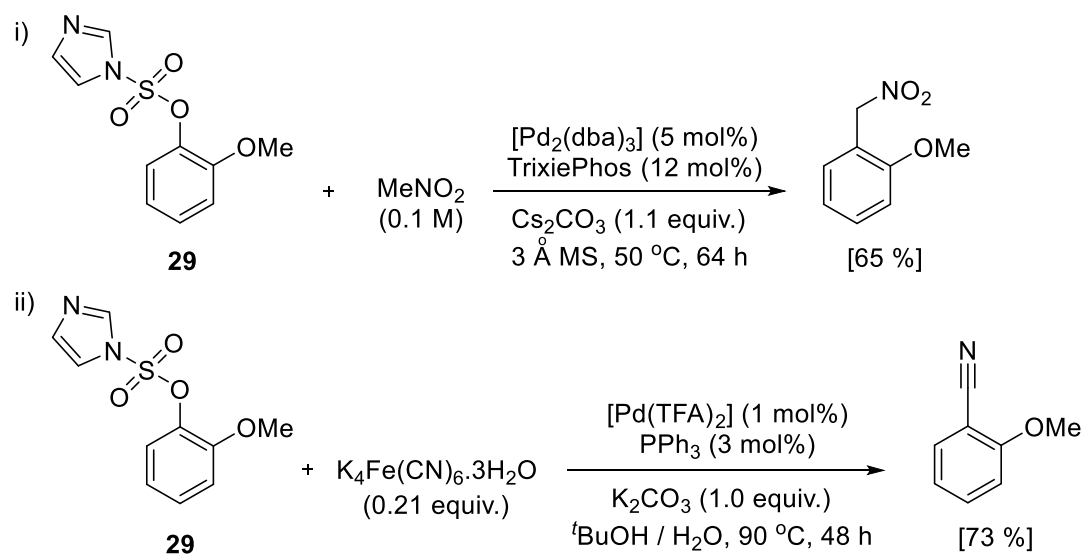
Albaneze-Walker and co-workers reported the first use of imidazole-sulfonates as effective electrophilic partners in metal-catalysed cross-coupling reactions.⁵⁷ Suzuki-Miyaura and Negishi cross-couplings were performed in high yield involving numerous different substrates containing the imidazole-sulfonate functionality (Scheme 2.2).



Scheme 2.2 – The use of aryl imidazole-sulfonates as electrophiles in the i) Suzuki-Miyaura cross-coupling and ii) Negishi cross-coupling reactions.⁵⁷

The success of these reactions resulted in the extension of the use of imidazole-sulfonates as electrophilic partners to a wide range of cross-coupling reactions including Sonogashira,¹³⁵ Hiyama,¹³⁵ direct C-H arylation,¹³⁶ and amination.⁵⁸

A co-worker on this project previously developed high-yielding cyanation (using the cheap, non-toxic potassium ferrocyanate as cyanide source) and nitromethylation reactions of the activated guaiacol substrate, 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**29**) (Scheme 2.3).¹³⁷



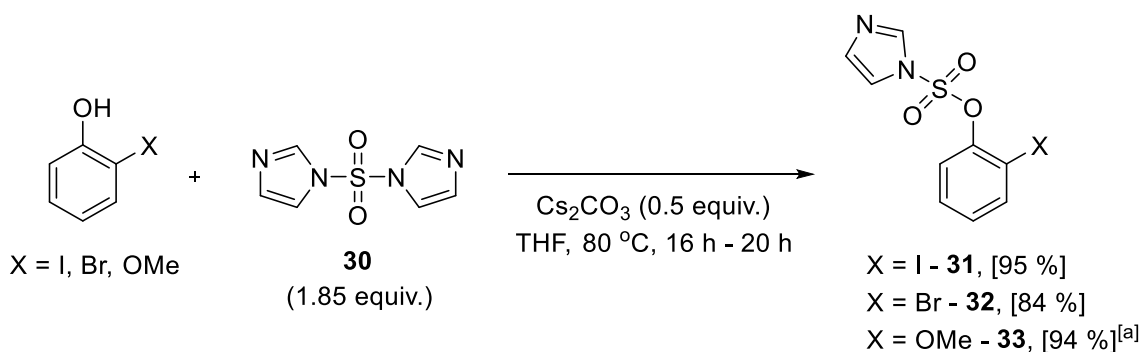
Scheme 2.3 – Catalytic reactions of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**29**) with i) nitromethane and ii) cyanide source, K₄Fe(CN)₆·3H₂O.¹³⁷

Imidazole-sulfonates have not been used in Grignard cross-coupling reactions and thus the initial aim of this project was to investigate the coupling of relatively economic Grignard reagents with guaiacol imidazole sulfonates, to selectively cleave both C_{aryl}-O bonds.

2.2 – Results and discussion

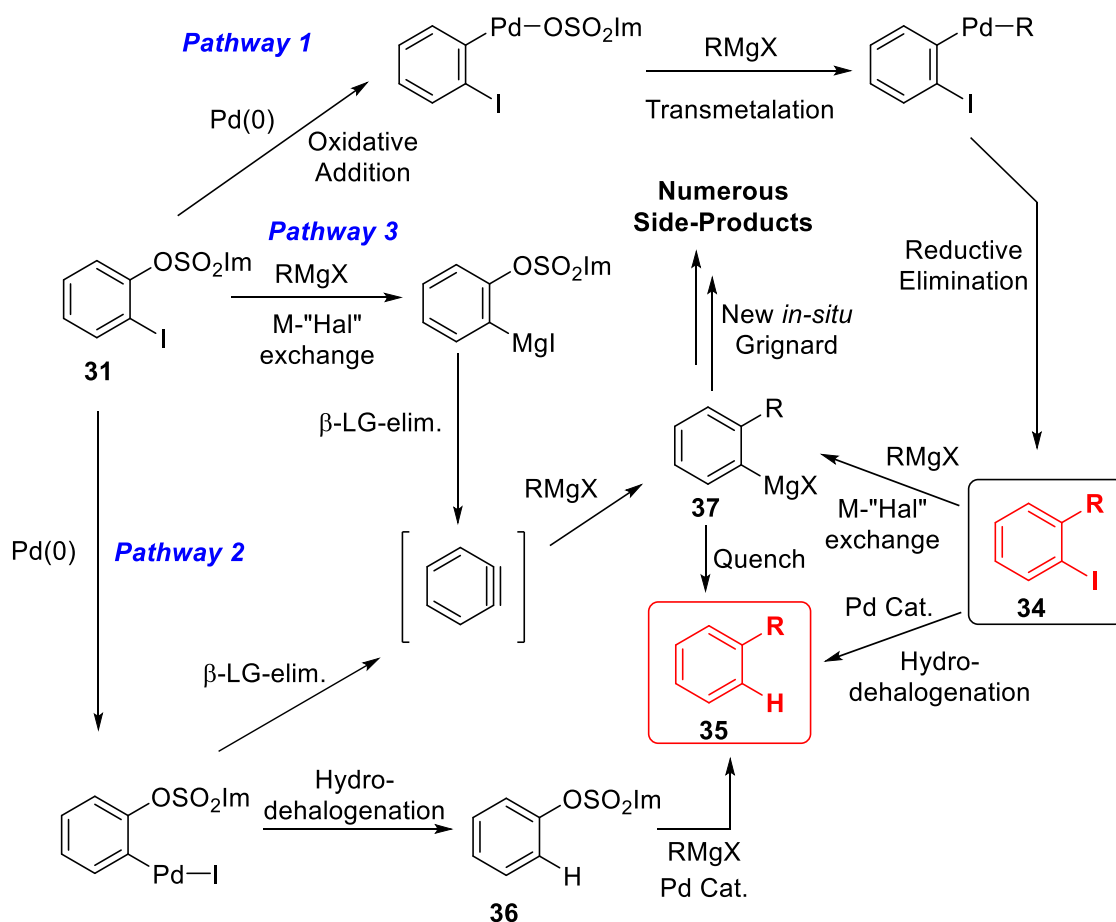
2.2.1 – Grignard cross-coupling of vicinal dielectrophiles

To initially determine the reactivity of imidazole-sulfonates as electrophiles for Grignard cross-coupling in vicinal systems, *ortho*-substituted phenols were reacted with 1,1'-sulfonyldiimidazole (SDI) (**30**), in the presence of base, to give the desired dielectrophiles in good to excellent yields (Scheme 2.4).

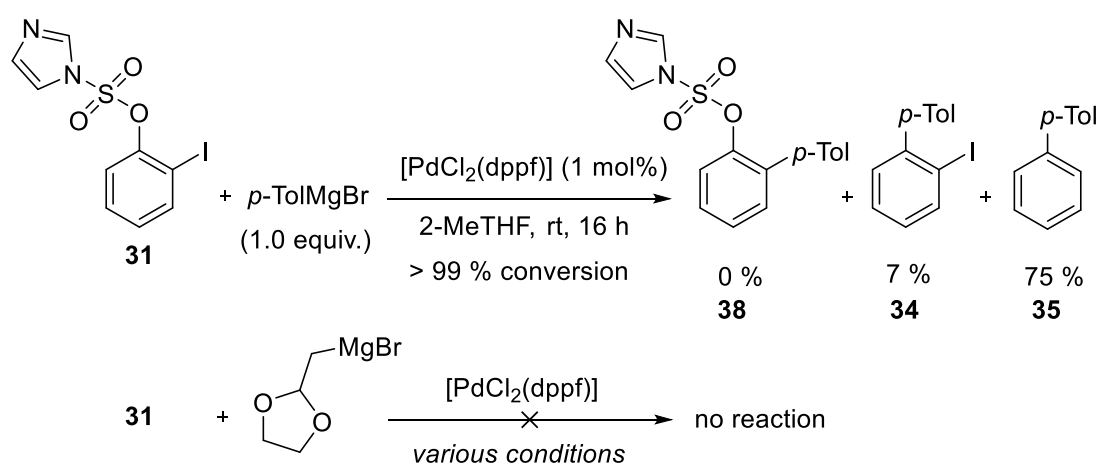


Scheme 2.4 – Synthesis of *ortho*-substituted aryl imidazole-sulfonates. ^[a] Reaction carried out at room temperature.

Selective cross-coupling of dielectrophiles is challenging, especially for *ortho*-substituted substrates. This is rendered even more difficult by the use of a reactive nucleophile like a Grignard reagent.¹³⁸⁻¹⁴⁴ Some of the possible side reactions are illustrated in Scheme 2.5. In order to assess this difficulty, the Grignard cross-coupling of 2-iodo-1*H*-imidazole-1-sulfonate (**31**) was briefly examined (Scheme 2.6).



Scheme 2.5 – Selectivity challenges that need to be overcome in the Grignard cross-coupling of 1,2-dielectrophiles such as 2-iodophenyl-1*H*-imidazole-1-sulfonate (**31**). *RMgX* = *p*-TolMgBr in this example.



Scheme 2.6 – Grignard cross-coupling of 2-iodophenyl-1*H*-imidazole-1-sulfonate (**31**) with *p*-TolMgBr and (1,3-dioxolan-2-ylmethyl)magnesium bromide, catalysed by [PdCl₂(dppf)] (**39**). ¹H NMR yields compared to an internal standard are shown. rt = room temperature.

Full consumption of starting material (**31**) was apparent when reacted with *p*-TolMgBr at room temperature with 1 mol% of [PdCl₂(dppf)] (**39**) (dppf = 1,1'-*bis*(diphenylphosphino)ferrocene). However, no desired product (**38**) was detected (Scheme 2.6). It was interesting to note that the coupling appeared to go through the imidazole-sulfonate functionality rather than the (more reactive) iodide. This was evident from the presence of 7 % of 2-iodo-4'-methylbiphenyl (**34**), with none of the desired coupling detected by ¹H NMR spectroscopy, as well as 75 % of 4-methylbiphenyl (**35**) being formed in high yield. A selective cross-coupling (*pathway 1*) could have occurred to give **34**, followed by fragmentation caused by hydro-dehalogenation, yielding **35** (Scheme 2.5). However, another possibility (*pathway 2*) was that the initial aryl iodide **31** was fragmenting by hydro-dehalogenation resulting in **36**, which was then subsequently coupled through the only possible electrophile, the imidazole-sulfonate. Successful coupling may have taken place to give **34** (*pathway 1*), with another Grignard reagent (**37**) subsequently being formed *in situ*, by magnesium inserting into the C-I bond, which was then capable of further transformations. In any case, this reaction was problematic. In contrast, coupling of the functionalised Grignard reagent (1,3-dioxolan-2-ylmethyl)magnesium bromide gave no reaction at all (Scheme 2.6). This Grignard reagent has been found to have low reactivity by others.^{145, 146}

The ultimate reason for the above undesired reactions was that the 1,2-dielectrophile **31** was simply too reactive to gain any form of selectivity due to two highly reactive functionalities. Therefore, in an attempt to control the high reactivity, coupling through the slightly less reactive bromide-derivative (**32**), was attempted. Bromide has been shown to be less likely to undergo metal-halogen exchange with Grignard reagents in comparison to iodide so it was predicted that there would be a lower impediment to the coupling.¹⁴⁷ However, no considerable improvements were made.

2.2.2 – Cross-coupling of the activated guaiacol derivative, 2-methoxyphenyl-1*H*-imidazole-1-sulfonate

We were keen to progress to more attractive substrates such as the renewable feedstock guaiacol, derived from lignin. Although a challenging 1,2-dielectrophile, the reactivity

difference between an aryl methyl ether and an activated phenol would result in complete chemoselectivity through the imidazole-sulfonate functionality of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**). The success of this first coupling would bring hope that tandem cross-coupling reactions could be strived for, albeit with potential forcing conditions for the second cross-coupling reaction.

2.2.2.1 – Palladium-catalysed Grignard cross-coupling

Planar chiral, 4,12-*bis*(diphenylphosphino)[2.2]paracyclophane, (Phanephos) (Figure 2.2 i), has become a well-established ligand for ruthenium- and rhodium-catalysed asymmetric hydrogenation reactions, since its discovery in 1997 by Pye and co-workers.¹⁴⁸ Palladium-catalysed amination reactions,¹⁴⁹ as well as a domino intramolecular asymmetric Heck – intermolecular Heck reaction,^{150, 151} have also utilised this ligand.

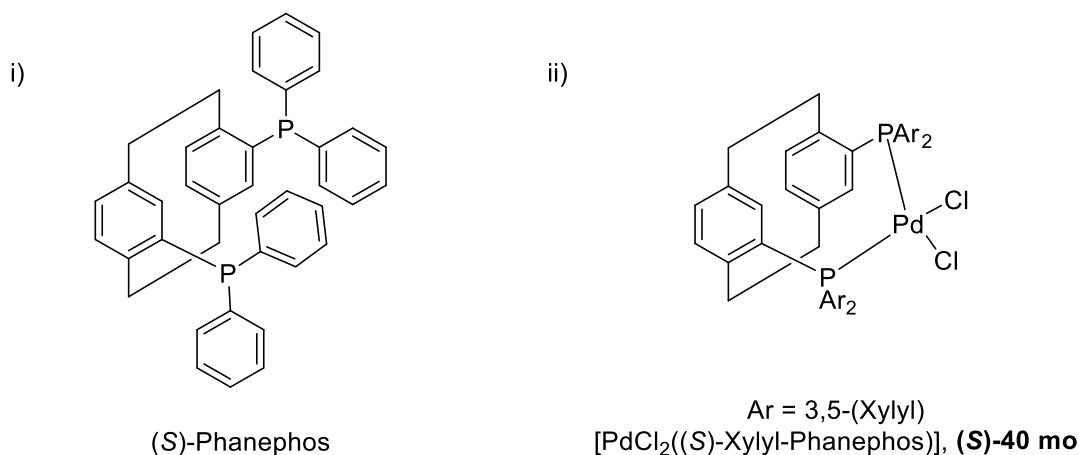
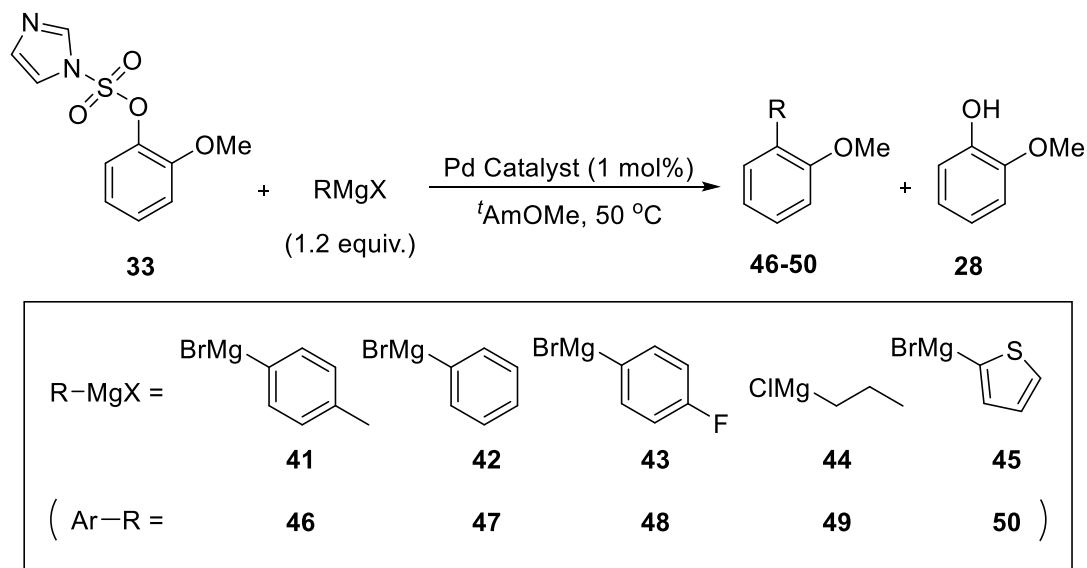


Figure 2.2 – i) (S)-Phanephos ligand. ii) Mono palladium(II) complex of Xylyl-Phanephos, (S)-40 mo

The Clarke group have created several Pd-Phanephos catalysts varying in steric and electronic properties, each resulting in differing regioselectivity, enantioselectivity and overall activity for the hydroxy/methoxy-carbonylation of alkenes, discussed further in Chapter V.¹⁵²⁻¹⁵⁴

However, these Phanephos ligands are still relatively untested in C-C bond forming reactions, especially in cross-coupling reactions, and have never been tested in Grignard cross-coupling reactions. Both the well known [PdCl₂(dppf)] (**39**), and [PdCl₂(Xylyl-Phanephos)] (**40 mo**), (Figure 2.2 ii) were examined in the desired Grignard cross-coupling of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**) (Table 2.1).

Table 2.1 – Palladium-catalysed Grignard cross-coupling of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**).



Entry ^[a]	Grignard (M) (Solvent)	Catalyst	t (h)	Conversion (%)	Product (%)	28 (%)
1 ^[b]	41 (0.5) (Et ₂ O)	39	23	76	< 5	11
2 ^[b]	41 (0.5) (Et ₂ O)	(<i>S</i>)- 40 mo	23	75	< 5	11
3 ^[c]	41 (0.5) (Et ₂ O)	39	17	21	11	10
4	41 (0.5) (Et ₂ O)	(<i>S</i>)- 40 mo	17	> 99	> 99 [63]	0
5	41 (0.5) (Et ₂ O)	(<i>S</i>)- 40 mo	1	> 99	94	0
6 ^[c]	42 (1.7) (Et ₂ O)	39	1	> 99	94	4
7 ^[c]	42 (1.7) (Et ₂ O)	(<i>S</i>)- 40 mo	1	> 99	93	0
8 ^[d]	42 (1.7) (Et ₂ O)	<i>rac</i> - 40 mo	16	> 99	99 [65]	0
9 ^[c]	42 (1.1) (THF)	(<i>S</i>)- 40 mo	19	86	3	43
10	43 (0.5) (Et ₂ O)	39	20	54	16	34
11	43 (0.5) (Et ₂ O)	(<i>S</i>)- 40 mo	16	85	80 [63]	5
12 ^[c]	43 (0.7) (THF)	(<i>S</i>)- 40 mo	17	66	4	46
13 ^[c]	44 (1.6) (Et ₂ O)	39	18	60	0	54
14 ^{[c][d]}	44 (1.6) (Et ₂ O)	<i>rac</i> - 40 mo	18	92	67 [40]	18
15	45 (0.9) (Et ₂ O)	39	4	88	82	0
16 ^[d]	45 (0.9) (Et ₂ O)	<i>rac</i> - 40 mo	4	> 99	99 [79]	0
17 ^[e]	45 (0.9) (THF)	(<i>S</i>)- 40 mo	23	73	17	19
18 ^{[c][f]}	45 (0.9) (THF)	39	23	13	< 5	7
19 ^{[c][f]}	45 (0.9) (THF)	(<i>S</i>)- 40 mo	23	24	16	6

^[a] Reaction conditions: 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (0.50 mmol), Grignard reagent (0.60 mmol), Pd catalyst (0.005 mmol) in *t*-AmOMe (1.0 mL). Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. ^[b] Reaction carried out in 2-MeTHF (500 μL) at room temperature. ^[c] 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (0.25 mmol) scale. ^[d] Racemic catalyst used. ^[e] 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (1.0 mmol) scale. ^[f] 20 °C.

It was found that with 2-MeTHF as the reaction solvent at room temperature, very little product was formed using *p*-TolMgBr (**41**). Starting material consumption was high (Table 2.1 entries 1 and 2), with guaiacol (**28**) the only identifiable side-product. Switching solvent to *t*-AmOMe resulted in significantly fewer side products, however [PdCl₂(dppf)] (**39**) still yielded little product (entry 3). [PdCl₂((*S*)-Xylyl-Phanephos)] (**39**) was significantly more active and selective, giving excellent yields in as little as one hour (entries 4 and 5). This superior activity was extended to several other Grignard reagents including, often troublesome, alkyl and heterocyclic nucleophiles (entries 13-16). Interestingly, both catalysts were very active for the reaction with PhMgBr (**42**), with [PdCl₂(dppf)] showing comparable activity (entries 6 and 7). However, when the electronically modified Grignard reagent **43** was reacted, the clear preference for [PdCl₂((*S*)-Xylyl-Phanephos)] was evident (entries 10 and 11).

The larger phosphine bite angle of 103.9° for [PdCl₂(Xylyl-Phanephos)]¹⁵⁵ compared to 99.1° for [PdCl₂(dppf)]²⁹ could offer an explanation for the difference in reactivity between the two catalysts. Kumada and co-workers reported that the high efficiency and selectivity of [PdCl₂(dppf)] in Grignard cross-coupling reactions was due to its large P-Pd-P angle.^{28,29} They found that the catalyst was particularly effective for alkyl Grignards like *sec*-butylmagnesium chloride, in what was the first application of dppf as a ligand in cross-coupling chemistry. Brown and Guiry showed that an increase in the P-Pd-P angle reduced the R-Pd-R' angle for a range of diphosphine palladium-complexes, including [PdCl₂(dppf)], accelerating the bond forming reaction that is reductive elimination.¹⁵⁶ In line with this, research by van Leeuwen and co-workers showed that “*both activity and selectivity increased with increasing bite angle*” for the palladium-catalysed cross-coupling of *sec*-butylmagnesium chloride with bromobenzene.¹⁵⁷ However, it is important to note that this trend was apparent up to 102.7° (bite angle of DPEphos). They noticed that any larger angled diphosphines tested resulted in lower activity and selectivity, and increased homocoupling of the substrate. Although van Leeuwen and co-workers screened several ligands with varying bite angles, their next ligand after DPEphos was Sixantphos which has a bite angle of 106.5°. Thus Xylyl-Phanephos at 103.9° could actually be the optimal value for high activity and selectivity in Grignard (and other) cross-coupling processes.

Research by Hoy and Hartwig on the Grignard cross-coupling of aryl tosylates showed that the scope was limited by transmetalation or reductive elimination, and not the previously considered oxidative addition.¹⁵⁸ Therefore, the apparent success of [PdCl₂(Xylyl-Phanephos)] is likely due to an increase in the rate of the reductive elimination. This is linked with the relative success of the cross-coupling using ^tPrMgCl (**44**) with [PdCl₂(Xylyl-Phanephos)], with regard to minimum β-hydride elimination, suggesting that the reductive elimination step is promoted using this wide bite angle catalyst, hindering this competing side reaction (Table 2.1 entry 14).

Although very active, the reactions with [PdCl₂(Xylyl-Phanephos)] had to occur at 50 °C to gain any considerable success. This was due to the partial solubility of the substrate in the non-polar ^tAmOMe, as well as the potential electron-donating ability and sterics imposed by the *ortho*-methyl ether in 2-methoxyphenyl-1*H*-imidazole-1-sulfonate. There appeared to be a strong requirement for the absence of furanic solvents: either in the bulk reaction solvent, or simply in the Grignard reagent. Any reaction containing 2-MeTHF or THF gave low product yields and resulted in side product formation. This was rectified by the use of the less coordinating ethers, ^tAmOMe (as bulk solvent) and Et₂O (as Grignard solvent), where high product yields were obtained, especially when using [PdCl₂(Xylyl-Phanephos)]. The more strongly coordinating solvents such as THF, render the Grignard reagent more reactive and susceptible to side reactions (imidazole-sulfonate decomposition), compared to the bulkier, less coordinating ^tAmOMe and Et₂O.

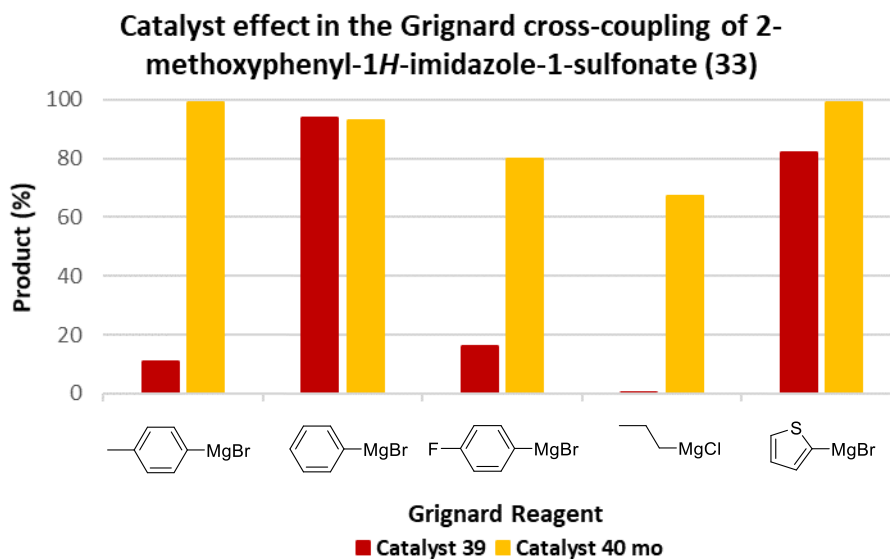
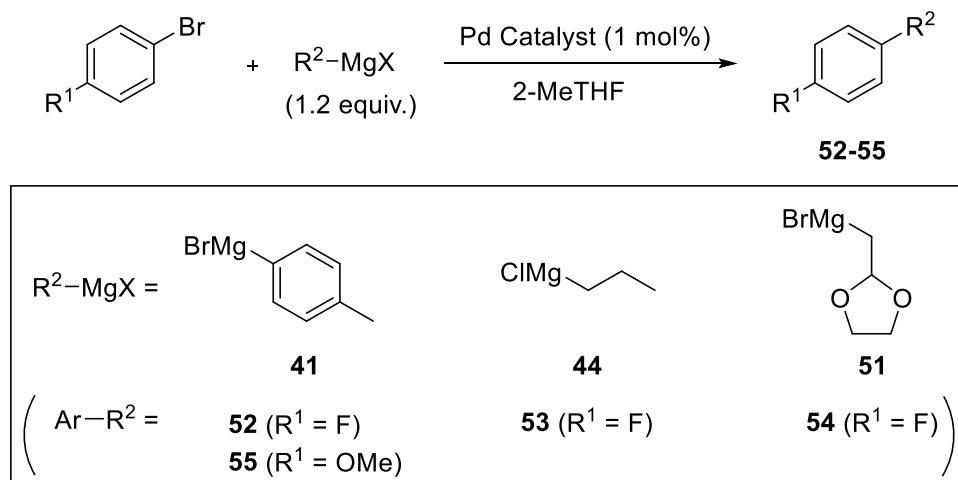


Figure 2.3 – The catalyst effect between [PdCl₂(Xylyl-Phanephos)] (**40 mo**), and [PdCl₂(dppf)] (**39**) for the Grignard cross-coupling of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**) in absence of furanic solvents. *Values taken from Table 2.3.*

Excellent results were obtained using the previously unexplored Grignard cross-coupling catalyst [PdCl₂(Xylyl-Phanephos)] (**40 mo**) for a range of Grignard reagents of varying electronic and steric properties (Figure 2.3). The high performance of [PdCl₂(Xylyl-Phanephos)] was not limited to imidazole-sulfonates only; a selection of reactions using aryl bromides, also demonstrated similar patterns (Table 2.2).

Table 2.2 – Catalyst effect in the Grignard cross-coupling of aryl bromides.



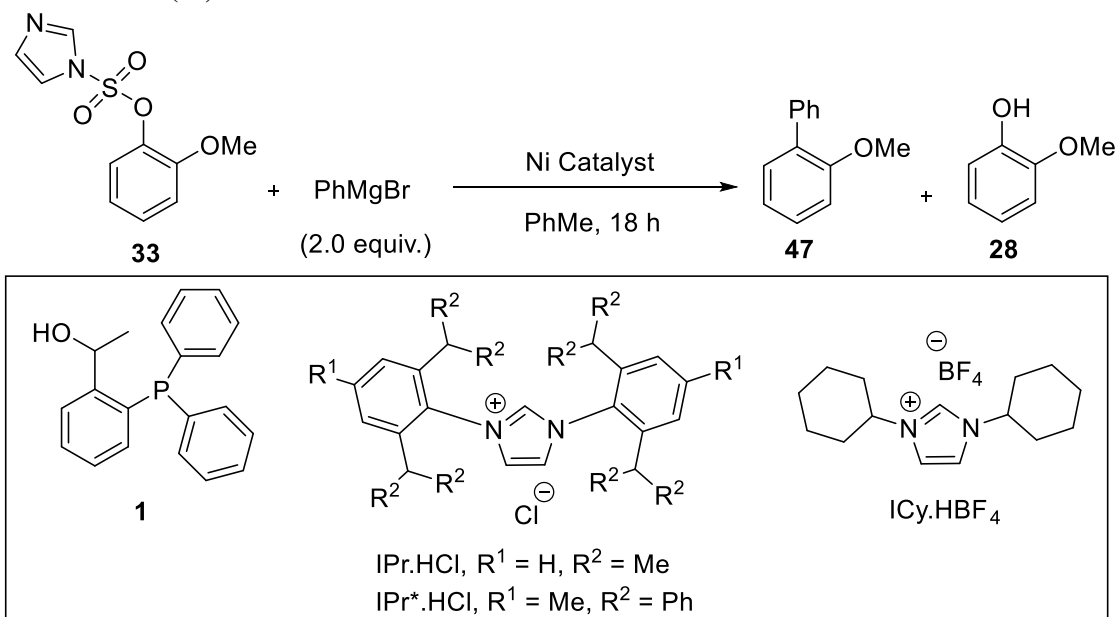
Entry ^[a]	R ¹	Grignard (M)	Catalyst	T (°C)	t (h)	Conversion (%)	Product (%)
1	F	41 (0.5)	39	20	24	67	n.d. ^[b]
2	F	41 (0.5)	<i>(S)</i> - 40 mo	20	4	95	[60] ^[c]
3 ^[d]	F	44 (1.6)	39	20	4	23	5
4 ^[d]	F	44 (1.6)	<i>(S)</i> - 40 mo	20	4	94	94 [74] ^[c]
5 ^[e]	F	51 (0.5)	39	80	24	< 5	0
6 ^[e]	F	51 (0.5)	<i>(S)</i> - 40 mo	80	24	< 5	0
7	OMe	41 (0.5)	39	20	18	25	18
8	OMe	41 (0.5)	<i>(S)</i> - 40 mo	20	18	75	69
9	OMe	41 (0.5)	39	40	4	51	43
					22	> 99	91
10	OMe	41 (0.5)	<i>(S)</i> - 40 mo	40	4	89	77
					22	> 99	88 [88] ^[c]

^[a] Reaction conditions: aryl bromide (0.50 mmol), Grignard reagent (0.60 mmol, Et₂O), Pd catalyst (0.005 mmol) in 2-MeTHF (500 μL). Conversions and yields were determined by ¹H NMR using 1-fluoronaphthalene or 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. ^[b] Due to overlapping of multiple signals in the ¹H NMR, the product yield was not determined. ^[c] Isolated yield from separate experiment without an internal standard. ^[d] aryl bromide (1 mmol) scale. ^[e] Grignard reagent in THF.

2.2.2.2 – Nickel-catalysed Grignard cross-coupling

Functionalising both C_{aryl}-O bonds in activated guaiacol derivatives in a tandem process would likely involve the use of nickel catalysts, since they are expected to be required for the second coupling of the aryl methyl ether. Nickel catalysis has come to the forefront, as a cost-efficient, earth-abundant alternative to palladium, but has not been examined in the cross-coupling of imidazole-sulfonates. Recently, Nakamura and co-workers reported a bimetallic nickel species containing the hydroxyphosphine ligand **1**, to facilitate Grignard cross-coupling reactions of phenolic electrophiles such as carbamates and phosphates.⁶⁵ It was hoped that this methodology could be successfully expanded to aryl imidazole-sulfonates and provide a nickel-catalysed constructive deoxygenation reaction (Table 2.3).

Table 2.3 – Nickel-catalysed Grignard cross-coupling of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**).

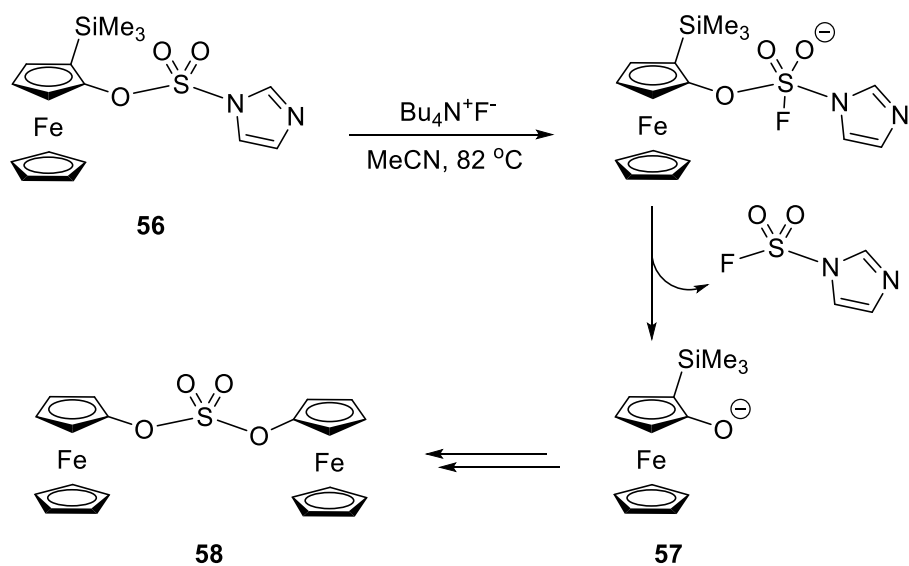


Entry ^[a]	Catalyst	Catalyst Loading (mol%)	T (°C)	Conversion (%)	Product (%)	28 (%)
1 ^[b-d]	Ni(acac) ₂ / 1	3 / 3	25	61	26	35
2 ^{[b][d-e]}	Ni(acac) ₂ / 1	3 / 3	50	59	33	26
3 ^{[b][d]}	Ni(acac) ₂ / 1	3 / 3	20	71	40	29
4 ^[d]	Ni(acac) ₂ / 1	3 / 3	20	68	38	28
5 ^[d]	Ni(acac) ₂ / 1	3 / 3	80	89	40	40
6	Ni(acac) ₂ / 1	3 / 3	20	96	59	37
7 ^[f]	Ni(acac) ₂ / 1	3 / 3	20	> 99	57	40
8	Ni(acac) ₂ / 1	3 / 4.5	20	97	63	33
9	Ni(acac) ₂ / 1	3 / 4.5	0	91	57	34
10	Ni(cod) ₂	3	20	79	13	60
11 ^[g]	Ni(cod) ₂ / 1	3 / 4.5	20	96	56	39
12	NiCl ₂ (PCy ₃) ₂	5	20	93	38	47
13 ^[h]	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	5	20	95	5	75
14 ^[h]	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	5	80	99	11	86
15	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	5	20	69	13	48
16	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	5	80	86	12	65
17	Ni(acac) ₂ / IPr.HCl	3 / 3.3	20	82	17	52
18	Ni(acac) ₂ / IPr*.HCl	3 / 3.3	20	75	14	45
19	Ni(acac) ₂ / ICy.HBF ₄	3 / 3.3	20	78	16	44
20	-	-	20	40	0	34

^[a] Reaction conditions: 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (0.25 mmol), Grignard reagent (0.50 mmol, 1.7 M in Et₂O), Ni catalyst in PhMe (500 μL). Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard. ^[b] 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (0.50 mmol) scale. ^[c] Et₂O as reaction solvent. ^[d] 1.5 equiv. Grignard. ^[e] *t*-AmOMe as reaction solvent. ^[f] 3.0 equiv. Grignard. ^[g] 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (0.31 mmol) scale. ^[h] 2-MeTHF as reaction solvent.

Unfortunately, conditions that were reported by Nakamura and co-workers to be successful with other phenolic electrophiles, yielded relatively little desired product (**47**), along with guaiacol (**28**) (Table 2.3 entry 1). Changing solvent from Et₂O to PhMe increased product yield, however higher temperatures had little effect (entries 3-5). Two equivalents of Grignard reagent appeared to be optimal (entries 6 and 7), while increasing the loading of ligand **1** gave the highest yield of 63 % (entry 8). However, there was a recurring problem with selectivity, with large quantities of guaiacol being consistently formed, even at 0 °C (entry 9). In an attempt to inhibit this side product formation, other nickel catalysts were tested (entries 12-19). These electron-rich catalysts have found application in aryl methyl ether cross-coupling reactions, which would be the subsequent reaction (Chapter IV). However, these were all low yielding, giving often larger quantities of guaiacol. The frequency and consistency of this side product formation, suggested an uncatalysed, direct attack of the Grignard reagent on the reactive imidazole-sulfonate species; similar to that observed in the palladium-catalysed process with THF as a solvent (Table 2.1). This was confirmed by an uncatalysed reaction in PhMe giving 34 % of guaiacol (Table 2.3 entry 20), that was representative of the values obtained in the previous nickel-catalysed processes.

This reactivity of imidazole-sulfonates has been previously reported in a similar manner. Werner and Butenschon¹⁵⁹ serendipitously found that the -SO₂- functionality of ferrocenyl imidazole-sulfonates, such as in 2-(trimethylsilyl)ferrocenyl imidazole-sulfonate (**56**), was an extremely good electrophile. Nucleophilic attack by fluoride occurred on the -SO₂- functionality even in the presence of trimethylsilyl groups (Scheme 2.7). The ferrocenolate **57** produced, subsequently reacted with another equivalent of starting ferrocenyl imidazole-sulfonate **56**, leading to the formation of the diferrocenyl sulfate **58**, *via* desilylation. However, the formation of guaiacol in the nickel-catalysed Grignard cross-coupling of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate could stem from a similar reaction mechanism, with the phenolate quenched upon aqueous work-up.



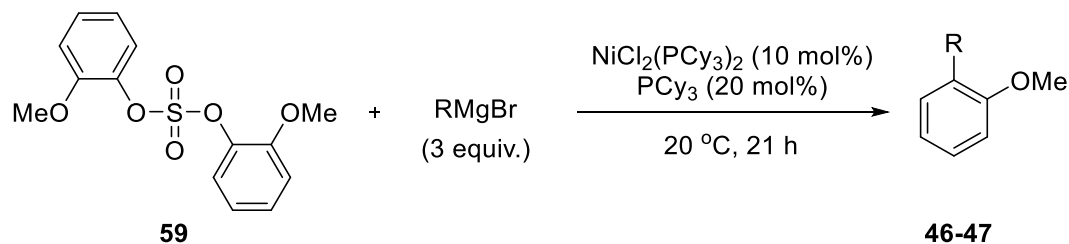
Scheme 2.7 – Unanticipated reactivity of 2-(trimethylsilyl)ferrocenyl imidazole-sulfonate (**56**) reported by Werner and Butenschon.¹⁵⁹

The metal-catalysed processes are in direct competition with guaiacol formation, and the higher product yields obtained with palladium must be due to reactivity differences between the two metal catalysts.

In attempts to overcome this problem, inspiration was taken from Shi and co-workers¹⁶⁰ who used diaryl sulfates to enable a concise and green, nickel-catalysed cross-coupling; with non-toxic inorganics MgSO_4 and MgBr_2 as the only by-products. One of the benchmark catalysts for aryl methyl ether cross-coupling, $[\text{NiCl}_2(\text{PCy}_3)_2]$, (discussed in depth in Chapter IV) was utilised, which made this methodology very attractive, looking ahead.

Three equivalents of guaiacol were reacted with SDI (**30**) to obtain *bis*(2-methoxyphenyl)sulfate (**59**) in a 68 % isolated yield (see Chapter VII, Experimental). This substrate was then subjected to nickel-catalysed Grignard cross-couplings (Table 2.4).

Table 2.4 – Nickel-catalysed Grignard cross-coupling of *bis*(2-methoxyphenyl)sulfate (**59**).



Entry ^[a]	Grignard (M)	Solvent	Conversion (%)	Product (%)
1 ^[b]	42	PhMe	– ^[c]	[18]
2 ^[d]	42	Et ₂ O	17	8
3	42	Et ₂ O	> 99	45
4 ^[d]	41 (0.5)	Et ₂ O	2	2

^[a] Reaction conditions: *bis*(2-methoxyphenyl)sulfate (0.25 mmol), Grignard reagent (0.75 mmol, 1.7 M in Et₂O), [NiCl₂(PCy₃)₂] (0.025 mmol), PCy₃ (0.05 mmol) in solvent (2.5 mL). Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. ^[b] No internal standard. ^[c] [48 %] starting material recovered. ^[d] *bis*(2-methoxyphenyl)sulfate (0.20 mmol) scale, [NiCl₂(PCy₃)₂] (0.01 mmol), PCy₃ (0.02 mmol).

Disappointingly, no improvement in product yield was observed with this substrate, with an exact literature repeat using 5 mol% catalyst and 10 mol% PCy₃, giving no reaction (Table 2.4 entry 4). This is in stark contrast to the literature value of 75 % isolated product. There was no clear indication of guaiacol formation by NMR spectroscopy, however yields of the desired substituted anisole were low. The relatively low mass balance obtained in entry 3 could possibly be due to poor chemoselectivity as Shi and co-workers did detect quantities of cross-coupling through the methyl ether bond also, which is understandable considering the electron-rich [NiCl₂(PCy₃)₂] was used.

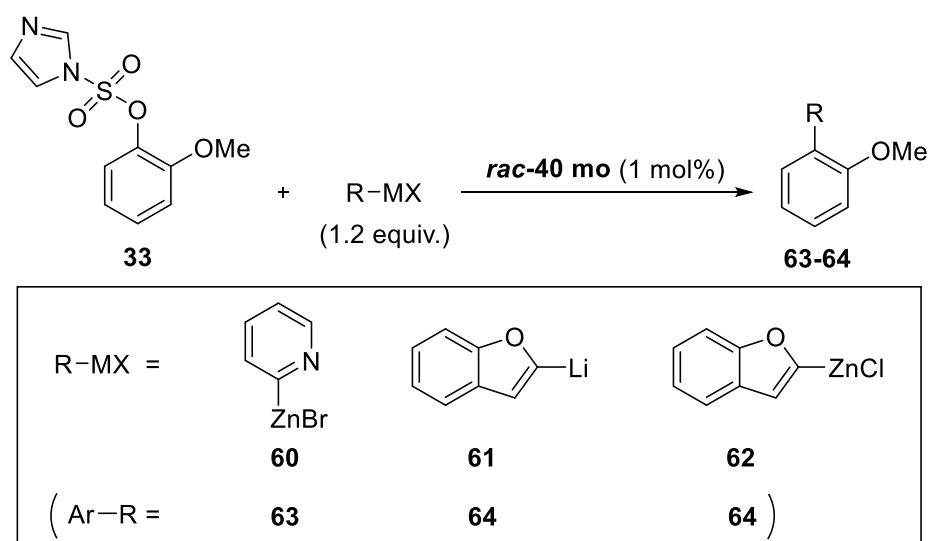
2.2.2.3 – [PdCl₂(Xylyl-Phanephos)]-catalysed cross-coupling of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate with other nucleophiles

To expand the scope of the successful palladium-catalysed constructive deoxygenation of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate, other nucleophiles were tested. Negishi cross-couplings of imidazole-sulfonates have previously been shown by Albanez-Walker and co-workers⁵⁷ (Scheme 2.2 ii), however there have been no reported reactions of organolithiums. Secondly, it was desirable to functionalise with an adjacent heterocycle,

which could increase the possibilities of chelation-assisted/directing group reactions, potentially aiding the challenging coupling of the aryl methyl ether in future functionalisations.

Attempts to synthesise 2-pyridylmagnesium bromide failed, therefore the commercially available 2-pyridylzinc bromide (**60**) was tested in the synthesis of 2-(2-methoxyphenyl)pyridine (**63**) (Table 2.5).

Table 2.5 – Palladium-catalysed Grignard cross-coupling of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**) with organozinc and organolithium reagents.



Entry ^[a]	Nucleophile (M)	Solvent	T (°C)	t (h)	Conversion (%)	Product (%)
1 ^{[b][c]}	60 (0.5)	<i>t</i> AmOMe	50	18	27	26
2 ^[b-d]	60 (0.5)	<i>t</i> AmOMe	50	18	29	24
3	60 (0.5)	<i>t</i> AmOMe	86	23	> 99	83
4 ^[e]	60 (0.5)	<i>t</i> AmOMe	100	23	> 99	84
5	60 (0.5)	2-MeTHF	80	23	> 99	92 [64]
6 ^{[b][f]}	61 (0.6)	<i>t</i> AmOMe	50	18	54	0 ^[g]
7 ^{[b][f]}	61 (0.6)	<i>t</i> AmOMe	-78 ^[h]	18	25	0 ^[i]
8 ^[j]	62 (0.3)	2-MeTHF	80	23	> 99	96
9 ^[k]	62 (0.3)	2-MeTHF	80	23	86	71 [70]

^[a] Reaction conditions: 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (0.25 mmol), nucleophile (0.30 mmol, in THF), [PdCl₂(*rac*-Xylyl-Phanephos)] (0.0025 mmol) in solvent (500 μL). Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. ^[b] 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (0.50 mmol) scale. ^[c] [PdCl₂(*S*)-Xylyl-Phanephos)] used. ^[d] Organozinc **60** in Et₂O. ^[e] Reaction performed in a sealed microwave vial with crimp cap. ^[f] Organolithium **61** in Et₂O. ^[g] 34 % guaiacol by ¹H NMR. ^[h] Reaction temperature had reached -10 °C after 18 h. ^[i] 3 % guaiacol by ¹H NMR. ^[j] 2 equiv. organozinc **62**. ^[k] 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (2.0 mmol) scale with [PdCl₂(*rac*-Xylyl-Phanephos)] (0.005 mmol).

Initially, attempts were made to avoid the use of furanic solvents, as they resulted in low product yields in the palladium-catalysed Grignard cross coupling process. Using the successful conditions from Table 2.1 but with 2-pyridylzinc bromide (**60**) in Et₂O as the nucleophile, the reaction was clean, but low yielding (Table 2.5, entries 1 and 2). However, increasing the reaction temperature significantly enhanced the reaction, with high yields of 2-(2-methoxyphenyl)pyridine (**63**) obtained (entries 3-5). This requirement for elevated temperatures is most likely due to 2-pyridyl organometallics being less reactive than the simpler aryl Grignard reagents used in the earlier reaction shown in Table 2.1. The reaction was in fact tolerant to furanic solvents, with 2-MeTHF giving the highest conversion to product (entry 6). Whilst the presence of furanic solvents renders the Grignard reagent too reactive for successful cross-coupling (Tables 2.1 and 2.3), 2-pyridylzinc bromide is less reactive, at least with the S-O bond of the imidazole-sulfonate.

Consistent with this, benzofuran-2-yl lithium (**61**) when reacted with 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**) at 50 °C in *t*-AmOMe, yielded 34 % of guaiacol, even when no furanic solvents were present (Table 2.5 entry 6). Consequently, benzofuran-2-yl zinc chloride (**62**) was synthesised by reacting benzofuran-2-yl lithium with anhydrous zinc chloride. The resulting organozinc reagent (**62**) was reacted with 2-methoxyphenyl-1*H*-imidazole-1-sulfonate at elevated temperatures to give excellent yields of 2-(2-methoxyphenyl)benzo[*b*]furan (**64**), even at 0.25 mol% catalyst loading (entries 8 and 9). These results give an indication of the utility of [PdCl₂(Xylyl-Phanephos)] (**40 mo**) to not only facilitate successful Grignard cross-coupling reactions, but to also catalyse Negishi cross-couplings.

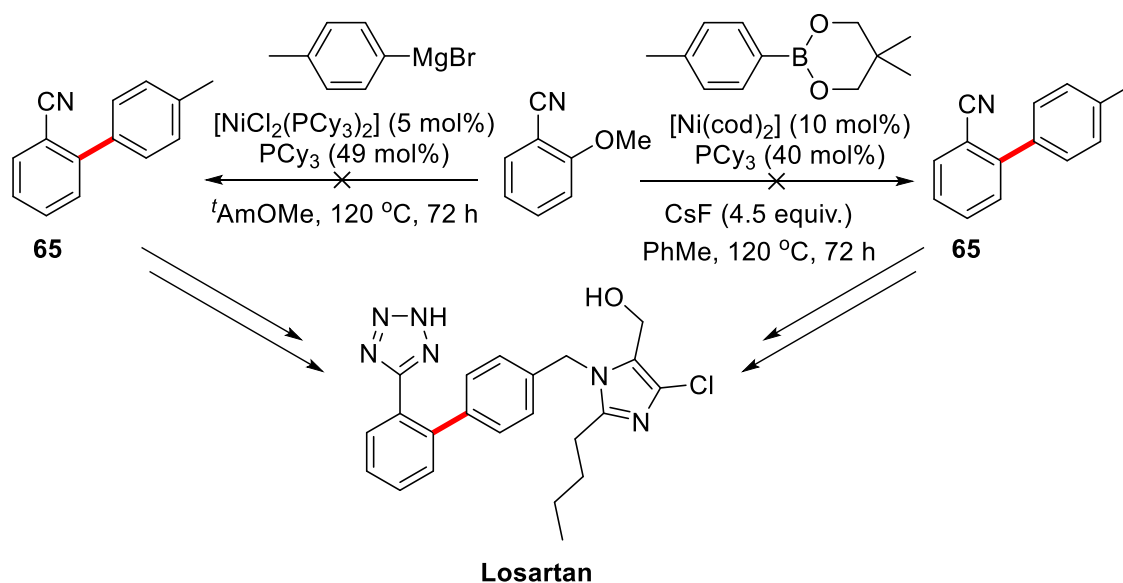
2.3 - Summary and future work

Guaiacol is a main feedstock from lignin and methods to functionalise this were developed. Novel Grignard cross-coupling reactions have been developed on imidazole-sulfonates and these can be added to the list of economic nucleophiles used to functionalise activated guaiacol. Initial reactions on reactive 1,2-dielectrophiles proved challenging, due to poor chemoselectivity, with multiple unknown side products apparent. Switching to the activated guaiacol derivative, 2-methoxyphenyl-1*H*-imidazole-1-sulfonate enabled selective Grignard cross-coupling reactions using the previously untested [PdCl₂(Xylyl-Phanephos)] catalyst. The reactions were significantly higher yielding when ^tAmOMe was used as a solvent. Furanic solvents had to be avoided, due to rendering the Grignard reagent more reactive and encouraging direct nucleophilic attack on the imidazole-sulfonate, leading to side products including guaiacol. [PdCl₂(Xylyl-Phanephos)] showed superior activity to [PdCl₂(dppf)] for a range of Grignard reagents and this trend was extended to aryl bromides.

Nickel-catalysed Grignard cross-coupling of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate was also attempted. This would open up more of a possibility of successful sequential cross-coupling reactions, through further functionalisation of the methyl ether. Moderate yields were apparent, relative to the palladium-catalysed process, with problems arising from the competing uncatalysed nucleophilic attack of the imidazole-sulfonate by the Grignard reagent, giving guaiacol; even with the exclusion of furanic solvents.

[PdCl₂(Xylyl-Phanephos)] was also able to catalyse the Negishi cross-coupling of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate with heterocyclic organozinc reagents. The use of milder organozinc reagents allowed the reactions to be performed successfully in furanic solvents, with negligible guaiacol formation. Meanwhile, the attempted coupling of the more nucleophilic benzofuran-2-yl lithium gave high quantities of guaiacol under standard reaction temperatures, again confirming that imidazole-sulfonate attack is problematic with reactive nucleophiles.

Future work could involve finding new, cost-effective nucleophiles that can facilitate this first constructive deoxygenation (as well as expanding the scope of those already tested). Methods to then link this methodology to the synthesis of specific target fine chemicals is also desirable. For example, one target that a co-worker made attempts to produce was the key fine chemical 2-(*p*-tolyl)benzonitrile (**65**), used in the synthesis of Losartan, by the route shown in Scheme 2.8. However, the difficulty of the methyl ether coupling means the choice of nucleophile caused compatibility issues with the nitrile functionality.



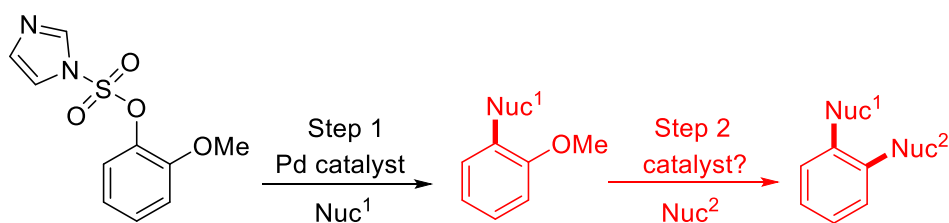
Scheme 2.8 – Attempted syntheses of 2-(*p*-tolyl)benzonitrile (**65**), a potential key intermediate in the synthesis of the blockbuster drug Losartan.

There are numerous compounds that can potentially be created from 1,2-dielectrophiles, however chemoselectivity issues can be apparent in a sequential substitution. A clear benefit from using guaiacol is that it is almost guaranteed that the more active C_{aryl}-O bond will react selectively. However, attempts must be made to functionalise the aryl methyl ether, in a second constructive deoxygenation. C-C bond forming reactions on unactivated aryl methyl ethers are challenging and hence were researched later in Chapter IV. Before taking on the challenge of a very broad catalytic method, directed nucleophilic aromatic substitution of aryl methyl ethers was also researched and this is described next in Chapter III.

Chapter III: Constructive deoxygenation of lignin-derived phenols: nucleophilic aromatic substitution of *ortho*-substituted aryl ethers

3.1 - Introduction

Chapter II reported effective methods to convert lignin-derived 2-methoxyphenol (guaiacol) into less-oxygenated, but still functionalised products by catalytically coupling through the activated phenol in the form of an imidazole-sulfonate. This leads on to the next challenge of functionalising through the relatively inert aryl methyl ether, in a further constructive deoxygenation reaction.



Scheme 3.1 – General scheme for constructive deoxygenation reactions, with the focus now on functionalisation through the challenging aryl methyl ether bond.

As discussed in Chapter I, the Meyers reaction, a directed nucleophilic aromatic substitution (S_NAr), uses a heterocyclic oxazoline to activate an *ortho* leaving group through chelation with the desired nucleophile, such as a Grignard reagent or organolithium. However, several other functionalities have now been developed and utilised to perform the same task. Attractive attributes to S_NAr reactions include high atom economy as well as a reverse in reactivity compared to traditional metal-catalysed cross-coupling reactions. Generally, the more difficult the oxidative addition step for a given functionality, the better the leaving group in S_NAr (e.g. fluoride).¹⁶¹ However, nucleophilic cleavage of aryl ethers has been suggested to be relatively challenging due to the low nucleofugacity of the functionality as well as the partial double bond character of the $C_{aryl}-O$ bond, as a result of resonance.¹⁶² The use of an activating group that can direct and assist the nucleophilic attack through chelation has resulted in this cleavage of aryl ethers becoming more favourable. Successful examples of activating, chelating groups include: sulfonyls,¹⁶² phosphine oxides,¹⁶³ ketones,¹⁶⁴ esters,¹⁶⁵ nitro groups,¹⁶⁶

nitriles,^{167, 168} aldimines,¹⁶⁹ and tetrazoles.¹⁷⁰ Some of these are specific to activated aromatics such as naphthalenes, with the Meyers reaction using oxazolines by far the most general method.

One approach to the desired difunctionalisation of guaiacol derivatives was rather than to perform a catalytic C_{aryl}-O bond activation of the methyl ether in step 2 of Scheme 3.1, to make use of a Meyers-type reaction. Within this goal, extending this ether cleavage to other activating and chelating heterocycles was desired, as well as to gain a better understanding on what can and cannot facilitate this S_NAr reaction.

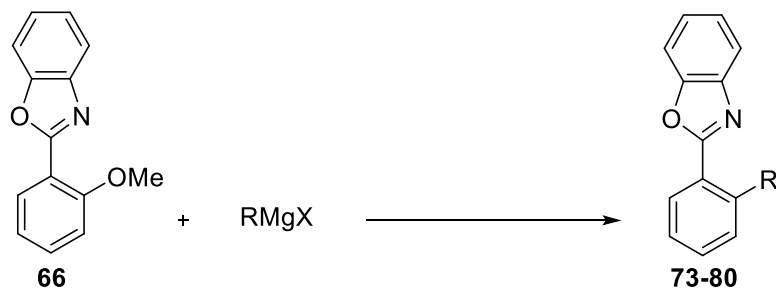
3.2 – Results and discussion









3.2.1 - Modified Meyers reaction with benzoxazole

It was envisaged that this directed S_NAr methodology could be extended to 2-(2-methoxyphenyl)benzo[*d*]oxazole (**66**). This could be made using a known C-H functionalisation of benzoxazole with 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**).¹³⁶ The substrate was therefore synthesised according to the literature,¹³⁶ with some attempts made to improve the reaction. If a one-pot or tandem process for difunctionalisation was to be attempted, the use of *N*-methyl-2-pyrrolidone (NMP) could severely hinder this, since the Grignard reagents required in the second step could react with the solvent.¹⁷¹⁻¹⁷³ Less toxic, more compatible solvents such as 2-MeTHF or PhMe were tested but gave **66** in lower yields relative to NMP, even with increased catalyst and ligand loadings and forcing conditions.

Working alongside myself, Leckie and Clarke initially discovered that a modification of the Meyers reaction was indeed achievable on the guaiacol-derived 2-(2-methoxyphenyl)benzo[*d*]oxazole (selected examples in Scheme 3.2).¹³⁷ However, it was important to increase the scope of the reaction further, as well as finding conditions that could possibly support one-pot/sequential constructive deoxygenations of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (Table 3.1).

Table 3.1 – Expanding the scope and further optimisation of the modified Meyers reaction of 2-(2-methoxyphenyl)benzo[*d*]oxazole (**66**) with a range of Grignard reagents.

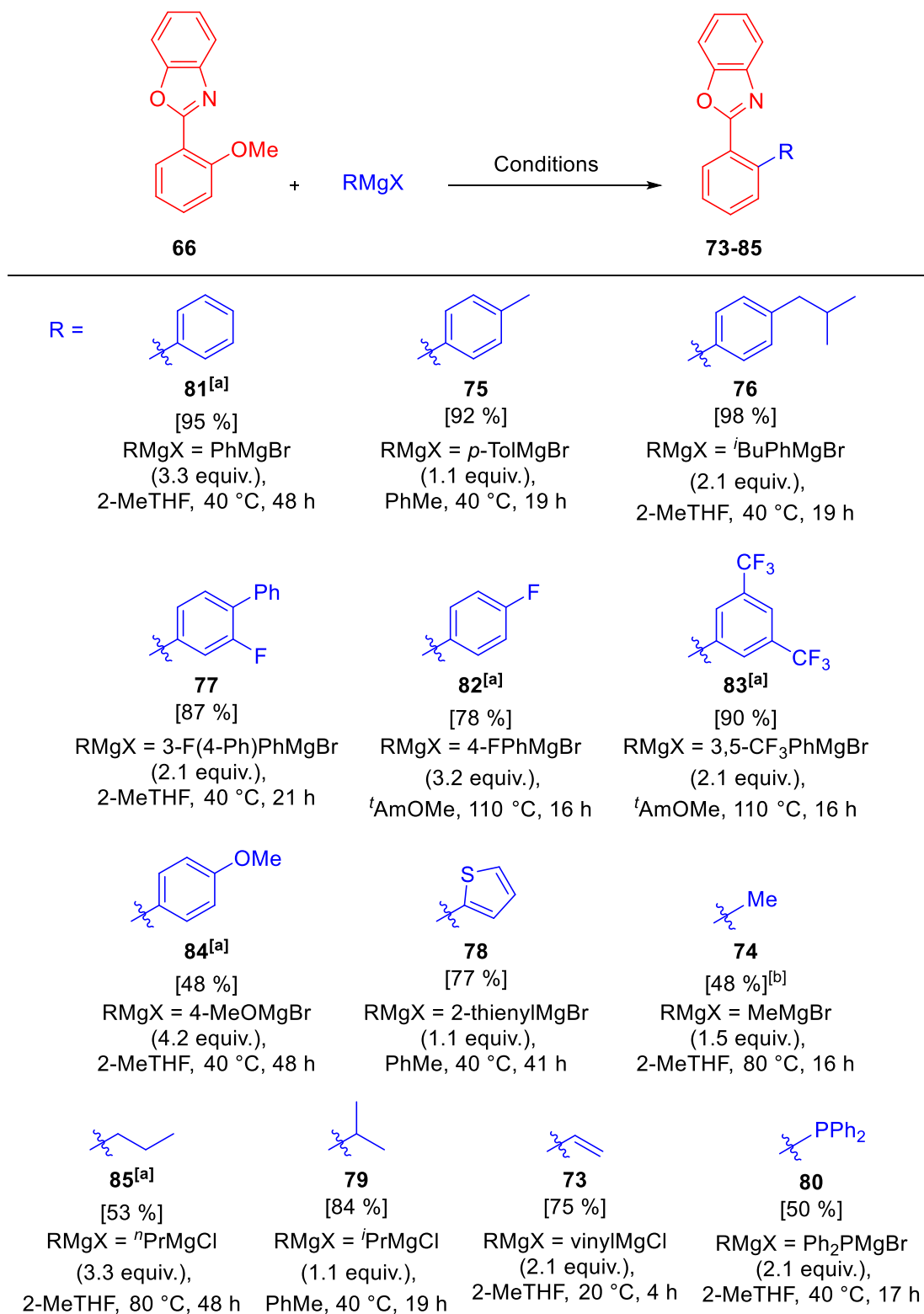


R =									
(X =		Cl	Br	Br	Br	Br	Br	Cl	Br
RMgX =		67	68	41	69	70	45	71	72
(Ar-R =		73	74	75	76	77	78	79	80)

Entry ^[a]	Grignard (M)	Grignard Equiv.	Solvent	T (°C)	t (h)	Conversion (%)	Product (%)
1 ^{[b][c]}	67 (1.6)	2.1	2-MeTHF	20	17	> 99	91
2 ^{[b][d]}	67 (1.6)	2.1	2-MeTHF	20	4	> 99	[75]
3	68 (2.4)	1.5	mesitylene	20	16	0	0
4	68 (2.4)	1.5	2-MeTHF	20	16	< 5	3
5	68 (2.4)	1.5	mesitylene	80	16	0	0
6	68 (2.4)	1.5	2-MeTHF	80	16	94	57
7 ^[e]	68 (2.4)	1.5	2-MeTHF	80	16	> 99	49 [48]
8	68 (2.4)	2.1	2-MeTHF	80	16	96	65
9 ^[f]	41 (0.5)	2.1	2-MeTHF	0	66	52	41
10 ^[b]	41 (0.5)	2.1	2-MeTHF	20	4	54	50
11	41 (0.5)	2.1	^t AmOMe	20	4	15	15
12	41 (0.5)	2.1	2-MeTHF	40	1	96	87
13 ^[d]	41 (0.5)	2.1	PhMe	40	4	> 99	[92]
14 ^{[d][g]}	41 (0.5)	1.1	PhMe	40	19	> 99	[92]
15 ^{[d][h]}	69 (0.7)	2.1	2-MeTHF	40	19	> 99	[98]
16 ^{[d][g-h]}	69 (0.7)	1.1	PhMe	40	41	> 99	[93]
17 ^{[d][h]}	70 (0.6)	2.1	2-MeTHF	40	21	> 99	[87]
18 ^{[c-d][g]}	45 (0.9)	1.1	PhMe	40	41	> 99	[77]
19 ^{[d][i]}	71 (0.6)	1.1	PhMe	40	19	> 99	[84]
20 ^{[c][f]}	72 (0.3)	2.1	2-MeTHF	20	140	> 99	68
21 ^{[c][f]}	72 (0.3)	1.2	2-MeTHF	40	17	> 99	71 [50]

^[a] Reactions conditions: 2-(2-methoxyphenyl)benzo[*d*]oxazole (0.50 mmol), Grignard reagent (0.5 M in Et₂O), solvent (2.25 mL). Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. ^[b] 2-(2-methoxyphenyl)benzo[*d*]oxazole (0.22 mmol) scale. ^[c] Grignard in THF. ^[d] No internal standard. ^[e] NiCl₂(PCy₃)₂ (0.025 mmol) present. ^[f] 2-(2-methoxyphenyl)benzo[*d*]oxazole (0.25 mmol) scale. ^[g] 2-(2-methoxyphenyl)benzo[*d*]oxazole (2 mmol) scale. ^[h] Grignard in 2-MeTHF. ^[i] 2-(2-methoxyphenyl)benzo[*d*]oxazole (1 mmol) scale.

