

Expanding the Scope of Coupling Partners in Catalytic Cross-Coupling Reactions

Xi Ye Hua

A thesis submitted to the Faculty of Graduate Studies in partial
fulfillment of the requirements for the degree of

MASTER OF SCIENCE

in Chemistry

Department of Chemistry and Biomolecular Sciences, University of
Ottawa, 10 Marie-Curie, Ottawa, Ontario, Canada, K1N 6N5.

August 2016

Thesis supervisor: Stephen G. Newman

© Xi Ye Hua, Ottawa, Canada, 2016

Table of Contents

List of Schemes	v
List of Figures.....	vii
List of Tables	ix
Abstract.....	x
Acknowledgements	xi
List of Publication	xii
Abbreviations	xiii
Introduction.....	1
Chapter 1: Intermolecular Cross-Coupling Between Aldehydes and Aryl Halides/Pseudohalides	4
1.1 Introduction	4
1.1.1 Traditional approaches to the synthesis of ketones	4
1.1.2 The Heck reaction.....	7
1.1.3 Pd-catalyzed acylation reactions.....	11
1.1.4 Research goal.....	16
1.2 Results and discussion.....	18
1.2.1 High-throughput screening using Pd catalysts.....	18
1.2.2 Troubleshooting	23

1.2.3 Optimization using Ni catalysts	31
1.2.4 Other approaches	38
1.4 Summary and future work	40
1.5 Experimental	44
Chapter 2: Inherent vs. Apparent Chemoselectivity: Expanding the Scope of the Kumada-Corriu Cross-Coupling Reaction	50
2.1 Introduction	50
2.1.1 Traditional Kumada-Corriu cross-coupling	51
2.1.2 Applications of the Kumada-Corriu reaction in industry	53
2.1.3 Comparison to other organometallic reagents	55
2.1.4 Recent advances in Kumada-Corriu cross-coupling	58
2.1.5 Research goals	59
Results and discussion	63
2.2 Robustness screen	63
2.2.1 Advantages of robustness screen	63
2.2.2 Robustness screen for the Kumada-Corriu coupling	64
2.2.3 Limitations of robustness screen	67
2.3 Slow addition experiments	68
2.3.1 Catalyst system optimization	68
2.3.2 Effect of Grignard addition rate	71
2.3.3 Effect of elevated temperature	77
2.3.4 Scope and chemoselectivity in Kumada-Corriu coupling	80
2.3.5 Scope limitations	88

2.4 ESI-MS experiments	90
2.4.1 ESI monitoring of Kumada-Corriu coupling reactions.....	90
2.4.2 ESI monitoring of PhLi coupling reactions	96
2.4.3 Advantages and Limitations	99
2.5 Summary and future work.....	100
2.6 Experimental	104
2.6.1 General considerations.....	104
2.6.2 Robustness screen experiments	105
2.6.3 Preparation of chemical reagents	115
2.6.4 Slow addition experiments.....	124
2.6.5 ESI-MS experiments.....	126
2.6.6 Characterization of Kumada-Corriu cross-coupling products	130
Appendices.....	148
NMR Spectra	148

List of Schemes

Scheme 1. The general cross-coupling reaction	2
Scheme 2. The Friedel-Crafts acylation.....	5
Scheme 3. The Grignard reaction of acid derivatives.....	6
Scheme 4. The Weinreb–Nahm ketone synthesis.....	7
Scheme 5. Early works and development of the Heck reaction	9
Scheme 6. Mechanism of the Heck reaction.....	10
Scheme 7. Examples of Pd-catalyzed acylation using boronic acids	12
Scheme 8. Synthesis of alkyl aryl ketones by direct acylation of aryl halides with aldehydes.....	13
Scheme 9. Pd-catalyzed intramolecular acylation of aryl halides	15
Scheme 10. Pd-catalyzed coupling of aryl bromides with N-tert-butylhydrazones	16
Scheme 11. Proposed new Oxa-Heck reaction: direct acylation of aldehydes and aryl halides	17
Scheme 12. Proposed mechanism for the new reaction: oxa-Heck reaction	18
Scheme 13. Proposed mechanism for 1,2 addition reaction	25
Scheme 14. Ni-catalyzed dehydrogenative cross-coupling of aldehydes.....	38
Scheme 15. Best reaction conditions for direct acylation of aldehydes and PhOTf.....	40
Scheme 16. Selection of organic bases to facilitate reductive elimination.....	41
Scheme 17. Selection of ligands for future screening.....	42
Scheme 18. Early works of Ni- and Pd-catalyzed Kumada-Corriu reaction	52
Scheme 19. The general mechanism of Pd-catalyzed Kumada-Corriu coupling	53
Scheme 20. Selected industrial applications of Ni-catalyzed Kumada coupling.....	54

