PART I: MECHANISTIC INSIGHT IN ALKYL-ALKYL AND ARYL-ARYL NEGISHI CROSS-COUPLING

PART II: LARGE SCALE SYNTHESIS OF NHC PRECURSORS: 2,6-DI(3-PENTYL)ANILINE AND 2,6-DI(4-HEPTYL)ANILINE

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ABSTRACT

Part I: An efficient method for alkyl-alkyl Negishi cross-coupling reaction of unactivated primary alkyl halides with higher-order zincate species (synthesized from dialkylzinc and a non-coordinating halide salt *in situ*) using *Pd-PEPPSI-IPent* (**P**yridine-**E**nhanced **P**re-catalyst **P**reparation **S**tabilization and **I**nitiation) pre-catalyst has been developed. The method requires no additive (such as LiX) or use of a polar co-solvent (such as THF/DMI) and reactions proceed in THF solvent alone. The transmetalating species in alkyl-alkyl Negishi cross-coupling has been identified and the catalytic cycle has been amended to include the formation of the higher-order zincate species.

Subsequent investigation into diarylzinc as reagents in Negishi cross-coupling have shown they transmetalate directly without the use of halide additive in THF alone producing arylzinc halide as a resting state. Once the dielectric of the solvent becomes sufficiently polar, coupling resumes, and the aryl moiety transmetalates to palladium. The optimized protocol using *Pd-PEPPSI-IPent* allowed for the coupling of a variety of alkyl- and aryl- organozinc reagents providing the corresponding products in good to quantitative yields. Moreover, the developed protocol is generally applicable and tolerant of a variety of functional groups including esters, and nitriles.

Part II: An improved and efficient method for the preparation of sterically demanding Pd *PEPPSI-IPent, IPent^{Cl}, IHept, and IHept^{Cl}* pre-catalysts are presented and the results of optimization for the multi-gram synthesis of 2,6-disubstituted anilines is discussed.

DEDICATION

I wish to dedicate this work to my loving family. I thank my caring mother, Suzanne for always reminding me of the importance of education, and to prioritize it over everything else. I thank my father, Jeff for supporting me in whatever career path I chose to follow. Whether it was music, acting, carpentry or science (or even politics), I have never felt that I would disappoint you by following my heart.

To Grand-mom and Grand-dad, for attending every birthday, Christmas pageant or football game, I remember you there at almost every single one. I was very proud I to tell both of you that I was successful in my PhD defense.

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To my aunts: Mary-Lou and Virginia. I am grateful for your support and interest my academic achievement. I will pay forward your kindness and wisdom. Thank you.

I warmly dedicate this work to my loving partner, Dr. Sherry Boodram. You have supported me in every dream, every endeavour, every practice, and every commitment. Our shared experience has made this a journey to remember for a life-time.

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TABLE OF CONTENTS

Abstract....i

Dedication....iii

Acknowledgements....iv

Table of Contents....v

List of Tables....ix

List of Figures....xii

List of Schemes....xiii

List of Abbreviations....xvi

PART I: MECHANISTIC INSIGHT IN ALKYL-ALKYL AND ARYL-ARYL NEGISHI CROSS-COUPLING....1

Chapter 1:Evidence for High-Order Zincates in Alkyl-alkyl Negishi Cross-coupling....2

1.1 Background Information....3

1.1.1 Selected Highlights in the History of Cross-coupling....3

1.1.2 Transition Metal Mediated $C(sp^3)$-$C(sp^3)$ Cross-coupling....4

1.1.3 Oxidative Addition to an Organohalide....7

1.1.4 Reductive Elimination Step....8

1.1.5 Transmetalation....9

1.1.6 The Active TM in Suzuki-Miyaura Cross-coupling....10

1.1.7 Difficulties in Alkyl-alkyl Cross-coupling....12

1.1.8 Negishi Cross-coupling....14

1.1.9 The Synthesis of Organozinc Reagents....15

1.1.10 The Importance of Salt By-products in Negishi Cross-coupling....17

1.1.11 Evidence for the Isolation of a Higher-order Zincate Species....22

1.2 Plan of Study....26

1.3 Results and Discussion....27

1.3.1 Spectrometric Titration – The Formation of $[EtZnBr_3]^{2-}$ $2[PPh_4]^+$....27

*1.3.2 Evaluation of the Reactivity of **13** Relative to Other Alkylzincs....30*

1.3.3 The Importance of the Cation in the Reactivity of Zincates....32

*1.3.4 The Reactivity of Di(tetra-*n*-butylammonium)ethylzinc Tribromide (**17**) in Negishi Cross-coupling* 38
1.3.5 The Proposed Catalytic Cycle of Alkyl-alkyl Negishi Cross-coupling 44
1.4 Conclusion 45

Chapter 2:Experimental Procedures 47

2.1 General Experimental 48
2.2 Synthetic Procedures 49
2.2.1 General procedure for the Preparation of Organozinc Halides[38a] 49
2.2.2 General Negishi Cross-coupling Procedures A and B 52
2.2.3 General Negishi Cross-coupling Procedure C 52
2.2.4 General Negishi Cross-coupling Procedure D 53
2.2.5 General Negishi Cross-coupling Procedure E 53
*2.2.6 Control Experiment for the Addition of PPh_4Br to the Cross-coupling of **14** (Ethylzinc Bromide) with **7** (1-Bromo-3-phenylpropane).* 54
*2.2.7 Titration of Tetra-n-butylammonium Bromide and Zinc Bromide with Diethylzinc (**11**)* 55
2.2.8 Spectral and Physical Data for Alkyl-alkyl Negishi Cross-coupling Products 56

Chapter 3:Aryl-aryl Negishi Cross-Coupling 58

3.1 Introduction 59
3.2 Plan of Study 59
3.3 Results and Discussion 59
3.3.1 Zinc Insertion in to sp^2 Carbon-Bromide Bonds 59
3.3.2 Mono-arylzinc Species Preparation and Reactivity 60
3.3.3 The Effect of $ZnBr_2$ on Alkyl-alkyl Negishi Cross-coupling 62
3.3.4 Solvent Effects in Aryl-aryl Negishi Cross-coupling 63
3.3.5 Aryl-aryl Negishi Cross-coupling Using Diarylzinc Species 64
3.3.6 Isolating Other Diarylzinc Species 67
3.3.7 On Structure and Stability of Diarylzincs 69
3.3.8 ^{1}H-NMR Spectroscopy Halide Salt Doping Studies of Mono- and Diarylzinc Species 70
3.4 Conclusion 75

Chapter 4:Experimental Procedures for Aryl-aryl Negishi Cross-coupling..... 77

4.1 General Experimental 78

4.2 Synthetic Procedures..... 79

4.2.1 Preparation of Arylzinc Halides..... 79

4.2.2 Negishi Coupling Containing MgX_2..... 79

4.2.3 Negishi Reaction with MgX_2 Removed, then Re-added..... 81

4.2.4 Negishi Coupling with MgX_2 Removed and DMI Aadded..... 82

4.2.5 General Procedure for the Preparation of Diarylzincs: 82

4.2.6 Spectral and Physical Data of Diarylzincs 84

4.2.7 Negishi Coupling to Provide Table 7, Entries 1 and 2: 86

4.2.8 Negishi Coupling to Provide Table 7, Entry 3:..... 86

4.2.9 Negishi Coupling to Provide Table 7, Entry 4:..... 87

4.2.10 Negishi Coupling to Provide Table 7, Entry 5:..... 88

4.2.11 Negishi Coupling to Provide Table 7, Entry 6:..... 89

4.2.12 Negishi Coupling to Provide Table 7, Entry 7:..... 89

4.2.13 Negishi Coupling to Provide Table 7, Entry 8:..... 90

4.2.14 Negishi Coupling to Provide Table 7, Entry 9:..... 91

4.2.15 Negishi Coupling to Provide Table 7, Entry 10:..... 92

4.2.16 General Cross-Coupling Procedure..... 92

PART II: LARGE SCALE SYNTHESIS OF NHC PRECURSORS: 2,6-DI(3-PENTYL)ANILINE AND 2,6-DI(4-HEPTYL)ANILINE.....96

Chapter 5:Introduction and General Background..... 97

5.1 The Use of Ancillary Ligands in Catalyst Design 98

5.1.1 Phosphine Ligands: An Introduction to Ancillary Ligands..... 98

5.1.2 A Brief Summary of the Evolution N-Heterocyclic Carbene (NHC) 99

5.1.3 NHC Based Catalysts in Cross-coupling Reactions..... 100

5.1.4 The Structure Activity Relationship in Pd-PEPPSI Pre-catalysts..... 103

5.1.5 The Effect of NHC Backbone Modification..... 104

5.1.6 Assembly of the Imidazolium Salt..... 104

5.1.7 The Challenges and Improvements in the Synthesis 2,6-Dialkylanilines..... 106

5.1.8 Pd-PEPPSI Pre-catalysts and Secondary Alkyl Cross-coupling..... 110

5.1.9 Plan of study ... *113*

5.2 Results and Discussion ... 114

*5.2.1 Towards the Synthesis of 2,6-Diisopropylaniline, (**80**)* ... *114*

*5.2.2 Preparation of 2,6-Di(3-pentyl)aniline (**56**)* ... *115*

*5.2.3 Preparation and Optimization Studies of 2,6-Di(4-heptyl)aniline (**74**)* ... *117*

*5.2.4 Re-optimizing the Synthesis of the Organozinc (**88**)* ... *122*

*5.2.5 Optimzation of 3-Pentylzinc Bromide (**84**) Negishi Cross-coupling en route Towards Substituted 2,6-Di(3-pentyl)aniline (**56**)* ... *124*

5.3 Conclusions ... 126

5.3.1 Other Anilines of Interest ... *127*

5.3.2 Future Work in this Area ... *128*

Chapter 6:Experimental Procedures ... 130

6.1 General Experimental ... 131

6.2 Experimental Procedures ... 132

6.2.1 Large Scale Preparation of 2,6-Di(4-heptyl)aniline Precursors ... *132*

6.2.2 General Preparation of Secondary Alkylzinc Halides ... *134*

*6.2.3 General Coupling Procedure for 2,6-Disubstituted Anilines (**80**, **56**, and **74**)* *136*

6.2.4 General Procedure for the Attempted Synthesis of Alkylbromides ... *138*

References ... 140

Appendix ... 149

A.1. - Structure Index ... 150

LIST OF TABLES

Table 1. Alkyl-alkyl Suzuki cross-coupling reactions of unactivated alkyl iodides with butyl-9-BBN 13

Table 2. Alkyl-alkyl Negishi cross-coupling reactions of unactivated alkyl iodides with butylzinc chloride..... 13

Table 3. Comparing the reactivity of **13** with that of other alkylzincs in Negishi cross-coupling..... 31

Table 4. Evaluating the role of phosphine additives in Negishi cross-coupling with *Pd-PEPPSI-IPr* pre-catalyst 33

Table 5. The impact of different halide sources in alkyl-alkyl Negishi cross-coupling. 35

Table 6. Substrate scope of diethyl zinc in alkyl-alkyl Negishi cross-coupling with selected additives 41

Table 7. Cross-coupling of diphenylzinc (**35**) with anisole (**33**) under different conditions..... 65

Table 8. Ligation of $PdCl_2$ with various imidazolium salts en route to *Pd-PEPPSI* pre-catalysts..... 105

Table 9. Selectivity evaluation of several *Pd-PEPPSI* pre-catalysts[a] 112

Table 10. Initials results coupling 2-propylzinc bromide (**75**) with 2,6-dibromoaniline (**68**)..... 115

Table 11. Coupling 3-pentylzinc bromide (**84**) with 2,6-dibromoaniline (**68**) 116

Table 12. A 1 g scale coupling of 3-pentylzinc bromide (**84**) with 2,6-dibromoaniline (**68**)..... 117

Table 13. Optimization of catalyst loading and temperature for a 50 mg scale cross coupling with 4-heptylzinc bromide (**88**) and 2,6-dibromoaniline **(68**) 120

Table 14. The effect of solvent composition and catalyst loading on conversion of **68** for a 50 mg scale cross-coupling with 4-heptylzinc bromide (**88**) 121

Table 15. Optimization of scale-up conditions 122

Table 16. Optimization of 2,6-di-(3-pentyl)aniline (**51**) for synthesis on a ten gram scale..... 125

LIST OF FIGURES

Figure 1. A palladium mediated catalytic cycle 5

Figure 2. General catalytic cycle of Pd-catalyzed, alkyl-alkyl cross-coupling reactions 6

Figure 3. General Suzuki-Miyaura reaction and its catalytic cycle 12

Figure 4. *Pd-PEPPSI* family of pre-catalysts 14

Figure 5. The catalytic cycle of Pd in the Negishi cross-coupling reaction..... 19

Figure 6. The impact of the incremental addition of LiBr and $ZnBr_2$ on the conversion of cross-coupling reactions involving *n*-BuZnBr and starting material (**7**)..... 21

Figure 7. Negative ion mass spectra showing the change in the ratio of the *n*-$BuZnBr_2^-$ to $ZnBr_3^-$ ion intensities as a function of changing amounts of LiBr..... 24

Figure 8. X-Ray crystal structure of **12** and **13**..... 25

Figure 9. ^{1}H-NMR Chemical shift perturbation of diethyl zinc with $PPh_4^+Br^-$ 28

Figure 10. ^{1}H-NMR Chemical shift perturbation of diethyl zinc with $PPh_4^+Br^-$.. 37

Figure 11. The impact of $ZnBr_2$ on the isolated yields of **19** from cross-coupling compounds alkylhalide **7** and organozinc **17**..... 43

Figure 12. Proposed catalytic cycle for the alkyl–alkyl Negishi reaction 44

Figure 13. Proposed transition state (**TS**) for alkyl-alkyl Negishi Cross-coupling with *Pd-PEPPSI-IPent*^{Cl} 45

Figure 14. ^{1}H NMR titration of Ph_2Zn (**35**) with LiBr in THF-d_8 72

Figure 15. ^{1}H NMR titration of Ph_2Zn (**35**) with DMI in THF-d_8 72

Figure 16. ^{1}H NMR titration of PhZnBr (**32**) with LiBr in THF-d_8..... 73

Figure 17. Superimposed ^{1}H NMR spectra: PhZnBr (**32**) and $Zn(Ph)_2$ (**35**) 73

Figure 18. The proposed catalytic cycle for the Negishi coupling of arylzinc reagents including the role of salt additives and solvent dielectric. 75

Figure 19. Various 5-membered N-heterocyclic carbenes 100

Figure 20. Highlighted imidazolidine based carbenes 101

Figure 21. Selection of examples of *Pd-PEPPSI* pre-catalysts 102

Figure 22. General mechanism for the Negishi cross-coupling of 2-propylzinc bromide (**75**) 111

Figure 23. Stability of organozinc reagents toward aniline 126

Figure 24. Synthetic targets **91**-**93** for future work 127

LIST OF SCHEMES

Scheme 1. General Rieke protocol for producing organozincs 16

Scheme 2. General $ZnBr_2$ transmetalation reaction for synthesizing organozincs 16

Scheme 3. Huo's protocol for the synthesis of alkylzincs..... 16

Scheme 4. Model Negishi cross-coupling reaction using **8** from Rieke Metals 17

Scheme 5. The synthesis of **9** using Huo's protocol followed by treatment of **8** with an organohalide **7** under Negishi cross-coupling conditions..... 17

Scheme 6. Rieke's protocol for the formation of organozinc **8** 18

Scheme 7. Cross-coupling of **8** from Huo's protocol in the presence of LiBr..... 18

Scheme 8. Reaction of diethylzinc and tetraphenylphosphonium bromide 25

Scheme 9. Formation of zincate species **15** and **13** by adding halide ions to diethyl zinc 29

Scheme 10. Preliminary cross-coupling results using TBAB with diethyl zinc in alkyl-alkyl Negishi cross-coupling..... 38

Scheme 11. Evaluating *Pd-PEPPSI-IPent* as a catalyst for zincate cross-coupling .. 39

Scheme 12. Reduced loading of organozinc species relative to the alkyl bromide ... 39

Scheme 13. Cross-coupling zincate **17** with low catalyst loading 40

Scheme 14. Zincate **17** converts alkyl halide **1** to **9** in THF solvent only..... 42

Scheme 15. Treatment of an aryl halide with conditions outlined by Huo to promote the direct insertion of Zn across the C-X bond..... 60

Scheme 16. The synthesis of **32** and subsequent cross-coupling to **33** with *Pd-PEPPSI-IPent* (**3**) 61

Scheme 17. Coupling of **32** with mineral salts removed..... 61

Scheme 18. Coupling MgX_2-free **32** in the presence of $MgCl_2$ 62

Scheme 19. $ZnBr_2$ as an additive in Negishi cross-coupling of salt-free arylzinc halide (**32**) 63

Scheme 20. DMI as an additive in Negishi cross-coupling of salt-free arylzinc halide (**32**) 63

Scheme 21. General procedure for the synthesis of diarylzincs. Shown are the synthesized diarylzincs and their yield. 68

Scheme 22. Cross-coupling of diarylzincs with arylhalides promoted by *Pd-PEPPSI-IPent* under salt-free conditions in THF at rt. 69

Scheme 23. Acid mediated condensation followed by formation of the imidazolium salt 105

Scheme 24. Steele and co-workers' route to synthesis of 2,6-di(3-pentyl)aniline (**56**) from 2,6-dimethylaniline (**55**) 106

Scheme 25. Synthesis of 2,6-di(3-pentyl)aniline (**56**) using a Grignard addition 107

Scheme 26. Synthesis of 2,6-di(3-pentyl)aniline (**56**) using Suzuki-Miyaura cross-coupling 108

Scheme 27. Synthesis of 2,6-di(4-heptyl)aniline (**74**) using a *Pd-PEPPSI* mediated Kumada-Tamao-Corriu coupling of alkenylmagnesium (**72-*E/Z)*** 109

Scheme 28. Retrosynthetic analysis en route to 2,6-di(4-alkyl)anilines 113

Scheme 29. The preparation of *2*-propylzinc bromide (**75**) and its titre. 114

Scheme 30. Preparation of 3-pentylzinc bromide (**84**) 115

Scheme 31. Reduction of 4-heptanone (**69**) with sodium borohydride 117

Scheme 32. Synthesis of 4-bromoheptane (**87**) from 4-heptanone (**69**) 118

Scheme 33. The preparation of 4-heptylzinc bromide, **88**, on a 500 g scale..... 118

Scheme 34. Preparation of **88** using Li/X exchange 123

Scheme 35. Preparation of **88** *via* Grignard reagent formation..... 123

Scheme 36. Reacting **88**, prepared from the organolithium or Grignard reagent, with **68**..... 123

Scheme 37. Bromination of compounds **95**, **97**, and **99**..... 128

Scheme 38. Alternative methods of bromination 129

LIST OF ABBREVIATIONS

Ac	acetyl
atm	atmospheric pressure
9-BBN	9-borabicyclo[3.3.1]nonane
BHE	β-hydride elimination
°C	degree Celsius
CAM	ceric ammonium molybdate
Cat.	catalytic
cod	1,5-cyclooctadiene
Cy	cyclohexyl
d	day(s)
dba	dibenzylideneacetone
DMI	N,N'-dimethylimidazolidin-2-one
DME	dimethoxyethane
DMF	dimethylformamide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DFT	density functional theory
equiv	molar equivalents
FT	Fourier transformed
GC/MS	Gas Chromatography/Mass Spectrometry
h	hour(s)
HRMS	high-resolution mass spectrometry
IHept	1,3-bis(2,6-di(4-heptyl)phenyl)imidazole-2-ylidene
IMe	1,3-dimethylimidazol-2-ylidine
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPent	1,3-bis(2,6-di(3-pentyl)phenyl)imidazole-2-ylidene
$IPent^{Cl}$	1,3-bis(2,6-di(3-pentyl)phenyl)-4,5-dichloroimidazol-2-ylidene
$IPent^{Me}$	1,3-bis(2,6-di(3-pentyl)phenyl)-4,5-dimethylimidazol-2-ylidene
IPr	1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidine
IPr^{Cl}	1,3-bis(2,6-diisopropylphenyl)-4,5-dichloroimidazol-2-ylidene
IPr^{Me}	1,3-bis(2,6-diisopropylphenyl)-4,5-dimethylimidazol-2-ylidene

IR	infrared spectroscopy
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride ($LiAlH_4$)
LiX	lithium halide salt, X = bromide (Br) and/or chloride (Cl)
MgX	magnesium halide salt, X = bromide (Br) and/or chloride (Cl)
MI	migratory insertion
min	minute(s)
Ms	Methylsulfonyl (mesyl)
NFSI	N-fluorobenzenesulfonimide
NHC	N-heterocyclic carbene
NMI	N-methylimidazole
NMP	N-methylpyrrolidine
NMR	Nuclear magnetic resonance
No-D NMR	NMR without deuterated solvent
PEPPSI	pyridine-enhanced pre-catalyst preparation, stabilization, and initiation
ppm	parts per million
psi	pounds per square inch
OA	oxidative addition
Quant.	Quantitative
rt	room temperature
RE	reductive elimination
sec	second(s)
S_N2	bimolecular nucleophilic substitution
t	tertiary
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TEP	Tolman's electronic parameter
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran

TLC	thin-layer chromatography
TM	transmetalation
TMS	trimethylsilyl
TON	turn-over number
TS	transition state
Ts	para-toluenesulfonyl (tosyl)

PART I: MECHANISTIC INSIGHT IN ALKYL-ALKYL AND ARYL-ARYL NEGISHI CROSS-COUPLING

Chapter 1:
Evidence for High-Order Zincates in Alkyl-alkyl Negishi Cross-coupling

1.1 Background Information

1.1.1 Selected Highlights in the History of Cross-coupling

The formation of carbon-carbon bonds *via* nucleophilic substitution is a fundamental process in organic chemistry. The Wurtz reaction (*ca*. 1855), which involves two alkyl halides in the presence of sodium to form an alkane, is the oldest reported protocol to form a bond between two sp^3-hybridized carbon centers. The primary drawbacks for this transformation are that significant amounts of homo-coupled and elimination products are observed.[1] However, a variant of this process called the Wurtz-Fittig reaction,[2] which involves an alkyl and aryl halide in the presence of sodium metal, does not lead to the same by-product formation.[3] In the time that followed the work by Wurtz, the organometallic reagents investigated for C-C bond formation included those of lithium and potassium.[4] However, the reactivity of organometallic reagents was overshadowed by their tedious preparation and handling along with their tendency to decompose upon exposure to the conditions typically encountered when working out on the bench, making their use less practical. Much later, in 1954, Kharasch began experimenting with the use of organo-alkalis together with transition metals. He developed a coupling reaction that featured an organomagnesium and an organohalide, which at the time was considered to be the best route for alkyl-alkyl coupling.[5] The application of this method for synthetic purposes presents yet another limitation because the coupling partner to the Grignard reagent must be activated, such as allylic or benzylic halides or some unhindered primary alkyl halides.[6] Kochi was successful in developping a modified procedure involving primary alkyl halides and Grignard reagents in combination with Li_2CuCl_4. Although it generates negligibly small

quantities of homo-dimers, functional group compatibility continued to be a concern with these types of reactions.[7]

The S_N2 reaction between an organometallic such as an organolithium or organomagnesium is limited to unhindered alkyl halides and are subject to many undesirable side reactions such as non-selective metal-halogen exchange, disproportionation, and β-hydride elimination (BHE).[8] As one might expect, the high propensity of organolithium and organomagnesiums reagents to engage most electrophilic functional groups such as ketones, esters, and aldehydes limits the scope of the coupling reactions. Tamao and Kumada discovered a more promising route to achieving alkyl-alkyl cross-coupling using a Ni-based catalyst that offered improved selectivity over other methods. However, concerns for substrate tolerance for particularly electrophilic functional groups remained unaddressed.[9] Nonetheless this work was pivotal in leading cross-coupling down a fruitful path over the last 40 years. The gradual movement from nickel to palladium as the catalytic metal improved the generality of cross coupling leading to seemingly limitless applications in the synthesis of natural products, pharmaceuticals and materials. These efforts in cross-coupling culminated when the Nobel prize was awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki "for palladium-catalyzed cross-couplings in organic chemistry" in 2010. New and innovative variations of this pivotal transformation continue today.

1.1.2 Transition Metal Mediated $C(sp^3)$-$C(sp^3)$ Cross-coupling

It has been well established that transition metal mediated cross-coupling is a powerful tool for carbon-carbon bond formation.[33a,10] The three key processes are 1) the oxidative addition of a low-valent transition metal across an electrophilic carbon-halide

or pseudohalide bond (e.g. OTf, OTs, OMs etc..), 2) transmetalation of the organometallic nucleophile to the oxidative addition intermediate, and 3) reductive elimination to form a carbon-carbon bond. After process 3) the active Pd^0 catalyst is regenerated and continues in the catalytic cycle (see Figure 1). The coupling of activated C(sp^2) and C(sp) carbon centres is fast and proceeds in a concerted fashion.

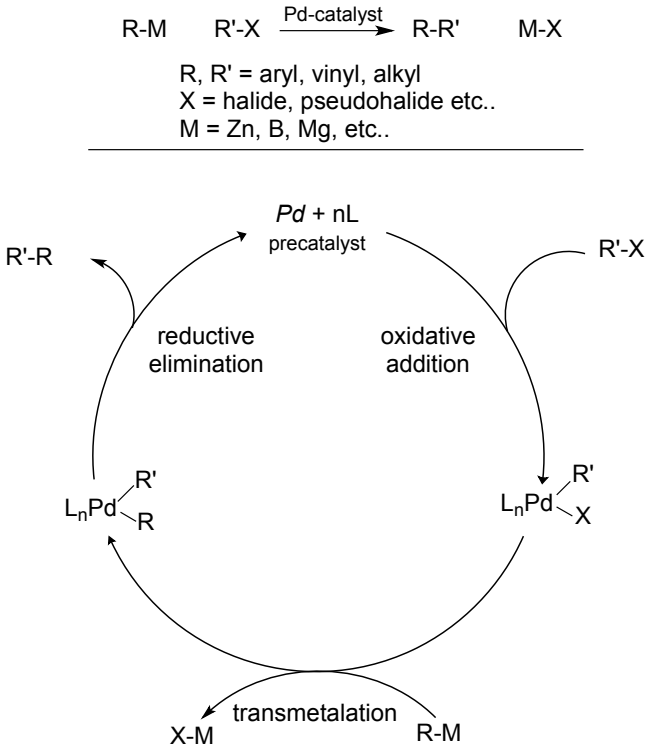


Figure 1. A palladium mediated catalytic cycle

In contrast, the coupling of C(sp^3) centres is wrought with many new challenges not seen in the C(sp^2) counterparts. The first challenge associated with haloalkanes is the reluctance carbon-halogen bonds have to oxidative addition.[10] Second, as in the Wurtz coupling, reactions with non-equivalent partners lead to poor conversions to the desired product and are plagued with side reactions such as β-hydride elminiation (BHE, see Figure 2). The reaction takes place via a catalytic cycle with several

possible paths. Amongst these are the route to the desired product (**Path A**), to the BHE product (**Path B**), which is unique to alkyl-alkyl cross-coupling, to the product of protodemetalation (**Path C**), and most abundant side reaction path that leads to the homocoupling product (**Path D**). To understand the propensity for side-reactions to occur, it is necessary to develop a firm understanding of the individual processes involved in the catalytic cycle and how a process can affect those that follow it.

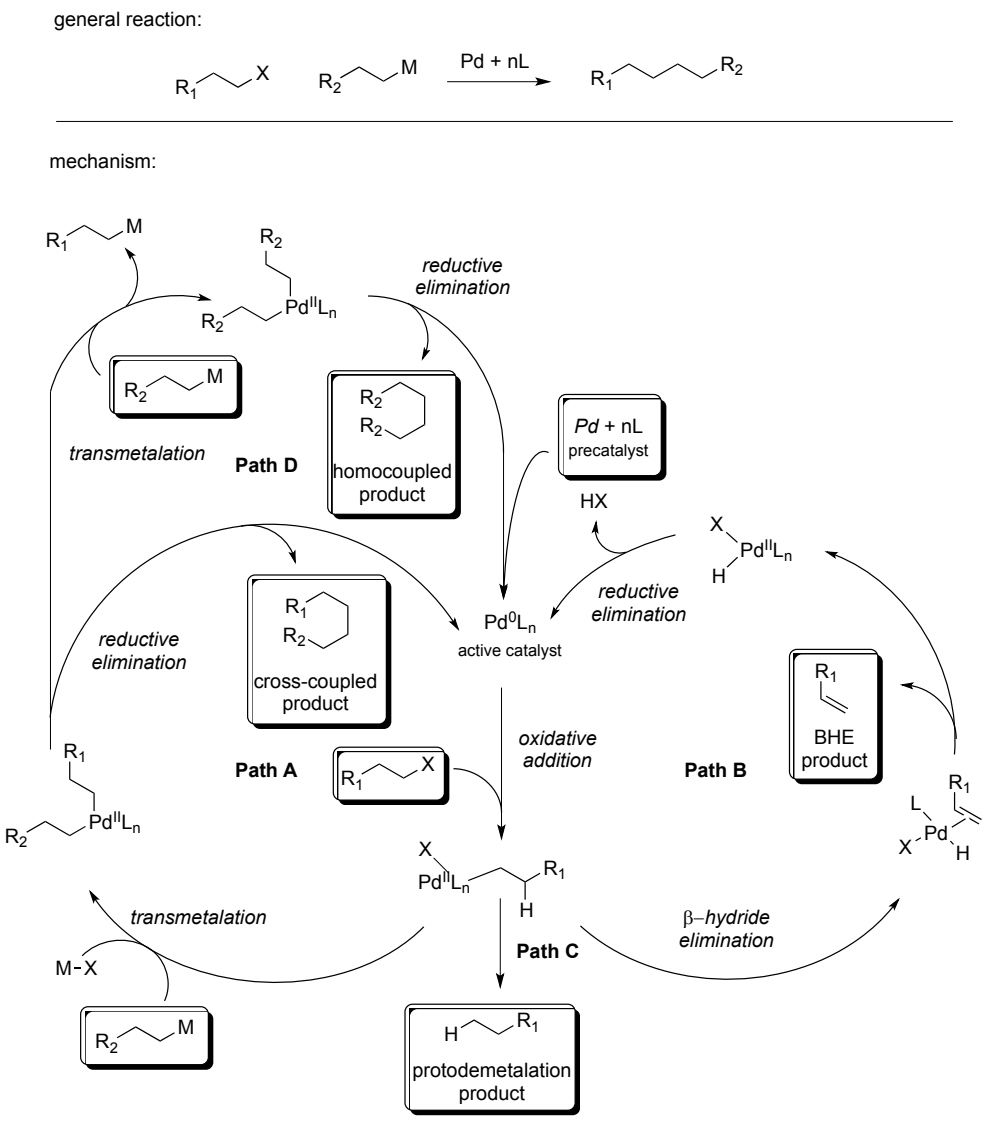


Figure 2. General catalytic cycle of Pd-catalyzed, alkyl-alkyl cross-coupling reactions

1.1.3 Oxidative Addition to an Organohalide

Generally speaking, oxidative addition (OA) creates two metal-ligand bonds by insertion in an organic fragment. The formation of a Grignard reagent from an alkyl halide and Mg metal is an analogous example. Mg^0 metal is oxidized to the Mg^{2+} state and it would appear that the metal has inserted itself between the C-X bond. In the context of palladium-mediated cross-coupling, OA is used to refer part of the catalytic cycle in which the metal undergoes the loss of two-electrons. The process occurs immediately after the formation of Pd(0), and is followed by a change in oxidation state from *n* to *n+2,* the number of *d*-electrons formally held within the palladium valence shell, decreases by two. The process with alkyl halides and pseudohalides can occur by an S_N2 mechanism in which the halide is the electrophile and the metal is the electron-rich nucleophile, a process that is accelerated in polar solvents due to the stabilization they provide of reactive intermediates. OA of substrates that cannot undergo S_N2 pathways alternatively can proceed by the formation of a three-centered transition state. This is almost always the case with aryl halides when nucleophilic aromatic substitution is impossible (e.g. bromobenzene) especially when d^{10} palladium(0) complexes are present.[11] The argument for a radical pathway of OA with aryl halides still lacks strong evidence, although this has been reported with other transition metals such as Pt, Rh, Ni and Ir.[12,13]

The process of catalytic oxidative addition for the purposes of cross-coupling reveals clues as to how NHC ligands are designed. Typically, the process occurs with a Pd(0) species on a 14-electron complex. The rate of oxidative addition is most often independent of the nucleophile though it has been postulated that it is a turnover-

limiting step. If the ligands of the metal are more electron-rich, this will accelerate oxidative addition by increasing electron density at the palladium metal centre. Counter intuitively, bulky ligands will encourage the formation of a 12-electron [LPd(0)] species which undergo oxidative addition more rapidly than [L_2Pd(0)] species.

1.1.4 Reductive Elimination Step

The process of reductive elimination (RE) is the product-forming step in the catalytic cycle of cross-coupling reactions that regenerates the Pd(0) species. The intermediates and transition states for RE and OA are the same for both processes. A *cis* orientation of two ligands is required for RE to occur via a three-centered, concerted mechanism. Complexes in which the two ligands are *trans* to one another undergo RE by isomerization of the complex to the *cis* isomer or by a stepwise mechanism that facilitates a *cis* relationship. RE involves the formation of a covalent bond between two ligands bonded to a metal center forming the product, which leaves the coordination sphere of the metal and vacates sites for the oxidative addition of another organohalide to occur. For metals, first row complexes will typically undergo RE more quickly than second row metals, which react more quickly than complexes of third row metals. In palladium-mediated cross-coupling, the process occurs by a 2-electron change and the oxidation state of the metal centre changes from n+2 to n.

The factors that control the rates of RE include the steric and electronic properties of the metal centre, which generally are the opposite properties that promote OA. For ligands, more sterically bulky ones produce more congested metal centres that reductively eliminate faster than complexes bearing less bulky ligands. Traditionally, the steric demands of a metal centre are modified with the use of phosphanes or NHC

ligands. The steric strain around a metal centre is relieved when two ligands reductively eliminate and this is a driving force for this process. By contrast, if the alkyl halide is sterically demanding then an appropriate geometry cannot be readily adopted and OA will proceed slowly. Electronically, RE is accelerated by electron-poor metal centres as the process of RE creates a metal complex that exhibits increased electron density about the metal centre. That is, the more electron-poor a complex is, the faster the process of RE relative to an electron-rich complex.