The novel Meyers reactions were shown to be efficient at near ambient temperatures for a range of aromatic, heteroaromatic, alkenyl and alkyl Grignard reagents, and provide a method to perform the challenging second constructive deoxygenation of guaiacol-derived compounds (Table 3.1 and Scheme 3.2). MeMgBr (**68**) required more forcing temperatures of 80 °C to gain any considerable conversion, in what was the most challenging Grignard reagent tested (Table 3.1, entries 7 and 8). VinylMgCl (**67**) gave good yields of 2-(2-vinylphenyl)benzo[*d*]oxazole (**73**), which then opens up the possibility of further functionalisation (entries 1 and 2). Similar to this, Ph₂PMgBr (**72**), synthesised from reacting KPPh₂ with anhydrous MgBr₂, successfully participated in the S_NAr reaction to give 2-(2-(diphenylphosphanyl)phenyl)benzo[*d*]oxazole (**80**) (entry 21). This again could be functionalised further or could find application as a P-N ligand in catalysis, similar to phosphinoxazoline (PHOX) ligands.¹⁷⁴ Reactions were shown to perform best in 2-MeTHF or PhMe and Grignard reagent equivalents could be reduced to as low as 1.1 in some cases.



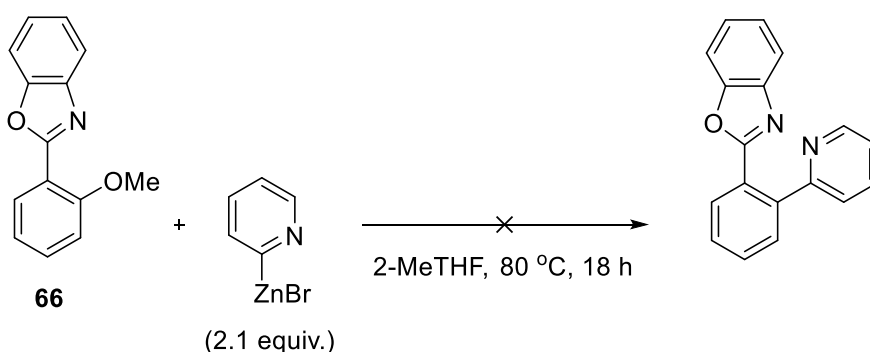
Scheme 3.2 – Overview of the modified Meyers reaction of 2-(2-methoxyphenyl)benzo[*d*]oxazole (**66**) with a range of Grignard reagents. ^[a] Reaction performed by Dr Stuart Leckie. ^[b] NiCl₂(PCy₃)₂ (0.025 mmol) present during reaction.

This Meyers reaction relied on chelation-controlled nucleophilic aromatic substitution in which the lone pair of electrons on the nitrogen from the benzoxazole, and the oxygen from the methyl ether, acted as donors to create a six-membered complex with the magnesium ion. The “R” group from the Grignard reagent is then held in a favourable position for nucleophilic insertion into the C_{aryl}-O bond of the methyl ether, resulting in the formation of desired product and magnesium salts.

Arylated benzoxazoles have wide-spread applications including in anti-inflammatory and fluorescent materials.^{175, 176} However, if desired, the resulting benzoxazole can be hydrolysed under forcing conditions to give the respective *ortho*-substituted benzoic acid ester and 2-aminophenol.¹⁷⁷

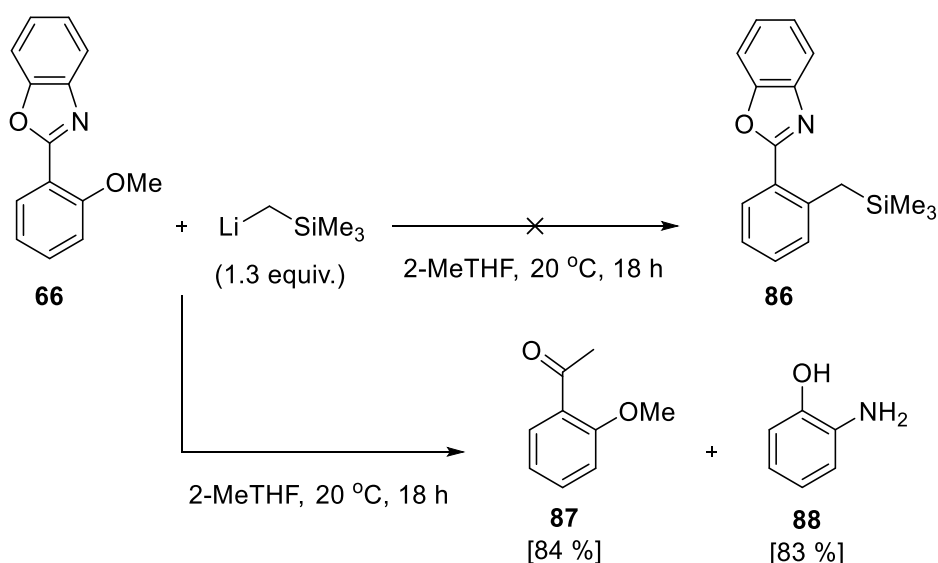
3.2.2 - Extension of the modified Meyers reaction to other nucleophiles

The Meyers reaction is known to occur with Grignard reagents and organolithiums. Firstly, it was of interest to determine if this could be further expanded to organozinc reagents such as 2-pyridylzinc bromide, in an attempt to functionalise with more complex moieties. If successful this would provide a di-heterocyclic substituted benzene that may, for example, find use as a bidentate ligand in catalysis. However, no reaction occurred, yielding only starting material **66**, even under forcing conditions (Scheme 3.3). It is predicted that although able to favourably coordinate to **66**, the organozinc reagent was not nucleophilic enough to displace the aryl methyl ether.



Scheme 3.3 – Attempted modified Meyers reaction with 2-pyridylzinc bromide.

Consequently, the more nucleophilic (trimethylsilyl)methyl lithium was chosen in an attempt to expand this methodology (Scheme 3.4). (trimethylsilyl)methyl lithium was recently successfully used as a coupling partner in the nickel-catalysed cross-coupling of challenging aryl ethers, including examples lacking extended π -conjugation.¹⁰⁷ Thus, it was hoped that, even if the uncatalysed reaction was unsuccessful, the nickel-catalysed cross-coupling reaction of the aryl methyl ether, directed by the adjacent benzoxazole would possibly give the desired product, 2-(2-((trimethylsilyl)methyl)phenyl)benzo[d]oxazole (**86**).

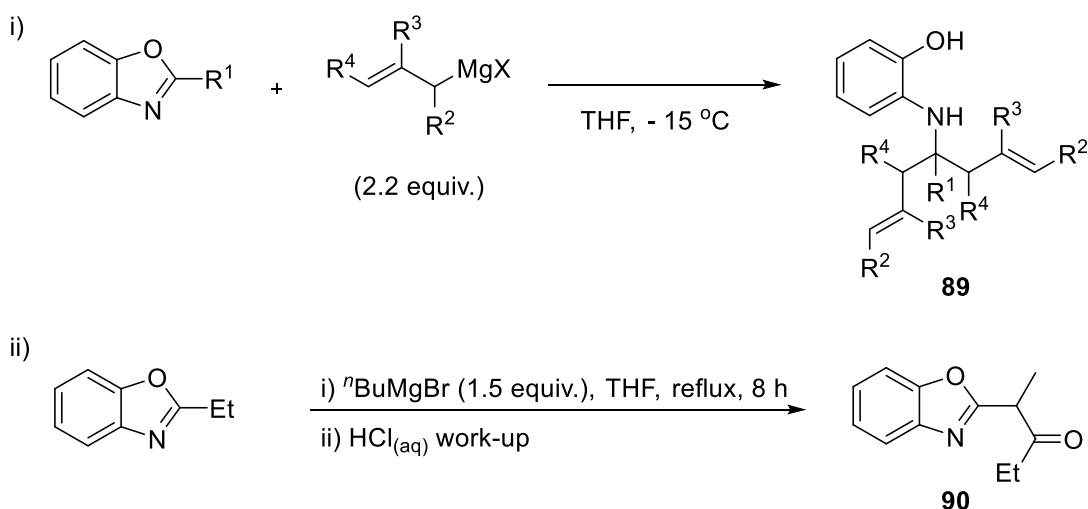


Scheme 3.4 – Attempted modified Meyers reaction using (trimethylsilyl)methyl lithium actually yielded the unexpected benzoxazole cleavage products **87** and **88** in high isolated yields.

The desired substitution of the methyl ether did not occur, with or without the presence of a nickel catalyst. It was serendipitously found that this organolithium cleaves the benzoxazole functionality, resulting in 2'-methoxyacetophenone (**87**) and 2-aminophenol (**88**) upon work-up with aqueous acid (Scheme 3.4 and Table 3.2 entries 1-3). Thus, direct attack on the benzoxazole must be occurring in preference to the methyl ether. It has been reported in the literature that benzoxazoles are remarkably stable to Grignard reagents (except allylic) and organolithiums, something that has limited their use as a protecting group. Florio reported that allylic Grignards directly attack the C=N bond due to the formation of a six-membered cyclic transition state through coordination of the nitrogen

lone pair of electrons to the Mg^{2+} ion.¹⁷⁸ Di-substitution occurred due to a second attack on the subsequent Schiff base produced by the initial ring cleavage, to give *N*-diallylalkyl-*o*-aminophenols (**89**) (Scheme 3.5 i). However, it was also shown that if a second equivalent of Grignard reagent was unable to react, the resulting ketone was created, most likely due to the hydrolysis of the Schiff base upon work-up.

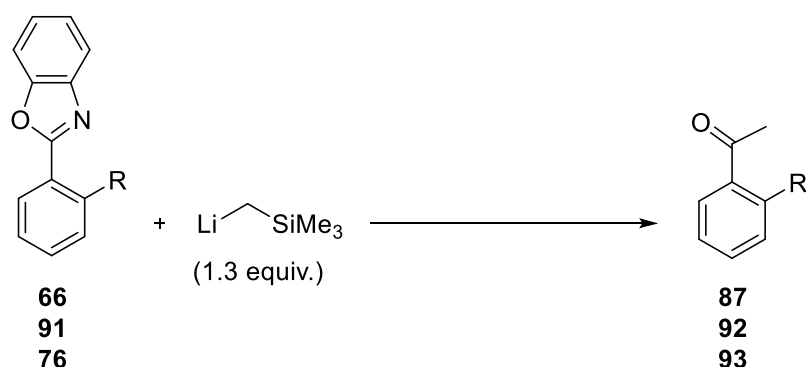
This methodology was then extended by the same author, and co-workers, a year later showing that 2-alkylbenzoxazoles can undergo Claisen-type self-condensations when reacted with $nBuMgBr$, to give benzoxazolylalkyl alkyl ketones such as **90**, when quenched with aqueous HCl (Scheme 3.5 ii).¹⁷⁹



Scheme 3.5 –Findings by Florio and co-workers involving the ring opening of benzoxazoles by Grignard reagents: i) allyl Grignards allow direct attack *via* a six-membered transition state. ii) $nBuMgBr$ was found to facilitate self-condensation of alkyl benzoxazoles followed by ketone formation upon acidic work-up.

To investigate the utility of the new reaction in Scheme 3.4, other 2-(aryl)benzo[*d*]oxazoles were tested (Table 3.2). It was important to determine if the coordinating ability of the methyl ether was required for this cleavage reaction to occur. If this was the case, then this reaction would not be of great synthetic use, being limited in substrate scope to *ortho*-benzoxazolyl substituted anisoles.

Table 3.2 – Cleavage of 2-(aryl)benzo[*d*]oxazoles by nucleophilic attack of (trimethylsilyl)methyl lithium.



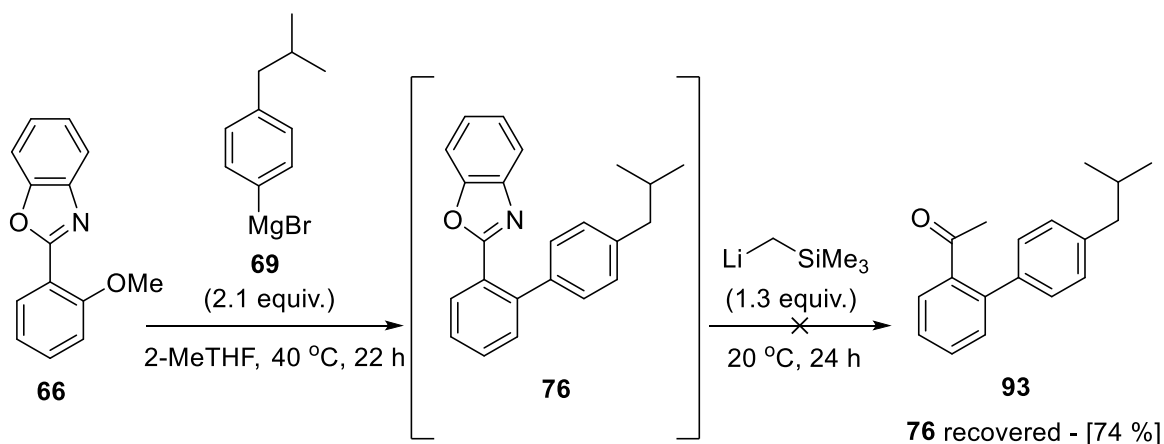
Entry ^[a]	R	Solvent	T (°C)	t (h)	Conversion (%)	Product (%)
1 ^{[b][c]}	OMe (66)	PhMe	80	18	97	61 [60]
2 ^[d]	OMe (66)	PhMe	20	18	-	[76]
3 ^[d]	OMe (66)	2-MeTHF	20	18	> 99	[84]
4 ^[d]	H (91)	2-MeTHF	20	21	-	[43]
5 ^[d]	H (91)	PhMe	20	21	-	[64]
6	H (91)	PhMe	80	19	96	81 [64]
7 ^{[d][e]}	4- ⁱ BuPh (76)	PhMe	20	21	-	[44]
8 ^{[d][f]}	4- ⁱ BuPh (76)	PhMe	80	21	-	[54]

^[a] Reactions conditions: 2-(aryl)benzo[*d*]oxazole (1.0 mmol), LiCH₂SiMe₃ (0.6 M in pentane), solvent (6 mL). Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. ^[b] 2-(2-methoxyphenyl)benzo[*d*]oxazole (0.25 mmol) scale. ^[c] Ni(cod)₂ (0.006 mmol) present. ^[d] No internal standard. ^[e] 2-(4'-isobutyl-[1,1'-biphenyl]-2-yl)benzo[*d*]oxazole (0.36 mmol) scale. ^[f] 2-(4'-isobutyl-[1,1'-biphenyl]-2-yl)benzo[*d*]oxazole (0.50 mmol) scale.

2-phenylbenzo[*d*]oxazole (**91**) was subjected to the cleavage reactions and gave acetophenone (**92**) in good isolated yield in PhMe (Table 3.2 entries 5 and 6). 2-(4'-isobutyl-[1,1'-biphenyl]-2-yl)benzo[*d*]oxazole (**76**), which was isolated from the modified Meyers reaction in a 98 % yield (Table 3.1), was also reacted with (trimethylsilyl)methyl lithium to give the substituted acetophenone, 1-(4'-isobutyl-[1,1'-biphenyl]-2-yl)ethan-1-one (**93**) in moderate yield (entries 7 and 8). Although the reaction performs better with 2-(2-methoxyphenyl)benzo[*d*]oxazole (**66**), implying there is a benefit to having the methyl ether available for coordination, there does not seem to be a requirement for chelation-assistance in order for the organolithium to react directly with the benzoxazole functionality (Scheme 3.6).

3.2.3 – Modified Meyers – benzoxazole cleavage

A modified Meyers reaction with Grignard reagent **69** was carried out and the subsequent product mixture subjected to (trimethylsilyl)methyl lithium cleavage (Scheme 3.7). Unfortunately, the second step was unsuccessful, returning 74 % of intermediate 2-(4'-isobutyl-[1,1'-biphenyl]-2-yl)benzo[*d*]oxazole (**76**).



Scheme 3.7 – Attempted one-pot modified Meyers – benzoxazole cleavage reaction.

The reaction was also tested in PhMe, with only 1.1 equivalents of the less-sterically hindered aryl Grignard *p*-TolMgBr however this also only gave intermediate (this time 2-(4'-methyl-[1,1'-biphenyl]-2-yl)benzo[*d*]oxazole (**75**)). Therefore, incompatibility of the Grignard reagent and organolithium could be ruled-out. It was then predicted that the magnesium salts produced as a by-product in the first step could be interfering with the cleavage reaction, possibly by blocking (required) chelation to the arylbenzoxazole. Preliminary additional experiments using *p*-TolMgBr, involving cannula filtration after the modified Meyers reaction and additional equivalents of (trimethylsilyl)methyl lithium showed some promise, in the sense that the intermediate arylbenzoxazole was being consumed; however, no desired product could be isolated. As will be discussed in Chapter V, tandem or sequential reactions can very easily be hampered by incompatibility issues.

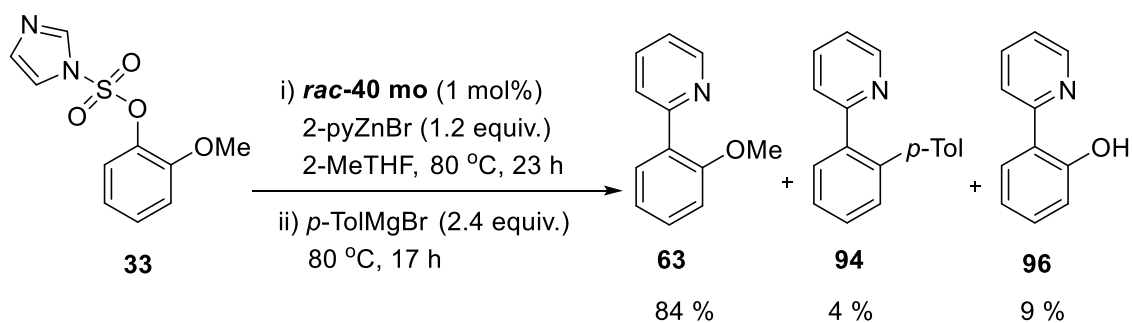
3.2.4 – Extension of the modified Meyers reaction to other heterocycles

It was shown in Chapter II (Table 2.5) that 2-(2-methoxyphenyl)pyridine (**63**) could be synthesised effectively by a palladium-catalysed Negishi cross-coupling of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**). Thus, it was of interest to determine if this product could be reacted further, with a second constructive deoxygenation reaction. Cao and co-workers demonstrated the utility of pyridine-directed C_{aryl}-F bond cleavage with Grignard reagents, in an uncatalysed manner.¹⁸⁰ However, this reaction has never been extended to aryl ether cleavage. It was predicted that this inherent directing ability of pyridine could facilitate another modified Meyers reaction, similar to what was seen with benzoxazole (Table 3.3).

directly on the methyl ether,¹⁷⁰ and is supported by the detection of methyldiphenylphosphine. The forcing conditions required are likely to be favouring this competing insertion into the C_{aryl}O-Me bond.

The required forcing conditions also resulted in THF fragmentation by BrMgPPh₂ to give 4-hydroxybutyldiphenylphosphine (**97**) (entry 11). Purdum and Berlin showed that this fragmentation was very dependent upon the duration of refluxing, with higher yields of 4-hydroxybutyldiphenylphosphine apparent after prolonged reaction times.¹⁸¹ Attempts were made to synthesise the desired Grignard reagent **72** in Et₂O and PhMe but with little success. This fragmentation was not apparent to any considerable extent in the reaction with 2-(2-methoxyphenyl)benzo[*d*]oxazole as the reaction performed well at lower temperatures, in which the fragmentation was deemed less likely (Table 3.1, entries 20 and 21). This therefore seems to be an inherent issue that will occur, due to the lower reactivity of 2-(2-methoxyphenyl)pyridine (**63**), and thus higher temperatures are required, although time could potentially be reduced in future.

This new type of Meyers reaction could provide a wide range of functionalised phenylpyridines,^{182, 183} initially stemming from guaiacol, assuming scope could be increased. Further examples were not tested due to the desire to pursue the greater challenges of undirected C_{aryl}-OMe cleavage. To make this methodology more attractive, again efforts were made to sequentialise part of the synthesis. This time, it was proposed that both constructive deoxygenation reactions could occur in a two-step, one-pot manner. This idea showed advantages over the efforts to couple a C-H functionalisation with a modified Meyers, in the sense that the Grignard compatible solvent 2-MeTHF could be used throughout (Scheme 3.8).

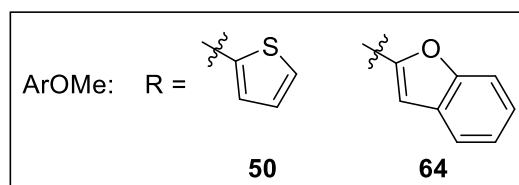
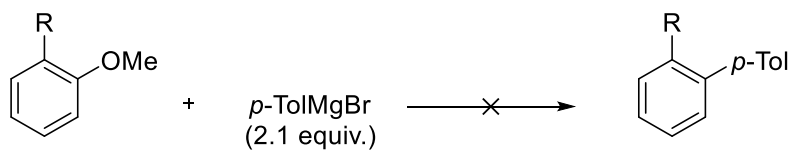


Scheme 3.8 – Attempted one-pot Pd-catalysed Negishi – modified Meyers reaction.

Similar to that observed with the benzoxazole as directing group, the reaction effectively ceased after the first functionalisation. High yields of the Negishi cross-coupling product 2-(2-methoxyphenyl)pyridine (**63**) were apparent, however only 4 % of **94** was observed. 9 % of the demethylation product **96** was understandable considering the quantities obtained in Table 3.3. An explanation for the unsuccessful second step could be the presence of zinc salts (e.g. BrZnOMe, ZnBr₂, Zn(OMe)₂) produced in the Negishi cross-coupling reaction, which compete and thus block the desired N,O coordination of the substrate to the Grignard reagent.

Section 3.1 gave examples of several different functionalities that can participate in this adaptation of the Meyers reaction. This research has shown the first examples of this with benzoxazole and pyridine functionalities to substitute an aryl methyl ether. To probe the relative importance of coordinating groups or resonance stabilisation (Scheme 3.9), and to gain a better understanding of functional groups that can and cannot participate in this reaction, 2-(2-methoxyphenyl)thiophene (**50**) and 2-(2-methoxyphenyl)benzo[*b*]furan (**64**), which were prepared from constructive deoxygenation reactions of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**) (Chapter II), were tested in the modified Meyers reaction (Table 3.4). Both of these substrates lack the ability to participate in productive extended conjugation, and thus will only be able to facilitate attack onto the C_{aryl}-OMe (in a more typical S_NAr manner).

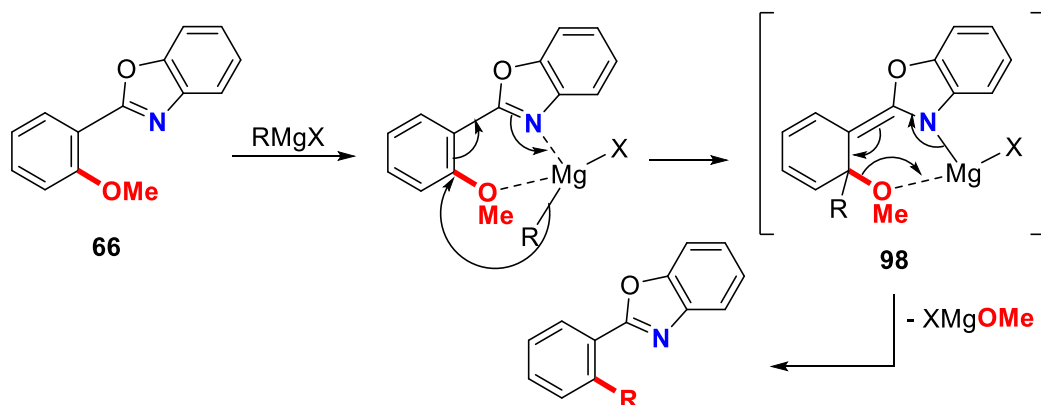
Table 3.4 – Investigation of the ability of other heterocycles to participate in the modified Meyers reaction, without the ability to effectively stabilise the developing negative charge.



Entry ^[a]	Ar-OMe	Solvent	T (°C)	t (h)	Conversion (%)	Product (%)
1 ^[b]	50	PhMe	20 100	22 48	0	0
2 ^[c]	64	PhMe	110	18	0	0
3 ^{[c][d]}	64	PhMe	110	18	0	0
4 ^[c]	64	2-MeTHF	80	64	0	0
5 ^{[c][d]}	64	2-MeTHF	110	18	0	0

^[a] Reactions conditions: aryl ether (0.25 mmol), *p*-TolMgBr (0.53 mmol, 0.5 M in Et₂O), solvent (1.13 mL). Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. ^[b] 1.2 equiv. Grignard. ^[c] 2-(2-methoxyphenyl)benzo[*b*]furan (0.15 mmol) scale. ^[d] Reaction performed in a sealed microwave vial with crimp cap.

Under conditions that were previously successful for Meyers-type cleavage of aryl methyl ethers, both 2-(2-methoxyphenyl)thiophene and 2-(2-methoxyphenyl)benzo[*b*]furan were unreactive. This highlights that an ability for the directing group to stabilise the negative charge *via* a Meisenheimer-type complex (**98**), was crucial for productive Meyers-type reactions (Scheme 3.9).



Scheme 3.9 - The proposed mechanism for the uncatalysed reaction of 2-(2-methoxyphenyl)benzo[*d*]oxazole (**66**) with Grignard reagents.

3.3 - Summary and future work

Methods to remove the aryl ether of some anisoles easily made from guaiacol have been established. These make use of an uncatalysed constructive deoxygenation on anisoles that contain an adjacent heterocycle, with C-C bond formation using Grignard reagents. Modifications of the Meyers reaction, utilising a benzoxazole, or pyridine directing group (successfully synthesised from 2-methoxyphenyl-1*H*-imidazole-1-sulfonate, in Chapter II) resulted in a range of products, with no original phenolic bonds from guaiacol remaining. Importantly, these products could then be functionalised further if so desired, either by cleavage of the benzoxazole or by further reaction e.g. lithiation of the pyridine ring or C-H activation, and this is something that would be desirable to determine in future work. It was found that other heterocyclic directing groups such as benzofuran and thiophene were unable to facilitate this Meyers reaction, due their inability to effectively stabilise the negative charge formed *via* a Meisenheimer-type transition state.

Presently, it appears as though this modified Meyers reaction only occurs with Grignard reagents, as attempts with other nucleophiles such as organozincs and organolithiums failed; future work could try to increase the reaction scope further. The reaction of 2-(2-methoxyphenyl)benzo[*d*]oxazole with (trimethylsilyl)methyl lithium resulted in the nucleophilic attack of the benzoxazole directly, leading to 2'-methoxyacetophenone after work up. This cleavage reaction was then extended to other arylbenzoxazoles lacking a methyl ether (as this would have been removed prior to benzoxazole cleavage), with moderate to good success, however highest yields were when the potentially coordinating methyl ether was present.

After this discovery of benzoxazole cleavage, attempts were made to perform a modified Meyers - benzoxazole cleavage two-step, one-pot process, however no success was apparent, with the conditions tested only returning the substituted arylbenzoxazole intermediate.

While the S_NAr reactions throughout this Chapter represent convenient procedures to remove aryl methyl ethers, and exemplify one of the project aims (transforming guaiacol

to *ortho*-substituted benzenes), they are not very broad in scope since a heterocycle is required. Nickel-catalysed cross-coupling has become a powerful method to cleave aryl ethers, allowing a degree of variation in terms of functionalisation. Hence the nickel-catalysed Grignard cross-coupling of aryl methyl ethers, particularly *ortho*-substituted anisoles, was researched in Chapter IV.

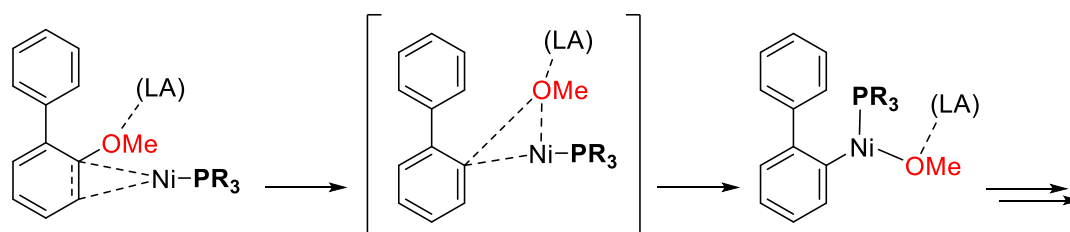
Chapter IV: New nickel catalysts for the cross-coupling of aryl methyl ethers with Grignard reagents

4.1 – Introduction

Chapter III described methodology to remove the ether functionality from guaiacol-derived feedstocks: specific directing groups were required. However, it is more synthetically useful if a general method for substituting aryl ethers with Grignard reagents is available.

As the research discussed in Chapter I has shown, aryl methyl ether cross-coupling is in an exciting era of development. Recently, many key contributions have been made to the field. Despite this, there are still challenges regarding the cross-coupling of non-activated anisole derivatives, with very specific nucleophiles or Grignard reagents being required.

Several possible mechanisms are speculated.^{123, 125, 184} One theory is that a classical mechanism is operating, which involves a typical cross-coupling catalytic cycle consisting of oxidative addition, transmetalation and reductive elimination. The key oxidative addition step involves a three-coordinate transition state, which may or may not be accelerated by a Lewis acid (LA) (Scheme 4.1).^{109, 121, 122}

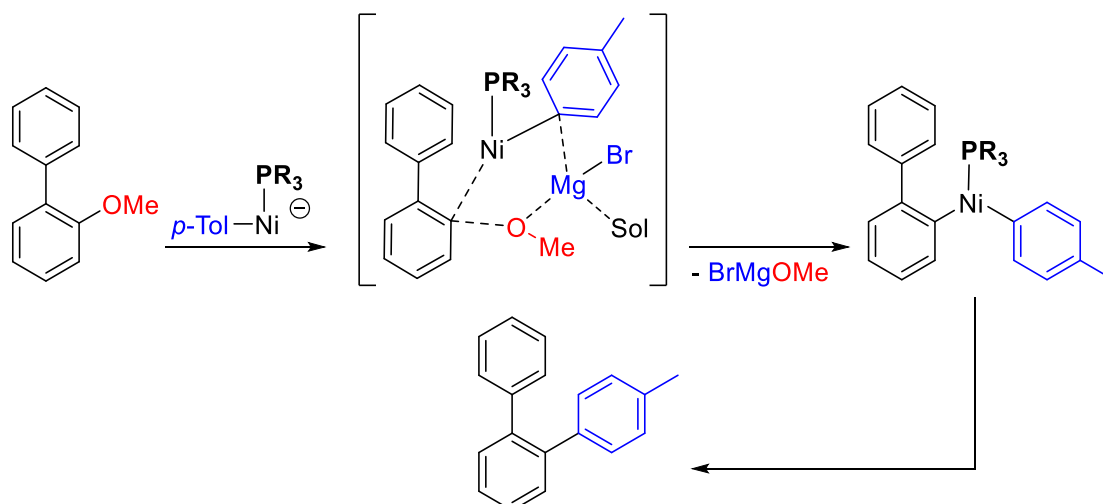


Scheme 4.1 – “Classical”, direct oxidative addition of an etheric C(sp²)-OMe bond to Ni⁰ involving the three-centred transition state. A marginally lower activation energy path is apparent with a Lewis acid (LA) to assist the C(sp²)-OMe bond activation.¹²⁵

This mechanism has been shown to occur under certain circumstances, but has also been ruled out by others, with facile β -hydride elimination from an ArNi(OMe) species being

observed.^{119, 123} Recent reports have put this direct oxidative addition mechanism into question as it does not explain the greater tendency and wider scope for Grignard cross-coupling to occur, as opposed to e.g. Suzuki-Miyaura reactions, even with Lewis acid additives.¹⁰¹

Uchiyama and co-workers have shown that reactions involving an anionic $[\text{Ni}^0\text{-ate}]^-$ species allow this insertion of nickel into the $\text{C}_{\text{aryl}}\text{-OMe}$ bond to occur in a significantly lower energy process.¹²⁵ This $[\text{Ni}^0\text{-ate}]^-$ species is formed by attack of the Grignard reagent on the metal centre and facilitates $\text{C}_{\text{aryl}}\text{-OMe}$ bond activation through a bimetallic, push-pull mechanism (Scheme 4.2), similar to that discussed by Nakamura and co-workers.⁶⁵



Scheme 4.2 – Calculated mechanism by Uchiyama and co-workers¹²⁵ for $\text{C}_{\text{aryl}}\text{-OMe}$ bond cleavage, involving the $\text{Ni}^0\text{-ate}$ species formed prior to insertion into $\text{C}_{\text{aryl}}\text{-OMe}$. This cleavage involves a “push-pull interaction” via a 5-membered ring transition state.

Regardless of mechanism, it is clear that nickel has a much better heritage than palladium in aryl methyl ether cross-coupling, with no successful reports to date involving palladium catalysts. Within the already challenging anisole-derivatives, *ortho*-substitution has been found to be another step-up in difficulty, which is represented by the relatively few examples in the literature. The effect of ligand cone angle on catalytic activity has only been briefly studied by Dankwardt in 2004, using 6-methoxy-1,2,3,4-tetrahydronaphthalene as the substrate, with tricyclohexylphosphine (PCy_3) being the optimal ligand.⁸⁹ This has led to PCy_3 being the main phosphine tested in the cross-

coupling catalysis of methyl ethers. It is unknown if the same reactivity patterns exist when *ortho*-substituted aryl ethers are used.

Although Dankwardt reported a range of phosphines varying in cone angle, from PCy₃ to trimethylphosphine (PMe₃), triⁿbutylphosphine (PⁿBu₃) was not discussed. This phosphine, as well as its derivatives, have somewhat surprisingly not been utilised previously throughout the literature. PⁿBu₃ has almost as strong σ -donating abilities as PCy₃ but has the benefit of being considerably smaller in terms of cone angle (Figure 4.1). It seemed possible that this reduced cone angle could aid in the coupling of challenging *ortho*-substituted aryl methyl ethers, potentially derived from guaiacol. Subsequently, the large bulk associated with PCy₃ and other successful ligands e.g. the N-heterocyclic carbene (NHC) 1,3-*bis*(2,6-diisopropylphenyl)-imidazol-2-ylidene (IPr), is possibly the reason why there are so few successful examples of coupling of *ortho*-substituted anisoles with Grignard reagents.

The aim of the work described in this chapter is to improve reactivity and scope of challenging *ortho*-substituted anisoles, that could be derived from guaiacol, through phosphine, and ultimately catalyst, variation.

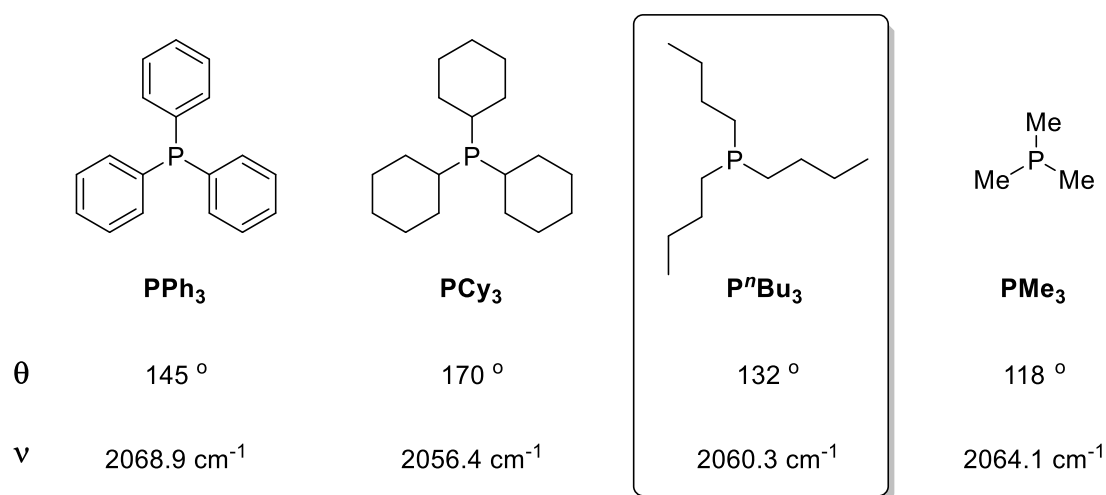
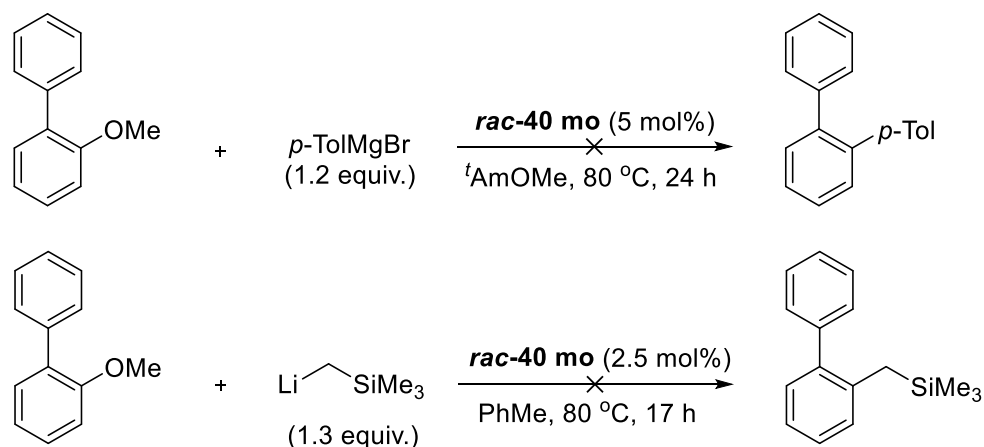


Figure 4.1 – Tolman cone angle (θ) and electronic parameter (ν) for a range of monodentate phosphines.³²

4.2 - Results and discussion

4.2.1 – Attempted Pd-Phanephos catalysed cross-coupling of 2-methoxybiphenyl

[PdCl₂(Xylyl-Phanephos)] (**40 mo**) was shown in Chapter II to be an excellent catalyst for the cross-coupling of imidazole-sulfonates of phenols, and so was tested here, since it might allow a catalytic tandem or sequential process for both constructive deoxygenations of lignin derived guaiacol. If successful it would be the first Pd-catalysed cross-coupling of any aryl ether. However, brief experiments using *rac*-**40 mo** gave none of the desired products (Scheme 4.3).



Scheme 4.3 – Unsuccessful attempts at Pd-catalysed cross-coupling of 2-methoxybiphenyl.

The results were not surprising as palladium has no real heritage in ether cross-coupling, compared to nickel. There are large energy barriers that must be overcome with ether cross-coupling, particularly in the C_{aryl}-OMe bond breaking step, and Uchiyama and co-workers have demonstrated the large differences between nickel and palladium in overcoming these.¹²⁵ Palladium is also more electronegative than nickel and consequently does not readily give up electron density to facilitate oxidative addition processes, which is often rate-limiting in the cross-coupling of less-reactive electrophiles. Palladium has also been shown to be less efficient at back-donating electron density to π -acceptors such as aryl ethers (Figure 4.2).¹⁸⁵

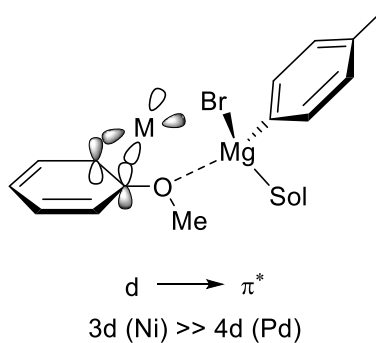
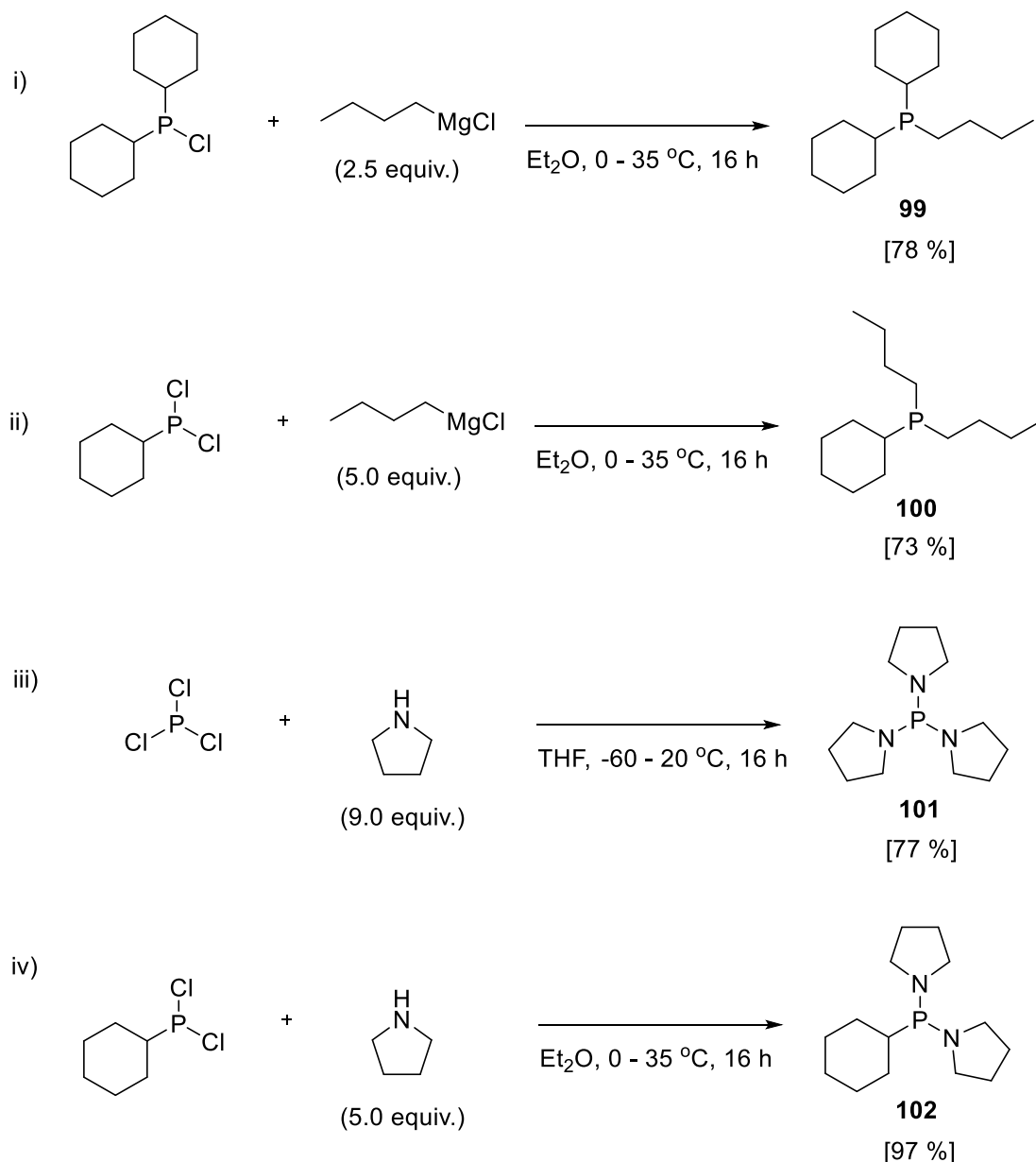


Figure 4.2 – η^2 -interaction between catalyst and aryl ether substrate, with Ni donating electron density more favourably.¹²⁵

The establishment of this η^2 -interaction is predicted to be key in facilitating the cross-coupling of aryl ethers as considerable stabilisation of intermediates and transition states can occur.^{125, 186} Avenues involving nickel-catalysis had to be explored.

4.2.2 – Ligand preparation

As $[\text{NiCl}_2(\text{PCy}_3)_2]$ is one of the most successful phosphine-based catalysts for methyl ether cleavage, alkyl phosphines based on PCy_3 were synthesised, with slight variations in cone angle as well as σ -donating ability (Scheme 4.4, i and ii). Nucleophilic substitution of the respective chlorophosphines with excess $n\text{BuMgCl}$ gave phosphines **99** and **100** in satisfactory isolated yields.



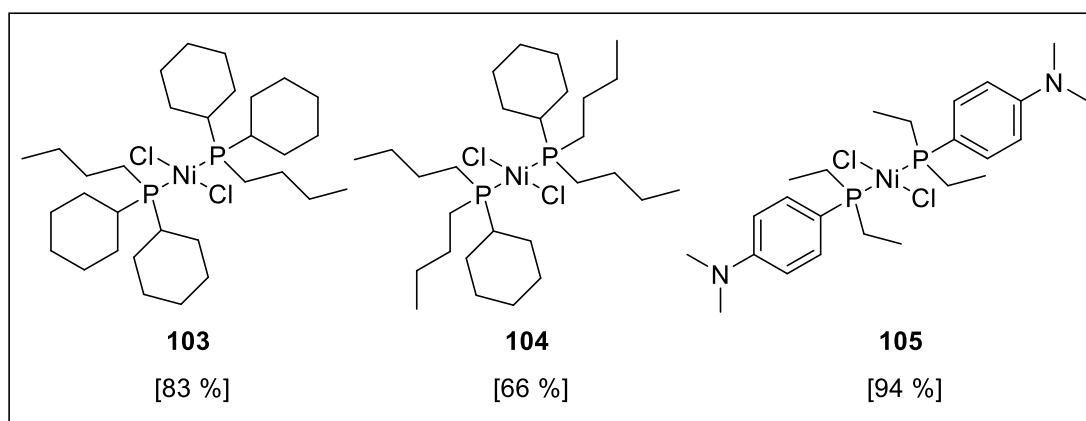
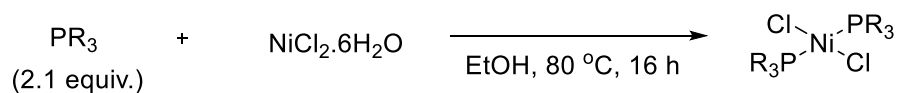
Scheme 4.4 – Synthesis of a range of strongly σ -donating phosphines, varying in cone angle.

Tris(alkylamino)phosphines such as **101** have been found to be electron-rich, strong σ -donor ligands, predominately due to electron density donation from the nitrogen lone pair of electrons to the phosphorus atom. However, it was found that in these systems, the phosphorus atom could only gain significant electron density from two of the nitrogen lone pairs.¹⁸⁷ Woollins and co-workers established a range of novel hybrid *bis*(*N*-pyrrolidinyl)alkylphosphines, and reported them to be extremely σ -donating ligands when complexed to various metals.^{187, 188} Therefore, inspiration was taken from these findings and cyclohexyldichlorophosphine was reacted with excess pyrrolidine to obtain

cyclohexyl(dipyrrolidinyl)phosphine (**102**) in near-quantitative isolated yield (Scheme 4.4 iv).

4.2.3 – Preparation of nickel complexes

All nickel(II) complexes were prepared according to Scheme 4.5, adapting a literature procedure reported by Jamison and co-workers.¹⁸⁹ Overall, these were high yielding reactions with crystal structures for complexes **103**, **104** and **105** confirming an expected square planar *trans*-configuration, due to sterics of the phosphines (Figures 4.3-4.5).



Scheme 4.5 – Nickel-complexation reactions to create *trans*-substituted nickel(II)-precatalysts, with configurations supported by crystal structure analysis.

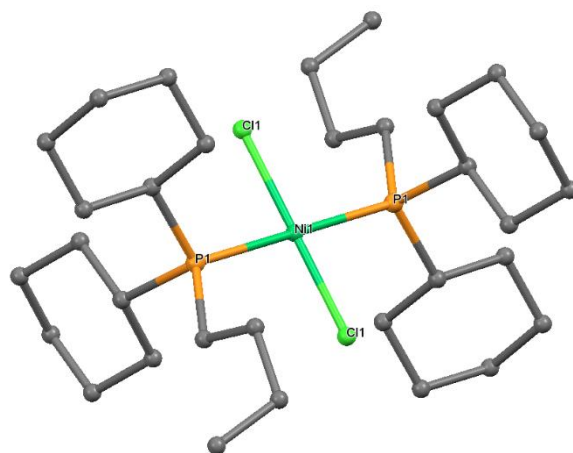


Figure 4.3 – Crystal structure of $[\text{NiCl}_2(\text{PCy}_2^i\text{Bu})_2]$ (**103**) (protons removed for clarity). Ni-P = 2.2519(4) Å, Ni-Cl = 2.1657(6) Å.

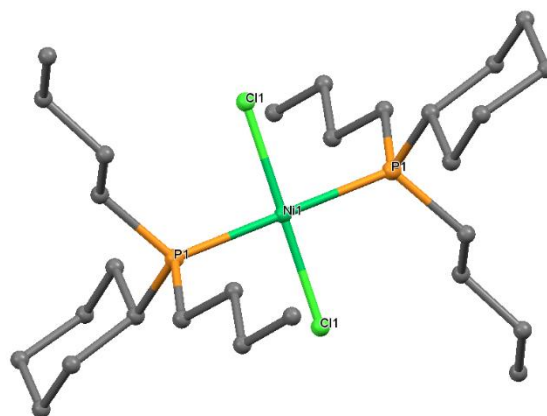


Figure 4.4 – Crystal structure of $[\text{NiCl}_2(\text{PCy}^i\text{Bu})_2]$ (**104**) (protons removed for clarity). Ni-P = 2.2295(3) Å, Ni-Cl = 2.1622(3) Å.

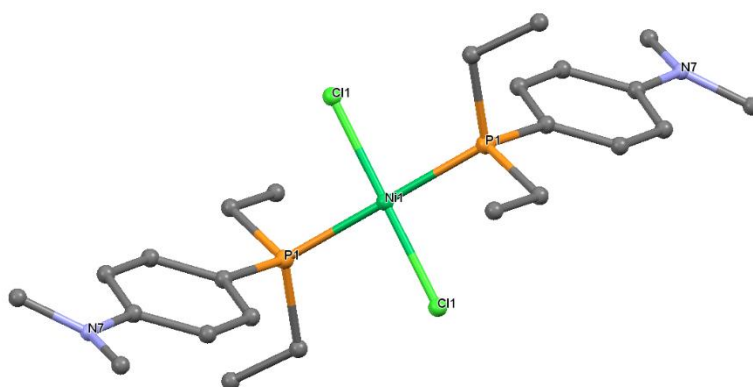


Figure 4.5 – Crystal structure of $[\text{NiCl}_2(\text{PEt}_2\text{Ar})_2]$, Ar = 4-(NMe₂)C₆H₄ (**105**) (protons removed for clarity). Ni-P = 2.2439(8) Å, Ni-Cl = 2.1647(8) Å.

Problems arose when trying to complex the pyrrolidine-based ligands **101** and **102**, with numerous species apparent in the ^{31}P NMR spectra. Several nickel-precursors were tested, ranging from anhydrous NiCl_2 , NiCl_2 glyme, to $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$. However, the desired complex was unable to be isolated in all cases. The strongly electron donating capabilities, and subsequent air- and moisture-sensitive nature of these ligands could have been problematic during complexation. Crystal structure analysis suggested phosphine decomposition, with $[\text{NiCl}_2(\text{pyrrolidinyl})_3]$ (**106**) being apparent (Figure 4.6). Thus, these nickel catalysts had to be tested *in situ* using $[\text{Ni}(\text{cod})_2]$.

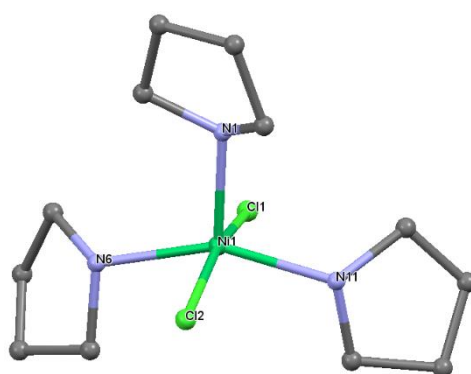


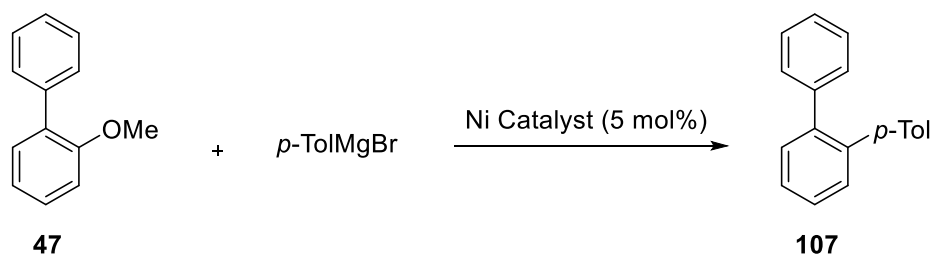
Figure 4.6 – Crystal structure of one of the isolated products from the attempted Ni complexation of cyclohexyl(dipyrrolidinyl)phosphine (**106**) indicating phosphine decomposition, (protons removed for clarity).

4.2.4 – Catalysis studies

4.2.4.1 – Effect of phosphine cone angle on the nickel-catalysed Grignard cross-coupling of 2-methoxybiphenyl

The model substrate chosen was 2-methoxybiphenyl (**47**) as it is relevant to guaiacol functionalisation, having been prepared in Chapter II. Initial optimisation involved testing the success of the well-renowned $[\text{NiCl}_2(\text{PCy}_3)_2]$ catalyst in the Grignard cross-coupling of this challenging *ortho*-substituted anisole (Table 4.1). However, it soon became apparent that the commercially available, relatively untested $[\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2]$ was a significantly better catalyst.

Table 4.1 – Optimisation of nickel-catalysed cross-coupling of 2-methoxybiphenyl (**47**) with *p*-TolMgBr.



Entry ^[a]	Catalyst	Grig. equiv.	Solvent	T (°C)	t (h)	Conversion (%)	Product (%)
1	NiCl ₂ (PCy ₃) ₂	2.1	^t AmOMe	100	19	25	10
2 ^[b]	NiCl ₂ (PCy ₃) ₂	2.1	^t AmOMe	100	19	27	21
3 ^[b]	NiCl ₂ (PCy ₃) ₂	2.1	^t AmOMe	100	45	33	22
4 ^{[b][c]}	NiCl ₂ (PCy ₃) ₂	2.1	^t AmOMe	100	42	44	23 [13]
5 ^[b]	NiCl ₂ (PCy ₃) ₂	3.0	^t AmOMe	100	42	30	8
6	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	2.1	^t AmOMe	100	45	70	52
7	NiCl ₂ (PCy ₃) ₂	2.1	PhMe	100	16	13	10
8	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	2.1	PhMe	100	16	65	49
9	NiCl ₂ (PCy ₃) ₂	2.1	2-MeTHF	100	16	36	15
10 ^[b]	NiCl ₂ (PCy ₃) ₂	2.1	2-MeTHF	100	16	37	30
11	NiCl ₂ (PCy ₃) ₂	2.1	2-MeTHF	100	45	22	10
12 ^[b]	NiCl ₂ (PCy ₃) ₂	2.1	2-MeTHF	100	45	45	26
13	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	2.1	2-MeTHF	100	16	88	78
14	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	2.1	2-MeTHF	100	45	96	80
15 ^[d]	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	2.1	2-MeTHF	100	45	98	84 [84]
16	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	2.1	2-MeTHF	125	16	88	77
17	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	4.2	2-MeTHF	100	16	70	67
18	NiCl ₂ (PCy ₃) ₂	1.5	2-MeTHF	100	16	34	5
19	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	1.5	2-MeTHF	100	16	85	79
20 ^[e]	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	1.5	2-MeTHF	100	16	80	66
21 ^[f]	NiCl ₂ (PCy ₃) ₂	1.5	2-MeTHF	80	16	29	19
22 ^[f]	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	1.5	2-MeTHF	80	16	54	43
23	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	1.5	2-MeTHF	80	16	53	38

^[a] Reactions conditions: 2-methoxybiphenyl (0.50 mmol), *p*-tolylmagnesium bromide (0.5 M in Et₂O), Ni catalyst (0.025 mmol), solvent (2.25 mL) in a sealed microwave vial with crimp cap. Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. ^[b] PCy₃ (0.05 mmol, 10 mol%) added. ^[c] Grignard reagent (0.5 M in ^tAmOMe). ^[d] P^{*n*}Bu₃ (0.05 mmol, 10 mol%) added. ^[e] MgI₂ (0.75 mmol) added. ^[f] Reaction performed in a Schlenk flask, since at 80 °C.

Initially, conditions similar to those reported by Dankwardt⁸⁹ were investigated, with *tert*-amyl methyl ether (^tAmOMe) as the solvent. However, poor results were obtained with [NiCl₂(PCy₃)₂], even with large equivalents of Grignard reagent, additional ligand for

stabilisation and prolonged time (Table 4.1, entries 1-5). Changing the solvent to toluene (PhMe) or 2-methyltetrahydrofuran (2-MeTHF) did not give any considerable improvements in yield with $[\text{NiCl}_2(\text{PCy}_3)_2]$ (entries 7 and 9-12). Few examples of *ortho*-substituted anisoles were coupled in the original study reporting on the Ni/PCy₃ system.⁸⁹ Furthermore, none of these examples, as well as several other anisole derivatives, were actually isolated. $[\text{NiCl}_2(\text{PCy}_3)_2]$, should not be considered a broadly viable catalyst for the coupling of deactivated aryl methyl ethers with Grignard reagents.

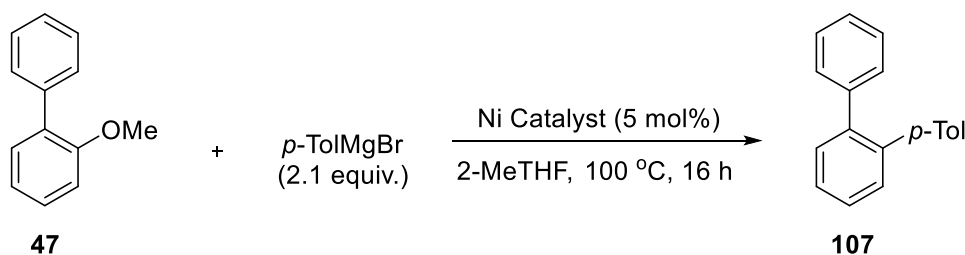
The more streamlined $[\text{NiCl}_2(\text{P}^i\text{Bu}_3)_2]$ considerably increased yields, and couplings in 2-MeTHF worked especially well. Adding 10 mol% of free ligand increased yields when using the Ni/PCy₃ system (entries 10 and 12), but desirably was not found to be necessary using $[\text{NiCl}_2(\text{P}^i\text{Bu}_3)_2]$.

Longer reaction times and elevated temperatures did not seem to have a significant effect on productivity. Pleasingly, lowering the equivalents of Grignard reagent to 1.5 increased product formation with $[\text{NiCl}_2(\text{P}^i\text{Bu}_3)_2]$ (entries 13, 17 and 19), in contrast to Dankwardt's findings.⁸⁹ Decreasing the reaction temperature to 80 °C gave low yields using either catalyst and MgI_2 ¹⁰⁰ did not improve performance (entry 20).

There is a pronounced difference in performance between the two nickel(II) complexes in the cross-coupling of this *ortho*-substituted anisole, lacking extended π -conjugation, and thus not benefitting from the "naphthalene effect". The more often utilised $[\text{NiCl}_2(\text{PCy}_3)_2]$, containing the strongly σ -donating phosphine PCy₃, seems to perform poorly compared to the under-utilised, more compact, $[\text{NiCl}_2(\text{P}^i\text{Bu}_3)_2]$. Regardless of conditions, $[\text{NiCl}_2(\text{PCy}_3)_2]$ only gave a maximum of 30 % of 4-methyl-1,1':2',1''-terphenyl (**107**) while $[\text{NiCl}_2(\text{P}^i\text{Bu}_3)_2]$ yielded a maximum of 84 %.

The fact that the slimmer PⁱBu₃-based catalyst performed better, could suggest that there is an optimum ligand cone angle for this cross-coupling. Therefore, other phosphines, varying in cone angle, were tested to determine if ligands with smaller cone angles than PCy₃ gave more active catalysts (Table 4.2).

Table 4.2 – Effect of ligand cone angle (θ) on the nickel-catalysed Grignard cross-coupling of 2-methoxybiphenyl (**47**) with *p*-TolMgBr.



Entry ^[a]	Catalyst	θ ($^\circ$)	Conversion (%)	Product (%)
1	NiCl ₂ (PCy ₃) ₂	170	36	15
2	103	157	23	21
3	104	145	59	51
4	NiCl ₂ (PPh ₃) ₂	145	8	1
5	105	139	61	47
6	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	132	88	78
7	NiCl ₂ (PMe ₃) ₂	118	20	7
8	Ni(cod) ₂	-	17	0
9 ^[b]	Ni(cod) ₂ / PCy ₃	170	28	8
10 ^[b]	Ni(cod) ₂ / P ^{<i>n</i>} Bu ₃	132	81	63
11 ^[b]	Ni(cod) ₂ / 102	151	7	1
12 ^[b]	Ni(cod) ₂ / 101	142	7	0

^[a] Reactions conditions: 2-methoxybiphenyl (0.50 mmol), *p*-tolylmagnesium bromide (1.05 mmol, 0.5 M in Et₂O), Ni catalyst (0.025 mmol), 2-MeTHF (2.25 mL) in a sealed microwave vial with crimp cap, 100 °C, 16 h. Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard. ^[b] 11 mol% of phosphine.

Pleasingly a trend was apparent: with decreasing cone angle, yields generally increased (Figure 4.7). The only real deviations from this trend were when catalysts **105** and [NiCl₂(PMe₃)₂] were used. With a cone angle of 139 ° catalyst **105** should lie between catalyst **104** and [NiCl₂(P^{*n*}Bu₃)₂], however electronic properties are also significant in this area of cross-coupling, as electron-rich nickel species are still required for successful insertion into the C_(aryl)-OMe bond; regardless of the proposed mechanism. As catalyst **105** contains an aryl phosphine component (albeit with an electron-donating *para*-dimethylamine functionality), the σ -donating properties of this phosphine could be reduced. The lower σ -donating ability of [NiCl₂(PMe₃)₂] could also be the reason it underperforms in this catalysis (Table 4.2, entry 7). To support this, a catalyst derived from PPh₃, a significantly weaker σ -donor relative to P^{*n*}Bu₃, was tested and gave negligible product, even with a reasonably desirable cone angle of 145 ° (Table 4.2, entry 4).