Scheme 21. Sample industrial application of Pd-catalyzed Kumada coupling	55
Scheme 22. Comparison of Kumada and Suzuki coupling for the synthesis of biaryl.....	57
Scheme 23. Kumada-couplings of aryl iodide by Buchwald group	58
Scheme 24. Kumada-couplings of aryl bromide by Knochel group.....	59
Scheme 25. Previous work in Pd-catalyzed Kumada-Corriu couplings with aryl chlorides.....	61
Scheme 26. Our strategy for the Pd-catalyzed Kumada-Corriu coupling	62
Scheme 27. Reaction conditions of the Kumada-Corriu robustness screen	64
Scheme 28. Influence of Grignard addition rate on pyrazine derivatives.....	76
Scheme 29. Additives and ligands screening for future experiments.....	102

List of Figures

Figure 1. The process of high-throughput screening	19
Figure 2. Variable selection details for 1 st , 2 nd and 3 rd high-throughput screening	21
Figure 3. Selected ligands in 1 st , 2 nd and 3 rd high-throughput screening	23
Figure 4. Details of 4 th high-throughput screening using preformed Pd-precursors	29
Figure 5. Structures of screened Pd-precursors	30
Figure 6. Details of 5 th and 6 th high-throughput screening using Ni catalyst	32
Figure 7. Details of 7 th highthrough-put screening using Ni catalyst	35
Figure 8. Overcoming chemoselectivity issues by controlling presence of catalytic intermediate.....	39
Figure 9. Cross-couplings with different nucleophiles.....	56
Figure 10. Comparison of traditional screen and robustness screen.....	63
Figure 11. A robustness screen revealed functional group tolerance issues in the Kumada-Corriu coupling of aryl chlorides.....	66
Figure 12. Effect of Grignard addition rate on ketone 26 for 4-chlorobenzophenone coupling.....	72
Figure 13. Effect of Grignard addition rate on side product 29 for 4-chlorobenzophenone coupling.....	72
Figure 14. Effect of Grignard addition rate on product 31 yield for methyl 4-chlorobenzoate coupling	73
Figure 15. Effect of Grignard addition rate on side product 29 for methyl 4-chlorobenzoate coupling.....	74
Figure 16. Influence of Grignard addition rate on yield of chemoselective coupling for aryl chlorides bearing nitrile groups	75
Figure 17. Unsuccessful aryl chlorides in slow addition experiments.....	89
Figure 18. Mechanistic interpretation of selectivity by slow addition of Grignard.....	91

Figure 19. ESI-MS monitoring for coupling of 4-chlorobenzonitrile.....	93
Figure 20. ESI-MS monitoring for coupling of 5-chloro-2-methylbenzooxazole.....	95
Figure 21. ESI-MS monitoring for coupling of chloronaphthalene with PhLi.....	98
Figure 22. Rational design for Kumada-Corriu couplings under flow conditions	103
Figure 23. Screening plate for the robustness screen.....	106
Figure 24. Experimental setup for real-time mass spectroscopic monitoring of cross-coupling reactions	126
Figure 25. Observed and calculated isotope patterns for the species monitored by ESI-MS.....	129

List of Tables

Table 1. Growth in the total number of publications and patents on cross-coupling reactions through July 2016.	3
Table 2. Optimization for 1,2 addition and oxa-Heck reactions.....	26
Table 3. Optimization for the reaction of 3-fluorobenzaldehyde and PhOTf.....	33
Table 4. Screening of the aldehydes with PhOTf.....	34
Table 5. Optimization for the reaction of 4-cyanobenzaldehyde and PhOTf.....	37
Table 6. Sample reaction studied for optimization: 4-chlorobenzophenone	69
Table 7. Sample reaction studied for optimization: 2-chlorobenzonitrile	70
Table 8. Reaction optimizations of selected substrates with elevated temperature	77
Table 9. Scope of sensitive aryl chlorides for Kumada-Corriu coupling reactions	82
Table 10. Scope of Grignard reagents.....	87
Table 11. Quantitation thresholds for classification of additives in robustness screen. .	108
Table 12. Complete robustness screen results	109

Abstract

Carbon-carbon (C-C) bond formation is among the most important processes in organic chemistry. Transition metal catalyzed C-C bond formation is an active research area that shows great potential due to high selectivity and relatively mild conditions.

In Chapter 1, a new reaction for direct acylation of aryl halides is discussed. Specifically, the catalytic reaction between aryl halides/pseudohalides and aldehydes is explored. The choice of ligand, base, solvent, temperature, catalyst and substrates are important factors for optimizing this catalytic reaction. The various combinations of all these factors have, therefore, been examined by high-throughput screening (HTS) in order to develop the new C-C coupling reaction.