1.1.5 Transmetalation

Transmetalation (TM) with a metal is one of the simplest ways to prepare a variety of organometallic reagents (see eq. 1). This reaction can be used to prepare alkyls of Li, Na, K, Be, Mg, Al, Ga, Zn, Cd, Te, Sn and so on, by transferring ligands from one metal to another (see eq. 1). The RM' compound can be successfully prepared when M' is above M in the electromotive series, unless some other way is found to shift the equilibrium.

$$RM + M' \rightleftharpoons RM' + M \quad \text{(eq. 1)}$$

Perhaps more common in cross-coupling reactions is the TM or exchange of ligands between two inorganic reagents, commonly an organometallic compound and a metal halide (see eq. 2).

$$RM + M'X \rightleftharpoons RM' + MX \quad \text{(eq. 2)}$$

Popular examples of this reaction include substrates such as Grignard reagents and organolithium compounds however, among others, alkyls of Be,[14] Zn,[15] Cd,[16] Hg,[17] Al,[18] Sn,[19] Pb,[20] Co,[21] Pt,[22] and Au[23] have been prepared by the treatment of Grignard

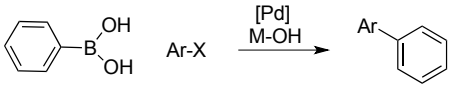
reagents and the appropriate metal halide.[24] The methods presented have been used to prepare many alkyls of non-transition metals, alkyls of metalloids and of non-metals, including Si, B,[25] Ge, P, As, Sb, and Bi.[26]

1.1.6 The Active TM in Suzuki-Miyaura Cross-coupling

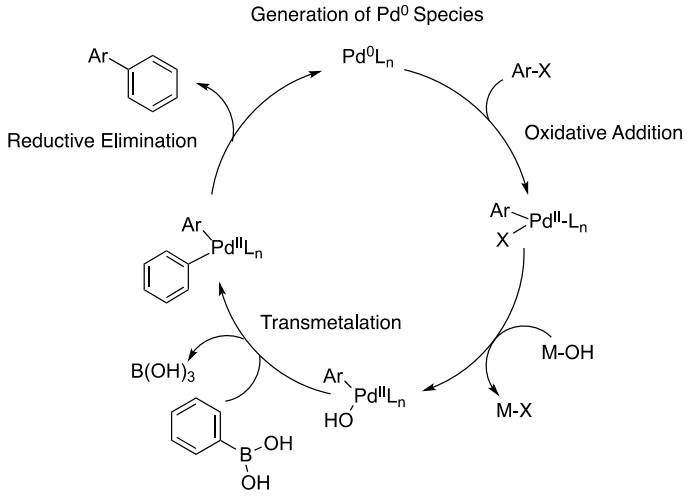
The Suzuki-Miyaura reaction is arguably the most-widely used method for catalytic C-C bond formation (see Figure 3). The mechanism and the intricacies of a catalytic process have been a subject of debate in chemistry. Much attention has been focused on the TM step as it considered being turnover-limiting. The optimization of conditions for Suzuki-Miyaura cross-coupling reactions depended on the efficiency of this step in the catalytic cycle. Typically, two pathways have been considered in the TM part: [**Path A**] the formation of a nucleophilic (trihydroxy)borate from the addition of an exogenous base followed by an attack on a palladium halide complex, or [**Path B**] a conversion of a palladium halide complex to a nucleophilic palladium hydroxo complex that will go on to react with a neutral organoboron species. In a study by Hartwig and Carrow, the relative rates of the different stoichiometric reactions between these isolated compounds were determined. By varying the relative populations of palladium and organoboron species generated under common reaction conditions, and measuring the relative rates constants for the stoichiometric reactions between the two classes (the trihydroxyborate vs. the palladium hydroxo complex), it was determined that the palladium hydroxyl complex and not the trihydroxyborate species accounts for the TM in transition metal catalyzed Suzuki-Miyaura reactions.[27] Though these results

were dependent on the strength of the exogenous base used, this study underlines the importance of the TM step.

Example Reaction:



Catalytic Cycle:



Transmetalation:

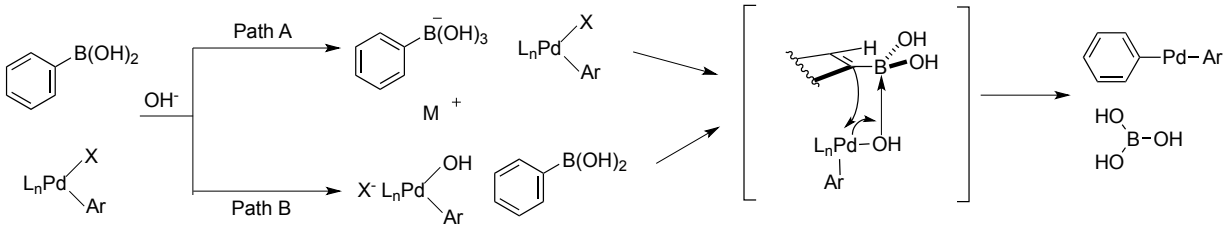


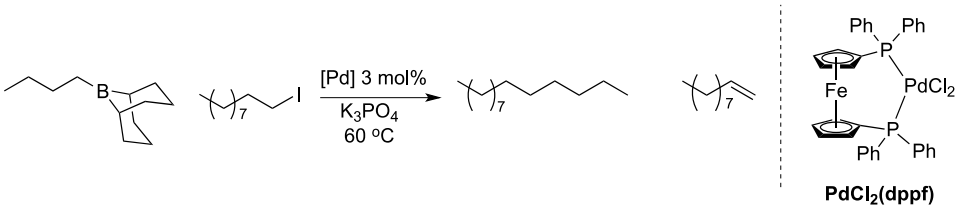
Figure 3. General Suzuki-Miyaura reaction and its catalytic cycle

1.1.7 Difficulties in Alkyl-alkyl Cross-coupling

Earlier work in the area of alkyl-alkyl cross-coupling helps to highlight the challenges in this reaction. In a study performed by Suzuki and co-workers, [28] it was determined that despite high conversion of starting material, the coupling of a alkyliodide with

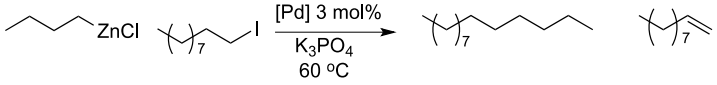
either an alkylboron or alkylzinc, led to significant amount of BHE product (see Table 1 and Table 2). In some cases, upwards of 90% of the BHE product was isolated (see Table 1, Entry 2), which demonstrates the difficulty of this reaction across both forms of alkyl-alkyl cross-coupling.

Table 1. Alkyl-alkyl Suzuki cross-coupling reactions of unactivated alkyl iodides with butyl-9-BBN



Entry	Catalyst	Solvent	Conversion (%)	Desired Product (%)	Elimination Product (%)
1	$Pd(PPh_3)_4$	dioxane	92	50	36
2	$PdCl_2$(dppf)	THF	94	4	90

Table 2. Alkyl-alkyl Negishi cross-coupling reactions of unactivated alkyl iodides with butylzinc chloride

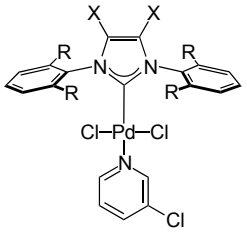


Entry	Catalyst	Solvent	Conversion (%)	Desired Product (%)	Elimination Product (%)
1	$Pd(PPh_3)_4$	dioxane	96	11	76
2	$PdCl_2$(dppf)	THF	93	10	80

It became more obvious that the choice of palladium catalyst was key to avoiding undesired products. The Negishi cross-coupling of two alkyl fragments was

successfully performed by Organ and co-workers employing $Pd(dba)_2$ in the presence of IPr•HCl, an N-heterocyclic carbene (NHC) salt that was seen as a necessary ligand to resist side reactions such as BHE.[29]

Subsequently, Organ and co-workers developed the first defined palladium based pre-catalyst that was active in these couplings called *Pd-PEPPSI-IPr* (Pyridine-Enhanced Pre-catalyst Preparation Stabilization and Initiation), which lead to the development of the *Pd-PEPPSI* family of pre-catalysts (see Figure 4). The *Pd-PEPPSI* family of catalysts featured a series of NHCs ligated to the metal centre of $Pd(II)Cl_2$ and 3-chloropyridine as a stabilizing "throw away" ligand. These catalysts were the first of their type to be effective in alkyl-alkyl Negishi cross-coupling as they have the tendency to resist BHE (see Figure 2, **Path B)**.[30, 31]



Most Commonly Employed Pd-PEPPSI Precatalysts

Pd-PEPPSI-IPr (**1**), R = *i*-propyl X = H
Pd-PEPPSI-IPr^{Cl} (**2**), R = *i*-propryl X = Cl
Pd-PEPPSI-IPent (**3**), R = *i*-pent X = H
Pd-PEPPSI-IPent^{Cl} (**4**), R = *i*-pent X = Cl
Pd-PEPPSI-IHept (**5**), R = *i*-heptyl X = H
Pd-PEPPSI-IHept^{Cl} (**6**), R = *i*-heptyl X = Cl

Figure 4. *Pd-PEPPSI* family of pre-catalysts

1.1.8 Negishi Cross-coupling

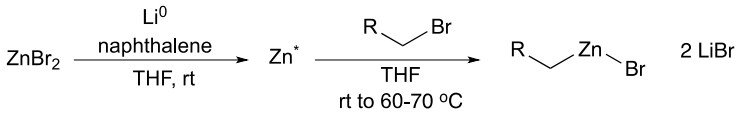
The Negishi cross-coupling reaction is a widely used transition metal mediated (most often Pd), cross-coupling reaction of an organozinc reagent and an aryl/alkyl halide resulting in the formation of carbon-carbon bonds.[32] While organozinc species are not as air and moisture stable as their organoboron analogues, they generally exhibit excellent reactivity at mild reaction temperatures, often reacting at room temperature.

Although many forms of cross-coupling have been developed and are still widely used, Negishi cross-coupling specifically offers the benefits of a highly nucleophilic organozinc centre yet these organometallics exhibit a broad tolerance for reactive functional groups such as nitriles, aldehydes and esters.[33]

When the reaction was initially developed, Negishi reported using Ni catalysts but shortly he, Cassar,[34] Heck,[35] Sonogashira,[36] and Murahashi[37] demonstrated the advantages of palladium catalysts over nickel catalysts for cross-coupling. Palladium overall is less sensitive to oxygen, and its complexes are thought to be less toxic than nickel complexes. Furthermore, nickel catalysts can promote the formation of radical intermediates that can lead to the formation of side-products such as those from homocoupling, products that have undergone racemization at a saturated carbon or the loss of stereochemistry at a vinylic carbon.

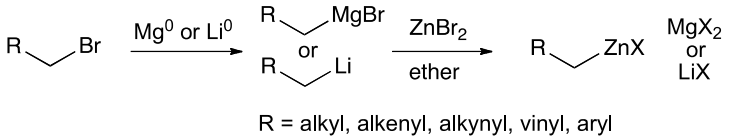
1.1.9 The Synthesis of Organozinc Reagents

Alkylzinc halide species for Negishi cross-coupling are most commonly prepared one of three ways. The first method, called the Rieke protocol, for treatment of the Lewis acid, zinc bromide (though $ZnBr_2$ will be discussed in this work, other Lewis acids include $ZnCl_2$, ZnI_2, etc.) with lithium metal and naphthalene (an electron carrier) in an ethereal solvent, most often THF (see Scheme 1).[38] $ZnBr_2$ is reduced to a highly active form of Zn(0) by the lithium naphthalenlide species formed *in situ* before it is oxidatively added across the C-X bond (where X = I, Br, or even Cl) after extended periods at refluxing temperatures.



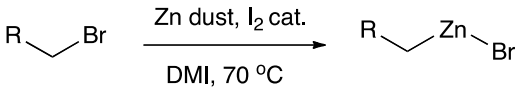
Scheme 1. General Rieke protocol for producing organozincs

The second method is a TM involving a 1:1 ratio of $ZnBr_2$ and an organo-magnesium or lithium reagent to produce a mono-organozinc bromide (see Scheme 2).



Scheme 2. General $ZnBr_2$ transmetalation reaction for synthesizing organozincs

The third reaction for synthesizing organozincs, and perhaps the most popular, is Huo's protocol (see Scheme 3). Huo's protocol for the formation of alkylzinc halides utilizes zinc dust activated with a catalytic amount of I_2, and has become one of the more widely used protocol for reagents of this type due its easy use, though it is limited to alkylzinc formation.[39a,b]

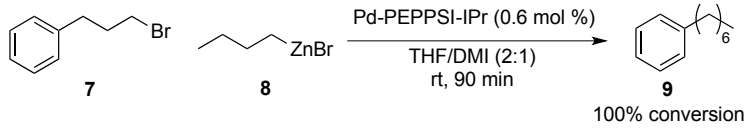


Scheme 3. Huo's protocol for the synthesis of alkylzincs

These synthetic protocols presented above, their by-products, and their reactivity, form the landscape that has become the basis for the work in this dissertation towards understanding the intricacies of the structure of organozinc reagents and how this impacts alkyl-alkyl and aryl-aryl Negishi cross-coupling.

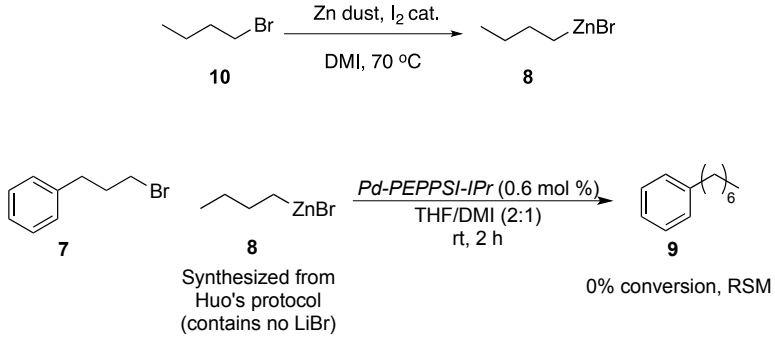
1.1.10 The Importance of Salt By-products in Negishi Cross-coupling

Cross-coupling was performed with *n*-butylzinc halide (**8** purchased from Rieke Metals Inc.) and 3-bromo-1-phenylpropane (**7**). Quantitative conversion of the starting material to the desired alkyl-alkyl coupled product **9**, as determined by GC/MS, was observed after 90 min (see Scheme 4).[40]



Scheme 4. Model Negishi cross-coupling reaction using **8** from Rieke Metals, Inc.

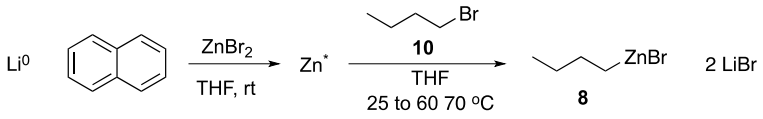
Surprisingly, this reactivity was not observed for the same organozinc prepared in house. Using Huo's protocol and subjected to the same conditions in Scheme 4. Indeed, the reaction failed to proceed with any observable coupling and **7** was recovered quantitatively (see Scheme 5).



Scheme 5. The synthesis of **9** using Huo's protocol followed by treatment of (**8**) with an organohalide (**7**) under Negishi cross-coupling conditions

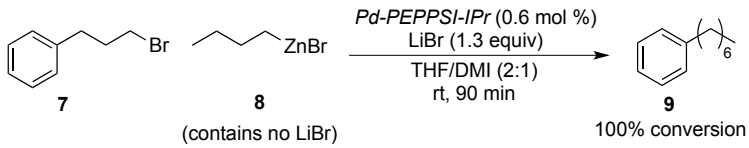
Rieke's procedure for the synthesis of organozincs was repeated and the respective organozinc (**8)** was prepared (see Scheme 6) and treated with the same cross-coupling

conditions (see Scheme 4). Again, the reaction proceeded to quantitatively convert the bromoalkane (**7**) into the desired, cross-coupled product (**9**).



Scheme 6. Rieke's protocol for the formation of organozinc **8**

Upon careful evaulation of the solvents and the titre of the organozinc formed our attention was turned to the salt by-product from this procedure, LiBr, and considered it may be playing a non-innocent role. When a superstoichiometric amount of lithium bromide was added to the organozinc (**8**, synthesized from Huo's protocol), the reactivity of the zinc reagent was restored and complete conversion of the alkyl halide to the desired cross-coupled product, **9**, was observed (see Scheme 7). When **8** was prepared from the Grignard reagent (organomagnesium) or respective organolithium, the results were identical to that seen when using the organozinc prepared from Rieke's protocol, as these methods all generate halide salt by-products. From this point, our attention was focused on the role of LiBr in alkyl-alkyl Negishi cross-coupling.



Scheme 7. Cross-coupling of **8** from Huo's protocol in the presence of LiBr

Initially, some research groups have argued that salt additives are necessary to break apart aggregates, prevent dimerization or even more vaguely, to activate the organozinc center by weakening the Zn-C bond.[41] Knochel's research group has shown

that the addition of coordinating ions (LiX for example, where X denotes Cl, Br, and/or I, etc.) to reactions of organometallic compounds can result in enhanced reactivity of an organometallic reagent. LiX not only promotes zinc and magnesium insertion into C-X bonds, but LiX salts can promote TM of the resulting organozinc reagent to palladium(0) by forming a more reactive intermediate.[42] Rieke's method for organozinc synthesis leads to the formation two equivalents of LiBr by-product. Organozinc prepared by this synthetic protocol require *no additive* to be reactive in Negishi cross coupling reactions.[39a]

The role that palladium plays in these reactions is reasonably well understood however, the active transmetalating species is, at present, a subject of debate in the organic chemistry community. Palladium mediated Negishi cross-coupling has an alkylzinc halide of the form RZnBr that transmetalates its organic moiety to the Pd centre and ZnX_2 leaves the cycle as a by-product. The product R-R$^{'}$ is formed as the metal centre undergoes RE, regenerating the Pd(0) species and reentering the catalytic cycle (see Figure 5).

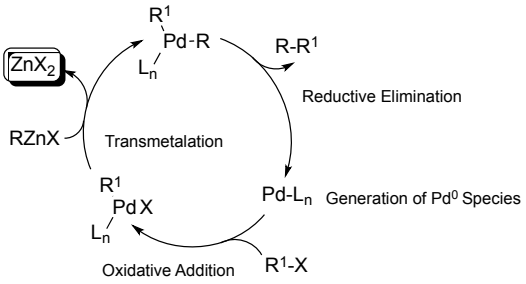


Figure 5. The catalytic cycle of Pd in the Negishi cross-coupling reaction

The mechanism of transmetalation in Negishi cross-coupling is not understood, that is if the active transmetalation species was a zincate species, of the form $RZnBr_2^-$,

analogous to the boronate in Suzuki-Miyaura cross-coupling or, if the organozinc species transmetalates directly. This, however, is valuable information to understand how to fine-tune the conditions to alter selectivity, introduce substrate discrimination, and easily predict products. The reaction requires that halide salts (i.e. LiX), if not already present as a by-product in organozinc preparation, are added before the addition of palladium to enhance the reactivity of the organozincs toward transmetalation.[43]

The Koszinowski research group has shown evidence that the active transmetalator was an anionic zinc species of the form $RZnX_2^-$.[44] To add to this, in 2010, Organ and co-workers evaluated the reactivity of the organozinc species formed (**8**) using both of the more common synthetic protocols (see Scheme 1 and 3), and evaluated the reactivity of the salt-free organozinc (**8**, synthesized by Huo's synthetic protocol, Scheme 3) with several halide salts to compare how they promote the reaction differently. It was shown that LiBr can promote the cross-coupling of the organozinc (**8**, see Scheme 7). It was important to see how much LiBr was required to promote the reaction. If the reaction was catalytic in LiBr then at least some of the LiBr present should be enough to facilitate the quantitative conversion for the desired cross-coupled product (**9**). A titration study was performed wherein various stoichiometries of LiBr were doped into the cross-coupling conditions presented in Scheme 5.

Butylzinc bromide synthesized from Huo's protocol was coupled with an alkylbromide (**8**) in the presence of *Pd-PEPPSI-IPr* pre-catalyst (0.6 mol%) and a various amounts of LiBr. With the first experiment beginning with no LiBr present and increasing in 0.1

increments, the conversions of **7** to **9** were plotted as a function of equivalents of LiBr present in the reaction media (see Figure 6).[40]

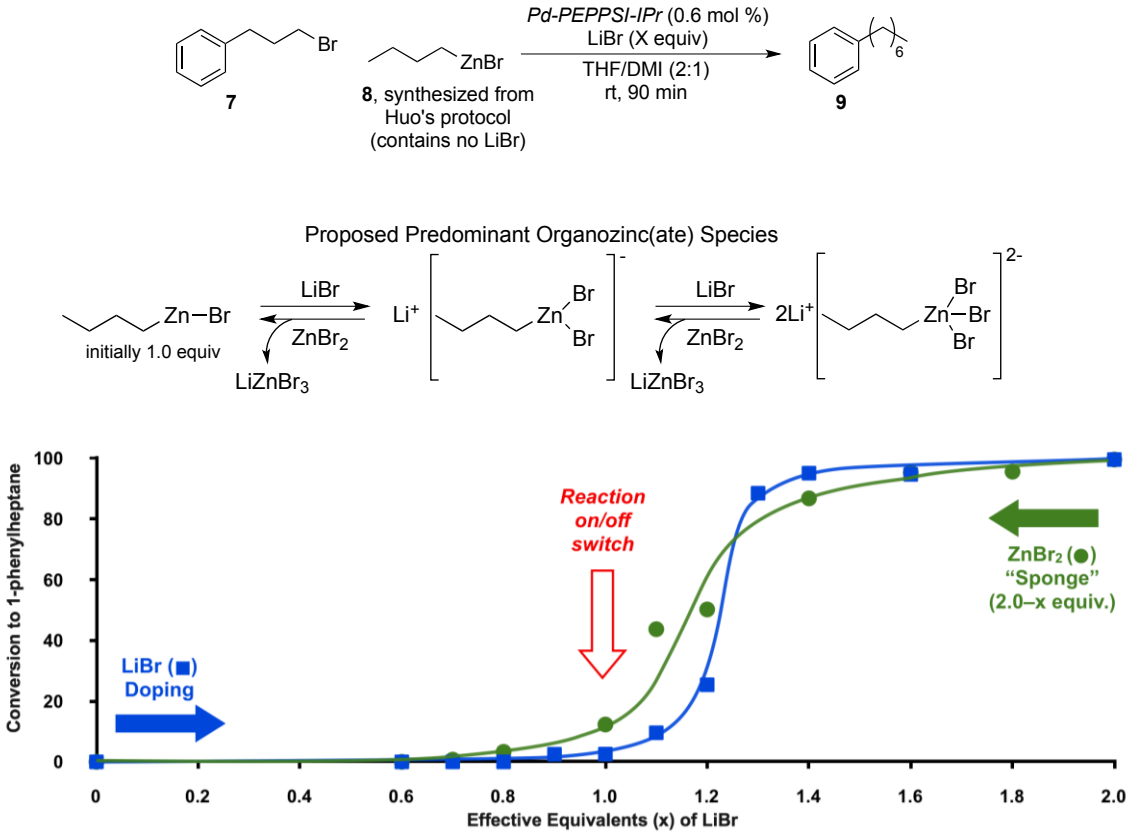


Figure 6. The impact of the incremental addition of LiBr and $ZnBr_2$ on the conversion of cross-coupling reactions involving *n*-BuZnBr and starting material (**7**)

The amount of LiBr present in solution played a vital role in the conversion of organozincs from Huo's method as no conversion of **7** to **9** occurred in its absence.[2, 43a] It was noted that the Negishi cross-coupling reaction had an "On/Off switch", that is, any reactions with less than one equivalent of LiBr showed no coupling to the desired product **9**. While there was some coupling above one equivalent of LiBr, it was noted that the conversions increased exponentially with each successive 0.1 equivalent of LiBr above 1.0 equivalent. The reaction proceeds most quickly *and* to completion

when at least 1.3 equivalents of LiBr were present. Now, if the sole purpose of LiX additive was to break up polymeric aggregates and that the active TM agent was of the form $RZnBr_2^-$, then simply adding a substoichiometric (i.e. catalytic) quantity of lithium halide should be sufficient to facilitate *some* conversion to the product **9**. Since no product is detectable in samples that contained less that 1.0 equivalent of a halide salt there was corroborating evidence that a higher-order zincate of the form $[Li^+]_2[RZnBr_3]^{2-}$ is more likely the active TM agent. From the curve (see Figure 6) the salt additive dependence was highlighted by further titrating zinc bromide into the reaction that already contains 2.0 equivalents of LiBr. Zinc bromide ($ZnBr_2$), we propose, is a sequestering agent and spontaneously forms $ZnBr_3^{-1}$ and, to a lesser extent, $ZnBr_4^{2-}$, outcompeting the organozincate ($RZnBr^-$) for halide ions. When bromide ions become unavailable, organozincates are broken down to organozincs, the reaction shuts off, and no conversion of the starting material (**7**) to product (**9**) is observed. This study indicated that the although the anion is important in driving the transmetalation and thus, the cross-coupling, the cation, at least form the evidence so far, was mechanistically benign and likely did not play a role in the TM step. This was supported by the work of Organ when they observed no effect on the conversions of **7** to **9** when crown ethers were used as a second additive in a few selected examples.[30, 40, 43, 45]

1.1.11 Evidence for the Isolation of a Higher-order Zincate Species

There has been only kinetic and spectroscopic evidence to support the existence of the high-order zincate until recently.[44] In a follow-up study by Organ and co-workers, solutions constructed to mimic Negishi reaction conditions were prepared using *n*-

BuZnBr and LiBr in solvents THF, DMI, or NMP (as well as combinations in a solvent/co-solvent mixture). The ESI-MS negative-ion mass spectra offered evidence of the rapid formation of *n*-$BuZnBr_2^-$ and $ZnBr_3^-$ (see Figure 7).

Using ^{1}H-NMR spectroscopy as a complimentary method, it was shown that the addition of LiBr to *n*-BuZnBr showed that high-order zincates were formed spontaneously in the presence of DMI or NMP (highly polar solvents) and not in THF alone owing to the need of a polar solvent/co-solvent system to stabilize high-order zincates such as *n*-$BuZnBr_2^-$ and *n*$BuZnBr_3^{2-}$. Observations of the ratio of *n*-$BuZnBr_2^-$ to $ZnBr_3^-$ changing from approximately 1:8 (Figure 7a) to 5:1 (Figure 7e) resulted from an increased addition of LiBr. There is a notable quantity of *n*-$BuZnBr_2^-$ at 0.5 equivalents, which does not support it is the active transmetalating agent. There is corroborating evidence to further suggest that the zincate that undergoes TM is of the form *n*-$BuZnBr_3^{2-}$ although the peak seen for this ion was very small in the negative ion spectra. However, this would be anticipated even if significant amounts of this higher-order zincate were present as Coloumbic repulsion was forcing this doubly charged ion to fragment, in the gas phase in particular. Nonetheless, its parent ion was detected albeit in small quantities and large amounts of *n*-$BuZnBr_2^-$ were observed, which is the product of fragmentation of the higher-order zincate.

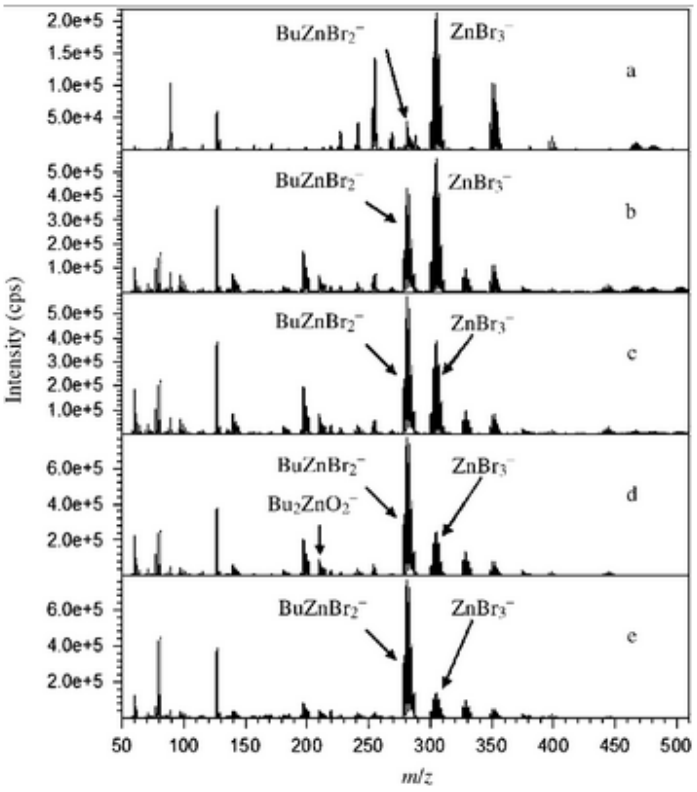
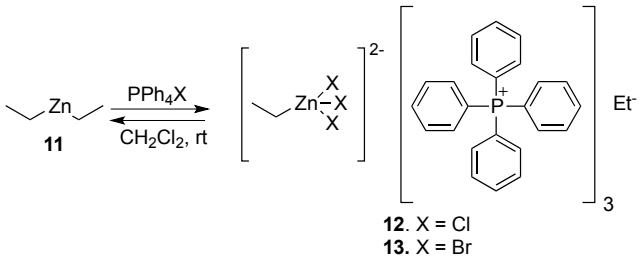


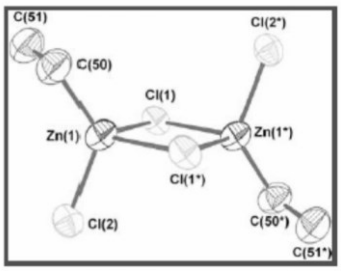
Figure 7. Negative ion mass spectra showing the change in the ratio of the *n*-$BuZnBr_2^-$ to $ZnBr_3^-$ ion intensities as a function of changing amounts of LiBr. The data collected with *n*-BuZnBr in DMI solvent with the following equivalents of LiBr added: a) 0; b) 0.5; c) 0.75; d) 1.0; and e) 1.5.

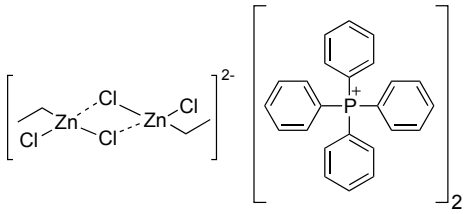
In a two-part study by Koszinowski and Böhrer,[44, 45] anion-mode electrospray ionization mass spectroscopy was used to identify various species including ZnR_n^- and $LiZnR_n^-$ species (R = X, alkyl). Clyburne and co-workers published results describing the isolation and characterization of $[EtZnBr_3^{2-}][PPh_4]^+_2$ and $[Et(Cl)Zn(\mu\text{-}Cl)_2ZnEt][PPh_4]^+_2$ (see Scheme 8) isolated from an ionic solution containing Et_2Zn and the respective phosphonium salt.



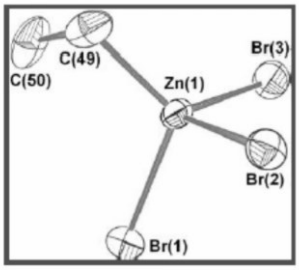
Scheme 8. Reaction of diethylzinc and tetraphenylphosphonium bromide

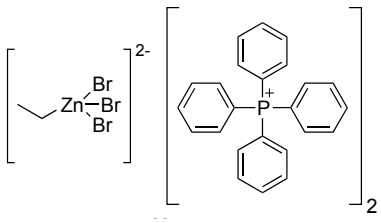
This report was accompanied by extensive characterization of the higher-order zincates by X-ray crystallography data (see Figure 8), melting point, elemental analysis and ^{1}H-NMR spectroscopic data.[46] However, there was no account for how any of the isolated species were formed. Before this report by Clyburne, there were no recorded isolation nor characterization of a higher order zincate.





12





13

Figure 8. X-Ray crystal structure of **12** and **13**

However, as with a catalyst, having a well-defined species will minimize any uncertainty in relation to the active transmetalating agent. The ability to couple the high-order zincate salts directly would be beneficial by shedding light on the formation of species involved in the Negishi cross-coupling catalytic cycle and would help to confirm the structure of the active transmetalating species, and provide a more accurate description of the Negishi catalytic cycle.

1.2 Plan of Study

Organozinc reagents are currently used in organic synthesis as sources of functionalized carbanions.[47] The kinetics of Negishi cross coupling have been studied quite thoroughly. However, the mechanism, the roles and the identity of the intermediary species remain a subject of debate.[48] Explicit understanding of the mechanism and the elucidation of the active transmetalating species of the Negishi cross coupling reaction will provide novel insight into the reaction. As a consequence, we can hope to expand the scope of the reaction, and eliminate induction periods by using more reactive organozincates.

To this end, zincates of the form $[A^+]_2[RZnBr_3^{2-}]$ will be synthesized and characterized using a procedure similar to that outlined by Clyburne and co-workers.[46] Thus, higher-order zincates will then be assessed for their viability as coupling partners in C(sp^3)-C(sp^3), C(sp^2)-C(sp^2) and C(sp^3)-C(sp^2), Negishi-style coupling reactions. The active transmetalators in alkyl-alkyl Negishi cross-coupling would be identified, and the role of lithium halides in this reaction would be defined. If this study provides concrete proof of the structure of the active transmetalators in Negishi cross-coupling, then direct application of this technology could include the commercialization of the

preformed zincate species by chemical suppliers for direct use in cross-couplings reactions. Such a product would eliminate the need to synthesize a desired organozinc species and titrations would not be necessary, therefore simplifying the reaction.