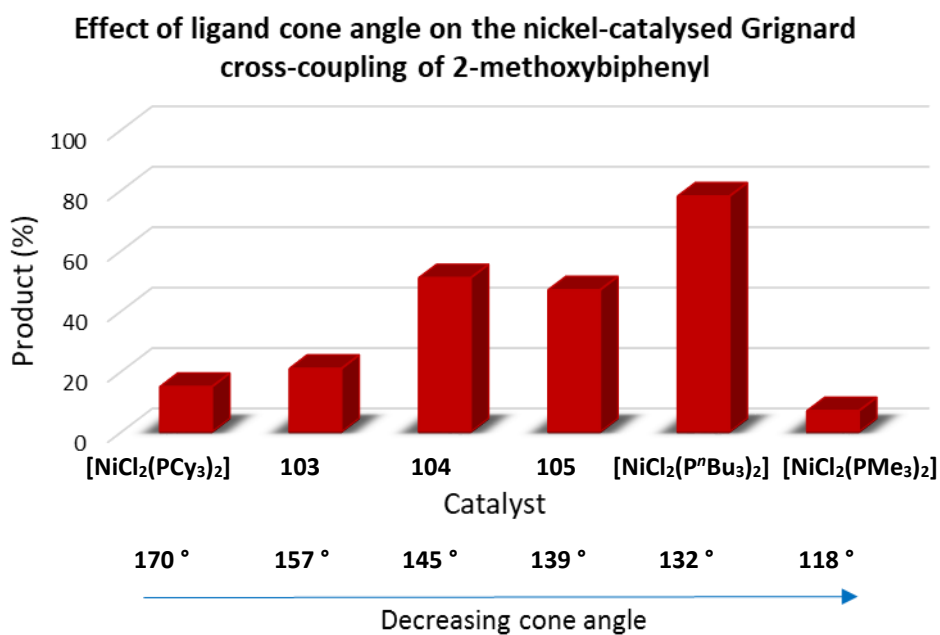


Figure 4.7 – Graphical representation of cone angle trend, clearly showing a bias towards nickel catalysts containing phosphines with a smaller cone angle relative to PCy_3 . $[\text{NiCl}_2(\text{PPh}_3)_2]$ was not plotted as it is significantly impeded by the low σ -donating ability of PPh_3 .

This requirement for strong σ -donating ligands is why Wenkert's seminal conditions using $[\text{NiCl}_2(\text{PPh}_3)_2]$ are now considered to be relatively poor, requiring high catalyst loadings even for easier naphthalene substrates, and thus struggling to find further application within the field.⁸⁸ Consequently, strongly electron donating ligands like PCy_3 , and NHCs such as IPr, have given good results. However, these results suggest smaller cone angle phosphines to be worthy of investigation.

In order to test the strongly σ -donating, relatively compact, pyrrolidine-based phosphines **101** and **102**, attempts were made to form the desired nickel catalysts *in situ*. To do this, $[\text{Ni}(\text{cod})_2]$ was chosen as the Ni^0 source, as it is heavily utilised for aryl methyl ether cross-coupling catalysis. Martin and co-workers have suggested that 1,5-cyclooctadiene (cod) can act as a non-innocent ancillary ligand within the catalytic cycle,^{112, 190} and have shown that it can stabilise the catalyst resting state in the $\text{Ni}(\text{cod})_2/\text{PCy}_3$ -catalysed reductive cleavage of C-O bonds with silanes.¹²³ Rueping and co-workers have also utilised $[\text{Ni}(\text{cod})_2]$ in the reaction of (trimethylsilyl)methyl lithium with a range of aryl methyl ethers.¹⁰⁷ However, $[\text{Ni}(\text{cod})_2]$ alone, gave no product in the Grignard cross-

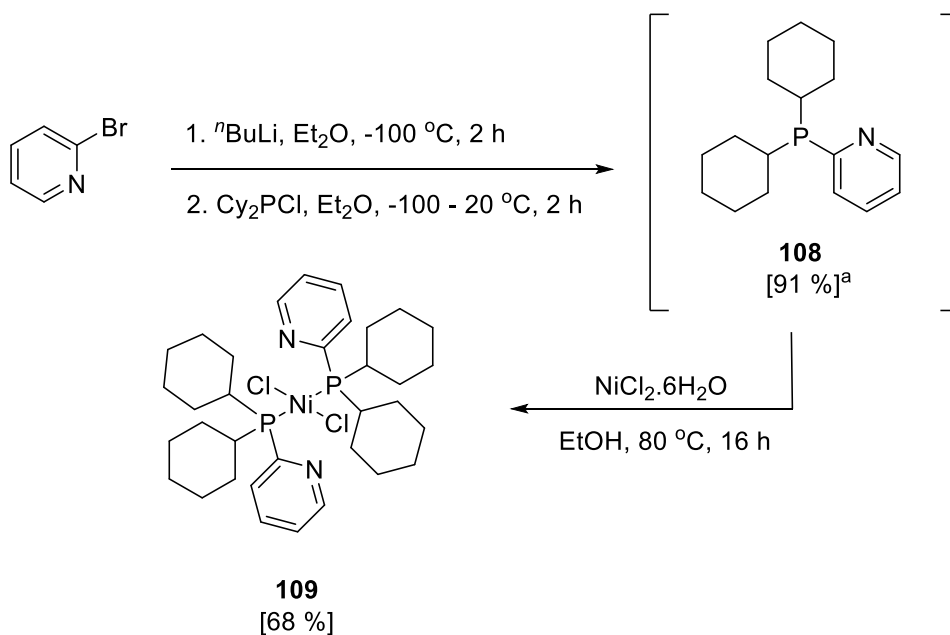
coupling of 2-methoxybiphenyl (Table 4.2, entry 8), reiterating the requirement for electron-donating ligands to facilitate this Grignard cross-coupling reaction.

As a control experiment for the *in situ* reactions using $[\text{Ni}(\text{cod})_2]$, ligands PCy_3 and P^nBu_3 were tested (Table 4.2, entries 9 and 10), and compared to the results with the pre-formed Ni^{II} -catalysts (Table 4.2, entries 1 and 6 respectively). Yields decreased slightly however the catalytic preference for P^nBu_3 -based catalysts still remained. The slight decrease is most probably due to inefficiencies in the phosphine displacing *cod* to form the desired catalytic species $\text{Ni}(\text{PR}_3)_2$. This displacement has been previously shown to be surprisingly challenging, computationally, as well as experimentally.¹²³ Alternatively, the very air sensitive nature of $[\text{Ni}(\text{cod})_2]$ may mean slightly less active catalyst is formed, due to small amounts of decomposition.

The pyrrolidine-based complexes (potentially) created *in situ* from $[\text{Ni}(\text{cod})_2]$ were both unsuccessful in catalysis (Table 4.2, entries 11 and 12). Numerous factors could have caused this, including the inability to form the desired complex, as well as the instability of the phosphine ligands with Grignard reagents. Nucleophilic substitution of the pyrrolidine by the Grignard reagent can possibly occur under these forcing conditions, cleaving the P-N bond and hindering catalysis.

The apparent strong dependence on the cone angle of the phosphine for the cross-coupling of 2-methoxybiphenyl is in contrast to the usual dogma in cross-coupling, where bulky, electron-rich ligands often thrive. Much of this catalysis operates through mono-ligated intermediates, with bulkier ligands maximising stability and the amounts of such species.

A range of potentially bidentate ligands were also worthy of investigation, for comparison. While 2-pyridyl phosphines and the hydroxyphosphine ligand **1** can act as P,N- or P,O-chelates respectively, it was also possible they could bind Mg at some point in the cycle, in a favourable manner.⁶⁵ Thus, *bis*(2-pyridyldicyclohexylphosphine)nickel(II) dichloride (**109**) was synthesised (Scheme 4.6).



Scheme 4.6 – Synthesis of *bis*(2-pyridyldicyclohexylphosphine)nickel(II) dichloride (**109**).
^a 91 % yield isolated with 2-bromopyridine impurity; total phosphine **108** obtained = 81 %.

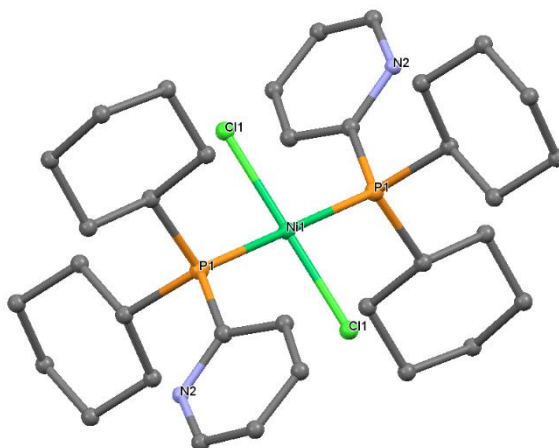
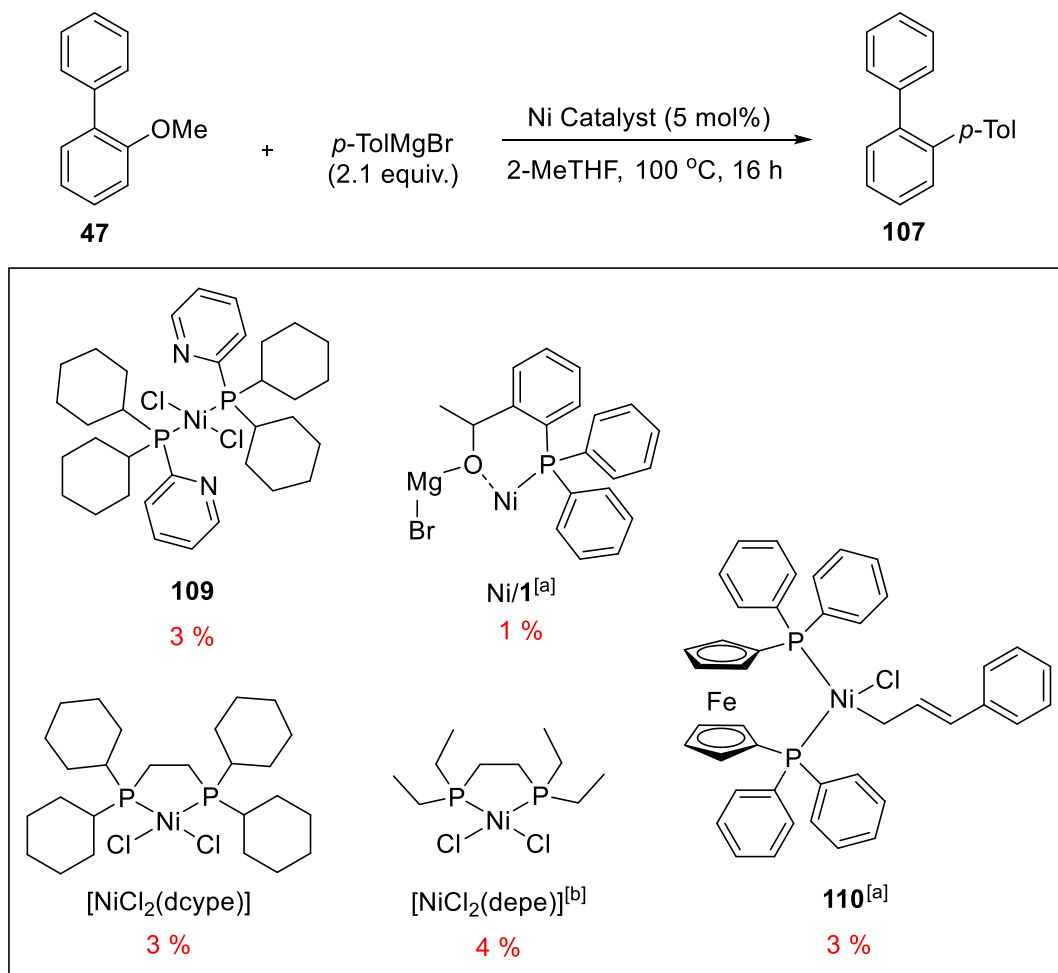


Figure 4.8 – Crystal structure of $[\text{NiCl}_2(\text{P}(2\text{-py})\text{Cy}_2)_2]$ (**109**) (protons removed for clarity).
 Ni-P = 2.237(2) Å, Ni-Cl = 2.167(4) Å.

Although pure by ^{31}P { ^1H } NMR spectroscopy, the phosphine intermediate **108** showed ~ 20 % impurity by ^1H NMR spectroscopy which was predominately from the starting material 2-bromopyridine (Scheme 4.6). Deemed unlikely to cause too many issues in the complexation reaction, the mixture was then reacted with $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ in the same manner as in Section 4.2.2. The crystal structure showed a *trans bis*-ligated system with the pyridine functionality not coordinated to the metal, similar to that often observed with the well-known aryl derivative in literature (Figure 4.8).^{191, 192} This complex, along with the

hydroxyphosphine ligand **1**, was then tested in the cross-coupling of 2-methoxybiphenyl (**47**) (Scheme 4.7).



Scheme 4.7 – Ni-catalysed Grignard cross-coupling of 2-methoxybiphenyl (**47**) with *p*-TolMgBr, with hemi-labile and bidentate catalytic systems. ^[a] 45 hours. ^[b] 1.5 equiv. Grignard reagent. Yields determined by ¹H NMR using 1-methylnaphthalene as an internal standard are shown in red.

Catalyst **109** performed very poorly, only yielding 3 % of desired product. It is likely that the aryl component of the pyridyl phosphine significantly limited catalysis. The 2-pyridyl substituent is known to be less σ -donating than a phenyl substituent on the phosphorus.¹⁹¹ Also, the pyridyl functionality may have competed with the Grignard reagent for binding to the methyl ether, resulting in the potential Lewis acid effect to facilitate ether cleavage, being weakened. Intramolecular chelation of the pyridyl functionality to the nickel to form a bidentate complex, resulting in the blocking of a potential vacant site on the nickel is also a strong possibility. Although heavily ring-strained, this subsequent 4-membered

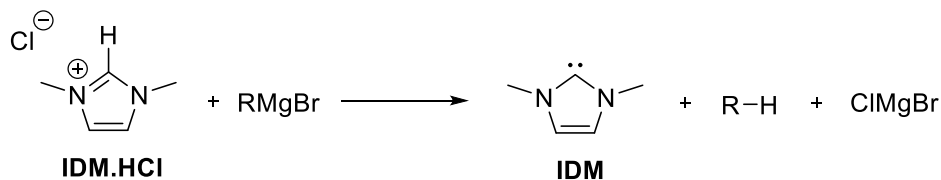
chelate has been shown to occur with the analogous diphenyl-2-pyridylphosphine (and derivatives) in a range of metal complexes, including nickel.¹⁹²⁻¹⁹⁵ This could severely restrict the capabilities of substrate coordination and subsequent [Ni-ate]⁻ formation, in what is considered the most likely mechanism of oxidative addition.

Similar to that observed by Nakamura and co-workers,⁶⁵ ligand **1** did not facilitate ether cleavage. [NiCl₂(dcype)] and [NiCl₂(depe)] were also considered as they offer similar σ -donating capabilities to [NiCl₂(P^{*n*}Bu₃)₂] but are bidentate.³² Dicyclohexylphosphinoethane (dcype) has been reported to provide good results in the nickel-catalysed alkylative cross-coupling of anisole derivatives,^{100, 109} whilst the compact diethylphosphinoethane (depe), has recently given good results in the nickel-catalysed cross-coupling of aryl chlorides using organolithiums.¹⁹⁶ However, both catalysts were unreactive, again suggesting that bidentate phosphines do not readily facilitate the formation of key interactions that aid oxidative addition processes, be it [Ni-ate]⁻ formation or Lewis acid-assisted oxidative addition. A vacant coordination site is lacking, relative to a monophosphine-based system, due to the chelate effect, which could also be severely hindering performance.

Recently, there has been growing interest in Ni^{II} pre-catalysts that offer very efficient methods to generate active Ni⁰ species. One of these, [(dppf)Ni(cinnamyl)Cl] (**110**), developed by Ge and Hartwig¹⁹⁷ was also tested in the cross-coupling of 2-methoxybiphenyl, however it also gave low yields of product. In future, the more general nickel pre-catalyst developed by Doyle and co-workers, [(TMEDA)Ni(*o*-tolyl)Cl], should be considered in order to benefit not only from the rapid formation of Ni⁰ but also to be able to tailor the desired catalyst with specific ligands, e.g. small, σ -donating monophosphines.¹⁹⁸

Significant focus and success in the field has surrounded the use of Ni-NHC catalytic systems that can facilitate methyl ether cross-coupling with a wide range of challenging nucleophiles, often under milder reaction conditions.^{93, 97, 98, 103, 199} To probe whether ligand dissociation effects are important (as well as sterics), replacing one of the

monophosphines in $[\text{NiCl}_2(\text{PR}_3)_2]$ with a small but electron donating NHC ligand *in situ* was attempted.



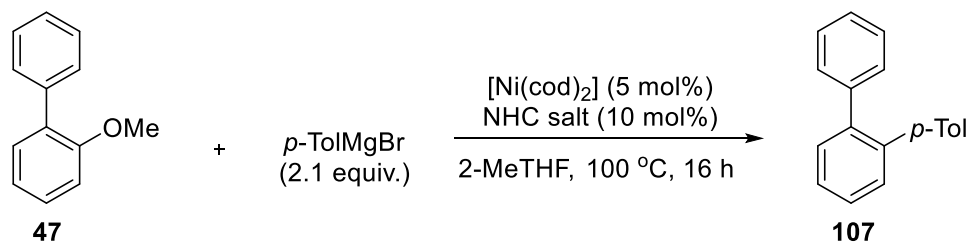
Scheme 4.8 – Creation of the small, σ -donating NHC, IDM, through *in situ* deprotonation by Grignard reagent.

5 mol% of the imidazolium salt 1,3-dimethylimidazolium chloride (IDM·HCl), which would generate the carbene *in situ* after reaction with the Grignard reagent (Scheme 4.8), was added to both $[\text{NiCl}_2(\text{PCy}_3)_2]$ and $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$ (Table 4.3, entries 8 and 9). Different yields were obtained when compared to using just the Ni-phosphine complex alone, which indicated that the NHC created, 1,3-bis(methyl)imidazol-2-ylidene (IDM), had an effect on the catalysis. IDM is more σ -donating than either of the monophosphines (IDM $\nu = 1946 \text{ cm}^{-1}$)²⁰⁰, and has a comparable % buried volume (% V_{bur}), and thus steric profile, to PMe_3 .³⁶ It was envisaged that IDM would compete with the phosphines for coordination to nickel. As NHCs undergo less facile ligand dissociation relative to phosphines,²⁰¹ a possible synergic effect could be established between the two ligands, similar to that reported by Zhang and co-workers.⁹⁴ Although a negative effect was apparent compared to $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$, the presence of IDM enhances the reaction relative to with $[\text{NiCl}_2(\text{PCy}_3)_2]$ alone. One possibility is that IDM does not provide enough steric bulk, compared to P^nBu_3 , but the reduced size and increased electronics do appear to aid the PCy_3 -ligated system, due to a much more open environment for catalysis to occur. However, another possibility is that due to the small, σ -donating nature of IDM, both phosphines are displaced to some extent, forming a tightly bound $\text{Ni}^0\text{-(IDM)}_2$ species, in differing amounts.

Other common NHC salts with varying steric properties were then considered to discover if the trend in ligand steric effects on productivity was more general. Pleasingly, a similar trend was apparent, again veering away from the preconceived requirement of bulky ligands. IMes (1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene), IDM and ICy all gave

improved results relative to the frequently employed IPr* (1,3-*bis*(2,6-*bis*(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene), SIPr and IPr (Table 4.3). ICy, which has recently been utilised by Chatani and co-workers in aryl methyl ether cleavage reactions using alkynyl and alkyl Grignard reagents,^{97, 98} has a %V_{bur} similar to PⁿBu₃ (23.5 vs 30.4 at 2.00 Å respectively),³⁶ as well as strong σ-donating properties (ν_(CO) 2049.6 cm⁻¹ vs 2060.3 cm⁻¹ respectively).^{32, 34} ICy was found to be the most successful carbene tested, giving 79 % of product (Table 4.3, entry 5). This result was comparable to when [NiCl₂(PⁿBu₃)₂] was used, however it must be noted that the use of ICy·HCl yielded more side products, consuming all of the starting material **47**. Also, the fact that the cheap, air-stable and commercially available [NiCl₂(PⁿBu₃)₂] gives comparable results, must be taken into consideration when looking at overall catalyst performance moving forward.

Table 4.3 – Further investigation of nickel catalytic systems as a function of ligand steric effects.



Entry ^[a]	NHC Salt	Structure	% V_{bur} ^[b] for M-NHC length at: 2.00 Å 2.28 Å		Conversion (%)	Product (%)
1	IPr*·HCl		50.4 ^[c]	-	20	8
2	SIPr·HCl		47.0	41.5	41	10
3	IPr·HCl		44.5	39.0	79	42
4	IMes·HCl		36.5	31.2	> 99	64
5	ICy·HCl		27.4	23.5	> 99	79
6	ICy·HBF ₄		27.4	23.5	> 99	72
7	IDM·HCl		26.3	22.7	80	50
8 ^{[d][e]}	IDM·HCl		26.3	22.7	78	43
9 ^{[e][f]}	IDM·HCl		26.3	22.7	84	68

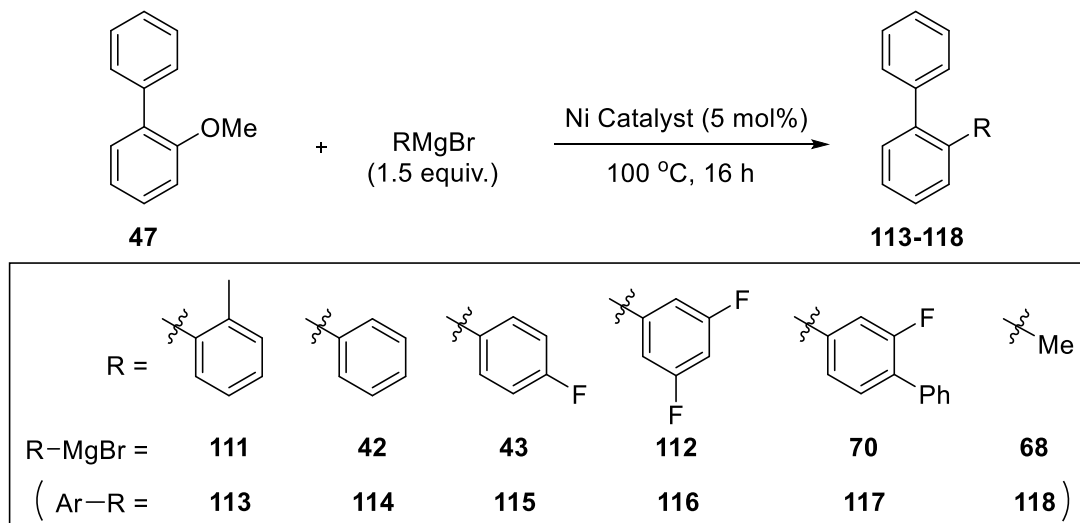
^[a] Reactions were carried out on the scale of 2-methoxybiphenyl (0.50 mmol), *p*-TolMgBr (1.05 mmol), 2-MeTHF (2.25 mL) in sealed microwave vials with crimp cap unless otherwise noted. Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard. ^[b] % V_{bur} for NHC in [(NHC)AuCl] complexes.³⁶ ^[c] % V_{bur} value obtained from ²⁰². ^[d] [NiCl₂(PCy₃)₂] (5 mol%) as Ni precursor and NHC·HCl (5 mol%). ^[e] 1.5 equiv. Grignard reagent. ^[f] [NiCl₂(P^{*t*}Bu₃)₂] (5 mol%) as Ni precursor and NHC·HCl (5 mol%).

4.2.4.2 – Effect of Grignard reagent on the nickel-catalysed cross-coupling of 2-methoxybiphenyl

As there appears to be a steric effect in the transition state, the effect of the nucleophile (Grignard reagent) was also studied. The role of the (often) crucial Lewis-acidic nucleophile has been relatively ignored so far in this chapter. It has been shown in the literature that the nucleophile of choice can sometimes be the difference between reaction success or failure. The success in Grignard cross-coupling, relative to the Suzuki-Miyaura coupling, suggests a Lewis acid-assisted oxidative addition. When Lewis acid additives are added to other processes e.g. Suzuki-Miyaura reactions, little beneficial effect is apparent.¹⁰¹ Although other nucleophiles such as organolithiums,^{107, 108, 196} organozincs,¹⁰⁶ AlMe₃,^{109, 199} organoborons,¹¹² and silyl boronates,¹¹³ are beginning to yield some success, Grignard cross-coupling of aryl ethers is more well-established. The use of Grignard reagents has evolved since work by Wenkert⁸⁸ and Dankwardt⁸⁹ who reported on solely aryl Grignard reagents. This has now progressed to the use of a limited range of Grignard or organolithium reagents including MeMgBr, alkynylMgBr and Me₃SiCH₂Li, being coupled successfully, particularly on easier naphthalene-based substrates.^{96-98, 100} However, it must be noted that there has been limited success on *ortho*-substituted anisoles, and consequently an investigation into the effect of the Grignard reagent was commenced (Table 4.4).

Initially, aryl Grignards were studied. Varying the steric and electronic properties could establish the scope, as well as the influence of the sterics imposed by the phosphine and substrate. It has been previously reported that Grignard reagent sterics can play a key role,^{65, 89} but relating this to the cone angle of the phosphine within the catalyst has not been heavily studied for aryl methyl ether cross-coupling. Results were compared to those using *p*-TolMgBr in Table 4.1.

Table 4.4 – The effect of Grignard reagent in the nickel-catalysed Grignard cross-coupling of 2-methoxybiphenyl (**47**), under optimised conditions.



Entry ^[a]	Grignard (M)	Catalyst	Solvent	Conversion (%)	Product (%)
1	111 (2.0)	NiCl ₂ (PCy ₃) ₂	2-MeTHF	23	8
2	111 (2.0)	NiCl ₂ (P ⁿ Bu ₃) ₂	2-MeTHF	25	21 [21]
3	111 (0.5)	NiCl ₂ (P ⁿ Bu ₃) ₂	2-MeTHF	30	26
4	42 (1.7)	NiCl ₂ (P ⁿ Bu ₃) ₂	2-MeTHF	97	96 [86]
5	43 (0.5)	NiCl ₂ (P ⁿ Bu ₃) ₂	2-MeTHF	10	n.d. ^[b]
6	112 (0.8)	NiCl ₂ (P ⁿ Bu ₃) ₂	2-MeTHF	24	n.d. ^[b]
7	117 (0.7)	NiCl ₂ (P ⁿ Bu ₃) ₂	2-MeTHF	13	n.d. ^[b]
8 ^[c]	68 (2.4)	NiCl ₂ (PCy ₃) ₂	2-MeTHF	21	19
9 ^[c]	68 (2.4)	NiCl ₂ (P ⁿ Bu ₃) ₂	2-MeTHF	12	10
10 ^[d]	68 (2.4)	NiCl ₂ (PCy ₃) ₂	mesitylene	12	12
11 ^[c]	68 (2.4)	NiCl ₂ (PCy ₃) ₂	PhMe	9	3
12 ^[c]	68 (2.4)	NiCl ₂ (P ⁿ Bu ₃) ₂	PhMe	48	46 [27] ^[f]

^[a] Reactions conditions: 2-methoxybiphenyl (0.50 mmol), Grignard reagent (0.75 mmol, in Et₂O), Ni catalyst (0.025 mmol), solvent (2.25 mL) in a sealed microwave vial with crimp cap, 100 °C, 16 h. Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. ^[b] Due to overlapping of multiple signals in the ¹H NMR, the product yield was not determined. ^[c] 2.1 equiv. Grignard added. ^[d] 110 °C. ^[f] 27 % yield isolated with 1-methylnaphthalene impurity; total product obtained = 24 %.

It is clear that the sterics in the Grignard reagent play a pivotal role as yields were dramatically reduced when switching from *p*-TolMgBr to *o*-TolMgBr (**111**) (Table 4.4, entry 2). Therefore, in order to obtain high yields for this challenging *ortho*-substituted anisole, crowded sterics in the Grignard reagent must be avoided. The effect of volume of Et₂O was studied to ensure that no extra stabilisation, from changes in the Schlenk equilibrium, was gained when comparing the two Grignard reagents *p*-TolMgBr (0.5 M

in Et₂O) and *o*-TolMgBr (2.0 M in Et₂O). It was also important to ensure that the propensity for the solvent to coordinate and thus modify the Lewis-acidic ability of the Grignard reagent was not affected. As a control, *o*-TolMgBr was diluted with Et₂O to give a 0.5 M solution which was then reacted and gave comparable results to the 2.0 M batch (Table 4.4, entry 3). This ruled out any additional benefit gained from extra solvent in the *p*-TolMgBr (0.5 M) Grignard reagent. Therefore, the differences apparent in yield were due to the steric nature of the Grignard reagent. This is further confirmed when the sterics were reduced, with PhMgBr (**42**) giving excellent yields of the resulting *ortho*-terphenyl **114** (Table 4.4, entry 4).

Unfortunately, as well as struggling with the bulkier aryl Grignard reagent, attempts to couple fluorinated Grignard reagents all resulted in low conversion and no noticeable product (Table 4.4, entries 5-7). The reason for the apparent failure to synthesise **115-117** is likely to be the electron-deficient nature of the Grignard reagents, rendering them less nucleophilic and thus inactive. Finally, potential insertion of nickel into the C_{Ar}-F bond of either the Grignard reagent itself or any desired product, could severely hinder the catalysis of ether cross-coupling. It has been shown in literature that nickel catalysts can be effective for C-F cross-coupling.^{65, 94, 96}

To investigate this steric effect further, a significantly smaller Grignard reagent, MeMgBr (**68**) was studied. This has the drawbacks of being an alkyl Grignard which are renowned for being more challenging, with only one successful methylation using MeMgBr in the literature.⁹⁶ MeMgBr cannot undergo β-hydride elimination, which is a recurring problem in the nickel-catalysed cross-coupling of anisoles that is just beginning to be solved,^{100, 109} so despite low activity, leads to few detrimental side reactions.

Inspiration was taken from one of the key papers published in the last decade in which Shi and co-workers reported the first methylation of aryl methyl ethers using [NiCl₂(PCy₃)₂].⁹⁶ To assess if this methodology could be extended to 2-methoxybiphenyl, both [NiCl₂(PCy₃)₂] and [NiCl₂(P^{*i*}Bu₃)₂] were tested. There was optimism about this challenging coupling because Shi reported good yields for substrates such as 2-methylanisole in as little as 20 minutes using [NiCl₂(PCy₃)₂]; which has been found to be

less effective than $[\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2]$ for the cross-coupling of 2-methoxybiphenyl. Also, it was stated that steric changes in the aromatic ring of the anisole did not play a critical role in the cross-coupling.

Unfortunately, the desired reaction was unsuccessful under a wide range of conditions, including those used in literature by Shi using 2-methylanisole (Table 4.4, entry 10). To obtain any considerable conversion, $[\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2]$ had to be used with PhMe as the solvent at 100 °C, for a prolonged time and with increased Grignard reagent equivalents. It is clear that these cross-coupling reactions are less successful when you deviate from an aryl Grignard. $[\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2]$ yet again outperformed $[\text{NiCl}_2(\text{PCy}_3)_2]$, this time in PhMe, but it is clear that the reaction is not very efficient. Perhaps the increased sterics of an *ortho*-phenyl substituent limit the success of the methylation reaction. Chatani and co-workers have shown the alkylation of aryl methyl ethers to be very susceptible to the sterics imposed by the substrate, with no successful examples involving *ortho*-substituted anisoles or naphthalenes.¹⁰⁰ Also, the mechanism suggested by Uchiyama and co-workers¹²⁵ relies on strong interaction between the nickel centre and Grignard substituent, which is potentially considerably less favoured by an alkyl Grignard.

4.2.4.3 – Extending this nickel-catalysed Grignard cross-coupling to other challenging anisoles

With the discovery of $[\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2]$ as an effective catalyst for the cross-coupling of 2-methoxybiphenyl, attempts were made to extend this methodology to other challenging (predominately) *ortho*-substituted anisoles. In the literature, there has been limited success for anisole-derivatives, let alone with *ortho*-substitution.^{60, 120, 124} The success of this catalyst so far has been shown to be due to the small cone angle of the phosphine. To evaluate the effect of the substrate, two catalysts at the opposite end of the cone angle spectrum $[\text{NiCl}_2(\text{PCy}_3)_2]$ and $[\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2]$, were tested in the cross-coupling of anisoles, varying in steric and electronic parameters (Table 4.5).

Table 4.5 – The effect of substrate variation in the nickel-catalysed Grignard cross-coupling of substituted anisoles with *p*-TolMgBr (**41**), MeMgBr (**68**) and *o*-TolMgBr (**111**).

Ar-OMe 119-123	+	RMgBr (1.5 equiv.)	$\xrightarrow[\text{2-MeTHF, 100 }^\circ\text{C}]{\text{Ni Catalyst (5 mol\%)}}$	Ar-R 124-130
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Ar =					
Ar-OMe =	119	120	121	122	123
(Ar-R =	124 (R = <i>p</i> -Tol)	125 (R = <i>p</i> -Tol)	126 (R = Me) 127 (R = <i>p</i> -Tol)	128 (R = <i>p</i> -Tol)	129 (R = <i>p</i> -Tol) 130 (R = <i>o</i> -Tol)

Entry ^[a]	Ar-OMe	Grignard (M)	Catalyst	t (h)	Conversion (%)	Product (%)
1 ^[b]	119	41	NiCl ₂ (PCy ₃) ₂	16	69	16
2 ^[b]	119	41	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	16	77	48
3	119	41	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	40	79	55 [40]
4 ^[b]	120	41	NiCl ₂ (PCy ₃) ₂	16	29	13
5 ^[b]	120	41	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	16	67	44 [7]
6 ^[c]	121	68 (2.4)	NiCl ₂ (PCy ₃) ₂	16	0	0
7 ^[d]	121	68 (2.4)	NiCl ₂ (PCy ₃) ₂	16	0	0
8 ^[e]	121	68 (2.4)	NiCl ₂ (PCy ₃) ₂	16	15	0
9 ^[f]	121	41	NiCl ₂ (PCy ₃) ₂	16	10	4
10 ^[f]	121	41	104	16	18	15
11 ^[f]	121	41	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	16	41	29
12 ^[f]	121	41	NiCl ₂ (PCy ₃) ₂	64	9	3
13 ^{[f][g]}	121	41	NiCl ₂ (PCy ₃) ₂	64	18	1
14 ^[f]	121	41	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	64	50	29
15 ^{[f][g]}	121	41	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	64	76	56 [40] ^[h]
16 ^[f]	122	41	NiCl ₂ (PCy ₃) ₂	16	76	23
17 ^{[f][g]}	122	41	NiCl ₂ (PCy ₃) ₂	16	61	9
18 ^[f]	122	41	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	16	95	32 [58] ^[i]
19 ^{[f][g]}	122	41	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	16	78	37
20	123	41	NiCl ₂ (PCy ₃) ₂	16	59	34
21	123	41	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	16	84	70 [65]
22	123	111 (2.0)	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	16	51	49 [43]

^[a] Reactions conditions: aryl ether (0.50 mmol), Grignard reagent (0.75 mmol, 0.5 M in Et₂O), Ni catalyst (0.025 mmol), 2-MeTHF (2.25 mL) in a sealed microwave vial with crimp cap, 100 °C. Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. ^[b] Reaction carried out by a 4th year MChem undergraduate student under my supervision and guidance. ^[c] Reaction performed in PhMe at 110 °C. ^[d] Reaction performed in mesitylene at 110 °C. ^[e] Reaction performed in mesitylene at 125 °C. ^[f] 2.1 equiv. of Grignard added. ^[g] 10 mol% Ni catalyst. ^[h] 40 % yield isolated with 1-methylnaphthalene impurity; total product obtained = 38 %. ^[i] 58 % yield isolated with 1-methylnaphthalene impurity; total product obtained = 26 %.

Initially, the electronic properties of the substrate were probed whilst trying to mimic the steric environment of 2-methoxybiphenyl. **119** and **120** were selected as good candidates. It was envisaged that by altering the electronic properties of the anisole, successful cleavage of the C_{Ar}-OMe bond would be altered, providing further mechanistic insight and aiding coupling. The electron-donating dimethylaniline functionality of **119** was anticipated to render the C_{Ar}-OMe bond stronger whilst the electron-withdrawing trifluoromethylphenyl group was expected to weaken the bond, thus aiding cleavage. Electron-withdrawing/activating groups have aided cross-coupling of aryl ethers previously in the literature.^{101, 110-112, 203}

There was no considerable difference between the coupling of the two substrates, however [NiCl₂(PⁿBu₃)₂] was the better performing catalyst again (Table 4.5, entries 2, 3 and 5). Both of these substrates appeared to be considerably worse than 2-methoxybiphenyl which initially suggests electronic properties within the substrate is not a significant factor in C_{aryl}-OMe cleavage; similar to that reported by Martin.¹¹³

To gauge the effect of sterics on the already hindered *ortho*-substituted anisole derivatives, less sterically hindered 2-methylanisole (**121**) was tested. This lacks any form of extended π -conjugation (unlike biaryls and particularly naphthalenes) and thus successful examples are rare.^{60, 120, 124} Despite this, the lower sterics present in 2-methylanisole could possibly aid the already crowded transition states involved in the Grignard cross-coupling of aryl methyl ethers.

Firstly, 2-methylanisole was reacted with MeMgBr (**68**). This methylation had already been successfully reported by Shi and co-workers with [NiCl₂(PCy₃)₂] as catalyst, yielding 71 % of product **126**.⁹⁶ However, under a range of forcing conditions, including a repeat of the literature (Table 4.5, entry 7), no reaction occurred. These discrepancies, as well as those in Table 4.5, do put this paper under scrutiny, which only reported yields by GC for the reactions of simpler anisole substrates, with no isolation of products.

Due to the unsuccessful attempts to methylate 2-methylanisole, the aryl Grignard *p*-TolMgBr (**41**) was tested. Unfortunately, low yields were apparent. However, the ligand

cone angle trend still remained (Table 4.5, entries 9-11). Increasing the reaction time did not increase productivity (entries 12 and 14). However, doubling the catalyst loading of $[\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2]$ increased yields to 56 % (entry 15), compared to only 1 % with $[\text{NiCl}_2(\text{PCy}_3)_2]$ (entry 13).

The failure of 2-methylanisole suggests a strong requirement for biaryl-type or π -extended substrates to facilitate strong η^2 -coordination with the metal centre, or provide extra stabilisation of intermediates and transition states, potentially involving other dearomatising pathways.

The electron-deficient 2-trifluoromethylanisole (**122**) was also tested, hypothesising that the electronic properties could mimic the electron withdrawing benefits of a biphenyl. A strongly electron-withdrawing group directly adjacent to the methyl ether was predicted to amplify the weakening of the $\text{C}_{\text{aryl}}\text{-OMe}$ bond relative to 2-methylanisole, if the classical oxidative addition mechanism operates. Also, this trifluoromethyl group could aid in the oxidative addition process by stabilising the increased negative charge transferred from the metal to the substrate.²⁰³

Again, the cone angle trend was apparent between the two nickel catalysts at 100 °C. There was a slight increase in conversion to product at 5 mol%, compared to with 2-methylanisole (Table 4.5, entries 16-19). However, there were significant side products. Detection of these was attempted but proved inconclusive. It appears that having an electron-withdrawing substrate that isn't very sterically demanding (which hypothetically would be desired), did not facilitate smooth coupling to desired product.

The high product yields observed with the relatively sterically encumbered 2-methoxybiphenyl could be due to a considerable stabilisation gained from π -stacking interactions between the *ortho*-phenyl group of substrate and aryl Grignard. Also, potentially this is why aryl Grignards have yielded considerably more success throughout the literature. To test if there was any benefit of *ortho*-phenyl substitution, the substitution was switched to the *para*-position. 4-methoxybiphenyl (**123**) was coupled with *p*-TolMgBr (**41**), under optimised conditions. Relatively high yields resulted with

[NiCl₂(PⁿBu₃)₂] which reinforces the requirement for biphenyl systems to gain considerable product yields (Table 4.5, entry 21). Extra benefit from a π-π system with the nickel-coordinated substrate and aryl Grignard seems more unlikely as it shouldn't be influential in both *ortho*- and *para*- positions. [NiCl₂(PCy₃)₂] was also tested to probe the cone angle influence (Table 4.5, entry 20). It was predicted that the relief of sterics in the substrate should facilitate better coupling with this bulkier catalyst and pleasingly, this was indeed the case (relative to 2-methoxybiphenyl, Table 4.1, entry 18). However, [NiCl₂(PⁿBu₃)₂] was still a better catalyst under these conditions. Increased sterics introduced by the use of *o*-TolMgBr (**111**) again resulted in a decrease in yield, therefore confirming that sterics in the Grignard reagent is more influential than in the substrate (Table 4.5, entry 22).

4.2.4.4 – Heterocyclic/chelating effect

A potential benefit of trying to functionalise *ortho*-substituted anisoles is that there is the possibility of chelation assistance. *Ortho*-directing groups have found extensive use in C-H activation reactions, with many researchers utilising heterocycles within the substrate to facilitate binding to the transition-metal catalyst.²⁰⁴ This interaction can enhance catalyst efficiency as well as control selectivity. However, it must be noted that catalytic examples involving nickel are scarce,²⁰⁵⁻²⁰⁷ with the first example utilising a 2-pyridylmethylamine functionality as directing group.²⁰⁵

It was desirable to use nickel's credentials in catalytic ether cleavage to try to facilitate directed oxidative addition into the C_{aryl}-OMe bond. Johnstone and co-workers reported the use of heteroaromatic ethers in nickel-catalysed substitution reactions with organometallic reagents including Grignards.^{208, 209} It must be noted that the directing group was part of the ether functionality, however it is an example of how heterocycles can be used to facilitate ether cleavage in conjunction with nickel catalysts. Oxidative addition of an aryl ether was first definitively observed by Chatani and co-workers using Ru in a carbonyl-directed manner.²¹⁰ These studies have now progressed to show stoichiometric cleavage of aryl methyl ethers with pendant phosphines, facilitated by nickel and directed by the phosphine-nickel interaction.¹¹⁹

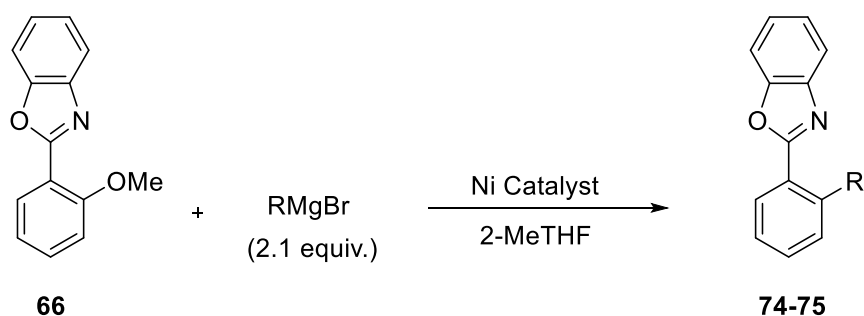
Two important results in the nickel-catalysed reductive cleavage of aryl methyl ethers provided the inspiration for this investigation involving the potential benefits of *ortho*-heterocycles. Martin and Alvarez-Bercedo,¹¹⁴ and Chatani and co-workers,¹¹⁵ independently demonstrated that an adjacent directing group, such as 2-pyridyl, facilitated the C_{aryl}-OMe oxidative addition step of challenging anisoles (Chapter I, Scheme 1.36). Significantly lower activity was apparent when these directing groups were moved to *meta*- or *para*- positions. Thus, it was of interest to investigate if the directing groups discussed in Chapter III, that were shown to enhance C_{aryl}-OMe bond cleavage in a Meyers-type manner, could in fact enhance nickel-catalysed Grignard cross-coupling of challenging anisoles. It was hoped that the ease of initial nickel-coordination and thus insertion into the ether bond could be accelerated through a substrate-mediated interaction.

Whilst in Chapter III, specific successful examples of uncatalysed coupling were described, if this chelation effect also helps the catalyst, then perhaps broader reactivity to include weaker nucleophiles and milder conditions could be found.

4.2.4.4.1 Nickel-catalysed cross-coupling of 2-(2-methoxyphenyl)benzo[*d*]oxazole

2-(2-methoxyphenyl)benzo[*d*]oxazole (**66**) was initially investigated, which could enable ether cleavage successfully in a S_NAr reaction using a wide range of Grignard reagents, as shown in Chapter III. The effect of adding in catalytic amounts of nickel was studied using the aryl Grignard *p*-TolMgBr (**41**) and alkyl Grignard MeMgBr (**68**) (Table 4.6).

Table 4.6 – Investigation of the effect of nickel catalysts in the reaction of Grignard reagents with 2-(2-methoxyphenyl)benzo[*d*]oxazole (**66**).



Entry ^[a]	Grignard (M)	Catalyst	Catalyst Loading (mol%)	T (°C)	t (h)	Conversion (%)	Product (%)
1 ^[b]	41	-	-	40	16	-	[96]
2	41	NiCl ₂ (PCy ₃) ₂	5	40	16	> 99	29
3	41	NiCl ₂ (P ^{<i>n</i>} Bu) ₃) ₂	5	40	16	> 99	76
4	41	-	-	40	1	96	87
5	41	NiCl ₂ (PCy ₃) ₂	10	40	1	> 99	29
6	41	-	-	20	4	54	50
7	41	NiCl ₂ (PCy ₃) ₂	10	20	4	76	21
8 ^[c]	41	NiCl ₂ (PCy ₃) ₂	10	20	4	73	20
9 ^[c]	41	Ni(cod) ₂	10	20	4	67	27
10	41	Ni(cod) ₂	10	20	4	60	41
11	41	-	-	0	66	52	41
12	41	NiCl ₂ (PCy ₃) ₂	5	0	66	47	14
13	41	NiCl ₂ (PCy ₃) ₂	20	0	66	61	3
14 ^[d]	41	NiCl ₂ (PCy ₃) ₂	20	0	16	19	18
15 ^[d]	68 (2.4)	-	-	80	16	94	57
16 ^[d]	68 (2.4)	NiCl ₂ (PCy ₃) ₂	5	80	16	> 99	49 [48]
17 ^[d]	68 (2.4)	-	-	20	16	5	3
18 ^[d]	68 (2.4)	NiCl ₂ (PCy ₃) ₂	5	20	16	65	30
19 ^[d]	68 (2.4)	NiCl ₂ (PCy ₃) ₂	5	0	16	7	7

^[a] Reactions conditions: aryl ether (0.50 mmol), Grignard reagent (1.05 mmol, 0.5 M in Et₂O), 2-MeTHF (2.25 mL). Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. ^[b] No 1-methylnaphthalene. ^[c] 20 mol% of PCy₃ added. ^[d] 1.5 equiv. of Grignard used.

The uncatalysed process with *p*-TolMgBr (**41**) has shown to be very successful, with an isolated yield of 96 % product (**75**) apparent after 16 hours at 40 °C (Table 4.6, entry 1). Unfortunately, it appeared as though the nickel catalysts tested hinder the formation of product. [NiCl₂(PCy₃)₂] was tested under a range of different conditions and gave lower yields than the uncatalysed modified-Meyers process. To investigate if the benefits of the

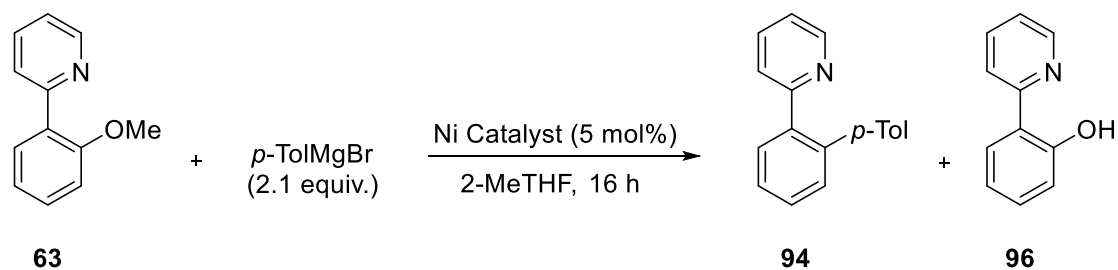
nickel catalyst were apparent at lower temperatures, 20 °C as well as 0 °C were tested. A ligand-less system was also tested, with [Ni(cod)₂] giving an increased yield relative to [NiCl₂(PCy₃)₂], implying that PCy₃ renders the catalyst more active to side reactions (entries 7-10). Finally, [NiCl₂(PⁿBu₃)₂], was tested at 40 °C and gave more promising results, however it is likely that it simply hinders the uncatalysed process to a lesser extent (entry 3).

The alkyl Grignard MeMgBr (**68**) was also tested. The uncatalysed Meyers reaction required higher temperatures and only resulted in moderate yields of **74**. Therefore, it was hypothesised that the presence of a nickel catalyst could possibly benefit this difficult reaction. At 80 °C reactions were comparable with the uncatalysed processes (Table 4.6, entries 15 and 16). However, at 20 °C there appears to be a benefit to having the nickel catalyst present with 30 % of product (**74**) obtained, as opposed to only 3 % without (entries 17 and 18). This therefore suggests that in Meyers-type reactions that are relatively unreactive, lower temperatures can be used in partnership with nickel catalysts; possibly due to a change in mechanism involving organonickel(II) species.²¹¹⁻²¹³ Yields are likely to increase if the more successful [NiCl₂(PⁿBu₃)₂] is utilised.

4.2.4.4.2 Nickel-catalysed cross-coupling of 2-(2-methoxyphenyl)pyridine

Encouraged by the previous result with 2-(2-methoxyphenyl)benzo[*d*]oxazole and MeMgBr at 20 °C, 2-(2-methoxyphenyl)pyridine (**63**) also fits this criteria: the uncatalysed process is not highly active and requires elevated temperatures (Chapter III and Table 4.7, entry 1). It was therefore predicted that the use of a nickel catalyst could lower activation barriers for product formation and facilitate the ether cleavage/substitution.

Table 4.7 – Investigation of the effect of nickel catalysts in the reaction of *p*-TolMgBr with 2-(2-methoxyphenyl)pyridine (**63**).



Entry ^[a]	Catalyst	T (°C)	Conversion (%)	Product (%)	96 (%)
1	-	80	> 99	88	7
2	NiCl ₂ (PCy ₃) ₂	80	79	7	6
3	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	80	88	15	6
4	-	20	< 5	0	0
5	NiCl ₂ (PCy ₃) ₂	20	85	21	17
6	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	20	85	42	15

^[a] Reactions conditions: aryl ether (0.50 mmol), *p*-TolMgBr (1.05 mmol, 0.5 M in Et₂O), 2-MeTHF (2.25 mL). Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets].

Firstly, both nickel catalysts were compared at 80 °C, for the Meyers-type process. Disappointingly, both catalysts appeared to favour the formation of 2-(pyridine-2-yl)phenol (**96**) (Table 4.7, entries 2 and 3). Again, lowering the temperature to 20 °C facilitated product (**94**) formation in the reactions containing nickel. Yields of 42 % could be reached at this temperature with [NiCl₂(P^{*n*}Bu₃)₂] (entry 6), compared to < 5 % in the uncatalysed process (entry 4). Perhaps the lower temperature enabled a stronger interaction between the substrate pyridine ring and the nickel catalyst, facilitating more favoured η² interaction with the aryl methyl ether. Efforts in future should be made to increase selectivity to product, however the presence of a nickel catalyst does appear to allow lower temperatures to be utilised.

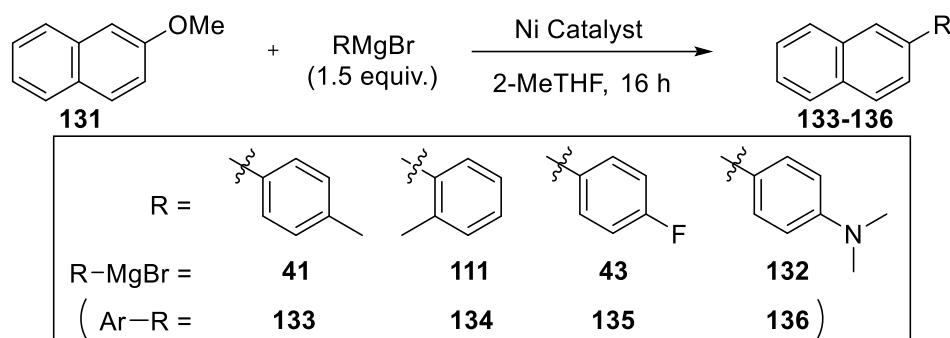
4.2.4.5 – Nickel-catalysed cross-coupling of methoxynaphthalenes

To further compare the capabilities of [NiCl₂(P^{*n*}Bu₃)₂] with [NiCl₂(PCy₃)₂], easier naphthalene derivatives were investigated. Methoxynaphthalenes have been widely

coupled in the literature, with the benefits of extended π -conjugation often referred to as the “naphthalene effect”.

The heavily tested 2-methoxynaphthalene (**131**) was subjected to the cross-coupling conditions used with challenging anisoles in previous sections (Table 4.8). It was hoped that the success apparent with $[\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2]$ for more challenging anisoles would allow milder reaction conditions and lower catalyst loadings to be used for this more active substrate.

Table 4.8 – Nickel-catalysed Grignard cross-coupling of 2-methoxynaphthalene (**131**).



Entry ^[a]	Grignard (M)	Catalyst	Catalyst Loading (mol%)	T (°C)	Conversion (%)	Product (%)
1 ^[b-d]	41	NiCl ₂ (PCy ₃) ₂	5	80	> 99	96 [89]
2 ^{[c][d]}	41	110	5	80	60	50
3 ^{[c][d]}	41	NiCl ₂ (PCy ₃) ₂	2.5	80	> 99	90
4 ^{[c][d]}	41	NiCl ₂ (P ^{<i>i</i>} Bu ₃) ₂	2.5	80	> 99	93
5 ^[d]	41	NiCl ₂ (PCy ₃) ₂	1	80	91	81
6 ^[d]	41	NiCl ₂ (P ^{<i>i</i>} Bu ₃) ₂	1	80	88	81
7 ^{[d][e]}	41	NiCl ₂ (PCy ₃) ₂	1	80	64	57
8 ^{[d][e]}	41	NiCl ₂ (P ^{<i>i</i>} Bu ₃) ₂	1	80	64	48
9	41	NiCl ₂ (PCy ₃) ₂	1	80	84	71
10	41	NiCl ₂ (P ^{<i>i</i>} Bu ₃) ₂	1	80	48	37
11 ^{[d][f]}	41	NiCl ₂ (PCy ₃) ₂	1	20	27	17
12 ^{[d][f]}	41	NiCl ₂ (P ^{<i>i</i>} Bu ₃) ₂	1	20	5	5
13 ^[d]	111 (2.0)	NiCl ₂ (PCy ₃) ₂	1	80	> 99	95
14 ^[d]	111 (2.0)	NiCl ₂ (P ^{<i>i</i>} Bu ₃) ₂	1	80	> 99	97 [82]
15 ^[d]	41	NiCl ₂ (PCy ₃) ₂	0.5	80	85	73
16 ^[d]	41	NiCl ₂ (P ^{<i>i</i>} Bu ₃) ₂	0.5	80	68	54
17	41	NiCl ₂ (PCy ₃) ₂	0.5	80	39	38
18	41	NiCl ₂ (P ^{<i>i</i>} Bu ₃) ₂	0.5	80	17	16
19	41	NiCl ₂ (PCy ₃) ₂	0.5	100	75	59
20	41	NiCl ₂ (P ^{<i>i</i>} Bu ₃) ₂	0.5	100	93	89
21	43 (0.5)	NiCl ₂ (P ^{<i>i</i>} Bu ₃) ₂	0.5	100	n.d. ^[g]	39
22	41	NiCl ₂ (P ^{<i>i</i>} Bu ₃) ₂	0.25	100	83	71
23 ^[h]	41	NiCl ₂ (P ^{<i>i</i>} Bu ₃) ₂	0.25	100	92	86
24 ^{[i][j]}	132 (0.3)	NiCl ₂ (P ^{<i>i</i>} Bu ₃) ₂	0.25	100	> 99	97 [41]
25 ^[i-k]	132 (0.3)	NiCl ₂ (P ^{<i>i</i>} Bu ₃) ₂	0.25	100	> 99	> 99
26 ^{[h][l]}	41	NiCl ₂ (P ^{<i>i</i>} Bu ₃) ₂	0.10	115	65	57

^[a] Reactions conditions: aryl ether (0.50 mmol), Grignard reagent (0.75 mmol, 0.5 M in Et₂O), 2-MeTHF (2.25 mL). Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. ^[b] 64 h. ^[c] 2.1 equiv. of Grignard used. ^[d] Reaction performed in a Schlenk flask. ^[e] PhMe as reaction solvent. ^[f] 70 h. ^[g] Due to overlapping of multiple signals in the ¹H NMR, the conversion of starting material was not determined. GCMS analysis of crude mixture indicated the presence of starting material, desired product and further coupling though C_{aryl}-F of product to give 2-[4-(4-fluorophenyl)phenyl]naphthalene. ^[h] 1.5 equiv. of MgI₂ added. ^[i] Reaction carried out by a 4th year MChem undergraduate student under my supervision and guidance. ^[j] Grignard reagent in THF. ^[k] 4 h. ^[l] 59 h.

The reactive nature of the substrate allowed reactions to be initially tested under milder conditions (at 80 °C) similar to many reports in literature. Excellent yields were apparent using 2.5 mol% of either $[\text{NiCl}_2(\text{PCy}_3)_2]$ or $[\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2]$ with *p*-TolMgBr (**41**) under these conditions (Table 4.8, entries 3 and 4). The Ni^{II}-precatalyst $[(\text{dppf})\text{Ni}(\text{cinnamyl})\text{Cl}]$ (**110**) struggled even at relatively high loadings of 5 mol% (entry 2). This was again likely to be due to the lack of σ -donating ability, as well as the bidentate nature potentially blocking a required vacant site during the catalysis. Encouraged by these results involving the trialkylphosphine catalysts, catalyst loadings were reduced to 1 mol% hoping that this would emphasise a difference in catalyst performance. At 80 °C, yields were found to be promoted by the use of Schlenk flasks under an argon atmosphere instead of in sealed microwave vials with crimp caps. More importantly, what became apparent was that at 80 °C $[\text{NiCl}_2(\text{PCy}_3)_2]$ outperformed $[\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2]$, regardless of reaction vessel (entries 5-10). Commonly used PhMe was again found to be an inferior solvent, with lower yields apparent with both catalysts. This could be due to unwanted interactions involving the aromatic ring of the solvent. This catalyst trend was extended to reactions at 20 °C as well, although yields were considerably lower (entries 11 and 12). Sterics in the Grignard reagent were shown to be extremely detrimental to the coupling of challenging anisoles such as 2-methoxybiphenyl, in Section 4.2.3.2. However pleasingly, *o*-TolMgBr (**111**) was reacted very successfully with either catalyst, regardless of cone angle, suggesting that the reduced steric hindrance of the less-substituted 2-methoxynaphthalene (**131**), resulted in less-crowded transition states for the key C_{aryl}-OMe bond breaking process (entries 13 and 14).

Under milder conditions of 80 °C, $[\text{NiCl}_2(\text{PCy}_3)_2]$ is a good catalyst for coupling this less-challenging, naphthalene substrate. To study this further, catalyst loadings were reduced. At 0.5 mol% $[\text{NiCl}_2(\text{PCy}_3)_2]$ was again the more active catalyst at 80 °C, regardless of reaction vessel, with a maximum yield of 73 % of 2-(*p*-tolyl)naphthalene (**133**), compared to 54 % for $[\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2]$ (Table 4.8, entries 15-18). However, in attempts to increase yields, the temperature was increased to 100 °C, which was required for the more challenging anisole substrates. An intriguing result followed: a major switch in catalyst productivity from $[\text{NiCl}_2(\text{PCy}_3)_2]$ to $[\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2]$. A significant increase in catalytic performance was apparent for $[\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2]$ with yields of **133** drastically increasing

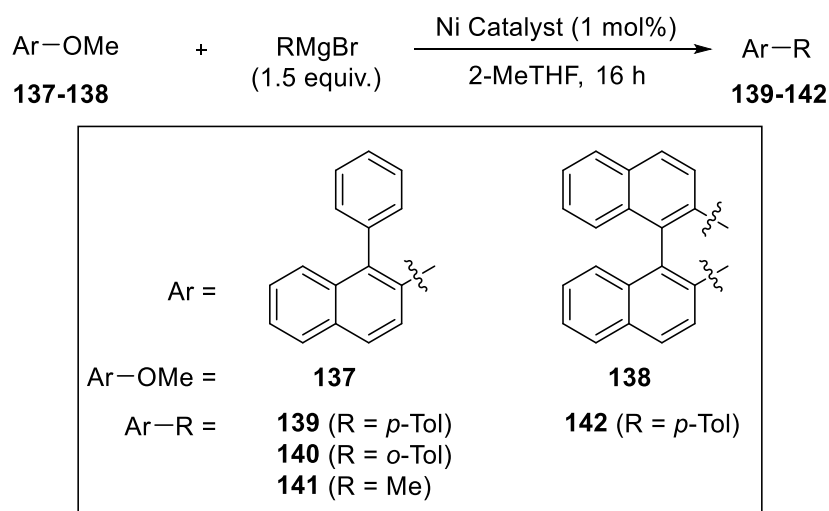
from 16 % to 89 %, with an increase of only 20 °C (entry 20). This, coupled with the results in previous sections suggest that $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$ performs optimally at slightly higher temperatures than what is often considered the norm when coupling highly activated naphthyl methyl ethers. Perhaps it is possible to create more stable and productive catalysts, of various metals, that only operate above a temperature threshold, by revisiting ligands such as P^nBu_3 . This temperature dependence could be the reason for the apparent under-utilisation of P^nBu_3 in the literature for aryl methyl ether cross-coupling, and a whole new realm of reactions could be revisited by trying this nickel-phosphine combination.

It was intriguing to investigate how much lower catalyst loadings of $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$ could be decreased, without sacrificing activity. Therefore, using only 0.25 mol% was attempted in the reaction of 2-methoxynaphthalene (**131**) and *p*-TolMgBr (**41**) at 100 °C, resulting in 71 % of desired product (**133**) (Table 4.8 entry 22). This could be increased to 86 % by the use of MgI_2 as a Lewis-acidic additive (entry 23). Interestingly, this benefit was not apparent when coupling 2-methoxybiphenyl (Table 4.1 entry 20), which perhaps suggests a difference in mechanism between the two substrate types. This additive allows loadings to be decreased further to just 0.1 mol% and still get meaningful conversion to product (entry 26). MgI_2 was not required for the reaction involving the electron-rich Grignard 4-*N,N*-dimethylaminophenylmagnesium bromide (**132**) with 0.25 mol% nickel catalyst, in which a quantitative yield of 2-(4-*N,N*-dimethylaminophenyl)naphthalene (**136**) was apparent after just 4 hours (entry 25). This electron-rich, and thus more nucleophilic Grignard reagent (in THF) must rapidly form the $[\text{Ni-ate}]^-$ complex and readily aid oxidative addition into the $\text{C}_{\text{aryl}}\text{-OMe}$ bond. Such a significant increase in reactivity by changing the electronic properties of the Grignard reagent, strongly suggests that the ease and rate of $[\text{Ni-ate}]^-$ formation is of high importance to the reaction outcome.

These loadings (0.25 – 0.1 mol%) are the lowest catalyst loadings reported for aryl methyl ether cross-coupling, with the vast majority of the literature often requiring ≥ 1 mol%. It may be argued that forcing conditions are used, however low catalyst loadings are of the utmost importance regarding cost and safety, as nickel complexes are often highly toxic.²¹⁴

In an attempt to replicate the original *ortho*-steric constraints present with guaiacol-derived feedstocks, the investigation was progressed to 1-phenyl-2-methoxynaphthalene (**137**). It was predicted that this extra steric hindrance would provide a clearer insight into catalyst preference, depending on cone angle, as well as gaining a clearer benefit of the naphthalene effect when compared to 2-methoxybiphenyl (Table 4.9).