In Chapter 2, a new methodology is reported in order to expand the scope of the Kumada-Corriu cross-coupling reaction. The strategy to achieve this goal is mechanistically based, matching oxidative addition rates with the rate of syringe pump addition of the Grignard to minimize the exposure of sensitive groups to the aggressive nucleophile. Aryl chlorides containing esters, amides, nitriles, pyrazines, carbamates, ketones, and other sensitive functionalities are all demonstrated to undergo chemoselective cross-coupling with this technique. The mechanistic reason for the effectiveness of this strategy is uncovered by continuous-infusion ESI-MS studies.

Acknowledgements

I would first like to thank my thesis advisor Professor Stephen G. Newman for the continuous support of my study and research. It has been an honor to be his first Master student. He has taught me, both consciously and unconsciously, how good experimental chemistry is done. The door to his office was always open whenever I ran into a trouble spot or had a question about my research or writing. His patience, passion, and immense knowledge have always amazed me. I could not have imagined having a better advisor and mentor for my graduate study.

My sincere thanks also go to Jeanne Masson-Makdissi and Ryan J. Sullivan, for all the awesome contributions and insights in this project, especially helping me writing and proofreading the manuscript and supporting information for the publication. I also would like to thank my fellow labmates in Newman Group: Wanying Zhang, Taoufik Ben Halima, Eric Isbrandt, Sara Omaiche, Claudia Meloche, Samantha Brix, for the stimulating discussions about chemistry and for all the fun we have had in the last two years.

Finally, I must express my very profound gratitude to my parents, grandparents and to my boyfriend for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them.

List of Publication

Chapter 2 of this thesis has been published in scientific reports as specified below.

“ *Inherent vs Apparent Chemoselectivity in the Kumada–Corriu Cross-Coupling Reaction,* ” **Hua, X.Y.**; Masson-Makdissi, J.; Sullivan, R.; Newman, S.G. *Org. Lett.*, **2016**, *18*, 5312–5315.

Abbreviations

aq.	aqueous
Ar	aryl
atm	atmosphere(s)
Bn	benzyl
Boc	tert-butyloxycarbonyl
Bu	butyl
Bz	benzoyl
Cy	cyclohexyl
dba	dibenzylideneacetone
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DIBAL	diisobutylaluminum hydride
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
eq.	equivalent(s)
ESI	electrospray ionization

EtOAc	ethyl acetate
g	gram(s)
GC-MS	gas chromatography coupled with mass spectrometry
GC-FID	gas chromatography coupled with flame ionization spectrometry
h	hour(s)
IR	infrared
J	coupling constant (NMR spectrometry)
L	generic ligand
M	generic metal, or molecular ion, or molar
MeCN	acetonitrile
Me	methyl
MHz	megahertz
min	minute(s)
mL	millilitre(s)
mol	mole(s)
mp	melting point
MS	molecular sieves or mass spectrometry
m/z	mass over charge

NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
Ph	phenyl
Piv	pivaloyl
ppm	parts per million
Py	pyridyl
R	generic chemical group
r.t.	room temperature
s	seconds
sat.	saturated
tBu	tert-butyl
T	temperature
THF	tetrahydrofuran
TLC	thin-layer chromatography
X	generic halogen/heteroatom
Y	generic halogen/heteroatom

Introduction

Organic chemistry studies all carbon-based compounds, where carbon is the most essential element for living things on earth. The study of life, the chemical reactions related to life, the natural carbon compounds and also the enormous, daily increasing number of synthetic carbon-containing compounds all deal with organic chemistry. The majority of organic synthesis involves building complex molecules from relatively simple molecules via carbon-carbon bond formation. The awarding of many Nobel Prizes in Chemistry during the previous century evidences the significance of carbon-carbon bond formation. These include: the Grignard reaction (1912)¹ which produces a carbon-carbon bond in which organomagnesium attacks aldehydes or ketones, the Diels-Alder reaction (1950)² which forms a cyclohexene system between a conjugated diene and a substituted alkene, and the Wittig reaction (1979)³ which synthesizes alkene from an aldehyde or ketone with a triphenyl phosphonium ylide.

The development of catalytic C-C bond forming processes has become a key focus during the last 50 years. Catalysts, when added in small quantities to a reaction, affect its rate and selectivity without being consumed.⁴ Lower activation energy can be achieved by using catalysts as compared to the uncatalysed reaction and provide an

¹ Grignard, V. *Compt. Rend.*, **1900**, 130, 1322-1325.

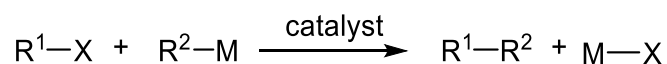
² Diels, O.; Alder, K. *Justus Liebigs Annalen der Chemie.*, **1928**, 460, 98-122.

³ Georg Wittig, Ulrich Schöllkopf. *Chemische Berichte.*, **1954**, 87 (9), 1318.