1.3 Results and Discussion

1.3.1 Spectrometric Titration – The Formation of $[EtZnBr_3]^{2-}$ $[PPh_4]_2^+$

The first ever synthesis, isolation and characterization of $[EtZnBr_3]^{2-}$ $2[PPh_4]^+$ by Clyburne and co-workers using diethylzinc and tetraphenylphosphonium bromide, in equimolar amounts, in dichloromethane was recently reported (see Scheme 8). The procedure states that slow evaporation of the reaction solvent in the glovebox lead to the formation of orange/yellow crystals that were harvested, and washed with solvents to remove impurities. After the crystals were formed, they were then characterized by ^{1}H-NMR spectroscopy and X-ray crystallography. Although the procedure appeared simple and easily reproducible, there was difficulty in obtaining quality crystals fit for characterization. After several attempts of isolating crystals, we moved to monitor the *in situ* formation of the zincate by ^{1}H-NMR spectroscopy. This was done by titrating diethylzinc and aliquots of tetraphenylphosphonium bromide in deuterated methylene chloride to observe the perturbation of the chemical shift of the methyl and methylene resonances in hopes of potentially identifying other intermediary species forming. The ^{1}H-NMR spectroscopy experiments were superimposed and calibrated to the same deuterated solvent and are shown in **Figure 9**

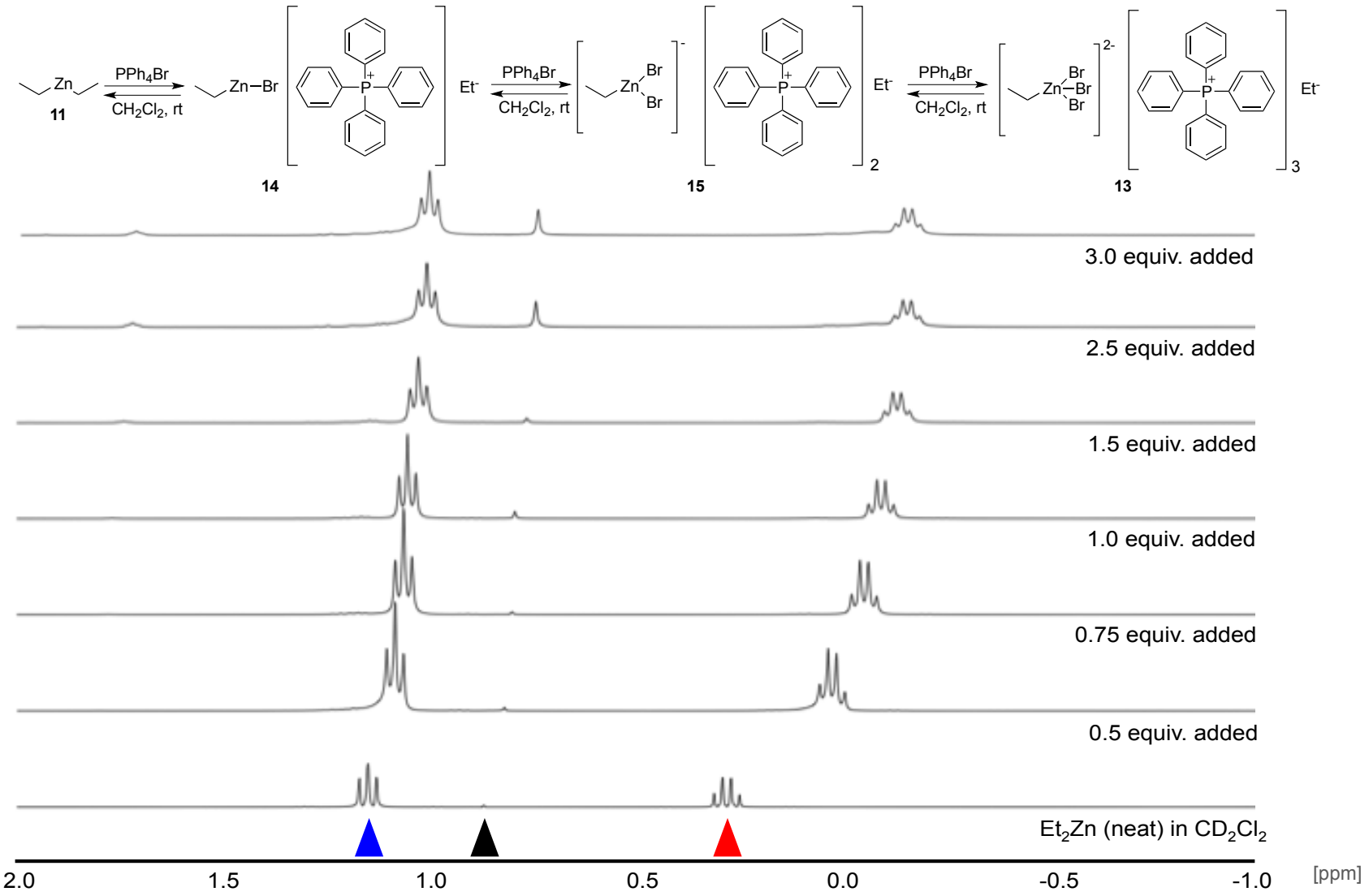
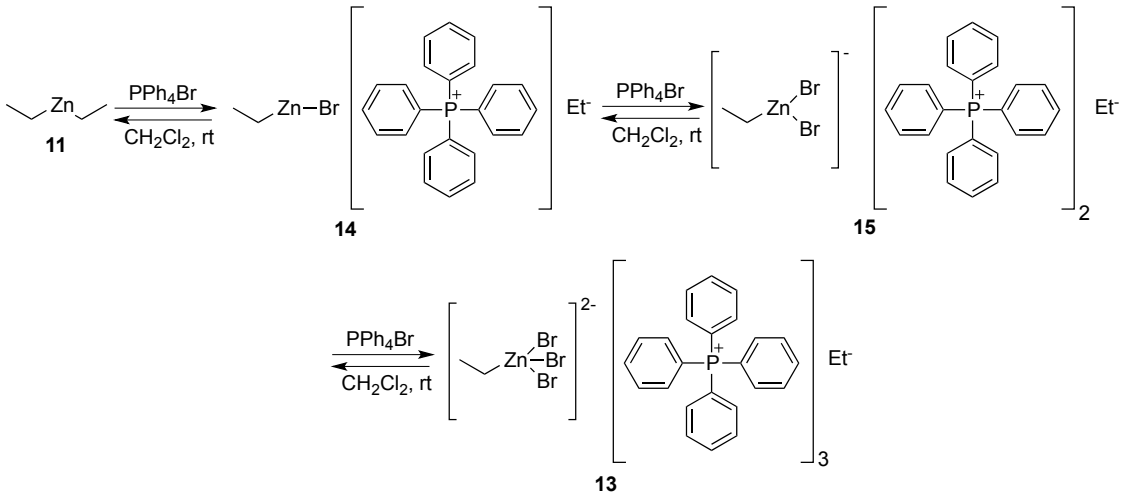


Figure 9. ^{1}H-NMR Chemical shift perturbation of diethyl zinc titrated with $PPh_4^+Br^-$ ^{1}H-NMR (400 MHz, CD_2Cl_2) δ = 1.12 (t, H_a = methyl, 3H, blue), 0.92 (s, ethane, black), 0.38 (q, H_b= methylene, 2H, red) ppm.

The resonances observed of **15** in ^{1}H-NMR spectroscopy highlight the equilibrium between it and the starting material **11** (**Figure 9**). The spectra show one resonance for the methyl and methylene protons of the ethyl group, even though the material in solution exists in equilibrium between several species (see Scheme 9). This represents the average state of the equilibrium that exists as seen on the NMR timescale. The progressively upfield chemical shift migration of the methylene groups adjacent to zinc can be explained by the metal centre becoming more electron rich as we increase the amount of PPh_4Br added because the zinc centre has an increasing number of halide ions coordinated to it.[49,23a]



Scheme 9. Formation of zincate species **15** and **13** by adding halide ions to diethyl zinc

Despite the transformation only yielding 42% of **13**, no side products could be isolated making it challenging to propose a mechanism for this unique reaction. In the spectroscopic studies performed (see **Figure 9**) we saw evidence for the formation of ethane, presumably through the decomposition of the methylene chloride solvent with Et^- that manifested itself as a singlet at 0.85 ppm, which intensified as PPh_4Br was

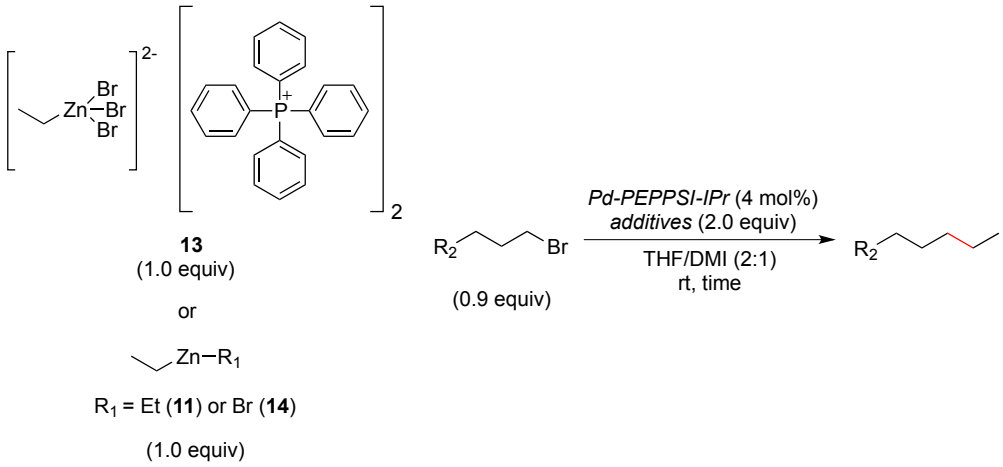
added.[50] No resonances were observed for ethyl bromide, which is another potential by-product that could form.

Crystals of **13** were carefully prepared by the slow evaporation of the reaction solvent under an inert atmosphere after which they were washed with freshly distilled and degassed hexanes, PhMe and THF. The isolated orange crystals were characterized by ^{1}H-NMR and their data was in agreement with the literature.[46] It was important that the crystals were only washed quickly and never full solubilized, as they reportedly are not isolable once they have been fully re-solvated in solvents such as THF.[50]

*1.3.2 Evaluation of the Reactivity of **13** Relative to Other Alkylzincs*

Confident that we have **13** in hand, we proceeded to evaluate its activity relative to that of **11** and **14** in Negishi cross-coupling conditions with *Pd-PEPPSI-IPr* pre-catalyst (see Table 3). We repeated the spectroscopic titration of **11** with TBAB to prepare **13** in THF, DMI and THF/DMI but have reported the studies performed in methylene chloride for the illustrative purposes of having a simpler figure. The chemical shift changes were analogous in when the titration was performed in THF, in DMI or a 1:1 combination of both solvents. As a control, we compared the reactivity of several similar organozinc species and that of compound **13** (prepared in THF) with a suitable electrophile to determine the approximate conversions (see Table 3).

Table 3. Comparing the reactivity of **13** with that of other alkylzincs in Negishi cross-coupling



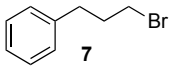
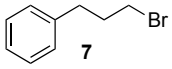
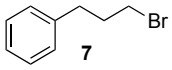
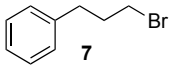
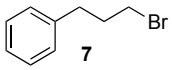
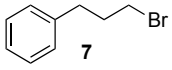
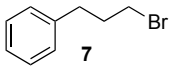
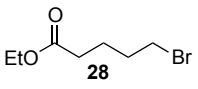
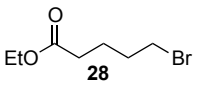
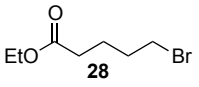
Entry	Alkyl zinc	Additive	Time (h)	Alkyl bromide	Conversion[a] (%)
1	EtZnBr (**14**)	LiBr	0.5	 **7**	99
2	EtZnBr (**14**)	*(none)*	0.5	 **7**	0
3	Et_2Zn (**11**)	*(none)*	12	 **7**	0
4	Et_2Zn (**11**)	LiBr	12	 **7**	20
5	**13** (in THF)	*(none)*	24	 **7**	0
6	EtZnBr (**14**)	PPh_4Br	24	 **7**	0
7	EtZnBr (**14**)	PPh_4Br, LiBr	24	 **7**	0
8	EtZnBr (**14**)	LiBr	0.5	 **28**	80
9	**13** (in THF)	*(none)*	24	 **28**	0

Table 4 continues on next page

10	EtZnBr (**14**)	LiBr PPh_4Br	24	 **28**	0

[a] Conversions determined by ^{1}H-NMR spectroscopic analysis. In entries with low or no conversion, the starting alkyl bromide was recovered and no other side products were observed.

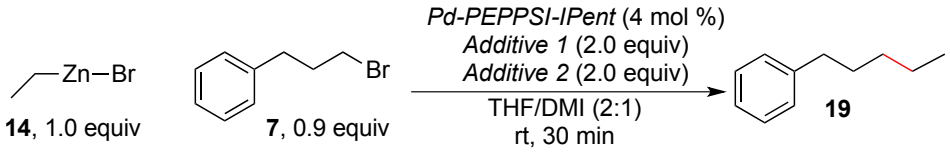
The ethylzinc bromide (**14**) used was prepared salt-free using Huo's protocol of organozinc preparation. As discussed, when LiBr is added to the reaction, the coupling proceeds. When no halide salts are present in the reaction media, the starting material (**7**) is quantitatively recovered (see Entries 1 and 2). Neat diethylzinc (**11)** was unable to generate the cross-coupled product, independent of whether LiBr was present or not (see Entries 3 and 4). Surprisingly, we found that the use of **13** in Negishi cross-coupling with two different substrates (**7** or **28**) failed to provide any quantifiable amount of the desired cross-coupling partner and the starting material was quantitatively recovered in both cases (see Entries 5 and 9). No difference was observed in conversions when **13** was prepared from methylene chloride, DMI or a combination of THF/DMI (as in Entry 5). Evaluating **14** in the cross-coupling of **7** we noted that when PPh_4Br was present, even in the presence of LiBr, the coupling did not proceed (see Entries 6, 7 and 10).

1.3.3 The Importance of the Cation in the Reactivity of Zincates

In light of this lack of reactivity with **13**, we suspected that the PPh_4^+ cation might be playing a deleterious role through an unknown mechanism. We suspected that it might be playing an active role as an inhibitor, perhaps by interfering with the catalyst. Several control reactions were performed to evaluate the stability of this salt, or more specifically the cation, when it was treated with alkyl-alkyl Negishi cross-coupling

conditions (see Table 4). Using **14** synthesized from Huo's method in the presence of LiBr leads to complete conversion to **19** yet if PPh_4Br or PPh_3 are present the reaction fails (see Entries 1-4). No information on the preparation of PPh_4Br was made available by the manufacturer upon request thus we assumed that the methods reported in the literature were used in its preparation from triphenylphosphine and the respective aryl halide using a transition metal mediated process.[51]

Table 4. Evaluating the role of phosphine additives in Negishi cross-coupling with *Pd-PEPPSI-IPr* pre-catalyst



Entry	Additive 1	Additive 2	Conversion[a] (%)
1	LiBr	-	99
2	PPh_4Br	-	0
3	LiBr	PPh_4Br	0
4	LiBr	PPh_3	0

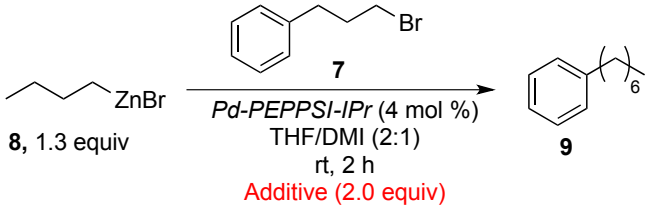
[a] Conversions determined by TLC and ^{1}H-NMR spectroscopy, experiments repeated in duplicate with the average conversion of the runs reported

It became apparent that the use of PPh_4Br, even as a spectator species was deleterious to the reaction completely inhibiting the coupling process (see Entry 3, Table 4). In subsequent studies, including ^{31}P-NMR spectroscopy it was determined that the PPh_4^+ counter ion was unstable and decomposing to form PPh_3 under the reaction conditions. From Entry 4 it was clear that a super-stoichiometric amount of PPh_3 was sufficient to completely poison the Pd catalyst. Thus, it would appear that PPh_4Br degrades to produce a large quantity of PPh_3 that shuts down any possible oxidative additions thereby halting coupling. The use of phosphine additives have been reported with non-NHC based catalysts as additives in cross-coupling reactions to sterically and

electronically tune the transition metal, yet in large quantities, can make the Pd catalyst unavailable to participate in the catalytic cycle.[52]

This result was surprising as much of the evidence we have seen to this point suggested that the cation played an innocent, non-participatory role. Until now we had only seen cations act as a spectator species as they do with several mineral salts. Alternative bromide sources were evaluated to form the zincate and use in the subsequent coupling step. Based on work by Organ and co-workers in which the reactivity of several halide sources was evaluated, we turned to *n*-Bu_4NBr (TBAB) as it offered the highest conversion (see Table 5).

Table 5. The impact of different halide sources in alkyl-alkyl Negishi cross-coupling.



Entry	*n*-BuZnBr source	Additive	Conversion[a] (%)
1[b]	Rieke's method	-	Quant.
2[b]	Huo's method	-	0
3[b]	"	LiBr/Cl	Quant.
4	"	LiOAc	0
5	"	LiI	5
6	"	$MgBr_2$	92
7	"	NaBr	0
8	"	KBr	0
9	"	$MgCl_2$	15
10	"	MgI_2	0
11	"	TBAB	79
12	"	TBAC	34
13	"	TBAI	2
14	"	THAB	65
15	"	LiBr + 15-crown-5	84

[a] Conversions determined by TLC and ^{1}H-NMR spectroscopy.[45a] [b] The results were similar when *Pd-PEPPSI-IPent* was used

Upon initial inspection, LiBr/Cl would appear to be the most suitable source of halide, yet, when preparing the organozinc halide and thereby the zincate from dialkyl zinc, we only observed traces of the desired cross-coupled product (discussed further in p. 41, Entry 2 of Table 6). Other suitable options were considered and our attention turned to another non-coordinating salt, TBAB (Entry 11, Table 5). TBAB appeared as though it was a suitable candidate as a bromide source since it met our criteria, that a) it did not inhibit the reaction and b) it facilitated the reaction as a halide source with a conversion of 79% in the reaction outlined in Table 5

The production of the zincates was followed by 1H-NMR spectroscopy in a similar fashion as was reported earlier for the PPh_4Br study (see **Figure 9**) and a similar result was observed (see Figure 10). The incremental addition of TBAB causes a progressive shift upfield, especially for the methylene protons adjacent to the metal centre. Again, this was interpreted to be the formation of zincates that makes the metal centre more electron rich this shielding the adjacent methylene protons. Additionally, after the three full equivalents of TBAB were added relative to diethyl zinc, an equivalent of $ZnBr_2$ was added causing a downfield shift of the methylene proton signals. This shift was very significant as it suggested that adding $ZnBr_2$ shifts the equilibrium to the left and the mono-organozincate species formed. The chemical shifts of this top curve very closely resemble the shifts shown in the curve second from the bottom in which 0.5 equiv of TBAB had been added (highlighted by the red circles).

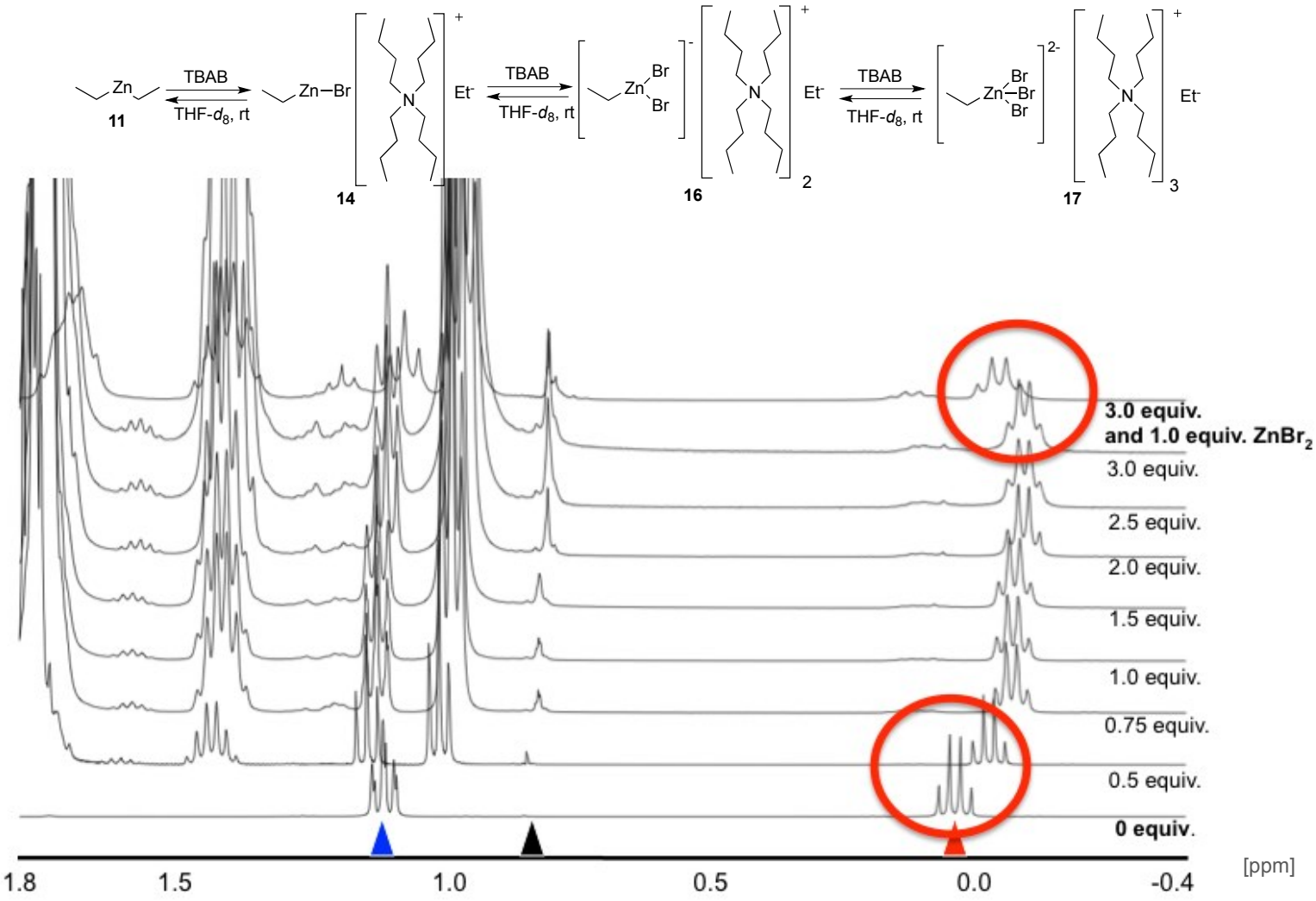
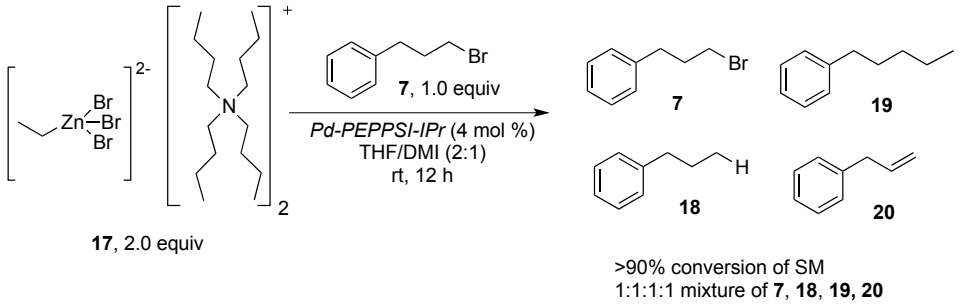


Figure 10. ^{1}H-NMR Chemical shift perturbation of diethyl zinc titrated with $PPh_4^+Br^-$. ^{1}H-NMR (400 MHz, THF-d_8) δ = 1.12 (t, H_a = methyl, 3H, blue), 0.8 (s, ethane, black), 0.05 (q, H_b= methylene, 2H, red) ppm.

The zincate/ammonium complex did not provide crystals upon slow evaporation in the glovebox as was observed with its PPh_4Br counterpart (**13**). Rather, a clear and colourless reactive oil was obtained that contained crystallized $ZnBr_4^{2-}$ and tetrabutylammonium solids that were confirmed by X-ray crystallography.

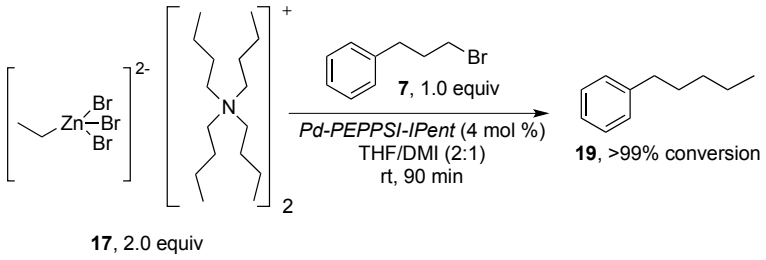
*1.3.4 The Reactivity of Di(tetra-*n*-butylammonium)ethylzinc Tribromide (**17**) in Negishi Cross-coupling*

Subjecting ammonium zincate, **17**, to the same cross-coupling conditions as seen in Table 3 (see Scheme 10) resulted in a mixture of four compounds that were present in equal amounts, the desired cross-coupled product (**19**), the starting material (**7**), the elimination product (**20**) and reduced product (**18**).



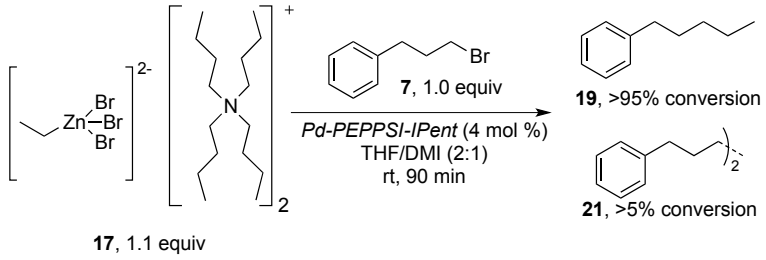
Scheme 10. Preliminary cross-coupling results using TBAB with diethyl zinc in alkyl-alkyl Negishi cross-coupling

When the catalyst was switched for the more reactive *Pd-PEPPSI-IPent catalyst* (see Scheme 11), complete conversion of the starting material to the desired cross-coupled product occurred.



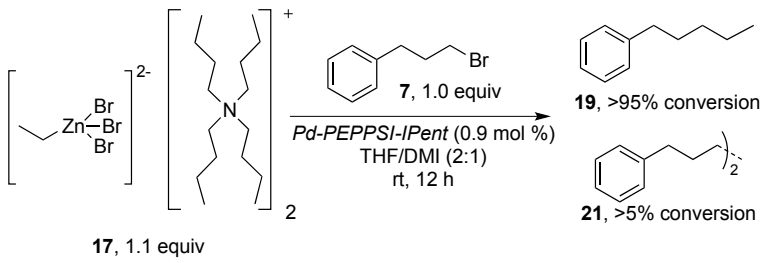
Scheme 11. Evaluating *Pd-PEPPSI-IPent* as a catalyst for zincate cross-coupling

This was an encouraging result as the reaction not only proceeded to completion but also proceeded quickly, completing in less than 90 minutes as verified by TLC and ^{1}H-NMR spectroscopic analysis. Next, we looked to improve atom economy by improving the zincate/alkyl bromide ratio from 2:1 to 1.1:1 (see Scheme 12). Although some homo-coupled alkyl halide (**21**) was observed in trace amount, the reaction proceeded well without any other undesired side products (such as **18** or **20**).



Scheme 12. Reduced loading of organozinc species relative to the alkyl bromide

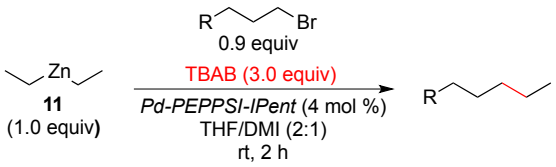
With the ratio of **17**:**7** lowered to 1.1:1, the catalyst load was next adjusted to less than 1 mol% (see Scheme 13). The reaction proceeded to completion after 12 hours producing the same reaction outcome as seen in Scheme 12.

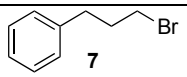
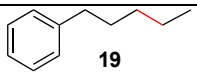
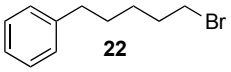
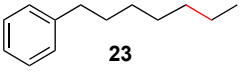
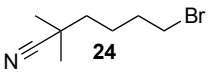
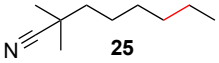
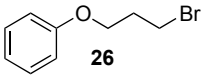
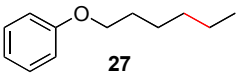
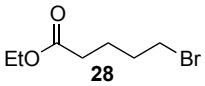
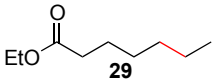
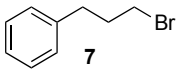
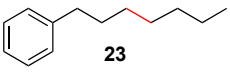


Scheme 13. Cross-coupling zincate **17** with low catalyst loading

With a strong understanding of the reaction in hand, we next evaluated the scope of the coupling. Entry 1 summarizes the result from Scheme 12. The use of zincate **17** in Negishi cross-coupling worked equally well for alkyl bromides with sensitive functional groups (see Entries 3, 5 and 7, Table 6). Recall that commercially available diethylzinc (**11**) alone does not couple with **7** in the presence of **3** (see Entry 3, Table 3). This result suggests that the commercially available product itself likely does not contain halide salts as a by-product of its own preparation. To confirm this, **11** was carefully distilled by bulb-to-bulb leaving no salt-residues. The species formed from **11** and LiBr is not as active as the species formed with tetra-*n*-butylammonium bromide (see Entry 2, Table 3) although some coupling did occur. These results confirm the unique role of *n*-Bu_4NBr as the halide source. So, not only is Br^- to promote coupling, the salt cation must promote the formation and stabilization of $EtZnBr_3^{-2}$ species without inhibiting the catalyst under Negishi cross-coupling conditions. For entry 6 of Table 6, commercially available di-*n*-butylzinc was used to from *n*-butyltribromo zincate from TBAB.

Table 6. Substrate scope of diethyl zinc in alkyl-alkyl Negishi cross-coupling with selected additives

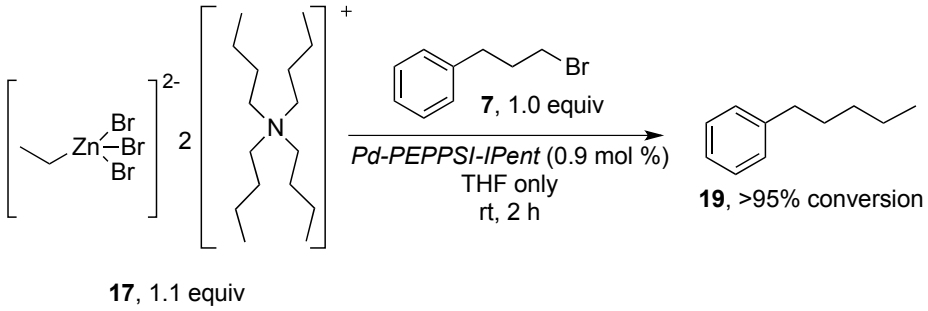


Entry	Additive	Electrophile	Product	% Conversion (% yield)
1	TBAB	 **7**	 **19**	100% (92%)[a]
2	TBAB	 **22**	 **23**	99% (94%)[a]
3	TBAB	 **24**	 **25**	99% (99%)
4	TBAB	 **26**	 **27**	99% (99%)
5	TBAB	 **28**	 **29**	86% (77%)
6	TBAB	 **7**	 **23**	74% (72%)[a]

[a] Conversions are determined by quenching an aliquot of the reaction with SiO_2 and integrating the area under curve of GC/MS spectra using undecane was used as an internal standard.

In a revealing experiment, cross-coupling of di(*n*-butylammonium)ethylzinc tribromide and alkylbromide (**7**) in *only* THF solvent was successful (see Scheme 14). We observed the zincate **17** to be fully reactive under these conditions as excellent conversion to the desired coupling product **9** was observed. Organozinc preparation is performed with the use of a polar, coordinating solvents such as THF or DMI (i.e. Huo's and Rieke's protocol). However, this result was most significant because

organozinc halides such as EtZnBr, require a highly polar co-solvent (such as DMI) in order for Negishi alkyl-alkyl cross-coupling to proceed. Without this co-solvent system (i.e. without DMI), the organozinc will not undergo cross-coupling and will begin to decompose slowly under these conditions. DMI has been thought to activate the organozinc by coordinating to the organometallic by polarizing the Zn-C bond, making the carbon more nucleophilic.[2, 8, 53] To date, there are no alkyl-alkyl Negishi cross-coupling reactions that have proceeded in straight THF.

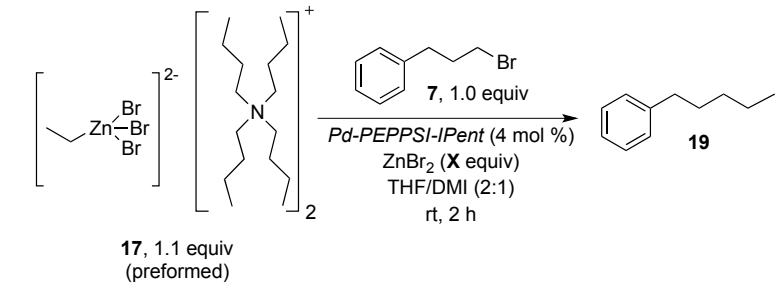


Scheme 14. Zincate **17** converts alkyl halide **1** to **9** in THF solvent only

Adding to the corroborating evidence that we have formed the higher-order zincate in THF alone using a new method acquiring access to the higher-order species, was the evidence that **17** will undergo cross-coupling directly. Because **17** was pre-formed, we were able to cross-couple the zincate directly and without the use of the polar co-solvent that is typically required.

The presence of zinc bromide, as with *n*-butylzinc bromide (**8**, Figure 6), showed a similar inhibition of the coupling with zincate **17**. The addition of increasing amounts of $ZnBr_2$ to the coupling reaction with **17** led to progressively lower coupling (see Figure 11).

Reaction:



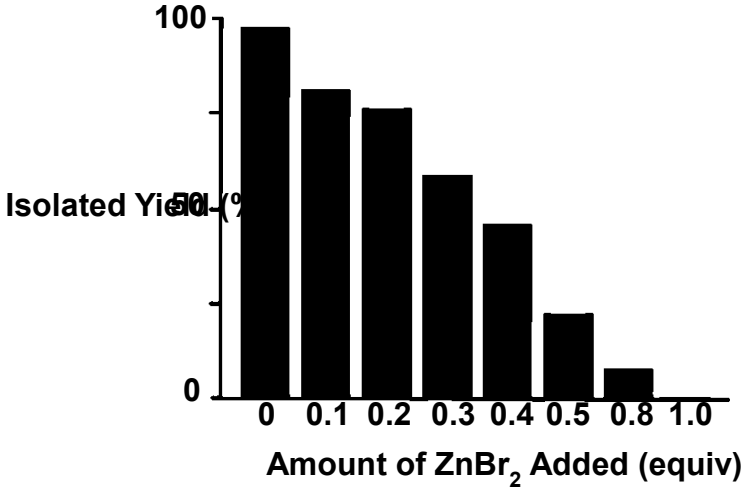


Figure 11. The impact of $ZnBr_2$ on the isolated yields of **19** from cross-coupling compounds alkylhalide **7** and organozinc **17**

1.3.5 The Proposed Catalytic Cycle of Alkyl-alkyl Negishi Cross-coupling

With the above results in hand, a more complete mechanism for the Negishi alkyl-alkyl cross-coupling reaction catalytic cycle has emerged. Clearly any mechanism must account for the necessity and role of halide salts in this process (see Figure 12).

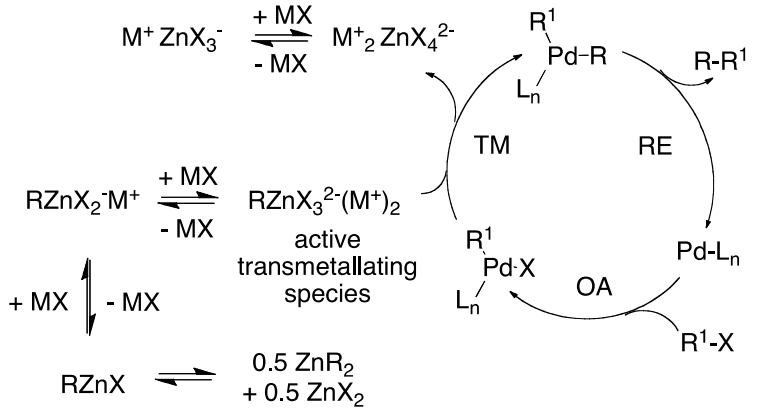


Figure 12. Proposed catalytic cycle for the alkyl–alkyl Negishi reaction. R = alkyl, M = Mg, Li, n-Bu_4N, X = Cl, Br. OA = oxidative addition, TM = transmetalation, RE = reductive elimination.

We believe that the evidence above supports the need for the formation of a higher-order zincate [$RZnX_3^{2-}(M^+)_2$] and that it is this species that transmetalates to Pd. This species can be prepared and added to the reaction flask (in the absence of any $ZnBr_2$ thus keeping the equilibrium toward the higher-order zincate) by the unique mechanism of the Clyburne procedure, and transmetalated to Pd in THF solvent alone. It is proposed that the transmetalation step operates under a dissociative mechanism involving a four-coordinate transition state. For this to occur, it is envisioned that the zinc becomes coordinated to the palladium metal centre through an uninterrupted η-interaction (or bridging) with an adjacent bromide. This bridging halide stabilizes the metal complex permits the transmetalation of the organic fragment from zinc to

palladium. Considered, are the reagents and conditions from the reaction outlined in Scheme 14 (see Figure 13).

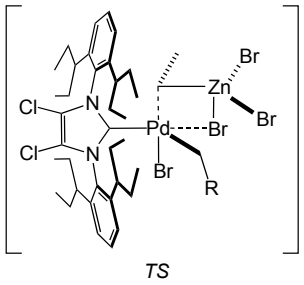


Figure 13. Proposed transition state (**TS**) for alkyl-alkyl Negishi Cross-coupling with *Pd-PEPPSI-IPentCl*

The proposed transition state (**TS**) was developed from previous DFT investigations of alkyl-alkyl Negishi cross-coupling.[54] This result from Scheme 14 was most significant because no other alkylzinc cross-coupling has ever proceeded in straight THF. Because higher-order zincates cannot form we propose that the organozinc will remain inactive until a polar co-solvent (such as DMI or NMP) is added.