Table 4.9 – Nickel-catalysed Grignard cross-coupling of substituted methoxynaphthalenes with *p*-TolMgBr (**41**), *o*-TolMgBr (**111**) and MeMgBr (**68**).



Entry ^[a]	Ar-O-Me	Grignard (M)	Catalyst	T (°C)	Conversion (%)	Product (%)
1 ^{[b][c]}	137	41	NiCl ₂ (PCy ₃) ₂	80	94	87
2 ^{[b][c]}	137	41	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	80	77	69
3 ^[c]	137	41	NiCl ₂ (PCy ₃) ₂	80	82	70
4 ^[c]	137	41	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	80	54	41
5	137	41	NiCl ₂ (PCy ₃) ₂	100	70	60
6	137	41	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	100	91	85 [83]
7 ^[c]	137	111 (2.0)	NiCl ₂ (PCy ₃) ₂	80	48	27
8 ^[c]	137	111 (2.0)	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	80	31	15
9	137	111 (2.0)	NiCl ₂ (PCy ₃) ₂	100	59	40
10	137	111 (2.0)	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	100	76	61 [59]
11 ^[c]	137	68 (2.4)	NiCl ₂ (PCy ₃) ₂	80	10	n.d. ^[d]
12 ^[c]	137	68 (2.4)	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	80	< 5	n.d. ^[d]
13	137	68 (2.4)	NiCl ₂ (PCy ₃) ₂	100	9	n.d. ^[d]
14	137	68 (2.4)	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	100	12	n.d. ^[d]
15 ^[e]	138	41	NiCl ₂ (PCy ₃) ₂	100	19	n.d. ^[d]
16 ^[e]	138	41	NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂	100	0	n.d. ^[d]

^[a] Reactions conditions: aryl ether (0.50 mmol), Grignard reagent (0.75 mmol in Et₂O), 2-MeTHF (2.25 mL). Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. ^[b] 2.5 mol% catalyst. ^[c] Reaction performed in a Schlenk flask. ^[d] Due to overlapping of multiple signals in the ¹H NMR, the product yield was not determined. ^[e] aryl ether (0.25 mmol) scale, 5 mol% catalyst and 4.2 equiv. of Grignard used.

Again, at 80 °C there appears to be a preference for [NiCl₂(PCy₃)₂] (Table 4.9, entries 1-4). However, when the temperature was increased to 100 °C there was a considerable switch in product yield between the two catalysts, with [NiCl₂(P^{*n*}Bu₃)₂] giving 85 % of 1-phenyl-2-(*p*-tolyl)naphthalene (**139**) at 1 mol% compared to only 60 % for

[NiCl₂(PCy₃)₂] (Table 4.9, entries 5 and 6). It is clear that the increased sterics due to *ortho*-substitution make a difference here when compared to 2-methoxynaphthalene, albeit only marginally. However, this steric effect becomes considerable when attempting to react the more hindered *o*-TolMgBr (**111**) with both catalysts, with both temperatures giving often considerably lower yields of 1-phenyl-2-(*o*-tolyl)naphthalene (**140**) (entries 7-10). The higher temperature of 100 °C did seem to counter this effect slightly, however yields were still lower compared to when *p*-TolMgBr (**41**) was used. In theory, this substrate has more extended π -conjugation in the sense that it combines the desirable attributes of a naphthalene backbone with a “biaryl-type” unit, and thus electronically, should facilitate rapid cross-coupling. The lack of success, albeit only at 1 mol%, gives an indication of the challenge apparent with simpler anisoles such as 2-methoxybiphenyl and even 2-methylanisole.

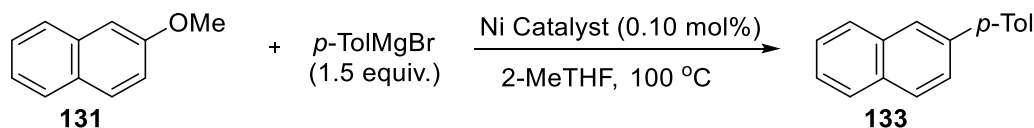
Methylation attempts were unsuccessful using MeMgBr (**68**), regardless of catalyst, with very low conversions apparent (Table 4.9, entries 11-14). However, the struggles to methylate aryl ethers have been presented throughout this chapter, including for non-activated, less-substituted anisoles. Perhaps, as discussed earlier, there is a strong requirement for aryl Grignards in this catalytic system, similar to what Dankwardt initially reported.⁸⁹ It is speculated that the Grignard reagent, although virtually steric free, cannot facilitate in any beneficial interaction to lower TSs or aid the bond breaking process in the oxidative addition step.

To further increase sterics, the coupling of 2,2'-dimethoxy-1,1'-binaphthalene (**138**) was investigated. This substrate possessed sterics in the *ortho*-position but interestingly this time conjugated to another naphthalene ring. This was a good test to investigate steric influences vs the enhanced naphthalene effect. Unfortunately, the coupling was unsuccessful with both catalysts, even with increased loadings of 5 mol% (Table 4.9, entries 15 and 16). This therefore implies that the steric crowding and restricted rotation imposed severely hinders catalysis, most likely again due to inability to form key interactions within transition states that facilitate oxidative addition processes.

4.2.4.6 Time profile analysis

To gain a better understanding of $[\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2]$, time profiling reactions were performed at a catalyst loading of just 0.1 mol%. Samples were taken after the desired time periods and analysed by ^1H NMR spectroscopy against 1-methylnaphthalene as the internal standard (Table 4.10). To avoid the sampling process impacting upon the course of these air and moisture sensitive reactions, a limited number of samples were taken for each reaction, which enabled reproducible data to be obtained (*the full dataset is shown in the Experimental Section 7.7.3*).

Table 4.10 – Time profile analysis for the reaction of 2-methoxynaphthalene (**131**) with *p*-TolMgBr using 0.10 mol% of nickel catalysts. See *Experimental for full details*.



Entry ^[a]	Additive (equiv.)	Catalyst	t (h)	Conversion (%)	Product (%)
1	-	[NiCl ₂ (PCy ₃) ₂]	4	5	0
			16	3	0
			28	10	1
			69	46	30
			90	68	43
2 ^[b]	-	[NiCl ₂ (PCy ₃) ₂]	16	3	0
			28	13	2
			69	56	34
			90	67	43
3	-	[NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂]	4	0	0
			16	11	4
			28	19	12
			69	64	50
4 ^[c]	MgI ₂ (1.5)	[NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂]	11	25	22
			45	83	70
			59	85	72
			90	85	72
5 ^[d]	MeOH (0.3)	[NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂]	4	9	7
			16	39	36
			28	65	59
			69	83	72
			90	84	72
6 ^[e]	BrMg(OMe) (0.3)	[NiCl ₂ (P ^{<i>n</i>} Bu ₃) ₂]	4	0	0
			16	12	10
			28	28	24
			69	81	72
			90	81	72
7 ^[f]	MgI ₂ (1.5)	-	90	0	0

^[a] Reaction conditions: 2-methoxynaphthalene (0.50 mmol), *p*-TolMgBr (0.75 mmol, 0.5 M in Et₂O), Ni catalyst (0.0005 mmol), solvent (2.25 mL) in a sealed microwave vial with crimp cap, 100 °C. Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard. ^[b] Reaction spiked with P^{*n*}Bu₃ (0.033 mol%, in 25 μL) after 49 h. ^[c] MgI₂ (0.75 mmol) added prior to start of reaction. ^[d] MeOH (0.15 mmol) added to the solution containing catalyst and substrate, prior to addition of Grignard reagent (0.90 mmol). ^[e] MeOH (0.15 mmol) added to the Grignard reagent (0.90 mmol) prior to the addition of catalyst and substrate. ^[f] No nickel catalyst.

Initially, the two catalysts were tested against each other and yet again, $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$ appeared to outperform $[\text{NiCl}_2(\text{PCy}_3)_2]$ at each time interval (Table 4.10, entries 1 and 3). Interestingly, it became apparent that these reactions showed signs of an induction period, which is quite unusual for this type of catalysis (Figure 4.9 – blue and red lines). Since the reduction of Ni^{II} pre-catalysts to Ni^0 using a Grignard reagent is usually considered a fast reaction, it is unlikely to cause the observed induction period. The data seems to suggest good catalyst stability, with the catalysts laying effectively dormant for ~ 16 hours. After this time, the reactions appear to accelerate and continue to be catalytic for substantial periods of time, perhaps due to the willingness of the dissociated ligand to re-coordinate and stabilise a resting state.

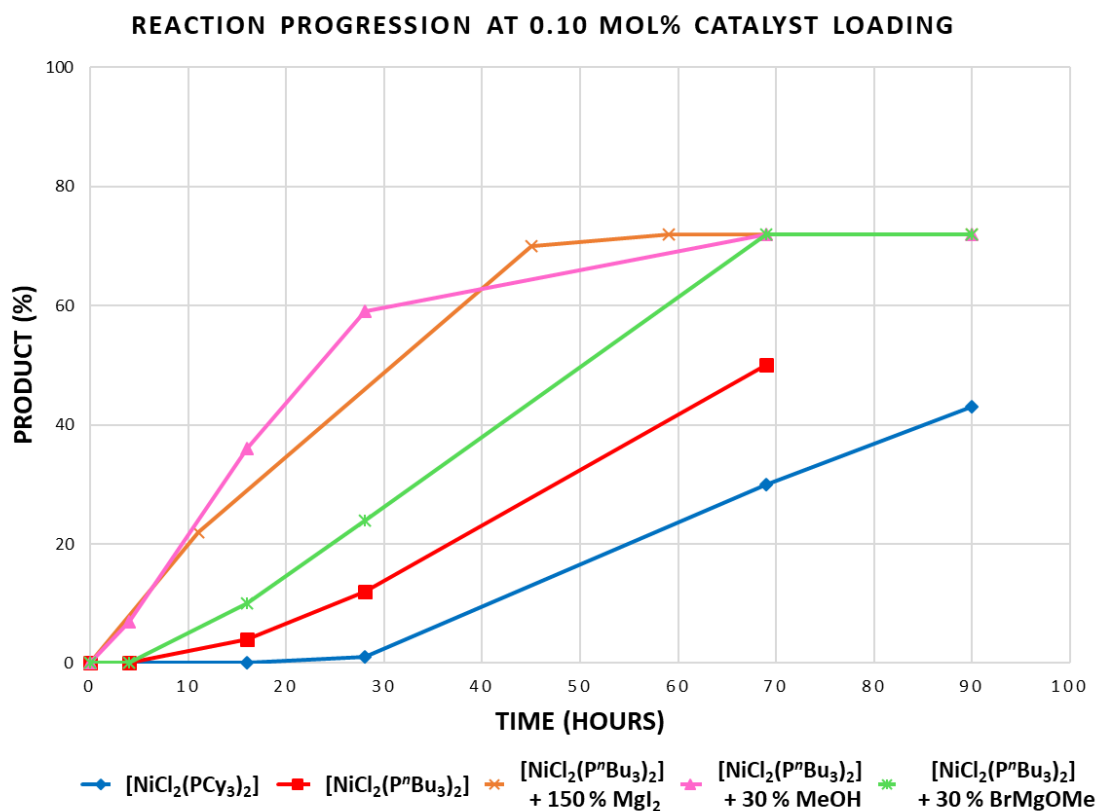


Figure 4.9 – Plot of 2-(*p*-tolyl)naphthalene (**133**) yield vs time from reaction of 2-methoxynaphthalene (**131**) with *p*-TolMgBr under optimised reaction conditions in Table 4.10, using different Ni-catalysts (0.10 mol%). (Orange) – 1.5 equiv. MgI_2 added. (Pink) – 0.3 equiv. MeOH added to solution of catalyst and substrate prior to Grignard reagent (1.8 equiv.) addition. (Green) – 0.3 equiv. MeOH added to the Grignard reagent (1.8 equiv.) prior to addition of solution containing catalyst and substrate.

An explanation for the induction periods observed could be that the reactions were catalysed by heterogeneous nanoparticles or clusters. Induction periods are often very indicative of this type of catalysis, which has been suggested by many in the field, particularly for reductive cleavage reactions.^{117, 123, 215} Hartwig and co-workers showed a ligandless, heterogeneous nickel-catalytic system to be successful in the hydrogenolysis of aryl ethers.¹¹⁷ This type of catalysis enabled lower catalyst loadings of 0.25 mol% to be utilised, similar to that seen here with the Grignard cross-coupling reactions. Often these heterogeneous systems require high temperatures and can display poor selectivity (e.g. C-F cleavage),¹¹⁷ which are two factors that the results over this chapter have shown, therefore again displaying some similarities.

To fully rule out heterogeneous catalysis, further studies are required; a brief attempt to poison/disrupt the potential nanoparticles with a sub-catalytic amount of P^tBu_3 (0.03 mol%) did not show strong inhibition, more consistent with a homogeneous mechanism, but at the high reaction temperature this result should be treated with caution (Table 4.10, entry 2). Mercury poisoning^{123, 216, 217} is often used to indicate heterogeneous catalysis. However, this can also be inconclusive at high temperatures and could have posed a safety concern due to the forcing conditions utilised. Other methods, such as transmission electron microscopy (TEM) and nano filtration should be tested in future work.

Reaction progression appeared to be coinciding with a solid precipitating from the reaction mixture. This therefore suggested that the observed induction periods may be due to the requirement of inorganic Lewis acid formation to facilitate the desired reaction. This was supported by the fact that excess MgI_2 , found to be advantageous as a promoter in the alkylative cross-coupling of anisoles,¹⁰⁰ showed no induction period (Table 4.10 entry 4, and Figure 4.9 – *orange line*). The profile indicates normal homogeneous catalysis with the reaction ceasing at ~45 hours, therefore suggesting that the magnesium salts produced during the reaction could be important in the mechanism. To achieve a more accurate representation of the effect of the inorganics formed during the reaction, 30 mol% of MeOH was added to create $BrMg(OMe)$ *in situ* (upon reaction with the Grignard reagent). The reaction in which MeOH was added to the solution containing $[NiCl_2(P^tBu_3)_2]$ and 2-methoxynaphthalene prior to Grignard addition (Table 4.10 entry

5, and Figure 4.9 – *pink line*), also showed no induction period and a time profile again indicating homogeneous catalysis. The success apparent with MeOH eliminates the requirement for magnesium iodide, which was suggested by Chatani and co-workers.¹⁰⁰ Substoichiometric amounts of MeOH (and thus magnesium inorganic salts) greatly enhanced the rate of product formation, therefore supporting the suggestion that this beneficial effect was due to inorganic Lewis acid formation, and not through Grignard reagent enhancement (e.g. by bromide exchanging with iodide). A very short induction period was initially observed in the experiment involving the addition of 30 mol% of MeOH directly to the Grignard reagent, prior to the addition of catalyst and substrate (Table 4.10 entry 6, and Figure 4.9 – *green line*). However, the reaction soon accelerated at a greater rate compared to the $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$ -catalysed reaction containing no additives. This again demonstrated the benefit of inorganic Lewis acids being present during the reaction. To ensure that this process was nickel-catalysed, a control experiment solely with MgI_2 was carried out, giving no reaction after 90 hours (Table 4.10 entry 7). This is consistent with Chatani and co-workers who showed that the presence of Grignard reagents were required for the ether cleavage reaction.¹⁰⁰

4.3 – Summary and future work

In this chapter, several nickel catalysts, varying in cone angle as well as σ -donating capabilities, were synthesised and subsequently tested in the cross-coupling of challenging aryl methyl ether substrates. A trend became apparent with cone angle; productivity increasing as ligand cone angles were reduced to 132°. For *ortho*-substituted 2-methoxybiphenyl, it became apparent that a smaller cone angle was favourable up until P^nBu_3 , with PMe_3 appearing to fall outside of the trend, probably due to the considerable decrease in σ -donating ability as well as dissociation capabilities. This steric dependence was extended to N—heterocyclic carbenes, in which the slimmer ICy, which has broadly comparable steric and electronic properties to P^nBu_3 , showed highest activity.

The two key catalysts of comparison were $[NiCl_2(PCy_3)_2]$ and $[NiCl_2(P^nBu_3)_2]$, which were at opposite sides of the cone angle spectrum. The somewhat previously untested $[NiCl_2(P^nBu_3)_2]$ was significantly more active for a wide range of substrates at elevated temperatures. The lowest catalyst loadings (0.1 mol%) ever reported for nickel-catalysed Grignard cross-coupling of an aryl methyl ether were apparent with the use of this Ni- P^nBu_3 catalyst, further enhanced by magnesium salt additives. Therefore, this catalyst should be considered in future when attempting to establish a successful cross-coupling reaction of aryl methyl ethers, especially for *ortho*-substituted anisoles.

It has become clear that for *ortho*-substituted aryl ether substrates, the extra sterics imposed undoubtedly have an effect as shown for 1-phenyl-2-methoxynaphthalene. However, removing these phenyl-based sterics in the example of 2-methylanisole appeared to have a negative effect on the coupling, suggesting a requirement for biaryl methyl ethers in order to mimic the extended π -conjugation apparent in fused naphthyl substrates. Electron-withdrawing substituents in the *ortho*-position did not provide an alternative to the requirement of extended π -conjugation or biaryl substrates, with low yields apparent with 2-trifluoromethylanisole. However, it must be noted that poor results may have been due to side reactions involving C-F bond cleavage, as there seems to be a low tolerance to certain functional groups.

There appears to be a clear preference for aryl Grignards which aligns with the majority of the literature. Sterics within the Grignard reagent appeared to have a significant effect in the success of the reaction of *ortho*-substituted aryl ethers, even when the more streamlined $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$ catalyst was used. However, methylations were surprisingly unsuccessful throughout. The extremely low steric hindrance from MeMgBr was predicted to favour cross-coupling, however the inability for sufficient coordination of this Grignard reagent to the methyl ether, as well as the nickel catalyst, is thought to have resulted in low yields. This poor coordination is supported by lower than expected yields in the uncatalysed Meyers-type processes involving 2-benzoxazolyl and 2-pyridyl directing groups, as well as the rarity of successful methylations in the literature, especially involving simpler anisoles.^{96, 199} Electronic properties of the Grignard reagent were also investigated, with electron-deficient (fluorinated) Grignard reagents giving low yields in the coupling of 2-methoxybiphenyl. The electron-rich Grignard reagent 4-*N,N*-dimethylaminophenylmagnesium bromide gave enhanced activity in the coupling with 2-methoxynaphthalene, with excellent yields in as little as 4 hours, using just 0.25 mol% of $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$.

The benefit of an adjacent heterocycle was investigated. Significant, unidentifiable side products often occurred, however the presence of a nickel catalyst appears to aid challenging $\text{S}_{\text{N}}\text{Ar}$ reactions when performed at lower temperatures. Future work will look to expand this methodology to other substrates, e.g. to hopefully catalytically cross-couple *p*-TolMgBr with 2-methoxybenzotrile, giving 4'-methyl-[1,1'-biphenyl]-2-carbonitrile, a key building block for the production of the hypertension drug Losartan. However, functional group tolerance is a problem in Grignard cross-coupling and will have to be overcome.

Time profiles for 2-methoxynaphthalene at 0.1 mol% catalyst loading have shown that induction periods are present. Both $[\text{NiCl}_2(\text{PCy}_3)_2]$ and $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$ displayed excellent stability and gave similar reaction profiles, with $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$ giving greater reaction rates and yields. This induction period was not present when a stoichiometric amount of MgI_2 (1.5 equiv.) or catalytic amount of MeOH ($\text{BrMg}(\text{OMe})$ created *in situ*) (30 mol%) was added, with a more predictable time profile for homogenous catalysis

being present, as well as higher rates and overall yields. This therefore suggested that the reactions required a high concentration of Lewis-acidic magnesium salts to initiate significant activity, thus agreeing with the sigmoidal shape of the time profiles and apparent autocatalytic behaviour of the reactions without additives. Future work could involve investigating the effect of other Lewis acid additives that have proven to benefit methyl ether cross coupling, such as AlMe_3 .^{105, 109, 117, 122}

Another possibility is that these reactions are actually heterogenous, most probably through the formation of nickel nanoparticles or multinuclear species. Induction periods are very common in this type of catalysis and should be investigated further, through more in-depth poisoning studies

Overall, the results show a clear trend favouring less-bulky ligands, that is contrasting to the usual prerequisites for cross-coupling catalysis. Poor results with heterocyclic based phosphines, hemi-labile ligands as well as bidentate phosphines seem to suggest that the active cycle requires a monoligated system. It is envisaged that the reactions proceed through intermediates with one coordinated phosphine. The reason for the success of $[\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2]$ at elevated temperatures is thought to be due to the threshold for phosphine dissociation being reached, thus providing a reactive and open environment for the reaction to proceed. There is now an argument for re-examining ligands such as P^tBu_3 in other reactions at higher temperatures, as well as developing new ligands inspired by its success. More hybrid phosphine ligands, this time primarily based upon P^tBu_3 , could be synthesised and tested to probe the cone angle/ligand dissociation limit further. As well as this, mixed NHC/ P^tBu_3 nickel-complexes should also be investigated and subsequently subjected to fine-tuning, with an attractive possibility being $[\text{NiCl}_2(\text{P}^t\text{Bu}_3)(\text{ICy})]$.

Chapter V: Synthesis of (*S*)-Flurbiprofen utilising a highly enantioselective palladium-catalysed methoxycarbonylation

5.1 – Introduction

5.1.1 - Flurbiprofen

Flurbiprofen is a member of the nonsteroidal anti-inflammatory drug (NSAID) family and can be further categorised as a “profen” drug (Figure 5.1). Since its Food and Drug Administration (FDA) approval in 1988, it has been widely sold as a racemate for treatment of pain and inflammation in a range of conditions from arthritis to dental pain, even finding use in throat lozenges.²¹⁸⁻²²⁰ Like all NSAIDs, Flurbiprofen works by inhibiting the cyclooxygenase (COX) enzymes,²²¹⁻²²³ and is known to be particularly potent.^{224, 225}

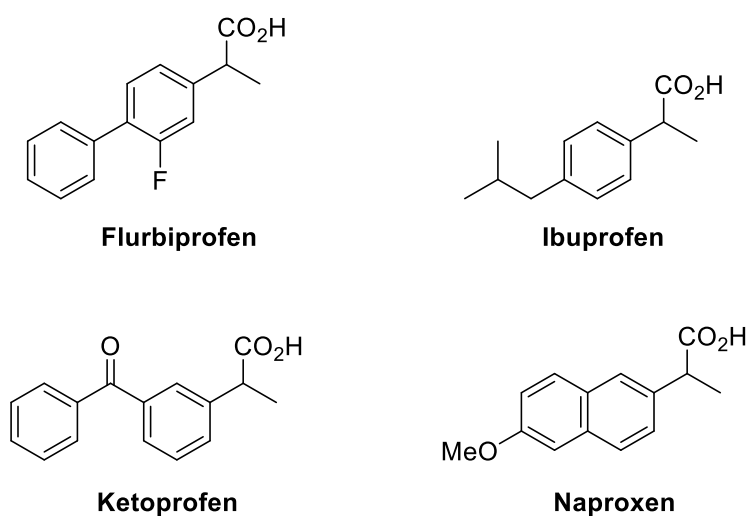


Figure 5.1 – Examples of nonsteroidal anti-inflammatory drugs, specifically “profens”, containing the aryl propanoic acid functionality.

Unlike Ibuprofen, Flurbiprofen does not undergo enzymatic-chiral inversion *in vivo*; a characteristic that means it is often studied to compare different activities of NSAID enantiomers. The anti-inflammatory action for all NSAIDs resides almost exclusively with the (*S*)-enantiomer.²²⁶⁻²³⁰ (*S*)-Flurbiprofen is 500 times more potent at COX

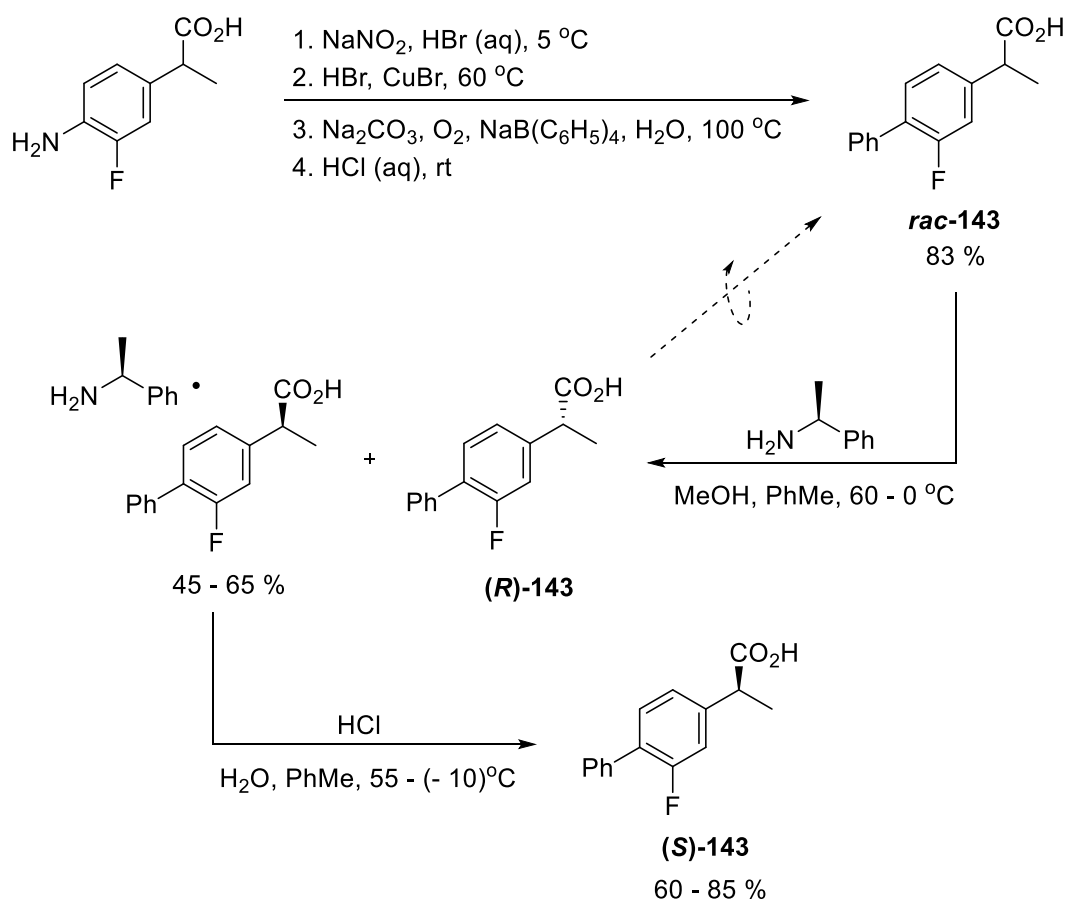
inhibition than its (*R*)-counterpart.²²⁹ A better side-effect profile²³¹⁻²³⁶ is thought to be possible using single enantiomer drugs, especially in the case of NSAIDs such as Flurbiprofen that do not racemise *in vivo*.

(*R*)-Flurbiprofen has been shown to possess significantly differing properties than its (*S*) enantiomer. Tests have displayed anti-tumour tendencies (particularly in the colon) and much research is ongoing for its use in Alzheimer's disease (AD) treatment. The anti-tumour properties arise from induction of apoptosis and reducing prostaglandin biosynthesis.^{237, 238} (*R*)-Flurbiprofen has been shown to reduce levels of the pathogenic peptide A β 42, responsible for neurodegeneration in AD, through modulating the activity of a key enzyme, γ -secretase.²²⁵ Myriad Genetics & Laboratories reached phase III clinical trials in 2008 with (*R*)-Flurbiprofen (FlurizanTM) for the treatment of AD before being discontinued, predominately due to low blood-brain-barrier penetration.²³⁹ Intensive research into new Flurbiprofen derivatives to try and improve this efficacy is now being prioritised.²⁴⁰⁻²⁴² When not used as an anti-inflammatory, a desirable feature of (*R*)-Flurbiprofen is that it does not inhibit the COX enzymes, significantly lowering gastrointestinal and kidney side-effects.²⁴³ These differing properties show that there are other modes of (potentially undesired/unrequired) action likely to occur elsewhere in the body (due to the (*R*)-enantiomer), when taking *rac*-Flurbiprofen for anti-inflammatory purposes (inherent to the (*S*)-enantiomer). Thus, the desire for single-enantiomer Flurbiprofen is growing rapidly.

Taisho Pharmaceutical have now marketed a single-enantiomer Flurbiprofen medication, in the form a single-dose patch for the treatment of osteoarthritis.²⁴⁴ Containing (*S*)-Flurbiprofen (40 mg) and mentha oil, the gel patch shows improvement compared to the racemic patch in terms of overall lasting effects (rehabilitation), as well as speed of action through faster absorption.^{245, 246} Fewer side-effects were apparent compared to a racemic oral dose.²⁴⁷⁻²⁴⁹

5.1.2 - Asymmetric routes to Flurbiprofen

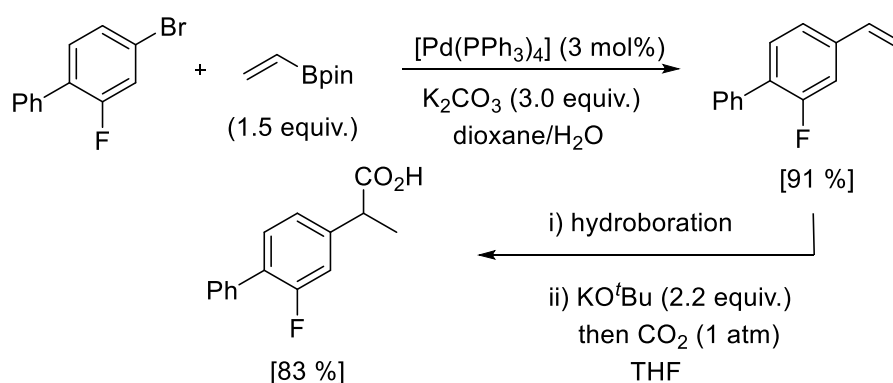
The synthesis of Flurbiprofen can involve numerous steps, often resulting in moderate yields.²⁵⁰⁻²⁵³ Additionally, chiral resolution is still required if single-enantiomers are desired.²⁵⁴⁻²⁵⁸ A current representative synthesis is shown in Scheme 5.1 that utilises a Sandmeyer reaction followed by biaryl synthesis using sodium tetraphenylborate.²⁵⁹ Chiral resolution of racemic Flurbiprofen (*rac*-143) was carried out using (*S*)-1-phenylethylamine to yield enantiopure drug ((*S*)-143) after acidification. The (*R*)-enantiomer ((*R*)-143) could be racemised in refluxing methanolic sulfuric acid to aid in the efficiency of the overall process.²⁵⁵



Scheme 5.1 – Current synthesis of (*S*)-Flurbiprofen ((*S*)-143).²⁶⁰

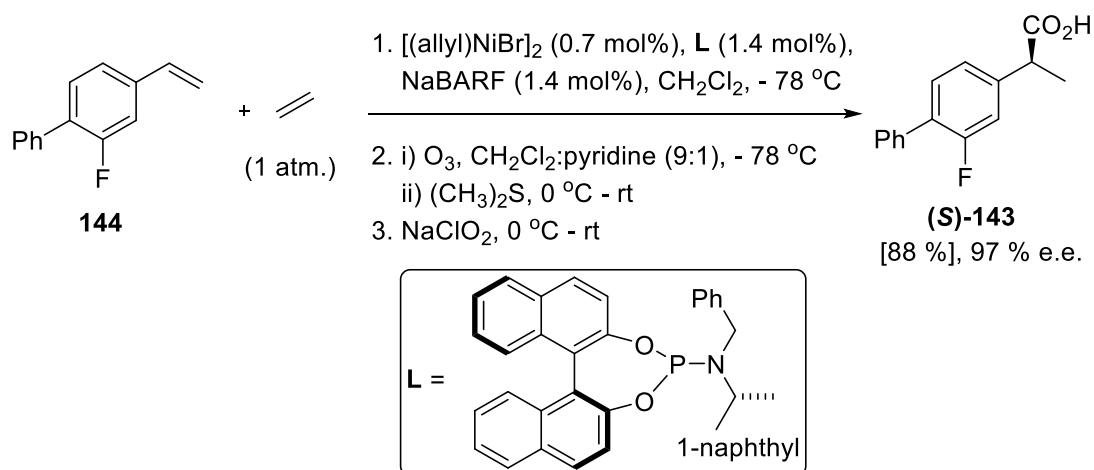
Catalytic methods to Flurbiprofen are more attractive but reasonably scarce. Xu and co-workers reported a five-step synthesis of *rac*-Flurbiprofen, utilising a Suzuki-Miyaura reaction with Pd/C in water to construct the biaryl fragment of the drug.²⁶¹ Schlosser *et*

al., reported a seven-step synthesis of *rac*-Flurbiprofen from inexpensive 3-fluorotoluene that also utilised a Suzuki-Miyaura reaction.²⁶² In 2012, Schomaker and co-workers developed a three-step, two-pot synthesis involving a Suzuki-Miyaura cross-coupling and hydroboration with an overall yield of 76 % (Scheme 5.2).²⁶³ Although these processes are quite attractive and high yielding, they are not enantioselective and thus don't yield an enantiopure drug.



Scheme 5.2 – Three step, two pot synthesis of *rac*-Flurbiprofen. i) Hydroboration: HBPIn (1.2 equiv.), CuCl (3 mol%), dppBz (3mol%), NaO^tBu (6 mol%).²⁶³

Catalytic asymmetric syntheses of enantiomerically enriched Flurbiprofen are relatively rare and generally have some problems that would make scale-up less appealing; such as requiring a large number of steps or reagents that are generally not preferred at large scale. Kennedy and co-workers²⁶⁴ utilised a Sharpless asymmetric dihydroxylation as well as catalytic hydrogenolysis in a highly enantioselective synthesis of (*S*)-Flurbiprofen (98 % e.e.) from commercially available 4-bromo-2-fluoro-1,1'-biphenyl. However, the synthesis required seven steps and thus produced extensive waste. Smith and RajanBabu²⁶⁵ showed a three-step procedure for the synthesis of highly enantioenriched (*S*)-Flurbiprofen (**(*S*)-143**) (97 % e.e.) from the advanced intermediate 3-fluoro-4-phenylstyrene (**144**) *via* asymmetric hydrovinylation followed by ozonolysis then oxidation (Scheme 5.3).

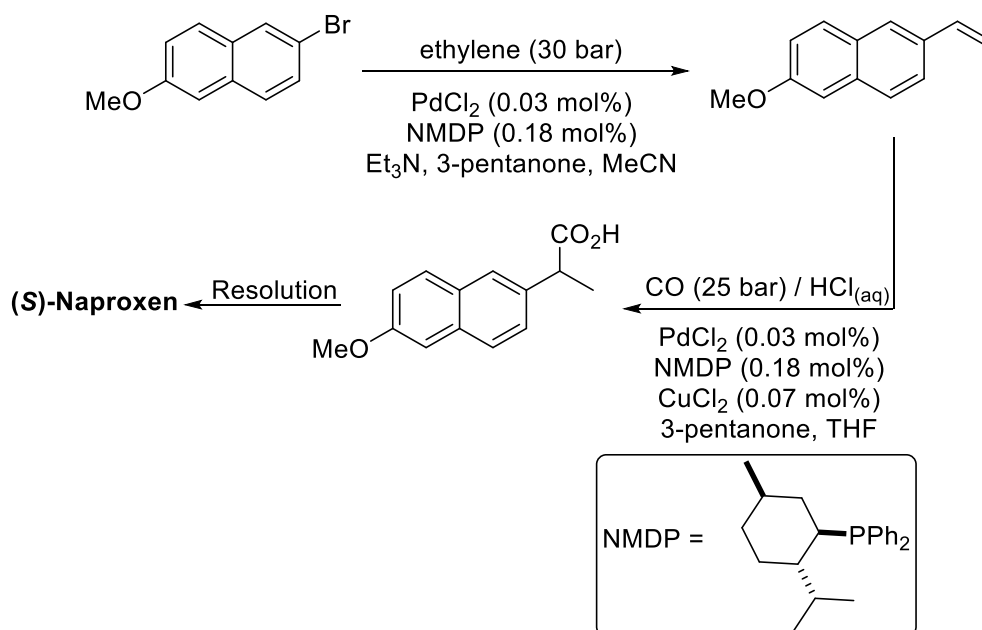


Scheme 5.3 – RajanBabu’s synthesis of (*S*)-Flurbiprofen (**(S)-143**) in good yield and excellent enantioselectivity.²⁶⁵

Although excellent results were apparent, there are a few drawbacks including the use of an air sensitive nickel precatalyst for the hydrovinylation, low reaction temperatures (-78 °C) and the handling of two gases, ethylene and ozone. Furthermore, oxidative processes are not preferred at large scale due to safety concerns. Although branded as a three-step synthesis, yields are taken from the vinyl arene **144**, which would also have to be prepared.

It has long been recognised that direct conversion of vinyl arenes to branched carboxylic acid derivatives via catalytic hydroxycarbonylation is potentially a more attractive procedure for making profen type drugs. This reaction takes two very cheap reagents, carbon monoxide and water, and converts them into products of real value, in an extremely atom-efficient manner. Consequently, various racemic profens have been made in this way industrially.^{21, 22, 266-274}

Some particularly attractive examples include the one-pot processes by Albemarle^{21, 269-271} (Heck cross-coupling – hydroxycarbonylation) (Scheme 5.4) and Beller²⁶⁷ (carbonylative Suzuki-Miyaura cross-coupling – hydroxycarbonylation).



Scheme 5.4 – Albemarle synthesis of *rac*-Naproxen utilising the same catalyst to perform the initial Heck cross-coupling followed by hydroxycarbonylation. Additional resolution is required to obtain (*S*)-Naproxen.²⁷¹

It must be noted that an additional chiral resolution step was required to get to the desired (*S*)-Naproxen in the Albemarle process. A more elegant approach could be to perform this in a single asymmetric step, catalytically.

5.1.3 – Asymmetric hydroxy-/methoxycarbonylation of vinyl arenes

Significant research has gone into the asymmetric hydroxy- and alkoxy carbonylation of vinyl arenes since the first reports in the 1970s. In general, it was found that chiral monophosphines gave enhanced branched regioselectivity as well as activity, but with low levels of enantioselectivity. Vinyl arenes give predominately branched products with monophosphines which is thought to be due to the increased thermodynamic stability of the branched metal complex as a result of the π -benzylic species being formed.^{275, 276} Methoxycarbonylation of olefins, particularly vinyl arenes, are generally regarded as being more active than their counterpart hydroxycarbonylation reactions. Consequently, loadings as low as 0.05 mol% can be applied with near perfect branched regioselectivity using Pd-precatalysts involving the commercially available phosphine 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxo-6-phospha-adamantane; with no excess ligand

required.²⁷⁷ Cometti *et al.*,²⁷⁸ were the first to report asymmetric methoxycarbonylation of styrene with a chiral monophosphine ligand (**145**) (Figure 5.2 i). In 2004, Hiyama and co-workers²⁷⁹ utilised chiral binaphthol-derived phosphines such as **146** to deliver solely branched products with moderate e.e. in the asymmetric methoxycarbonylation of styrene (46 % e.e.) and 2-methoxy-6-vinylnaphthalene (53 % e.e.), using relatively mild conditions. At the time, ligand **146** gave the best combination of branched regioselectivity and enantioselectivity. Several chiral phosphetane ligands, for example **147**, have been studied by Claver and were the first examples of an isolated catalyst containing a chiral monophosphine being used in these reactions.²⁸⁰ However, yields decreased whenever there was any meaningful degree of enantiocontrol. Ligand **149**, (Figure 5.2 ii), was utilised by Alper and Hamel in 1990 to give extremely promising results for the challenging hydroxycarbonylation of 2-methoxy-6-vinylnaphthalene to yield Naproxen.²⁸¹ High enantioselectivities (up to 91 %, recorded by optical rotation) were obtained with perfect selectivity to branched product. However, the system was found to be relatively inactive, requiring extremely specific, harsh conditions (13 mol% catalyst as well as undesired Cu additives and concentrated HCl) that wouldn't be feasible industrially. In addition, the results have not been reproduced by several groups. It is thought that either these specific conditions or error within the analytical method, may have resulted in the lack of reproducibility of this reaction.^{282, 283}

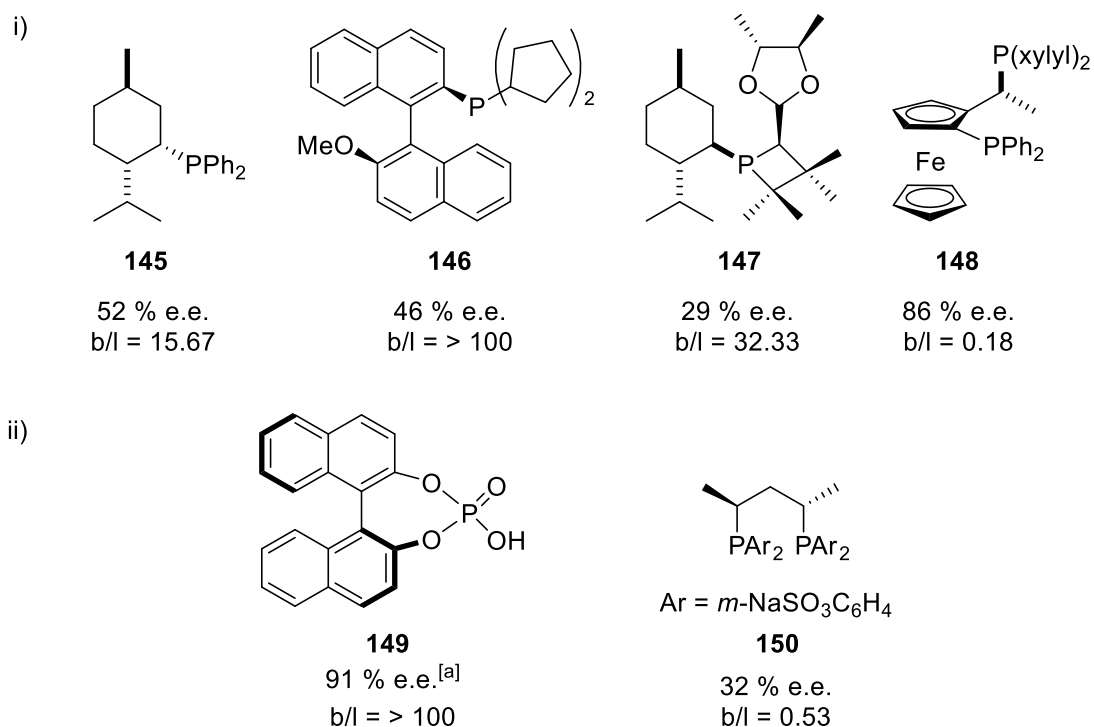


Figure 5.2 – Notable ligands for the asymmetric i) methoxycarbonylation, ii) hydroxycarbonylation of styrene. ^[a] Hydroxycarbonylation of 4-isobutylstyrene; methoxycarbonylation of styrene only gave 38 % e.e. and b/l = 2.33.²⁸³

Chiral diphosphines can favour enantioselectivity because of the increased rigidity of the catalytic species. Frustratingly, although high enantioselectivities can be obtained, branched selectivity is often low. Chiral ferrocene-based diphosphines such as **148** seem to provide high levels of enantioselectivity in the methoxycarbonylation of vinyl arenes but are severely hindered by low activity (yields) and linear selectivity.²⁸⁴⁻²⁸⁶ Similar observations regarding low branched selectivity were found in hydroxycarbonylation, e.g. with the use of diphosphine **150**.²⁷⁶ The problem of palladium catalysts derived from diphosphines delivering high linear selectivity, is that it results in a wide array of chiral, potentially highly enantioselective ligands that cannot be used. This has been suggested to be predominately down to sterics in the transition states disfavoring the branched intermediate as well as chelate coordination increasing the hydridic nature of the Pd-H intermediate, and thus promoting anti-Markovnikov addition, giving linear products.^{275,}

276

Significant research has focussed on trying to make diphosphine systems more branched selective. Some success was apparent when incorporating electron-deficient diphosphines

in styrene methoxycarbonylation. Significantly higher branched selectivity was observed when using *m*-(CF₃)₂C₆H₃ aryl groups such as in ligand **151** (bite angle 100 °) compared to just phenyl rings, but to the cost of e.e. (3 % down from 30 %) (Figure 5.3 i).²⁸⁷ Clarke and co-workers designed bulky fluorinated diphosphines e.g. **152** (bite angle 97 °) which proved to be high yielding with satisfactory branched regioselectivity in the hydroxycarbonylation of styrene (Figure 5.3 ii).²⁸⁸ Chiral, enantiopure variants were not synthesised.

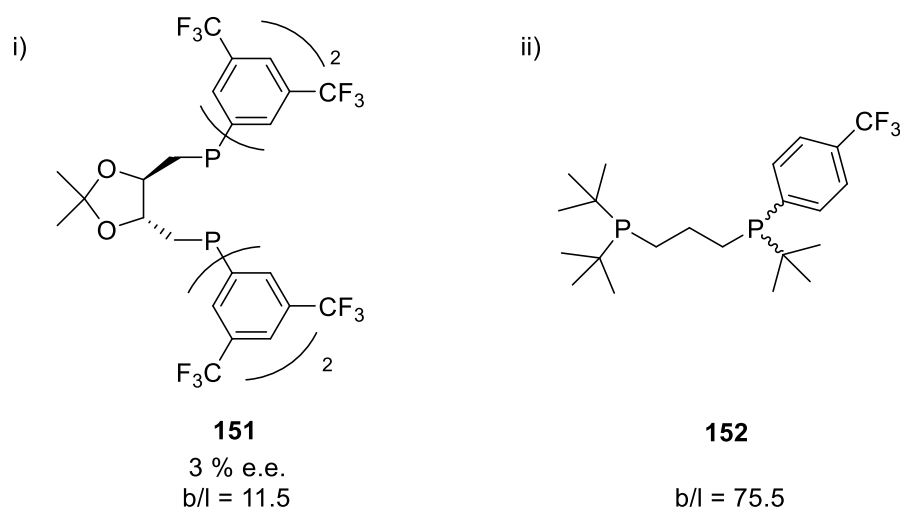


Figure 5.3 – Notable electron-deficient ligands in the attempts to increase branched selectivity in i) methoxycarbonylation, ii) hydroxycarbonylation of vinyl arenes.

Major improvements were made by Clarke and co-workers in 2010 and 2013 using a Pd-Phanephos catalytic system (Figure 5.4).^{152, 153}

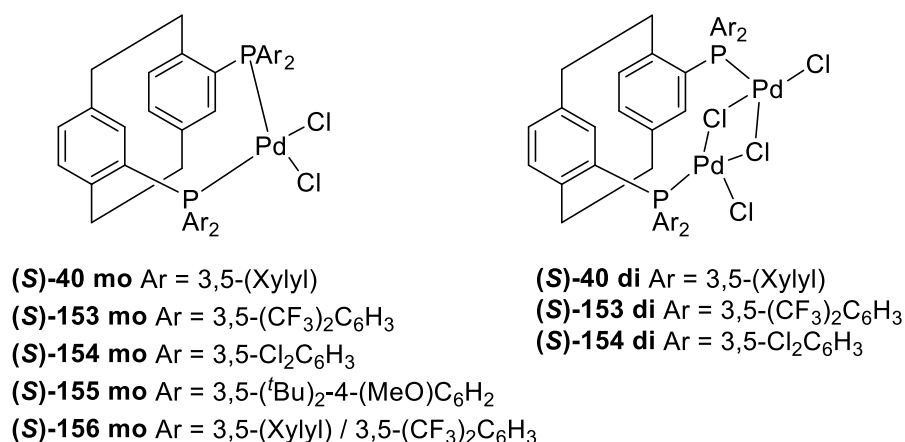


Figure 5.4 – Pd-Phanephos catalysts synthesised by Clarke and co-workers in order to try and establish simultaneous control of enantio- and regioselectivity.^{152, 153}

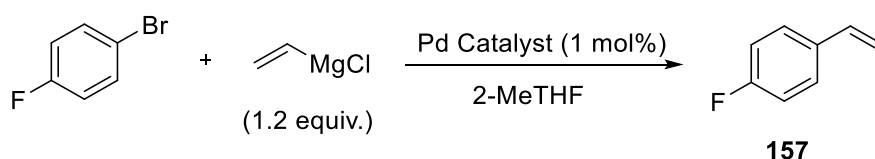
The aim of this part of the project was to utilise the capabilities of the Pd-Phanephos catalysts to perform the alkene installation to yield 3-fluoro-4-phenylstyrene (**144**) and then hopefully couple this with an enantioselective carbonylation, using the same catalyst. The desired tandem manner of this synthesis would effectively lower catalyst use thus making the process more industrially attractive.

5.2 - Results and discussion

5.2.1 - Grignard cross-coupling to obtain vinyl arene

The use of Pd-Phanephos catalysts in coupling vinyl Grignard reagents with aryl bromides to obtain substituted styrene derivatives was investigated. Based on the results in Chapter II, [PdCl₂(Xylyl-Phanephos)] (**40 mo**) was expected to outperform [PdCl₂(dppf)] (**39**), this time in the coupling of vinylmagnesium chloride. The ultimate aim would be to perform a sequential one-pot Grignard cross-coupling - hydroxycarbonylation reaction to give chiral aryl propanoic acids enantioselectively. Test reactions were performed on the model substrate 1-bromo-4-fluorobenzene (Table 5.1).

Table 5.1 – Scoping the initial success of [PdCl₂(Xylyl-Phanephos)] (**40 mo**) in the Grignard cross-coupling of an aryl bromide with vinylmagnesium chloride.



Entry ^[a]	Catalyst	T (° C)	t (h)	Conversion (%)	Product (%)
1 ^[b]	39	rt	18	< 5	< 5
2 ^[b]	(S)-40 mo	rt	18	< 5	< 5
3 ^[c]	39	rt	24	< 5	< 5
4 ^[c]	(S)-40 mo	rt	24	< 5	< 5
5 ^[d]	39	80	4	96	69
6 ^[d]	(S)-40 mo	80	22	> 99	57 [48]
			4	53	5
			22	66	13

^[a] Reaction conditions: 1-bromo-4-fluorobenzene (0.50 mmol), vinylmagnesium chloride (0.60 mmol, 1.6 M in THF), Pd catalyst (0.005 mmol) in 2-MeTHF (500 μL). Conversions and yields were determined by ¹H NMR using 1-fluoronaphthalene as an internal standard. rt = room temperature. ^[b] Results taken from ¹⁹F NMR. ^[c] ZnCl₂ (0.50 mmol) added. ^[d] 1-bromo-4-fluorobenzene (1.00 mmol) scale.

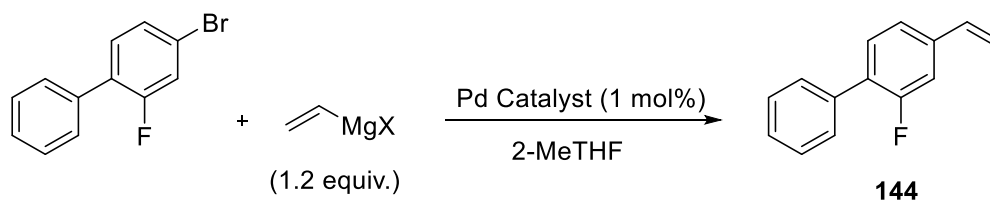
Unfortunately, the reactions were unreactive and required heat. Also, the trend appeared to switch from what was seen on this substrate in Chapter II, with [PdCl₂(dppf)] performing better and yielding more product (**157**) (entry 5). It was hoped that similar to the work of Farrell and Miller²⁸⁹ addition of ZnCl₂ to the reaction mixture would aid the

reaction at room temperature. Organozinc reagents have been shown to facilitate transmetalation more readily than other nucleophilic organometallics due to empty low-lying p orbitals on the zinc.²⁹⁰ Consequently, challenging reactions can be performed successfully at lower temperatures, often chemoselectively. However, the addition of ZnCl₂ (anhydrous) did not increase conversion at room temperature in this reaction.

Although moderate product yields were obtained in entry 5, poor mass balance was observed. Despite only 57 % of product being formed, there were no other significant peaks present in the ¹H NMR and ¹⁹F NMR spectra. However, the high conversion implied that side reactions must have occurred. Initial thoughts were that volatiles were created, e.g. fluorobenzene, and evaporated under the sustained high reaction temperatures.

Vinyl Grignards were also reacted with the Flurbiprofen precursor 4-bromo-2-fluoro-1,1'-biphenyl. Again, the capabilities of [PdCl₂(Xylyl-Phanephos)] (**40 mo**) were compared to [PdCl₂(dppf)] (**39**) (Table 5.2).

Table 5.2 – Attempts at synthesising 3-fluoro-4-phenylstyrene (**144**) via the Grignard cross-coupling of 4-bromo-2-fluoro-1,1'-biphenyl with a vinylic Grignard.



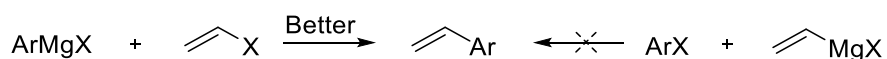
Entry ^[a]	X =	Catalyst	T (° C)	t (h)	Conversion (%)	Product (%)
1	Cl ^{[d][e]}	39	80	17	> 99	0
2	Cl ^{[d][e]}	<i>rac-40 mo</i>	80	17	76	0
3	Br ^[d]	39	80	18	> 99	< 5
4	Br ^[d]	<i>rac-40 mo</i>	80	18	> 99	0
5	Br ^[d]	39	20	18	> 99	< 5
6	Br ^[d]	<i>rac-40 mo</i>	20	18	39	9
7	Br	39	80	89	> 99	77
8	Br	<i>rac-40 mo</i>	80	89	87	44
9 ^[b]	Br	39	80	18	> 99	[54]
10 ^[c]	Br ^[f]	39	80	16	> 99	[61]

^[a] Reaction conditions: 4-bromo-2-fluorobiphenyl (0.25 mmol), vinylic Grignard (0.30 mmol, in THF), Pd catalyst (0.0025 mmol) in 2-MeTHF (500 μ L). Conversions were determined by ¹⁹F NMR and yields were determined by ¹H NMR using either 1-methylnaphthalene or 1-fluoronaphthalene as an internal standard, [yield of isolated product in square brackets]. ^[b] 4-bromo-2-fluorobiphenyl (5.00 mmol) scale and no internal standard. ^[c] 4-bromo-2-fluorobiphenyl (5.50 mmol) scale and no internal standard. ^[d] Commercially available Grignard used, purchased from Sigma Aldrich. ^[e] 2.4 equiv. of Grignard added. ^[f] 1.05 equiv. of Grignard added.

Unfortunately, as with 1-bromo-4-fluorobenzene, neither catalyst worked particularly well; both producing numerous unidentifiable side products. Again, [PdCl₂(dppf)] was the slightly better performing catalyst and there seemed to be a requirement for the Grignard reagent to be made and used fresh rather than purchased.

The apparent failure of [PdCl₂(Xylyl-Phanephos)] to effectively react with vinyl Grignards could be due to the fact that, inherently as a carbonylation catalyst, it favours olefin coordination. Consequently, the Grignard reagent may in fact compete with organic halide for coordination to the metal centre, potentially causing side reactions, especially at elevated temperatures.

In an initial report, Kumada stated that: “*vinyl Grignards exhibited relatively low reactivity and vinylmagnesium chloride in THF is one of the least reactive ones*”.²⁹¹ He therefore proposed, from a synthetic point of view, that the reaction should be reversed in order to introduce an alkene functionality. Vinyl arenes should therefore be prepared from an aryl Grignard and a vinylic halide rather than from an aryl halide and a vinylic Grignard (Scheme 5.6).

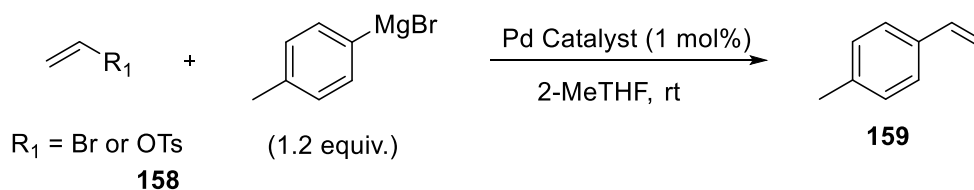


Scheme 5.6 – Kumada’s initial proposal to circumvent the use of unreactive vinylmagnesium chloride.

Kumada also reported that vinyl chloride “*is one of the most reactive halides*”.²⁹¹ The large difference in reactivity between vinyl Grignards and vinyl halides is thought to be due to the stabilising interaction that can occur between the vinyl halide and metal complex which favours the catalytic process.

Therefore, a new strategy was to attempt the coupling of commercially available vinyl bromide solution (1.0 M in THF) with the aryl Grignard *p*-TolMgBr using [PdCl₂(*S*)-Xylyl-Phanephos] ((*S*)-**40 mo**) as catalyst. It was predicted that [PdCl₂(*S*)-Xylyl-Phanephos] would perform well since results in Chapter II demonstrated that it readily catalyses the Kumada-Corriu coupling of aryl Grignards. Also, the fact that vinyl halides are amongst the best coupling substrates makes this reaction very attractive. It is pleasing to note that Grignard cross-coupling reactions involving vinyl chloride have been scaled-up effectively for use on the industrial scale (Figure 1.1).¹⁸

Table 5.3 – Investigation of the capabilities of [PdCl₂((*S*)-Xylyl-Phanephos)] ((*S*)-**40 mo**) in the Grignard cross-coupling of vinyl halides and pseudo-halides.



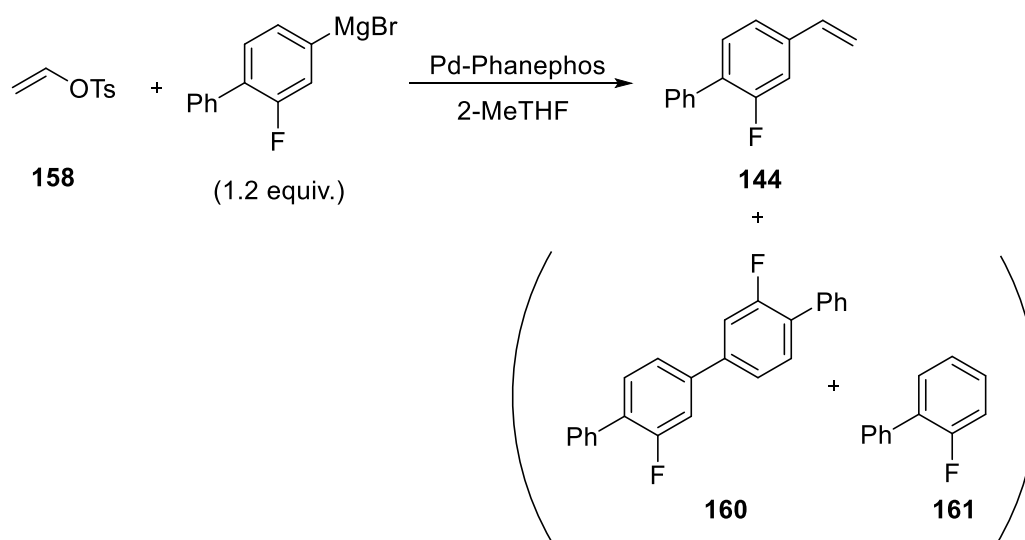
Entry ^[a]	R ¹	Catalyst	t (h)	Conversion (%)	Product (%)
1 ^[b]	Br	(<i>S</i>)- 40 mo	25	n.d. ^[c]	63
2 ^{[b][d]}	Br	(<i>S</i>)- 40 mo	19	n.d. ^[c]	[46]
3	OTs (158)	39	4	> 99	43
4	OTs (158)	(<i>S</i>)- 40 mo	4	> 99	66
5	OTs (158)	(<i>S</i>)- 40 mo	19	> 99	73
6	OTs (158)	(<i>S</i>)- 40 mo	19	> 99	[54]

^[a] Reaction conditions: vinyl bromide solution (0.50 mmol, 1.0 M in THF) or vinyl tosylate (0.50 mmol), *p*-TolMgBr (0.60 mmol, 0.5 M in Et₂O), Pd catalyst (0.005 mmol) in 2-MeTHF (1.0 mL), rt. rt = room temperature. Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard, [yield of isolated product in square brackets]. ^[b] 2-MeTHF (500 μL). ^[c] Due to the volatility of SM, the conversion was not determined. ^[d] vinyl bromide solution (1.00 mmol, 1.0 M in THF) scale.

The poorer than expected yields in Table 5.3 entries 1 and 2, along with the volatility of vinyl bromide resulted in an alternative, more stable substrate, being sought. In 2005, Hartwig and co-workers showed successful Grignard cross-couplings of alkenyl tosylates with aryl and alkyl Grignard reagents using strongly electron donating and sterically hindered *bis*phosphines.²⁹² Vinyl tosylate (**158**) was not reported. Skrydstrup and co-workers demonstrated the Heck coupling of vinyl tosylate as a method to obtain functionalised butadienes,²⁹³ as well as obtaining a range of styrene derivatives *via* Suzuki-Miyaura coupling of vinyl tosylate with arylboronic acids.²⁹⁴ More recently, the utility of vinyl tosylate has been expanded to palladium-catalysed C-H functionalisation of substituted benzoxazoles.²⁹⁵ An added bonus is that vinyl tosylate is a relatively cheap, non-toxic oil (derived from the fragmentation of THF) which would enormously aid handling. Pleasingly there was an improvement in product yield, with [PdCl₂((*S*)-Xylyl-Phanephos)] ((*S*)-**40 mo**) being the better performing catalyst (Table 5.3, entries 4 vs 3). This is the first example of vinyl tosylate being used in a Grignard cross-coupling reaction.

Keen to progress, efforts were made to synthesise the desired vinyl arene, 3-fluoro-4-phenylstyrene (**144**). The aryl Grignard (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide was synthesised from the commercially available bromide, 4-bromo-2-fluoro-1,1'-biphenyl, and magnesium turnings with a catalytic amount of iodine as the initiator. Envisaging the one-pot/tandem cross-coupling – carbonylation that was trying to be established, 2-MeTHF was chosen as the solvent for Grignard reagent preparation as it has been shown to be effective for Grignard cross-couplings¹³⁷ and hydroxycarbonylation reactions,¹⁵⁴ using Pd-Phanephos catalysts. The desired cross-coupling reaction proceeded, on the whole, very well (Table 5.4).

Table 5.4 – Pd-Phanephos-catalysed Grignard cross-coupling of vinyl tosylate (**158**) with (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide.



Entry ^[a]	Catalyst	Catalyst Loading (mol%)	T (° C)	t (h)	Conversion (%)	Product (%)
1	(S)- 40 mo	1	20	17	> 99	99
2 ^[b]	(S)- 40 mo	1	20	17	> 99	96
3 ^[c]	(S)- 40 mo	1	20	17-21	> 99	92
4	(S)- 40 mo	1	20	2	97	88
5 ^[d]	(S)- 40 mo	1	0	17	69	50
6 ^{[d][e]}	(S)- 40 mo	1	20	17	> 99	77
7 ^[d]	<i>rac</i> - 40 mo	1	50	21	> 99	78
8 ^{[f][g]}	(S)- 40 mo	1	20	17	> 99	[90] ^[h]
9 ^{[g][i]}	(S)- 40 mo	1	20	18	> 99	[75] ^[j]
10	(S)- 40 mo	0.25	20	20	> 99	83
11	(S)- 40 mo	0.1	20	19	47	40
12	(S)- 40 mo	0.1	50	3	> 99	65
13 ^{[b][d]}	(R)- 153 mo	1	20	19	> 99	82
14 ^{[d][g]}	(R)- 153 mo	1	20	17	> 99	[79] ^[k]

^[a] Reactions conditions: vinyl tosylate (0.50 mmol), (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide (0.60 mmol in 2-MeTHF, molarity determined by titration before use), Pd catalyst, in 2-MeTHF (1.0 mL). Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. ^[b] Reaction performed in a sealed microwave vial with crimp cap. ^[c] Average yield of 13 experiments (t 17-21 h) = 92 %. ^[d] Vinyl tosylate (0.25 mmol) scale. ^[e] Grignard added at 0 °C. ^[f] Vinyl tosylate (0.76 mmol) scale. ^[g] No internal standard. ^[h] 90 % yield isolated with 2-fluorobiphenyl impurity; total product obtained = 68 %. ^[i] Vinyl tosylate (2.25 mmol) scale vinyl tosylate with 0.67 equiv. Grignard. ^[j] 75 % yield isolated with 2-fluorobiphenyl impurity; total product obtained = 68 %. ^[k] 79 % yield isolated with 2-fluorobiphenyl impurity; total product obtained = 63 %.