1.4 Conclusion

Since the 1970s it has been well recognized that organometallic cross-coupling partners such as organoboron, organosilicons and organozincs require the addition of exogenous base to promote reactions *via* the formation of 'ate' complexes. These complexes form and weaken the M-C bond, which aids in facilitating transmetalation.[43a, 45a]

We have shown for the first time the direct involvement of higher-order zincates in the alkyl-alkyl Negishi cross-coupling reaction. By synthesizing, isolating and subjecting pure $RZnBr_3^{2-}$ zincates, from non-coordinating solvents such as CH_2Cl_2 we have been

able to strictly exclude salts present in all commercially produced organozinc reagents. The commercial reagents contain by-products occurring from respective Grignard transmetalations and the Rieke protocol that have, until now, been very well-hidden and non-innocent. These commercial preparations lead to the production of LiX or MgX salts that are, in fact, necessary to promote Negishi couplings to completion and without the need of other additives.

Most important from these results is that we were able to couple **17** in straight THF in the absence of any additives. The cross-coupling of **17** proceeds quickly and cleanly to completion. The absence of salt required to promote equilibration to the simple, low-order zincate, $RZnBr_2^{-1}$ or even further to RZnBr or R_2Zn (see Figure 12) suggests that **17** is the active transmetalating species and not any other species in the Schlenk equilibrium. These results now have provided valuable insight into the Negishi reaction and a facile and highly useful means to use alkyl-alkyl Negishi cross-coupling.

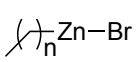
Chapter 2:
Experimental Procedures

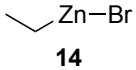
2.1 General Experimental

All reactions were run under argon with scrupulous exclusion of moisture from reagents and glassware using standard Schlenk techniques for manipulating air-sensitive compounds.[55] All glassware was stored in an oven and was flame-dried and purged with argon prior to use. Anhydrous solvents were obtained by distillation over sodium/benzophenone (ether, THF) or used directly from ampoules ($CDCl_3$, CD_2Cl_2, DMSO-d_6, THF-d_8, Sigma-Aldrich) or Sure/Seal™ bottles (DMI, Sigma-Aldrich) without further purification. Analytical thin-layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed using UV absorbance, ceric ammonium molybdate (CAM) solution, or an aqueous potassium permanganate solution. Flash column chromatography was performed using Silicycle™ silica gel 60 (230-400 mesh) and the indicated solvent system according to a standard technique.[56] Nuclear magnetic resonance spectra (^1H, ^{13}C, ^{31}P) were recorded on Bruker 300 or 400 MHz AVANCE spectrometers equipped with a DUAL probe. Chemical shifts for ^1H NMR spectra are recorded in parts per million (ppm) using the residual proton signal of the solvent as the internal standard ($CDCl_3$, δ = 7.26 ppm, CD_2Cl_2, δ = 5.32 ppm, THF-d_8 = 3.58, DMSO, δ = 2.50 ppm). Chemical shifts for ^{13}C NMR spectra are recorded in parts per million by calibrating the central peak of CD_2Cl_2 to 54.00 ppm or THF-d_8 to 67.40 ppm. Chemical shifts for ^{31}P spectra are recorded in ppm relative to 85% phosphoric acid (H_3PO_4, δ = 0.00 ppm), which was used as an internal standard in a sealed capillary.

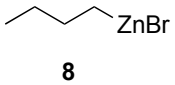
2.2 Synthetic Procedures

2.2.1 General procedure for the Preparation of Organozinc Halides[39a]

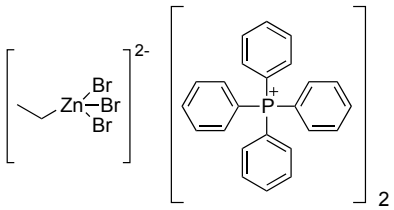
 (n = 1, 3) – In a glovebox, a flame-dried vial was charged with a stir bar and zinc dust (990 mg, 15 mmol, 1.5 equiv.) and sealed with a screw cap. The flask was removed from glovebox and I_2 (125 mg, 0.50 mmol, 0.05 equiv.) was added under a cone of argon. The flask was covered with a septum and sealed with electrical tape before it was purged with argon (3x). A syringe equipped with a long needle was used to add DMI (9 mL) and the resultant yellow solution was stirred for 10 min at rt, at which time the yellow colour faded to light grey. The alkyl bromide (0.75 mmol, 1.0 equiv.) was added and the vial was heated to 70 ° C for 16 h.


14

Ethylzinc bromide (14) was synthesized following the general procedure for organozinc halides. The spectroscopic data was in agreement with the literature.[57] ^{1}H-NMR (400 MHz, in DMI with a sealed capillary of $CDCl_3$ in order to lock the spectrometer) δ 1.12 (t, *J* = 7.4 Hz, 3H), 0.07 (q, *J* = 7.4 Hz, 2H) ppm.

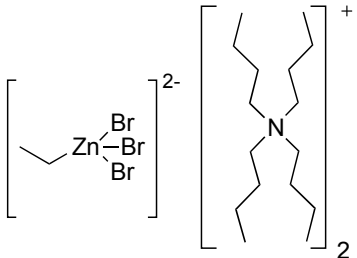

8

Butylzinc bromide (8). ^{1}H-NMR (400 MHz, in DMI with a sealed capillary of CD_2Cl_2 in order to lock the spectrometer) δ = 2.06 (m, *J* = 7.5 Hz, 2 H), 1.86 (m, *J* = 7.5 Hz, 2 H), 1.41 (q, *J* = 7.5 Hz, 3H), 0.66 (t, *J* = 7.5 Hz, 2H) ppm.[4,58]



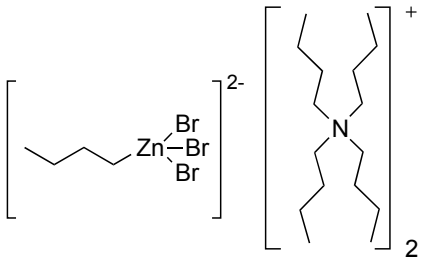
13

Di(tetraphenylphosphonium)ethylzinc tribromide (**13**): A flame-dried vial was charged with a stir bar and PPh_4Br (1.26 g, 3.0 mmol, 3.0 equiv.) before being covered with a septum, sealed with electrical tape, and purged with argon (3x). THF (2.4 mL) and diethylzinc (102 μL, 1.0 mmol, 0.5 equiv.) were added *via* syringe in succession leading to a light-yellow solution. A syringe equipped with a long needle was used to transfer 0.7 mL of the resultant solution to a sealed NMR tube under a positive pressure of argon and a ^{1}H-NMR spectrum was acquired to confirm the formation of **13**. ^{1}H-NMR (400 MHz, CD_2Cl_2) δ 7.89 (t, J = 7.9 Hz, 8H), 7.78 (td, J = 7.7, 3.5 Hz, 16H), 7.61 (dd, J = 8.4 Hz, 4.4 Hz, 16H) 1.00 (t, J = 8.0 Hz, 3H), -0.15 (q, J = 8.0 Hz, 2H) ppm, ^{13}C-NMR (100 MHz, CD_2Cl_2) δ 136.1, 136.0, 134.8, 134.7, 131.1, 131.0, 118.3, 117.4, 12.2, 6.9 ppm, ^{31}P-NMR (162 MHz, CD_2Cl_2 with a sealed capillary of H_3PO_4 for reference) δ -23.7 ppm. Following analysis, **13** was used in the next step without further manipulation or the vial was left sitting and, after 48 h, the solution darkened to amber and crystals formed on the walls of the vial. The vial was transferred to a glovebox and the crystals were harvested from the mother liquor and were washed with hexane, toluene and THF (2 x 10 mL portions). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.98 (m, 8H), 7.83 (m, 16H), 7.79 (m, 16H), 1.02 (t, J = 8.0, 3H), -0.26 (q, J = 8.0 Hz, 2H) ppm. The spectral and physical data for these crystals were in agreement with the literature.[59]



17

Di(tetra-*n*-butylammonium)ethylzinc tribromide (**17**): A flame-dried vial was charged with *n*-Bu_4NBr (966 mg, 3.0 mmol, 3.0 equiv.) and a stir bar, after which it was covered with a septum, sealed with electrical tape, and purged with argon (3X). THF (2.4 mL) was injected *via* syringe and the resultant white suspension solubilised completely following the addition of diethyl zinc (102 μL, 1.0 mmol, 1.0 equiv.) and was left to stir for 10 min. at rt. Di(tetra-*n*-butylammonium)ethylzinc tribromide was characterized as a clear, light grey, reactive solution that was used in the next step without additional manipulation or purification. Evaporation of the solvent gave a reactive oil. ^{1}H-NMR (300 MHz, CD_2Cl_2) δ 3.23 (m, 18H), 1.56 (m, 18H), 1.32 (m, 18H), 1.03 (t, J = 8.1 Hz, 3H), 0.89 (t, J = 7.3 Hz, 26H), -0.15 (q, J = 8.1 Hz, 2H) ppm, ^{13}C-NMR (75 MHz, CD_2Cl_2) δ 59.0, 24.1, 19.7, 13.4, 12.7, 6.7 ppm.



30

Di(tetra-*n*-butylammonium)butylzinc tribromide (**30**): To a flame-dried vial equipped with a stir bar, and covered with a septum, and sealed with electrical tape was added di-*n*-butylzinc (1 M in heptanes, 1.0 mmol, 1.0 equiv). Di-*n*-butylzinc was concentrated in the vial by slowly bubbling argon through the solution with a long needle for 4 h until only traces of heptanes remained (as seen by ^{1}H-NMR spectroscopy) at which time the concentrated solution turned from colourless to light yellow. Solubulized *n*-Bu_4NBr (966 mg, 3.0 mmol, 3.0 equiv) in THF (2.4 mL) was added *via* syringe and the resultant solution was left to stir at room temperature for 10 min. Di(tetra-*n*-

butylammonium)butylzinc tribromide was characterized by NMR spectroscopy in solution and was used in the next step without additional manipulation or purification. Evaporation of the solvent gave a reactive oil. ^{1}H-NMR (400 MHz, CD_2Cl_2) δ 3.23 (m, 18H), 1.64 (m, 18H), 1.43 (t, J = 7.5 Hz, 2H), 1.32 (sextet, J = 7.4 Hz, 18H), 1.09 (t, J = 7.9 Hz, 3H), 0.89 (t, J = 7.4 Hz, 26H), 0.73 (m, 2H), 0.04 (q, J = 7.9 Hz, 2H) ppm.

2.2.2 General Negishi Cross-coupling Procedures A and B

To a sealed vial containing a solution of either alkyl zinc bromide (**14**, 1.0 mmol) in THF (2.4 mL), (Procedure A) or di(tetra-*n*-butylammonium)ethylzinc tribromide (**17**, 1.0 mmol) in THF (2.4 mL) (Procedure B) was added *via* syringe a solution containing *Pd-PEPPSI-IPent* (**3**, 32 mg, 4 mol%) and the alkylbromide (0.9 equiv) in THF (1.0 mL). Immediately after the addition, the solution bubbled slightly and darkened to a medium brown colour that continued to darken over 10 min to deep brown. The resultant solution was stirred for 2 h at which time a precipitate developed and TLC analysis showed complete consumption of the alkyl bromide. The reaction mixture was filtered through 1 cm of Celite sitting atop of 3 cm of silica gel in a fine fritted filter funnel. The vial and the plug were rinsed with diethyl ether (2 x 10 mL). The resultant solution was concentrated *in vacuo* to provide the product that was shown to be analytically pure.

2.2.3 General Negishi Cross-coupling Procedure C

In the glovebox, LiBr (140 mg, 1.50 mmol, 3.0 equiv) was added to a flame-dried vial equipped with a stir bar and then the vial was removed from the glovebox. *Pd-PEPPSI-IPr* (**1**, 14 mg, 0.02 mmol, 4 mol%) was added to the vial under a cone of argon after which it was covered with a septum, sealed with electrical tape, and purged

with argon (3x). THF (1.6 mL), the alkylzinc bromide (0.8 mL, 0.8 mmol, 1M in DMI, 1.3 equiv), and the alkyl bromide (0.5 mmol, 1.0 equiv) were then added; the reaction gently exothermed and changed from a light yellow to dark brown. The reaction flask was left to stir for the time indicated in Table 3. GC-MS analysis was performed by adding undecane (50 μL) to the crude solution, then 300 μL of the crude reaction mixture was removed by a syringe and was flushed through a 3 cm pad of silica with 1.5 mL of EtOAc. An 800 μL aliquot of the filtrate was transferred to a GC vial containing 1 mL of EtOAc, sealed with a plastic screw-cap lined with a Teflon™ cover, and the resulting solution was subjected to GC-MS analysis.

2.2.4 General Negishi Cross-coupling Procedure D

To a sealed vial containing a solution of **13** (1.0 mmol) in THF (2.4 mL), was added *via* syringe a solution containing *Pd-PEPPSI-IPent (***3**, 32 mg, 4 %mol) and the alkylbromide (0.9 equiv) in THF (1.0 mL). Immediately after the addition, the solution bubbled slightly and darkened to a medium brown colour that continued to darken over 10 min. to deep brown. The resultant solution was stirred for 2 h, at which time the reaction mixture was filtered through 1 cm of Celite sitting atop of 3 cm of silica gel in a fine fritted filter funnel. The vial and the plug were rinsed with diethyl ether (2 x 10 mL). The resultant solution was concentrated *in vacuo* and revealed no sign of the cross-coupled product by GC-MS and ^{1}H-NMR spectroscopic analysis.

2.2.5 General Negishi Cross-coupling Procedure E

To a sealed vial containing a solution of **17** (1.0 mmol) in THF (2.4 mL), was added *via* syringe a solution of zinc bromide (X mg, Y mmol, see Figure 11 for stoichiometries). Exactly ten seconds later, a solution containing *Pd-PEPPSI-IPent (***3**,

32 mg, 4 %mol) and 1-bromo-5-phenylpentane (**22**, 167 μL, 0.9 mmol, 0.9 equiv) in THF (1.0 mL) was added *via* syringe. Immediately after the addition, the solution darkened to a medium brown colour that continued to darken over 10 min. to deep brown. The resultant solution was stirred for 2 h, at which time a precipitate developed and TLC analysis showed complete consumption of the alkyl bromide. The reaction mixture was filtered through 1 cm of Celite sitting atop of 3 cm of silica gel in a fine fritted filter funnel. The vial and the plug were rinsed with diethyl ether (2 x 10 mL). The resultant solution was concentrated *in vacuo* and purified by SiO_2 chromatography (500:1 → 300:1 pentanes/diethyl ether).

*2.2.6 Control Experiment for the Addition of PPh_4Br to the Cross-coupling of **14** (Ethylzinc Bromide) with **7** (1-Bromo-3-phenylpropane).*

In the glovebox, LiBr (87 mg, 1.0 mmol, 2.0 equiv) was added to a flame-dried vial equipped with a stir bar and then the vial was removed from the glovebox. PPh_4Br (419 mg, 1.0 mmol, 2.0 equiv) and *Pd-PEPPSI-IPr* (**1**, 14 mg, 0.02 mmol, 4 mol%) were added to the vial under a cone of argon after which the vial was covered with a septum, sealed with electrical tape, and purged with argon (3x). THF (1.6 mL), the alkylzinc bromide (0.8 mL, 0.8 mmol, 1M in DMI, 1.3 equiv), and 1-bromo-3-phenylpropane (**7**, 75 μL, 0.5 mmol, 1.0 equiv) were then added; the reaction bubbled slightly and changed from a light yellow to dark brown immediately. The reaction flask was left to stir for the time indicated in Table 3, at which time TLC analysis indicated no consumption of the starting material. The reaction mixture was filtered through 1 cm of Celite sitting atop of 3 cm of silica gel in a fine fritted filter funnel. The vial and the plug were rinsed with diethyl ether (2 x 10 mL). The resultant solution

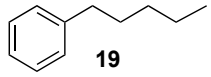
was concentrated *in vacuo* to reveal only starting material; no detectable cross-coupled product was observed by GC-MS or ^{1}H-NMR spectroscopic analysis.

*2.2.7 Titration of Tetra-n-butylammonium Bromide and Zinc Bromide with Diethylzinc (**11**)*

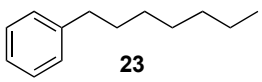
To a flame-dried vial equipped with a stir bar, covered with a septum and sealed with electrical tape was added THF-d_8 (1 mL) and diethylzinc (**11**, 102 μL, 1 mmol, 1 equiv). Under a positive pressure of argon, a syringe equipped with a long needle was used to transfer 0.7 mL of the resultant solution to a flame-dried, septum-sealed NMR tube and the ^{1}H-NMR spectrum was acquired. Using a syringe equipped with a long needle, the solution was removed from the NMR tube and returned to the vial under a positive pressure of argon. To a flame-dried, septum-sealed vial was added a 0.5 M solution of *n*-Bu_4NBr (966 mg, 3.0 mmol, 3.0 equiv) in THF-d_8 (6 mL). The solution was sonicated and warmed gently (and, if subsequently necessary, cooled to room temperature) until the salt was completely dissolved. To the vial containing diethylzinc in THF-d_8 was added an aliquot of the *n*-Bu_4NBr solution (1.0 mL, 0.5 equiv.) and the resultant solution stirred for 15 min before a ^{1}H-NMR spectrum was acquired (as described above). This was repeated to complete the titration series whereby 0.75, 1.0, 1.5, 2.0, 2.5 and 3.0 equivalent solutions of *n*-Bu_4NBr were added and the ^{1}H-NMR spectra acquired. In the glovebox, a vial was charged with zinc bromide (225 mg, 1.0 mmol, 1.0 equiv) before being sealed with a septum. THF-d_8 (1.0 mL) was added to the vial containing zinc bromide and the resultant mixture was sonicated until it was completely dissolved. The zinc bromide solution was taken up in a syringe and added

to the vial containing the ammonium zincate. The resultant mixture was permitted to stir for 15 min and a ^{1}H-NMR spectrum was then acquired as described above.

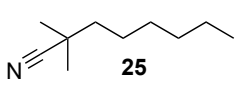
2.2.8 Spectral and Physical Data for Alkyl-alkyl Negishi Cross-coupling Products


19

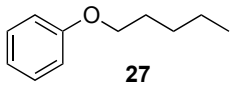
(Table 6, Entry 1) **Pentylbenzene**, (**19**): Following coupling procedure A, 92 mg of **19** (68% yield, 99% conversion) were isolated as a clear, colourless oil. ^{1}H-NMR (400 Hz, $CDCl_3$) δ 7.32 (m, 2H), 7.23 (m, 3H), 2.64 (t, J = 7.6 Hz, 2H), 1.66 (tq, J = 6.4, 7.6 Hz 2H), 1.36 (m, 4H), 0.94 (t, J = 6.4 Hz, 3H) ppm, ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.9, 128.4, 128.2, 125.5, 35.9, 31.5, 31.2, 25.5, 14.0 ppm. Spectra and physical data are in agreement with the literature.[60]


23

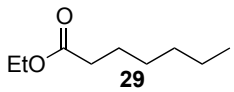
(Table 6, Entries 2 and 6) **Heptylbenzene** (**23**): Following coupling procedure A, 149 mg of **23** (94% yield, 99% conversion) were isolated as a clear, colourless oil. Following coupling procedure B, 114 mg of **23** were isolated (72% yield, 74% conversion). Following coupling procedure C, GC/MS analysis showed complete conversion to product (quant.). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 2H), 7.19 (qt, J = 7.6 Hz, 3H), 2.61 (t, J = 7.8 Hz, 2H), 1.62 (m, 2H), 1.31 (m, 8H), 0.88 (t, J = 6.7 Hz, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.9, 128.3, 128.1, 125.5, 35.9, 31.8, 31.5, 29.4, 29.1, 22.6, 14.0 ppm. Spectra and physical data are in agreement with the literature.[61]



(Table 6, Entry 3) **2,2-Dimethyloctanenitrile**, (**25**): Following coupling procedure A, 153 mg of **25** (99% yield, 99% conversion) were isolated as a clear, colourless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.49 (m, 4H), 1.30-1.33 (m, 8H), 0.88 (qt, J = 6.1, 7.4 Hz, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ 125.2, 41.03, 31.5, 29.2, 26.6, 25.3, 25.1, 22.4, 14.0 ppm. Spectra and physical data are in agreement with the literature.[62]



(Table 6, Entry 4) **Phenoxy-1-pentane**, (**27**): Following coupling procedure A, 153 mg of **27** (99% yield, 99% conversion) were isolated as a clear, colourless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 2H), 6.95 (m, 3H), 3.98 (t, J = 8.8 Hz, 2H), 1.80 (tq, J = 7.5, 8.8 Hz, 2H), 1.45 (m, 4H), 0.97 (t, J = 7.5 Hz, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.1, 129.4, 120.4, 114.5, 67.8, 29.0, 28.2, 22.5, 14.0 ppm. Spectra and physical data are in agreement with the literature.[63]



(Table 6, Entry 5) **Ethyl heptanoate**, (**29**): Following coupling procedure A, 125 mg of **29** (77% yield, 86% conversion) were isolated as a clear, colourless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.12 (q, J = 7.0 Hz, 2H), 2.35 (t, J = 7.8 Hz, 2H), 1.59-1.65 (m, 2H), 1.33 (m, 9H), 0.89 (t, J = 7.0 Hz, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ 185.3, 59.7, 33.8, 33.2, 29.1, 24.6, 21.4, 14.1, 13.5 ppm. Spectra and physical data are in agreement with the literature.[64]

Chapter 3:
Aryl-aryl Negishi Cross-Coupling

3.1 Introduction

With overwhelming corroborating evidence that the Negishi cross-coupling of alkyl-organozinc compounds (RZnX) occurs via the formation of a higher-order zinc species of the form ($RZnX_3^{2-}$) we next wanted to investigate whether the same was true with arylzinc reagents as this has been a subject of debate in the chemistry community.

3.2 Plan of Study

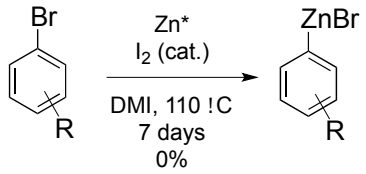
To begin our study, it would be necessary to evaluate how mono- and diarylzinc species are formed and isolated. Once pure, we would subject these organozinc species to Negishi cross-coupling conditions using pre-catalyst **3**, and observe how salt additives such as LiBr, that is formed during the TM of organometallics to ZnX_2, affects reactivity. Additionally, in order to gain an understanding of the species present in the aryl cross-coupling solution salts will be added to the mixture and the evolution and disappearance of organozinc materials followed by ^{1}H-NMR spectroscopy. It would be logical to assume that mono- and diarylzinc species will form higher order zincate species prior to the TM to Pd in Negishi cross-coupling. Such information is supported by the reactivity of alkyl organozinc species as seen in Chapters 1-2 of this work.

3.3 Results and Discussion

3.3.1 Zinc Insertion in to sp^2 Carbon-Bromide Bonds

It has been speculated that the coupling of sp^2-hybridized organozincs would be facile compared to its sp^3 counterparts, as the cross-coupling of sp^3-hybridized zincs is

plagued with various side reactions (see Figure 2).[30, 65, 66] On the other hand, the preparation of sp^2-hybridized organozincs is complicated because this invariably leads to the formation of salt by-products as the direct Zn insertion across an sp^2 hybridized C-X bond fails even under more forcing conditions[11] (see Scheme 15).

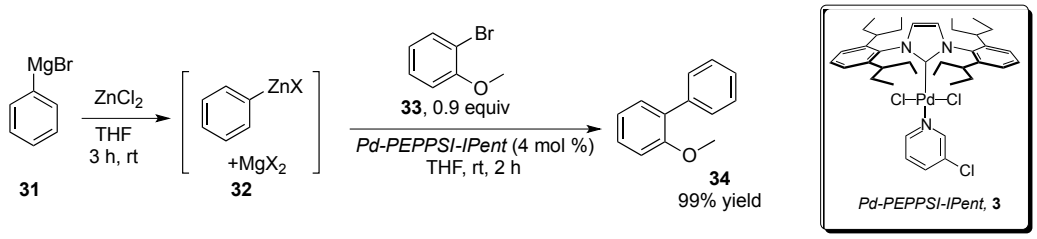


Scheme 15. Treatment of an aryl halide with conditions outlined by Huo to promote the direct insertion of Zn across the C-X bond[39]

The inability to undergo direct insertion means that vinyl- and arylzinc halides cannot be prepared salt-free. Consequently, arylzinc halide species are most typically obtained *via* the transmetalation of the respective organolithium or organomagnesium compound that also produces and equivalent of the corresponding salt (e.g. LiBr, $MgBr_2$).[67]

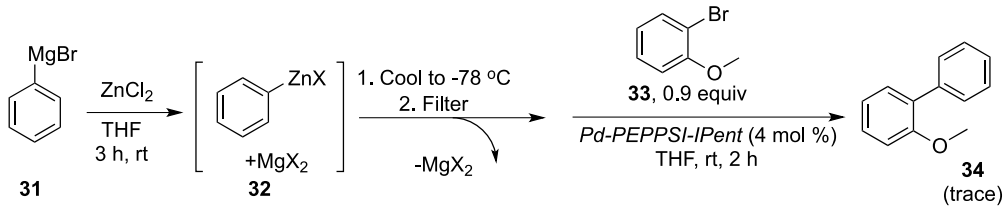
3.3.2 Mono-arylzinc Species Preparation and Reactivity

Compound **32** was formed by treatment of Grignard reagent **31** and one equivalent of $ZnCl_2$. During the preparation, a white precipitate (presumably MgX_2 where X = Cl or Br) forms. The slurry containing **32** was treated with *Pd-PEPPSI-IPent* pre-catalyst (**3**) and 2-bromoanisole (**33**) that led to quantitative conversion to **34**, which occurred concomitantly with the dissipation of the salt suspension (see Scheme 16).



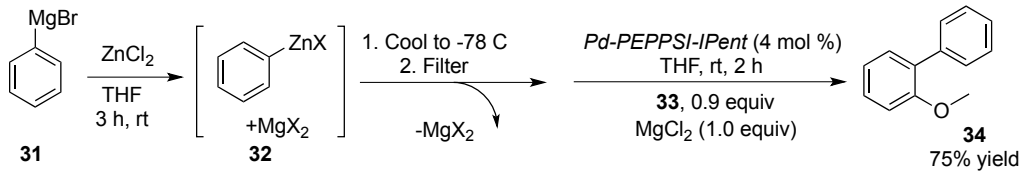
Scheme 16. The synthesis of **32** and subsequent cross-coupling to **33** with *Pd-PEPPSI-IPent* (**3**)

In a separate operation, the vessel containing the slurry of salts and **32** was cooled to -78 °C and most if not all of the MgX_2 precipitated. These salts were pelleted to the bottom of the reaction vessel through centrifugation and the vessel was cooled again to -78 °C. The solution of **32** was carefully cannulated (so as not to disturb the salt-pellet) through a septum-sealed, dry, fine-frit funnel filled with glass-wool into an argon-filled, dry, flask containing pre-catalyst **3** and **33**. With the salts absent from the reaction the cross-coupling failed and **33** was almost completely recovered (Scheme 17). This reaction served as a control experiment, as when the salts from TM are absent, cross-coupling cannot proceed. This result confirmed that we had removed the salts almost entirely.



Scheme 17. Coupling of **32** with mineral salts removed

If the MgX_2-free zinc solution of **32** was filtered into a flask containing the pre-catalyst, **33**, and $MgCl_2$ (see Scheme 18), coupling was restored as it had previously when the salts remained present (see Scheme 16).



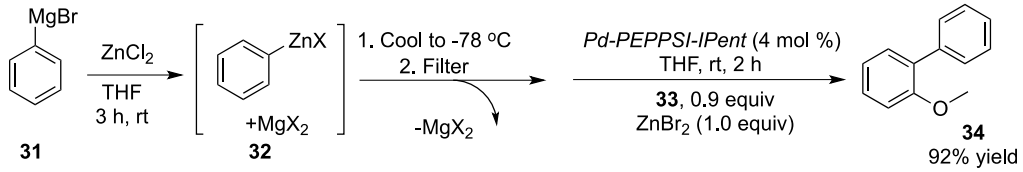
Scheme 18. Coupling MgX_2-free **32** in the presence of $MgCl_2$

These experiments highlight the importance of salts for the cross-coupling reaction of arylzinc halide species. Initially, we suspected a similar mechanism of TM to palladium with arylzincs as with alkylzinc species that involved a higher-order zincate species. To test this hypothesis we revisited the role of ZnX_2 in the mechanism of couplings.

3.3.3 The Effect of $ZnBr_2$ on Aryl-aryl Negishi Cross-coupling

In the case of alkyl-alkyl Negishi couplings, we have shown an inversely proportional relationship to the sub-stoichiometric amount of ZnX_2 present and the success of the coupling (see Figure 11).[16] $ZnBr_2$ shut down alkyl Negishi coupling, we propose by sequestering Br^- out of solution and away from the higher-order zincate due to its highly electrophilic nature, thus pushing left on the Schlenk equilibrium away from the zincate and back toward dialkylzinc (see Scheme 8). The exothermic process forms ZnX_3^- and subsequently $ZnBr_4^{2-}$ preventing transmetalation of the alkylzinc with palladium. We repeated the process as in Scheme 18 except we added $ZnBr_2$ as an additive instead of $MgCl_2$ and nearly quantitative coupling was observed (see Scheme 19). This result is in stark constrast to the alkylzinc coupling and suggests that the

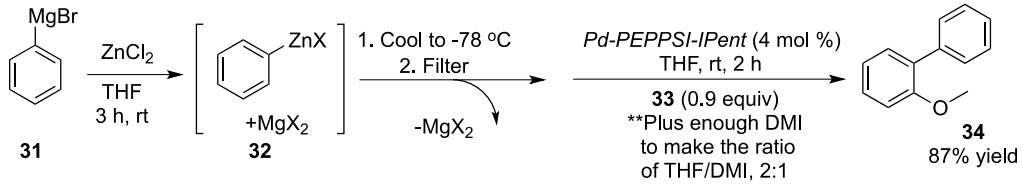
arylzinc species are not forming a zincate prior to transmetalation as it does in the alkylzinc case.



Scheme 19. $ZnBr_2$ as an additive in Negishi coupling of salt-free arylzinc halide (**32**)

3.3.4 Solvent Effects in Aryl-aryl Negishi Cross-coupling

With evidence that $ZnBr_2$ was promoting the reaction of **32**, we hoped to evaluate how the use of very polar co-solvent would affect the cross-coupling reaction with electrophile **33**. By preparing **32** using the salt-free protocol described above, the arylzinc species was filtered into a flask containing the *Pd-PEPPSI-IPent* pre-catalyst, **33**, and THF/DMI in a 2:1 ratio. TLC analysis indicated that the reaction had completed after only 2 h with complete conversion of the starting material, **34** was isolated in 87% yield (see Scheme 20).



Scheme 20. DMI as an additive in Negishi coupling of salt-free arylzinc halide (**32**)

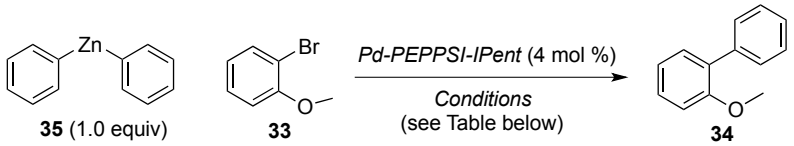
Since we observed that both $ZnBr_2$ (see Scheme 19) a very polar co-solvent (THF/DMI, 2:1, as in Scheme 20), as in the reactions above, provided the product **34** in good yield. This suggested that the mono-arylzinc species **32** was likely aggregating and the use of either a Lewis acid or polar solvent system facilitated the coupling by breaking apart

the organozinc species from polymeric, trimeric or dimeric forms to allow Zn and Pd to transmetalate. The heightened polarization of the C(sp^2)-Zn bond (as in **32**) relative to the C(sp^3)-Zn bond could account for the increased aggregation in this species relative to the alkyl counterpart in ethylzinc bromide (**14**).

3.3.5 Aryl-aryl Negishi Cross-coupling Using Diarylzinc Species

With the arylzinc halide results in hand, we decided to approach arylzinc coupling with the diarylzinc species to observe any differences in reactivity under similar conditions. Diphenylzinc (**35**) was prepared from the respective Grignard reagent (**31**), and sublimed to purify it of the transmetalation salts prior to the treatment of Negishi coupling conditions with aryl halide **32**. An additive study was done with **35** as it was with **32** (see Table 7).

Table 7. Cross-coupling of diphenylzinc (**35**) with anisole (**33**) under different conditions



35 (1.0 equiv) **33** **34**

Entry	Equivalents of ArBr (**33**)	Solvent	Time (h)	Additive (1 equiv)	Yield[a] (%)
1	0.9	THF	2	-	99
2	1.9	THF	8	-	47
3	1.9	THF	8	LiBr	87
4	1.9	THF	8	*n*-Bu_4NBr	90
5	1.9	THF	8	$ZnBr_2$	90
6	1.9	THF/DMI (2:1)	8	*n*-Bu_4NBr	84
7	1.9	THF/DMI (1:2)	8	-	81
8	1.9	THF/DMI (2:1)	8	-	80
9	1.9	DMI	8	-	88
10	1.9	1. THF then 2. THF/DMI (now 2:1)	2 6 (8 h total)	-	81

[a] Yields are determined after purification of the products on silica gel

Surprisingly, we noticed that the coupling of diphenylzinc (**35**) proceeded in straight THF with full conversion to **34** based on **33** as the limiting reagent (Table 7, Entry 1). Under the assumption that $ZnPh_2$ (**35**) will generate PhZnBr (**32**) after completing the catalytic cycle with Pd, we envisioned that both PhZnBr and $ZnPh_2$ moieties should be able to transmetalate. When the amount of **33** was doubled, the overall amount of cross-coupled biaryl (**34)** recovered was roughly half, what would be expected if only $ZnPh_2$ was transmetalating (Entry 2). In entries 3 and 4, the reaction was carried out with LiBr and TBAB respectively providing complete conversion of the starting material (**33**) and good yields the desired product. Much to our surprise, when $ZnBr_2$ was evaluated to determine if it would inhibit the transmetalation of the arylzinc with

Pd, the cross-coupling reaction proceeded well providing good conversions of **33** to **34**. This result strongly suggests that the aryl-aryl Negishi cross-coupling mechanism was proceeding by a different mechanism than its alkylzinc counterpart. The use of THF/DMI (2:1) co-solvent system *and* TBAB as an additive (Entry 6) did not improve the overall yield compared to the entry in which TBAB was present but DMI co-solvent was absent (Entry 4). Noted, was that the use of a very polar co-solvent (i.e. DMI) in the absence of a halide salt additive was sufficient to drive the reaction to completion (Entries 7 - 9). To add to this, we subjected **35** to two equivalents of **33** in straight DMI and both phenyl moieties were transmetalated to Pd, with complete conversion to **34** (Entry 9). Lastly, the reaction was started in THF solvent only, and the progress of the coupling reaction was followed by TLC analysis. After two hours, roughly half of the electrophile **33** had been converted to the cross-coupled product **34**. After presumably all of the $ZnPh_2$ had reacted and produced PhZnBr, the solvent system was adjusted to incorporate DMI (such that the co-solvent system was 2:1, THF/DMI) **34**, the cross-coupling reaction resumed and proceeded to convert the unreacted aryl halide to the desired product (**34**, see Entry 12).

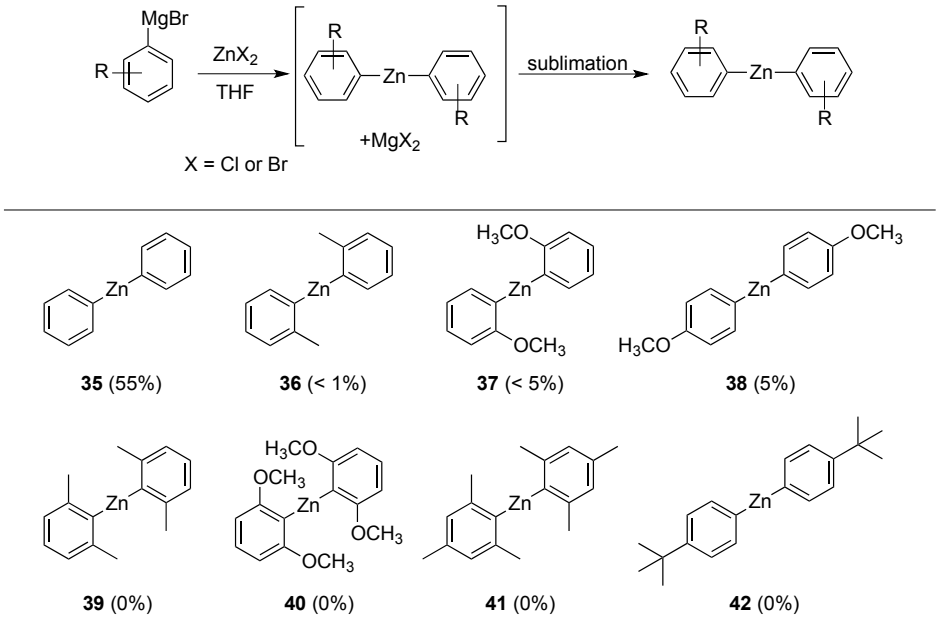
At this point, it was suggested that **35** in THF transmetalates to Pd directly without the use of a polar co-solvent or a salt-additive. The by-product of the transmetalation of $ZnPh_2$ was PhZnBr, which remained inactive in the catalytic cycle unless either a) a salt and/or b) a polar co-solvent was added. Now, with sufficient evidence to disprove formation of a higher-order zincate in aryl Negishi cross-coupling, we proposed a dielectric dependence of PhZnBr for transmetalation to Pd to occur. If the resulting mixture containing PhZnBr is not sufficiently polar, coupling will not proceed. An

explanation for this observation is that $ZnPh_2$ is likely forming aggregates that are less strong that those formed by PhZnBr, owed to the less polarized C-Zn bond relative to the Zn-Br case. In PhZnBr, the process of aggregation minimizes dipoles and stabilizes the system. Therefore, it would make sense that under the Negishi reaction conditions, the aggregates formed with $ZnAr_2$ species are easily broken down to facilitate transmetalation in relatively non-polar solvent (i.e. ε THF = 7.5 relative to ε DMI = 37.6).[68] As the organozinc species participate as the nucleophile in Negishi cross-coupling, it is understandable that a metal center bearing a highly electronegative ligand (i.e. ArZnX species) would be less easily transmetalated to an electrophilic metal centre (such as Pd^{II}). ArZnX species require *either* a high dielectric solvent *or* a lower polarity solvent with enough additive to increase the medium's ion-solubilizing ability to break down the residual ArZnX aggregates.

3.3.6 Isolating Other Diarylzinc Species

After providing evidence that arylzincs are not required to form the respective higher-order zincates before transmetalation we investigated the substrate scope with various diaryl zinc species. The synthesis of several diarylzincs was attempted with limited success (see Scheme 21). The sublimations of diarylzinc species on the whole proved challenging because of a) the strong coordination of THF solvent to the diarylzinc species. The diarylzinc species, even though dried on high vacuum contained residual THF and would not sublime as they were unable to crystallize on the glass surface of the cold finger in a sublimator, and b) the temperature of sublimation was very close to the temperature of decomposition for the organozincs. Though reproducibility was

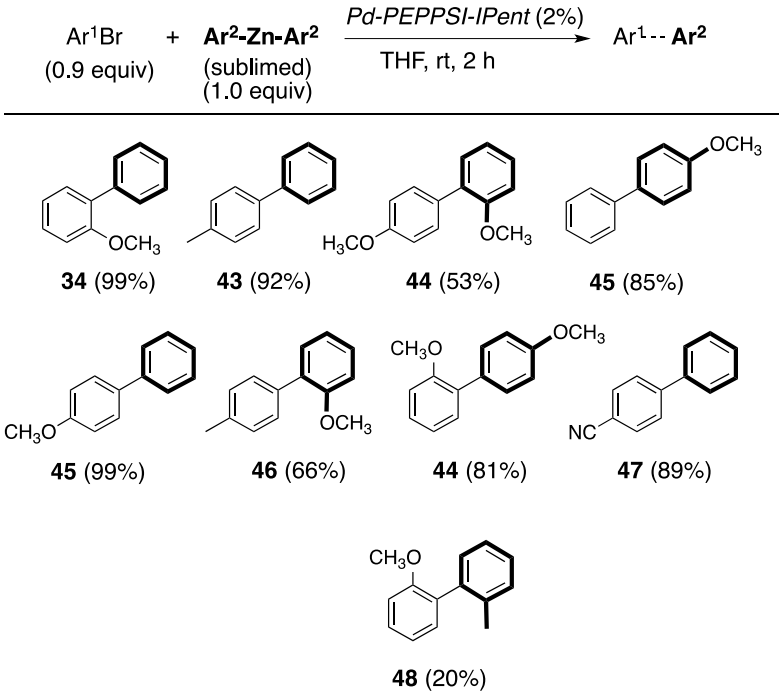
challenging, we were able to successfully synthesize, isolate, purify and cross-couple several diarylzincs (see Scheme 21).



[a] Yields, with the exception of **35**, are estimated based on their mass and ^{1}H-NMR spectra, if a yield of 0% is reported, the diarylzinc decomposed during sublimation and was not isolated.

Scheme 21. General procedure for the synthesis of diarylzincs. Shown are the synthesized diarylzincs and their yield.

Diarylzincs such as diphenylzinc (**35**) and mono-substituted diarylzincs with an electron donating methoxy group in the ortho or para position were more easily isolated relative to those that were diortho-substituted or alkylsubstituted (in the case of the *t*-Bu groups in **42**). Once compounds **36**, **37**, and **38** had sublimed they immediately began to decompose as evidenced by their discolouration within minutes following their sublimation. Several diarylzinc species decomposed during sublimation and their spectra could not be obtained (**39**, **40**, **41** and **42**). Of the successfully synthesized diarylzinc species, a substrate scope was developed to demonstrate the utility of reaction (see Scheme 22).



Scheme 22. Cross-coupling of diarylzincs with arylhalides promoted by *Pd-PEPPSI-IPent* under salt-free conditions in THF at rt.

3.3.7 On Structure and Stability of Diarylzincs

Of the diarylzincs **35** through **38**, only **35** is commercially available as a pure, solid. Compound **35** was the most robust of the arylzinc species and the least of these were compounds **36**, **37**, and **38**. Furthermore, **35** was the easiest to purify, provided the cleanest spectrum and afforded the highest yields after treatment to cross-coupling conditions with the selected electrophiles. Of the diarylzinc compounds isolated, **36** was the most difficult to purify and the results were lowest when subjected to cross-coupling conditions. It is possible that the presence of the methoxy groups in compounds **37** and **38** provided stabilization to aid in their isolation from the reaction media. Of all the diarylzinc species, with the exception of **35**, decomposition began as the THF solvent was removed and compounds, once devoid of any solvent quickly began to decompose within minutes. This was highlighted most clearly in compound

36 that began to show visual changes suggesting its decomposition immediately when dried *in vacuo*. When the isolation/sublimation of diarylzinc compounds prepared in a non-coordinating solvent (e.g. ether or toluene) was performed, they were not isolable. Unless there was at least *some* THF present, the diarylzincs decomposed with heating during the sublimation process. This observation speaks to how important coordination, in terms of bearing functional groups or the solvent used in their preparation, was fundamental to their relative stability. This is supported by several reports that zinc species are often 4-coordinate species and often dimerize or trimerize.[69,70] From this we can hypothesize that the diorthosubstituted compounds, even in the case of **40** bearing 2,6-dimethoxy groups, disrupt zinc's pseudo-tetrahedral coordination contributing to the compound's overall instability.

3.3.8 ^{1}H-NMR Spectroscopy Halide Salt Doping Studies of Mono- and Diarylzinc Species

Initially, when the dependence of LiX and MgX_2 salts was noted in arylzinc halide Negishi cross-coupling we presumed that zincate formation was occurring prior to the Zn/Pd transmetalation step. Due to our understanding of the role these salts play in the alkyl systems (in carefully titrated control reactions) we initially believed that a salt-dependance indicated zincate formation in the sp^2 system as well.[40,71,72] Once we had confirmation that solvent was playing a key role in the transmetalation to Pd of monarylzinc species, we reasoned that the chemical shifts of these zinc species in presence of varying amounts of salts or solvents would be important.

To observe the ^{1}H-NMR chemical shift perturbation of Ph_2Zn **(35)**, a titration experiment was conducted much as it was for **14**. A solution of LiBr in THF-d_8 was

added in aliquots to **35** to observe if the presence of Br^- had any affect on the resonance of the protons of the aryl moiety. We observed that as the concentration of LiBr increased in solution, the chemical shift of the aromatic protons shifted (see Figure 14).

The titration of **35** was repeated again with DMI (see Figure 15) and a very similar shift of the aryl protons was observed. When LiBr aliquots were added to a solution containing PhZnBr (**32**), the spectroscopic perturbation was similar in the case of LiBr addition (**35**) (see Figure 16). Though it's not shown here, when $ZnBr_2$ was added at the end of the titrations presented above, the chemical shifts continued to be perturbed in much the same as when LiBr or DMI were added and peak broadening occurred.

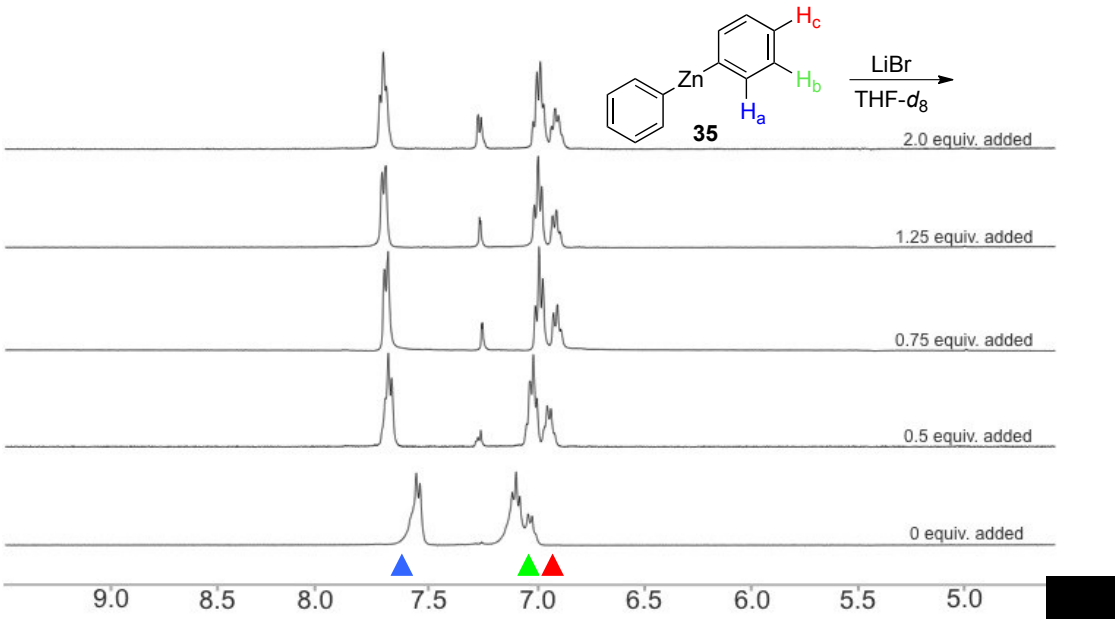


Figure 14. ^{1}H NMR titration of Ph_2Zn (**35**) with LiBr in THF-d_8

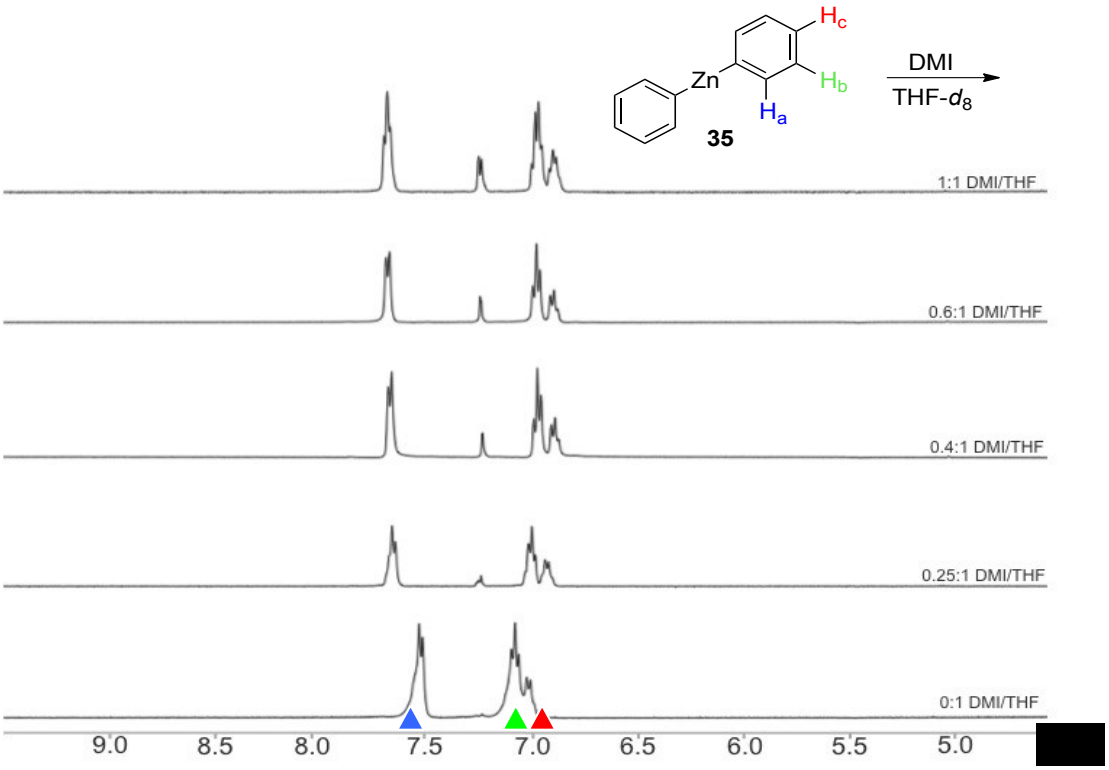


Figure 15. ^{1}H NMR titration of Ph_2Zn (**35**) with DMI in THF-d_8

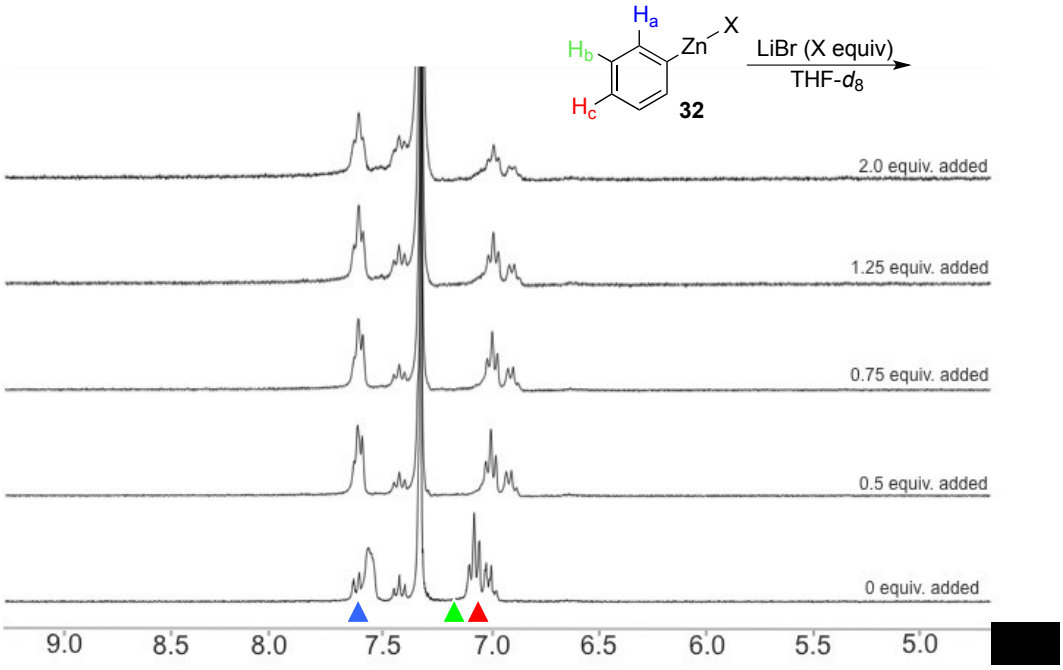


Figure 16. ^{1}H NMR titration of PhZnBr (**32**) with LiBr in THF-d_8

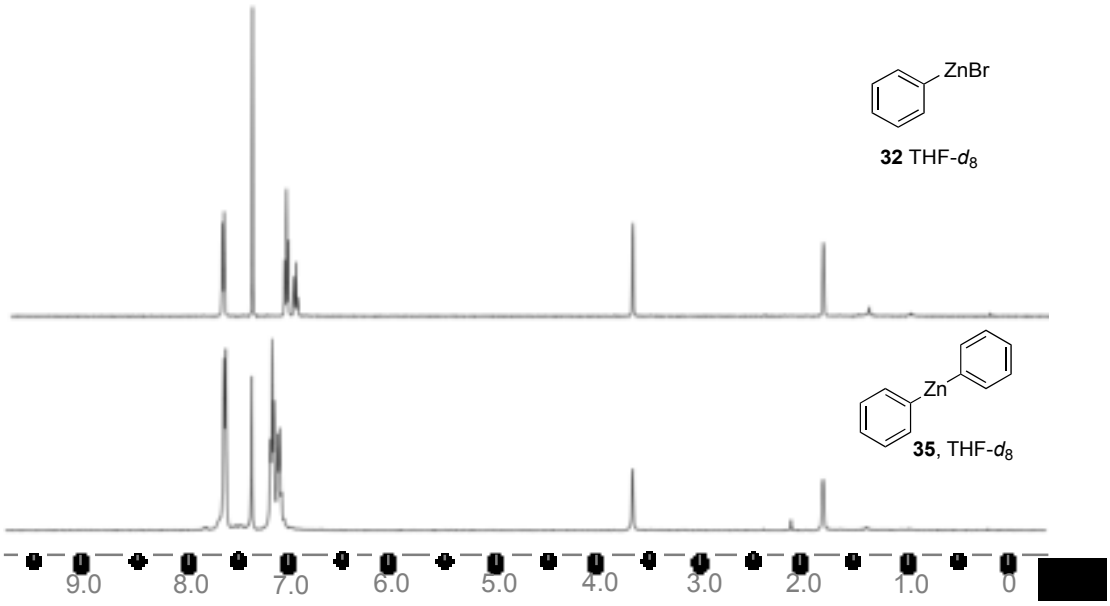


Figure 17. Superimposed ^{1}H NMR spectra: PhZnBr (**32**) and $Zn(Ph)_2$ (**35**)

This is in stark contrast to the case of the alkylzinc species (see Figure 9 and 10) in which the addition of $ZnBr_2$ caused a shift upfield of the methyl and methylene proton resonances in **13** and **17** at the end of the halide salt titration, resembling more closely the starting organozinc species (**11)**. Furthermore, the addition of $ZnBr_2$ to a flask containing **32** (see Scheme 19 and Table 7, Entry 5) casts doubt that an arylzincate must form prior to transmetalating with Pd. At this time we cannot rule out a mechanism that involves that disproportionation of **35** in the presence of $ZnBr_2$. What we propose instead is that the coupling activity seen in the monoarylzinc species **(32)** is dependent on the dielectric of the reaction media. The chemical shift perturbation seen in the monoarylzinc species **(32)** with LiBr, DMI or $ZnBr_2$ (see Figures 14, 15, and 16) is largely the result of aggregates of the organozinc species breaking apart. The cross-coupling of **32** is promoted when the above-mentioned additives were present, that is when the solution's dielectric constant becomes sufficiently high. Although the proton resonances between species **32** and **35** are significant enough to be identifiable (see Figure 17) it is noteworthy that in a mixture containing **32** or **35** with LiBr, $ZnBr_2$ or DMI, the resonances become nearly indistinguishable.

We have proposed a new catalytic cycle that incorporates the difference in reactivity between mono- and di-arylated zinc species that incorporates the role of the dielectric of the solvent (see Figure 18).

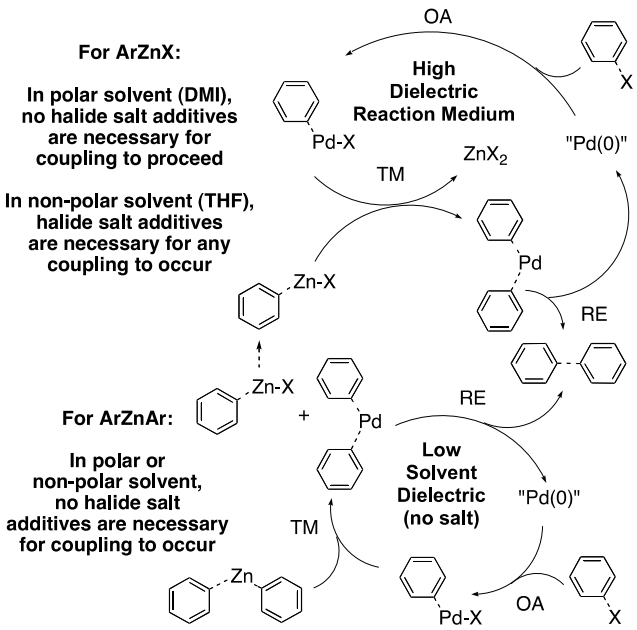


Figure 18. The proposed catalytic cycle for the Negishi coupling of arylzinc reagents including the role of salt additives and solvent dielectric.[73]

3.4 Conclusion

We have inferred that $ZnPh_2$ (**35**) will form aggregates that are less strong, owed to the less polarized C-Zn bond relative to the Zn-Br case. This argument supports the observation that **35** will undergo cross-coupling in THF solvent alone. In PhZnBr (**32**), the process of aggregation minimizes dipoles and stabilizes the system. Therefore, it would make sense that under the Negishi reaction conditions, the aggregates formed with $ZnAr_2$ species are easily broken down to facilitate transmetalation in relatively non-polar solvent (i.e. ε THF = 7.5 relative to ε DMI = 37.6).[68] As the Zn partners in coupling participate as the nucleophile, it is our understanding that a metal center bearing a highly electronegative ligand (i.e. ArZnX species) would be less easily transmetalated to an electrophilic metal centre (such as Pd^{II}). ArZnX species require *either* a high dielectric solvent *or* a lower polarity solvent with enough additive to

increase the medium's ion-solubilizing ability to break down residual ArZnX aggregates.

On the whole, while higher-order zincates have been shown to readily form in the presence of halide ions and are postulated to be the active transmetalating species in alkylzinc couplings, there is no evidence to invoke arylzincates in the mechanism of Negishi cross-coupling.

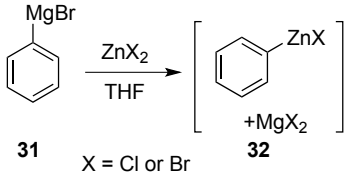
Chapter 4:
Experimental Procedures for Aryl-aryl Negishi Cross-coupling

4.1 General Experimental

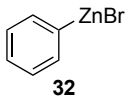
All reactions were run under argon with scrupulous exclusion of moisture from reagents and glassware using standard Schlenk techniques for manipulating air-sensitive compounds.[55] All glassware was stored in a drying oven, flame-dried, and purged with argon prior to use. Anhydrous ether and THF were obtained by distillation over sodium/benzophenone, or used directly from ampoules in the case of THF-d_8 (Sigma-Aldrich). DMI was purchased in *Sure/Seal*™ bottles from Sigma-Aldrich and used directly without further purification. Analytical thin-layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed using UV absorbance and ceric ammonium molybdate (CAM) or aqueous potassium permanganate stains. Flash column chromatography[56] was performed using Silicycle™ silica gel 60 (230-400 mesh) and the indicated solvent system. Nuclear magnetic resonance spectra (^{1}H, ^{13}C) were recorded on Bruker 300 or 400 MHz AVANCE spectrometers equipped with a DUAL probe. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million (ppm) using the residual proton signal of the solvent as the internal standard ($CDCl_3$, δ = 7.26 ppm, CD_2Cl_2, δ = 5.32 ppm, THF-d_8 δ = 3.58 ppm). Chemical shifts for ^{13}C NMR spectra are recorded in parts per million (ppm) by calibrating the central peak of $CDCl_3$ (77.00 ppm), CD_2Cl_2 (54.00 ppm) or THF-d_8 (67.40 ppm).

4.2 Synthetic Procedures

4.2.1 Preparation of Arylzinc Halides

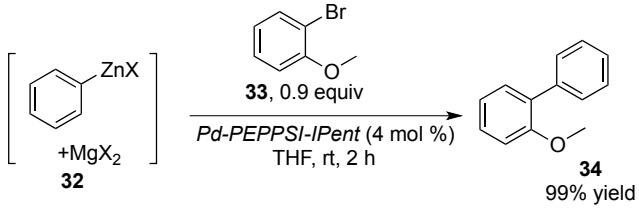


In a glove box, a flame-dried vial was charged with a stir bar and zinc bromide (225 mg, 1.0 mmol, 1.0 equiv.) or zinc chloride (136 mg, 1.0 mmol, 1.0 equiv.) and the vial was closed with a rubber septum. The vial was removed from the glove box, connected to a vacuum line and purged. The vial contents were heated gently with a flame until they became free-flowing (but not melted), cooled to rt, and backfilled with argon. To the vial, THF (2 mL) was added and the resulting clear, colourless solution was stirred. PhMgBr (2.0 mL, 2.0 equiv., 2.0 M in THF) was added *via* syringe resulting in a visual change in the mixture's appearance from clear and colourless to dark-yellow with a white precipitate. The vial contents were stirred at rt for 30 minutes and carried forward to the next reaction (purification as indicated).

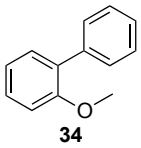


Phenylzinc bromide (**32**), ^{1}H-NMR (400 MHz, THF-d_8) δ 7.45 (d, J = 6.4 Hz, 2H), 7.29 (benzene) 7.09 (t, J = 7.2 Hz, 2H), 7.04 (t, J = 7.2 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, THF-d_8) δ 153.4, 139.3, 129.1 (benzene), 127.6, 126.7 ppm.

*4.2.2 Negishi Coupling Containing MgX_2 (**Scheme 16**):*

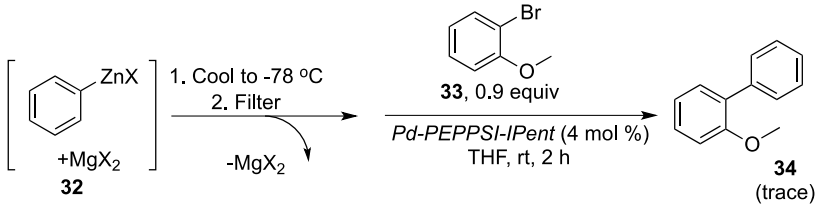


To a vial containing freshly prepared arylzinc halide (0.25 mmol, 1 equiv.) a clear, yellow THF solution (totalling 1 mL) containing *Pd-PEPPSI-IPent* (8 mg, 0.01 mmol, 4 mol%), and **33** (43 mg, 28 μL, 0.23 mmol, 0.9 equiv.) was added *via* syringe resulting in a visual change in the mixture's appearance from bright-yellow to dark-brown. The vial contents were stirred at rt for 2 h under argon, at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was concentrated *in vacuo* and purified using flash chromatography (silica gel, 200:1 pentane/Et_2O) providing 42 mg of **34** (99% yield, 100% conversion based on **3**) as a clear, colourless oil.


34

2-methoxy-1,1'-biphenyl, (**34**), ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.6 Hz, 2 H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.33 (m, 3H), 7.13-7.00 (m, 2H), 3.86 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.5, 138.6, 130.9, 130.8, 129.6, 128.7, 128.0, 126.9, 120.9, 111.3, 55.6 ppm. Spectra and physical data are in agreement with the literature.[74]

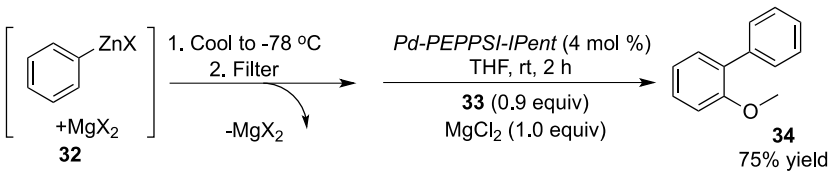
4.2.2.1 Negishi Reaction with MgX_2 removed ***(Scheme 17):***



A vial containing freshly prepared arylzinc halide (0.25 mmol, 1.0 equiv.) was chilled to – 20 °C for 4 hours in a freezer. The vial was centrifuged (2000 rpm, 5 min) and then chilled to – 78 °C in a dry ice/acetone bath. The cold solution was cannulated through a glass wool plug held in a septum-sealed, fine-frit filter funnel connected to a

septum-sealed, two-neck round-bottom flask equipped with a stir bar. To this flask, a clear, yellow THF solution (totaling 1.0 mL) containing *Pd-PEPPSI-IPent* (8 mg, 0.01 mmol, 4 mol%) and **33** (43 mg, 28 μL, 0.23 mmol, 0.9 equiv.) was added *via* syringe resulting in a visual change in the mixture's appearance from bright-yellow to dark-brown. The reaction was stirred at rt for 2 h under argon at which time it was concentrated *in vacuo* and purified using flash chromatography (silica gel, 200:1 pentane/Et_2O) providing 3 mg of **34** (9% yield, based on **33**) as a clear, colourless oil, and 31 mg of **33** (75% recovered).

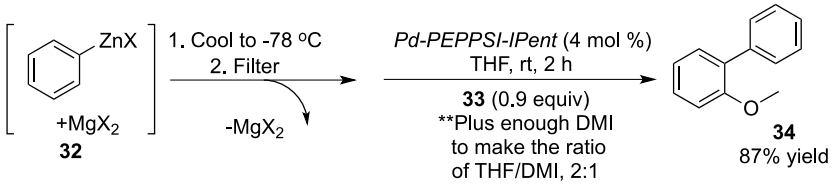
4.2.3 Negishi Reaction with MgX_2 Removed, then Re-added (Scheme 18):



A vial containing freshly prepared arylzinc halide (0.25 mmol, 1.0 equiv.) in THF was chilled to – 20 °C for 4 hours in a freezer. The vial was then centrifuged (2000 rpm, 5 min) and then chilled to – 78 °C in a dry ice/acetone bath. The solution was cannulated through a glass wool plug held in a septum-sealed, fine-frit filter funnel connected to a septum-sealed, two-neck round-bottom flask equipped with a stir bar. To the flask, a cloudy, yellow THF solution (totaling 1.0 mL), *Pd-PEPPSI-IPent* (8 mg, 0.01 mmol, 4 mol%), **33** (43 mg, 28 μL, 0.23 mmol, 0.9 equiv.), and $MgCl_2$ (24 mg, 0.25 mmol, 1.0 equiv.) was added *via* syringe resulting in a visual change of the solution's appearance from bright-yellow to dark-brown. The resulting solution was stirred at rt for 2 h under argon, at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was concentrated *in vacuo* and was purified using flash

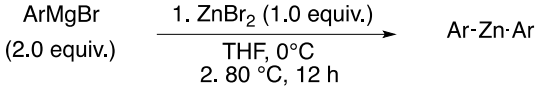
chromatography (silica gel, 200:1 pentane/Et_2O) providing 31 mg of **34** (75% yield, 77% conversion based on **33**) as a clear, colourless oil.

4.2.4 Negishi Coupling with MgX_2 Removed and DMI Aadded (Scheme 20):



A vial containing freshly prepared arylzinc halide (0.25 mmol, 1 equiv.) was chilled to – 20 °C for 4 hours in a freezer. The vial was then centrifuged (2000 rpm, 5 min) and then chilled to – 78 °C. The solution was cannulated through a glass wool plug held in a septum-sealed, fine-frit filter funnel connected to a septum-sealed, two-neck, round-bottom flask equipped with a stir bar. To the vial, a clear, yellow DMI solution (totalling 1 mL) containing *Pd-PEPPSI-IPent* (8 mg, 0.01 mmol, 4 mol%), **33** (43 mg, 28 μL, 0.23 mmol, 0.9 equiv.) was added *via* syringe resulting in a visual change in the mixture's appearance from bright-yellow to dark-brown. The resulting solution was stirred at rt for 2 h under argon, at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was concentrated *in vacuo* and purified using flash chromatography (silica gel, 200:1 pentane/Et_2O) providing 37 mg of **34** (87% yield, 90% conversion based on **33**) as a clear, colourless oil.

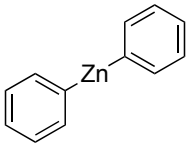
4.2.5 General Procedure for the Preparation of Diarylzincs:



Zinc bromide (4.95 g, 22 mmol, 1.0 equiv.) was weighed into an oven-dried 20 mL vial inside the glovebox. The vial was sealed with a Teflon®-lined plastic screw cap and removed from the glove box. The vial contents were transferred under a cone of argon to a flame-dried 24/40 necked, 250 mL round-bottom flask equipped with a large stir bar. The flask was fitted with a septum-sealed, cold-water condenser closed with a rubber septum. The flask purged under high-vacuum and zinc halide was gently heated by flame until it was free flowing but not melted. The flask was cooled to rt and backfilled with argon. To the flask was added THF (50 mL) and the contents were stirred until a clear and colourless solution was attained. The flask was cooled to 0 °C in an ice bath and ArMgBr (44 mmol, 2.0 equiv. 0.5-2.0 M in THF or ether) was added slowly *via* syringe resulting in a visual change of the mixture's appearance from clear and colourless to medium-brown with a white precipitate. The resulting solution was heated quickly to reflux (80 °C) for 12 h with vigorous stirring. The flask was cooled to rt. While under a blanket of argon, the sealed flask containing freshly prepared $Zn(Ar)_2$ was fitted quickly with a septum-sealed three-way adapter, a cold-water condenser and a vacuum adapter connected to a 250 mL round-bottom receiving flask that was immersed in an ice bath. The apparatus was purged under vacuum (1.0 mm Hg) and backfilled with argon (3x) while stirring and the flask was heated to 200 °C over 1 h. At this time the apparatus was purged under high vacuum (0.1 mmHg) until the solvent was fully removed leaving a viscous, yellow oil. The flask was cooled to rt and backfilled with argon. Quickly and under a cone of argon, the flask containing the diarylzinc was fitted with a clean, septum-sealed three-way adapter connected to a receiving, septum-sealed, two-neck, round-bottom flask. The apparatus was purged

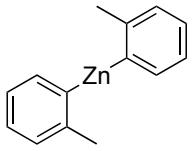
under high-vacuum (0.1 mmHg) and the receiving, two-neck flask was cooled to -78 °C. The flask containing the diarylzinc was heated carefully with a heat gun (850 Watts) because the heat required to sublime the material surpassed the safe operating conditions of an oil bath or heating mantle. The flask was heated around the sidewall and bottom of the round bottom flask in a continuous, side-to-side motion. As white, diarylzinc vapour began to sublime up into three-way adapter, the apparatus was backfilled with argon and the vapours settled in the cold collection flask. Once the vapours had condensed in the receiving flask, the system was depressurized under high vacuum. The pump, heat, and backfill procedure was repeated until the all of the diarylzinc had sublimed/distilled over to the collection flask leaving behind any salts and decomposed product. The apparatus was carefully transferred to the glove box and the diarylzinc was transferred to tightly sealed, screw-cap vials and characterized by ^{1}H and ^{13}C-NMR spectroscopy in sealed, argon-filled NMR tubes.