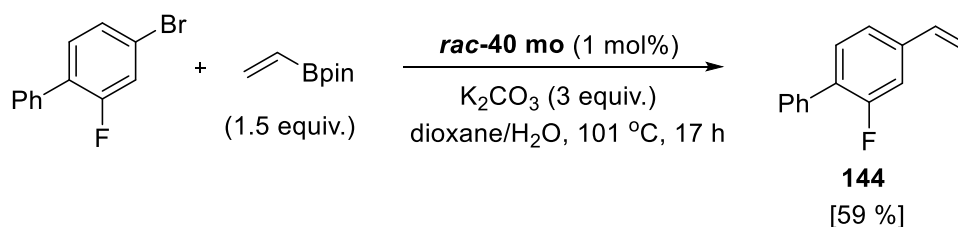
Yields fluctuated slightly when using 1 mol% of [PdCl₂(Xyl)yl-Phanephos)] (**40 mo**) at 20 °C, possibly due to variation in the Grignard reagents from batch to batch, although

they were titrated prior to use. Consequently, an overall average conversion to product of 92 % was recorded at 1 mol%, from thirteen experiments (Table 5.4, entry 3) (*see Appendix for data on these thirteen experiments*). There was often complete conversion of starting material but no real indication of side product by NMR spectroscopy and GCMS, apart from the Grignard homocoupling product 3',3''-difluoro-[1,1';4',1'';4'',1''']quaterphenyl (**160**) and 2-fluorobiphenyl (**161**). Significant quantities of homocoupling/dimerisation of the Grignard reagent can occur from undesired secondary transmetalations during the catalytic cycle,²⁹⁶ while quenching of unreacted Grignard reagent results in 2-fluorobiphenyl. Because of these (often inherent) side products, isolation of pure alkene was very challenging by chromatography, with a difficult to separate mixture of alkene **144**, **160** and **161** being formed. However, looking forward to a sequential process, it was assumed that these inert impurities would not affect subsequent carbonylation reactions. In attempts to limit the formation of undesired side products, fewer equivalents of Grignard reagent were added. However, the reaction still gave some 2-fluorobiphenyl. Pleasingly, the catalyst loading of **40 mo** could be successfully lowered from 1 – 0.25 – 0.1 mol% with the latter requiring some heat (Table 5.4, entries 10-12).

It was interesting to note that other Pd-Phanephos derivatives that tend to give better results in carbonylation reactions could also facilitate this Grignard cross-coupling. Pleasingly, at the regular loading for carbonylation with the Pd-Phanephos catalytic systems (1 mol%), [PdCl₂((*R*)-F₂₄-Phanephos)] ((*R*)-**153 mo**) also gave desired vinyl arene **144**, albeit in slightly lower yields. This electron-withdrawing diphosphine renders the palladium more electron-deficient, presumably resulting in slower oxidative addition, which is often the rate-determining step in Grignard cross-coupling reactions. This could be an explanation for the lower yields apparent, but, it must be noted that there was full conversion of vinyl tosylate (**158**). Since **153 mo** is one of the more active carbonylation catalysts,¹⁵³ it possibly facilitates alkene coordination and thus side product formation more readily.

To initially investigate the carbonylation reactions of 3-fluoro-4-phenylstyrene, an alternative synthesis of the vinyl arene was performed to ensure high purity.²⁶³ The aryl

bromide was subjected to a Suzuki-Miyaura reaction with vinylboronic acid pinacol ester, catalysed by 1 mol% of [PdCl₂(*rac*-Xylyl-Phanephos)] (***rac*-40 mo**), giving 59 % of pure vinyl arene **144** (Scheme 5.7). There appeared to be significant catalyst decomposition after a few hours, as well as several other vinylic peaks in the crude ¹H NMR spectrum. The high temperature of the reaction is presumed to have had a detrimental effect on the selectivity as it has been shown that lower temperatures avoid unwanted Heck reactions.²⁹⁷ This reaction was not optimised further but it does at least show that Pd-Phanephos catalysts have the potential to catalyse yet more cross-coupling reactions. When a literature procedure using 3 mol% of [Pd(PPh₃)₄] was followed, an isolated yield of 83 % was obtained. **144** obtained from this Suzuki-Miyaura cross-coupling reaction was easier to purify using column chromatography.



Scheme 5.7 – Pd-Phanephos-catalysed Suzuki-Miyaura cross-coupling of 4-bromo-2-fluoro-1,1'-biphenyl with vinylboronic acid pinacol ester. Reaction following literature procedure with [Pd(PPh₃)₄] (3 mol%) gave 83 % isolated yield.

5.2.2 Catalytic carbonylation

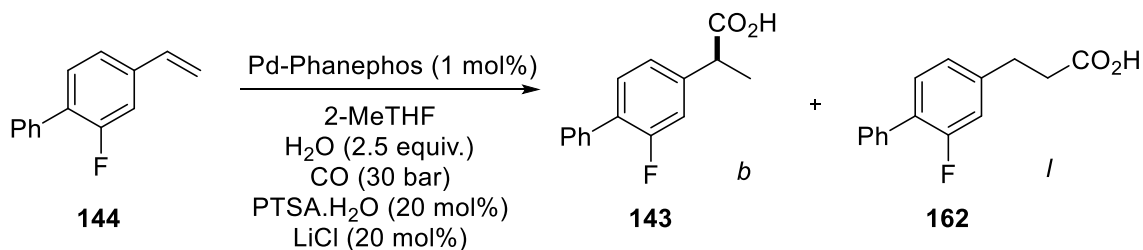
5.2.2.1 - Hydroxycarbonylation

Previous work on the hydroxy-/methoxycarbonylation of 3-fluorostyrene using Pd-Phanephos catalysts has been shown to be relatively successful with high yields (> 99 %) and enantioselectivities (up to 73 %), with near perfect regio-control.¹⁵³ Thus, it was anticipated that the extra phenyl substituent in the 4-position would not create too significant an issue and give similar, if not better, results.

In previous work on the hydroxycarbonylation of styrene, [Pd₂Cl₄(F₂₄-Phanephos)] (**153 di**) was clearly identified as the best catalyst for this type of process in terms of

productivity, rate, and high regioselectivity. It was therefore examined and compared to other Pd-Phanephos catalysts in the hydroxycarbonylation of vinyl arene **144** (Table 5.5).

Table 5.5 – Synthesis of Flurbiprofen (**143**) by enantioselective hydroxycarbonylation using Pd-Phanephos catalysts.



Entry ^[a]	Catalyst	T (° C)	t (h)	Conversion (%)	Product [%]	b/l	e.e. (%)
1 ^{[b][c]}	<i>rac</i> - 40 mo	110	19	> 99	80 [56]	0.31	0
2	(<i>S</i>)- 40 mo	80	17	49	21 [13]	0.73	55
3 ^[d]	(<i>S</i>)- 40 mo	80	17	18	14 [6]	0.50	56
4	(<i>S</i>)- 40 mo	60	42	16	9	1.20	75
5 ^[d]	(<i>S</i>)- 40 mo	60	42	2	4	0.67	76
6	(<i>S</i>)- 40 mo	60	65	30	14 [10]	0.96	72
7 ^[c]	(<i>S</i>)- 40 mo	60	65	25	18 [11]	1.05	78
8	(<i>R</i>)- 153 mo	60	65	97	97 [69]	79	47
9	(<i>R</i>)- 153 mo	60	17	69	67 [56]	80	52
10	(<i>R</i>)- 153 di	60	65	93	91 [69]	55	42
11	(<i>R</i>)- 156 mo	60	65	> 99	> 99 [73]	39	32

^[a] Reaction conditions: 3-fluoro-4-phenylstyrene (0.25 mmol), Pd-Phanephos (0.0025 mmol), H₂O (0.63 mmol), PTSA·H₂O (0.05 mmol), LiCl (0.05 mmol), CO (30 bar) in 2-MeTHF (750 μL). Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets after acid-base extraction]. b/l ratio determined by ¹H NMR. Enantiomeric excess determined by chiral HPLC. (*S*)-configured catalysts give (*S*)-configured product and *vice versa*. ^[b] Racemic catalyst used. ^[c] 10 equiv. H₂O. ^[d] Butanone as solvent.

As was the case with styrene, the electron deficient Pd-F₂₄Phanephos catalysts (**R**)-**153 mo** and (**R**)-**153 di**, were among the highest performing (Table 5.5, entries 8-10). High yields as well as excellent regioselectivity towards the branched isomer were apparent. In contrast to previous studies, the monomeric palladium complex (**R**)-**153 mo** was higher yielding and more regio-/enantioselective than the dipalladium complex (**R**)-**153 di**. The degree of enantioselectivity using (**R**)-**153 di** was lower and reactions were less active, requiring higher temperatures and longer times compared to with styrene. This apparent low activity could hinder any future desire to increase enantioselectivity by lowering temperatures. Reactions could be performed in 2-MeTHF which could aid tandem

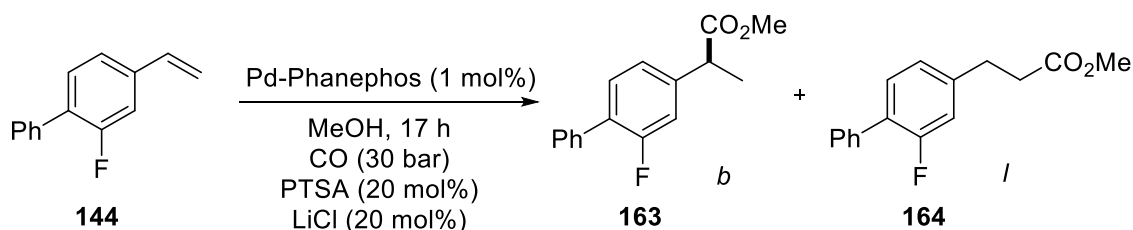
capabilities as it is a Grignard-compatible solvent. (*S*)-**40 mo** gave the highest enantioselectivity (Table 5.5, entries 4 and 5) but regioselectivity and activity were low, with high temperatures required in order to obtain any meaningful conversion (Table 5.5, entry 1).

In order to try and increase the enantioselectivity whilst preserving a high preference for Flurbiprofen (**143**), the non-symmetric catalyst (*R*)-**156 mo**, containing both an electron-poor phosphine and an electron-rich phosphine was tested. It was hoped that this would provide the specific characteristics of both Pd-F₂₄Phanephos and Pd-XylylPhanephos required for high regio- and enantioselectivity respectively. Unfortunately, instead of giving the “best of both”, it resulted in low enantioselectivity, although activity was high (Table 5.5, entry 11).

5.2.2.2 - Methoxycarbonylation

While the results for hydroxycarbonylation are reasonably good in the context of this challenging reaction, the moderate enantioselectivity was not sufficient to be synthetically useful. Methoxycarbonylation reactions are known to be more active and it was hoped that lower temperatures could aid in raising enantioselectivities (Table 5.6).

Table 5.6 – Enantioselective methoxycarbonylation of 3-fluoro-4-phenylstyrene (**144**).



Entry ^[a]	Catalyst	T(° C)	Conversion(%)	Product [%]	b/l	e.e.(%)
1	<i>rac</i> - 40 mo	60	95	88 [79]	1.09	0
2	(<i>S</i>)- 40 mo	60	> 99	98	1.17	91
3 ^[b]	(<i>S</i>)- 40 mo	60	> 99	> 99	1.37	93
4 ^{[b][c]}	(<i>S</i>)- 40 mo	60	62	59	1.27	92
5 ^{[c][d]}	(<i>S</i>)- 40 mo	60	72	67	1.27	91
6 ^{[c][e]}	(<i>S</i>)- 40 mo	60	17	13	1.17	85
7 ^[e]	(<i>S</i>)- 40 mo	60	> 99	> 99	1.35	93
8	(<i>S</i>)- 40 mo	40	88	81 [71] ^[f]	1.39	95
9 ^[g]	(<i>S</i>)- 40 mo	40	62	61	1.54	96
10 ^[h]	(<i>S</i>)- 40 mo	45	82	83 [78] ^[i]	1.31	95
11 ^[c]	(<i>S</i>)- 40 mo	40	84	81	1.63	96
12 ^[j]	(<i>S</i>)- 40 mo	40	12	9	1.33	92
13 ^[k]	(<i>S</i>)- 40 mo	40	85	82	1.56	96
14 ^{[l][m]}	(<i>S</i>)- 40 mo	40	1	< 1	-	-
15 ^{[m][n]}	(<i>S</i>)- 40 mo	40	2	< 2	-	-
16 ^{[m][o]}	(<i>S</i>)- 40 mo	40	0	0	-	-
17 ^[p]	(<i>S</i>)- 40 mo	40	73	68 [59] ^[q]	1.50	96
18 ^[r]	(<i>S</i>)- 40 mo	40	67	64	1.64	95
19	(<i>S</i>)- 40 mo	20	15	14	1.69	98
20	(<i>S</i>)- 40 di	40	39	27	1.62	96
21	(<i>R</i>)- 153 mo	40	16	8	> 100	51
22 ^{[l][s]}	(<i>R</i>)- 153 mo	40	15	7	> 100	58
23	(<i>R</i>)- 153 mo	20	2	< 2	-	-
24 ^{[l][s]}	(<i>R</i>)- 153 di	40	10	10	> 100	40
25	(<i>R</i>)- 154 mo	40	6	6	2.78	83
26	(<i>R</i>)- 154 di	40	9	8	3.38	74
27	(<i>R</i>)- 155 mo	40	10	6	7.19	74
28 ^[t]	(<i>R</i>)- 156 mo	40	19	17	6.23	77

[a] Reaction conditions: 3-fluoro-4-phenylstyrene (0.25 mmol), Pd-Phanephos (0.0025 mmol), PTSA·H₂O (0.05 mmol), LiCl (0.05 mmol), CO (30 bar) in MeOH (750 μL). Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. b/l ratio determined by ¹H NMR. Enantiomeric excess determined by chiral HPLC. (*S*)-configured catalysts give (*S*)-configured product and *vice versa*. ^[b] 70 bar CO. ^[c] No PTSA·H₂O. ^[d] 4:1, CO:H₂, 87.5 bar. ^[e] 4:1, CO:H₂, 70 bar. ^[f] Includes 32 % regioisomerically pure branched product **163**. ^[g] Al(OTf)₃ (20 mol%) as acid. *MsOH* (20 mol%) inactive. ^[h] 3-fluoro-4-phenylstyrene (1 mmol) scale. ^[i] Includes 39 % regioisomerically pure branched product **163**. ^[j] 10 bar CO. ^[k] 27 h. ^[l] 2-MeTHF as solvent. ^[m] 10 equiv. MeOH. ^[n] Butanone as solvent. ^[o] PhMe as solvent. ^[p] 3-fluoro-4-phenylstyrene (0.52 mmol) scale (0.68 mmol of a 73:27 mixture of vinyl arene and 2-fluorobiphenyl). ^[q] Includes 26 % regioisomerically pure branched product **163**. ^[r] Reaction performed alongside entry 16. ^[s] 2.5 equiv. MeOH. ^[t] 3-fluoro-4-phenylstyrene (0.10 mmol) scale.

In previous work using Pd-Phanephos catalysts, methoxycarbonylation and hydroxycarbonylation of a given alkene have tended to give similar regioselectivity and enantioselectivity. The results in the methoxycarbonylation (Table 5.6) were therefore surprising on several levels. Most catalysts showed very disappointing activity with only [PdCl₂((*S*)-Xylyl-Phanephos)] (**(*S*)-40 mo**) yielding any considerable product, with methanol as the solvent. The dipalladium complex (**(*S*)-40 di**), containing the same xylyl aryl groups as (**(*S*)-40 mo**), failed to give high yields. The use of (**(*R*)-153 mo**) gave only low yields of the branched isomer **163**. The fact methanol had to be used as solvent was detrimental to the vision of a tandem process as it involved Grignard reagents. Yields were extremely low when 2-MeTHF, butanone or PhMe were used, even with ten equivalents of methanol. However, (**(*S*)-40 mo**) was found to show excellent enantioselectivity ranging from 91 – 98 % e.e. (Table 5.6). Yields increased with temperature when using (**(*S*)-40 mo**), only at the slight expense of regio- and enantioselectivity. Isolation of pure branched ester was possible by column chromatography, albeit in only moderate yields due to the lower regioselectivity of the reactions when using (**(*S*)-40 mo**).

Various different catalysts were tested to try to increase regioselectivity whilst keeping enantioselectivity high, however there appears to be a trade-off in this process, and yields decreased significantly (Table 5.6, entries 21-28). The low yields using F₂₄-Phanephos catalysts (**(*R*)-153 mo**) and (**(*R*)-153 di**) are likely due to an unfavourable electronic effect hindering some part of the cycle to a much greater degree than is observed with styrene. Consistent with this, catalysts (**(*R*)-154 mo**) and (**(*R*)-154 di**) that are likely to be isosteric with (**(*S*)-40 mo**) and (**(*S*)-40 di**) respectively, but with more electron-withdrawing *meta* dichlorophenyl groups, also gave low yields relative to (**(*S*)-40 mo**). The very bulky, electron-rich catalyst (**(*R*)-155 mo**), although low yielding gave moderately high regioselectivity and an e.e. of 74 %. The significant decrease in enantioselectivity from (**(*S*)-40 mo**) to (**(*R*)-153 mo**) was a slight surprise in the sense that usually extra bulk within a ligand typically encourages higher selectivity. Since enantioselection is a subtle event, the differences in enantioselectivity, while striking, represent very small energy differences, but do reveal that this substrate is very nicely matched to the chiral pocket of (**(*S*)-40 mo**).

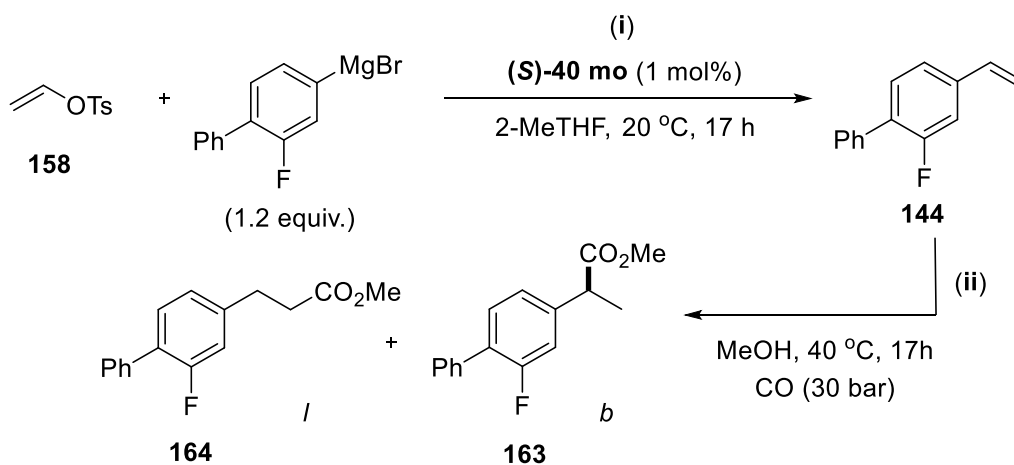
Increasing CO pressure can lead to higher branched selectivity by increasing the rate of carbonyl insertion as well as suppressing the fast β -hydride elimination of the branched Pd-alkyl species that can often occur. Indeed, higher CO pressures increased regioselectivity to branched ester, but not considerably (Table 5.6, entries 2-3 and 8 & 11). Low CO pressure (10 bar) resulted in low yields (Table 5.6, entry 12). Other acid co-catalysts were tested, however they all gave poorer results compared to PTSA·H₂O (entry 9). Pleasingly, the reaction could occur without PTSA·H₂O, provided there was an increase in CO pressure (70 bar). However, only moderate yields were apparent at 60 °C (entry 4). Syngas could be used as an alternative to PTSA·H₂O to generate the palladium hydride species, albeit with decreased yields. When using syngas, it appears as if there was a requirement for a large partial pressure of CO as shown by the differences in yield of entries 4 and 5.

5.2.2.3 – Attempts at a one-pot, consecutive cross-coupling - carbonylation reaction

The capabilities of Pd-Phanephos to perform both the Grignard cross-coupling and the subsequent carbonylation in a tandem/one-pot process was investigated.

As a result of the high enantioselectivity (95 % - 98 %) apparent with the methoxycarbonylation of 3-fluoro-4-phenylstyrene (**144**) with [PdCl₂((*S*)-Xylyl-Phanephos)] ((*S*)-**40 mo**), a tandem cross-coupling – methoxycarbonylation was initially attempted (Table 5.7). Re-using the catalyst would reduce its cost contribution and make the overall synthesis more productive and attractive industrially. Pd-Phanephos catalysts have been partly limited by the relatively high loadings (0.25 – 1.0 mol%) required for carbonylation reactions and this is a possible solution. It was envisaged that the Lewis-acidic magnesium salts produced from the initial Grignard cross-coupling could possibly act as an alternative to the co-promoters LiCl and PTSA·H₂O. Holzapfel and co-workers showed that the Lewis acid Al(OTf)₃ could be used in the methoxycarbonylation of styrene and actually gave higher rates and yields.²⁹⁸ PTSA could also be produced upon quenching the predicted transmetalation side product (*p*-TsOMgBr) with methanol.

Table 5.7 – Attempts to couple the Grignard cross-coupling step with methoxycarbonylation, re-using the Pd-Phanephos catalyst, (*S*)-**40 mo**. For full set of results: See Chapter VII, Experimental section.



Entry ^[a]	Step (i)		Step (ii)		Overall		
	Conversion (i) (%)	144 (i) (%)	Conversion (ii) (%)	Product (ii) (%)	Product (over steps i and ii) (%)	b/l	e.e. (%)
1 ^[b]	> 99	89	32	31	17 ^[c]	1.66	94
2 ^{[b][d]}	89	88	40	29	18 ^[c]	1.23	94
3 ^[e]	> 99	[90] ^[f]	73	68 [59] ^[g]	47 [40] ^[h]	1.50	96

^[a] Reaction conditions: (i) vinyl tosylate (0.50 mmol), (*S*)-**40 mo** (0.005 mmol), 2-fluoro-1,1'-biphenyl magnesium bromide (0.60 mmol in 2-MeTHF, molarity determined by titration before use) in 2-MeTHF (1.0 mL), 20 °C, 17 h. (ii) CO (30 bar), MeOH (1.5 mL). Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. b/l ratio determined by ¹H NMR. Enantiomeric excess determined by chiral HPLC. (*S*)-configured catalysts give (*S*)-configured product and *vice versa*. For full set of results: See Experimental section.

^[b] After Grignard cross-coupling the reaction was quenched with MeOH (400 μL) and concentrated *in vacuo*. 2-MeTHF (3.00 mL) was added and the reaction mixture was filtered by cannula under argon and concentrated *in vacuo*. MeOH (1.50 mL) was added and the resulting solution was added to a microwave vial with crimp cap equipped with stirrer bar, PTSA·H₂O (0.20 mmol) and LiCl (0.10 mmol), and subsequently methoxycarbonylated as in (ii).

^[c] Compared to external standard, 1,3,5-trimethoxybenzene (0.50 mmol).

^[d] Reaction time for Grignard cross-coupling step (i) = 2 h. PTSA·H₂O (0.50 mmol).

^[e] Vinyl tosylate (0.76 mmol) scale and no internal standard for (i). Isolated mixture obtained after cross-coupling step was re-charged with (*S*)-**40 mo** (1 mol%) prior to methoxycarbonylation as in (ii) with PTSA·H₂O (0.10 mmol) and LiCl (0.10 mmol).

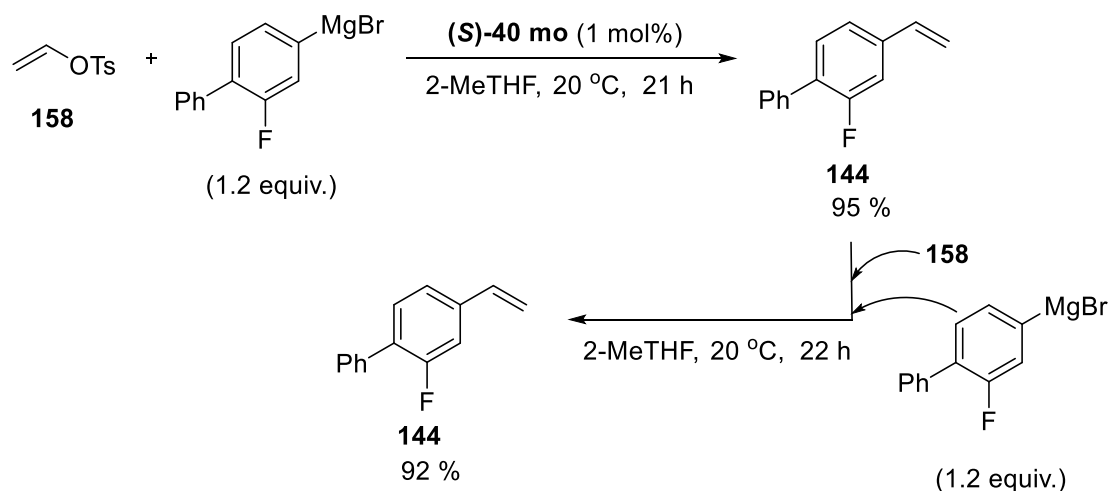
^[f] 90 % yield isolated with 2-fluorobiphenyl impurity; total product obtained = 68 %.

^[g] Includes 26 % regioisomerically pure branched product **163**, based on 3-fluoro-4-phenylstyrene.

^[h] Includes 17 % regioisomerically pure branched product **163**, based on vinyl tosylate.

Unfortunately, it became clear that a one-pot reaction was not possible, returning unreacted vinyl arene **144** under various conditions (see Chapter VII, Table 7.3, entries 1-4). Various complications were apparent: the methoxycarbonylation reaction did not readily occur in 2-MeTHF (Table 5.6, entries 14 and 15), so it was not simply a process of just adding methanol to the reaction mixture. Also, the magnesium salts produced appear to hinder the process as negligible product was obtained unless there was cannula filtration (Table 5.7, entries 1 and 2). As well as filtration, increased loadings of PTSA·H₂O were added (40 mol% entry 1, 1 equiv. entry 2) to counter the presence of methoxide (MeO⁻) formed from quenching the reaction with methanol. It was thought that the MeO⁻ formed could be reacting with the PTSA·H₂O and hindering the desired reaction. To discover whether Mg salts or the presence of MeO⁻ was hindering the process, a one-pot reaction with elevated PTSA·H₂O equivalents could have been performed. However, low yields were apparent with both factors considered and so this was not investigated. It was hoped that quenching the reaction with H₂O and extracting with 2-MeTHF would remove any unwanted Mg salts and also avoid MeO⁻ being able to react with the Brønsted acid (Chapter VII, Table 7.3, entry 6). But, the subsequent methoxycarbonylation was unsuccessful and this was probably due to decomposition of the sensitive Pd⁰ catalyst upon work up. Acidic conditions were also tested to quench the Grignard cross-coupling reaction, avoiding MeO⁻ formation, however this was also unsuccessful in the methoxycarbonylation (Table 7.3, entry 5). A shorter reaction time for the Grignard cross-coupling step was not beneficial to the overall process (Table 5.7, entry 2).

To discover if the catalyst was still active after the Grignard cross-coupling, a second Grignard cross-coupling step was performed in a sequential manner. If low yields were apparent then catalyst deactivation from the first cycle could be causing the inabilities in the methoxycarbonylation reactions. After the first cycle, the reaction was doped with another equivalent of vinyl tosylate (**158**) and Grignard reagent and continued for another 22 h (Scheme 5.8).



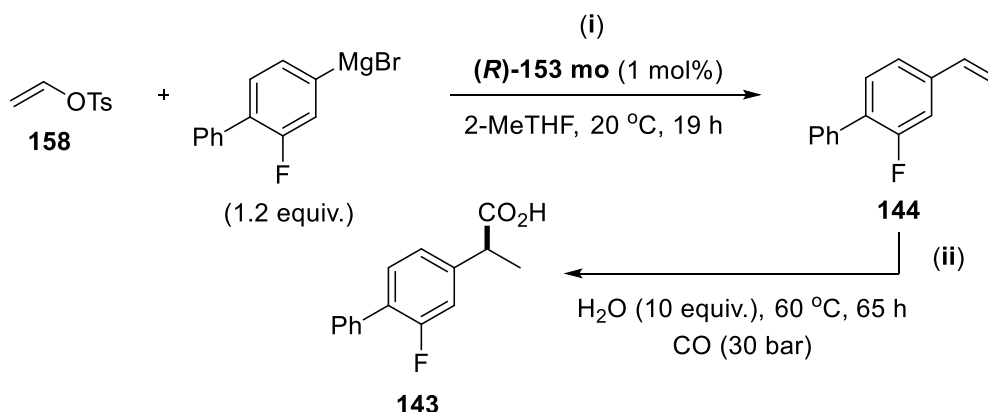
Scheme 5.8 – A sequential Grignard cross-coupling as a control to check that the catalyst is still active after the first reaction.

Only a 3 % decrease in product yield was apparent which indicated that the catalyst was indeed still active. Therefore, another factor must have caused the lower than expected yields, that is yet to be determined.

Consequently, a two-step process was established, re-charging the isolated mixture of vinyl arene **144** and 2-fluorobiphenyl **161** obtained after the Grignard cross-coupling, with 1 mol% [PdCl₂((*S*)-Xylyl-Phanephos)] ((*S*)-**40 mo**) (Table 5.7, entry 3). This resulted in a moderate yield of Flurbiprofen methyl ester, displaying excellent enantioselectivity. Further optimisation of this reaction to increase yields should be addressed in future.

The low yields apparent in the attempted tandem cross-coupling – methoxycarbonylation resulted in a switch of focus to a subsequent hydroxycarbonylation. Although the hydroxycarbonylation of pure vinyl arene **144** only gave moderate enantioselectivity, almost exclusively branched Flurbiprofen (**143**) could be synthesised using (*R*)-**153 mo**, without the need for an additional ester hydrolysis step. It has been shown that the hydroxycarbonylation reactions of the vinyl arene can be performed in 2-MeTHF which could possibly aid the desired tandem/one-pot process, particularly in the transition between the two reactions. Ideally, just water would need to be added to quench the Grignard reagent and to also be the reactant in the hydroxycarbonylation process.

Table 5.8 – Attempts to couple the Grignard cross-coupling step with hydroxycarbonylation, re-using the Pd-Phanephos catalyst.



Entry ^[a]	Step (i)		Step (ii)		Overall		
	Conversion (i) (%)	144 (i) (%)	Conversion (ii) (%)	Product (ii) (%)	Product (over steps i and ii) (%)	b/l	e.e. (%)
1 ^[b]	> 99	82	13	n.d. ^[c]	-	-	-
2 ^[d]	> 99	73	69	69 [28] ^[e]	50 [21] ^[f]	6.08	41
3 ^{[g][h]}	> 99	76	39	34	16 ^[i]	7.08	47
4 ^{[g][j]}	> 99	77	20	10	6 ^[i]	8.70	18

^[a] Reaction conditions: (i) vinyl tosylate (0.25 mmol), **(R)-153 mo** (0.0025 mmol), 2-fluoro-1,1'-biphenyl magnesium bromide (0.30 mmol in 2-MeTHF, molarity determined by titration before use) in 2-MeTHF (500 μ L), 20 °C, 19 h. (ii) CO (30 bar), H₂O (5.0 mmol), 60 °C, 65 h. Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets after acid-base extraction], b/l ratio determined by ¹H NMR. Enantiomeric excess determined by chiral HPLC. (*S*)-configured catalysts give (*S*)-configured product and *vice versa*.

^[b] Tandem, one-pot process re-using the catalyst: Grignard cross-coupling performed in sealed microwave vial with crimp cap. The reaction was then quenched with H₂O (2.50 mmol) and subsequently hydroxycarbonylated as in (ii).

^[c] Due to overlapping of multiple signals in the ¹H NMR, the product yield was not determined.

^[d] After Grignard cross-coupling the reaction was quenched with H₂O (1.25 mmol) and the reaction mixture was filtered by cannula under argon into a microwave vial with crimp cap equipped with stirrer bar, PTSA·H₂O (0.05 mmol) and LiCl (0.05 mmol). H₂O (1.25 mmol) was added and the reaction mixture subsequently hydroxycarbonylated as in (ii).

^[e] Based on 3-fluoro-4-phenylstyrene.

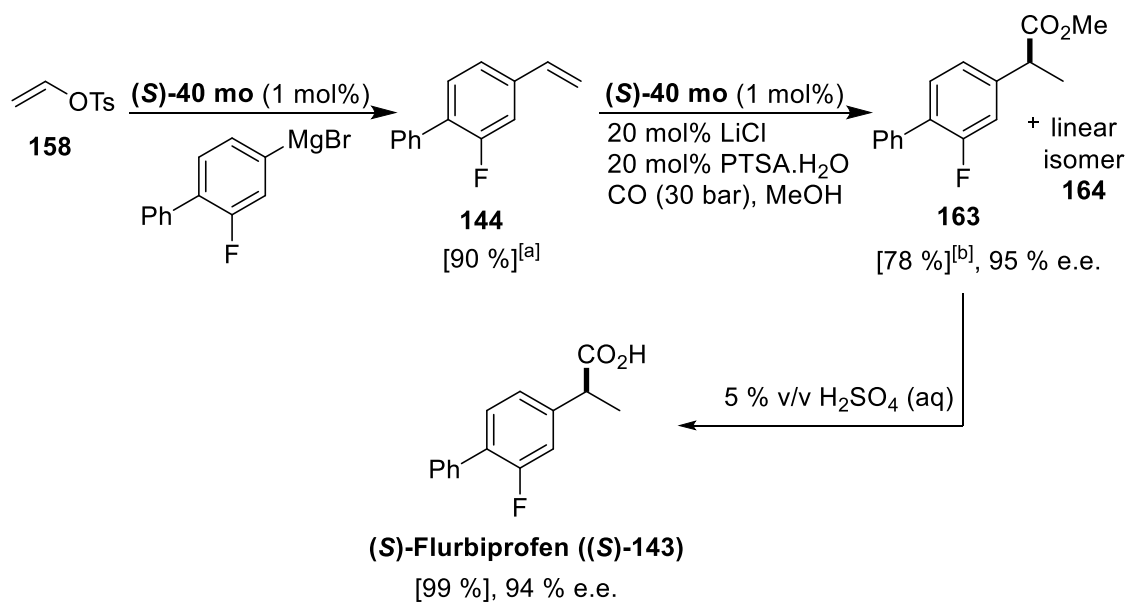
^[f] Based on vinyl tosylate.

^[g] Vinyl tosylate (0.50 mmol) scale. Reaction time for Grignard cross-coupling step (i) = 4 h.

^[h] After Grignard cross-coupling the reaction was quenched with H₂O (2.50 mmol) and the reaction mixture was filtered by cannula under argon into a microwave vial with crimp cap equipped with stirrer bar, PTSA·H₂O (0.50 mmol) and LiCl (0.10 mmol). H₂O (5.00 mmol) was added and the reaction mixture subsequently hydroxycarbonylated as in (ii).

^[i] Compared to external standard, 1,3,5-trimethoxybenzene (0.50 mmol).

^[j] After Grignard cross-coupling the reaction was quenched with H₂O (1.5 mL) and extracted three times with 2-MeTHF (3 x 1.5 mL). The combined organics were concentrated *in vacuo*. 2-MeTHF (1.5 mL) was added and the resulting solution was transferred under argon to a microwave vial with crimp cap equipped with stirrer bar, PTSA·H₂O (0.50 mmol) and LiCl (0.10 mmol). H₂O (5.00 mmol) was added and the reaction mixture subsequently hydroxycarbonylated as in (ii).



Scheme 5.10 – Three-step synthesis of (*S*)-Flurbiprofen (**(S)-143**), from THF-derived vinyl tosylate (**158**). $[\text{PdCl}_2((S)\text{-Xylyl-Phanephos})]$, (*S*)-**40 mo**, was used to synthesise the vinyl arene intermediate **144** and to also perform the subsequent enantioselective methoxycarbonylation. Isolated yields shown are highest values obtained in separate experiments. ^[a] 90 % yield isolated with 2-fluorobiphenyl impurity; total product (**144**) obtained = 68 %. ^[b] Includes 39 % regioisomerically pure branched product **163**.

5.3 - Summary and future work

This chapter has expanded on the discovered capabilities of [PdCl₂(Xylyl-Phanephos)] to catalyse a range of Grignard cross-coupling reactions described in Chapter II. The versatility of Pd-Phanephos catalysts to perform both a Grignard cross-coupling of vinyl tosylate as well as a hydrox-/methoxycarbonylation of the subsequent vinyl arene, 3-fluoro-4-phenylstyrene, has been shown. Although the desired simultaneous control of regio- and enantioselectivity was not possible here, careful choice of Pd-Phanephos catalysts can facilitate either near-perfect regioselectivity (> 99 % branched using [PdCl₂((*R*)-F₂₄-Phanephos)]) in the hydroxycarbonylation (albeit it with only 52 % e.e.), or excellent enantioselectivity (up to 98 % using [PdCl₂((*S*)-Xylyl-Phanephos)]) in the methoxycarbonylation. The high e.e. values are among the best in the literature for asymmetric methoxycarbonylation reactions.

A highly enantioselective synthesis of (*S*)-Flurbiprofen methyl ester can be obtained catalytically in two steps from commercially available 4-bromo-2-fluoro-1,1'-biphenyl using [PdCl₂((*S*)-Xylyl-Phanephos)]. The moderate regioselectivity apparent, results in only moderate yields of the desired branched isomer, but with excellent e.e. This could then be hydrolysed quantitatively to give (*S*)-Flurbiprofen (94 % e.e.).

Exploitation of both the cross-coupling and carbonylative capabilities of Pd-Phanephos catalysts was attempted in tandem/one-pot reactions, transforming vinyl tosylate to the desired drug or prodrug directly. One-pot reactions failed to give any considerable product but cannula filtration after the initial Grignard cross-coupling allowed the catalyst to be re-used for the subsequent carbonylation reaction. Higher yields for the overall process were apparent when the subsequent step was a hydroxycarbonylation using [PdCl₂((*R*)-F₂₄-Phanephos)]. This resulted in moderate enantioselectivity, whilst there was a considerable decrease in regioselectivity relative to the hydroxycarbonylation reaction alone.

Future work should be primarily focussed on trying to find electron-deficient analogues of [PdCl₂((*S*)-Xylyl-Phanephos)]. Increasing branched selectivity without affecting the

key asymmetric transition states leading to excellent enantioselectivities in the methoxycarbonylation of 3-fluoro-4-phenylstyrene would be extremely desirable. A possible solution could be to make the paracyclophane backbone of [PdCl₂((*S*)-Xylyl-Phanephos)] more electron-deficient and thus not modifying the key xylyl functionalities. If it is possible to raise the regioselectivity (and thus desired branched product yields) of [PdCl₂((*S*)-Xylyl-Phanephos)], as well as lower catalyst loadings, this catalytic cross-coupling – methoxycarbonylation methodology could be an extremely attractive possibility for the synthesis of enantiopure Flurbiprofen.

Chapter VI: Conclusions and future work

Methods to successfully functionalise 2-methoxyphenol (guaiacol) derivatives, replacing C_{aryl}-O bonds (constructive deoxygenation), have been developed using transition metal-catalysed cross-coupling, and chelation-assisted nucleophilic aromatic substitution.

Imidazole-sulfonates are an attractive alternative to common phenolic activating groups, such as triflates and tosylates, in regards to cost, stability and toxicity, and were thus used to activate guaiacol. 1,2-dielectrophiles are often regarded as challenging substrates in terms of selectivity. However, since methyl ethers are of such low reactivity, guaiacol-derived 2-methoxyphenyl-1*H*-imidazole-1-sulfonate underwent completely selective functionalisation in palladium-catalysed cross-coupling. Several different Grignard reagents were successfully coupled with 2-methoxyphenyl-1*H*-imidazole-1-sulfonate to give *ortho*-substituted anisole derivatives. [PdCl₂(Xylyl-Phanephos)], previously only utilised as an enantioselective carbonylation catalyst, was found to be an excellent catalyst for this cross-coupling and often showed significantly higher activity than the commonly used [PdCl₂(dppf)]. High yields could be obtained in as little as one hour, as long as no furanic solvents were present. This high activity is likely to be because of the large bite angle present in [PdCl₂(Xylyl-Phanephos)], accelerating reductive elimination and hindering potential side reactions such as β-hydride elimination. Heteroarylzinc reagents could also be successfully reacted with 2-methoxyphenyl-1*H*-imidazole-1-sulfonate, in what were the first examples of Negishi cross-coupling reactions with [PdCl₂(Xylyl-Phanephos)], at loadings as low as 0.25 mol%, showing the versatility of this catalyst for cross-coupling reactions. A range of nickel catalysts were also tested, however it became apparent that they were not as active as the competing uncatalysed nucleophilic attack of the Grignard reagent on the imidazole sulfonate, resulting in significant quantities of guaiacol as a side product.

In order to functionalise through the second, more challenging C_{aryl}-OMe bond, other methods were required. The use of an *ortho*-directing benzoxazole allowed the methyl ether to be substituted by a wide range of Grignard reagents, without the requirement of a metal catalyst, and often under relatively mild conditions. This modified Meyers

reaction was also applied to 2-(2-methoxyphenyl)pyridine, in what was the first example of a 2-pyridyl group being used to facilitate methyl ether cleavage in this manner. There is some precedent for benzoxazole cleavage, and this thesis also presents a new method to create *ortho*-substituted acetophenones by cleavage of benzoxazoles. However, this nucleophilic aromatic substitution methodology is limited by the requirement of an *ortho*-directing group.

To broaden the scope of aryl methyl ether functionalisation, nickel-catalysed Grignard cross-coupling was investigated. The relatively untested $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$ showed high activity for a range of aryl methyl ethers, including challenging *ortho*-substituted anisoles, at the elevated temperature of 100 °C. The reduced steric hindrance invoked by the small cone-angled P^nBu_3 (132 °) was proposed to aid the Grignard cross-coupling of aryl methyl ethers, particularly for *ortho*-substituted anisoles that can suffer from crowded transition states. This was confirmed by a trend in phosphine cone angle showing productivity increasing as ligand cone angles were reduced to 132 °, with the commonly used $[\text{NiCl}_2(\text{PCy}_3)_2]$ often giving poor yields (cone angle of $\text{PCy}_3 = 170$ °). This steric dependence was also extended to N-heterocyclic carbenes (NHCs), with the relatively small ICy giving highest yields. Many different Grignard reagents were tested, with non-sterically encumbered aryl Grignard reagents giving highest yields. These results are of broader interest since bulky ligands dominate catalytic C-C bond forming reactions, but smaller ligands could be worthy of reinvestigation. Even in cases where smaller ligands have not given great results at lower temperatures, it is possible that high turnover numbers (TONs) may be possible at higher temperatures.

The superiority of $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$ over $[\text{NiCl}_2(\text{PCy}_3)_2]$ was also demonstrated in the Grignard cross-coupling of more reactive methoxynaphthalene substrates at 100 °C. It is envisaged that these Grignard cross-coupling reactions proceed through intermediates with one coordinated ligand. $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$ is suggested to only dissociate at 100 °C. Once this has occurred it creates a vacant site and relatively open environment for catalysis to occur. Catalyst loadings could be reduced to 0.25-0.1 mol%, with high yields reported with $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$. Time profiling analysis was carried out on the reaction of 2-methoxynaphthalene with *para*-tolylmagnesium bromide, using both $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$

and $[\text{NiCl}_2(\text{PCy}_3)_2]$ at 0.1 mol%. Induction periods were apparent with both catalysts laying dormant for ~ 16 hours. However, once initiated, both reactions accelerated for substantial periods of time, indicating good stability. $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$ was the more active catalyst. Induction periods were removed by the addition of a Lewis acid, with more normal catalytic profiles apparent, indicating a Lewis acid-assisted mechanism.

The discovery of the capabilities of $[\text{PdCl}_2(\text{Xylyl-Phanephos})]$ to facilitate the Grignard cross-coupling of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (and also aryl bromides), resulted in efforts to use the same catalyst for two different C-C bond forming reactions. (*S*)-Flurbiprofen was successfully synthesised in high enantioselectivity, with $[\text{PdCl}_2((\text{S})\text{-Xylyl-Phanephos})]$ catalysing both the Grignard cross-coupling of THF-derived vinyl tosylate, and subsequent methoxycarbonylation, in the three-step synthesis. Efforts to do this in a tandem/one-pot manner, re-using the catalyst, were not successful, with low yields apparent with the use of either hydroxy- or methoxycarbonylation.

Future work could focus on expanding the scope of nucleophile for the first constructive deoxygenation of 2-methoxyphenyl-1*H*-imidazole-1-sulfonate, with more specific target fine chemicals in mind, and then subsequently utilising the high activity of $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$ to couple through the methyl ether. Finding new processes for this first constructive deoxygenation step that could be catalysed effectively by $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$ could enable a tandem/one-pot process, although it has been shown that it is often difficult to predict and control reactivity in these processes.

The success of $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$ in the Grignard cross-coupling of aryl methyl ethers warrants further investigation. Expanding the scope of both the nucleophile and challenging anisole substrate could be prioritised. This could possibly be achieved by the creation of further hybrid phosphine ligands, this time based on P^nBu_3 , or by combining the success of P^nBu_3 with an NHC ligand such as ICy, in a mixed $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)(\text{ICy})]$ complex. The activity of $[\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2]$ at elevated temperatures in other processes could also be tested as it appears that this catalyst performs well after a certain threshold, that may not have necessarily been previously examined.

Finally, the effect of other Lewis acid additives in the nickel-catalysed cross-coupling of aryl methyl ethers could be investigated, with attempts to lower the catalyst loading required for 2-methoxynaphthalene beyond 0.1 mol%.

Chapter VII: Experimental

7.1 – General information

All catalytic reactions were set up under an argon atmosphere using standard vacuum line techniques and carried out either under argon or carbon monoxide atmospheres. Unless otherwise stated, all glassware used was flame dried and cooled under vacuum before use. When required, solvents were thoroughly degassed before use by either freeze-pump-thaw or rigorous purging with nitrogen. 2-MeTHF (anhydrous $\geq 99\%$, inhibitor free, Sigma-Aldrich) was degassed by freeze-pump-thaw before use. ¹AmOMe (produced by INEOS Oligomers, $\geq 99.0\%$ (GC), Sigma-Aldrich) was dried over CaH₂ and degassed by freeze-pump-thaw before use. CH₂Cl₂, hexane and PhMe were dried using an Innovative Technologies Puresolve 400 solvent purification system. MeOH was refluxed over Mg for 5 h, then distilled under N₂ and stored over 3 angstrom molecular sieves, before being rigorously purged with N₂ prior to use. THF and Et₂O were distilled under Ar from sodium/benzophenone. Reagent grade solvents were used for chromatography and work-up procedures under aerobic conditions. Following aerobic work-up procedures, solvents were removed using a Heidolph Laborota 4000 rotary evaporator.

Unless otherwise stated chemicals were purchased from commercial sources and used without further purification. All purchased organometallic reagents were used as supplied (Aldrich and Acros) and titrated before use, unless stated otherwise. Pd-Phanephos catalysts (Figure 5.4) were available “in house” or prepared according to literature procedure.^{152, 153} Conditions were obtained using an oil bath equipped with a contact thermometer. Analytical thin layer chromatography (TLC) was performed on pre-coated aluminium plates (POLYGRAM SIL G/UV₂₅₄). TLC visualisation was carried out with ultraviolet light (254 nm), followed by staining with a 1% aqueous KMnO₄ solution or vanillin stain. Flash silica chromatography was performed on Kieselgel 60 silica in the solvent system stated.

¹H, ¹³C, ³¹P and ¹⁹F nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (300 MHz ¹H, 75 MHz ¹³C, 121 MHz ³¹P and 282 MHz ¹⁹F), a

Bruker Avance II 400 (400 MHz ^1H , 100 MHz ^{13}C , 162 MHz ^{31}P and 376 MHz ^{19}F), Bruker Ultrashield 500 (500 MHz ^1H , 125 MHz ^{13}C , 202 MHz ^{31}P and 470 MHz ^{19}F) or a Bruker Ultrashield 700 (700 MHz ^1H , 125 MHz ^{13}C , 283 MHz ^{31}P and 470 MHz ^{19}F) spectrometer at ambient temperature in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) relative to the residual solvent as the internal standard. Where appropriate, coupling constants, J , are quoted in Hz and reported high to low and to the nearest 0.1 Hz. Multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), or a combination of these. The abbreviation app is used to denote apparent. Infrared spectra (ν_{max}) were recorded on a Shimadzu IRAffinity-1 using a Pike attenuated total reflectance (ATR) accessory. Only characteristic absorbances are quoted. Melting points were recorded on a Stuart SMP30 melting point apparatus and are uncorrected. Mass spectrometric (m/z) data were acquired by electrospray ionisation (ESI), electron impact (EI) or chemical ionisation (CI) (atmospheric solids analysis probe (ASAP)) either at the University of St Andrews Mass Spectrometry facility or at the EPSRC National Mass Spectrometry Service Centre, Swansea (NMSF-Swansea). At the University of St Andrews, high resolution ESI was carried out on a Micromass LCT spectrometer and high resolution EI and CI were carried out on a Micromass GCT spectrometer. At the EPSRC National Mass Spectrometry Service Centre, high resolution EI was carried out on a Waters GCT Premier and high resolution CI on a Waters Xevo G2-S spectrometer with ASAP probe. Values are quoted as a ratio of mass to charge in Daltons. Elemental analyses were carried out by the Elemental Analysis Service at the London Metropolitan University. X-ray crystallography, and refinement of data was performed by Dr David Cordes and Prof. Alexandra Slawin at the University of St Andrews. X-ray diffraction data were collected at either 173 K or 93 K by using a Rigaku FR-X Ultrahigh brilliance Microfocus RA generator/confocal optics and Rigaku XtaLAB P200 system, with Mo $K\alpha$ radiation ($\lambda = 0.71075 \text{ \AA}$). Optical rotations were measured on a Perkin Elmer 241-polarimeter at room temperature using a 1 mL cell with a 1 dm path length, using the sodium D-line, with concentrations reported in grams per 100 mL of solvent. HPLC analysis was carried out using a Varian Prostar operated by Galaxie workstation PC software. Gas chromatography was performed on a Thermo Scientific Trace GC Ultra equipment (split/splitless injector, Restek Rtx[®] -1, 100 % dimethyl polysiloxane column with 30 m

× 0.25 mm × 0.25 μm dimensions, carrier gas – He, F.I.D. detector). Data was analysed using a Chromeleon data system.

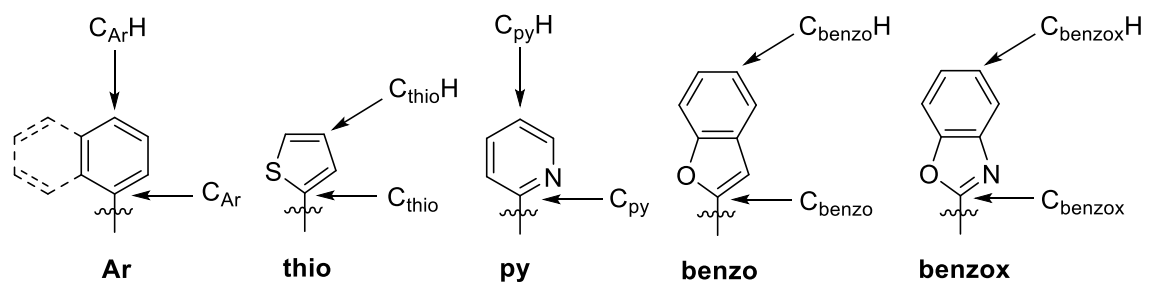
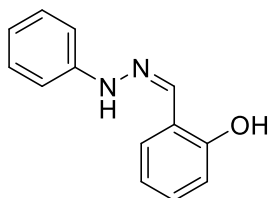


Figure 7.1 – Key for NMR spectroscopy interpretation.

7.2 – Preparation of organometallic reagents

7.2.1 – Preparation of titrating agent, salicylaldehyde phenylhydrazone (**165**):



Prepared following a literature procedure.³⁰⁰ To a solution of phenylhydrazine (5.8 mL, 42.89 mmol) in EtOH (20 mL) was added a solution of salicylaldehyde (6.6 g, 42.89 mmol) in EtOH (30 mL). The reaction was stirred at room temperature for 30 minutes and then cooled to -15 °C. The precipitate was collected by vacuum filtration, washed with ice cold EtOH (20 mL) and dried under reduced pressure to give salicylaldehyde phenylhydrazone (**165**) (7.5 g, 89 %) as an off-white solid with spectroscopic data in agreement with the literature.³⁰⁰

mp 144-145 °C {lit³⁰¹ 139-141 °C}; δ_{H} (400 MHz, CDCl₃) 10.89 (1H, br s, OH), 7.83 (1H, s, CH), 7.49 (1H, br s, NH), 7.34–7.28 (2H, m, C_{Ar}H), 7.25 (1H, ddd, *J* 8.2, 7.5, 1.7, C_{Ar}H), 7.15 (dd, *J* 7.7, 1.7, CHC_{Ar}C_{Ar}H), 7.04 (1H, dd, *J* 8.2, 1.1, OC_{Ar}C_{Ar}H), 7.03–6.97 (2H, m, C_{Ar}H), 6.96–6.87 (2H, m, C_{Ar}H); δ_{C} (100 MHz, CDCl₃) 157.1 (C_{Ar}O), 143.5 (C_{Ar}NH), 141.3 (CH), 130.1 (C_{Ar}H), 129.7 (2C, C_{Ar}H), 129.5 (CHC_{Ar}C_{Ar}H), 121.0 (C_{Ar}H), 119.6 (C_{Ar}H), 118.6 (NHC_{Ar}), 116.7 (OC_{Ar}C_{Ar}H), 112.8 (2C, HNC_{Ar}C_{Ar}H); *m/z* HRMS (ESI⁺) C₁₃H₁₃ON₂⁺ ([M+H]⁺) requires 213.1022; found 213.1019 (–1.4 ppm).

7.2.2 – Preparation of Grignard reagents

When required, Grignard reagents were prepared by reacting magnesium turnings, activated by a crystal of iodine, in anhydrous and degassed etheric solvents with the required halide.

Ph₂PMgBr (**72**) was prepared by reacting potassium diphenylphosphide with anhydrous magnesium bromide in anhydrous and degassed THF.

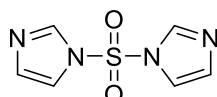
7.2.3 – Preparation of benzofuran-2-yllithium (**61**) and benzofuran-2-ylzinc chloride (**62**)

To a solution of benzofuran in anhydrous and degassed THF was slowly added *n*BuLi. This yielded benzofuran-2-yllithium (**61**), which could then be reacted further with the addition of anhydrous zinc chloride (1.2 equiv.) to give benzofuran-2-ylzinc chloride (**62**).

7.3 – Transition metal-catalysed Grignard cross-coupling of aryl/vinyl electrophiles

7.3.1 – Preparation of substrates

1,1'-sulfonyldiimidazole (**30**):



Prepared following a literature procedure.³⁰² To a 0 °C solution of imidazole (10.0 g, 147.0 mmol) in CH₂Cl₂ (105 mL), a solution of sulfonyl chloride (2.5 mL, 30.8 mmol) in CH₂Cl₂ (14 mL) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 16 hours. The obtained mixture was filtered and concentrated under reduced pressure. The resulting solid (6.41 g) was crystallised from isopropanol (50 mL) to give white needles which were filtered, washed with cold isopropanol and dried under reduced pressure to give 1,1'-sulfonyldiimidazole (**30**) (4.69 g, 77 %), with spectroscopic data in accordance with the literature.³⁰³

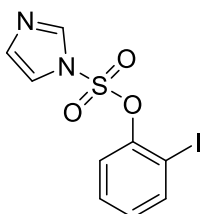
mp 139-140 °C {lit³⁰⁴ 143-144 °C}; δ_{H} (500 MHz, CDCl₃) 8.04-8.03 (2H, m, N=CHN), 7.31 (2H, m, SO₂NCH=CH), 7.16-7.15 (2H, m, SO₂NCH=CH); δ_{C} (125 MHz, CDCl₃) 136.7 (2C, N=CHN), 132.6 (2C, SO₂NCH=CH), 117.5 (2C, SO₂NCH=CH); m/z HRMS (ESI⁺) C₆H₇O₂N₄S⁺ ([M+H]⁺) requires 199.0284; found 199.0283 (–0.5 ppm).

7.3.1.1 – General procedure 1: synthesis of aryl imidazole-sulfonates

To a solution of *ortho*-substituted phenol in THF was added caesium carbonate (0.5 equiv.) then 1,1'-sulfonyldiimidazole (**30**) (2.0 equiv.). The reaction mixture was refluxed for 16 hours. Reaction completion was confirmed by TLC analysis and the reaction mixture was then concentrated under reduced pressure. EtOAc was added and the mixture was cooled to 0 °C and saturated aqueous ammonium chloride solution was added. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organics were washed with water and then brine. The organic layer was dried

over sodium sulfate and then concentrated under reduced pressure to give a crude solid which was purified by column chromatography on silica gel.

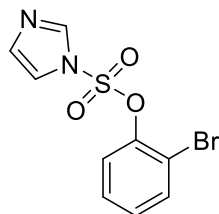
2-iodophenyl-1*H*-imidazole-1-sulfonate (31):



Prepared following **general procedure 1** at 66 °C for 16 hours with 2-iodophenol (128 μ L, 1.14 mmol), THF (5 mL), caesium carbonate (185 mg, 0.57 mmol) and 1,1'-sulfonyldiimidazole (**30**) (450 mg, 2.28 mmol). Purification *via* column chromatography on silica gel (eluent EtOAc:hexane, 40:60) gave 2-iodophenyl-1*H*-imidazole-1-sulfonate (**31**) as a white crystalline solid (378 mg, 95 %).

mp 71-74 °C; ν_{max} (ATR) 3138 (w), 3125 (w), 1423 (m), 1148 (m), 1053 (m), 880 (m), 864 (s), 777 (m), 743 (s), 608 (s), 602 (s); δ_{H} (500 MHz, CDCl₃) 7.89-7.88 (1H, m, N=CHN), 7.84 (1H, dd, *J* 7.9, 1.6, C_{Ar}HC_{Ar}I), 7.38 (1H, ddd, *J* 8.2, 7.5, 1.6, C_{Ar}H), 7.30-7.28 (1H, m, NCH=CH), 7.19-7.16 (1H, m, NCH=CH), 7.09 (1H, ddd, *J* 7.9, 7.5, 1.5, C_{Ar}H), 7.05 (1H, dd, *J* 8.2, 1.5, C_{Ar}HC_{Ar}O); δ_{C} (100 MHz, CDCl₃) 149.8 (C_{Ar}O), 140.8 (C_{Ar}HC_{Ar}I), 137.7 (NCH=N), 131.5 (HC=CHN), 130.2 (C_{Ar}H), 129.9 (C_{Ar}H), 122.3 (C_{Ar}HC_{Ar}O), 118.9 (NCH=CH), 89.3 (C_{Ar}I); *m/z* HRMS (ESI⁺) C₉H₈O₃N₂IS⁺ ([M+H]⁺) requires 350.9295; found 350.9292 (-0.9 ppm).

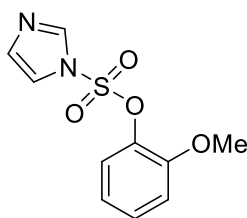
2-bromophenyl-1*H*-imidazole-1-sulfonate (**32**):



Prepared following **general procedure 1** at 66 °C for 20 hours with 2-bromophenol (528 μ L, 4.56 mmol), THF (20 mL), caesium carbonate (740 mg, 2.28 mmol) and 1,1'-sulfonyldiimidazole (**30**) (1.80 g, 9.12 mmol). Purification *via* column chromatography on silica gel (eluent EtOAc:hexane, 30:70) gave 2-bromophenyl-1*H*-imidazole-1-sulfonate (**32**) as a white crystalline solid (1.16 g, 84 %).

mp 61-64 °C; ν_{\max} (ATR) 3138 (w), 3117 (w), 1425 (m), 1150 (m), 1042 (m), 866 (m), 745 (m), 611 (s), 602 (s); δ_{H} (500 MHz, CDCl_3) 7.85-7.84 (1H, m, N=CHN), 7.61 (1H, dd, J 8.0, 1.6, $\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{Br}$), 7.35 (1H, td, J 8.0, 1.6, $\text{C}_{\text{Ar}}\text{H}$), 7.29-7.28 (1H, m, NCH=CH), 7.23 (1H, td, J 8.0, 1.5, $\text{C}_{\text{Ar}}\text{H}$), 7.17-7.16 (1H, m, NCH=CH), 7.10 (1H, dd, J 8.0, 1.5, $\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{O}$); δ_{C} (125 MHz, CDCl_3) 146.6 ($\text{C}_{\text{Ar}}\text{O}$), 137.5 (NCH=N), 134.5 ($\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{Br}$), 131.5 (HC=CHN), 129.7 ($\text{C}_{\text{Ar}}\text{H}$), 129.2 ($\text{C}_{\text{Ar}}\text{H}$), 123.3 ($\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{O}$), 118.7 (NCH=CH), 116.2 ($\text{C}_{\text{Ar}}\text{Br}$); m/z HRMS (ESI⁺) $\text{C}_9\text{H}_8\text{O}_3\text{N}_2^{79}\text{BrS}^+$ ($[\text{M}+\text{H}]^+$) requires 302.9434; found 302.9430 (-1.3 ppm).

2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**):

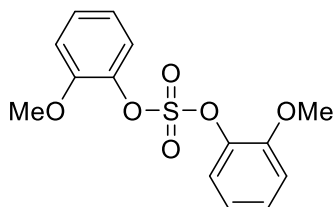


Prepared following **general procedure 1** at room temperature for 16 hours with 2-methoxyphenol (2.50 g, 20.14 mmol), THF (50 mL), caesium carbonate (3.28 g, 10.07 mmol) and 1,1'-sulfonyldiimidazole (**30**) (7.40 g, 37.34 mmol). Purification *via* column chromatography on silica gel (eluent EtOAc:hexane, 30:70) gave 2-methoxyphenyl-1*H*-

imidazole-1-sulfonate (**33**) as a white crystalline solid (4.81 g, 94 %), with spectroscopic data in accordance with the literature.³⁰⁵

mp 71-72 °C; δ_{H} (500 MHz, CDCl_3) 7.82-7.79 (1H, m, N=CHN), 7.31 (1H, ddd, J 8.3, 7.8, 1.5, $\text{C}_{\text{Ar}}\text{H}$), 7.27-7.25 (1H, m, NCH=CH), 7.15-7.09 (2H, m, NCH=CH, $\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{OS}$), 6.96 (1H, td, J 7.8, 1.5, $\text{C}_{\text{Ar}}\text{H}$), 6.91 (1H, dd, J 8.3, 1.5, $\text{CH}_3\text{OC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 3.60 (3H, s, OCH_3); δ_{C} (125 MHz, CDCl_3) 151.5 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 137.8 ($\text{C}_{\text{Ar}}\text{O}$), 137.7 (NCH=N), 130.5 ($\text{HC}=\text{CHN}$), 129.6 ($\text{C}_{\text{Ar}}\text{H}$), 123.6 ($\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{O}$), 120.9 ($\text{C}_{\text{Ar}}\text{H}$), 119.0 (NCH=CH), 112.7 ($\text{CH}_3\text{OC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 55.7 (OCH_3); m/z HRMS (ESI⁺) $\text{C}_{10}\text{H}_{11}\text{O}_4\text{N}_2\text{S}^+$ ($[\text{M}+\text{H}]^+$) requires 255.0434; found 255.0430 (-1.6 ppm).