4.2.6 Spectral and Physical Data of Diarylzincs



35

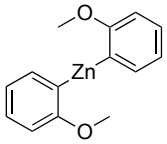
Diphenylzinc, (**35**): Sublimes as a pure, white solid 2.66 g (55% yield): ^{1}H-NMR (400 MHz, CD_2Cl_2) δ 7.69 (dd, *J* = 7.6, 2.0 Hz, 4H), 7.40 (benzene), 7.37 (t, *J* = 5.5 Hz, 2H) 7.35 (dd, *J* = 7.6, 2.0 Hz, 4H) ppm; ^{13}C-NMR (100 MHz, CD_2Cl_2) δ = 147.9, 137.7, 128.2, 128.0 (benzene), 127.6 ppm. Spectra and physical data are in agreement with the literature.[74]



36

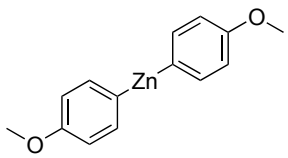
***bis*-(2-Methylphenyl)zinc**, (**36**) Distils as a clear and colourless liquid with THF, forming a white solid when concentrated under vacuum that decomposes within minutes.[74] ^{1}H-NMR (400 MHz, CD_2Cl_2) δ ^{1}H-NMR (400 MHz, CD_2Cl_2) δ = 7.69 (d, *J* = 7.5 Hz, 2H), 7.37 (m, 1 H) 7.35 (dd, *J* = 7.5

Hz, J = 2.0 Hz, 2H), 2.36 (s, 3H) ppm; ^{13}C-NMR (100 MHz, CD_2Cl_2) δ 137.6, 129.6, 127.9, 127.8, 125.8, 124.6, 20.9 ppm.



37

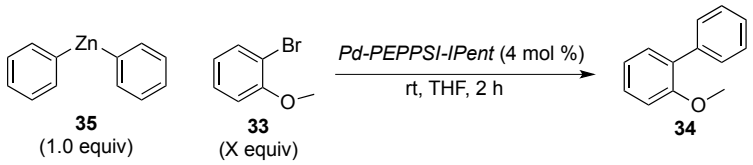
***bis*-(2-Methoxyphenyl)zinc**, (**37**) Distils as a clear and colourless liquid with THF containing traces of anisole, forming a white solid when concentrated under vacuum that decomposes within minutes.[74] ^{1}H-NMR (400 MHz, CD_2Cl_2) δ 7.34-7.31 (m, 2H), 7.19 (dd, J = 6.0, 1.6 Hz, 2H), 6.98 (d, J = 8.0 Hz, 4H), 3.75 (s, 6H) ppm; ^{13}C-NMR (100 MHz, CD_2Cl_2) δ 149.6, 131.2, 128.4, 127.8, 120.1, 110.8, 55.4 ppm.



38

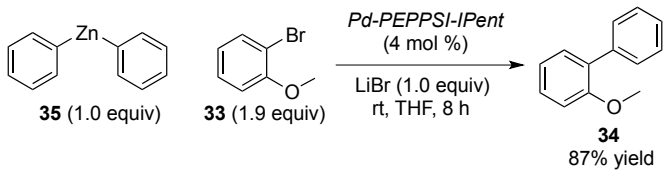
***bis*-(4-Methoxyphenyl)zinc**, (**38**) Distils as a clear and colourless liquid with THF, forming a white solid when concentrated under vacuum. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.8 Hz, 4H), 6.96 (d, J = 8.8 Hz, 4H), 3.84 (s, 6H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.6, 133.4, 127.6, 114.0, 55.2 ppm.

4.2.7 Negishi Coupling to Provide Table 7, Entries 1 and 2:



In the glove box, freshly sublimed $Zn(Ph)_2$ (**35**, 55 mg, 0.25 mmol, 1.0 equiv.) was added to a flame-dried vial equipped with a stir bar after which the vial was closed with a rubber septum and removed from the glove box. The sealed vial was charged with argon and the contents dissolved in THF (2 mL) forming a clear, colourless solution. To this vial, a clear, yellow THF solution (totaling 1 mL) containing *Pd-PEPPSI-IPent* (**3**, 8 mg, 0.01 mmol, 4 mol%), and **33** (Entry 1: 43 mg, 29 μL, 0.24 mmol, 0.9 equiv., or Entry 2: 89 mg, 59 μL, 0.48 mmol, 1.9 equiv.) was added *via* syringe resulting in a visual change in the mixture's appearance from bright-yellow to light-brown. The solution was stirred for 8 h at rt at which time the reaction mixture was concentrated on silica gel (1 g) *in vacuo* and the product was purified by flash chromatography (silica gel, 200:1 → 100:1 pentane/Et_2O) providing **34** as a clear, colourless oil. Entry 1: 43 mg (98% yield, >99% conversion based on **33**). Entry 2: 44 mg (47% yield, 49% conversion based on **33**).

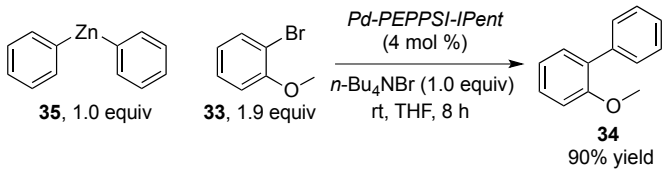
4.2.8 Negishi Coupling to Provide Table 7, Entry 3:



In the glove box, freshly sublimed $Zn(Ph)_2$ (**35**, 55 mg, 0.25 mmol, 1.0 equiv.) was added to a flame-dried vial equipped with a stir bar after which the vial was closed

with a rubber septum and removed from the glove box. The sealed vial was charged with argon and the contents dissolved in THF (2 mL) forming a clear, colourless solution. A clear, yellow THF solution (totaling 1 mL) containing *Pd-PEPPSI-IPent* (**3**, 8 mg, 0.01 mmol, 4 mol%), **33** (89 mg, 59 μL, 0.48 mmol, 1.9 equiv.), and LiBr (21 mg, 0.24 mmol, 1.0 equiv.), was added *via* syringe resulting in a visual change in the mixture's appearance from bright-yellow to dark-brown. The solution was stirred for 8 h at rt at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was concentrated on silica gel (1 g) *in vacuo* and the product was purified by flash chromatography (silica gel, 200:1 pentane/Et_2O) providing 76 mg of **34** (87% yield, 90% conversion based on **33**) as a clear, colourless oil.

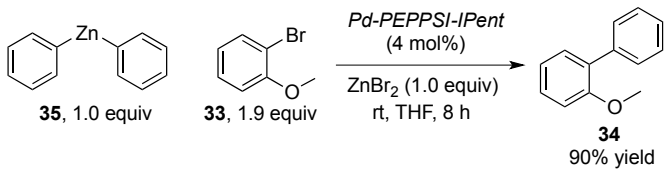
4.2.9 Negishi Coupling to Provide Table 7, Entry 4:



In the glove box, freshly sublimed $Zn(Ph)_2$ (**35**, 55 mg, 0.25 mmol, 1.0 equiv.) was added to a flame-dried vial equipped with a stir bar after which the vial was closed with a rubber septum and removed from the glove box. The sealed vial was charged with argon and the contents dissolved in THF (2 mL) forming a clear, colourless solution. A clear, yellow THF solution (totaling 1 mL) containing *Pd-PEPPSI-IPent* (**3**, 8 mg, 0.01 mmol, 4 mol%), **33** (89 mg, 59 μL, 0.48 mmol, 1.9 equiv.), and *n*-Bu_4NBr (77 mg, 0.24 mmol, 1.0 equiv.), was added *via* syringe resulting in a visual change in the mixture's appearance from bright-yellow to dark-brown. The solution

was stirred for 8 h at rt at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was concentrated on silica gel (1 g) *in vacuo* and the product was purified by flash chromatography (silica gel, 200:1 pentane/Et_2O) providing 79 mg of **34** (90% yield, 93% conversion based on **33**) as a clear, colourless oil.

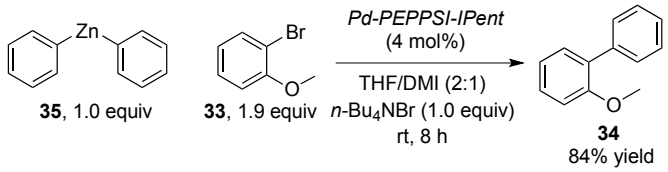
4.2.10 Negishi Coupling to Provide Table 7, Entry 5:



35, 1.0 equiv **33**, 1.9 equiv **34** 90% yield

In the glove box, freshly sublimed $Zn(Ph)_2$ (**35**, 55 mg, 0.25 mmol, 1.0 equiv.) was added to a flame-dried vial equipped with a stir bar, after which the vial was closed with a rubber septum and it was then removed from the glove box. The sealed vial was charged with argon and the contents dissolved in THF (2 mL) forming a clear, colourless solution. A clear, yellow THF solution (totaling 1 mL) containing *Pd-PEPPSI-IPent* (**3**, 8 mg, 0.01 mmol, 4 mol%), **33** (89 mg, 59 μL, 0.48 mmol, 1.9 equiv.), and $ZnBr_2$ (54 mg, 0.24 mmol, 1.0 equiv.) was added *via* syringe resulting in a visual change in the mixture's appearance from bright-yellow to dark-brown. The solution was left stirring 8 h at rt, at which time TLC analysis indicated complete consumption of starting material. The reaction mixture was concentrated on silica gel (1 g) *in vacuo* and the product was purified by flash chromatography (silica gel, 200:1 pentane/Et_2O) yielding 79 mg of **34** (90% yield, 94% conversion based on **33**) as a clear, colourless oil.

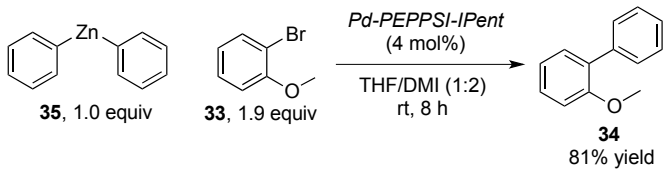
4.2.11 Negishi Coupling to Provide Table 7, Entry 6:



35, 1.0 equiv **33**, 1.9 equiv **34** 84% yield

In the glove box, freshly sublimed $Zn(Ph)_2$ (**35**, 55 mg, 0.25 mmol, 1.0 equiv.) was added to a flame-dried vial equipped with a stir bar, after which the vial was closed with a rubber septum and it was then removed from the glove box. The sealed vial was charged with argon and the contents dissolved in THF (2 mL) forming a clear, colourless solution. To this vial, a clear, yellow DMI solution (totaling 1 mL) containing *Pd-PEPPSI-IPent* (**3**, 8 mg, 0.01 mmol, 4 mol%), **33** (89 mg, 59 μL, 0.48 mmol, 1.9 equiv.) and *n*-Bu_4NBr (77 mg, 0.24 mmol, 1.0 equiv.) was added *via* syringe resulting in a visual change in the mixture's appearance from bright-yellow to dark-brown. The solution was left stirring 8 h at rt, at which time TLC analysis indicated the complete consumption of starting material. The reaction mixture was concentrated on silica gel (1 g) *in vacuo* and the product was purified by flash chromatography (silica gel, 200:1 pentane/Et_2O) yielding 73 mg of **34** (84% yield, 89% conversion based on **33**) as a clear, colourless oil.

4.2.12 Negishi Coupling to Provide Table 7, Entry 7:

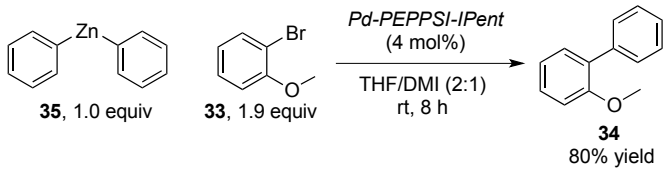


35, 1.0 equiv **33**, 1.9 equiv **34** 81% yield

In the glove box, freshly sublimed $Zn(Ph)_2$ (**35**, 55 mg, 0.25 mmol, 1.0 equiv.) was added to a flame-dried vial equipped with a stir bar, after which the vial was closed

with a rubber septum and it was then removed from the glove box. The sealed vial was charged with argon and the contents dissolved in THF (1 mL) forming a clear, colourless solution. To this vial, a clear, yellow DMI solution (totaling 2 mL) containing *Pd-PEPPSI-IPent* (**3**, 8 mg, 0.01 mmol, 4 mol%), **33** (89 mg, 59 μL, 0.48 mmol, 1.9 equiv.) was added *via* syringe resulting in a visual change in the mixture's appearance from bright-yellow to dark-brown. The solution was left stirring 8 h at rt, at which time TLC analysis indicated the complete consumption of starting material. The reaction mixture was concentrated on silica gel (1 g) *in vacuo* and the product was purified by flash chromatography (silica gel, 200:1 pentane/Et_2O) yielding 73 mg of **34** (84% yield, 88% conversion based on **33**) as a clear, colourless oil.

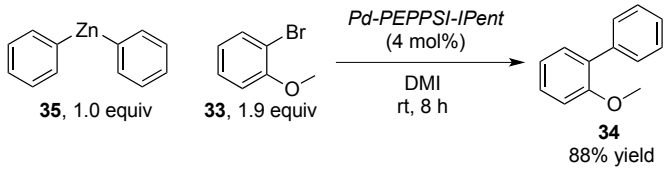
4.2.13 Negishi Coupling to Provide Table 7, Entry 8:



In the glove box, freshly sublimed $Zn(Ph)_2$ (**35**, 55 mg, 0.25 mmol, 1.0 equiv.) was added to a flame-dried vial equipped with a stir bar, after which the vial was closed with a rubber septum and it was then removed from the glove box. The sealed vial was charged with argon and the contents dissolved in THF (2 mL) forming a clear, colourless solution. To this vial, a clear, yellow DMI solution (totaling 1 mL) containing *Pd-PEPPSI-IPent* (**3**, 8 mg, 0.01 mmol, 4 mol%) and **33** (89 mg, 59 μL, 0.48 mmol, 1.9 equiv.) was added *via* syringe resulting in a visual change in the mixture's appearance from bright-yellow to dark-brown. The solution was left stirring 8 h at rt, at which time TLC analysis indicated the complete consumption of starting

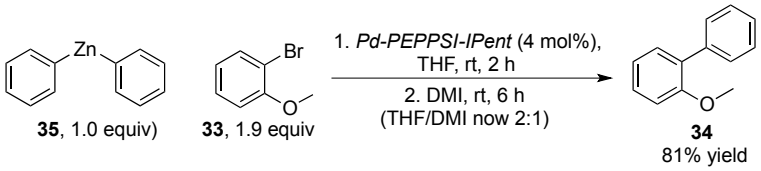
material. The reaction mixture was concentrated on silica gel (1 g) *in vacuo* and the product was purified by flash chromatography (silica gel, 200:1 pentane/Et_2O) yielding 70 mg of **34** (80% yield, 85% conversion based on **33**) as a clear, colourless oil.

4.2.14 Negishi Coupling to Provide Table 7, Entry 9:



In the glove box, freshly sublimed $Zn(Ph)_2$ (**35**, 55 mg, 0.25 mmol, 1.0 equiv.) was added to a flame-dried vial equipped with a stir bar, after which the vial was closed with a rubber septum and it was then removed from the glove box. The sealed vial was charged with argon and the contents dissolved in DMI (2 mL) forming a clear, colourless solution. To this vial, a clear, yellow DMI solution (totaling 1 mL) containing *Pd-PEPPSI-IPent* (**3**, 8 mg, 0.01 mmol, 4 mol%) and **33** (89 mg, 59 μL, 0.48 mmol, 1.9 equiv.) was added *via* syringe resulting in a visual change in the mixture's appearance from bright-yellow to dark-brown. The solution was left stirring 8 h at rt, at which time TLC analysis indicated the complete consumption of starting material. The reaction mixture was concentrated on silica gel (1 g) *in vacuo* and the product was purified by flash chromatography (silica gel, 200:1 pentane/Et_2O) yielding 77 mg of **34** (88% yield, 93% conversion based on **33**) as a clear, colourless oil.

4.2.15 Negishi Coupling to Provide Table 7, Entry 10:



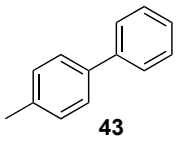
35, 1.0 equiv) **33**, 1.9 equiv **34** 81% yield

In the glove box, freshly sublimed $Zn(Ph)_2$ (**35**, 55 mg, 0.25 mmol, 1.0 equiv.) was added to a flame-dried vial equipped with a stir bar, after which the vial was closed with a rubber septum and it was then removed from the glove box. The sealed vial was charged with argon and the contents dissolved in THF (2 mL) forming a clear, colourless solution. To the vial, a clear, yellow THF solution (totaling 1 mL) containing *Pd-PEPPSI-IPent* (8 mg, 0.01 mmol, 4 mol%) and **33** (89 mg, 59 μL, 0.48 mmol, 1.9 equiv.) was added *via* syringe resulting in a visual change in the mixture's appearance from bright-yellow to light-orange. The solution was left stirring 2 h at rt, at which time TLC analysis indicated approximately one-half of the starting material was consumed. DMI (1.5 mL) was added *via* syringe and the reaction was further stirred for 6 h. At this time TLC analysis showed complete consumption of the starting material. The reaction mixture was concentrated on silica gel (1 g) *in vacuo* and purified by flash chromatography (silica gel, 200:1 pentane/Et_2O) yielding 71 mg of **34** (81% yield, 82% conversion based on **3**) as a clear, colourless oil.

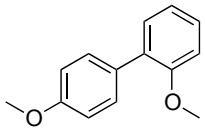
4.2.16 General Cross-Coupling Procedure for Scheme 21:

To a flame-dried, septum-sealed vial containing freshly prepared $Zn(Ar)_2$ (0.25 mmol, 1.0 equiv.) was added a clear, yellow THF solution (totalling 1 mL) containing *Pd-PEPPSI-IPent* (4 mg, 0.005 mmol, 2 mol%) and arylbromide (0.23 mmol, 0.9 equiv.), resulting in a visual change in the mixture's appearance from bright-yellow to dark-

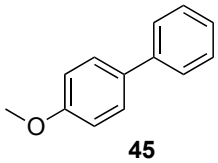
brown. The resulting solution was stirred at rt for 2 h under argon, and followed by TLC analysis. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (silica gel, using pentane/Et_2O: concentrations as indicated).


43

4-Methyl-1,1'-biphenyl, (**43**): Following the above general coupling procedure with $Zn(Ph)_2$ (**35**), 36 mg of **43** (92% yield, 95% conversion) were obtained after flash chromatography (200:1 pentane/Et_2O, R_f= 0.65) as a white solid. Mp: 46-48 °C (lit: 45-48 °C)[75]; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41 (t, *J* = 7.4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.27 (q, *J* = 7.5 Hz, 2H), 7.20-7.14 (m, 1H), 7.08 (d, *J* = 7.0 Hz, 2H), 2.23 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.1, 138.2, 136.9, 129.3, 128.6, 127.2, 127.1, 126.9, 21.0 ppm. Spectra and physical data are in agreement with the literature.[75]

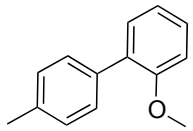

44

2,4'-Dimethoxy-1,1'-biphenyl, (**44**): Following the above general coupling procedure with *bis*-(2-methoxyphenyl)zinc (**37**), 26 mg of **44** (53% yield, 55% conversion based on arylbromide) were obtained after flash chromatography (50:1 pentane/Et_2O, R_f= 0.40) as a white solid. Following the above general coupling procedure with *bis*-(4-methoxyphenyl)zinc, 40 mg of **7** (81% yield, 82% conversion based on arylbromide) were obtained after flash chromatography (50:1 pentane/Et_2O, R_f= 0.40) as a white solid. Mp: 78-79 °C (lit: 72-74 °C);[75] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.6 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.05-6.96 (m, 4H), 3.86 (s, 3H), 3.83 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.5, 156.3, 130.8, 130.6, 130.5, 130.2, 128.1, 120.7, 113.4, 111.1, 55.4, 55.2 ppm. Spectra and physical data for compound **7** are in agreement with the literature.[75]



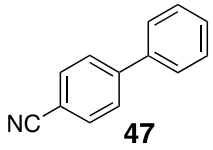
45

4-Methoxy-1,1'-biphenyl, (**45**): Following the general coupling procedure with $Zn(Ph)_2$, 42 mg of **45** (99% yield, 100% conversion based on arylbromide) were obtained after flash chromatography (50:1 pentane/Et_2O, R_f = 0.45,) as a white solid. Following the general coupling procedure with *bis*-(4-methoxyphenyl)zinc (**38**), 36 mg of **45** (85% yield, 86% conversion based on arylbromide) were obtained after flash chromatography (50:1 pentane/Et_2O) as a white solid. Mp = 87-88 °C (lit: 86-90 °C);[76] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 4H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 2H), 3.85 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.1, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.1, 55.2 ppm. Spectra and physical data for compound **45** are in agreement with the literature.[76]



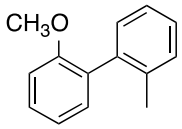
46

2-Methoxy-4'-methyl-1,1'-biphenyl, (**46)**: Following the general coupling procedure above with *bis*-(2-methoxydiphenyl)zinc (**37**), 30 mg of **46** (66% yield, 70% conversion) were obtained after flash chromatography (200:1 pentane/Et_2O, R_f = 0.60) as a white solid. Mp = 71-72 °C (lit: 73-74 °C);[77] ^{1}H-NMR (400 MHz, CD_2Cl_2) δ 7.44 (d, *J* = 7.9 Hz, 2H), 7.33-7.30 (m, 4H), 7.05-6.98 (m, 2H), 3.82 (s, 3H), 2.41 (s, 3H) ppm; ^{13}C-NMR (100 MHz, CD_2Cl_2) δ 156.4, 136.5, 135.5, 130.7, 130.6, 129.3, 128.7, 128.3, 120.7, 111.1, 55.5, 21.1 ppm. Spectra and physical data are in agreement with the literature.[77]



47

4-Phenylbenzonitrile, (**47**): Following the general coupling procedure with $Zn(Ph)_2$ (**35**), 37 mg of **47** (89% yield, 90% conversion) were obtained after flash chromatography (25:1 pentane/Et_2O, R_f= 0.35) as a white solid. Mp = 84-87 °C (lit: 85-87 °C);[78] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2 H), 7.68 (d, *J* = 8.1 Hz, 2H) 7.58 (d, *J* = 7.4 Hz, 2H), 7.48 (t, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.1 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 145.6, 139.1, 132.5, 129.0, 128.6, 127.6, 127.1, 118.8, 110.8 ppm. Spectra and physical data are in agreement with the literature.[78]



48

2-Methyl-2'-methoxybiphenyl, (**48)**: Following the general coupling procedure with *bis*-(2-Methylphenyl)zinc **(36)**, 9 mg of **48** (20% yield, 20% conversion) were obtained after flash chromatography (100:1 pentanes/Et_2O, R_f= 0.55), as a white solid, Mp = 69-71 °C (lit: 74-76 °C);[79] ^{1}H-NMR (400 MHz, CD_2Cl_2) δ 7.49 (d, *J* = 8.6 Hz, 2 H), 7.31 (t, *J* = 5 Hz, 2H), 7.05-6.96 (m, 4H), 3.86 (s, 3H), 3.83 (s, 3H) ppm. ^{13}C-NMR (100 MHz, CD_2Cl_2) δ 156.4, 138.7, 136.5, 135.5, 130.7, 130.0, 129.3, 128.7, 128.3, 125.5, 120.7, 111.1, 55.5, 21.1 ppm. Spectra and physical data are in agreement with the literature.[79]

PART II: LARGE SCALE SYNTHESIS OF NHC PRECURSORS: 2,6-DI(3-PENTYL)ANILINE AND 2,6-DI(4-HEPTYL)ANILINE

Chapter 5:
Introduction and General Background

5.1 The Use of Ancillary Ligands in Catalyst Design

5.1.1 Phosphine Ligands: An Introduction to Ancillary Ligands

In catalysis, ancillary ligands are important for the fine-tuning of the steric and electronic parameters of metal centres. Significant value has been placed on understanding how these parameters can be modified to exploit the requirements of the elementary steps of a catalytic cycle. Such an understanding has helped chemists predict and design new ligands that are best suited for specific cross-coupling reactions. Phosphines, most notably PPh_3, belong to a longstanding family of ancillary ligands used in a wide range of catalytic applications, making these a go-to reagent for many chemists in the field of cross-coupling. The reactivity of many metal complexes towards organic molecules is heavily influenced by the electronic properties of the metal. Many σ-donating phosphines such as PPh_3, that when used in transition metal mediated cross-coupling causes the centre of the transition metal complex to become increasingly rich with electron density and allows the process of OA to be much more greatly favoured (see Figure 1). The large cone of the triphenyl groups assist the transition metal complex to undergo RE of the coupling partners and aid in promotion of this step by influencing the steric environment about the metal centre. Although phosphines are perhaps the most widely used family of ancillary ligands in palladium catalysis, there are a number of concerns that arise with their use. Phosphines, specifically alkylphosphines, require special handling because they are pyrophoric in nature and will easily oxidize in air. Their use is generally limited to applications in an inert atmosphere where the use of a glove box or desiccator is generally required for their storage. Once bound, the steric bulk of the ligand is pointed away from the metal

centre preventing optimal 'steric shielding' of the metal. Since the steric bulk is pointed away from the metal, there is arguably little influence from the sterics of the ligand on the metal throughout the catalytic cycle. For this reason, the electronic influence rather than the steric influence of phosphines is often considered to be of greater importance.

Phosphines are typically considered to be strong σ-donors, however their tendency to stay bound to the metal centre throughout the catalytic cycle is inconsistent, particularly after the process of oxidative addition from Pd(0) to Pd(II) that results in the electron density becoming removed from the metal.[80] Thus the influence of phosphine ligands on the Pd centre is not consistent throughout cross-coupling mechanism. NHCs, ligate much more strongly with most transition metals relative to phosphines.[81]. Though phosphine-based ligands have been investigated as promoters of cross-coupling reactions for a longer period of time the favourable attributes to using newer, NHC catalysts cannot be ignored .[82]

5.1.2 A Brief Summary of the Evolution N-Heterocyclic Carbene (NHC)

NHC ligands are nitrogen-based and typically 5 membered heterocycles that are most often derived from the imidazole and the imidazolidine family (see Figure 19). Several examples of early NHC are outlined in Figure 20. The first use of NHC ligands for transition metal complexes was reported almost 60 years ago by Öfele[83] and Wanzlicke, although their synthetic use was limited.[84] These new compounds were purported to be mimics of phosphines. This attribute of NHCs inevitably lead to their evolution as useful organic molecules in synthesis for a wide variety of chemical transformations, including cross-coupling.[85]. In 1991, Arduengo's work of isolating the

first, free NHCs, led to synthetic strategies that furthered their preparation and development.[86] As ligands, NHCs have proven to be superior σ-donors to phosphines making the steric and electronic influence of NHCs on the Pd metal centre more consistent than their bulky phosphine ligand counterparts especially throughout the cross-coupling mechanism.[87,88] This advantage is attributed to the thermal stability of the NHC-Pd bond.[89] The electron rich NHC ligand helps the Pd centre to remain bound longer relative to phosphine ligands. This increase in binding activity of the catalyst to the ligand allows the complex to last longer during the reaction (a higher TON) and it allows for more consistent reactivity throughout the reaction.

Figure 19. Various 5-membered N-heterocyclic carbenes

5.1.3 NHC Based Catalysts in Cross-coupling Reactions

Initially, bulky R-group alkyl substituents of the nitrogen in NHCs (such as IAd, I*t*Bu and ICy) have been ligated to a Pd centre and studied (see Figure 20). However, these complexes were found to have poor catalytic activity, if any. Subsequently, Organ and co-workers have studied several aryl R-group substituents and the effects of increasing the steric bulk about the metal centre by modifying the ortho substituents and found this series to be of far greater value in organic transformations (such as IMe, IPr, IMes, ICPent, IPent and IHept).[90]

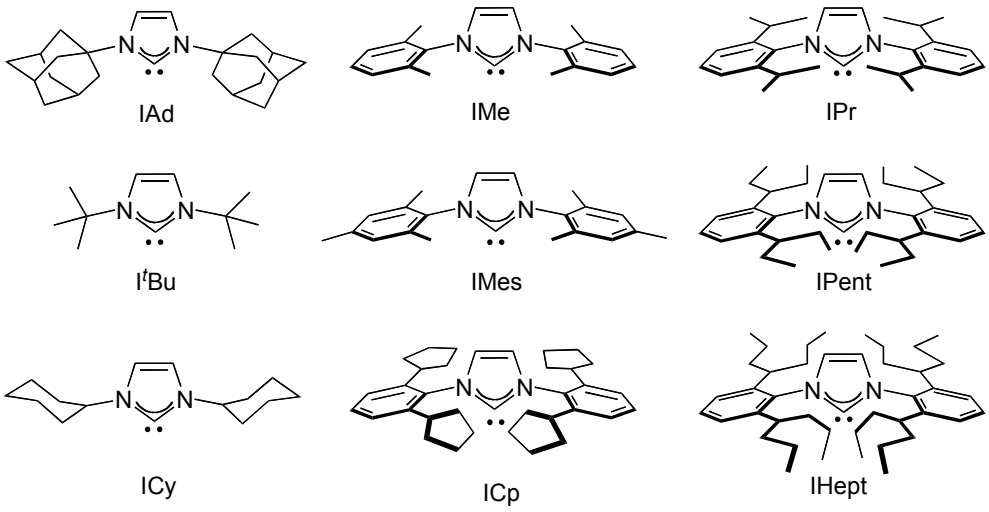


Figure 20. Highlighted imidazolidine based carbenes

This series of sterically demanding, mono-ligated NHC, Pd-based pre-catalysts, called *Pd-PEPPSI* (**P**yridine-**E**nhanced **P**re-catalyst **P**reparation **S**tabilization and **I**nitiation), have shown heightened reactivity and selectivity in various types of cross-coupling reactions. The heightened activity of these pre-catalysts can be attributed to their steric and electronic tunability. Selected examples of Pd-PEPPSI pre-catalysts are provided in Figure 21.

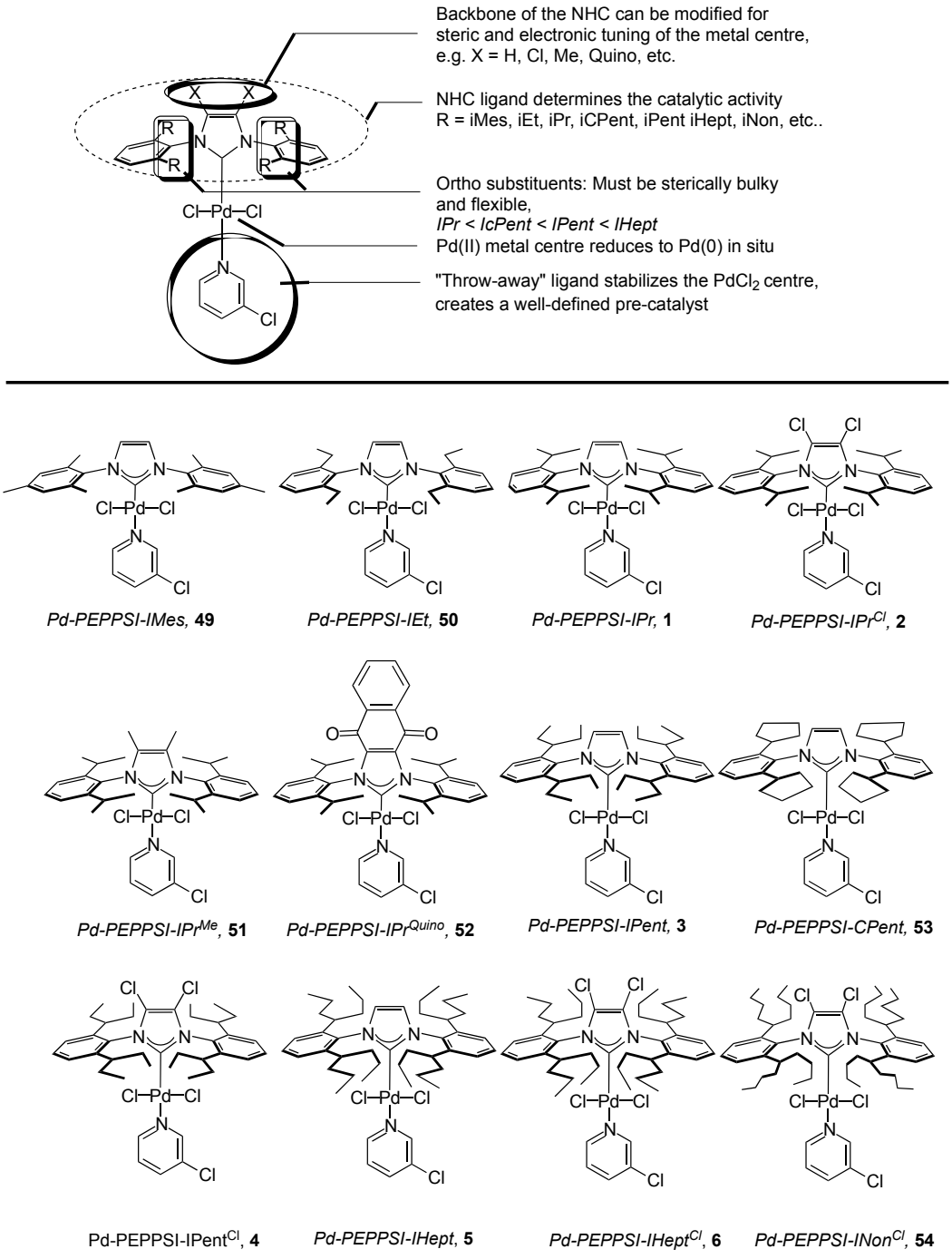


Figure 21. Selection of examples of *Pd-PEPPSI* pre-catalysts

In terms of tunability the most important aspects of the catalyst are attributed to the tuning of the NHC moiety. Of these are 1) the NHC ligand's ortho-aryl substituents, and 2) NHC backbone substitution.

5.1.4 The Structure Activity Relationship in Pd-PEPPSI Pre-catalysts

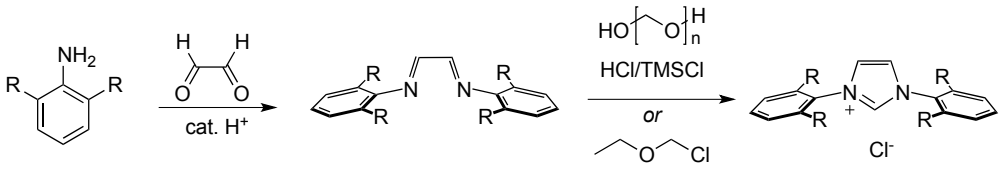
In a series of publications, *PEPPSI* based pre-catalysts were evaluated in Suzuki-Miyaura,[91] Kumada-Tamao-Corriu,[45b] Buchwald-Hartwig amination[92] and Negishi[93] reactions. A trend was established from these results indicating that as the bulk around the Pd metal centre increased, as did its catalytic activity and conversion of the starting materials to the desired products. Reactions that called for *PEPPSI-IPr* (**1**) resulted in much higher yields than reactions that used *PEPPSI-IMes* (**49**) or *PEPPSI-IEt* (**50**). Of these catalysts, **3** has been given significant attention for its superior performance in Suzuki-Miyaura,[94] Negishi,[63b,95] Stille-Migita,[96] and Buchwald-Hartwig[97] cross-coupling reactions. The trend of reactivity as a function of increased steric bulk from the *ortho*-aryl substituents has been well established for the *PEPPSI* complexes (i.e. IMe < IEt < IPr <IPent < IHept). Interestingly, when comparing the activities of **3**, **5**, **53** and **54**, an important structure-activity relationship was observed. First, *Pd-PEPPSI* complexes **3** and **53** were evaluated for their activity in Suzuki-Miyaura cross-coupling reactions. The results revealed that **3** was much more active than **53** despite the fact that the NHC *ortho*-alkyl substituents were almost identical (cyclopentyl vs. 3-pentyl). This result is consistent with the work of Glorius and co-workers that suggest that NHC substituents must be both bulky and flexible.[98] Second, by further increasing the size of the ortho-substituent from 3-pentyl (**3**) to 4-heptyl (**5**) to 5-nonyl (**54**), less significant increases in reactivity were observed indicating that reactivity as a function of increasing steric bulk had plateaued. Thus, further increasing the bulk of the ortho-aryl substituents would result in no increase of catalytic activity.[99]

5.1.5 The Effect of NHC Backbone Modification

Given the similar activity of catalysts **3** and **5**, Organ and co-workers set out to modify the catalyst elsewhere on the NHC core. Thus, the NHC backbones of several *Pd-PEPPSI* pre-catalysts were modified with substituents such as halogens and methyl groups to evaluate the change in the steric and electronic nature of the metal. Backbone modified NHC precursors IPr^{Cl}, IPr^{Me}, IPr^{Quino}, $IPent^{Cl}$, $IHept^{Cl}$ and their respective corresponding *Pd-PEPPSI* complexes were prepared in order to evaluate their catalytic activity in cross-coupling chemistry. It was determined that the addition of substituents on the backbone of the NHC resulted in a metal centre that was more sterically hindered and thus, more reactive *and* selective.[100] Generally, the substitution of a Cl gave rise to a pre-catalyst that was more reactive than the Me substituted backbone. Of these, *Pd-PEPPSI-IPent*^{Cl} (**4**) and *Pd-PEPPSI-IHept*^{Cl} (**6**) had been identified by Organ as the most reactive pre-catalysts for far, especially for the challenging secondary alkyl-alkyl Negishi cross-coupling reaction. As several variations of the *PEPPSI* complexes have been synthesized, there have been several improvements to the synthesis to access these pre-catalysts. The synthesis for these complexes requires the preparation of a 2,6-disubstituted aniline followed by a condensation, a ring closing event, and finally, the ligation of the NHC salt itself to the $PdCl_2$ metal centre.

5.1.6 Assembly of the Imidazolium Salt

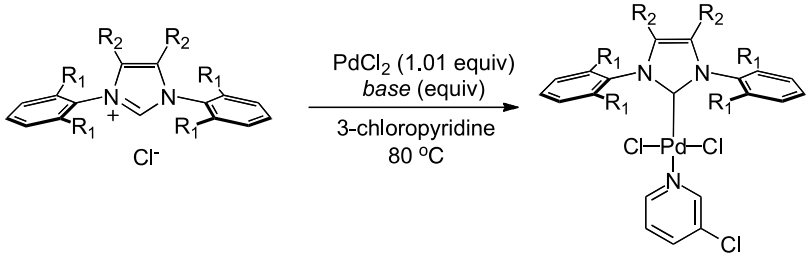
Once the 2,6-dialkyl-aniline is assembled, an acid catalyzed condensation followed by an acid-mediated ring-closing event can easily generate the imidazolium salt (see Scheme 23).



Scheme 23. Acid mediated condensation followed by formation of the imidazolium salt

Once the respective NHC salt is prepared, the ligation to the metal centre is performed simply in the presence of an excess of mineral base such as cesium carbonate (see Table 8).

Table 8. Ligation of $PdCl_2$ with various imidazolium salts en route to *Pd-PEPPSI* pre-catalysts



<u>*Pd-PEPPSI* Pre-catalysts</u>

IPent, (**3**) R_1 = i-pentyl R_2 = H
$IPent^{Cl}$, (**4**) R_1 = i-pentyl R_2 = Cl
IHept, (**5**) R_1 = i-heptyl R_2 = H
$IHept^{Cl}$, (**6**) R_1 = i-heptyl R_2 = Cl

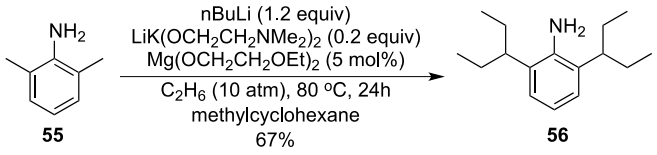
Entry	R_1	R_2	Base	% Yield
1	*i*Pr	H	$CsCO_3$	86
2	*i*Pr	Cl	K_2CO_3	81
3	*i*Pent	H	$CsCO_3$	84
4	*i*Pent	Cl	$CsCO_3$	81
5	*i*Hept	H	$CsCO_3$	70
6	*i*Hept	Cl	$CsCO_3$	55

The most recently employed synthesis of 2,6-dialkylanilines required to prepare the *Pd-PEPPSI* NHC ligands leaves room for improvement. Though the anilines have

been successfully prepared[101] in hundred gram batches despite the impracticalities of various steps of the synthesis.

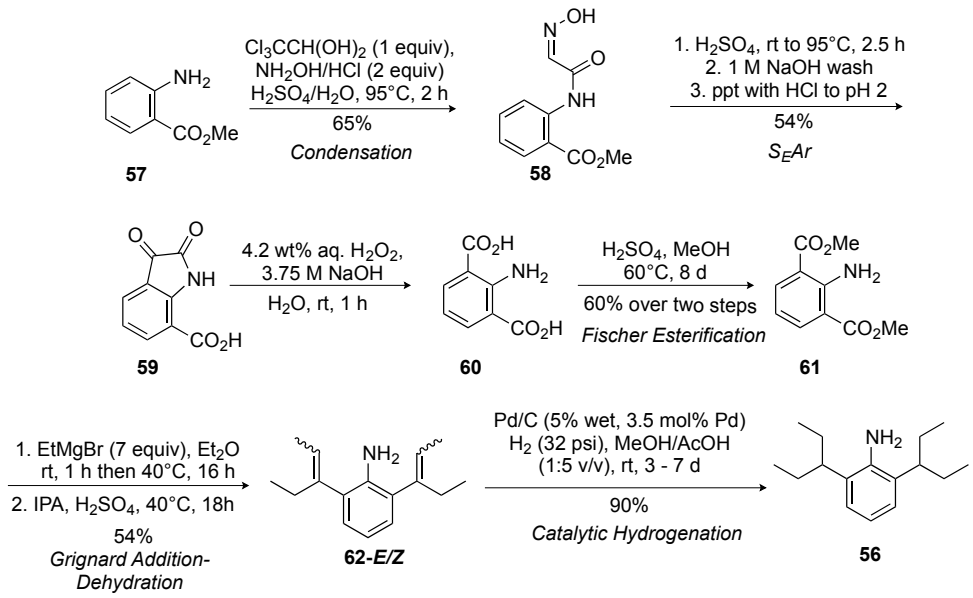
5.1.7 The Challenges and Improvements in the Synthesis 2,6-Dialkylanilines

Arguably, the most challenging step in the synthesis of Pd-PEPPSI complexes is the synthesis of the 2,6-dialkyl aniline, from which all NHC precursors are constructed. The only literature precedent for the preparation of **56** was reported in 2007 by Steele and co-workers. This synthesis involves a benzylic deprotonation followed by alkylation of inexpensive 2,6-dimethylaniline using the superbase BuLi/LiK($OCH_2CH_2NMe_2$)$_2$ under an atmosphere of ethylene (see Scheme 24).[102] This high-pressure step limits the scalability of the reaction by introducing considerable safety issues and the need for highly specialized reaction apparatus. As a result of these concerns, other options were explored.



Scheme 24. Steele and co-workers' route to synthesis of 2,6-di(3-pentyl)aniline (**56**) from 2,6-dimethylaniline (**55**)

In 2009, a more operationally practical synthesis of 2,6-di(3-pentyl)aniline was developed beginning with inexpensive and readily available methyl anthranilate (see Scheme 25). In the first step the sulfuric acid promoted the condensation of **57** with chloral hydrate and H_2NOH•HCl providing **58**. Treatment of this hydroxyimine with sulfuric acid initiated an intramolecular Friedel-Crafts reaction, to provide 2-carboxyisatin (**61**) after a subsequent hydrolysis step.



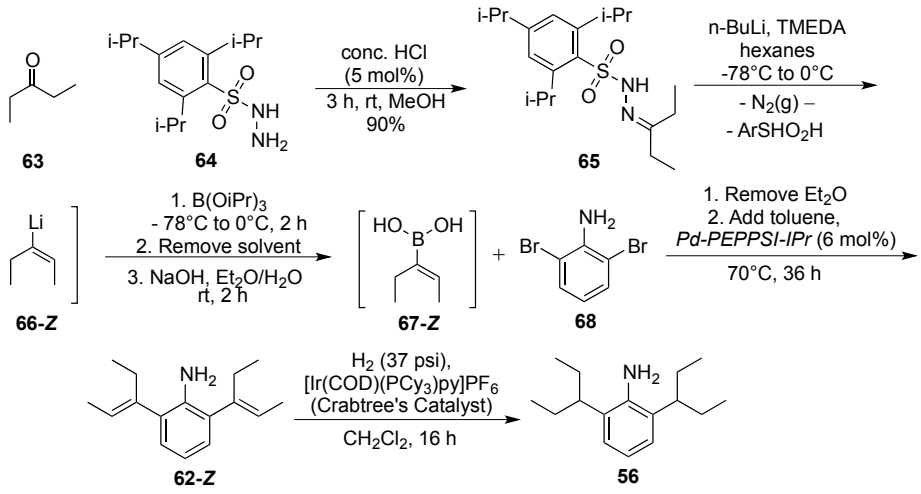
Scheme 25. Synthesis of 2,6-di(3-pentyl)aniline (**56**) using a Grignard addition[103]

Bayer-Villager oxidation of **59** followed by base promoted hydrolysis yielded the diacid **60**, which subsequently esterified to the dimethylester using Fischer's protocol to give **61** in good yield. The ester underwent exhaustive Grignard addition followed by Pd mediated hydrogenation to yield the 2,6-disubstituted aniline **62-*E/Z***. Though this provided a multi-gram synthetic route to acquire access to the aniline, the extended time to complete the synthesis (20 days) and the difficulties in the purification of intermediates led to poor reproducibility, especially in the hydrogenation step.

Organ and co-workers looked to construct the 2,6-di(3-pentylanililine) (**56**) synthetic unit by implementing a C(sp^2)-C(sp^2) Suzuki-Miyaura cross-coupling reaction between the alkenyl boronic acid **67-*Z*** and commercially available 2,6-dibromoaniline (**68**). Even though several steps were required to synthesize **67-*Z*** alone, the reaction addressed the safety concern associated with running a large scale reaction at 10 atm

(or nearly 150 psi) that Steel and co-workers had reported or performing the exothermic Grignard addition on large scale.

To prepare the aniline, an *in situ* Shapiro-Suzuki sequence in which the hydrazone was converted to an alkenylboronic acid through the alkenyllithium **66-*Z*** was strategized (see Scheme 26). Next, the cross-coupling of **67-*Z*** to the 2,6-dibromoaniline (**68**) generated the unsaturated aniline (**62-*Z*)**. The reduction of trisubstituted alkene was accelerated with the use of Crabtree's catalyst under an elevated pressure of hydrogen gas to afford **56**.

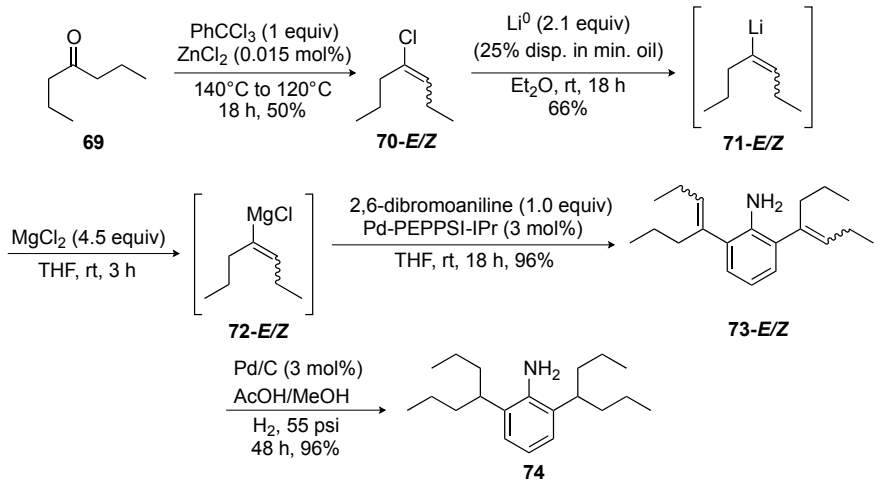


Scheme 26. Synthesis of 2,6-di(3-pentyl)aniline (**56**) using Suzuki-Miyaura cross-coupling[104]

Though the Organ group had discovered a new synthesis of 2,6-di(3-pentyl)aniline, the synthesis shown above caused concerns due to the cost of the reagents. To proceed with a kilogram scale-up would be prohibitively expensive due to the use of Crabtree's catalyst (Sigma-Aldrich, $404/g). Furthermore, the purification of intermediates in between steps was challenging and the reactions typically exhibited poor atom economy. More importantly, was the safety concern associated with the rapid evolution

of nitrogen gas and as the low temperature required for the Shapiro reaction. In light of these opportunities for improvement, Organ and co-workers explored another, more cost-effective synthetic route.

Organ and co-workers have moved to evaluating the formation of the alkenyl species *via* transmetalation from the respective alkenyllithium en route to 2,6-di(4-heptyl)aniline shown in Scheme 27. The transformation from **69** to **73-*E/Z*** proceeds *via* the exothermic S_N2 reaction involving a Grignard reagent and a low (3 mol%) *Pd-PEPPSI-IPr* loaded Kumada-Corriu cross-coupling reaction.



Scheme 27. Synthesis of 2,6-di(4-heptyl)aniline (**74**) using a *Pd-PEPPSI* mediated Kumada-Tamao-Corriu coupling of alkenylmagnesium (**72-*E/Z*)** [105]

Albeit high-yielding, the hydrogenation event to produce the 2,6-disubstituted aniline is still required in the synthesis presented in Scheme 27. Though catalytic hydrogenation is one of the most commonly practiced reactions in industry, the safety controls on a large scale are well established. Hydrogenation in an academic laboratory, especially on a kilogram scale at elevated pressure of material presents the risk of

explosion. If we could perform an efficient secondary alkyl-aryl cross-coupling reaction between 3-pentyl or 4-heptyl moieties with 2,6-dibromoaniline we could effectively eliminate the need for the hydrogenation step.

5.1.8 Pd-PEPPSI Pre-catalysts and Secondary Alkyl Cross-coupling

Perhaps the most significant advantage of the NHC backbone-modified Pd-PEPPSI based pre-catalysts is its selectivity in the coupling of secondary alkyl fragments. Pd-catalyzed cross-coupling of secondary alkyl nucleophiles remains one of the most expedient and atom-economical techniques for preparing substrates bearing secondary alkyl substitution.[106] However, the regiochemical outcome of these cross-coupling reactions continues to be the major pitfall of this strategy. Until recently, the suppression of undesirable side-reactions has been difficult to control, and very few examples have been reported that have successfully suppressed undesired rearrangement.[107] Among these, Buchwald and co-workers employed the CPhos ligand to overcome these undesired reactions. Though several examples exist for the Negishi cross-coupling of primary alkyl substituents, these techniques do not translate when a secondary organozinc is employed.[108] As highlighted in Figure 22, the process of alkyl rearrangement occurs after TM and prior to RE. This side-reaction occurs as a result of BHE followed by migratory insertion MI. If the rate of RE is slow enough, BHE can predominate to form **D**. Once **D** is formed, it is more energetically favourable for MI to proceed and leads to the formation of **E**, the linear product, than for **C** to reform. Thus, if RE is slow, predominantly **E** is formed, which leads to

irreversible formation of the linear product $\mathbf{P_L}$. However, if RE is fast, regiochemical retention is observed and the favoured branched product, $\mathbf{P_B}$, forms.

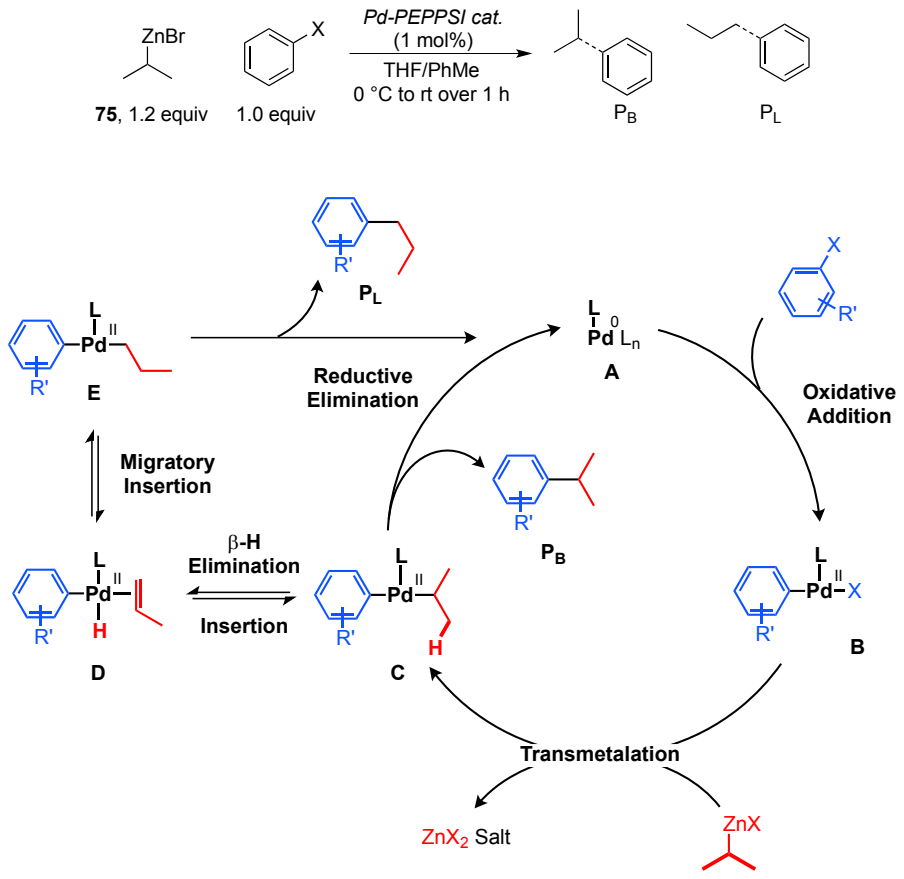
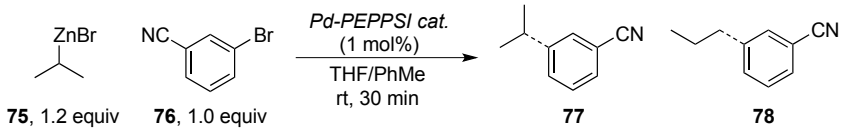


Figure 22. General mechanism for the Negishi cross-coupling of 2-propylzinc bromide (**75**)

The Organ group has recently evaluated the *Pd-PEPPSI* family of pre-catalysts in an attempt to capitalize on the unique steric topology of NHC ligands, however these studies showed that both *Pd-PEPPSI-IPr* and *Pd-PEPPSI-IPent* were both inferior to CPhos.[65] Pompeo and Organ evaluated the catalytic activity of the back-bone modified pre-catalysts **1**-**4**, **51** and **52** and observed both heightened reactivity and selectivity in the cross-coupling of secondary alkyls nucleophiles were observed (see Table 9).[65a] In

the reaction studied, 2-propylzinc bromide **75** was treated with aryl halide **76**, and though the yields were all roughly similar, the most important criteria was the relative amount of branch product **77**, versus the migratory inserted product **78**. *Pd-PEPPSI-IPr* (Entry 1) showed no preference for the immediate RE path (which leads irreversibly to **77**) versus the secondary BHE-MI path (leading to **78**). Increasing the steric bulk of the NHC ligand by switching to IPent (a catalyst with bulkier *ortho*-aryl R-groups on the NHC portion of the *Pd-PEPPSI* complex) and placing a substituent on the NHC backbone improves selectivity for the non-isomerized product in particular for the IPent^{Cl} pre-catalyst (Entries 2-6).

Table 9. Selectivity evaluation of several *Pd-PEPPSI* pre-catalysts[a]

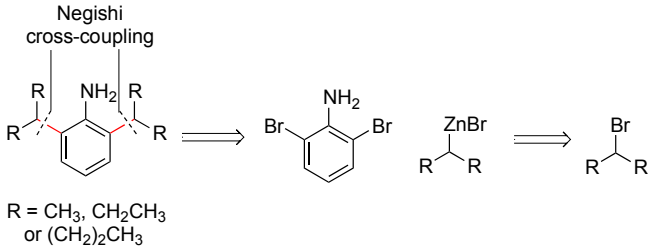


Entry	*Pd-PEPPSI* Complex	Yield (%)	**77**:**78**
1	IPr (**1**)	82	1:1.4
2	IPr^{Cl} (**2**)	81	15:1
3	IPr^{Me} (**51**)	70	15:1
4	IPr^{Quino} (**52**)	78	13:1
5	IPent (**3**)	66	11:1
6	IPent^{Cl} (**4**)	81	61:1

[a] The ratio of inseparable isomers was determined by ^{1}H-NMR spectroscopy after purification by flash chromatography. These results were repeated in duplicate and the average of the two runs are reported here.

5.1.9 Plan of study

Supported by the effectiveness of *Pd-PEPPSI-IPent*^{Cl} (**4**) in the cross-coupling of secondary alkylzincs, we hope to apply this strategy to the synthesis of the NHC precursors **56** and **74** from 2,6-dibromoaniline (**68**). If **4** is sufficiently reactive and selective in secondary alkyl-alkyl coupling, such that it can provide the branched product without any traces of the isomerized side-products, then we can simplify the synthesis of complexes **4** - **6** by eliminating the need for the hydrogenation step. For this, we would attempt to exhaustively couple both of the arylhalide centres one-pot (see Scheme 28). If successful, an obvious advantage would be a new and efficient synthetic route towards 2,6-dialkylanilines with fewer concerns for cost and safety. However, if unsuccessful, the cross-coupling reaction will lead to an inseparable mixture of isomers.



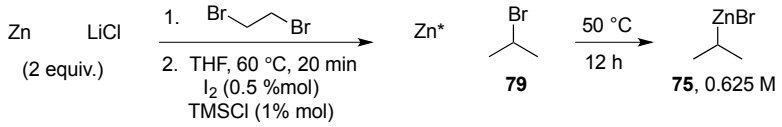
Scheme 28. Retrosynthetic analysis en route to 2,6-di(4-alkyl)anilines

5.2 Results and Discussion

*5.2.1 Towards the Synthesis of 2,6-Diisopropylaniline, (**80**)*

The coupling of 2-propylzinc bromide (**75**) is actually the most challenging secondary organometallic to cross-couple selectively as there are the maximum number of hydrides possible to allow for BHE to occur and thus, the rearranged linear product. To make this substrate more challenging would be the formation of the energetically favoured, 1° alkyl-metal species, which would lead to the BHE-MI product (**82**). Thus, if a catalyst could cleanly produce a single isomer of non-migratory insertion products in the cross-coupling of 2-propylzinc bromide and an arylhalide, this would be an excellent indicator to confirm the feasibility of this transformation to access 2,6-di(3-pentyl)aniline (**56**) and 2,6-di(4-heptyl)aniline (**74**).

Since 2-propylzinc halide (**75**) would be the most difficult to couple selectively we began our evaluation of the new synthetic protocol using this model. A modified version of the Knochel procedure for preparation of secondary organozincs was used to prepare **75** (See Scheme 29).[42,109]

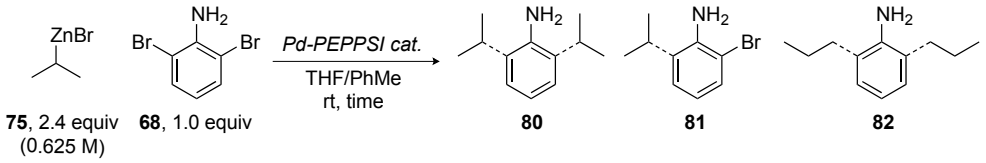


Scheme 29. The preparation of *2*-propylzinc bromide (**75**) and its titre.

With **75** in hand we subjected the organometallic to an initial screening (see Table 10). Initially we noted that *Pd-PEPPSI-IPent*^{Cl} provided an inseparable mixture of the linearized and branched product. However, in the presence of *Pd-PEPPSI-IHept*^{Cl}, we

observed excellent conversion of **75** to the bis-coupled product **80** with no formation of the linearized product when the appropriate conditions were used (Entries 2 and 3).

Table 10. Initials results coupling 2-propylzinc bromide (**75**) with 2,6-dibromoaniline (**68**)



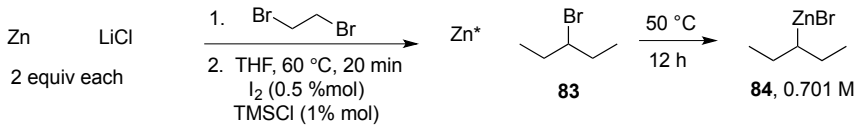
Entry	Pd-PEPPSI cat.	Catalyst Loading (mol %)	Time (h)	Conversion[a] (%)	**80**:**81**:**82**
1	**4**	2	2	100	1:0:1
2	**6**	1	12	90	9:1:0
3	**6**	3	1	100	1:0:0

[a] Conversions and ratio of **80**:**81**:**82** are determined by ^{1}H-NMR spectroscopic analysis. No isomerized product was observed by ^{1}H-NMR spectroscopy and GC/MS in entries 2-3.

With this result in hand, we turned our attention to the 3-pentylzinc bromide (**84**) preparation in hopes of observing complete conversion of the starting material to 2,6-di(3-pentyl)aniline (**56**). The 3-pentylzinc bromide (**84**) was prepared the same way as in the case of 2-propylzinc bromide (**75**), which was titred using iodometric titration to determine its concentration.

*5.2.2 Preparation of 2,6-Di(3-pentyl)aniline (**56**)*

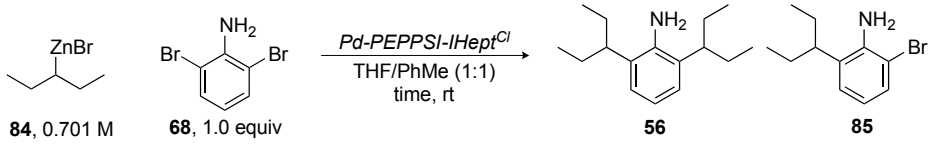
Next, **84** was prepared using the same procedure as **75** (see Scheme 30).



Scheme 30. Preparation of 3-pentylzinc bromide (**84**)

With a conversion of **83** to the organozinc that was comparable to that of **79**, we now had sufficient quantities of 3-pentylzinc bromide (**84**) to begin the cross-coupling optimization. The organozinc **84** was coupled with 2,6-dibromoaniline (**68**) at rt with various catalyst loadings and with varying equivalence of the organozinc species (see Table 11). An excess of the organozinc (roughly 3.0 equivalents) were necessary to obtain complete conversion of the starting bromide to the decoupled product (Entry 3) as less than this provided incomplete conversions of **57** (Entries 1 and 2). In all of the cases evaluated, none showed any instances of isomerization and reflected complete regiocontrol of the products when *Pd-PEPPSI-IHept*^{Cl} was used.

Table 11. Coupling 3-pentylzinc bromide (**84**) with 2,6-dibromoaniline (**68**)



84, 0.701 M **68**, 1.0 equiv **56** **85**

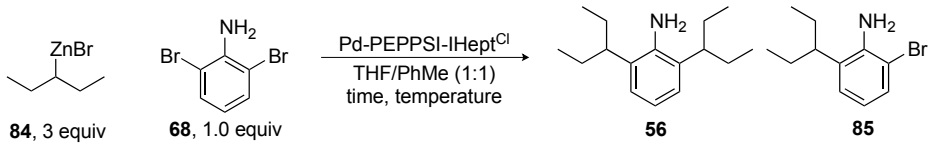
Entry	Equivalents of **84**	Catalyst Loading (mol %)	Time (h)	Conversion[a] (%)	**56**:**85**
1	2.4	1	12	100	9:1
2	3.6	1	3	100	95:5
3	3.0	2	1	100 (95%)	1:0

[a] Results are based on a 50 mg scale of aniline **68**; Conversions and ratio of **56**:**85** are determined by ^{1}H-NMR spectroscopic analysis. No isomerized product was observed by ^{1}H-NMR spectroscopy or GC/MS analysis

These were the conditions used for templating the 1 gram scale for coupling **84** and **68** (see Table 12). With 1 gram of substrate it was noted that 2 mol% of catalyst at room temperature was insufficient to completely convert the starting material to the di-coupled product **51** (see Table 12, Entry 1). At room temperature, with 3 mol% of catalyst added complete conversion of the starting dibromide (**68**) was observed (Entry 2). Lastly, by gentle heating to 40°C, 2 mol% catalyst was again sufficient to

completely convert the dibromide (**68**) to the di-coupled product (**56**) with no isomerization detected by ^{1}H-NMR spectroscopy or GC/MS (Entry 3).

Table 12. A 1 g scale coupling of 3-pentylzinc bromide (**84**) with 2,6-dibromoaniline (**68**)



84, 3 equiv **68**, 1.0 equiv **56** **85**

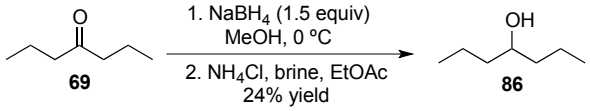
Entry	Equiv of **84**	Catalyst Loading (mol %)	Temp. (°C)	Time (h)	Conversion[a] (%)	Yield[b] (%)	**56**:**85**
1	3.0	2	22	24	100	-	3:1
2	3.0	3	22	2	100	98	1:0
3	3.0	2	40	2	100	95	1:0

[a] Based on a 1 g scale of aniline **68**; Conversions and ratio of **56**:**85** are determined by ^{1}H-NMR spectroscopic analysis. No isomerized product was observed by ^{1}H-NMR spectroscopy and GC/MS. [b] Determined after evaporation of solvent, filtration through a pad of silica, washing with hexane.

*5.2.3 Preparation and Optimization Studies of 2,6-Di(4-heptyl)aniline (**74**)*

Considering the synthesis of the IHept/IHept^{Cl} immidazolium salt precursor at large scale, we could not use 4-bromoheptane as a commercially available starting material, due to its prohibitive cost and very limited commercial offering. To this end we developed the preparation of **88** from 4-heptanone, which is widely available and very inexpensive.

Reduction of **69** with sodium borohydride lead to a disappointing 24% recovery of alcohol **86** (see Scheme 31).

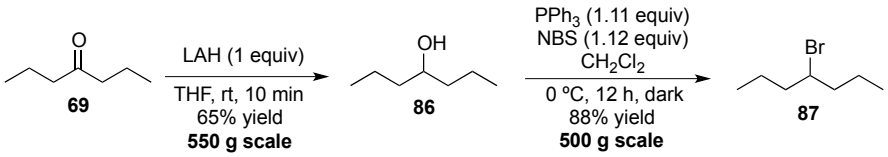


69 **86**

Scheme 31. Reduction of 4-heptanone (**69**) with sodium borohydride

Although the workup must be done with caution, we found that lithium aluminum hydride gave access to the alcohol in good yield on a 550 mL scale. Next, we treated

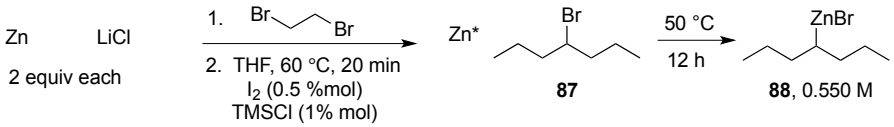
the alcohol with N-bromosuccinimide in the presence of triphenylphosphine to yield 88% of 4-bromoheptane (**87**) on a 500 g scale using a modified version of the Appel reaction (see Scheme 32).[110]



Scheme 32. Synthesis of 4-bromoheptane (**87**) from 4-heptanone (**69**)

Next, the organozinc was prepared as a 0.550 M solution in THF using the Knochel procedure (see Scheme 33). [42] Iodometric titration revealed that approximately 50% of the organozinc was formed.[111] Analysis of an aliquot of quenched product into heptane indicated that the remainder of the mass balance was unreacted bromide (**87**). Neither using different sources of zinc such as finer mesh (smaller particle size) nor altering the reaction time, temperature, order of addition, concentration had any effect on increasing the conversion. Fortunately, this titre did not decline when the procedure was scaled up. Once prepared and with suitable storage under static argon, a 500 g batch of **88** could be stored for months with negligible effect on the solution's titer.

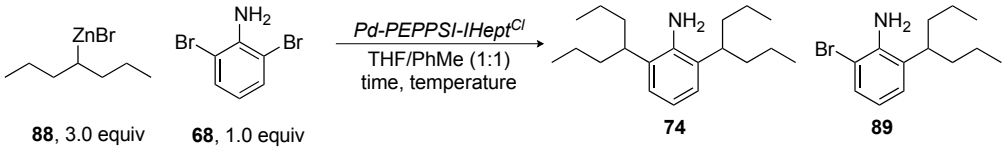
The preparation of 4-heptylzinc bromide (**88**) was performed using a modified version of Knochel's procedure.[107a, 106a] The iodometric titre was 0.550 M, the lowest observed for the secondary alkyl organozincs in this work (see Scheme 33).



Scheme 33. The preparation of 4-heptylzinc bromide, **88**, on a 500 g scale

With large quantities of **88** in hand, we evaluated the effect of catalyst loading and temperature on the cross-coupling reaction with **68** (see Table 13). We observed that at rt, we could easily obtain complete conversion of **68** to **74** after 16 h, using 3 mol% *Pd-PEPPSI-IHept*^{Cl} (Entries 1-4). Given this promising result, we hoped to be able to reduce the catalyst loading to achieve the same conversion by simply extending the reaction time. However, at catalyst loading of 1 mol%, an equimolar mixture of **74** and **89** was isolated after a reaction time of 7 days (Entry 5). Increasing both the catalyst loading to 2 mol% and the temperature to 50°C was sufficient to achieve full conversion of **68** to **74** after only 12 h (Entry 7) whereas the same reaction at rt led to only 90% conversion to **74** after 16 h (Entry 6). Interestingly, the reaction had completed by 90% after only 1 hour, and even with heating, we failed to obtain the desired product in quantitative conversion (Entries 8-10).