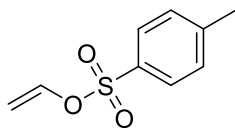
bis(2-methoxyphenyl)sulfate (59):



Prepared following a literature procedure,¹⁶⁰ and **general procedure 1** at 66 °C for 16 hours with 2-methoxyphenol (**28**) (3.72 g, 30.00 mmol), THF (10 mL), caesium carbonate (3.26 g, 10.00 mmol) and 1,1'-sulfonyldiimidazole (**30**) (1.98 g, 10.00 mmol). Purification *via* column chromatography on silica gel (eluent CH_2Cl_2) gave *bis*(2-methoxyphenyl)sulfate (**59**) as a white crystalline solid (2.11 g, 68 %), with spectroscopic data in accordance with the literature.¹⁶⁰

mp 55-56 °C; δ_{H} (500 MHz, CDCl_3) 7.42 (2H, dd, J 8.1, 1.6, $\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{OS}$), 7.28 (2H, ddd, J 8.3, 7.6, 1.6, $\text{C}_{\text{Ar}}\text{H}$), 7.02 (2H, dd, J 8.3, 1.5, $\text{CH}_3\text{OC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 6.96 (2H, ddd, J 8.1, 7.6, 1.5, $\text{C}_{\text{Ar}}\text{H}$), 3.85 (6H, s, OCH_3); δ_{C} (125 MHz, CDCl_3) 151.6 (2C, $\text{C}_{\text{Ar}}\text{OCH}_3$), 139.7 (2C, $\text{C}_{\text{Ar}}\text{O}$), 128.5 (2C, $\text{C}_{\text{Ar}}\text{H}$), 122.8 (2C, $\text{C}_{\text{Ar}}\text{H}$), 120.8 (2C, $\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{O}$), 113.2 (2C, $\text{CH}_3\text{OC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 56.1 (2C, OCH_3); m/z HRMS (ESI⁺) $\text{C}_{14}\text{H}_{14}\text{O}_6\text{SNa}^+$ ($[\text{M}+\text{Na}]^+$) requires 333.0403; found 333.0399 (-1.2 ppm).

vinyl tosylate (158):

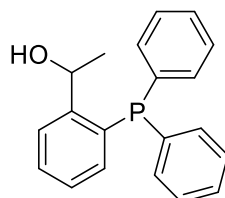


Prepared following a modified literature procedure.²⁹⁴ *n*BuLi (15.2 mL, 34.13 mmol, 2.3 M in hexane) was slowly added to dry and degassed THF (35 mL) under an argon atmosphere and the reaction mixture was stirred for 16 hours at 35 °C. The solution was then cooled to -78 °C and a solution of *p*-toluenesulfonyl chloride (5.01 g, 26.28 mmol) in THF (10 mL) was added dropwise over 15 minutes. The reaction mixture was stirred for 30 minutes, allowed to warm to room temperature, and then stirred for another 30 minutes. MeOH (5.0 mL) was slowly added and the mixture was concentrated under reduced pressure. Et₂O (140 mL) was added and the mixture was added to an ice/saturated aqueous NaHCO₃ mixture (90 mL). The aqueous layer was extracted with Et₂O (3 x 20 mL) and the combined organics were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification *via* column chromatography on silica gel (eluent EtOAc:hexane, 20:80) gave vinyl tosylate (**158**) as a colourless oil (1.01 g, 19 %), with spectroscopic data in accordance with the literature.²⁹⁴

δ_{H} (500 MHz, CDCl₃) 7.79 (2H, d, *J* 8.3, SO₂C_{Ar}C_{Ar}H), 7.36 (2H, d, *J* 8.1, CH₃C_{Ar}C_{Ar}H), 6.60 (1H, dd, *J* 13.5, 5.9, CH₂CH), 4.89 (1H, dd, *J* 13.5, 2.5, CH'H''CH), 4.68 (1H, dd, *J* 5.9, 2.5, CH'H''CH), 2.45 (3H, s, C_{Ar}CH₃); δ_{C} (125 MHz, CDCl₃) 145.5 (SO₂C_{Ar}), 141.7 (CH₂CH), 132.5 (C_{Ar}CH₃), 130.0 (2C, CH₃C_{Ar}C_{Ar}H), 128.1 (2C, SO₂C_{Ar}C_{Ar}H), 102.8 (CH₂CH), 21.7 (C_{Ar}CH₃); *m/z* HRMS (ESI⁺) C₉H₁₀O₃SNa⁺ ([M+Na]⁺) requires 221.0243; found 221.0239 (-1.8 ppm).

7.3.2 – Preparation of hydroxyphosphine ligand

1-(2-diphenylphosphinophenyl)ethanol (**1**):



To a 0 °C solution of 2-(diphenylphosphino)benzaldehyde (495 mg, 1.71 mmol) in dry and degassed Et₂O (6 mL) was added MeMgBr (1.20 mL, 2.05 mmol, 1.7 M in Et₂O) dropwise under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Anhydrous and degassed MeOH (1 mL) was added and the mixture was concentrated under reduced pressure. The resulting residue was washed with Et₂O (2 x 6 mL) and filtered by cannula under argon. The filtrate was then concentrated under reduced pressure to give 1-(2-diphenylphosphinophenyl)ethanol (**1**) as a white solid (288.6 mg, 55 %), with spectroscopic data in agreement with the literature.⁶⁵

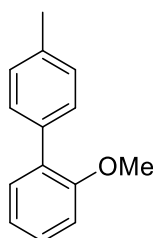
mp 93-95 °C {lit⁶⁵ 95-96 °C}; δ_{H} (500 MHz, CDCl₃) 7.65 (1H, ddd, J 7.7, 1.3, $J_{\text{H-P}}$ 4.2, HCC_{Ar}C_{Ar}H), 7.40 (1H, td, J 7.7, 1.3, C_{Ar}H), 7.36-7.32 (6H, m, C_{Ar}H), 7.30 – 7.24 (4H, m, C_{Ar}H), 7.18 (1H, td, J 7.7, 1.4, C_{Ar}H), 6.89 (1H, ddd, J 7.7, 1.4, $J_{\text{H-P}}$ 4.5, PC_{Ar}C_{Ar}H), 5.64 (1H, quint d, J 6.4, 3.0, CH), 2.02 (1H, d, J 3.0, OH), 1.34 (3H, d, J 6.4, CH₃); δ_{P} (202 MHz, CDCl₃) -17.2; δ_{C} (125 MHz, CDCl₃) 150.2 (d, $J_{\text{C-P}}$ 22.1, C_{Ar}), 136.9 (d, $J_{\text{C-P}}$ 9.7, C_{Ar}), 136.3 (d, $J_{\text{C-P}}$ 9.3, C_{Ar}), 134.2 (2C, d, $J_{\text{C-P}}$ 19.9, C_{Ar}H), 134.0 (C_{Ar}), 133.8 (2C, d, $J_{\text{C-P}}$ 19.5, C_{Ar}H), 133.6 (PC_{Ar}C_{Ar}H), 129.7 (C_{Ar}H), 129.1 (C_{Ar}H), 128.9 (C_{Ar}H), 128.8 (2C, d, $J_{\text{C-P}}$ 4.7, C_{Ar}H), 128.7 (2C, d, $J_{\text{C-P}}$ 5.1, C_{Ar}H), 127.8 (C_{Ar}H), 125.7 (d, $J_{\text{C-P}}$ 5.4, HCC_{Ar}C_{Ar}H), 67.6 (d, $J_{\text{C-P}}$ 26.1, CH), 24.5 (CH₃); m/z HRMS (ESI⁺) C₂₀H₂₀OP⁺ ([M+H]⁺) requires 307.1246; found 307.1241 (-1.6 ppm).

7.3.3 – General procedure 2: transition metal-catalysed Grignard cross-coupling of aryl/vinyl electrophiles

An aryl or vinyl electrophile and an internal standard were added to a flame dried Schlenk flask under an inert atmosphere. Degassed solvent was then added to make a solution. A t_0 sample (approximately 10 μL) was taken and analysed by ^1H NMR (to calibrate the ratio of internal standard to starting material). The desired transition metal catalyst was added to a second flame dried Schlenk flask and placed under an inert atmosphere. Solvent was then added. The solution containing the electrophile and internal standard was added to the catalyst solution *via* syringe. The requisite Grignard solution was added dropwise over 30 minutes. The reaction mixture was stirred at a specific temperature for a specific time; tracking the reaction progress by ^1H NMR. Following reaction completion (as determined by analysis of the ^1H NMR), the mixture was allowed to cool to ambient temperature and H_2O , saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ or $\text{HCl}_{(\text{aq})}$ (1.0 M) was added. The aqueous phase was extracted three times with ethyl acetate or diethyl ether, dried over sodium sulfate and concentrated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel.

7.3.4 – Product data

2-methoxy-4'-methyl-1,1'-biphenyl (46):

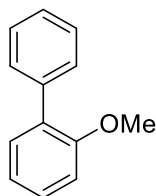


Following **General Procedure 2**, at 50 $^{\circ}\text{C}$ for 17 hours with 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**) (127.1 mg, 0.50 mmol), 1-methylnaphthalene (60 μL , 0.21 mmol), $[\text{PdCl}_2((S)\text{-Xylyl-Phanephos})]$ (4.3 mg, 0.005 mmol), $^i\text{AmOMe}$ (1.0 mL) and *p*-TolMgBr (1.2 mL, 0.60 mmol, 0.5 M in Et_2O). Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (5 mL) was added upon work-up and purification *via* column chromatography on silica gel (eluent

petrol:EtOAc, 100:0 to 99:1) gave 2-methoxy-4'-methyl-1,1'-biphenyl (**46**) as a white solid (62.2 mg, 63 %), with spectroscopic data in accordance with the literature.³⁰⁶

mp 81-82 °C {lit³⁰⁶ 81-82 °C}; δ_{H} (500 MHz, CDCl₃) 7.43 (2H, d, *J* 7.8, C_{Ar}H), 7.31 (2H, m, C_{Ar}H), 7.22 (2H, d, *J* 7.8, H₃CC_{Ar}C_{Ar}H), 7.02 (1H, td, *J* 7.4, 1.1, C_{Ar}H), 6.98 (1H, dd, *J* 8.7, 1.1, OC_{Ar}C_{Ar}H), 3.81 (3H, s, OCH₃), 2.39 (3H, s, CH₃); δ_{C} (100 MHz, CDCl₃) 156.6 (C_{Ar}O), 136.7 (C_{Ar}C_{Ar}), 135.7 (C_{Ar}C_{Ar}), 130.9 (C_{Ar}H), 130.8 (C_{Ar}CH₃), 129.5 (2C, H₃CC_{Ar}C_{Ar}H), 128.9 (2C, C_{Ar}H), 128.5 (C_{Ar}H), 120.9 (C_{Ar}H), 111.3 (OC_{Ar}C_{Ar}H), 55.7 (OCH₃), 21.3 (CH₃); *m/z* HRMS (ESI⁺) C₁₄H₁₄ONa⁺ ([M+Na]⁺) requires 221.0937; found 221.0930 (-3.2 ppm).

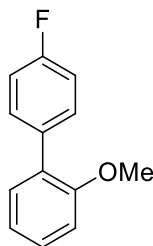
2-methoxybiphenyl (**47**):



Following **General Procedure 2**, at 50 °C for 16 hours with 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**) (127.1 mg, 0.50 mmol), 1-methylnaphthalene (60 μ L, 0.21 mmol), [PdCl₂(*rac*-Xylyl-Phanephos)] (4.3 mg, 0.005 mmol), ^tAmOMe (1.0 mL) and PhMgBr (350 μ L, 0.60 mmol, 1.7 M in Et₂O). Saturated NH₄Cl_(aq) (5 mL) was added upon work-up and purification *via* column chromatography on silica gel (eluent petrol:EtOAc, 100:0 to 98:2) gave 2-methoxybiphenyl (**47**) as a colourless oil (59.5 mg, 65 %), with spectroscopic data in accordance with the literature.³⁰⁷

δ_{H} (500 MHz, CDCl₃) 7.57–7.52 (2H, m, C_{Ar}H), 7.45–7.40 (2H, m, C_{Ar}H), 7.36–7.31 (3H, m, C_{Ar}H), 7.04 (1H, td, *J* 7.5, 1.1, C_{Ar}H), 7.00 (1H, dd, *J* 8.7, 1.1, OC_{Ar}C_{Ar}H), 3.82 (3H, s, OCH₃); δ_{C} (125 MHz, CDCl₃) 156.6 (C_{Ar}O), 138.7 (C_{Ar}C_{Ar}), 131.0 (C_{Ar}H), 130.8 (C_{Ar}C_{Ar}), 129.7 (2C, C_{Ar}H), 128.7 (C_{Ar}H), 128.1 (2C, C_{Ar}C_{Ar}H), 127.1 (C_{Ar}H), 120.9 (C_{Ar}H), 111.3 (OC_{Ar}C_{Ar}H), 55.7 (OCH₃); *m/z* HRMS (EI⁺) C₁₃H₁₂O⁺ ([M]⁺) requires 184.0888; found 184.0884 (-2.2 ppm).

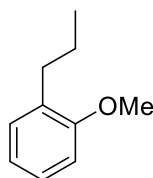
4'-fluoro-2-methoxy-1,1'-biphenyl (**48**):



Following **General Procedure 2**, at 50 °C for 16 hours with 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**) (127.1 mg, 0.50 mmol), 1-methylnaphthalene (60 μ L, 0.21 mmol), [PdCl₂((*S*)-Xylyl-Phanephos)] (4.3 mg, 0.005 mmol), ^tAmOMe (1.0 mL) and 4-FPhMgBr (1.2 mL, 0.60 mmol, 0.5 M in Et₂O). Saturated NH₄Cl_(aq) (5 mL) was added upon work-up and purification *via* column chromatography on silica gel (eluent petrol:EtOAc, 100:0 to 99:1) gave 4'-fluoro-2-methoxy-1,1'-biphenyl (**48**), as a white solid (63.8 mg, 63 %), with spectroscopic data in accordance with the literature.³⁰⁸

mp 58-59 °C {lit³⁰⁹ 58 °C}; δ_{H} (500 MHz, CDCl₃) 7.54–7.46 (2H, m, C_{Ar}C_{Ar}H), 7.34 (1H, ddd, *J* 8.2, 7.4, 1.8, C_{Ar}H), 7.30 (1H, dd, *J* 7.4, 1.8, C_{Ar}C_{Ar}H), 7.14–7.07 (2H, m, FC_{Ar}C_{Ar}H), 7.04 (1H, td, *J* 7.4, 1.1, C_{Ar}H), 6.99 (1H, dd, *J* 8.2, 1.1, OC_{Ar}C_{Ar}H), 3.82 (3H, s, OCH₃); δ_{F} (470 MHz, CDCl₃) –115.9; δ_{C} (125 MHz, CDCl₃) 162.1 (d, *J*_{C-F} 245.7, C_{Ar}F), 156.5 (C_{Ar}O), 134.5 (d, *J*_{C-F} 3.2, C_{Ar}C_{Ar}), 131.2 (2C, d, *J*_{C-F} 8.1, C_{Ar}C_{Ar}H), 130.9 (C_{Ar}C_{Ar}H), 129.8 (C_{Ar}C_{Ar}), 128.9 (C_{Ar}H), 121.0 (C_{Ar}H), 115.0 (2C, d, *J*_{C-F} 21.2, FC_{Ar}C_{Ar}H), 111.3 (OC_{Ar}C_{Ar}H), 55.7 (OCH₃); *m/z* HRMS (EI⁺) C₁₃H₁₁FO⁺ ([M]⁺) requires 202.0794; found 202.0796 (+ 1.0 ppm).

1-methoxy-2-propylbenzene (**49**):

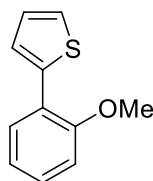


Following **General Procedure 2**, at 50 °C for 18 hours with 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**) (63.6 mg, 0.25 mmol), 1-methylnaphthalene (30 μ L, 0.11 mmol), [PdCl₂(*rac*-Xylyl-Phanephos)] (2.2 mg, 0.0025 mmol), ^tAmOMe (500 μ L) and

¹¹⁹PrMgCl (190 μ L, 0.30 mmol, 1.6 M in Et₂O). Saturated NH₄Cl_(aq) (2.5 mL) was added upon work-up and purification *via* column chromatography on silica gel (eluent petrol:EtOAc, 100:0 to 99:2) gave 1-methoxy-2-propylbenzene (**49**) as a colourless oil (15.1 mg, 40 %), with spectroscopic data in accordance with the literature.³¹⁰

δ_{H} (500 MHz, CDCl₃) 7.18 (1H, td, *J* 7.7, 1.8, C_{Ar}H), 7.14 (1H, dd, *J* 7.7, 1.8, C_{Ar}C_{Ar}H), 6.89 (1H, td, *J* 7.7, 1.1, C_{Ar}H), 6.85 (1H, dd, *J* 7.7, 1.1, OC_{Ar}C_{Ar}H), 3.83 (3H, s, OCH₃), 2.60 (2H, t, *J* 7.5, C_{Ar}CH₂), 1.62 (2H, app. hex, *J* 7.5, CH₂CH₃), 0.96 (3H, t, *J* 7.5, CH₂CH₃); δ_{C} (125 MHz, CDCl₃) 157.6 (C_{Ar}O), 131.2 (C_{Ar}CH₂), 130.0 (C_{Ar}C_{Ar}H), 126.9 (C_{Ar}H), 120.4 (C_{Ar}H), 110.3 (OC_{Ar}C_{Ar}H), 55.4 (OCH₃), 32.4 (C_{Ar}CH₂), 23.1 (CH₂CH₃), 14.3 (CH₂CH₃); *m/z* HRMS (EI⁺) C₁₀H₁₄O⁺ ([M]⁺) requires 150.1045; found 150.1046 (+ 0.7 ppm).

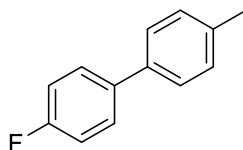
2-(2-methoxyphenyl)thiophene (**50**):



Following **General Procedure 2**, at 50 °C for 4 hours with 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**) (127.1 mg, 0.50 mmol), 1-methylnaphthalene (60 μ L, 0.21 mmol), [PdCl₂(*rac*-Xylyl-Phanephos)] (4.3 mg, 0.005 mmol), ^tAmOMe (1.0 mL) and 2-thienylMgBr (667 μ L, 0.60 mmol, 0.9 M in Et₂O). Saturated NH₄Cl_(aq) (5 mL) was added upon work-up and purification *via* column chromatography on silica gel (eluent petrol:EtOAc, 100:0 to 95:5) gave 2-(2-methoxyphenyl)thiophene (**49**) as a yellow oil (74.8 mg, 79 %), with spectroscopic data in accordance with the literature.³¹¹

δ_{H} (500 MHz, CDCl₃) 7.68 (1H, dd, *J* 7.7, 1.7, C_{Ar}C_{Ar}H), 7.53 (1H, dd, *J* 3.7, 1.2, C_{thio}H), 7.35 (1H, dd, *J* 5.1, 1.2, C_{thio}H), 7.29 (1H, ddd, *J* 8.2, 7.4, 1.7, C_{Ar}H), 7.12 (1H, dd, *J* 5.2, 3.7, C_{thio}H), 7.05–6.99 (2H, m, C_{Ar}H, OC_{Ar}H), 3.95 (3H, s, OCH₃); δ_{C} (125 MHz, CDCl₃) 155.7 (C_{Ar}O), 139.6 (C_{thio}), 128.7 (C_{Ar}C_{Ar}H), 128.5 (C_{Ar}H), 126.9 (C_{thio}H), 125.5 (C_{thio}H), 125.5 (C_{thio}H), 123.4 (C_{Ar}C_{thio}), 121.0 (C_{Ar}H), 111.7 (OC_{Ar}C_{Ar}H), 55.7 (OCH₃); *m/z* HRMS (ESI⁺) C₁₁H₁₁OS⁺ ([M+H]⁺) requires 191.0525; found 191.0524 (-0.5 ppm).

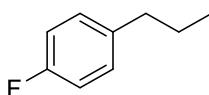
4-fluoro-4'-methyl-1,1'-biphenyl (**52**):



Following **General Procedure 2**, at 20 °C for 4 hours with 1-bromo-4-fluorobenzene (110 μ L, 1.00 mmol), 1-methylnaphthalene (120 μ L, 0.84 mmol), [PdCl₂((S)-Xylyl-Phanephos)] (8.7 mg, 0.01 mmol), 2-MeTHF (1.0 mL) and *p*-TolMgBr (2.2 mL, 1.10 mmol, 0.5 M in Et₂O). HCl_(aq) (5 mL, 1.0 M) was added upon work-up and purification *via* column chromatography on silica gel (eluent hexane) gave 4-fluoro-4'-methyl-1,1'-biphenyl (**52**) as a white solid (111.7 mg, 60 %), with spectroscopic data in agreement with the literature.³¹²

mp 77-78 °C {lit³¹² 73-75 °C}; δ_{H} (500 MHz, CDCl₃) 7.57-7.53 (2H, m, C_{Ar}H), 7.47 (2H, d, *J* 8.0, C_{Ar}H), 7.27 (2H, d, *J* 8.0, H₃CC_{Ar}C_{Ar}H), 7.17-7.11 (2H, m, FC_{Ar}C_{Ar}H), 2.42 (3H, s, C_{Ar}CH₃); δ_{F} (470 MHz, CDCl₃) -116.3; δ_{C} (125 MHz, CDCl₃) 162.4 (d, *J*_{C-F} 245.5, C_{Ar}F), 137.5 (C_{Ar}C_{Ar}), 137.4 (d, *J*_{C-F} 2.9, C_{Ar}C_{Ar}), 137.2 (C_{Ar}CH₃), 129.7 (2C, C_{Ar}H), 128.6 (2C, d, *J*_{C-F} 7.8, C_{Ar}H), 127.0 (2C, C_{Ar}H), 115.7 (2C, d, *J*_{C-F} 21.5, FC_{Ar}C_{Ar}H), 21.2 (CH₃); *m/z* HRMS (EI⁺) C₁₃H₁₁F⁺ ([M]⁺) requires 186.0845; found 186.0839 (-3.2 ppm).

1-fluoro-4-propylbenzene (**53**):

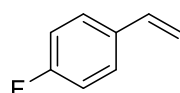


Following **General Procedure 2**, at 20 °C for 24 hours with 1-bromo-4-fluorobenzene (110 μ L, 1.00 mmol), 1-methylnaphthalene (120 μ L, 0.84 mmol), [PdCl₂((S)-Xylyl-Phanephos)] (8.7 mg, 0.01 mmol), 2-MeTHF (1.0 mL) and ⁿPrMgCl (600 μ L, 1.20 mmol, 2.0 M in Et₂O). HCl_(aq) (5 mL, 1.0 M) was added upon work-up and purification *via* column chromatography on silica gel (eluent CH₂Cl₂:hexane 70:30) gave 1-fluoro-4-propylbenzene (**53**) as a pale yellow oil (102.7 mg, 74 %).

ν_{max} (ATR) 2959 (w), 2928 (w), 1508 (m), 1499 (w), 1223 (w), 824 (w); δ_{H} (500 MHz, CDCl₃) 7.16-7.10 (2H, m, C_{Ar}H), 7.00-6.94 (2H, m, FC_{Ar}C_{Ar}H), 2.57 (2H, t, *J* 7.5,

$C_{Ar}CH_2$), 1.63 (2H, app. hex, J 7.5, $C_{Ar}CH_2CH_2$), 0.94 (3H, t, J 7.5, CH_3); δ_F (470 MHz, $CDCl_3$) -118.2; δ_C (125 MHz, $CDCl_3$) 161.3 (d, J_{C-F} 243.0, $C_{Ar}F$), 138.3 (d, J_{C-F} 3.2, $C_{Ar}CH_2$), 129.8 (2C, d, J_{C-F} 7.6, $C_{Ar}H$), 115.0 (2C, d, J_{C-F} 20.9, $FC_{Ar}C_{Ar}H$), 37.3 ($C_{Ar}CH_2$), 24.8 ($C_{Ar}CH_2CH_2$), 13.8 (CH_3); m/z HRMS (EI^+) $C_9H_{11}F^+$ ($[M]^+$) requires 138.0845; found 138.0840 (-3.6 ppm).

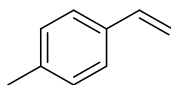
4-fluorostyrene (**157**):



Following **General Procedure 2**, at 80 °C for 22 hours with 1-bromo-4-fluorobenzene (110 μ L, 1.00 mmol), 1-methylnaphthalene (120 μ L, 0.84 mmol), $[PdCl_2(dppf)]$ (7.3 mg, 0.01 mmol), 2-MeTHF (1.0 mL) and vinylMgCl (750 μ L, 1.20 mmol, 1.6 M in THF). $HCl_{(aq)}$ (5 mL, 1.0 M) was added upon work-up and purification *via* column chromatography on silica gel (eluent EtOAc:hexane 5:95) gave 4-fluorostyrene (**157**) (58.6 mg, 48 %) as a colourless oil with spectroscopic data in agreement with the literature.³¹³

δ_H (500 MHz, $CDCl_3$) 7.41-7.35 (2H, m, $HCC_{Ar}C_{Ar}H$), 7.05-6.99 (2H, m, $FC_{Ar}C_{Ar}H$), 6.68 (1H, dd, J 17.6, 10.9, $CHCH_2$), 5.67 (1H, d, J 17.6, $CHCH'H''$), 5.22 (1H, d, J 10.9, $CHCH'H''$); δ_F (470 MHz, $CDCl_3$) -114.4; δ_C (125 MHz, $CDCl_3$) 162.59 (d, J_{C-F} 246.8, $C_{Ar}F$), 135.8 (CH), 133.85 (d, J_{C-F} 3.2, C_{Ar}), 127.86 (d, J_{C-F} 8.0, $HCC_{Ar}C_{Ar}H$), 115.54 (d, J_{C-F} 21.6, $FC_{Ar}C_{Ar}H$), 113.7 (d, J_{C-F} 1.9, CH_2); m/z HRMS (EI^+) $C_8H_7F^+$ ($[M]^+$) requires 122.0532; found 122.0534 (+1.6 ppm).

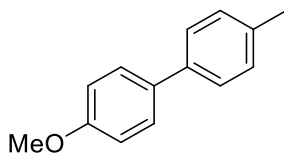
4-methylstyrene (**159**):



Following **General Procedure 2**, at room temperature for 19 hours with vinyl tosylate (**158**) (99.1 mg, 0.50 mmol), 1-methylnaphthalene (60 μ L, 0.42 mmol), [PdCl₂((*S*)-Xylyl-Phanephos)] (4.3 mg, 0.005 mmol), 2-MeTHF (1.0 mL) and *p*-TolMgBr (1.2 mL, 1.20 mmol, 0.5 M in Et₂O). Saturated NH₄Cl_(aq) (2.5 mL) was added upon work-up and purification *via* column chromatography on silica gel (eluent petroleum ether) gave 4-methylstyrene (**159**) (32.2 mg, 54 %) as a colourless oil with spectroscopic data in agreement with the literature.³¹⁴

δ_{H} (500 MHz, CDCl₃) 7.33 (2H, d, *J* 8.0, CHC_{Ar}C_{Ar}H), 7.15 (2H, d, *J* 8.0, H₃CC_{Ar}C_{Ar}H), 6.71 (1H, dd, *J* 17.6, 10.9, CHCH₂), 5.72 (1H, dd, *J* 17.6, 0.9, CHCH'H''), 5.20 (1H, dd, *J* 10.9, 0.9, CHCH'H''), 2.36 (3H, s, CH₃); δ_{C} (125 MHz, CDCl₃) 137.7 (CH₃C_{Ar}), 136.8 (CH), 134.9 (C_{Ar}), 129.3 (2C, H₃CC_{Ar}C_{Ar}H), 126.2 (2C, CHC_{Ar}C_{Ar}H), 112.9 (CH₂), 21.4 (CH₃); *m/z* HRMS (ESI⁺) C₉H₁₁⁺ ([M+H]⁺) requires 199.0855; found 119.0856 (+0.8 ppm).

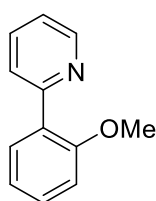
4-methoxy-4'-methyl-1,1'-biphenyl (**55**):



Following **General Procedure 2**, at 40 °C for 22 hours with 4-bromoanisole (126 μ L, 1.00 mmol), 1-methylnaphthalene (120 μ L, 0.84 mmol), [PdCl₂((*S*)-Xyl-Phanephos)] (8.7 mg, 0.01 mmol), 2-MeTHF (1.0 mL) and *p*-TolMgBr (2.4 mL, 1.20 mmol, 0.5 M in Et₂O). HCl_(aq) (5 mL, 1.0 M) was added upon work-up and purification *via* column chromatography on silica gel (eluent CH₂Cl₂:hexane 5:95) gave 4-methoxy-4'-methyl-1,1'-biphenyl (**55**) as a white solid (173.5 mg, 88 %) with spectroscopic data in accordance with the literature.³¹⁵

mp 110-111 °C {lit³¹⁵ 111-112 °C}; δ_{H} (500 MHz, CDCl₃) 7.54 (2H, d, J 8.8, C_{Ar}H), 7.48 (2H, d, J 8.0, C_{Ar}H), 7.26 (2H, d, J 8.0, H₃CC_{Ar}C_{Ar}H), 7.00 (2H, d, J 8.8 Hz, OC_{Ar}C_{Ar}H), 3.87 (3H, s, OCH₃), 2.42 (3H, s, CH₃); δ_{C} (125 MHz, CDCl₃) 159.0 (C_{Ar}O), 138.1 (C_{Ar}C_{Ar}), 136.5 (C_{Ar}C_{Ar}), 133.9 (C_{Ar}CH₃), 129.6 (2C, H₃CC_{Ar}C_{Ar}H), 128.1 (2C, C_{Ar}H), 126.7 (2C, C_{Ar}H), 114.3 (2C, OC_{Ar}C_{Ar}H), 55.5 (OCH₃), 21.2 (C_{Ar}CH₃); m/z HRMS (EI⁺) C₁₄H₁₄O⁺ ([M]⁺) requires 198.1045; found 198.1043 (-1.0 ppm).

2-(2-methoxyphenyl)pyridine (**63**):

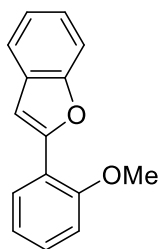


Following **General Procedure 2**, at 80 °C for 23 hours with 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**) (63.6 mg, 0.25 mmol), 1-methylnaphthalene (30 μ L, 0.11 mmol), [PdCl₂(*rac*)-Xylyl-Phanephos] (2.2 mg, 0.0025 mmol), 2-MeTHF (500 μ L) and 2-pyridylZnBr (600 μ L, 0.30 mmol, 0.5 M in THF). H₂O (2.5 mL) was added upon work-up and the combined organics were washed with brine. Purification *via* column chromatography on silica gel (eluent EtOAc:hexane, 20:80) gave 2-(2-methoxyphenyl)pyridine (**63**) as a pale yellow oil (29.6 mg, 64 %), with spectroscopic data in accordance with the literature.³¹⁶

δ_{H} (500 MHz, CDCl₃) 8.70 (1H, ddd, J 4.9, 1.9, 1.0, NC_{py}H)*, 7.81 (1H, dt, J 8.0, 1.0, NC_{py}C_{py}H)*, 7.76 (1H, dd, J 7.4, 1.8, C_{Ar}C_{Ar}H), 7.70 (1H, ddd, J 8.0, 7.5, 1.9, C_{py}H), 7.38 (1H, ddd, J 8.3, 7.4, 1.8, C_{Ar}H), 7.21 (1H, ddd, J 7.5, 4.9, 1.0, NC_{py}HC_{py}H), 7.08 (1H, td, J 7.4, 1.0, C_{Ar}H), 7.01 (1H, dd, J 8.3, 1.0, OC_{Ar}C_{Ar}H), 3.89 (OCH₃); δ_{C} (125 MHz, CDCl₃) 157.0 (C_{Ar}O), 156.2 (NC_{py}), 149.5 (NC_{py}H), 135.7 (C_{py}H), 131.2 (C_{Ar}C_{Ar}H), 130.0 (C_{Ar}H), 129.2 (C_{Ar}), 125.2 (NC_{py}C_{py}H), 121.7 (NC_{py}HC_{py}H), 121.1 (C_{Ar}H), 111.4 (OC_{Ar}C_{Ar}H), 55.7 (OCH₃); m/z HRMS (ESI⁺) C₁₂H₁₂NO⁺ ([M+H]⁺) requires 186.0913; found 186.0911 (-1.1 ppm).

* ⁵J_{H-H} confirmed by ¹H-¹H COSY NMR spectroscopy.

2-(2-methoxyphenyl)benzo[*b*]furan (64):



Following a modification of **General Procedure 2**, at 80 °C for 23 hours with 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**) (508.6 mg, 2.00 mmol), 1-methylnaphthalene (240 μ L, 1.68 mmol), [PdCl₂(*rac*-Xylyl-Phanephos)] (4.3 mg, 0.005 mmol), 2-MeTHF (4.0 mL) and 2-benzofuranylZnCl (7.7 mL, 2.40 mmol, 0.3 M in THF). After 23 hours, the reaction was cooled to room temperature and MeOH (2.5 mL) was slowly added. The mixture was concentrated under reduced pressure and EtOAc (5 mL) and saturated NH₄Cl_(aq) (5 mL) were added. The aqueous phase was extracted three times with EtOAc (3 x 5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification *via* column chromatography on silica gel (eluent EtOAc:hexane, 0:100 to 5:95) gave 2-(2-methoxyphenyl)benzo[*b*]furan (**64**) as a white solid (314.3 mg, 70 %), with spectroscopic data in accordance with the literature.³¹⁷

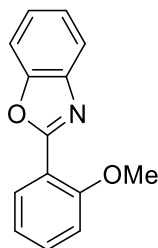
mp 80-81 °C {lit³¹⁷ 80-82 °C}; δ_{H} (500 MHz, CDCl₃) 8.08 (1H, dd, *J* 7.5, 1.7, C_{Ar}C_{Ar}H), 7.60 (1H, ddd, *J* 7.4, 1.4, 0.9, OC_{benzo}C_{benzo}H)*, 7.52 (1H, app. dq, *J* 8.1, 0.9, CHC_{benzo}C_{benzo}H)*, 7.36 (1H, d, *J* 0.9, CH), 7.34 (1H, ddd, *J* 8.3, 7.5, 1.7, C_{Ar}H), 7.28 (1H, ddd, *J* 8.1 7.4 1.4, C_{benzo}H), 7.22 (1H, td, *J* 7.4, 0.9, C_{benzo}H), 7.09 (1H, td, *J* 7.5, 1.1, C_{Ar}H), 7.02 (1H, dd, *J* 8.3, 1.1, OC_{Ar}C_{Ar}H), 4.02 (3H, s, OCH₃); δ_{C} (125 MHz, CDCl₃) 156.6 (C_{Ar}OCH₃), 154.0 (C_{benzo}O), 152.3 (OC_{benzo}C_{Ar}), 129.9 (C_{benzo}), 129.4 (C_{Ar}H), 127.1 (C_{Ar}H), 124.2 (C_{benzo}H), 122.8 (C_{benzo}H), 121.2 (OC_{benzo}C_{benzo}H), 120.9 (C_{Ar}H), 119.4 (OC_{Ar}C_{Ar}), 111.1 (OC_{Ar}C_{Ar}H), 110.9 (CHC_{benzo}C_{benzo}H), 106.4 (CH), 55.5 (OCH₃); *m/z* HRMS (ESI⁺) C₁₅H₁₃O₂⁺ ([M+H]⁺) requires 225.0916; found 225.0908 (-3.6 ppm).

* ⁵J_{H-H} confirmed by ¹H-¹H COSY NMR spectroscopy.

7.4 – Modified Meyers reaction

7.4.1 – Preparation of 2-(2-methoxyphenyl)benzo[d]oxazole

2-(2-methoxyphenyl)benzo[d]oxazole (**66**):



Following a modification of literature procedure.¹³⁶ [Pd(OAc)₂] (59.5 mg, 0.27 mmol), dppe (253.4 mg, 0.64 mmol), Cs₂CO₃ (3.45 g, 10.60 mmol), benzoxazole (630 mg, 5.30 mmol), and 2-methoxyphenyl-1*H*-imidazole-1-sulfonate (**33**) (1.52 g, 6.36 mmol) in NMP (20 mL) were stirred under argon at 100 °C for 16 h. H₂O (300 mL) was added at ambient temperature, and the resulting mixture was extracted with Et₂O (3 × 300 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography on silica gel (EtOAc:hexane 1:5) gave 2-(2-methoxyphenyl)benzo[d]oxazole (**66**) (923 mg, 78 %) as an off-white solid with spectroscopic data in agreement with the literature.¹³⁶

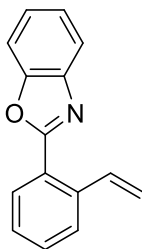
mp 65-67 °C {lit³¹⁸ 55-57 °C}; δ_H (400 MHz, CDCl₃) 8.14 (1H, dd, *J* 7.7, 1.8, NC_{benzox}C_{Ar}C_{Ar}H), 7.87–7.77 (1H, m, C_{benzox}H), 7.66–7.54 (1H, m, C_{benzox}H), 7.49 (1H, ddd, *J* 8.4, 7.4, 1.8, C_{Ar}H), 7.39–7.30 (2H, m, C_{benzox}H), 7.13–7.04 (2H, m, C_{Ar}H), 4.01 (3H, s, OCH₃); δ_C (100 MHz, CDCl₃) 161.6 (NC_{benzox}O), 158.5 (C_{Ar}O), 150.4 (C_{benzox}), 142.2 (C_{benzox}), 132.8 (C_{Ar}H), 131.4 (C_{Ar}C_{Ar}H), 125.0 (C_{benzox}H), 124.4 (C_{benzox}H), 120.8 (C_{Ar}H), 120.3 (C_{benzox}H), 116.3 (C_{Ar}C_{Ar}O), 112.1 (OC_{Ar}C_{Ar}H), 110.5 (C_{benzox}H), 56.3 (OCH₃); *m/z* HRMS (ESI⁺) C₁₄H₁₂NO₂⁺ ([M+H]⁺) requires 226.0868; found 226.0859 (-4.0 ppm).

7.4.2 – General procedure 3: modified Meyers reaction

To a solution of 2-(2-methoxyphenyl)benzo[*d*]oxazole (**66**) in anhydrous solvent was added the desired Grignard reagent dropwise, and the reaction mixture was stirred at a specific temperature for a specific time. After reaction completion, saturated NH₄Cl_(aq) was added upon work-up and the aqueous phase was extracted three times with EtOAc. The combined organics were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product. Purification *via* column chromatography on silica gel gave the desired product.

7.4.3 – Product data

2-(2-vinylphenyl)benzo[*d*]oxazole (**73**):

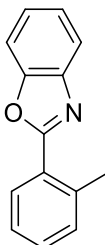


Following **General Procedure 3**, at 20 °C for 4 hours with 2-(2-methoxyphenyl)benzo[*d*]oxazole (**66**) (50.0 mg, 0.22 mmol), 2-MeTHF (1 mL) and vinylMgCl (300 μL, 0.47 mmol, 1.6 M in THF). Purification *via* column chromatography on Et₃N deactivated silica gel (eluent Et₃N:EtOAc:hexane 1:5:95) gave 2-(2-vinylphenyl)benzo[*d*]oxazole (**73**) (36.8 mg, 75 %) as a white solid.

mp 53-55 °C; ν_{\max} (ATR) 3028 (w), 2920 (w), 1545 (m), 1454 (m), 1236 (m), 1030 (s), 918 (s); δ_{H} (500 MHz, CDCl₃) 8.15 (1H, dd, *J* 7.7, 1.4, NC_{benzox}C_{Ar}C_{Ar}H), 7.89–7.78 (2H, m, C_{benzox}H, C_{Ar}CH), 7.76–7.70 (1H, m, CHC_{Ar}C_{Ar}H), 7.63–7.58 (1H, m, C_{benzox}H), 7.51 (1H, td, *J* 7.7, 1.4, C_{Ar}H), 7.43 (1H, td, *J* 7.7, 1.4, C_{Ar}H), 7.40–7.34 (2H, m, C_{benzox}H), 5.82 (1H, dd, *J* 17.4, 1.3, CH'H''), 5.48 (1H, dd, *J* 11.0, 1.3, CH'H''); δ_{C} (125 MHz, CDCl₃) 162.8 (NC_{benzox}O), 150.5 (C_{benzox}), 142.3 (C_{benzox}), 138.5 (C_{Ar}CH), 135.9 (C_{Ar}CH), 131.2 (C_{Ar}H), 130.1 (C_{Ar}C_{Ar}H), 127.9 (C_{Ar}H), 127.3 (CHC_{Ar}C_{Ar}H), 125.3 (C_{benzox}H), 125.1 (CHC_{Ar}C_{Ar}), 124.6 (C_{benzox}H), 120.4 (C_{benzox}H), 116.9 (CH'H''), 110.7

(C_{benzoxH}); *m/z* HRMS (ESI⁺) C₁₅H₁₂ON⁺ ([M+H]⁺) requires 222.0913; found 222.0917 (+1.8 ppm).

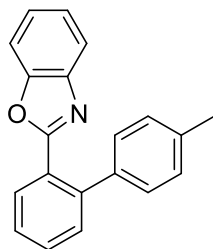
2-(*o*-tolyl)benzo[*d*]oxazole (74):



Following **General Procedure 3**, at 80 °C for 16 hours with 2-(2-methoxyphenyl)benzo[*d*]oxazole (**66**) (112.6 mg, 0.50 mmol), [NiCl₂(PCy₃)₂] (17.3 mg, 0.003 mmol), 2-MeTHF (4 mL) and MeMgBr (313 μL, 0.75 mmol, 2.4 M in Et₂O). Purification *via* column chromatography on silica gel (eluent EtOAc:hexane 1:99) gave 2-(*o*-tolyl)benzo[*d*]oxazole (**74**) (50.5 mg, 48 %) as an off-white crystalline solid with spectroscopic data in agreement with the literature.³¹⁸

mp 59-61 °C {lit³¹⁸ 58-60 °C}; δ_H (500 MHz, CDCl₃) 8.19 (1H, dd, *J* 8.1, 1.5, NC_{benzox}C_{Ar}C_{ArH}), 7.82 (1H, ddd, *J* 6.0, 3.2, 0.7, C_{benzoxH}), 7.63-7.58 (1H, m, C_{benzoxH}), 7.42 (1H, td, *J* 7.4, 1.5, C_{ArH}), 7.39-7.34 (4H, m, C_{ArH}, C_{benzoxH}), 2.36 (3H, s, CH₃); δ_C (125 MHz, CDCl₃) 163.5 (NC_{benzoxO}), 150.4 (C_{benzox}), 142.2 (C_{benzox}), 139.0 (C_{Ar}CH₃), 131.9 (CH₃C_{Ar}C_{ArH}), 131.0 (C_{ArH}), 130.0 (C_{Ar}C_{ArH}), 126.3 (CH₃C_{Ar}C_{Ar}), 126.2 (C_{ArH}), 125.1 (C_{benzoxH}), 124.5 (C_{benzoxH}), 120.2 (C_{benzoxH}), 110.6 (C_{benzoxH}), 22.4 (CH₃); *m/z* HRMS (ESI⁺) C₁₄H₁₂ON⁺ ([M+H]⁺) requires 210.0913; found 210.0911 (-1.0 ppm).

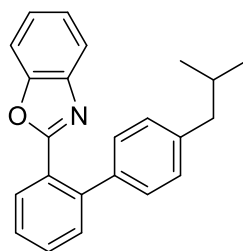
2-(4'-methyl-[1,1'-biphenyl]-2-yl)benzo[d]oxazole (75):



Following **General Procedure 3**, at 40 °C for 19 hours with 2-(2-methoxyphenyl)benzo[d]oxazole (**66**) (450.5 mg, 2.00 mmol), PhMe (9 mL) and *p*-TolMgBr (4.9 mL, 2.20 mmol, 0.5 M in Et₂O). Purification *via* column chromatography on silica gel (eluent EtOAc:hexane 5:95) gave 2-(4'-methyl-[1,1'-biphenyl]-2-yl)benzo[d]oxazole (**75**) (570.7 mg, 92 %) as an off-white crystalline solid with spectroscopic data in agreement with the literature.³¹⁹

mp 90-91 °C {lit³¹⁹ 88-90 °C}; δ_{H} (500 MHz, CDCl₃) 8.12 (1H, dd, *J* 7.7, 1.6, NC_{benzox}C_{Ar}C_{Ar}H), 7.81-7.75 (1H, m, C_{benzox}H), 7.64-7.56 (1H, m, C_{Ar}H), 7.54-7.46 (1H, m, C_{Ar}H), 7.36-7.31 (2H, m, C_{benzox}H), 7.31-7.27 (1H, m, C_{benzox}H), 7.22 (2H, d, *J* 8.0, C_{Ar}H), 7.16 (2H, d, *J* 8.0, CH₃C_{Ar}C_{Ar}H), 2.39 (3H, s, CH₃); δ_{C} (125 MHz, CDCl₃) 164.1 (NC_{benzox}O), 150.8 (C_{benzox}), 142.5 (C_{Ar}C_{Ar}C_{benzox}N), 141.8 (C_{benzox}), 138.0 (C_{Ar}C_{Ar}), 137.0 (C_{Ar}CH₃), 131.2 (C_{Ar}H), 131.1 (NC_{benzox}C_{Ar}C_{Ar}H), 131.0 (C_{Ar}H), 129.0 (2C, CH₃C_{Ar}C_{Ar}H), 128.7 (2C, C_{Ar}C_{Ar}H), 127.3 (C_{Ar}C_{Ar}H), 126.3 (C_{Ar}C_{benzox}N), 124.9 (C_{benzox}H), 124.3 (C_{benzox}H), 120.1 (C_{benzox}H), 110.6 (C_{benzox}H), 21.3 (CH₃); *m/z* HRMS (ESI⁺) C₂₀H₁₆ON⁺ ([M+H]⁺) requires 286.1226; found 286.1221 (-1.7 ppm).

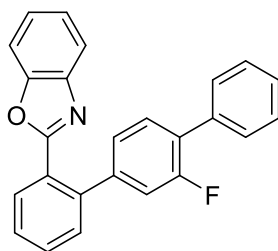
2-(4'-isobutyl-[1,1'-biphenyl]-2-yl)benzo[d]oxazole (76):



Following **General Procedure 3**, at 40 °C for 19 hours with 2-(2-methoxyphenyl)benzo[d]oxazole (**66**) (112.6 mg, 0.50 mmol), 2-MeTHF (2.3 mL) and 4-*i*BuPhMgBr (1.4 mL, 1.05 mmol, 0.7 M in 2-MeTHF). Purification *via* column chromatography on silica gel (eluent EtOAc:hexane 5:95) gave 2-(4'-isobutyl-[1,1'-biphenyl]-2-yl)benzo[d]oxazole (**76**) (160.5 mg, 98 %) as a light yellow oil.

ν_{\max} (ATR) 2953 (w), 1541 (w), 1466 (m), 1452 (s), 1242 (m), 1113 (w), 1032 (m), 1005 (w), 847 (m), 810 (m), 797 (m), 756 (s); δ_{H} (500 MHz, CDCl_3) 8.15 (1H, dd, J 7.7, 1.3, $\text{NC}_{\text{benzox}}\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 7.76 (1H, dt, J 7.9, 1.0, $\text{C}_{\text{benzox}}\text{H}$), 7.61 (1H, td, J 7.5, 1.3, $\text{C}_{\text{Ar}}\text{H}$), 7.56-7.49 (2H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.34 (1H, ddd, J 8.0, 6.3, 2.2, $\text{C}_{\text{benzox}}\text{H}$), 7.31-7.25 (2H, m, $\text{C}_{\text{benzox}}\text{H}$), 7.22 (2H, d, J 8.1, $\text{C}_{\text{Ar}}\text{H}$), 7.13 (2H, d, J 8.1, $\text{CH}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 2.53 (2H, d, J 7.2, CH_2), 1.97-1.86 (1H, m, CH), 0.95 (6H, d, J 6.6, CH_3); δ_{C} (125 MHz, CDCl_3) 164.2 ($\text{NC}_{\text{benzox}}\text{O}$), 150.9 (C_{benzox}), 142.7 ($\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{C}_{\text{benzox}}\text{N}$), 141.8 (C_{benzox}), 140.9 ($\text{C}_{\text{Ar}}\text{CH}_2$), 138.4 ($\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}$), 131.1 ($\text{C}_{\text{Ar}}\text{H}$), 131.1 (2C, $\text{NC}_{\text{benzox}}\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$, $\text{C}_{\text{Ar}}\text{H}$), 129.0 (2C, $\text{CH}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 128.6 (2C, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 127.4 ($\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 126.4 ($\text{C}_{\text{Ar}}\text{C}_{\text{benzox}}\text{N}$), 125.0 ($\text{C}_{\text{benzox}}\text{H}$), 124.4 ($\text{C}_{\text{benzox}}\text{H}$), 120.1 ($\text{C}_{\text{benzox}}\text{H}$), 110.6 ($\text{C}_{\text{benzox}}\text{H}$), 45.2 (CH_2), 30.4 (CH), 22.5 (CH_3); m/z HRMS (ESI⁺) $\text{C}_{23}\text{H}_{21}\text{NONa}^+$ ($[\text{M}+\text{Na}]^+$) requires 350.1515; found 350.1507 (-2.3 ppm).

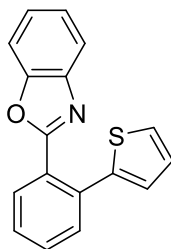
2-(3'-fluoro-[1,1':4',1''-terphenyl]-2-yl)benzo[d]oxazole (77):



Following **General Procedure 3**, at 40 °C for 21 hours with 2-(2-methoxyphenyl)benzo[d]oxazole (**66**) (112.6 mg, 0.50 mmol), 2-MeTHF (2.3 mL) and (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide (1.7 mL, 1.05 mmol, 0.6 M in 2-MeTHF). Purification *via* column chromatography on silica gel (eluent EtOAc:hexane 5:95) gave 2-(3'-fluoro-[1,1':4',1''-terphenyl]-2-yl)benzo[d]oxazole (**77**) (159.7 mg, 87 %) as a white solid.

mp 89-90 °C; ν_{\max} (ATR) 1551 (w), 1474 (m), 1454 (m), 1404 (m), 1231 (w), 1180 (w), 1022 (m), 810 (m), 760 (s), 750 (s); δ_{H} (500 MHz, CDCl_3) 8.16 (1H, dd, J 7.5, 1.2, $\text{NC}_{\text{benzox}}\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 7.74 (1H, m, $\text{C}_{\text{benzox}}\text{H}$), 7.65-7.59 (3H, m, $\text{C}_{\text{benzox}}\text{H}$, $\text{C}_{\text{Ar}}\text{H}$), 7.57 (1H, dd, J 7.5, 1.5, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 7.55-7.52 (1H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.50-7.44 (2H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.43-7.27 (5H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.18 (1H, dd, $J_{\text{H-F}}$ 11.5, 1.8, $\text{FC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 7.10 (1H, dd, J 7.9, 1.8, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$); δ_{F} (376 MHz, CDCl_3) -118.4; δ_{C} (125 MHz, CDCl_3) 163.4 ($\text{NC}_{\text{benzox}}\text{O}$), 159.5 (d, $J_{\text{C-F}}$ 248.2, $\text{FC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 150.8 (C_{benzox}), 142.2 (d, $J_{\text{C-F}}$ 8.3, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}$), 141.8 (C_{benzox}), 140.9 (d, $J_{\text{C-F}}$ 1.4, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}$), 135.6 ($\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}$), 131.2 ($\text{C}_{\text{Ar}}\text{H}$), 131.2 ($\text{NC}_{\text{benzox}}\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 131.2 ($\text{C}_{\text{Ar}}\text{H}$), 130.4 (d, $J_{\text{C-F}}$ 4.0, $\text{C}_{\text{Ar}}\text{H}$), 129.1 (2C, d, $J_{\text{C-F}}$ 3.1, $\text{C}_{\text{Ar}}\text{H}$), 128.6 (2C, $\text{C}_{\text{Ar}}\text{H}$), 128.2 ($\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 127.9 ($\text{C}_{\text{Ar}}\text{H}$), 126.3 ($\text{C}_{\text{Ar}}\text{C}_{\text{benzox}}\text{N}$), 125.3 ($\text{C}_{\text{benzox}}\text{H}$), 125.2 (d, $J_{\text{C-F}}$ 3.3, $\text{C}_{\text{Ar}}\text{H}$), 124.6 ($\text{C}_{\text{benzox}}\text{H}$), 120.3 ($\text{C}_{\text{benzox}}\text{H}$), 116.8 (d, $J_{\text{C-F}}$ 23.9, $\text{C}_{\text{Ar}}\text{FC}_{\text{Ar}}\text{H}$), 110.7 ($\text{C}_{\text{benzox}}\text{H}$); m/z . HRMS (ESI⁺) $\text{C}_{25}\text{H}_{16}\text{FNONa}^+$ ($[\text{M}+\text{Na}]^+$) requires 388.1108; found 388.1101 (-1.8 ppm).

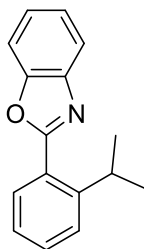
2-(2-(thiophen-2-yl)phenyl)benzo[d]oxazole (78):



Following **General Procedure 3**, at 40 °C for 41 hours with 2-(2-methoxyphenyl)benzo[d]oxazole (**66**) (450.5 mg, 2.00 mmol), PhMe (9 mL) and 2-thienylMgBr (3.1 mL, 2.20 mmol, 0.9 M in THF). Purification *via* column chromatography on silica gel (eluent EtOAc:hexane 5:95) gave 2-(2-(thiophen-2-yl)phenyl)benzo[d]oxazole (**78**) (428.0 mg, 77 %) as a light yellow solid.

mp 75-76 °C; ν_{\max} (ATR) 1532 (w), 1452 (m), 1423 (w), 1244 (m), 1233 (w), 1024 (m), 808 (m), 781 (m), 762 (s), 750 (s); δ_{H} (500 MHz, CDCl₃) 8.00 (1H, dd, *J* 7.6, 1.5, NC_{benzox}C_{Ar}C_{Ar}H), 7.80-7.77 (1H, m, C_{benzox}H), 7.62 (1H, dd, *J* 7.6, 1.4, C_{thio}C_{Ar}C_{Ar}H), 7.56 (1H, td, *J* 7.6, 1.4, C_{Ar}H), 7.49 (1H, td, *J* 7.6, 1.4, C_{Ar}H), 7.41 (1H, dd, *J* 8.1, 1.3, C_{benzox}H), 7.37-7.31 (2H, m, C_{benzox}H), 7.30 (1H, dd, *J* 5.0, 1.2, SC_{thio}H), 6.98 (1H, dd, *J* 5.0, 3.6, C_{thio}H), 6.94 (1H, dd, *J* 3.6, 1.2, C_{thio}C_{thio}H); δ_{C} (125 MHz, CDCl₃) 163.5 (NC_{benzox}O), 150.9 (C_{benzox}), 141.9 (C_{thio}), 141.8 (C_{benzox}), 135.0 (C_{thio}C_{Ar}), 131.4 (C_{thio}C_{Ar}C_{Ar}H), 131.4 (NC_{benzox}C_{Ar}C_{Ar}H), 131.1 (C_{Ar}H), 128.1 (C_{Ar}H), 127.4 (C_{thio}H), 126.9 (NC_{benzox}C_{Ar}), 126.9 (C_{thio}C_{thio}H), 126.2 (SC_{thio}H), 125.2 (C_{benzox}H), 124.5 (C_{benzox}H), 120.3 (C_{benzox}H), 110.8 (C_{benzox}H); *m/z* HRMS (ESI⁺) C₁₇H₁₁NOSNa⁺ ([M+Na]⁺) requires 300.0454; found 300.0446 (-2.7 ppm).

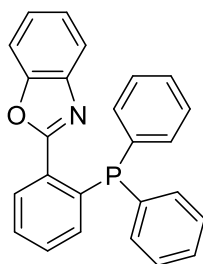
2-(2-isopropylphenyl)benzo[d]oxazole (79):



Following **General Procedure 3**, at 40 °C for 19 hours with 2-(2-methoxyphenyl)benzo[d]oxazole (**66**) (225.3 mg, 1.00 mmol), PhMe (4.5 mL) and ⁱPrMgCl (1.8 mL, 1.10 mmol, 0.6 M in Et₂O). Purification *via* column chromatography on silica gel (eluent EtOAc:hexane 5:95) gave 2-(2-isopropylphenyl)benzo[d]oxazole (**79**) (199.9 mg, 84 %) as a yellow oil.

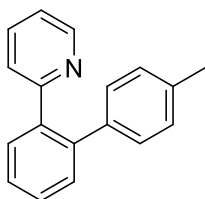
ν_{max} (ATR) 2965 (w), 1614 (w), 1545 (m), 1489 (m), 1474 (m), 1454 (s), 1441 (m), 1236 (s), 1192 (m), 1038 (m), 1024 (s), 1001 (w), 920 (m), 814 (m), 756 (s); δ_{H} (500 MHz, CDCl₃) 8.04 (1H, dd, *J* 7.8, 1.3, NC_{benzox}C_{Ar}C_{Ar}H), 7.88-7.81 (1H, m, C_{benzox}H), 7.65-7.59 (1H, m, C_{benzox}H), 7.57-7.49 (2H, m, C_{Ar}H, CHC_{Ar}C_{Ar}H), 7.41-7.37 (2H, m, C_{benzox}H), 7.35 (1H, ddd, *J* 8.3, 7.0, 1.6, C_{Ar}H), 4.16 (1H, septet, *J* 6.8, CH), 1.35 (6H, d, *J* 6.8, CH₃); δ_{C} (125 MHz, CDCl₃) 163.5 (NC_{benzox}O), 150.6 (C_{benzox}), 149.6 (C_{Ar}CH), 142.2 (C_{benzox}), 131.3 (C_{Ar}H), 130.5 (NC_{benzox}C_{Ar}C_{Ar}H), 126.5 (CHC_{Ar}C_{Ar}H), 125.9 (C_{Ar}H), 125.7 (CHC_{Ar}C_{Ar}), 125.1 (C_{benzox}H), 124.4 (C_{benzox}H), 120.3 (C_{benzox}H), 110.6 (C_{benzox}H), 29.6 (CH), 24.1 (CH₃); *m/z* HRMS (ESI⁺) C₁₆H₁₆ON⁺ ([M+H]⁺) requires 238.1226; found 238.1227 (+0.4 ppm).

2-(2-(diphenylphosphanyl)phenyl)benzo[d]oxazole (80):



Following **General Procedure 3**, at 40 °C for 17 hours with 2-(2-methoxyphenyl)benzo[d]oxazole (**66**) (56.3 mg, 0.25 mmol), 2-MeTHF (1.1 mL) and Ph_2PMgBr (1.2 mL, 0.30 mmol, 0.3 M in THF). Purification *via* column chromatography on silica gel (eluent EtOAc:petroleum ether 0:100 to 20:80) gave 2-(2-(diphenylphosphanyl)phenyl)benzo[d]oxazole (**80**) (47.8 mg, 50 %) as an off-white solid. mp 167-169 °C; ν_{max} (ATR) 1506 (w), 1449 (w), 1429 (m), 1236 (m), 1107 (w), 1082 (w), 1032 (m), 812 (w), 747 (s); δ_{H} (500 MHz, CDCl_3) 8.25 (1H, ddd, J 7.6, 3.6, 1.4, $\text{NC}_{\text{benzox}}\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 7.71-7.67 (1H, m, $\text{C}_{\text{benzox}}\text{H}$), 7.49 (1H, td, J 7.6, 1.3, $\text{C}_{\text{Ar}}\text{H}$), 7.46-7.42 (1H, m, $\text{C}_{\text{benzox}}\text{H}$), 7.41-7.35 (5H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.34-7.29 (6H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.30-7.26 (2H, m, $\text{C}_{\text{benzox}}\text{H}$), 7.07 (1H, ddd, J 7.8, 4.0, 1.3, $\text{PC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$); δ_{P} (202 MHz, CDCl_3) -5.6; δ_{C} (125 MHz, CDCl_3) 162.6 ($\text{NC}_{\text{benzox}}\text{O}$), 150.5 (C_{benzox}), 141.8 (C_{benzox}), 139.3 (d, $J_{\text{C-P}}$ 26.8, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{P}$), 137.5 (2C, d, $J_{\text{C-P}}$ 10.3, $\text{C}_{\text{Ar}}\text{P}$), 134.6 ($\text{PC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 134.2 (4C, d, $J_{\text{C-P}}$ 20.6, $\text{PC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 131.2 (d, $J_{\text{C-P}}$ 20.8, $\text{NC}_{\text{benzox}}\text{C}_{\text{Ar}}$), 130.3 (d, $J_{\text{C-P}}$ 3.3, $\text{NC}_{\text{benzox}}\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 128.8 ($\text{C}_{\text{Ar}}\text{H}$), 128.6 ($\text{C}_{\text{Ar}}\text{H}$), 128.6 (4C, $\text{C}_{\text{Ar}}\text{H}$), 125.1 ($\text{C}_{\text{benzox}}\text{H}$), 124.4 ($\text{C}_{\text{benzox}}\text{H}$), 120.5 ($\text{C}_{\text{benzox}}\text{H}$), 110.6 ($\text{C}_{\text{benzox}}\text{H}$); m/z HRMS (ESI⁺) $\text{C}_{25}\text{H}_{19}\text{ONP}^+$ ($[\text{M}+\text{H}]^+$) requires 380.1199; found 380.1192 (-1.8 ppm).

2-(4'-methyl-[1,1'-biphenyl]-2-yl)pyridine (94):

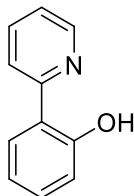


Following a modification of **General Procedure 3**. To an oven dried microwave vial equipped with a stirrer bar was added 2-(2-methoxyphenyl)pyridine (**63**) (46.31 mg, 0.25 mmol). The vial was sealed with a crimp cap and flushed with argon for 30 minutes. THF (1.13 mL) was then added to the vial to make a solution. *p*-tolylmagnesium bromide (1.2 mL, 0.60 mmol, 0.5 M in Et₂O) was added dropwise over 15 minutes and the reaction mixture was stirred vigorously in an oil bath at 80 °C for 67 hours. Upon cooling to rt, approximately 20 μL of the crude reaction mixture was added to a vial and quenched with CDCl₃. A ¹H NMR was run to assess the ratio between SM and desired product. The reaction mixture was then quenched with MeOH (3 mL) and concentrated under reduced pressure. Saturated aqueous ammonium chloride (3 mL) was added to the reaction mixture and the aqueous phase was extracted three times with ethyl acetate (3 x 3 mL), dried over sodium sulfate and concentrated under reduced pressure. Purification *via* column chromatography on silica gel (eluent EtOAc:petroleum ether, 20:80) gave 2-(4'-methyl-[1,1'-biphenyl]-2-yl)pyridine (**94**) (43.3 mg, 71 %) as a light yellow oil with spectroscopic data in accordance with the literature.³²⁰

δ_{H} (500 MHz, CDCl₃); 8.64 (1H, ddd, *J* 4.9, 1.9, 1.1, NC_{py}H)*, 7.73–7.65 (1H, m, C_{py}C_{Ar}C_{Ar}H), 7.47–7.42 (3H, m, C_{Ar}H, C_{Ar}C_{Ar}C_{Ar}H), 7.40 (1H, td, *J* 7.6, 1.9, C_{py}H), 7.11 (1H, ddd, *J* 7.6, 4.9, 1.1, C_{py}H), 7.05 (4H, s, C_{Ar}H), 6.91 (1H, dt, *J* 7.9, 1.1, NC_{py}C_{py}H)*, 2.32 (3H, s, CH₃); δ_{C} (100 MHz, CDCl₃) 159.5 (C_{py}N), 149.5 (NC_{py}H), 140.7 (C_{Ar}C_{Ar}C_{Ar}), 139.4 (NC_{py}C_{Ar}), 138.4 (C_{Ar}C_{Ar}C_{Ar}), 136.5 (C_{Ar}CH₃), 135.4 (C_{py}H), 130.6 (2C, C_{py}C_{Ar}C_{Ar}H, C_{Ar}H), 129.7 (2C, C_{Ar}C_{Ar}H), 128.9 (2C, C_{Ar}HC_{Ar}CH₃), 128.6 (C_{Ar}H), 127.5 (C_{Ar}H), 125.6 (C_{py}H), 121.4 (C_{py}H), 21.2 (C_{Ar}CH₃); *m/z* HRMS (ESI⁺) C₁₈H₁₆N⁺ ([M+H]⁺) requires 246.1277; found 246.1272 (-2.0 ppm).

* ⁵J_{H-H} confirmed by ¹H-¹H COSY NMR spectroscopy.

2-(pyridine-2-yl)phenol (**96**):

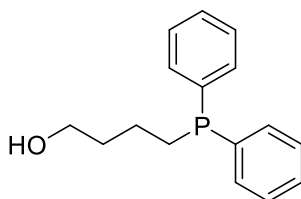


Following **General Procedure 3**, at 80 °C for 140 hours with 2-(2-methoxyphenyl)pyridine (**63**) (46.31 mg, 0.25 mmol), 2-MeTHF (1.1 mL) and Ph₂PMgBr (2.5 mL, 0.53 mmol, 0.2 M in THF). Purification *via* column chromatography on silica gel (eluent EtOAc:petroleum ether 15:85) gave 2-(pyridine-2-yl)phenol (**96**) (32.8 mg, 77 %) as a light yellow oil with spectroscopic data in accordance with the literature.³²¹

δ_{H} (500 MHz, CDCl₃); 14.38 (1H, br s, C_{Ar}OH), 8.51 (1H, dt, *J* 5.1, 1.3, NC_{py}H)*, 7.93–7.90 (1H, m, NC_{py}C_{py}H), 7.85–7.81 (1H, m, C_{py}H), 7.80 (1H, dd, *J* 8.1, 1.7, C_{Ar}C_{Ar}H), 7.31 (1H, ddd, *J* 8.6, 7.2, 1.7, C_{Ar}H), 7.27–7.20 (1H, m, NC_{py}HC_{py}H), 7.04 (1H, dd, *J* 8.4, 1.3, 1H), 6.91 (1H, ddd, *J* 8.1, 7.2, 1.3, C_{Ar}H); δ_{C} (125 MHz, CDCl₃) 160.1 (C_{Ar}OH), 158.0 (2C, NC_{py}, NC_{py}C_{Ar}), 145.9 (NC_{py}H), 137.9 (C_{py}H), 131.6 (C_{Ar}H), 126.2 (C_{Ar}C_{Ar}H), 121.6 (NC_{py}HC_{py}H), 119.2 (C_{py}C_{py}H), 118.9 (C_{Ar}H), 118.7 (HOC_{Ar}C_{Ar}H); *m/z* HRMS (ESI⁺) C₁₁H₁₀NO⁺ ([M+H]⁺) requires 172.0757; found 172.0751 (-3.4 ppm).

* ⁵J_{H-H} confirmed by ¹H-¹H COSY NMR spectroscopy.

4-hydroxybutyldiphenylphosphine (**97**):



Following **General Procedure 3**, at 80 °C for 140 hours with 2-(2-methoxyphenyl)pyridine (**63**) (46.31 mg, 0.25 mmol), 2-MeTHF (1.1 mL) and Ph₂PMgBr (2.5 mL, 0.53 mmol, 0.2 M in THF). Purification *via* column chromatography on silica gel (eluent EtOAc:petroleum ether 20:80) gave 4-hydroxybutyldiphenylphosphine (**97**)

(65.9 mg, 49 %) as a light yellow oil with spectroscopic data in accordance with the literature.³²²

δ_{H} (500 MHz, CDCl_3) 7.45–7.39 (4 H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.35–7.28 (6H, m, $\text{C}_{\text{Ar}}\text{H}$), 3.61 (2H, t, J 6.5, HOCH_2), 2.15–2.01 (2H, m, CH_2CH_2), 1.76–1.62 (2H, m, CH_2CH_2) 1.58–1.46 (2H, m, CH_2P); δ_{P} (202 MHz, CDCl_3) -16.3; δ_{C} (125 MHz, CDCl_3) 138.8 (2C, d, $J_{\text{C-P}}$ 12.6, C_{Ar}), 132.8 (4C, d, $J_{\text{C-P}}$ 18.3, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 128.6 (2C, $\text{C}_{\text{Ar}}\text{H}$), 128.5 (4C, d, $J_{\text{C-P}}$ 6.5, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 62.4 (HOCH_2), 34.2 (d, $J_{\text{C-P}}$ 12.4, CH_2CH_2), 27.9 (d, $J_{\text{C-P}}$ 11.2, CH_2CH_2), 22.4 (d, $J_{\text{C-P}}$ 16.6, CH_2P).

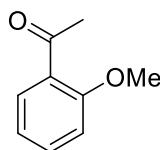
7.5 – Benzoxazole cleavage

7.5.1 – General procedure 4: Aryl benzoxazole cleavage

(trimethylsilyl)methyl lithium solution (1.3 equiv., 0.6 M in pentane) was added dropwise to a solution of aryl benzoxazole in anhydrous solvent, and the reaction mixture was stirred at a specific temperature for a specific time. After reaction completion, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ was added and the aqueous phase was extracted three times with EtOAc. The combined organics were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give the crude product. Purification *via* column chromatography on silica gel gave the desired product.

7.5.2 – Product data

2'-methoxyacetophenone (**87**):

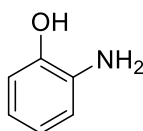


Following **General Procedure 4**, at 20 °C for 18 hours with 2-(2-methoxyphenyl)benzo[*d*]oxazole (**66**) (225.3 mg, 1.00 mmol), 2-MeTHF (6.0 mL) and (trimethylsilyl)methyl lithium (2.2 mL, 1.30 mmol, 0.6 M in pentane). Purification *via* column chromatography on silica gel (eluent EtOAc:hexane, 5:95 to 10:90) gave 2'-methoxyacetophenone (**87**) (126.7 mg, 84 %) as a pale yellow oil with spectroscopic data in agreement with the literature.³²³

δ_{H} (500 MHz, CDCl_3) 7.73 (1H, dd, *J* 7.7, 1.9, $\text{O}=\text{C}\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 7.45 (1H, ddd, *J* 8.3, 7.3, 1.8, $\text{C}_{\text{Ar}}\text{H}$), 7.02-6.92 (2H, m, $\text{C}_{\text{Ar}}\text{H}$, $\text{O}\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 3.90 (3H, s, OCH_3), 2.61 (3H, s, CH_3); δ_{C} (125 MHz, CDCl_3) 200.0 ($\text{O}=\text{C}$), 159.0 ($\text{O}\text{C}_{\text{Ar}}$), 133.8 ($\text{C}_{\text{Ar}}\text{H}$), 130.4 ($\text{C}_{\text{Ar}}\text{H}$), 128.3 ($\text{O}=\text{C}\text{C}_{\text{Ar}}$), 120.6 ($\text{C}_{\text{Ar}}\text{H}$), 111.6 ($\text{O}\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 55.6 (OCH_3), 32.0 (CH_3); *m/z* HRMS (ESI⁺) $\text{C}_9\text{H}_{10}\text{O}_2\text{Na}^+$ ($[\text{M}+\text{Na}]^+$) requires 173.0573; found 173.0569 (-2.3 ppm).

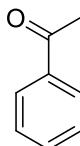
2-aminophenol (**88**) (90.0 mg, 83 %) was also isolated as a light brown crystalline solid (eluent increased to EtOAc:hexane, 80:20), with spectroscopic data in agreement with the literature.³²⁴

2-aminophenol (88):



mp 172-175 °C {lit³²⁵ 172-174 °C}; δ_{H} (400 MHz, DMSO-*d*₆) 8.94 (1H, br s, OH), 6.66 (1H, dd, *J* 7.7, 1.4, OC_{Ar}C_{Ar}H), 6.62–6.52 (2H, m, C_{Ar}H, NC_{Ar}C_{Ar}H), 6.41 (td, *J* 7.7, 1.9, C_{Ar}H), 4.47 (2H, br s, NH₂); δ_{C} (125 MHz, DMSO-*d*₆) 144.1 (OC_{Ar}), 136.6 (C_{Ar}N), 119.6 (C_{Ar}H), 116.6 (C_{Ar}H), 114.5 (OC_{Ar}C_{Ar}H), 114.5 (NC_{Ar}C_{Ar}H); *m/z* HRMS (ESI⁺) C₆H₈NO⁺ ([M+H]⁺) requires 110.0600; found 110.0599 (-0.9 ppm).

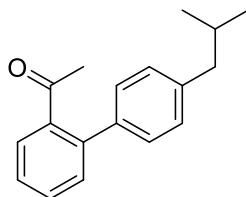
acetophenone (92):



Following **General Procedure 4**, at 20 °C for 18 hours with 2-phenylbenzo[*d*]oxazole (**91**) (195.2 mg, 1.00 mmol), PhMe (6.0 mL) and (trimethylsilyl)methyl lithium (2.2 mL, 1.30 mmol, 0.6 M in pentane). Purification *via* column chromatography on silica gel (eluent EtOAc:hexane, 0:100 to 5:95) gave acetophenone (**92**) (76.9 mg, 64 %) as a pale yellow oil with spectroscopic data in agreement with the literature.³²⁶

δ_{H} (500 MHz, CDCl₃) 7.98–7.94 (2H, m, C_{Ar}C_{Ar}H), 7.59–7.53 (1H, m, C_{Ar}H), 7.49-7.42 (2H, m, C_{Ar}H), 2.60 (3H, s, CH₃); δ_{C} (125 MHz, CDCl₃) 198.3 (O=C), 137.2 (O=CC_{Ar}), 133.2 (C_{Ar}H), 128.7 (2C, C_{Ar}H), 128.4 (2C, C_{Ar}H), 26.7 (CH₃); *m/z* HRMS (EI⁺) C₈H₈⁺ ([M]⁺) requires 120.0575; found 120.0578 (+2.5 ppm).

2'-(4'-isobutylphenyl)acetophenone (93):



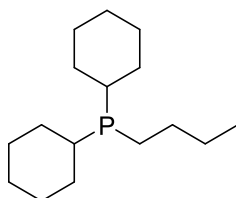
Following **General Procedure 4**, at 80 °C for 21 hours with 2-(4'-isobutyl-[1,1'-biphenyl]-2-yl)benzo[*d*]oxazole (**76**) (160.5 mg, 0.50 mmol), PhMe (3.0 mL) and (trimethylsilyl)methyl lithium (1.1 mL, 0.65 mmol, 0.6 M in pentane). Purification *via* column chromatography on silica gel (eluent EtOAc:hexane, 5:95 to 10:90) gave 2'-(4'-isobutylphenyl)acetophenone (**93**) (68.7 mg, 54 %) as a yellow oil.

ν_{\max} (ATR) 2953 (w), 1684 (s), 1508 (w), 1458 (w), 1354 (w), 1265 (m), 1233 (m), 849 (m), 800 (w), 756 (s); δ_{H} (500 MHz, CDCl_3) 7.57–7.48 (2H, m, $\text{O}=\text{CC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$, $\text{C}_{\text{Ar}}\text{H}$), 7.43–7.37 (2H, m, $\text{C}_{\text{Ar}}\text{H}$, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 7.25 (2H, d, J 8.5, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 7.20 (2H, d, J 8.5, $\text{CH}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 2.53 (2H, d, J 7.2, CH_2), 1.98 (3H, s, $\text{O}=\text{CCH}_3$), 1.91 (1H, m, CH), 0.93 (6H, d, J 6.6, CHCH_3); δ_{C} (125 MHz, CDCl_3) 205.5 ($\text{O}=\text{C}$), 141.7 ($\text{C}_{\text{Ar}}\text{CH}_2$), 141.1 ($\text{O}=\text{CC}_{\text{Ar}}$), 140.7 ($\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}$), 138.1 ($\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}$), 130.8 ($\text{C}_{\text{Ar}}\text{H}$), 130.3 ($\text{C}_{\text{Ar}}\text{H}$), 129.6 (2C, $\text{C}_{\text{Ar}}\text{H}$), 128.8 (2C, $\text{C}_{\text{Ar}}\text{H}$), 127.9 ($\text{C}_{\text{Ar}}\text{H}$), 127.4 ($\text{C}_{\text{Ar}}\text{H}$), 45.2 (CH_2), 30.5 ($\text{O}=\text{CCH}_3$), 30.4 (CHCH_3), 22.5 (2C, CHCH_3); m/z HRMS (ESI⁺) $\text{C}_{18}\text{H}_{20}\text{ONa}^+$ ($[\text{M}+\text{Na}]^+$) requires 275.1406; found 275.1400 (-2.2 ppm).

7.6 – Preparation of nickel complexes

7.6.1 – Preparation of phosphine ligands

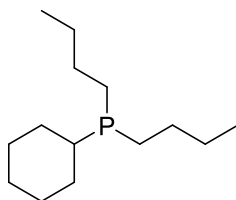
dicyclohexylⁿbutylphosphine (**99**):



To a 0 °C solution of chlorodicyclohexylphosphine (475 μ L, 2.15 mmol) in anhydrous and degassed Et₂O (3 mL) was added ⁿBuMgCl (4.0 mL, 5.38 mmol, 1.4 M in Et₂O) dropwise under an argon atmosphere. The reaction mixture was then stirred at 35 °C for 16 hours. Reaction completion was confirmed by a crude ³¹P NMR sample and then anhydrous and degassed MeOH (2 mL) was added dropwise at 0 °C. The mixture was concentrated under reduced pressure, washed with dry and degassed hexane (3 x 3 mL) and filtered by cannula under argon. The filtrate was concentrated under reduced pressure to give dicyclohexylⁿbutylphosphine (**99**) (421.2 mg, 78 %) as a colourless oil which was confirmed by ³¹P NMR, then complexed to nickel without further analysis.

δ_P (202 MHz, C₆D₆) -5.8.

cyclohexyldiⁿbutylphosphine (**100**):

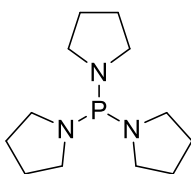


To a 0 °C solution of cyclohexyldichlorophosphine (664 μ L, 4.32 mmol) in anhydrous and degassed Et₂O (6 mL) was added ⁿBuMgCl (16.0 mL, 21.60 mmol, 1.4 M in Et₂O) dropwise under an argon atmosphere. The reaction mixture was then stirred at 35 °C for 16 hours. Reaction completion was confirmed by a crude ³¹P NMR sample and then

anhydrous and degassed MeOH (2 mL) was added dropwise at 0 °C. The mixture was concentrated under reduced pressure, washed with dry and degassed hexane (3 x 6 mL) and filtered by cannula under argon. The filtrate was concentrated under reduced pressure to give cyclohexyldiⁿbutylphosphine (**100**) (720.9 mg, 73 %) as a pale yellow oil.

δ_{H} (500 MHz, C_6D_6) 1.83–1.69 (4H, m, CH_2), 1.51–1.27 (15H, m, CH , CH_2), 1.23–1.15 (4H, m, CH_2), 0.90 (6H, t, J 7.2, CH_3); δ_{P} (202 MHz, C_6D_6) -19.6; δ_{C} (125 MHz, C_6D_6) 35.7 (d, $J_{\text{C-P}}$ 12.6, C_{cycloH}), 29.7 (2C, d, $J_{\text{C-P}}$ 11.8, $\text{C}_{\text{cycloH}_2}$), 29.2 (2C, d, $J_{\text{C-P}}$ 14.5, CH_2), 27.6 (2C, d, $J_{\text{C-P}}$ 9.3, $\text{C}_{\text{cycloH}_2}$), 27.0 ($\text{C}_{\text{cycloH}_2}$), 25.0 (2C, d, $J_{\text{C-P}}$ 10.8, CH_2), 24.5 (2C, d, $J_{\text{C-P}}$ 16.3, CH_2), 14.2 (2C, CH_3); m/z HRMS (EI^+) $\text{C}_{14}\text{H}_{29}\text{P}^+$ ($[\text{M}]^+$) requires 228.2007; found 228.2005 (-0.9 ppm).

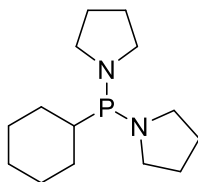
tripyrrolidinylphosphine (**101**):



*Prepared following a literature procedure.*³²⁷ To a -60 °C solution of trichlorophosphine (635 μL , 7.28 mmol) in anhydrous and degassed THF (15 mL) was added a solution of pyrrolidine (5.5 mL, 65.54 mmol) in THF (5 mL) dropwise under an argon atmosphere. The reaction mixture was then allowed to warm to room temperature and stirred for 16 hours. Reaction completion was confirmed by a crude ^{31}P NMR sample and then the mixture was filtered by cannula under argon and concentrated under reduced pressure. The resulting oil was washed with anhydrous and degassed hexane (2 x 10 mL) and filtered by cannula under argon. The filtrate was concentrated under reduced pressure to give tripyrrolidinylphosphine (**101**) (1.35 g, 77 %) as a colourless oil with spectroscopic data in agreement with the literature.³²⁸

δ_{H} (500 MHz, C_6D_6) 3.14-3.08 (12H, m, NCH_2), 1.63-1.57 (12H, m, NCH_2CH_2); δ_{P} (202 MHz, C_6D_6) 104.0; δ_{C} (125 MHz, C_6D_6) 47.8 (6C, d, $J_{\text{C-P}}$ 16.5, NCH_2), 26.4 (6C, d, $J_{\text{C-P}}$ 4.8, NCH_2CH_2); m/z HRMS (EI^+) $\text{C}_{12}\text{H}_{24}\text{N}_3\text{P}^+$ ($[\text{M}]^+$) requires 241.1708; found 241.1712 (+1.7 ppm).

cyclohexyl(dipyrrolidinyl)phosphine (**102**):



To a 0 °C solution of cyclohexyldichlorophosphine (664 μ L, 4.32 mmol) in anhydrous and degassed Et₂O (6 mL) was added pyrrolidine (1.8 mL, 21.60 mmol) dropwise under an argon atmosphere. The reaction mixture was then stirred at 35 °C for 16 hours. Reaction completion was confirmed by a crude ³¹P NMR sample and then the mixture was filtered by cannula under argon and concentrated under reduced pressure. The resulting oil was washed with anhydrous and degassed hexane (2 x 6 mL) and filtered by cannula under argon. The filtrate was concentrated under reduced pressure to give cyclohexyl(dipyrrolidinyl)phosphine (**102**) (1.06 g, 97 %) as a colourless oil.

δ_{H} (500 MHz, C₆D₆) 3.14-3.08 (8H, m, NCH₂), 1.87-1.77 (4H, m, CH₂), 1.71-1.66 (1H, m, CH), 1.60-1.50 (8H, m, NCH₂CH₂), 1.44-1.19 (6H, m, CH₂); δ_{P} (202 MHz, C₆D₆) 75.2; δ_{C} (125 MHz, C₆D₆) 49.7 (4C, d, $J_{\text{C-P}}$ 10.2, NCH₂), 34.9 (d, $J_{\text{C-P}}$ 2.5, CH), 29.2 (d, $J_{\text{C-P}}$ 19.0, CH₂), 27.5 (d, $J_{\text{C-P}}$ 12.0, CH₂), 27.2 (CH₂), 26.6 (d, $J_{\text{C-P}}$ 4.4, NCH₂CH₂); m/z HRMS (ESI⁺) C₁₄H₂₈N₂P⁺ ([M+H]⁺) requires 255.1985; found 255.1982 (-1.2 ppm).

7.6.2 – Preparation of nickel complexes

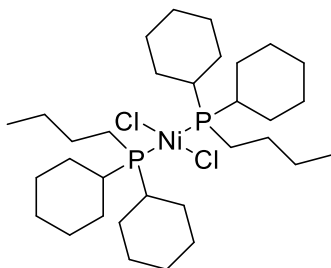
7.6.2.1 – General procedure 5: Preparation of nickel complexes

*Prepared following a modification of a literature procedure.*¹⁸⁹ NiCl₂·6H₂O, EtOH and a magnetic stir bar were added to a flame dried Schlenk flask. The solution was sparged with nitrogen for 15 minutes and a solution of phosphine (2.1 equiv.) in EtOH was added in one portion. The reaction mixture was stirred at 80 °C for 16 hours and then cooled to room temperature. Once cool, the flask was chilled to 0 °C for 10 minutes, after which the solid was collected by cannula filtration, washed twice with EtOH and twice with Et₂O. Drying under vacuum yielded the desired nickel(II) complex.

7.6.2.2 – Product data

As is normal with nickel (II) complexes, some broadness appears in the NMR spectra due to paramagnetic effects (either traces or not idealised square planar geometries).

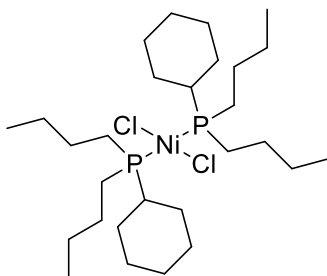
[NiCl₂(PCy₂ⁿBu)₂] (**103**):



Following **General Procedure 5**, with NiCl₂·6H₂O (94.0 mg, 0.40 mmol), EtOH (1 mL) and dicyclohexylⁿbutylphosphine (**99**) (210.6 mg, 0.83 mmol) in EtOH (2 mL), gave [NiCl₂(PCy₂ⁿBu)₂] (**103**) (208.5 mg, 83 %) as a fine, red powder.

mp 140-142 °C; ν_{\max} (ATR) 2914 (s), 2845 (m), 1458 (w), 1441 (m), 1206 (w), 1171 (w), 1049 (w), 1003 (m), 907 (w), 887 (w), 847 (m), 752 (m); δ_{H} (500 MHz, C₆D₆) 2.70-2.45 (4H, m, CH₂), 2.02-1.40 (40H, m, CH₂, CH), 1.36-1.16 (12H, m, CH₂), 0.99 (6H, m, CH₃); δ_{P} (202 MHz, C₆D₆) 9.5; δ_{C} (125 MHz, C₆D₆) 33.4 (CH), 30.1 (CH₂), 29.5 (CH₂), 28.2 (CH₂), 28.0 (CH₂), 27.7 (CH₂), 26.9 (CH₂), 25.7 (CH₂), 18.8 (CH₂), 14.2 (CH₃); m/z HRMS (APCI⁺) C₃₂H₆₂ClNiP₂⁺ ([M-Cl]⁺) requires 601.3369; found 601.3363 (-1.0 ppm); Anal. Calcd for C₃₂H₆₂Cl₂NiP₂: C, 60.21; H, 9.79; Found: C, 60.32; H, 9.90.

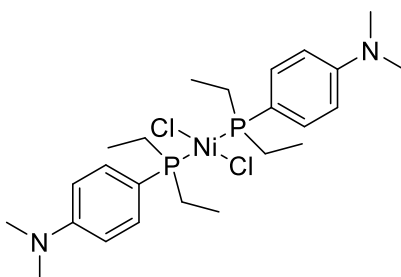
[NiCl₂(PCyⁿBu₂)₂] (104):



Following **General Procedure 5**, with NiCl₂·6H₂O (349.8 mg, 1.47 mmol), EtOH (4 mL) and cyclohexyldiⁿbutylphosphine (**100**) (705.9 mg, 3.09 mmol) in EtOH (2 mL), gave [NiCl₂(PCyⁿBu₂)₂], (**104**) (569.9 mg, 66 %) as a fine, red powder.

mp 68-69 °C; ν_{\max} (ATR) 2953 (m), 2918 (s), 2849 (m), 1449 (m), 1092 (w), 1061 (m), 1045 (w), 1001 (w), 907 (m), 891 (w), 777 (s); δ_{H} (500 MHz, C₆D₆) 2.30 (4H, app d, *J* 12.4, CH₂), 2.10-1.97 (6H, m, CH₂, CH), 1.83-1.67 (16H, m, CH₂), 1.65-1.58 (2H, m, CH₂), 1.52-1.39 (12H, m, CH₂), 1.28-1.16 (6H, m, CH₂), 0.96 (12H, t, *J* 7.3, CH₃); δ_{P} (202 MHz, C₆D₆) 5.9; δ_{C} (125 MHz, C₆D₆) 34.7 (CH), 29.3 (CH₂), 27.6 (CH₂), 27.4 (CH₂), 26.8 (CH₂), 25.3 (CH₂), 19.9 (CH₂), 14.1 (CH₃); *m/z* HRMS (APCI⁺) C₂₈H₅₈ClNiP₂⁺ ([M-Cl]⁺) requires 549.3056; found 549.3056 (±0.0 ppm); Anal. Calcd for C₂₈H₅₈Cl₂NiP₂: C, 57.36; H, 9.97; Found: C, 57.47; H, 9.89.

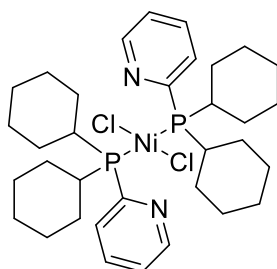
[NiCl₂(PEt₂Ar)₂], Ar = 4-(NMe₂)C₆H₄, (105):



Following **General Procedure 5**, with NiCl₂·6H₂O (134.7 mg, 0.57 mmol), EtOH (3 mL) and neat diethyl[4-(*N,N*-dimethylamino)phenyl]phosphine (244 μ L, 1.19 mmol), gave [NiCl₂(PEt₂Ar)₂], Ar = 4-(NMe₂)C₆H₄, (**105**) (291.5 mg, 94 %) as a fine, dark red powder. mp 108-110 °C; ν_{\max} (ATR) 2880 (w), 1595 (m), 1508 (m), 1447 (w), 1362 (m), 1227 (w), 1206 (m), 1105 (m), 1072 (w), 1036 (m), 1024 (m), 980 (w), 943 (w), 808 (s), 758

(m); δ_{H} (500 MHz, C_6D_6) 7.75 (4H, br d, J 8.2, $\text{C}_{\text{Ar}}\text{H}$), 6.57 (4H, br d, J 8.2, $\text{C}_{\text{Ar}}\text{H}$), 3.41-2.64 (8H, m, CH_2), 2.48 (12H, s, NCH_3), 1.27 (12H, br t, CH_3); δ_{C} (125 MHz, C_6D_6) 151.8 (2C, $\text{C}_{\text{Ar}}\text{N}$), 135.7 (4C, $\text{C}_{\text{Ar}}\text{H}$), 120.3 (2C, C_{Ar}), 112.2 (4C, $\text{C}_{\text{Ar}}\text{H}$), 39.6 (4C, NCH_3), 18.1 (4C, CH_2), 10.2 (4C, CH_3); Anal. Calcd for $\text{C}_{24}\text{H}_{40}\text{Cl}_2\text{N}_2\text{NiP}_2$: C, 52.59; H, 7.36; N, 5.11; Found: C, 52.72; H, 7.44; N, 5.14.

[NiCl₂(P(2-py)Cy₂)], py = pyridine, (**109**):



2-(dicyclohexylphosphino)pyridine, (**108**), was prepared following a literature procedure.³²⁹ To anhydrous and degassed Et₂O (2.2 mL) at -100 °C was added ⁿBuLi (1.6 mL, 2.15 mmol, 1.3 M in hexane) under an argon atmosphere and the mixture was stirred for 10 minutes. 2-bromopyridine (205 μL , 2.15 mmol) was added slowly to the cold solution. The resulting mixture was stirred for 2 hours at -90 °C. At this temperature, chlorodicyclohexylphosphine (474 μL , 2.15 mmol) was added slowly and stirred for 2 hours. After that, the solution was slowly warmed to 20 °C and the solution was then quenched with anhydrous and degassed MeOH (1 mL). The mixture was filtered by cannula under argon and the filtrate was concentrated under reduced pressure to give 2-(dicyclohexylphosphino)pyridine (**108**) (541.1 mg, 91 % yield isolated with 2-bromopyridine impurity; total product obtained = 81 %) as a brown oil, which was confirmed by ³¹P NMR and HRMS, then complexed to nickel without further analysis. Spectroscopic data in agreement with the literature:³²⁹

δ_{P} (162 MHz, C_6D_6) 7.0; m/z HRMS (EI⁺) $\text{C}_{17}\text{H}_{26}\text{NP}^+$ ($[\text{M}]^+$) requires 275.1803; found 275.1800 (-1.1 ppm).

[NiCl₂(P(2-py)Cy₂)] (**109**) was prepared following **General Procedure 5**, with NiCl₂·6H₂O (77.9 mg, 0.33 mmol), EtOH (1.5 mL) and 2-

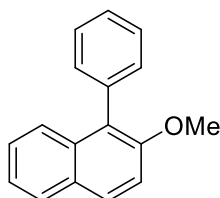
(dicyclohexylphosphino)pyridine (**108**) (270.6 mg, 0.98 mmol) in EtOH (1 mL) giving a fine, red powder (152.6 mg, 68 %).

mp 199-202 °C ; ν_{\max} (ATR) 2924 (s), 2847 (m), 1574 (m), 1559 (m), 1447 (s), 1418 (s), 1113 (m), 1003 (m), 887 (s), 847 (m), 756 (m); δ_{H} (500 MHz, C_6D_6) 8.59-8.45 (2H, m, $\text{NC}_{\text{py}}\text{H}$), 8.19 (2H, d, J 7.8, $\text{C}_{\text{py}}\text{H}$), 7.07 (2H, app t, J 7.8, $\text{C}_{\text{py}}\text{H}$), 6.59-6.44 (2H, m, $\text{C}_{\text{py}}\text{H}$), 3.65 (4H, br s, CH), 2.62 (4H, d, J 12.7, CH_2), 2.27 – 1.94 (12H, m, CH_2), 1.82 (8H, dd, J 45.9, 12.7, CH_2), 1.62 (4H, d, J 12.0, CH_2), 1.46-1.15 (12H, m, CH_2); δ_{C} (125 MHz, C_6D_6) 156.9 (2C, NC_{py}), 149.6 (2C, $\text{NC}_{\text{py}}\text{H}$), 134.1 (2C, $\text{C}_{\text{Ar}}\text{H}$), 133.5 (2C, $\text{C}_{\text{Ar}}\text{H}$), 123.7 (2C, $\text{C}_{\text{Ar}}\text{H}$), 32.7 (4C, CH), 30.9 (4C, CH_2), 29.6 (4C, CH_2), 27.9 (4C, CH_2), 27.8 (4C, CH_2), 27.0 (4C, CH_2); Anal. Calcd for $\text{C}_{34}\text{H}_{52}\text{Cl}_2\text{N}_2\text{NiP}_2$: C, 60.02; H, 7.70; N, 4.12; Found: C, 60.05; H, 7.80; N, 4.24.

7.7 – Nickel-catalysed Grignard cross-coupling of aryl methyl ethers

7.7.1 – Preparation of 1-phenyl-2-methoxynaphthalene

1-phenyl-2-methoxynaphthalene (**137**):



1-bromo-2-methoxynaphthalene (2.0 g, 8.44 mmol) and [PdCl₂(dppf)] (61.5 mg, 0.084 mmol) were added to a flame dried Schlenk flask equipped with a stirrer bar. Degassed 2-MeTHF (10 mL) was added and the solution was stirred. PhMgBr (15.7 mL, 26.88 mmol, 1.7 M in Et₂O) was added dropwise to the solution over 15 minutes. The reaction mixture was stirred overnight at 80 °C. The reaction mixture was allowed to cool to ambient temperature and saturated aqueous ammonium chloride solution (10 mL) was added and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organics were dried over Na₂SO₄ and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (eluent petroleum ether:EtOAc, 100:0 to 95:5) to give 1-phenyl-2-methoxynaphthalene (**137**) (1.59 g, 81 %) as a white solid, with spectroscopic data in accordance with the literature.³³⁰

mp 50-52 °C {lit³³¹ 50-51 °C}; δ_H (500 MHz, CDCl₃) 7.89 (1H, d, *J* 9.0, C_{Ar}H), 7.86-7.81 (1H, m, C_{Ar}H), 7.53-7.47 (3H, m, C_{Ar}H), 7.46-7.41 (1H, m, C_{Ar}H), 7.40-7.36 (3H, m, C_{Ar}H), 7.36-7.31 (2H, m, C_{Ar}H), 3.85 (3H, s, OCH₃); δ_C (125 MHz, CDCl₃) 153.8 (C_{Ar}O), 136.5 (C_{Ar}), 133.7 (C_{Ar}), 131.1 (2C, C_{Ar}H), 129.2 (C_{Ar}H), 129.1 (C_{Ar}), 128.3 (2C, C_{Ar}H), 128.0 (C_{Ar}H), 127.2 (C_{Ar}H), 126.4 (C_{Ar}H), 125.5 (C_{Ar}), 125.4 (C_{Ar}H), 123.6 (C_{Ar}H), 113.9 (OC_{Ar}C_{Ar}H), 56.9 (OCH₃); *m/z* HRMS (EI⁺) C₁₇H₁₄O⁺ ([M]⁺) requires 234.1045; found 234.1046 (+0.4 ppm).

7.7.2 – General procedures

7.7.2.1 - General procedure 6: nickel-catalysed Grignard cross-coupling of aryl methyl ethers

To an oven dried microwave vial equipped with a stirrer bar was added the desired nickel catalyst. The vial was sealed with a crimp cap and flushed with argon for 30 minutes. Aryl ether (0.50 mmol) and 1-methylnaphthalene (60 μ L, 0.42 mmol, internal standard) were added to a flame dried Schlenk flask under an inert atmosphere. Degassed solvent (2.25 mL) was then added to the Schlenk flask to make a solution. A t_0 sample (approximately 10 μ L) was taken and analysed by ^1H NMR (to calibrate the ratio of internal standard to starting material). The solution containing the electrophile and internal standard was added to the nickel catalyst *via* syringe. The requisite Grignard solution was added dropwise over 15 minutes. The reaction mixture was stirred vigorously in an oil bath at a specific temperature for the required period of time. Upon cooling to rt, approximately 20 μ L of the crude reaction mixture was added to a vial and quenched with CDCl_3 . The resulting mixture was then filtered through a small cotton wool plug into an NMR tube and a ^1H NMR was run to assess the ratio between SM and desired product. Saturated aqueous ammonium chloride (5 mL) was added to the reaction mixture and the aqueous phase was extracted three times with ethyl acetate (3 x 5 mL), dried over sodium sulfate and concentrated under reduced pressure. Purification *via* either column chromatography on silica gel or trituration yielded product. The initial crude ^1H NMR was then spiked with product to verify product peaks.

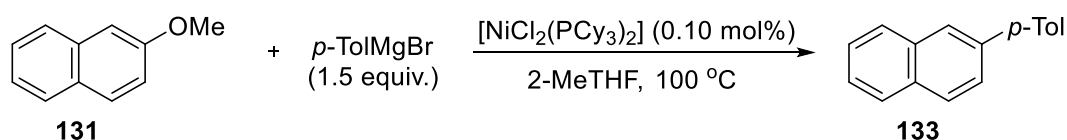
7.7.2.2 - General procedure 7: nickel-catalysed Grignard cross-coupling of aryl methyl ethers using NHC salts

NHC salt (10 mol%) was added to an oven dried microwave vial equipped with a stirrer bar and then sealed with a crimp cap and flushed with argon for 30 minutes. Under an inert atmosphere, a stock solution containing 6.88 mg mL^{-1} of $[\text{Ni}(\text{cod})_2]$ in 2-MeTHF was created. An aliquot (1 mL) of this solution was then added to the microwave vial. 2-methoxybiphenyl (**47**) (92.1 mg, 0.50 mmol) and 1-methylnaphthalene (60 μ L, 0.42

mmol, internal standard) were added to a separate flame dried Schlenk flask under an inert atmosphere. 2-MeTHF (1.25 mL) was then added to the Schlenk flask to make a solution. A t0 sample (approximately 10 μ L) was taken and analysed by ^1H NMR (to calibrate the ratio of internal standard to starting material). The solution containing the electrophile and internal standard was added to the microwave vial containing the nickel catalyst and NHC salt. *p*-TolMgBr (2.10 mL, 1.05 mmol, 0.5 M in Et₂O) was added dropwise over 15 minutes and the reaction mixture was stirred vigorously in an oil bath at 100 °C for 16 hours. Upon cooling to rt, approximately 20 μ L of the crude reaction mixture was added to a vial and quenched with CDCl₃. The resulting mixture was then filtered through a small cotton wool plug into an NMR tube and a ^1H NMR was run to assess the ratio between SM and desired product.

7.7.3 – Time profile analysis of the nickel-catalysed Grignard cross-coupling of 2-methoxynaphthalene (131) with *p*-TolMgBr.

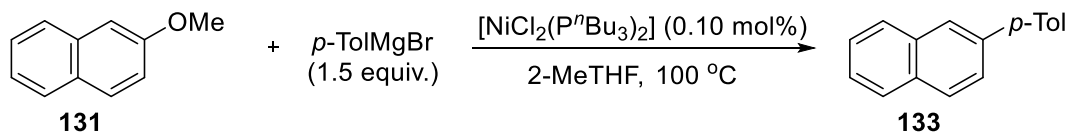
Table 7.1 – Time profile analysis for the reaction of 2-methoxynaphthalene (**131**) with *p*-TolMgBr using 0.10 mol% of [NiCl₂(PCy₃)₂].



Entry ^[a]	MgI ₂ (equiv.)	Catalyst	t (h)	Conversion (%)	Product (%)
1	0	[NiCl ₂ (PCy ₃) ₂]	4	3	0
			16	3	0
			28	10	1
			69	46	30
			90	68	43
2 ^[c]	0	[NiCl ₂ (PCy ₃) ₂]	16	3	0
			28	13	2
			69	56	34
			90	67	43
3	0	[NiCl ₂ (PCy ₃) ₂]	28	11	1
			69	66	40
			90	80	52
4	0	[NiCl ₂ (PCy ₃) ₂]	69	49	32
			90	68	42

^[a] Reactions were carried out on the scale of 2-methoxynaphthalene (0.50 mmol), *p*-TolMgBr (0.75 mmol in Et₂O, 0.5 M), Ni catalyst (0.0005 mmol), 2-MeTHF (2.25 mL) in sealed microwave vials with crimp cap unless otherwise noted. Data in **bold** used to produce Figure 4.9 in Section 4.2.3.5. ^[b] Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard. ^[c] Reaction spiked with P^{*n*}Bu₃ (0.033 mol%, in 25 μL) after 49 h.

Table 7.2 – Time profile analysis for the reaction of 2-methoxynaphthalene with *p*-TolMgBr using 0.10 mol% of [NiCl₂(PⁿBu₃)₂].



Entry ^[a]	Additive (equiv.)	Catalyst	t (h)	Conversion (%)	Product (%)
1	-	[NiCl ₂ (P ⁿ Bu ₃) ₂]	2	0	0
			4	0	0
			16	11	5
			28	19	15
			69	64	56
2	-	[NiCl ₂ (P ⁿ Bu ₃) ₂]	4	0	0
			16	11	4
			28	19	12
			69	64	50
3	-	[NiCl ₂ (P ⁿ Bu ₃) ₂]	16	0	0
			28	5	5
			69	34	33
4	-	[NiCl ₂ (P ⁿ Bu ₃) ₂]	28	15	12
			69	65	58
5 ^[c]	MgI ₂ (1.5)	[NiCl ₂ (P ⁿ Bu ₃) ₂]	11	25	22
			45	83	70
			59	85	72
			90	85	72
6 ^[c]	MgI ₂ (1.5)	[NiCl ₂ (P ⁿ Bu ₃) ₂]	11	23	21
			45	86	71
			59	88	73
			90	88	73
7 ^[d]	MeOH (0.3)	[NiCl ₂ (P ⁿ Bu ₃) ₂]	4	9	7
			16	39	36
			28	65	59
			69	83	72
			90	84	72
8 ^[e]	BrMg(OMe) (0.3)	[NiCl ₂ (P ⁿ Bu ₃) ₂]	4	0	0
			16	12	10
			28	28	24
			69	81	72
			90	81	72
9 ^[f]	MgI ₂ (1.5)	-	45	0	0

^[a] Reactions were carried out on the scale of 2-methoxynaphthalene (0.50 mmol), *p*-TolMgBr (0.75 mmol in Et₂O, 0.5 M), Ni catalyst (0.0005 mmol), 2-MeTHF (2.25 mL) in sealed microwave vials with crimp cap unless otherwise noted. Data in **bold** used to produce Figure 4.9 in Section 4.2.3.5. ^[b] Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard. ^[c] MgI₂ (0.75 mmol) added prior to the start of the reaction. ^[d] MeOH (0.15 mmol) added to the solution containing catalyst and substrate, prior to addition of Grignard reagent (0.90 mmol). ^[e] MeOH (0.15 mmol) added to the Grignard reagent (0.90 mmol) prior to the addition of catalyst and substrate. ^[f] No nickel catalyst.

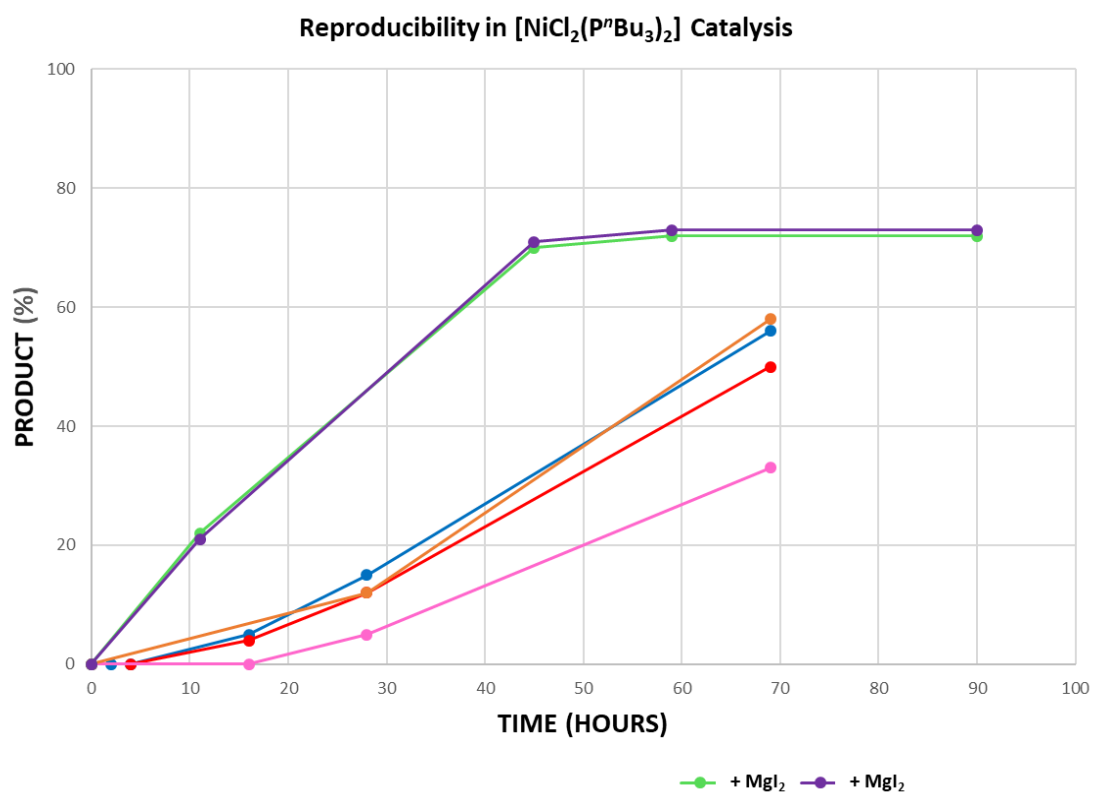
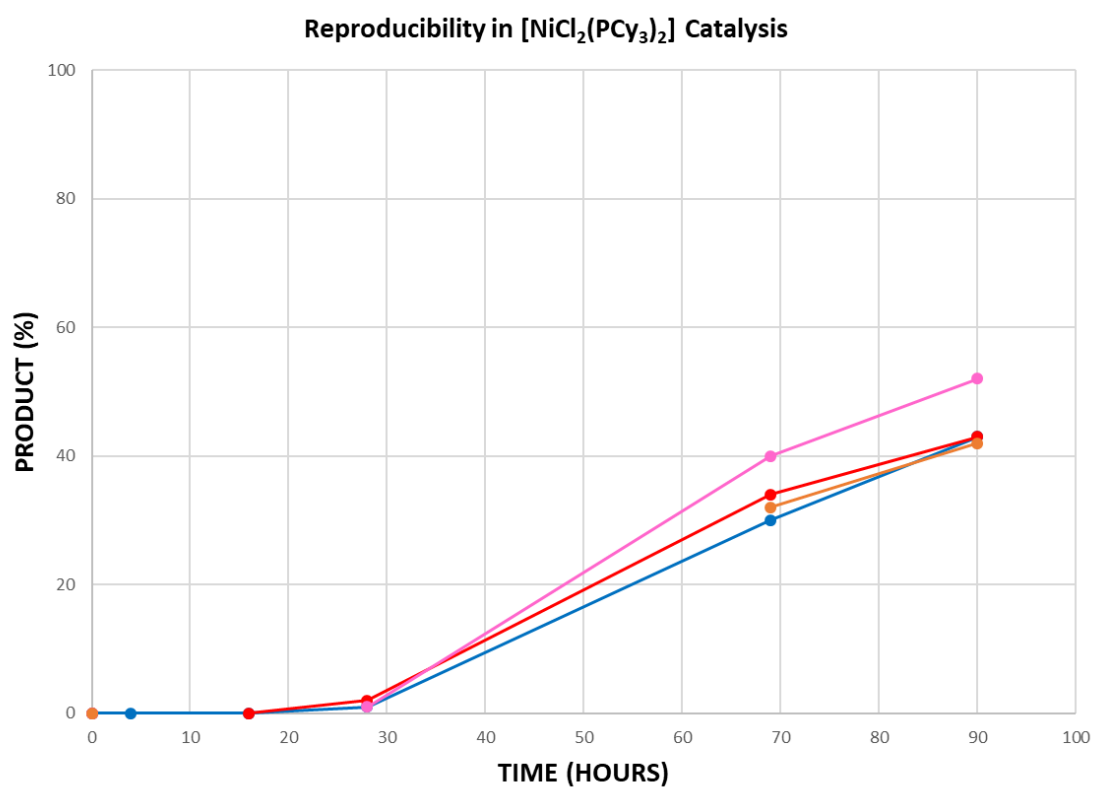
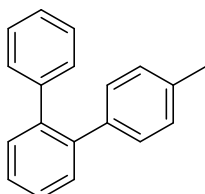


Figure 7.2 – Reproducibility in the reaction of 2-methoxynaphthalene with *p*-TolMgBr (1.5 equiv.) using 0.10 mol% of nickel catalyst. (Green and purple – 1.5 equiv. MgI₂ added prior to reaction). Results taken from Tables 7.1 (entries 1-4) and 7.2 (entries 1-6).

7.7.4 – Product data

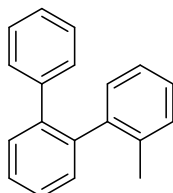
4-methyl-1,1':2',1''-terphenyl (**107**):



Prepared following **general procedure 6** at 100 °C for 16 hours with 2-methoxybiphenyl (**47**) (92.1 mg, 0.50 mmol), 1-methylnaphthalene (60 μ L, 0.42 mmol), 2-MeTHF (2.25 mL), $\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2$ (13.4 mg, 0.025 mmol) and *p*-tolylmagnesium bromide (1.50 mL, 0.75 mmol, 0.5 M in Et_2O). Purification *via* column chromatography on silica gel (eluent petroleum ether) gave 4-methyl-1,1':2',1''-terphenyl (**107**) (102.7 mg, 84 %) as a white crystalline solid with spectroscopic data in accordance with the literature.³³²

mp 70-73 °C {lit³³³ 60-62 °C}; δ_{H} (500 MHz, CDCl_3); 7.45-7.39 (4H, m, C_{ArH}), 7.26-7.20 (3H, m, C_{ArH}), 7.19-7.15 (2H, m, C_{ArH}), 7.06-7.01 (4H, m, C_{ArH}), 2.32 (3H, s, CH_3); δ_{C} (125 MHz, CDCl_3) 141.8 (C_{Ar}), 140.6 (2C, C_{Ar}), 138.7 (C_{Ar}), 136.2 (C_{Ar}), 130.8 (2C, C_{ArH}), 130.0 (2C, C_{ArH}), 129.9 (2C, C_{ArH}), 128.8 (2C, C_{ArH}), 128.0 (2C, C_{ArH}), 127.6 (C_{ArH}), 127.4 (C_{ArH}), 126.5 (C_{ArH}), 21.3 (CH_3); m/z HRMS (EI^+) $\text{C}_{19}\text{H}_{16}^+$ ($[\text{M}]^+$) requires 244.1252; found 244.1250 (-0.8 ppm).

2-methyl-1,1':2',1''-terphenyl (**113**):

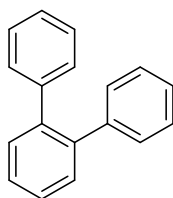


Prepared following **general procedure 6** at 100 °C for 16 hours with 2-methoxybiphenyl (**47**) (92.1 mg, 0.50 mmol), 1-methylnaphthalene (60 μ L, 0.42 mmol), 2-MeTHF (2.25 mL), $\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2$ (13.4 mg, 0.025 mmol) and *o*-tolylmagnesium bromide (375 μ L, 0.75 mmol, 2.0 M in Et_2O). Purification *via* column chromatography on silica gel (eluent

petroleum ether) gave 2-methyl-1,1':2',1''-terphenyl (**113**) (25.6 mg, 21 %) as a colourless oil with spectroscopic data in accordance with the literature.³³⁴

δ_{H} (500 MHz, CDCl_3); 7.49-7.38 (3H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.31 (1H, dd, J 7.4, 1.7, $\text{C}_{\text{Ar}}\text{H}$), 7.24-7.11 (8H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.08 (1H, d, J 7.8, $\text{C}_{\text{Ar}}\text{H}$), 1.92 (3H, s, CH_3); δ_{C} (125 MHz, CDCl_3) 141.5 (C_{Ar}), 141.4 (C_{Ar}), 141.1 (C_{Ar}), 140.4 (C_{Ar}), 135.9 (C_{Ar}), 130.8 ($\text{C}_{\text{Ar}}\text{H}$), 130.7 ($\text{C}_{\text{Ar}}\text{H}$), 130.1 ($\text{C}_{\text{Ar}}\text{H}$), 129.9 ($\text{C}_{\text{Ar}}\text{H}$), 129.5 (2C, $\text{C}_{\text{Ar}}\text{H}$), 127.8 (2C, $\text{C}_{\text{Ar}}\text{H}$), 127.6 ($\text{C}_{\text{Ar}}\text{H}$), 127.2 ($\text{C}_{\text{Ar}}\text{H}$), 127.1 ($\text{C}_{\text{Ar}}\text{H}$), 126.6 ($\text{C}_{\text{Ar}}\text{H}$), 125.4 ($\text{C}_{\text{Ar}}\text{H}$), 20.2 (CH_3); m/z HRMS (EI^+) $\text{C}_{19}\text{H}_{16}^+$ ($[\text{M}]^+$) requires 244.1252; found 244.1250 (-0.8 ppm).

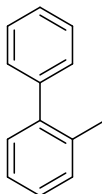
1,1':2',1''-terphenyl (**114**):



Prepared following **general procedure 6** at 100 °C for 16 hours with 2-methoxybiphenyl (**47**) (92.1 mg, 0.50 mmol), 1-methylnaphthalene (60 μL , 0.42 mmol), 2-MeTHF (2.25 mL), $\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2$ (13.4 mg, 0.025 mmol) and phenylmagnesium bromide (439 μL , 0.75 mmol, 1.7 M in Et_2O). Purification *via* column chromatography on silica gel (eluent petroleum ether) gave 1,1':2',1''-terphenyl (**114**) (98.6 mg, 86 %) as a colourless oil with spectroscopic data in accordance with the literature.³³⁵

δ_{H} (500 MHz, CDCl_3); 7.49-7.42 (4H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.26-7.20 (6H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.19-7.14 (4H, m, $\text{C}_{\text{Ar}}\text{H}$); δ_{C} (125 MHz, CDCl_3) 141.6 (2C, C_{Ar}), 140.7 (2C, C_{Ar}), 130.7 (2C, $\text{C}_{\text{Ar}}\text{H}$), 130.0 (4C, $\text{C}_{\text{Ar}}\text{H}$), 128.0 (4C, $\text{C}_{\text{Ar}}\text{H}$), 127.6 (2C, $\text{C}_{\text{Ar}}\text{H}$), 126.6 (2C, $\text{C}_{\text{Ar}}\text{H}$); m/z HRMS (EI^+) $\text{C}_{18}\text{H}_{14}^+$ ($[\text{M}]^+$) requires 230.1096; found 230.1092 (-1.7 ppm).

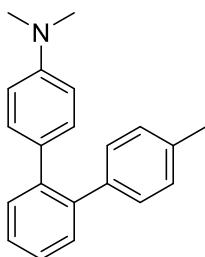
2-methylbiphenyl (**118**):



Prepared following **general procedure 6** at 100 °C for 16 hours with 2-methoxybiphenyl (**47**) (92.1 mg, 0.50 mmol), 1-methylnaphthalene (60 μ L, 0.42 mmol), PhMe (2.25 mL), $\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2$ (13.4 mg, 0.025 mmol) and methylmagnesium bromide (434 μ L, 1.05 mmol, 2.4 M in Et_2O). Purification *via* column chromatography on silica gel (eluent petroleum ether) gave a mixture of 2-methylbiphenyl (**118**) and 1-methylnaphthalene (88:12, ^1H NMR) (22.9 mg) [total product = 24 %] as a colourless oil with spectroscopic data in accordance with the literature.³³⁶

δ_{H} (500 MHz, CDCl_3); 7.48-7.41 (2H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.39-7.34 (3H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.32-7.24 (4H, m, $\text{C}_{\text{Ar}}\text{H}$), 2.31 (3H, s, CH_3); δ_{C} (125 MHz, CDCl_3) 142.1 (C_{Ar}), 142.1 (C_{Ar}), 135.5 (C_{Ar}), 130.4 ($\text{C}_{\text{Ar}}\text{H}$), 129.9 ($\text{C}_{\text{Ar}}\text{H}$), 129.3 (2C, $\text{C}_{\text{Ar}}\text{H}$), 128.2 (2C, $\text{C}_{\text{Ar}}\text{H}$), 127.4 ($\text{C}_{\text{Ar}}\text{H}$), 126.9 ($\text{C}_{\text{Ar}}\text{H}$), 125.9 ($\text{C}_{\text{Ar}}\text{H}$), 20.6 (CH_3); m/z HRMS (EI^+) $\text{C}_{13}\text{H}_{12}^+$ ($[\text{M}]^+$) requires 168.0939; found 168.0938 (-0.6 ppm).

2-(4-*N,N*-dimethylaminophenyl)-4'-dimethyl-1,1'-biphenyl (**124**):

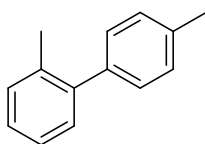


Prepared following **general procedure 6** at 100 °C for 16 hours with 4'-(*N,N*-dimethylamino)-2-methoxybiphenyl (113.7 mg, 0.50 mmol), 1-methylnaphthalene (60 μ L, 0.42 mmol), 2-MeTHF (2.25 mL), $\text{NiCl}_2(\text{P}^t\text{Bu}_3)_2$ (13.4 mg, 0.025 mmol) and *p*-tolylmagnesium bromide (1.50 mL, 0.75 mmol, 0.5 M in Et_2O). Purification *via* column chromatography on silica gel (eluent petroleum ether:EtOAc, 100:0 to 99:1) gave 2-(4-

N,N-dimethylaminophenyl)-4'-dimethyl-1,1'-biphenyl (**124**) (56.9 mg, 40 %) as a light yellow oil.

ν_{\max} (ATR) 2920 (w), 2245 (w), 1713 (w), 1611 (m), 1524 (m), 1477 (m), 1441 (w), 1352 (m), 1221 (w), 1196 (w), 907 (s), 818 (s), 758 (s); δ_{H} (500 MHz, CDCl_3) 7.46-7.34 (4H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.13-7.09 (2H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.09-7.04 (4H, m, $\text{C}_{\text{Ar}}\text{H}$), 6.67-6.61 (2H, m, $\text{NC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 2.95 (6H, s, NCH_3), 2.35 (3H, s, CH_3); δ_{C} (125 MHz, CDCl_3) 149.1 ($\text{C}_{\text{Ar}}\text{NCH}_3$), 140.6 (C_{Ar}), 140.3 (2C, C_{Ar}), 139.2 ($\text{CH}_3\text{C}_{\text{Ar}}$), 135.9 (C_{Ar}), 130.8 ($\text{C}_{\text{Ar}}\text{H}$), 130.7 (2C, $\text{C}_{\text{Ar}}\text{H}$), 130.6 ($\text{C}_{\text{Ar}}\text{H}$), 129.8 (2C, $\text{C}_{\text{Ar}}\text{H}$), 128.8 (2C, $\text{H}_3\text{CC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 127.4 ($\text{C}_{\text{Ar}}\text{H}$), 126.7 ($\text{C}_{\text{Ar}}\text{H}$), 112.9 (2C, $\text{NC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 40.7 (2C, NCH_3), 21.3 ($\text{C}_{\text{Ar}}\text{CH}_3$); m/z HRMS (ESI^+) $\text{C}_{21}\text{H}_{22}\text{N}^+$ ($[\text{M}+\text{H}]^+$) requires 288.1747; found 288.1741 (-2.1 ppm).

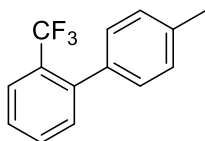
2,4'-dimethyl-1,1'-biphenyl (**127**):



Prepared following **general procedure 6** at 100 °C for 64 hours with 2-methylanisole (61.1 mg, 0.50 mmol), 1-methylnaphthalene (60 μL , 0.42 mmol), 2-MeTHF (2.25 mL), $\text{NiCl}_2(\text{P}^i\text{Bu}_3)_2$ (26.7 mg, 0.05 mmol) and *p*-tolylmagnesium bromide (2.10 mL, 1.05 mmol, 0.5 M in Et_2O). Purification *via* column chromatography on silica gel (eluent petroleum ether) gave a mixture of 2,4'-dimethyl-1,1'-biphenyl (**127**) and 1-methylnaphthalene (93:7, ^1H NMR) (36.8 mg) [total product = 38 %] as a colourless oil with spectroscopic data in accordance with the literature.³³⁷

δ_{H} (500 MHz, CDCl_3); 7.29-7.22 (8H, m, $\text{C}_{\text{Ar}}\text{H}$), 2.42 (3H, s, $\text{C}_{\text{Ar}}\text{CH}_3$), 2.30 (3H, s, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{CH}_3$); δ_{C} (125 MHz, CDCl_3) 142.0 (C_{Ar}), 139.1 (C_{Ar}), 136.5 (C_{Ar}), 135.5 (C_{Ar}), 130.4 ($\text{CH}_3\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 130.0 ($\text{C}_{\text{Ar}}\text{H}$), 129.2 (2C, $\text{C}_{\text{Ar}}\text{H}$), 128.9 (2C, $\text{CH}_3\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 127.2 ($\text{C}_{\text{Ar}}\text{H}$), 125.9 ($\text{C}_{\text{Ar}}\text{H}$), 21.3 ($\text{C}_{\text{Ar}}\text{CH}_3$), 20.7 ($\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{CH}_3$); m/z HRMS (EI^+) $\text{C}_{14}\text{H}_{14}^+$ ($[\text{M}]^+$) requires 182.1096; found 182.1098 (+1.1 ppm).

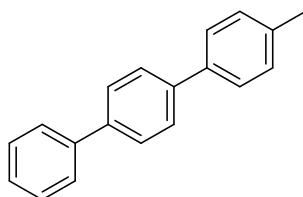
4'-methyl-2-(trifluoromethyl)-1,1'-biphenyl (**128**):



Prepared following **general procedure 6** at 100 °C for 16 hours with 2-(trifluoromethyl)anisole (88.1 mg, 0.50 mmol), 1-methylnaphthalene (60 μ L, 0.42 mmol), 2-MeTHF (2.25 mL), $\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2$ (13.4 mg, 0.025 mmol) and *p*-tolylmagnesium bromide (2.10 mL, 1.05 mmol, 0.5 M in Et_2O). Purification *via* column chromatography on silica gel (eluent petroleum ether) to give a mixture of 4'-methyl-2-(trifluoromethyl)-1,1'-biphenyl (**128**) and 1-methylnaphthalene (32:68, ^1H NMR) (69.0 mg) [total product = 26 %] as a colourless oil with spectroscopic data in accordance with the literature.³⁰⁶

δ_{H} (500 MHz, CDCl_3); 7.75 (1H, d, J 7.9, $\text{C}_{\text{Ar}}\text{H}$), 7.58-7.48 (1H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.46 (1H, app. t, J 7.6, $\text{C}_{\text{Ar}}\text{H}$), 7.35-7.32 (1H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.24 (4H, s, $\text{C}_{\text{Ar}}\text{H}$), 2.43 (1H, s, CH_3); δ_{F} (470 MHz, CDCl_3) -56.7; δ_{C} (125 MHz, CDCl_3) 141.6 (q, $J_{\text{C-F}}$ 1.7, C_{Ar}), 137.4 (C_{Ar}), 137.1 (C_{Ar}), 132.3 (2C, $\text{C}_{\text{Ar}}\text{H}$), 131.4 ($\text{C}_{\text{Ar}}\text{H}$), 128.9 (d, $J_{\text{C-F}}$ 1.9, $\text{C}_{\text{Ar}}\text{H}$), 128.6 (2C, $\text{C}_{\text{Ar}}\text{H}$), 128.5 (C_{Ar}), 127.3 ($\text{C}_{\text{Ar}}\text{H}$), 126.1 (q, $J_{\text{C-F}}$ 5.3, $\text{C}_{\text{Ar}}\text{H}$), 124.4 (q, $J_{\text{C-F}}$ 273.9, $\text{C}_{\text{Ar}}\text{CF}_3$), 21.4 (CH_3); m/z HRMS (EI^+) $\text{C}_{14}\text{H}_{11}\text{F}_3^+$ ($[\text{M}]^+$) requires 236.0813; found 236.0804 (-3.8 ppm).

4-methyl-1,1':4',1''-terphenyl (**129**):

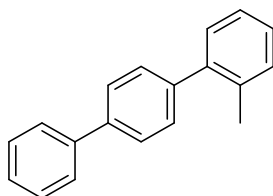


Prepared following **general procedure 6** at 100 °C for 16 hours with 4-methoxybiphenyl (92.1 mg, 0.50 mmol), 1-methylnaphthalene (60 μ L, 0.42 mmol), 2-MeTHF (2.25 mL), $\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2$ (13.4 mg, 0.025 mmol) and *p*-tolylmagnesium bromide (1.50 mL, 0.75 mmol, 0.5 M in Et_2O). Purification *via* filtration through a small plug of silica gel (eluent EtOAc), concentration under reduced pressure and trituration with petroleum ether (3 x

10 mL) gave 4-methyl-1,1':4',1''-terphenyl (**129**) (79.0 mg, 65 %) as a white solid with spectroscopic data in accordance with the literature.³¹²

mp 210-213 °C {lit³⁰² 214 °C}; δ_{H} (500 MHz, CDCl₃) 7.67 (4H, s, C_{Ar}H), 7.65 (2H, dd, *J* 8.3, 1.3, C_{Ar}C_{Ar}H), 7.57-7.53 (2H, m, C_{Ar}C_{Ar}H), 7.46 (2H, dd, *J* 8.3, 7.6, C_{Ar}C_{Ar}HC_{Ar}H), 7.39-7.33 (1H, m, C_{Ar}H), 7.30-7.26 (2H, m, H₃CC_{Ar}C_{Ar}H), 2.42 (3H, s, CH₃); δ_{C} (125 MHz, CDCl₃) 140.9 (C_{Ar}), 140.2 (C_{Ar}), 139.9 (C_{Ar}), 137.9 (C_{Ar}), 137.3 (C_{Ar}), 129.7 (2C, C_{Ar}H), 128.9 (2C, C_{Ar}H), 127.6 (2C, C_{Ar}H), 127.4 (3C, C_{Ar}H), 127.2 (2C, C_{Ar}H), 127.0 (2C, C_{Ar}H), 21.3 (CH₃); *m/z* HRMS (EI⁺) C₁₉H₁₆⁺ ([M]⁺) requires 244.1252; found 244.1253 (+0.4 ppm).