Table 13. Optimization of catalyst loading and temperature for a 50 mg scale cross coupling with 4-heptylzinc bromide (**88**) and 2,6-dibromoaniline **(68**)



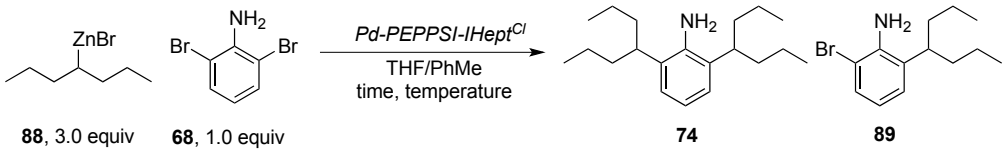
88, 3.0 equiv **68**, 1.0 equiv **74** **89**

Entry	Catalyst Loading (mol %)	Temperature (°C)	Time (h)	Conversion[a] (%)	**74**:**89**
1	3	22	1	100	3:2
2	3	22	2	100	4:3
3	3	22	3	100	4:1
4	3	22	16	100	1:0
5	1	22	7 days	100	1:1
6	2	22	16	100	9:1
7	2	50	12	100	1:0
8	2	50	1	100	9:1
9	2	60	1	100	9:1
10[b]	2	90	10 min	100	0

[a] Conversions and ratio of **74:89** are determined by ^{1}H-NMR spectroscopic analysis. No isomerized product was observed by ^{1}H-NMR spectroscopy and GC/MS. [b] Decomposition of the starting material was observed.

Entry 7 indicated an approximation for the ideal temperature and an approximate catalyst loading for the above reaction. Next, we optimized the ratio of THF and toluene that worked best with this system (see Table 14). Eliminating toluene as a co-solvent was deleterious to the reaction (Entry 2). Immediately, it became clear that adjusting the relative amounts of THF/PhMe to a ratio of 1:2 lead to full conversion of the starting material in a fraction of the time (Entries 3-9). From this, we were able to lower to the catalyst loading down to 0.25 mol%, albeit after a slightly longer reaction time, with no effect on the conversion to compound **74** (see Entries 3-7). Catalyst loadings lower than 0.25 mol% were unsuccessful at fully converting **88** and **68** to compound **74** even after extended reaction times (Entries 8 and 9).

Table 14. The effect of solvent composition and catalyst loading on conversion of **68** for a 50 mg scale cross-coupling with 4-heptylzinc bromide (**88**)



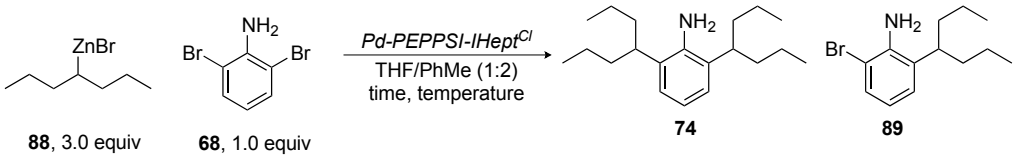
88, 3.0 equiv **68**, 1.0 equiv **74** **89**

Entry	Catalyst loading (%)	Temp	THF:PhMe	Time (h)	Conversion[a] (%)	**74**:**89**
1	2	60	1:1	1	100	9:1
2[b]	2	60	1:0	12	0	0:0
3	2	60	1:2	30 min	100	1:0
4	1.5	60	1:2	30 min	100	1:0
5	1.5	55	1:2	30 min	100	1:0
6	0.5	60	1:2	45 min	100	1:0
7	0.25	60	1:2	3	100	1:0
8[b]	0.05	60	1:2	48	80	1:1
9[b]	0.10	60	1:2	48	80	1:1

[a] Conversions and ratio of **74:89** were determined by ^{1}H-NMR spectroscopic analysis. No isomerized product was observed by ^{1}H-NMR spectroscopy and GC/MS. [b] Unreacted bromide, **68**, was recovered.

Once the solvent system was optimized (Entries 1-3) we were able to progressively lower the catalyst loading down to 0.25% relative to **68** (Entried 3-7). The next step was to move the transformation of compounds **88** and **68** to larger scale (see Table 15). The strategy used for scaling up the reaction was of every successful result involved increasing the mass of the starting bromide by a factor of three. No issues were seen for the first experiments (Entries 1 and 2), however, there was incomplete conversion of **68** that was observed at the 3 g scale. Simply doubling the catalyst loading at this scale lead to complete conversion of **68** to the desired product **74** (See Entry 4). The 0.5% *PEPPSI-IHept^{Cl}* catalyst loading worked for the scales of 3, 10 and 30 g.

Table 15. Optimization of scale-up conditions



88, 3.0 equiv **68**, 1.0 equiv **74** **89**

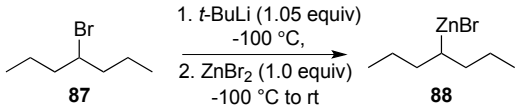
Entry	Mass of **68** (grams)	Catalyst Loading (mol %)	Temp. (°C)	Time (h)	Conversion[a] (%)	**74**:**89**
1	0.25	0.25	60	16	100	1:0
2	1	0.25	60	24	100	1:0
3	3	0.25	60	12	65	1:0
4	3	0.5	60	30 min	100	1:0
6	10	0.5	60	30 min	100	1:0
7	30	0.5	50	3	100	1:0

[a] Conversions and ratio of **74:89** were determined by ^{1}H-NMR spectroscopic analysis. No isomerized product was observed by ^{1}H-NMR spectroscopy and GC/MS.

*5.2.4 Re-optimizing the Synthesis of the Organozinc (**88**)*

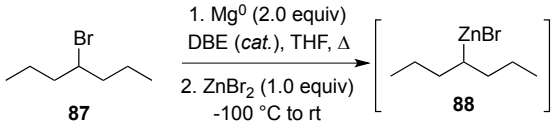
Having successfully optimized the large scale cross-coupling of **88** with **68**, we then turned our attention to improving the conversion of **88** from bromide **87**, which was obtained in only 50% using Knochel's modified direct Zn insertion protocol (see Scheme 33).[112] We attempted to metalate **87** with either Li or Mg then transmetalate to Zn since the formation of either the organolithium or the Grignard reaction should proceed quantitatively.

Lithium halogen exchange with **87** was performed in either ether or THF using *t*-BuLi at -100°C (see Scheme 34). The organolithium formed *in situ* and was transmetalated to zinc bromide. This transformation was confirmed by performing GC/MS analysis on a sample of the quenched material.



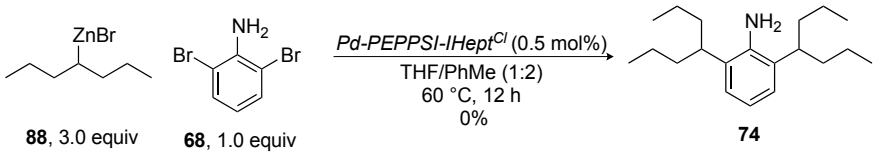
Scheme 34. Preparation of **88** using Li/X exchange

Comparatively, the organozinc was formed *via* the corresponding Grignard reagent that generating by treating **87** with Mg turnings (see Scheme 35).



Scheme 35. Preparation of **88** *via* Grignard reagent formation

Once transmetalated, the species **88**, prepared from the organolithium *or* the respective Grignard reagent, was then treated with the Negishi cross-coupling conditions (see Scheme 36).



Scheme 36. Reacting **88**, prepared from the organolithium or Grignard reagent, with **68**

In both cases, the organozinc formed from the Grignard reagent or the organolithium failed to provide the cross-coupled product. In the case of the organolithium we proposed that the use of ether had an adverse effect on the cross-coupling reaction. With ether, the delicate balance of THF and PhMe that was required for the reaction to proceed smoothly with low catalyst loading was disrupted (refer to Figure 20, Entries 1-3). In the case of the organolithium species in THF, we noted decomposition of the

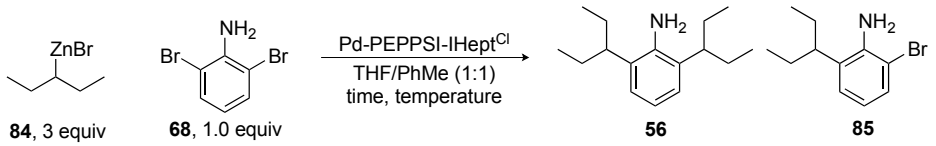
solvent followed by a sluggish, non-productive reaction after the reaction was slowly warmed to rt (see reaction scheme from Table 15). In the case of reaction outlined in Scheme 35, the resulting solution was so viscous, that it could not be cannulated to facilitate the separation the active organometallic species from unreacted magnesium, which was detrimental to the reaction. In light of these results, we were forced to work with Knochel's protocol for the formation of secondary alkyl organozincs, which at least allowed the recovery of the unreacted alkylbromide.

*5.2.5 Optimzation of 3-Pentylzinc Bromide (**84**) Negishi Cross-coupling en route Towards Substituted 2,6-Di(3-pentyl)aniline (**56**)*

After optimizing the large-scale preparation of 2,6-di(4-heptyl)aniline (**74**) using *Pd-PEPPSI-IHept*^{Cl} with no evidence of the formation of rearranged product, we focused on optimizing the Negishi cross-coupling of 3-pentylzinc bromide and 2,6-dibromoaniline which remained as yet unoptimized.

Our optimization studies began by using the coupling conditions shown to work well for the large-scale (30 g) of **74** (see Table 15, Entry 7 and Table 16).

Table 16. Optimization of 2,6-di-(3-pentyl)aniline (**51**) for synthesis on a ten gram scale



84, 3 equiv **68**, 1.0 equiv **56** **85**

Entry	Mass of **68** (g)	Equivalents of **84**	Catalyst Loading (mol %)	Temp. (°C)	Time (h)	Conversion[a] (%)	**56**:**85**
1	1	3.0	1	22	1	100	1:0
2	3	3.0	0.5	60	3	100	1:0
3	3	3.0	0.25	60	3	100	1:0
4	10	3.0	0.25	60	3	100	1:0
5	1	2.2	0.25	60	12	100	1:0

[a] Conversions and ratio of **56**:**85** were determined by ^{1}H-NMR spectroscopic analysis. No isomerized product was observed by ^{1}H-NMR spectroscopy and GC/MS.

We evaluated the efficacy of the catalyst at rt with a loading of 1 mol% and found complete conversion to **56** in only 1 h (Table 16, Entry 1). With heating to 60°C, loading of the catalyst could be lowered to 0.5 and 0.25 mol% (Entries 2 and 3 respectively). The conditions of Entry 3 were applied with success to the cross-coupling reaction at the 10-gram scale yielding 92% of **56** (Entry 4). Lastly, we returned to the 1-gram scale however, this time, using less of the organozinc when proceeding with the coupling. Only a slight excess of the organozinc is required to activate the catalyst *via* double TM followed by RE to invoke the Pd(0) species. Yet, at only 2.2 molar equivalents we see complete conversion to the single, non-isomerized, di-coupled product, **56**, indicating that side reactions involving the organozinc and the aniline are either negligible or not occurring. This is supported by the work of Knochel and co-workers that reported that alkylzinc halides are relatively stable to anilines and secondary alkyl alcohols (see Figure 23).

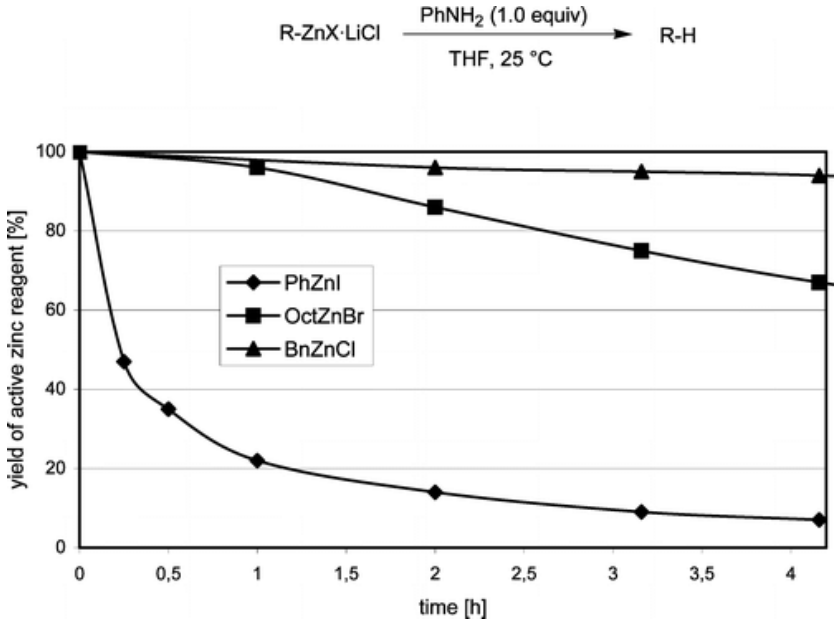


Figure 23. Stability of organozinc reagents toward aniline. Recovery of the organozincs were determined by quenching with CuCN/allyl bromide in THF and GC analysis with tetradecane as internal standard.[113]

5.3 Conclusions

An efficient, large-scale synthesis of bulky 2,6-dialkylanilines using *Pd-PEPPSI-IHept*^{Cl} pre-catalyst **(5)** has been achieved. The syntheses focus around the Negishi cross-coupling of secondary alkylzinc reagents with 2,6-dibromoaniline and with **6**, which resulted in no observable isomerization. This synthetic approach represents a significant improvement over the existing route to make bulky 2,6-dialkylanilines derivatives, especially on large scale. This method will be useful in the synthesis of many other substrates requiring the regiospecific installation of a secondary alkyl-aryl bond and lead to more complex and interesting NHC ligands for use in further studies as new *Pd-PEPPSI* pre-catalysts.

5.3.1 Other Anilines of Interest

Other anilines of potential interest are outlined in Figure 24. These anilines may create additional steric bulk around the Pd centre and facilitate difficult coupling reactions such as alkyl-alkyl Negishi cross-coupling. To acquire these anilines we applied a similar rational to their synthesis as was used in the case of compound **87** (see Scheme 28). The respective bromides are not available by any manufacturer however, the alcohol precursors for these anilines shown below are inexpensive and widely commercially available.

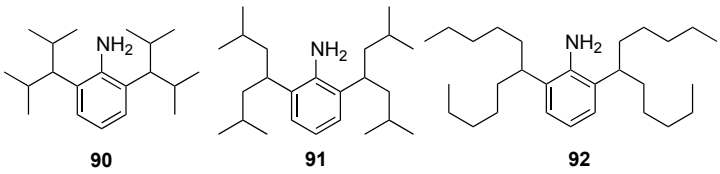
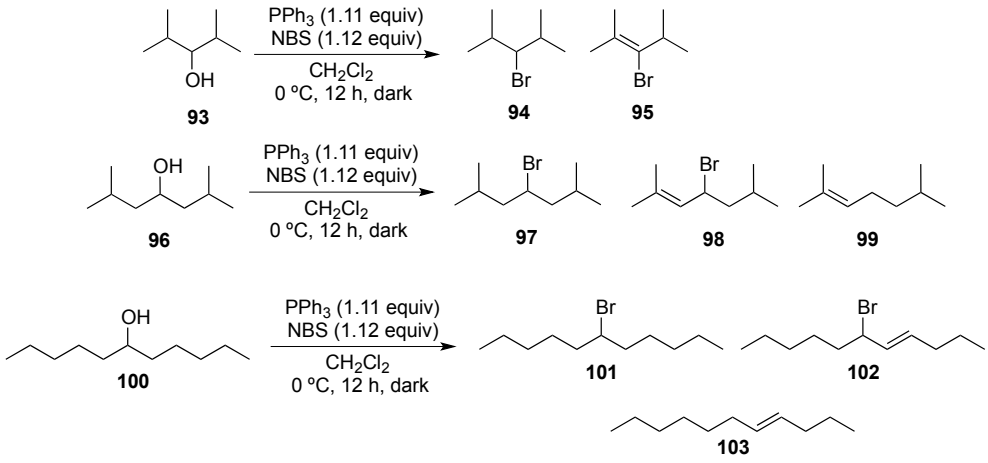


Figure 24. Synthetic targets **91**-**93** for future work[99b]

As with the synthesis presented for **74**, the alcohols were treated with NBS and PPh_3 in the dark at low temperature. Unfortunately, the Appel bromination procedure gave poor results when applied to compounds **90**, **91**, and **92**. This speaks to the limitation of the bromination reaction with bulky alcohols. The crude reaction mixture was analyzed by ^{1}H and ^{13}C-NMR spectroscopy revealing a mixture of isomers that were inseparable by fractional distillation or by flash chromatography (see Scheme 37). Had the reaction mixture contained the eliminated product as the only side-product, the crude reactions mixtures could have been used without further purification.

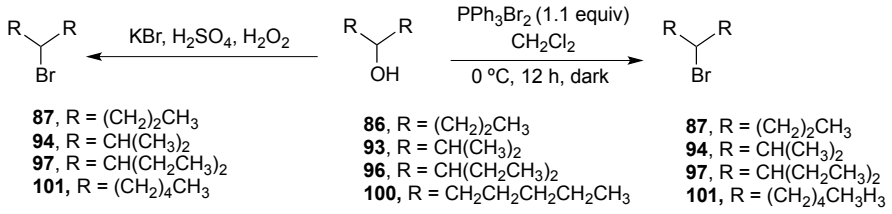


Scheme 37. Bromination of compounds **95**, **97**, and **99**

5.3.2 Future Work in this Area

Though the overall synthesis present is improved over previous methods, there are still many aspects of this work that could be improved. First, an alternative procedure for the reduction of 4-heptanone (**69**) would address concerns as the quench of $LiAlH_4$ requires time and caution (see Scheme 32).

Second, the Appel bromination reaction exhibits poor atom economical leading to vast amounts of PPh_3O that complicate the filtration aspect workup. Exploring other methods of brominating 4-heptanol (**86**) on large scale would be of value. Other methods may include producing a brominating reagent from sulfuric acid and KBr, or employing PPh_3Br_2 species, which can be made *in situ* by adding PPh_3 and Br_2 in dichloromethane prior to the addition of the alkyl alcohol (see Scheme 38).[114]



Scheme 38. Alternative methods of bromination

These anilines (**91-92**), once synthesized, will allow our group to expand the family *Pd-PEPPSI* pre-catalysts and further our understanding of the cross-coupling mechanism.

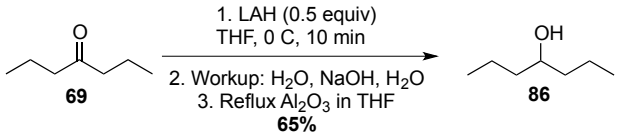
Chapter 6:
Experimental Procedures

6.1 General Experimental

All reactions were run under argon with scrupulous exclusion of moisture from reagents and glassware using standard Schlenk techniques for manipulating air-sensitive compounds.[55] All glassware was stored in an oven and was flame-dried and purged with argon prior to use. Anhydrous solvents were obtained by distillation over sodium/benzophenone (ether, THF) or used directly from Sigma-Aldrich Sure/Seal™ bottles (toluene, THF) without further purification unless indicated. Analytical thin-layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel plates coated with 254 nm indicator. Visualization of the developed chromatogram was performed using UV absorbance, a ceric ammonium molybdate (CAM) solution, an aqueous potassium permanganate solution or H_2SO_4 and heat provided by heat gun at 400 W. Flash column chromatography was performed using Silicycle™ silica gel 60 (230-400 mesh) and the indicated solvent system using the flash technique.[56] Nuclear magnetic resonance spectra (^1H, ^{13}C) were recorded on Bruker 300 or 400 MHz AVANCE spectrometers equipped with a DUAL probe. Chemical shifts for ^1H NMR spectra are recorded in parts per million (ppm) using the residual proton signal of the solvent as the internal standard ($CDCl_3$, δ = 7.26 ppm). Chemical shifts for ^{13}C NMR spectra are recorded in parts per million by calibrating the central peak of $CDCl_3$ to 77.00 ppm.

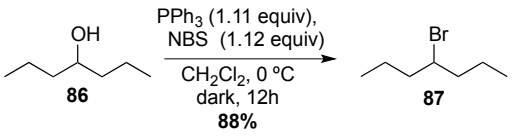
6.2 Experimental Procedures

6.2.1 Large Scale Preparation of 2,6-Di(4-heptyl)aniline Precursors



Synthesis of 4-heptanol, (86): Lithium aluminium hydride (75 g, 2.0 mol, 0.5 equiv) was added portion-wise to a flame dried, 3-neck, 5 L round bottom flask equipped with a magnetic stirrer, a ground glass joint fitted with a thermometer, and a 500 mL pressure equalizing addition funnel before being closed with a ground glass joint. The flask was cooled to 0 °C in an ice/water bath and reagent grade THF (1.5 L) was added dropwise over 30 min under a positive pressure of Ar with magnetic stirring. To the resulting grey suspension was added 4-heptanone (**69**, 550 mL, 450 g, 4.0 mol, 1.0 equiv) dropwise over 90 minutes. The resulting solution was stirred for an additional 10 minutes at which time TLC indicated the complete consumption of starting material. **EXTREME CAUTION**: Water (75 mL) was added slowly, dropwise via syringe at a rate of 1 mL/5 min for the initial 5 mL, followed by a rate of 1 mL/min thereafter such that the reaction temperature does not exceed 40°C, followed by a 1M solution of aqueous NaOH (75 mL) added a rate of 5 mL/min and water (225 mL) dropwise, added a rate of 25 mL/min, by pressure-equalizing, addition funnel adapter, causing a visual change in the mixtures appearance from a clear, colourless solution with a grey suspension to a clear, colourless solution with a thick, white precipitate. The flask contents were filtered through a coarse-frit sintered glass filter funnel and the white, crystalline cake was washed with ether (2 x 100 mL). The filtrate was stored in a round bottom flask with a rubber septum under Ar. The white filter cake was loaded into a 3-

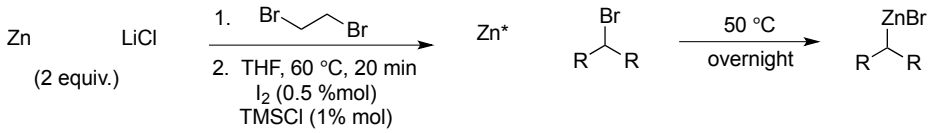
neck, 5 L round bottom flask equipped with a magnetic stir bar, a cold-water reflux condenser, a ground glass stopper, and THF (non-anhydrous, 2 L) before being closed with a ground glass stopper. The contents of the flask were stirred and heated to reflux for 12 h under a positive pressure of Ar at which time the contents were filtered through a coarse-frit, sintered glass filter funnel. The precipitate was washed with ether (2 x 100 mL) and the filtrate portions were combined and concentrated in vacuo to afford pure 4-heptanol (**86**, 298 g, 65%) as a clear, colourless oil that was used in the next step without further purification: R_f = 0.22 (10:1 pentane/ether), H_2SO_4/heat; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.61 (bs, 1H), 1.84-1.36 (m, 8H), 0.92 (t, J = 6.8 Hz) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 71.4, 39.6, 18.8, 14.1 ppm. Spectra and physical data are in agreement with the literature.[115]



Synthesis of 4-bromoheptane (87): PPh_3 (1.07 kg, 4.1 mol, 1.11 equiv) was added to a flame dried 3-neck 5 L round bottom flask equipped with a wide-neck glass funnel, a ground glass joint fitted with a thermometer, and a ground glass Ar inlet and a magnetic stirrer containing non-anhydrous CH_2Cl_2 (2 L). The outside of the flask was covered with aluminum foil prior to being cooled to 0 °C in an ice/water bath. The clear and colourless was stirred under a positive pressure of Ar. NBS (813 mg, 4.6 mol, 1.12 equiv) was added portion wise to the solution such that the internal temperature of the reaction did not surpass 35 °C. The addition of NBS caused the resulting solution to effervesce (exothermic) and resulted in a visual change in the mixture's appearance

from clear and colourless to clear and light orange. After the addition was complete (30 min) the colour of the resulting solution had darkened to an opaque, dark brown. The wide-neck glass funnel was removed and the flask was equipped with a 500 mL pressure equalizing addition funnel. 4-Heptanol (**86**, 500 mL, 427 g, 3.7 mol, 1.0 equiv) was added drop wise over 40 min at which time the flask was left to stir for 12 h while warming slowly to rt. The volume of the solution was concentrated by one-half in vacuo and to the resulting black sludge was added cold pentane (1 L) causing PPh_3O to precipitate. The resulting, bi-phasic solution was filtered through a coarse frit, sintered 500 mL glass filter funnel containing a 400 cm^3 plug of SiO_2 which was washed with pentane (1 L) that had been chilled in an ice bath to 0°C. The filtrate was concentrated *in vacuo* and purified using flash chromatography (SiO_2, pentane) to provide 4-bromoheptane (**87**, 583 g, 88%) as a clear, colourless oil: R_f = 0.81 (10:1 pentane/ether), CAM; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.05 (quint, 1H, J = 4.0 Hz), 1.83-1.74 (m, 4H), 1.56 (m, 2H), 1.44 (m, 2H), 0.92 (t, 3H, J = 7.3 Hz) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 58.3, 41.2, 20.8, 13.5 ppm. Spectra and physical data are in agreement with the literature.[116]

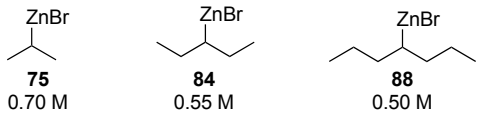
6.2.2 General Preparation of Secondary Alkylzinc Halides [42,107a]



To an oven-dried 4-neck, 5 L reaction flask equipped with a magnetic stirrer, a 500 mL septum-sealed pressure equalizing addition funnel, a septum sealed cold water condenser and a ground glass joint connected to an Ar/vacuum line was added zinc

dust (432 g, 6.6 mol, 2 equiv), and LiCl (280 g, 6.6 mol, 2 equiv) before being closed with a ground glass stopper. The flask was evacuated and heated by flame for 10 min, stopping every few minutes to shake the flask and mix its contents. The flask was left to cool to rt and then backfilled filled with Ar. After repeating the procedure once more, anhydrous THF (2 L) was cannulated into the now open addition funnel followed by an addition via syringe of 1,2-dibromoethane (6.7 mL, 0.17 mol). The reaction mixture was lowered into an oil bath heated to 60 °C for 20 min at which time the solution bubbled. The flask was removed from the oil bath and, after cooling to rt, freshly distilled TMSCl (2.5 mL, 0.03 mol) was added via syringe to the addition funnel followed by a solution of I_2 (21 g, 0.08 mol) in THF (250 mL) was added via cannula from a septum sealed, round bottom flask. The reaction mixture was heated with stirring to 60 °C for 20 min, removed from the oil bath and cooled to rt. Akyl bromide (3.3 mol) was cannulated into the addition funnel and added dropwise to the flask's contents over 10 min. The flask was stirred for 24 h at 50 °C under a positive Ar pressure. The resulting heterogenous solution was cooled to rt and left to settle for 24 h, at which time the resulting mixture's supernatant was clear and colourless with an insoluble grey layer that had settled on the bottom. The supernatant was titrated using Knochel's method for the iodometric titration of organozincs.[111]

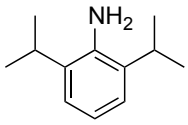
The solutions thus prepared are shown with their measured titre:



75 0.70 M **84** 0.55 M **88** 0.50 M

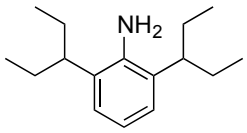
*6.2.3 General Coupling Procedure for 2,6-Disubstituted Anilines (**80**, **56**, and **74**)*

A 3-neck 22 L oven-dried round bottom flask was equipped with a septum-sealed 500 mL pressure equalizing addition funnel, ground glass joint equipped with a thermometer and an Ar/vacuum line before being evacuated and flame dried with a propane torch. The flask was cooled to room temperature and slowly backfilled with Ar (x2). Under a positive pressure of argon, the addition funnel was removed and replaced with a wide neck glass funnel, **68** (100 g, 0.40 mol, 1.0 equiv) and *Pd-PEPPSI-IHept*^{Cl} (**6**, Procedure for A for **80** and **56**, 194 mg, 0.25 mol% *or* Procedure B for **74**, 390 mg 0.5 mol%). The glass funnel was replaced with a pressure equalizing addition funnel and the flask was evacuated (45 minutes) and slowly backfilled with Ar (x2). Anhydrous toluene (4.8 L) was cannulated in 500 mL portions to the dropping funnel and added to the reaction mixture resulting in a clear, light yellow solution which was heated by mantle to 50 °C. Under a positive pressure of Ar, the thermometer fitted to the ground glass joint was removed and a septum sealed cold-water condenser was added. **Organozinc halide solution** (1.20 mol, 2.2 equiv) was added drop-wise via addition funnel resulting in a visual change in the solution's appearance from clear, yellow to opaque, white which changed to opaque, light brown after hours. After stirring overnight, TLC analysis indicated complete consumption of the starting material. The solution was taken up in ether (100 mL) and washed with sat. NH_4Cl (1 L), 1 M EDTA (2 x 1 L), brine (1 L), dH_2O (1 L), dried on $MgSO_4$ and filtered through a plug of $MgSO_4$ to afford the aniline as a clear, brown oil which was used in the next step without further purification:



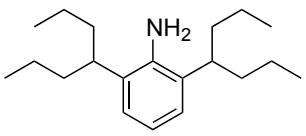
80

2,6-Diisopropylaniline (**80**): Following the general coupling Procedure A, 63 g (89% yield, 98% conversion) were obtained after the subsequent condensation step, Compound **80** is a clear, dark-brown oil; R_f =0.35 (100:1, pentane/ether); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 7.5 Hz, 2H), 6.81 (t, *J* = 7.7 Hz, 1H), 3.73 (bs, 2H), 2.93 (quint, *J* = 6.8 Hz, 2H), 1.29 (d, *J* = 6.9 Hz, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 140.2, 132.4, 122.7, 118.5, 27.9, 22.4 ppm. These spectral data are consistent with those reported in the literature.[117]



56

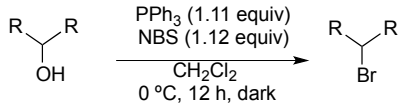
2,6-Di(3-pentyl)aniline (**56**): Following the general coupling Procedure A, 78 g (84% yield, 99% conversion) were obtained after the subsequent step. Compound **56** is a clear, dark-brown oil; R_f =0.41, (100:1, pentane/ether); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 7.8 Hz, 2H), 6.78 (t, *J* = 7.6 Hz, 1H), 3.15 (bs, 2H), 2.49 (quint, *J* = 6.2 Hz, 2H), 1.73-1.55 (m, 8H), 0.83 (t, *J* = 7.7 Hz, 12H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.4, 130.2, 123.9, 118.6, 42.3, 28.0, 12.1. These spectral data are consistent with those reported in the literature.[99b,102]



74

2,6-Di(4-heptyl)aniline (**74**): Following the general coupling Procedure B, 95 g (84% yield, 99% conversion) were obtained after the subsequent step. Compound **74** is a clear, dark-brown oil; R_f =0.40 (100:1, pentane/ether); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 7.8 Hz, 2H), 6.78 (t, *J* = 7.6 Hz, 1H), 3.15 (bs, 2H), 2.49 (quint, *J* = 6.2 Hz, 2H), 1.73-1.55 (m, 8H), 0.83 (t, *J* = 7.7 Hz, 12H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.4, 130.2, 123.9, 118.6, 42.3, 28.0, 12.1. These spectral data are consistent with those reported in the literature. [99b,102]

6.2.4 General Procedure for the Attempted Synthesis of Alkylbromides



Attempted synthesis of **3-bromo-2,4-dimethylpentane** (**94**), **4-bromo-2,6-dimethylheptane (97**) and **6-bromoundecane** (**102**): PPh_3 (70 mg, 0.27 mmol, 1.11 equiv) was added to a flame dried 50 mL 3-neck round bottom flask equipped with a removable glass funnel, a ground glass joint fitted with a thermometer, and a ground glass Ar inlet and a magnetic stirrer containing non-anhydrous CH_2Cl_2 (20 mL). The outside of the flask was covered with aluminum foil prior to being cooled to 0 °C in an ice/water bath. The clear and colourless was stirred under a positive pressure of Ar. NBS (49 mg, 0.28 mmol, 1.12 equiv) was added portion wise to the solution such that the internal temperature of the reaction did not surpass 35 °C. The addition of NBS caused the resulting solution to effervesce (exothermic) and resulted in a visual change in the mixture's appearance from clear and colourless to clear and light orange. After the addition was complete (5 min) the colour of the resulting solution had darkened to an opaque, dark brown. Alcohol (**93**, **96**, or **100**, 0.25 mmol, 1.0 equiv) was added drop wise over 5 min via syringe at which time the flask was left to stir for 12 h while warming slowly to rt. The volume of the solution was concentrated by one-half in vacuo and to the resulting black sludge was added cold pentane (100 mL) causing PPh_3O to precipitate. The resulting, bi-phasic solution was filtered through a coarse frit, sintered 250 mL glass filter funnel containing a 10 cm^3 plug of SiO_2, which was washed with pentane (50 mL) that had been chilled in an ice bath to 0°C. The filtrate was concentrated *in vacuo*. ^{1}H-NMR spectroscopic analysis indicated a mixture of

starting material, the desired alcohol and side-products, which were inseparable by flash chromatography or fractional distillation.

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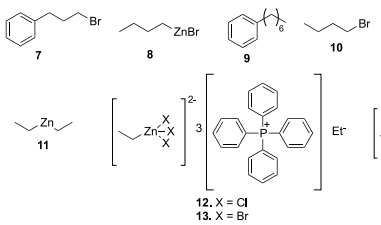
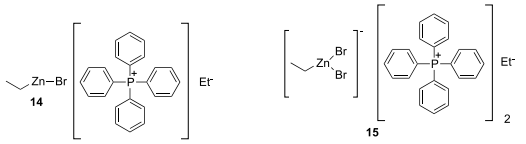
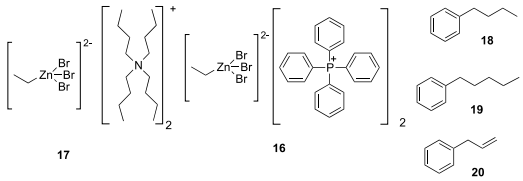
Appendix

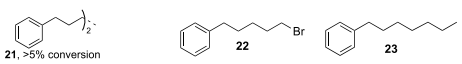
A.1 Structure Index

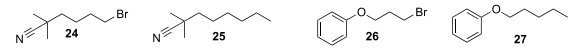
Pd-PEPPSI-IPr (**1**),
Pd-PEPPSI-IPr^{Cl} (**2**),
Pd-PEPPSI-IPent (**3**),
Pd-PEPPSI-IPent^{Cl} (**4**),
Pd-PEPPSI-IHept (**5**),
Pd-PEPPSI-IHept^{Cl} (**6**)

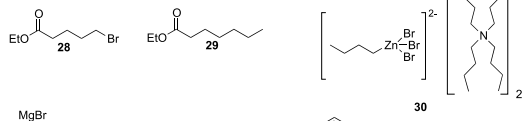


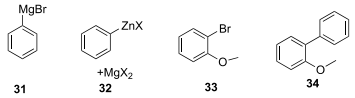


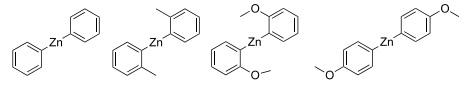


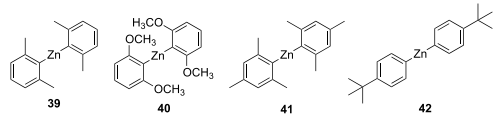


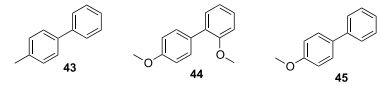


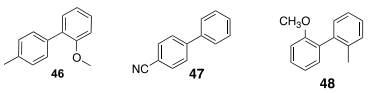












Pd-PEPPSI-IMes, **49**
Pd-PEPPSI-IEt, **50**
Pd-PEPPSI-IPr^{Me}, **51**
Pd-PEPPSI-IPr^{Quino}, **52**
Pd-PEPPSI-CPent, **53**
Pd-PEPPSI-INon^{Cl}, **54**