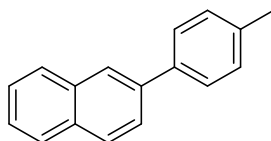
2-methyl-1,1':4',1''-terphenyl (**130**):



Prepared following **general procedure 6** at 100 °C for 16 hours with 4-methoxybiphenyl (92.1 mg, 0.50 mmol), 1-methylnaphthalene (60 μ L, 0.42 mmol), 2-MeTHF (2.25 mL), NiCl₂(P^{*n*}Bu₃)₂ (13.4 mg, 0.025 mmol) and *o*-tolylmagnesium bromide (375 μ L, 0.75 mmol, 2.0 M in Et₂O). Purification *via* column chromatography on silica gel (eluent petroleum ether) gave 2-methyl-1,1':4',1''-terphenyl (**130**) (52.2 mg, 43 %) as a white solid with spectroscopic data in accordance with the literature.³³⁸

mp 87-88 °C {lit³³⁹ 88-89 °C}; δ_{H} (500 MHz, CDCl₃) 7.70-7.64 (4H, m, C_{Ar}H), 7.51-7.45 (2H, m, C_{Ar}H), 7.45-7.41 (2H, m, C_{Ar}H), 7.41-7.36 (1H, m, C_{Ar}H), 7.33-7.27 (4H, m, C_{Ar}H), 2.35 (3H, s, CH₃); δ_{C} (125 MHz, CDCl₃) 141.6 (C_{Ar}), 141.1 (C_{Ar}), 141.0 (C_{Ar}), 139.7 (C_{Ar}), 135.5 (CH₃C_{Ar}), 130.5 (C_{Ar}H), 130.0 (C_{Ar}H), 129.8 (2C, C_{Ar}H), 128.9 (2C, C_{Ar}H), 127.5 (C_{Ar}H), 127.4 (C_{Ar}H), 127.2 (2C, C_{Ar}H), 126.9 (2C, C_{Ar}H), 126.0 (C_{Ar}H), 20.7 (CH₃); *m/z* HRMS (EI⁺) C₁₉H₁₆⁺ ([M]⁺) requires 244.1252; found 244.1250 (-0.8 ppm).

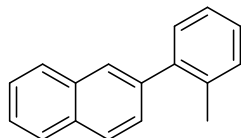
2-(*p*-tolyl)naphthalene (**133**):



NiCl₂(PCy₃)₂ (17.3 mg, 0.025 mmol) was added to a flame dried Schlenk flask under an argon atmosphere, equipped with a stirrer bar. 2-methoxynaphthalene (**131**) (79.1 mg, 0.50 mmol) and 1-methylnaphthalene (60 μL, 0.42 mmol, internal standard) were added to a separate flame dried Schlenk flask under an inert atmosphere. 2-MeTHF (2.25 mL) was then added to the Schlenk flask containing 2-methoxynaphthalene and internal standard to make a solution. A *t*₀ sample (approximately 10 μL) was taken and analysed by ¹H NMR (to calibrate the ratio of internal standard to starting material). The solution was added to the nickel catalyst *via* syringe. *p*-TolMgBr (2.10 mL, 1.05 mmol, 0.5 M in Et₂O) was added dropwise over 15 minutes and the reaction mixture was stirred vigorously in an oil bath at 80 °C for 16 hours. Upon cooling to rt, approximately 20 μL of the crude reaction mixture was added to a vial and quenched with CDCl₃. The resulting mixture was then filtered through a small cotton wool plug into an NMR tube and a ¹H NMR was run to assess the ratio between SM and desired product. Saturated NH₄Cl_(aq) (5 mL) was added to the reaction mixture and the aqueous phase was extracted three times with EtOAc (3 x 5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification *via* column chromatography on silica gel (eluent petroleum ether) gave 2-(*p*-tolyl)naphthalene (**133**) (97.4 mg, 89 %) as a white crystalline solid with spectroscopic data in accordance with the literature.³¹²

mp 93-94 °C {lit³⁴⁰ 92-94 °C}; δ_H (500 MHz, CDCl₃) 8.07 (1H, s, C_{Ar}C_{Ar}HC_{Ar}), 7.96-7.87 (3H, m, C_{Ar}H), 7.79 (1H, dd, *J* 8.5, 1.9, C_{Ar}H), 7.67 (2H, d, *J* 7.9, C_{Ar}C_{Ar}H), 7.57-7.48 (2H, m, C_{Ar}H), 7.34 (2H, d, *J* 7.9, CH₃C_{Ar}C_{Ar}H), 2.47 (3H, s, CH₃); δ_C (125 MHz, CDCl₃) 138.6 (C_{Ar}), 138.3 (C_{Ar}), 137.3 (C_{Ar}), 133.8 (C_{Ar}), 132.6 (C_{Ar}), 129.7 (2C, CH₃C_{Ar}C_{Ar}H), 128.5 (C_{Ar}H), 128.3 (C_{Ar}H), 127.8 (C_{Ar}H), 127.4 (2C, C_{Ar}C_{Ar}H), 126.4 (C_{Ar}H), 125.9 (C_{Ar}H), 125.7 (C_{Ar}H), 125.6 (C_{Ar}C_{Ar}HC_{Ar}), 21.3 (CH₃); *m/z* HRMS (EI⁺) C₁₇H₁₄⁺ ([M]⁺) requires 218.1096; found 218.1094 (-0.9 ppm).

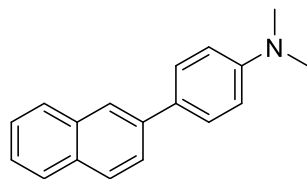
2-(*o*-tolyl)naphthalene (**134**):



$\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2$ (2.7 mg, 0.005 mmol) was added to a flame dried Schlenk flask under an argon atmosphere, equipped with a stirrer bar. 2-methoxynaphthalene (**131**) (79.1 mg, 0.50 mmol) and 1-methylnaphthalene (60 μL , 0.42 mmol, internal standard) were added to a separate flame dried Schlenk flask under an inert atmosphere. 2-MeTHF (2.25 mL) was then added to the Schlenk flask containing 2-methoxynaphthalene and internal standard to make a solution. A t_0 sample (approximately 10 μL) was taken and analysed by ^1H NMR (to calibrate the ratio of internal standard to starting material). The solution was added to the nickel catalyst *via* syringe. *o*-TolMgBr (375 μL , 0.75 mmol, 2.0 M in Et_2O) was added dropwise over 15 minutes and the reaction mixture was stirred vigorously in an oil bath at 80 $^\circ\text{C}$ for 16 hours. Upon cooling to rt, approximately 20 μL of the crude reaction mixture was added to a vial and quenched with CDCl_3 . The resulting mixture was then filtered through a small cotton wool plug into an NMR tube and a ^1H NMR was run to assess the ratio between SM and desired product. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (5 mL) was added to the reaction mixture and the aqueous phase was extracted three times with EtOAc (3 x 5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* column chromatography on silica gel (eluent petroleum ether) gave 2-(*o*-tolyl)naphthalene (**134**) (89.8 mg, 82 %) as a colourless oil with spectroscopic data in accordance with the literature.³⁴¹

δ_{H} (500 MHz, CDCl_3) 7.95-7.89 (3H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.83 (1H, d, J 1.7, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}$), 7.58-7.51 (3H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.40-7.31 (4H, m, $\text{C}_{\text{Ar}}\text{H}$), 2.37 (3H, s, CH_3); δ_{C} (125 MHz, CDCl_3) 142.0 ($\text{CH}_3\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}$), 139.6 (C_{Ar}), 135.7 ($\text{CH}_3\text{C}_{\text{Ar}}$), 133.4 (C_{Ar}), 132.4 (C_{Ar}), 130.5 ($\text{CH}_3\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 130.1 ($\text{C}_{\text{Ar}}\text{H}$), 128.1 ($\text{C}_{\text{Ar}}\text{H}$), 127.9 ($\text{C}_{\text{Ar}}\text{H}$), 127.9 ($\text{C}_{\text{Ar}}\text{H}$), 127.8 ($\text{C}_{\text{Ar}}\text{H}$), 127.6 ($\text{C}_{\text{Ar}}\text{H}$), 127.5 ($\text{C}_{\text{Ar}}\text{H}$), 126.3 ($\text{C}_{\text{Ar}}\text{H}$), 126.0 ($\text{C}_{\text{Ar}}\text{H}$), 126.0 ($\text{C}_{\text{Ar}}\text{H}$), 20.7 (CH_3); m/z HRMS (EI^+) $\text{C}_{17}\text{H}_{14}^+$ ($[\text{M}]^+$) requires 218.1096; found 218.1094 (-0.9 ppm).

2-(4-*N,N*-dimethylaminophenyl)naphthalene (**136**):

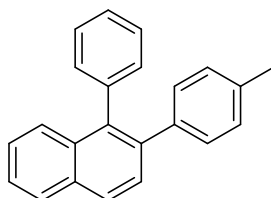


An oven dried microwave vial equipped with a stirrer bar was sealed with a crimp cap and flushed with argon for 30 minutes. In a flame dried Schlenk under an argon atmosphere, a stock solution containing 0.67 mg mL^{-1} of $\text{NiCl}_2(\text{P}^n\text{Bu}_3)_2$ in 2-MeTHF was created. An aliquot (1 mL) of this solution was then added to the microwave vial. 2-methoxynaphthalene (**131**) (79.1 mg, 0.50 mmol) and 1-methylnaphthalene (60 μL , 0.42 mmol, internal standard) were added to a separate flame dried Schlenk flask under an inert atmosphere. 2-MeTHF (1.25 mL) was then added to the Schlenk flask to make a solution. A t_0 sample (approximately 10 μL) was taken and analysed by ^1H NMR (to calibrate the ratio of internal standard to starting material). The solution containing the electrophile and internal standard was added to the microwave vial containing the nickel catalyst. 4-*N,N*-dimethylaminophenylmagnesium bromide (3.0 mL, 0.75 mmol, 0.3 M in THF) was added dropwise over 15 minutes and the reaction mixture was stirred vigorously in an oil bath at 100°C for 16 hours. Upon cooling to rt, approximately 20 μL of the crude reaction mixture was added to a vial and quenched with CDCl_3 . The resulting mixture was then filtered through a small cotton wool plug into an NMR tube and a ^1H NMR was run to assess the ratio between SM and desired product. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (5 mL) was added to the reaction mixture and the aqueous phase was extracted three times with EtOAc (3 x 5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* column chromatography on silica gel (eluent petroleum ether:Et₂O, 100:0 to 98:2) gave 2-(4-*N,N*-dimethylaminophenyl)naphthalene (**136**) (50.8 mg, 41 %) as an off-white solid with spectroscopic data in agreement with the literature.³⁴¹

mp $129\text{--}131^\circ\text{C}$; δ_{H} (500 MHz, CDCl_3) 8.00 (1H, s, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}$), 7.90-7.86 (2H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.84 (1H, d, J 8.1, $\text{C}_{\text{Ar}}\text{H}$), 7.75 (1H, dd, J 8.5, 1.9, $\text{C}_{\text{Ar}}\text{H}$), 7.67 (2H, d, J 8.8, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 7.49 (1H, ddd, J 8.2, 6.8, 1.5, $\text{C}_{\text{Ar}}\text{H}$), 7.44 (1H, ddd, J 8.1, 6.8, 1.4, $\text{C}_{\text{Ar}}\text{H}$), 6.90 (2H, d, J 8.8, $\text{NC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 2.47 (6H, s, CH_3); δ_{C} (125 MHz, CDCl_3) 149.8 ($\text{C}_{\text{Ar}}\text{N}$), 138.6 (C_{Ar}), 134.0 (C_{Ar}), 132.2 (C_{Ar}), 129.2 (C_{Ar}), 128.4 ($\text{C}_{\text{Ar}}\text{H}$), 128.2 (2C, $\text{NC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$),

128.1 ($C_{Ar}H$), 126.2 ($C_{Ar}H$), 125.4 ($C_{Ar}H$), 125.4 ($C_{Ar}H$), 124.4 ($C_{Ar}C_{Ar}HC_{Ar}$), 113.3 (2C, $NC_{Ar}C_{Ar}H$), 41.0 (CH_3); m/z HRMS (CI^+) $C_{18}H_{18}N^+$ ($[M+H]^+$) requires 248.1434; found 248.1434 (+0.8 ppm).

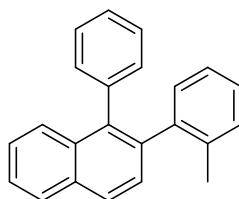
1-phenyl-2-(*p*-tolyl)naphthalene (139):



Prepared following **general procedure 6** at 100 °C for 16 hours with 1-phenyl-2-methoxynaphthalene (**137**) (117.2 mg, 0.50 mmol), 1-methylnaphthalene (60 μ L, 0.42 mmol), 2-MeTHF (2.25 mL), $NiCl_2(P^tBu_3)_2$ (2.7 mg, 0.005 mmol) and *p*-tolylmagnesium bromide (1.50 mL, 0.75 mmol, 0.5 M in Et_2O). Purification *via* column chromatography on silica gel (eluent petroleum ether) gave 1-phenyl-2-(*p*-tolyl)naphthalene (**139**) (122.2 mg, 83 %) as a white crystalline solid.

mp 92-93 °C; ν_{max} (ATR) 2920 (w), 1503 (w), 1441 (w), 1373 (w), 1024 (w), 957 (w), 829 (w), 806 (s), 789 (m), 758 (m); δ_H (500 MHz, $CDCl_3$) 7.97-7.91 (2H, m, $C_{Ar}H$), 7.68 (1H, dd, J 8.4, 1.2, $C_{Ar}H$), 7.60 (1H, d, J 8.5, $C_{Ar}H$), 7.50 (1H, ddd, J 8.0, 6.8, 1.2, $C_{Ar}H$), 7.42 (1H, ddd, J 8.4, 6.8, 1.5, $C_{Ar}H$), 7.37-7.29 (3H, m, $C_{Ar}H$), 7.26-7.22 (2H, m, $C_{Ar}H$), 7.08 (2H, d, J 8.0, $CH_3C_{Ar}C_{Ar}HC_{Ar}H$), 7.02 (2H, d, J 8.0, $CH_3C_{Ar}C_{Ar}H$), 2.31 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 139.3 (C_{Ar}), 139.1 (C_{Ar}), 138.3 (C_{Ar}), 137.6 (C_{Ar}), 135.9 ($C_{Ar}CH_3$), 132.8 (C_{Ar}), 132.8 (C_{Ar}), 131.6 (2C, $C_{Ar}H$), 130.1 (2C, $CH_3C_{Ar}C_{Ar}HC_{Ar}H$), 128.6 ($C_{Ar}H$), 128.5 (2C, $CH_3C_{Ar}C_{Ar}H$), 128.0 (2C, $C_{Ar}H$), 128.0 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 126.9 ($C_{Ar}H$), 126.8 ($C_{Ar}H$), 126.3 ($C_{Ar}H$), 125.7 ($C_{Ar}H$), 21.2 (CH_3); m/z HRMS (EI^+) $C_{23}H_{18}^+$ ($[M]^+$) requires 294.1409; found 294.1413 (+1.4 ppm).

1-phenyl-2-(*o*-tolyl)naphthalene (140):



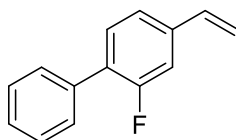
Prepared following **general procedure 6** at 100 °C for 16 hours with 1-phenyl-2-methoxynaphthalene (**137**) (117.2 mg, 0.50 mmol), 1-methylnaphthalene (60 μ L, 0.42 mmol), 2-MeTHF (2.25 mL), NiCl₂(P^{*n*}Bu₃)₂ (2.7 mg, 0.005 mmol) and *o*-tolylmagnesium bromide (375 μ L, 0.75 mmol, 2.0 M in Et₂O). Purification *via* column chromatography on silica gel (eluent petroleum ether) gave 1-phenyl-2-(*o*-tolyl)naphthalene (**140**) (87.5 mg, 59 %) as a white crystalline solid.

mp 120-121 °C; ν_{max} (ATR) 1489 (w), 1375 (w), 870 (w), 820 (m), 760 (m); δ_{H} (500 MHz, CDCl₃) 7.96 (1H, dd, *J* 8.2, 1.3, C_{Ar}H), 7.93 (1H, d, *J* 8.4, C_{Ar}H), 7.69 (1H, d, *J* 8.5, C_{Ar}H), 7.53 (1H, ddd, *J* 8.1, 6.7, 1.2, C_{Ar}H), 7.47-7.40 (2H, m, C_{Ar}H), 7.31-7.22 (4H, m, C_{Ar}H), 7.16-7.12 (1H, m, C_{Ar}H), 7.12-7.09 (2H, m, C_{Ar}H), 7.06-7.01 (2H, m, C_{Ar}H), 2.09 (3H, s, CH₃); δ_{C} (125 MHz, CDCl₃) 141.6 (CH₃C_{Ar}C_{Ar}), 138.9 (C_{Ar}), 138.5 (C_{Ar}), 138.1 (C_{Ar}), 135.8 (C_{Ar}CH₃), 133.0 (C_{Ar}), 132.8 (C_{Ar}), 131.6 (C_{Ar}H), 130.8 (C_{Ar}H), 130.2 (C_{Ar}H), 129.6 (CH₃C_{Ar}C_{Ar}H), 128.3 (C_{Ar}H), 128.1 (C_{Ar}H), 127.8 (C_{Ar}H), 127.5 (C_{Ar}H), 127.3 (C_{Ar}H), 126.9 (C_{Ar}H), 126.9 (C_{Ar}H), 126.8 (C_{Ar}H), 126.3 (C_{Ar}H), 125.7 (C_{Ar}H), 124.9 (C_{Ar}H), 20.6 (CH₃); *m/z* HRMS (EI⁺) C₂₃H₁₈⁺ ([M]⁺) requires 294.1409; found 294.1409 (\pm 0.0 ppm).

7.8 – Palladium-catalysed carbonylation of 3-fluoro-4-phenylstyrene

7.8.1 – Preparation of 3-fluoro-4-phenylstyrene

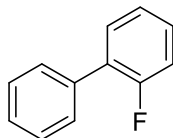
3-fluoro-4-phenylstyrene (**144**):



To a mixture of [PdCl₂(*rac*-Xylyl-Phanephos)] (8.7 mg, 0.01 mmol), 4-bromo-2-fluorobiphenyl (251.1 mg, 1.00 mmol) and K₂CO₃ (417.6 mg, 3.00 mmol) in anhydrous and degassed 1,4-dioxane (4.0 mL) was added a solution of vinylboronic acid pinacol ester (230.8 mg, 1.50 mmol) in anhydrous and degassed 1,4-dioxane (500 μL). Degassed H₂O (577 μL) was then added and the reaction mixture was stirred at 99 °C for 16 hours. The reaction was cooled to rt, quenched with water (4 mL), and extracted three times with Et₂O (3 x 5 mL). The combined organics were washed with brine (4 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification *via* column chromatography on silica gel (eluent petroleum ether) to give 3-fluoro-4-phenylstyrene (**144**) (117.5 mg, 59 %) as a colourless oil with spectroscopic data in agreement with the literature.³⁴²

δ_{H} (500 MHz, CDCl₃) 7.58-7.53 (2H, m, C_{Ar}C_{Ar}H), 7.47-7.35 (4H, m, C_{Ar}H), 7.25 (1H, dd, *J* 7.9, 1.7, CHC_{Ar}C_{Ar}H), 7.21 (1H, dd, *J*_{H-F} 11.9, 1.7, FC_{Ar}C_{Ar}H), 6.71 (1H, dd, *J* 17.6, 10.9, CH=CH₂), 5.80 (1H, dd, *J* 17.6, 0.7, CH=CH'H'), 5.33 (1H, dd, *J* 10.9, 0.7, CH=CH'H'); δ_{F} (376 MHz, CDCl₃) -118.4; δ_{C} (125 MHz, CDCl₃) 160.4 (d, *J* 247.6, C_{Ar}F), 139.0 (d, *J*_{C-F} 7.9, CHC_{Ar}), 135.7 (C_{Ar}C_{Ar}), 135.6 (d, *J*_{C-F} 2.2, CH=CH₂), 130.1 (d, *J*_{C-F} 4.1, FC_{Ar}C_{Ar}C_{Ar}H), 129.0 (2C, d, *J*_{C-F} 2.9, C_{Ar}C_{Ar}H), 128.6 (2C, C_{Ar}H), 128.4 (d, *J*_{C-F} 13.8, FC_{Ar}C_{Ar}), 127.8 (C_{Ar}H), 122.5 (d, *J*_{C-F} 3.1, CHC_{Ar}C_{Ar}H), 115.3 (CH=CH₂), 113.5 (d, *J*_{C-F} 23.3, FC_{Ar}C_{Ar}H); *m/z* HRMS (EI⁺) C₁₄H₁₁F⁺ ([M]⁺) requires 198.0845; found 198.0849 (+2.0 ppm).

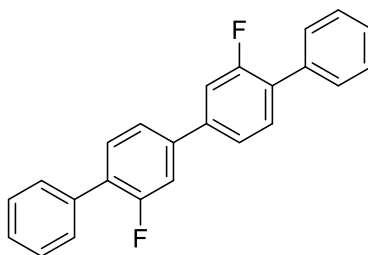
2-fluorobiphenyl (161):



Obtained as a side product (white solid) from the Grignard cross-coupling of vinyl tosylate (**158**) with (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide, with spectroscopic data in agreement with the literature.³⁴³

m.p. 73-74 °C {lit³⁴³ 72-73 °C}; δ_{H} (500 MHz, CDCl₃) 7.60-7.56 (2H, m, C_{Ar}H), 7.51-7.43 (3H, m, C_{Ar}H), 7.42-7.37 (1H, m, C_{Ar}H), 7.36-7.31 (1H, m, FC_{Ar}C_{Ar}HC_{Ar}H), 7.23 (1H, td, *J* 7.5, 1.2, C_{Ar}H), 7.21-7.14 (1H, m, FC_{Ar}C_{Ar}H); δ_{F} (470 MHz, CDCl₃) -118.1; δ_{C} (125 MHz, CDCl₃) 159.9 (d, *J*_{C-F} 247.8, C_{Ar}F), 135.9 (C_{Ar}C_{Ar}), 130.9 (d, *J*_{C-F} 3.1, FC_{Ar}C_{Ar}C_{Ar}H), 129.2 (FC_{Ar}C_{Ar}), 129.2 (2C, d, *J*_{C-F} 2.9, C_{Ar}C_{Ar}H), 129.1 (d, *J*_{C-F} 8.3, FC_{Ar}C_{Ar}HC_{Ar}H), 128.6 (2C, C_{Ar}H), 127.8 (C_{Ar}H), 124.5 (d, *J*_{C-F} 3.7, C_{Ar}H), 116.2 (d, *J*_{C-F} 22.8, FC_{Ar}C_{Ar}H); m/z HRMS (EI⁺) C₁₂H₉F⁺ ([M]⁺) requires 172.0688; found 172.0684 (-2.3 ppm).

3',3''-difluoro-[1,1';4',1'';4'',1''']quaterphenyl (160):



Obtained as a side product (white crystalline solid) from the Grignard cross-coupling of vinyl tosylate (**158**) with (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide, with spectroscopic data in agreement with the literature.³⁴⁴

m.p. 200-202 °C {lit³⁴⁴ 182 °C}; δ_{H} (500 MHz, CDCl₃) 7.63-7.59 (4H, m, C_{Ar}H), 7.55 (2H, app t, *J* 8.0, FC_{Ar}C_{Ar}C_{Ar}H), 7.51-7.46 (6H, m, C_{Ar}H), 7.46-7.38 (4H, m, C_{Ar}H); δ_{F} (376 MHz, CDCl₃) -117.5; δ_{C} (125 MHz, CDCl₃) 160.2 (2C, d, *J*_{C-F} 248.3, C_{Ar}F), 140.7 (2C, d, *J*_{C-F} 8.9, FC_{Ar}C_{Ar}HC_{Ar}), 135.4 (2C, C_{Ar}C_{Ar}), 131.3 (2C, d, *J*_{C-F} 4.0, FC_{Ar}C_{Ar}C_{Ar}H),

129.1 (4C, d, J_{C-F} 2.8, $C_{Ar}C_{Ar}C_{Ar}H$), 128.7 (4C, $C_{Ar}H$), 128.6 (2C, d, J_{C-F} 13.5, $FC_{Ar}C_{Ar}$), 128.0 (2C, $C_{Ar}H$), 122.9 (2C, d, J_{C-F} 3.0, $C_{Ar}C_{Ar}H$), 114.6 (2C, d, J_{C-F} 24.1 $FC_{Ar}C_{Ar}H$); m/z HRMS (EI⁺) $C_{24}H_{16}F_2^+$ ($[M]^+$) requires 342.1220; found 342.1221 (+0.3 ppm).

7.8.2 – Palladium-catalysed hydroxycarbonylation of 3-fluoro-4-phenylstyrene

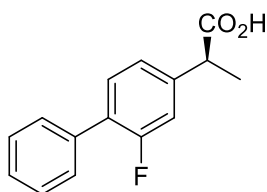
7.8.2.1 – General Procedure 8: Palladium-catalysed hydroxycarbonylation

Lithium chloride (20 mol%), *para*-toluenesulfonic acid monohydrate (20 mol%) and Pd-Phanephos catalyst (1 mol%) were weighed into a microwave vial equipped with a magnetic stirrer bar. The vial was sealed with a crimp cap and flushed with argon for 30 minutes. 3-fluoro-4-phenylstyrene (**144**) (1 equiv.) and 1-methylnaphthalene (0.84 equiv., internal standard) were added to a flame dried Schlenk flask under an inert atmosphere. Anhydrous and degassed solvent was then added to the Schlenk flask to make a solution. A t_0 sample (approximately 10 μ L) was taken and analysed by ¹H NMR (to calibrate the ratio of internal standard to starting material). The solution containing the vinyl arene and internal standard was added to the microwave vial *via* syringe. Degassed H₂O (2.5 – 10 equiv.) was then added to the reaction mixture. The crimp cap was pierced with two needles and quickly placed into an autoclave which had previously been placed under an argon atmosphere, before being opened under a flow of argon. The autoclave was sealed, purged three times with CO and then pressurised to 30 bar. The autoclave was then placed in an oil bath at a specific temperature for the required period of time, with constant stirring. Upon cooling to room temperature, the pressure was released slowly into a well-ventilated fume cupboard. The mixture was analysed by taking a sample, diluting in CDCl₃, and analysing by ¹H NMR to assess the ratio between SM and desired product, as well as regioselectivity. Solvent was removed under reduced pressure from the reaction mixture and the residue was dissolved in toluene and extracted 3 times with saturated NaHCO₃ solution. The combined extracts were acidified with concentrated HCl. The solution was then extracted 3 times with ethyl acetate and the combined organic layers were dried over Na₂SO₄, filtered and the solvent removed to give chemically pure regioisomers Flurbiprofen (**143**) and 3-(2-fluoro-[1,1'-biphenyl]-4-yl)propanoic acid (**162**) as a white crystalline solid. The enantiomeric excess was

determined by HPLC, using 2 x Chiracel OD-H columns, 250 x 4.6 mm, 5 μ m, 0.5 mL min^{-1} , 95:5:0.1 hexane : iso-propanol : trifluoroacetic acid, $t_{\text{R}}[(-)\text{-}R] = 29$ min, $t_{\text{R}}[(+)\text{-}S] = 31$ min, $t_{\text{R}}[\text{linear}] = 34$ min.

7.8.2.2 – Product data

(S)-(+)-Flurbiprofen ((S)-143):



(A mixture of regioisomers was prepared following **general procedure 8** to give a white crystalline solid.)

Pure Flurbiprofen was obtained by the acid-catalysed hydrolysis of highly enantioenriched methyl 2-(2-fluoro-biphenyl-4-yl)-propionate (Flurbiprofen methyl ester), obtained from methoxycarbonylation, following a literature procedure.²⁹⁹

A solution of (S)-(+)-Flurbiprofen methyl ester ((S)-163) (83.0 mg, 0.32 mmol, e.e. 95%) in dioxane (4 mL) was added to 5 % v/v aqueous H_2SO_4 (2.1 mL) and the mixture refluxed for 3 hours. After addition of water (4 mL) the reaction mixture was extracted three times with ethyl acetate (3 x 5 mL) and the combined organics dried over Na_2SO_4 , filtered and the solvent removed to give chemically pure (S)-(+)-Flurbiprofen ((S)-143) (78.0 mg, 99 %, e.e. 94 %) as a white solid, with spectroscopic data in accordance with the literature.²⁶³ m.p. 108-110 $^\circ\text{C}$ {lit.²⁶⁴ 108-110 $^\circ\text{C}$ }; δ_{H} (500 MHz, CDCl_3) 7.56-7.51 (2H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.47-7.34 (4H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.21-7.13 (2H, m, $\text{C}_{\text{Ar}}\text{H}$), 3.80 (1H, q, J 7.2, CHCH_3), 1.57 (3H, d, J 7.2, CH_3); δ_{F} (376 MHz, CDCl_3) -117.4; δ_{C} (125 MHz, CDCl_3) 180.3 (CO_2H), 159.8 (d, $J_{\text{C-F}}$ 248.5, $\text{C}_{\text{Ar}}\text{F}$), 141.0 (d, $J_{\text{C-F}}$ 7.7, CHC_{Ar}), 135.5 (C_{Ar}), 131.0 (d, $J_{\text{C-F}}$ 3.8, $\text{FC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 129.1 (2C, d, $J_{\text{C-F}}$ 2.8, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 128.6 (2C, $\text{C}_{\text{Ar}}\text{H}$), 128.3 (d, $J_{\text{C-F}}$ 13.6, $\text{FC}_{\text{Ar}}\text{C}_{\text{Ar}}$), 127.9 ($\text{C}_{\text{Ar}}\text{H}$), 123.8 (d, $J_{\text{C-F}}$ 3.5, $\text{CHC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 115.5 (d, $J_{\text{C-F}}$ 23.8, $\text{FC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 45.0 (CHCH_3), 18.2 (CHCH_3); m/z HRMS (ESI⁺) $\text{C}_{15}\text{H}_{13}\text{FO}_2\text{Na}^+$ ($[\text{M}+\text{Na}]^+$) requires 267.0792; found 267.0790 (-0.8 ppm). Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{FO}_2$: C, 73.76; H, 5.36;

Found: C, 73.69; H, 5.45. $[\alpha]_{\text{D}}^{20} = +44.4$ ($c = 1.00$, CHCl_3 , e.e. = 94 % (*S*)) {lit.²⁹⁹ $[\alpha]_{\text{D}}^{20} = +41.4$ ($c = 1.00$, CHCl_3 , e.e. = > 95 % (*S*))}.

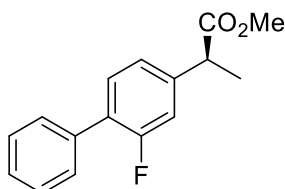
7.8.3 – Palladium-catalysed methoxycarbonylation of 3-fluoro-4-phenylstyrene

7.8.3.1 – General Procedure 9: Palladium-catalysed methoxycarbonylation

Lithium chloride (20 mol%), *para*-toluenesulfonic acid monohydrate (20 mol%) and Pd-Phanephos catalyst (1 mol%) were weighed into a microwave vial equipped with a magnetic stirrer bar. The vial was sealed with a crimp cap and flushed with argon for 30 minutes. 3-fluoro-4-phenylstyrene (**144**) (1 equiv.) and 1-methylnaphthalene (0.84 equiv., internal standard) were added to a flame dried Schlenk flask under an inert atmosphere. Anhydrous and degassed methanol was then added to the Schlenk flask to make a solution. A *t*₀ sample (approximately 10 μL) was taken and analysed by ¹H NMR (to calibrate the ratio of internal standard to starting material). The solution containing the vinyl arene and internal standard was added to the microwave vial *via* syringe. The crimp cap was pierced with two needles and quickly placed into an autoclave which had previously been placed under an argon atmosphere, before being opened under a flow of argon. The autoclave was sealed, purged three times with CO and then pressurised to 30 bar. The autoclave was then placed in an oil bath at a specific temperature for the required period of time, with constant stirring. Upon cooling to room temperature, the pressure was released slowly into a well-ventilated fume cupboard. The mixture was analysed by taking a sample, diluting in CDCl_3 , and analysing by ¹H NMR to assess the ratio between SM and desired product, as well as regioselectivity. Solvent was removed under reduced pressure and purification *via* column chromatography on silica gel (eluent petroleum ether:EtOAc, 100:0 to 90:10) gave branched methyl 2-(2-fluoro-biphenyl-4-yl)-propionate (**163**) as a white crystalline solid, linear methyl 3-(2-fluoro-biphenyl-4-yl)-propionate (**164**) as a colourless oil and a mixture of both regioisomers as a colourless oil. The enantiomeric excess was determined by HPLC, using a Chiracel OJ column, 250 x 4.6 mm, 10 μm , 0.5 mL min^{-1} , 95:5 hexane : iso-propanol, $t_{\text{R}}[(-)\text{-}R] = 23$ min, $t_{\text{R}}[(+)\text{-}S] = 27$ min, $t_{\text{R}}[\text{linear}] = 46$ min.

7.8.3.2 – Product data

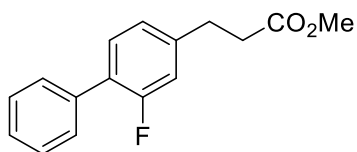
(S)-(+)-methyl 2-(2-fluoro-biphenyl-4-yl)-propionate ((S)-163):



Prepared following **general procedure 9**, to give a white crystalline solid with spectroscopic data in accordance with the literature.³⁴⁵

m.p. 39-40 °C {lit.³⁴⁶ 40 °C}; δ_{H} (500 MHz, CDCl_3) 7.56-7.51 (2H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.48-7.33 (4H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.17-7.09 (2H, m, $\text{C}_{\text{Ar}}\text{H}$), 3.77 (1H, q, J 7.2, CHCH_3), 3.71 (3H, s, OCH_3), 1.54 (3H, d, J 7.2, CHCH_3); δ_{F} (376 MHz, CDCl_3) -117.6; δ_{C} (125 MHz, CDCl_3) 174.6 (CO_2CH_3), 159.8 (d, $J_{\text{C-F}}$ 248.3, $\text{C}_{\text{Ar}}\text{F}$), 141.9 (d, $J_{\text{C-F}}$ 7.7, CHC_{Ar}), 135.6 ($\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}$), 131.0 (d, $J_{\text{C-F}}$ 3.9, $\text{FC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 129.1 (2C, d, $J_{\text{C-F}}$ 2.9, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 128.6 (2C, $\text{C}_{\text{Ar}}\text{H}$), 128.0 (d, $J_{\text{C-F}}$ 13.6, $\text{FC}_{\text{Ar}}\text{C}_{\text{Ar}}$), 127.8 ($\text{C}_{\text{Ar}}\text{H}$), 123.7 (d, $J_{\text{C-F}}$ 3.3, $\text{CHC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 115.4 (d, $J_{\text{C-F}}$ 23.6, $\text{FC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 52.4 (OCH_3), 45.1 (CHCH_3), 18.6 (CHCH_3); m/z HRMS (ESI^+) $\text{C}_{16}\text{H}_{16}\text{FO}_2$ ($[\text{M}+\text{H}]^+$) requires 259.1129; found 259.1126 (-1.2 ppm). Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{FO}_2$: C, 74.40; H, 5.85; Found: C, 74.51; H, 5.99. $[\alpha]_{\text{D}}^{20} = +46.2$ ($c = 1.00$, CHCl_3 , e.e. = 95 % (S)) {lit.²⁹⁹ $[\alpha]_{\text{D}}^{20} = -39.2$ ($c = 1.50$, CHCl_3 , e.e. = 76 % (R))}.

methyl 3-(2-fluoro-biphenyl-4-yl)-propionate (164):



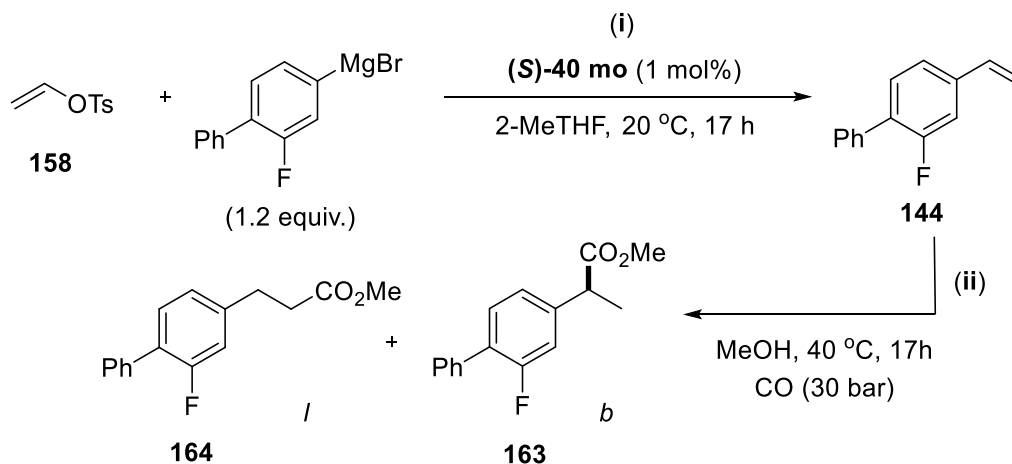
Prepared following **general procedure 9**, to give a colourless oil.

ν_{\max} (ATR) 1732 (s), 1485 (w), 1416 (m), 1265 (w) 1196 (m), 1153 (m), 1126 (m), 827 (w), 766 (s); δ_{H} (500 MHz, CDCl_3) 7.56-7.52 (2H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.47-7.42 (2H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.40-7.33 (2H, m, $\text{C}_{\text{Ar}}\text{H}$), 7.06 (1H, dd, J 7.8, 1.7, $\text{CH}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 7.02 (1H, dd, $J_{\text{H-F}}$ 11.5, 1.7, $\text{FC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 3.70 (3H, s, OCH_3), 3.00 (2H, t, J 7.8, $\text{C}_{\text{Ar}}\text{CH}_2$), 2.68 (2H, t, J 7.8, $\text{C}_{\text{Ar}}\text{CH}_2\text{CH}_2$); δ_{F} (376 MHz, CDCl_3) -118.2; δ_{C} (125 MHz, CDCl_3) 173.2 (CO_2CH_3), 159.8 (d, $J_{\text{C-F}}$ 248.0, $\text{C}_{\text{Ar}}\text{F}$), 142.2 (d, $J_{\text{C-F}}$ 7.7, CHC_{Ar}), 135.8 ($\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}$), 130.8 (d, $J_{\text{C-F}}$ 3.9, $\text{FC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 129.0 (2C, d, $J_{\text{C-F}}$ 3.0, $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 128.5 (2C, $\text{C}_{\text{Ar}}\text{H}$), 127.7 ($\text{C}_{\text{Ar}}\text{H}$), 127.0 (d, $J_{\text{C-F}}$ 13.5, $\text{FC}_{\text{Ar}}\text{C}_{\text{Ar}}$), 124.4 (d, $J_{\text{C-F}}$ 3.2, $\text{CH}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 116.0 (d, $J_{\text{C-F}}$ 22.8, $\text{FC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 51.9 (OCH_3), 35.4 ($\text{C}_{\text{Ar}}\text{CH}_2\text{CH}_2$), 30.4 ($\text{C}_{\text{Ar}}\text{CH}_2\text{CH}_2$); m/z HRMS (ESI⁺) $\text{C}_{16}\text{H}_{15}\text{FO}_2\text{Na}^+$ ($[\text{M}+\text{Na}]^+$) requires 281.0948; found 281.0944 (-1.4 ppm).

7.8.4 – Full experimental for tandem Grignard cross-coupling – carbonylation reactions

7.8.4.1 – Grignard cross-coupling – methoxycarbonylation

Table 7.3 – Attempts to couple the Grignard cross-coupling step with methoxycarbonylation, re-using the Pd-Phanephos catalyst, (*S*)-**40 mo**.



Entry ^[a]	Procedure	Step (i)		Step (ii)		Overall		
		Conv. (i) (%)	144 (i) (%)	Conv. (ii) (%)	P (ii) (%)	P (over steps i and ii) (%)	b/l	e.e. (%)
1	A	> 99	96	0	0	0	-	-
2	B	> 99	95	2	0	0	-	-
3	C	> 99	93	4	0	0	-	-
4	D	> 99	93	2	0	0	-	-
5	E	> 99	90	0	0	0	-	-
6	F	> 99	90	6	< 5	0	-	-
7	G	> 99	89	32	31	17 ^[b]	1.66	94
8 ^[c]	H	89	88	40	29	18 ^[b]	1.23	94
9 ^[d]	I	> 99	[90] ^[e]	73	68	47	1.50	96
					[59] ^[f]	[40] ^[g]		

^[a] Reactions were carried out on the scale of vinyl tosylate (0.50 mmol) and according to table and equation, unless otherwise noted. For each entry, see specific procedure below. Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets, based on either 3-fluoro-4-phenylstyrene (% product ii) or vinyl tosylate (% product over two steps)]. b/l ratio determined by ¹H NMR. Enantiomeric excess determined by chiral HPLC. (*S*)-configured catalysts give (*S*)-configured product and *vice versa*. ^[b] Compared to external standard, 1,3,5-trimethoxybenzene (0.50 mmol). ^[c] Reaction time for Grignard cross-coupling step (i) = 2 h. ^[d] 0.76 mmol scale and no internal standard for cross-coupling step (i). Isolated mixture obtained after cross-coupling step was re-charged with (*S*)-**40 mo** (1 mol%) prior to methoxycarbonylation. ^[e] 90 % yield isolated with 2-fluorobiphenyl impurity; total product obtained = 68 %. ^[f] Includes regioisomerically pure branched product (**163**) 26 %, based on 3-fluoro-4-phenylstyrene. ^[g] Includes regioisomerically pure branched product (**163**) 17 %, based on vinyl tosylate.

Procedure A:

Grignard cross-coupling was performed following **general procedure 2** at 20 °C for 17 hours in a microwave vial with a crimp cap, with vinyl tosylate (**158**) (99.1 mg, 0.50 mmol), 2-MeTHF (1.00 mL), (**S**)-**40 mo** (4.3 mg, 0.005 mmol) and (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide (760 µL, 0.60 mmol, 0.8 M in 2-MeTHF). The reaction was then quenched with degassed MeOH (400 µL, 9.89 mmol). The resulting mixture was concentrated *in vacuo* at 40 °C for 2 hours. Degassed MeOH (1.50 mL) was added to the microwave vial and a new t_0 sample was taken for ^1H NMR analysis. The resulting reaction mixture was carbonylated following **general procedure 9** at 40 °C for 17 hours.

Procedure B:

Grignard cross-coupling was performed following **general procedure 2** at 20 °C for 17 hours in a microwave vial with a crimp cap, with vinyl tosylate (**158**) (99.1 mg, 0.50 mmol), 2-MeTHF (1.00 mL), (**S**)-**40 mo** (4.3 mg, 0.005 mmol) and (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide (760 µL, 0.60 mmol, 0.8 M in 2-MeTHF). The reaction was then quenched with degassed MeOH (400 µL, 9.89 mmol). The resulting mixture was concentrated *in vacuo* at 40 °C for 2 hours. PTSA.H₂O (19.0 mg, 0.10 mmol) was quickly added to the microwave vial and a new cap was put on. The vial was then flushed with argon for 30 minutes. Degassed MeOH (1.50 mL) was added to the microwave vial and a new t_0 sample was taken for ^1H NMR analysis. The resulting reaction mixture was carbonylated following **general procedure 9** at 40 °C for 17 hours.

Procedure C:

Grignard cross-coupling was performed following **general procedure 2** at 20 °C for 17 hours in a microwave vial with a crimp cap, with vinyl tosylate (**158**) (99.1 mg, 0.50 mmol), 2-MeTHF (1.00 mL), (**S**)-**40 mo** (4.3 mg, 0.005 mmol) and (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide (760 µL, 0.60 mmol, 0.8 M in 2-MeTHF). The reaction was then quenched with degassed MeOH (400 µL, 9.89 mmol). The resulting mixture was concentrated *in vacuo* at 40 °C for 2 hours. LiCl (4.2 mg, 0.10 mmol) was quickly added to the microwave vial and a new cap was put on. The vial was then flushed with argon for 30 minutes. Degassed MeOH (1.50 mL) was added to the microwave vial

and a new t_0 sample was taken for ^1H NMR analysis. The resulting reaction mixture was carbonylated following **general procedure 9** at 40 °C for 17 hours.

Procedure D:

Grignard cross-coupling was performed following **general procedure 2** at 20 °C for 17 hours in a microwave vial with a crimp cap, with vinyl tosylate (**158**) (99.1 mg, 0.50 mmol), 2-MeTHF (1.00 mL), (**S**)-**40 mo** (4.3 mg, 0.005 mmol) and (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide (760 μL , 0.60 mmol, 0.8 M in 2-MeTHF). The reaction was then quenched with degassed MeOH (400 μL , 9.89 mmol). The resulting mixture was concentrated *in vacuo* at 40 °C for 2 hours. PTSA.H₂O (19.0 mg, 0.10 mmol) and LiCl (4.2 mg, 0.10 mmol) were quickly added to the microwave vial and a new cap was put on. The vial was then flushed with argon for 30 minutes. Degassed MeOH (1.50 mL) was added to the microwave vial and a new t_0 sample was taken for ^1H NMR analysis. The resulting reaction mixture was carbonylated following **general procedure 9** at 40 °C for 17 hours.

Procedure E:

Grignard cross-coupling was performed following **general procedure 2** at 20 °C for 17 hours with vinyl tosylate (**158**) (99.1 mg, 0.50 mmol), 2-MeTHF (1.00 mL), (**S**)-**40 mo** (4.3 mg, 0.005 mmol) and (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide (760 μL , 0.60 mmol, 0.8 M in 2-MeTHF). The reaction was then quenched with HCl/Et₂O (300 μL , 0.30 mmol, 1.0 M) and concentrated *in vacuo*. 2-MeTHF (3.00 mL) was added and the mixture was transferred by cannula filtration under argon into another Schlenk flask. The solution was then concentrated *in vacuo* and degassed MeOH (1.5 mL) was added. The solution was added to a microwave vial with crimp cap equipped with stirrer bar, PTSA.H₂O (38.0 mg, 0.20 mmol) and LiCl (4.2 mg, 0.10 mmol), which had been previously flushed with argon for 30 minutes. A new t_0 sample was taken for ^1H NMR analysis. The reaction mixture was carbonylated following **general procedure 9** at 40 °C for 17 hours.

Procedure F:

Grignard cross-coupling was performed following **general procedure 2** at 20 °C for 17 hours with vinyl tosylate (**158**) (99.1 mg, 0.50 mmol), 2-MeTHF (1.00 mL), (*S*)-**40 mo** (4.3 mg, 0.005 mmol) and (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide (760 µL, 0.60 mmol, 0.8 M in 2-MeTHF). The reaction was then quenched with degassed H₂O (1.50 mL) and extracted three times with 2-MeTHF (3 x 1.50 mL), under argon, into another Schlenk flask containing Na₂SO₄. The combined organics were then filtered by cannula under argon to another Schlenk flask and concentrated *in vacuo*. Degassed MeOH (1.50 mL) was added and the resulting solution was added to a microwave vial with crimp cap equipped with stirrer bar, PTSA.H₂O (38.0 mg, 0.20 mmol) and LiCl (4.2 mg, 0.10 mmol), which had been previously flushed with argon for 30 minutes. A new *t*₀ sample was taken for ¹H NMR analysis. The reaction mixture was carbonylated following **general procedure 9** at 40 °C for 17 hours.

Procedure G:

Grignard cross-coupling was performed following **general procedure 2** at 20 °C for 17 hours with vinyl tosylate (**158**) (99.1 mg, 0.50 mmol), 2-MeTHF (1.00 mL), (*S*)-**40 mo** (4.3 mg, 0.005 mmol) and (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide (760 µL, 0.60 mmol, 0.8 M in 2-MeTHF). The reaction was then quenched with degassed MeOH (400 µL, 9.89 mmol). The resulting mixture was concentrated *in vacuo*. Degassed 2-MeTHF (3.00 mL) was added and the reaction mixture was filtered by cannula under argon into another Schlenk flask. The resulting solution was concentrated *in vacuo*. Degassed MeOH (1.50 mL) was added and the resulting solution was added to a microwave vial with crimp cap equipped with stirrer bar, PTSA.H₂O (38.0 mg, 0.20 mmol) and LiCl (4.2 mg, 0.10 mmol), which had been previously flushed with argon for 30 minutes. A new *t*₀ sample was taken for ¹H NMR analysis. The reaction mixture was carbonylated following **general procedure 9** at 40 °C for 17 hours. The success of the overall reaction was determined by adding 1,3,5-trimethoxybenzene (84.1 mg, 0.50 mmol), as an external standard, to the reaction mixture and stirring vigorously to ensure solubility. A ¹H NMR was run to assess the ratio between SM, vinyl arene and desired product, against external standard.

Procedure H:

Grignard cross-coupling was performed following **general procedure 2** at 20 °C for 2 hours with vinyl tosylate (**158**) (99.1 mg, 0.50 mmol), 2-MeTHF (1.00 mL), (*S*)-**40 mo** (4.3 mg, 0.005 mmol) and (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide (800 µL, 0.60 mmol, 0.8 M in 2-MeTHF). The reaction was then quenched with degassed MeOH (500 µL, 12.36 mmol). The resulting mixture was concentrated *in vacuo*. Degassed 2-MeTHF (3.00 mL) was added and the reaction mixture was filtered by cannula under argon into another Schlenk flask. The resulting solution was concentrated *in vacuo*. Degassed MeOH (1.50 mL) was added and the resulting solution was added to a microwave vial with crimp cap equipped with stirrer bar, PTSA.H₂O (95.1 mg, 0.50 mmol) and LiCl (4.2 mg, 0.10 mmol), which had been previously flushed with argon for 30 minutes. A new *t*₀ sample was taken for ¹H NMR analysis. The reaction mixture was carbonylated following **general procedure 9** at 40 °C for 17 hours. The success of the overall reaction was determined by adding 1,3,5-trimethoxybenzene (84.1 mg, 0.50 mmol), as an external standard, to the reaction mixture and stirring vigorously to ensure solubility. A ¹H NMR was run to assess the ratio between SM, vinyl arene and desired product, against external standard.

Procedure I:

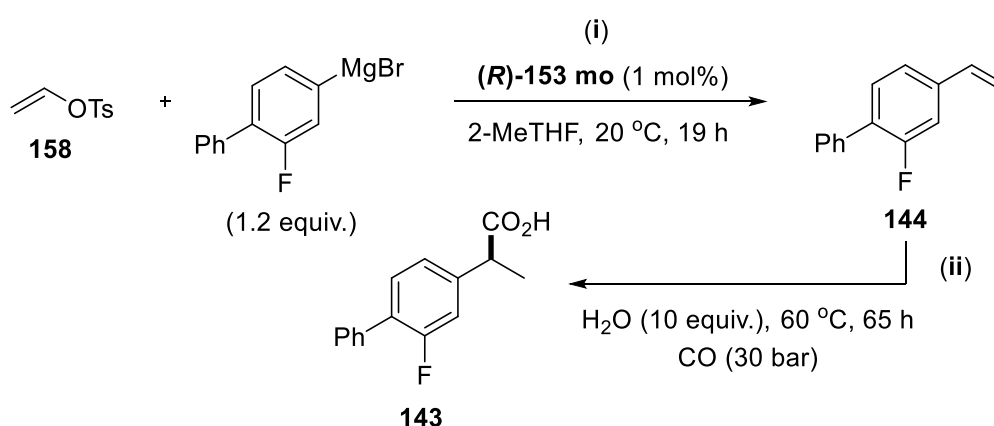
Grignard cross-coupling was performed following **general procedure 2** at 20 °C for 17 hours with vinyl tosylate (**158**) (150.7 mg, 0.76 mmol), 2-MeTHF (1.50 mL), (*S*)-**40 mo** (6.6 mg, 0.0076 mmol) and (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide (904 µL, 0.91 mmol, 1.0 M in 2-MeTHF), without the use of internal standard. Purification *via* column chromatography on silica gel (eluent petroleum ether) gave a mixture of vinyl arene (**144**) and 2-fluorobiphenyl (**161**) (73:27, ¹H NMR) (135.1 mg) [total product = 68 %] as a colourless oil. This mixture was then carbonylated following **general procedure 9** at 40 °C for 17 hours with PTSA.H₂O (19.8 mg, 0.10 mmol), LiCl (4.4 mg, 0.10 mmol), (*S*)-**40 mo** (4.51 mg, 0.0052 mmol) and degassed MeOH (1.56 mL). Purification *via* column chromatography on silica gel (eluent petroleum ether:EtOAc, 100:0 to 90:10) gave branched methyl 2-(2-fluoro-biphenyl-4-yl)-propionate (**163**) (34.3 mg, 26 %) as a white crystalline solid, linear methyl 3-(2-fluoro-biphenyl-4-yl)-propionate (**164**) (8.7

mg, 7 %) as a colourless oil and a mixture of both regioisomers (35.8 mg, 27 %) as a colourless oil.

Overall yield of desired branched methyl 2-(2-fluoro-biphenyl-4-yl)-propionate (**163**) from vinyl tosylate (**158**) was 34.3 mg, 17 %.

7.8.4.2 – Grignard cross-coupling – hydroxycarbonylation

Table 7.4 – Attempts to couple the Grignard cross-coupling step with hydroxycarbonylation, re-using the Pd-Phanephos catalyst.



Entry ^[a]	Procedure	Step (i)		Step (ii)		Overall		
		Conv. (i) (%)	144 (i) (%)	Conv. (ii) (%)	143 (ii) (%)	143 (over steps i and ii) (%)	b/l	e.e. (%)
1	J	> 99	82	13	n.d. ^[b]	-	-	-
2 ^[c]	K	> 99	73	69	69 [28] ^[d]	50 [21] ^[e]	6.08	41
3 ^{[c][f]}	L	> 99	76	39	34	16 ^[g]	7.08	47
4 ^[f]	M	> 99	77	20	10	6 ^[g]	8.70	18

^[a] Reactions were carried out on the scale of vinyl tosylate (0.50 mmol) and according to table and equation, unless otherwise noted. For each entry, see specific procedure below. Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets, based on either 3-fluoro-4-phenylstyrene (% product ii) or vinyl tosylate (% product over two steps)]. b/l ratio determined by ¹H NMR. Enantiomeric excess determined by chiral HPLC. (*S*)-configured catalysts give (*S*)-configured product and *vice versa*. ^[b] Due to overlapping of multiple signals in the ¹H NMR, the product yield was not determined. ^[c] vinyl tosylate (0.25 mmol) scale. ^[d] Based on 3-fluoro-4-phenyl styrene. ^[e] Based on vinyl tosylate. ^[f] Reaction time for Grignard cross-coupling step (i) = 4 h. ^[g] Compared to external standard 1,3,5-trimethoxybenzene (0.50 mmol).

Procedure J:

Grignard cross-coupling was performed following **general procedure 2** at 20 °C for 19 hours in a microwave vial with a crimp cap, with vinyl tosylate (**158**) (49.6 mg, 0.25 mmol), 2-MeTHF (500 μL), (**R**)-**153 mo** (3.2 mg, 0.0025 mmol) and (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide (417 μL, 0.30 mmol, 0.7 M in 2-MeTHF). Degassed H₂O (45 μL, 2.5 mmol) was added to the microwave vial and the resulting reaction mixture was carbonylated following **general procedure 8** at 60 °C for 65 hours.

Procedure K:

Grignard cross-coupling was performed following **general procedure 2** at 20 °C for 19 hours with vinyl tosylate (**158**) (49.6 mg, 0.25 mmol), 2-MeTHF (500 μL), (**R**)-**153 mo** (3.2 mg, 0.0025 mmol) and (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide (417 μL, 0.30 mmol, 0.7 M in 2-MeTHF). The reaction was then quenched with degassed H₂O (22.5 μL, 1.25 mmol). The resulting mixture was transferred *via* cannula filtration under argon to a microwave vial with crimp cap equipped with stirrer bar, PTSA.H₂O (9.5 mg, 0.05 mmol) and LiCl (2.1 mg, 0.05 mmol), which had been previously flushed with argon for 30 minutes. Degassed H₂O (22.5 μL, 1.25 mmol) was added to the microwave vial and the resulting reaction mixture was carbonylated following **general procedure 8** at 60 °C for 65 hours. Isolation *via* acid-base extraction gave a mixture of the acid regioisomers (**143 and 162**) (12.8 mg, 21 %) as a white solid.

Procedure L:

Grignard cross-coupling was performed following **general procedure 2** at 20 °C for 4 hours with vinyl tosylate (**158**) (99.1 mg, 0.50 mmol), 2-MeTHF (1.00 mL), (**R**)-**153 mo** (6.5 mg, 0.005 mmol) and (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide (706 μL, 0.60 mmol, 0.9 M in 2-MeTHF). The reaction was then quenched with degassed H₂O (45 μL, 2.5 mmol). The resulting mixture was transferred *via* cannula filtration under argon to a microwave vial with crimp cap equipped with stirrer bar, PTSA.H₂O (95.1 mg, 0.50 mmol) and LiCl (4.2 mg, 0.10 mmol), which had been previously flushed with argon for 30 minutes. A new t₀ sample was taken for ¹H NMR analysis. Degassed H₂O (90 μL, 5.0 mmol) was added to the microwave vial and the resulting reaction mixture was carbonylated following **general procedure 8** at 60 °C for 65 hours. The success of the

overall reaction was determined by adding 1,3,5-trimethoxybenzene (84.1 mg, 0.50 mmol), as an external standard, to the reaction mixture and stirring vigorously to ensure solubility. A ^1H NMR was run to assess the ratio between SM, vinyl arene and desired product, against external standard.

Procedure M:

Grignard cross-coupling was performed following **general procedure 2** at 20 °C for 4 hours with vinyl tosylate (**158**) (99.1 mg, 0.50 mmol), 2-MeTHF (1.00 mL), (**R**)-**153 mo** (6.5 mg, 0.005 mmol) and (2-fluoro-1,1'-biphenyl-4-yl)magnesium bromide (706 μL , 0.60 mmol, 0.9 M in 2-MeTHF). The reaction was then quenched with degassed H_2O (1.50 mL) and extracted three times with 2-MeTHF (3 x 1.50 mL), under argon, into another Schlenk flask. The combined organics were then concentrated *in vacuo* and fresh 2-MeTHF (1.50 mL) was added and the resulting mixture was added to a microwave vial with crimp cap equipped with stirrer bar, PTSA. $\cdot\text{H}_2\text{O}$ (95.1 mg, 0.50 mmol) and LiCl (4.2 mg, 0.10 mmol), which had been previously flushed with argon for 30 minutes. A new t_0 sample was taken for ^1H NMR analysis. Degassed H_2O (90 μL , 5.0 mmol) was added to the microwave vial and the resulting reaction mixture was carbonylated following **general procedure 8** at 60 °C for 65 hours. The success of the overall reaction was determined by adding 1,3,5-trimethoxybenzene (84.1 mg, 0.50 mmol), as an external standard, to the reaction mixture and stirring vigorously to ensure solubility. A ^1H NMR was run to assess the ratio between SM, vinyl arene and desired product, against external standard.

Chapter VIII: References

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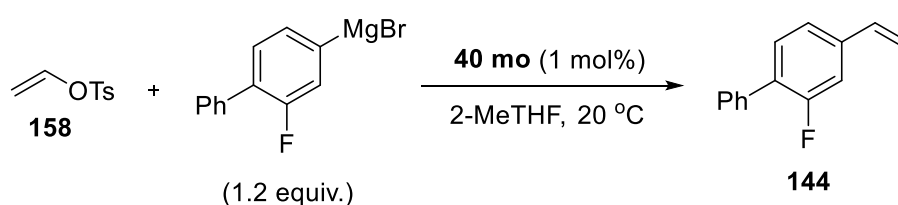
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Chapter IX: Appendix

9.1 – [PdCl₂(Xylyl-Phanephos)]-catalysed Grignard cross-coupling of vinyl tosylate with 2-fluoro-1,1'-biphenyl magnesium bromide, from which the average yield was obtained

Table 9.1 – [PdCl₂(Xylyl-Phanephos)] (**40 mo**)-catalysed Grignard cross-coupling of vinyl tosylate (**158**) with 2-fluoro-1,1'-biphenyl magnesium bromide.



Entry ^[a]	Catalyst	t (h)	Conversion (%)	Product (%)
1	(<i>S</i>)- 40 mo	17	> 99 %	99 %
2 ^[b]	(<i>S</i>)- 40 mo	21	> 99 %	95 %
3 ^[b]	(<i>S</i>)- 40 mo	21	> 99 %	92 %
4	(<i>S</i>)- 40 mo	17	> 99 %	96 %
5 ^[c]	(<i>S</i>)- 40 mo	17	> 99 %	96 %
6 ^[c]	(<i>S</i>)- 40 mo	17	> 99 %	95 %
7 ^[c]	(<i>S</i>)- 40 mo	17	> 99 %	93 %
8 ^[c]	(<i>S</i>)- 40 mo	17	> 99 %	93 %
9	(<i>S</i>)- 40 mo	17	> 99 %	90 %
10	(<i>S</i>)- 40 mo	17	> 99 %	90 %
11	(<i>S</i>)- 40 mo	17	> 99 %	89 %
12 ^[b]	<i>rac</i> - 40 mo	21	> 99 %	79 %
13 ^[b]	(<i>S</i>)- 40 mo	17	> 99 %	90 %
14^[e]	40 mo	17-21	> 99 %	92 %

^[a] Reactions conditions: vinyl tosylate (0.50 mmol), 2-fluoro-1,1'-biphenyl magnesium bromide (0.60 mmol in 2-MeTHF, molarity determined by titration before use), [PdCl₂(Xylyl-Phanephos)] (0.005 mmol), in 2-MeTHF (1.0 mL). Conversions and yields were determined by ¹H NMR using 1-methylnaphthalene as an internal standard. ^[b] Vinyl tosylate (0.25 mmol) scale. ^[c] Reaction performed in a sealed microwave vial with crimp cap. ^[e] Average yield of 13 experiments (t 17-21h).

9.2 – Publications

“Catalytic constructive deoxygenation of lignin-derived phenols: new C–C bond formation processes from imidazole-sulfonates and ether cleavage reactions.” Stuart M. Leckie, **Gavin J. Harkness** and Matthew L. Clarke, *Chem. Commun.*, 2014, **50**, 11511.

“A Highly Enantioselective Alkene Methoxycarbonylation Enables a Concise Synthesis of (*S*)-Flurbiprofen.” **Gavin J. Harkness** and Matthew L. Clarke, *Eur. J. Org. Chem.*, 2017, **2017**, 4859.

“Less hindered ligands give improved catalysts for the nickel-catalysed Grignard cross-coupling of aromatic ethers.” **Gavin J. Harkness** and Matthew L. Clarke, *Catal. Sci. Technol.*, 2018, Advance Article, *Accepted 2017*, DOI: 10.1039/C7CY01205E.

Beyond the scope of this thesis:

“A Highly Active Manganese Catalyst for Enantioselective Ketone and Ester Hydrogenation.” Magnus B. Widegren, **Gavin J. Harkness**, Alexandra M. Z. Slawin, David B. Cordes and Matthew L. Clarke, *Angew. Chem. Int. Ed.*, 2017, **56**, 5825.

9.3 – NMR spectra of novel compounds

NMR spectra of novel compounds are available on the attached disc.

9.4 – X-ray data for all crystal structures

X-ray data for all crystal structures are available on the attached disc.