⁴ Van Santen, R. Catalysis in perspective: Historic review. In *Catalysis: From Principles to Applications*, 1st ed.; Beller, M., Renken, A., van Santen, R., Beller, M., Renken, A., Van Santen, R., Eds.; Wiley-VCH: Weinheim, Germany, **2012**; p3-19.

alternative pathway to generate target molecules in fewer steps with less chemical waste.

Transition metals have made a huge impact on organic chemistry and have led many discoveries for creating different organic molecules and many industrially important chemicals through the development of a large number of catalytic reactions. For example, the 2001 Nobel Prize in Chemistry was awarded for the chirally catalyzed reactions. Also in 2005, the Nobel Prize was awarded for the development of olefin metathesis. Cross-coupling is a generic term for a variety of reactions where an organometallic species and an organohalide are coupled with the aid of a metal catalyst to form a new carbon-carbon and metal-halide bond (Scheme 1). However, some of the cross-coupling reactions such as Buchwald–Hartwig reaction, etc., do not fit into this simple reaction scheme or follow this generic definition. Distinguishing between cross-coupling and cross-coupling-like reactions is not always clear.



Scheme 1. The general cross-coupling reaction

Palladium was most commonly used early on for cross-coupling and has stimulated the rapid growth of these reactions. The 2010 Nobel Prize in Chemistry was awarded for the formation of carbon-carbon single bonds through palladium-catalyzed cross-coupling reactions developed by Professors Richard F. Heck (University of Delaware), Akira Suzuki (University of Hokkaido) and Ei-ichi Negishi (Purdue

University).⁵ Nickel also plays an important role in the field of transition metal catalysis; it can readily perform many of the same elementary reactions as palladium, while being less expensive.⁶ The field of cross-coupling has undoubtedly turned into an area appreciated by all organic chemists, irrespective of their prominence in academia or industry,⁷ as evidenced by the rapid growth in the total number of publications and patents on several cross-coupling reactions (Table 1).

Table 1. Growth in the total number of publications and patents on cross-coupling reactions through July 2016.⁸

	Through 2000	Through 2010	Through 2016
Kumada-Corriu	25	209	327
Negishi	102	490	499
Stille	639	1646	1351
Suzuki-Miyaura	1465	7137	7928
Hiyama	58	262	274
Heck	1132	5284	4634

Extensive new discoveries within the field of cross-coupling have not reached an end. Many new catalytic reactions have not yet been discovered. Chemists still need to

⁵ For Nobel lectures see: (a) E. Negishi, *Angew. Chem. Int. Ed.*, **2011**, 50, 6738. (b) A. Suzuki, *Angew. Chem. Int. Ed.*, **2011**, 50, 6722.

⁶ Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature*, **2014**, 509, 299.

⁷ Johansson Seechurn, C. C. C.; DeAngelis, A.; Colacot, T. J. In *New Trends in Cross-Coupling: Theory and Applications*; The Royal Society of Chemistry: **2015**, p1.

⁸ Web of Science Core Collection. <http://ipscience.thomsonreuters.com> (Accessed on 08/02/2016)

continue incorporating problematic nucleophilic and electrophilic reaction partners, developing more efficient and milder catalytic conditions, and improving the existing catalytic transformations. In this thesis, the development of new catalytic acylation reaction between aryl halides/pseudohalides and aldehydes is covered in Chapter 1. A new mechanistically based methodology with the aim of expanding the scope of Kumada-Corriu cross-coupling reaction is reported in Chapter 2.

Chapter 1: Intermolecular Cross-Coupling Between Aldehydes and Aryl Halides/Pseudohalides

1.1 Introduction

1.1.1 Traditional approaches to the synthesis of ketones

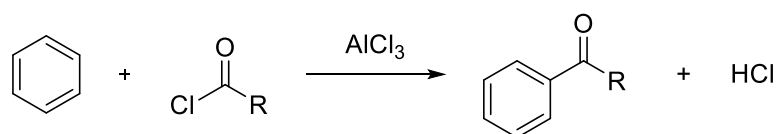
Ketones are important building blocks for the synthesis of pharmaceuticals, fine chemicals, polymers and many natural products that are produced at massive scale in the chemical industry.⁹ Acylation is an organic process that is used to add acyl functionalities to compounds and a number of well-known approaches are utilized to achieve this transformation.¹⁰ One of the common and traditional approaches to synthesize ketones is the Friedel-Crafts acylation of arenes (Scheme 2), which was reported by Charles Friedel and James Crafts.¹¹ This process usually requires AlCl₃, a Lewis acid, to enhance the electrophilicity of the acyl halide by complexing with the

⁹ Hardo Siegel, Manfred Eggersdorfer "Ketones" in Ullmann's Encyclopedia of Industrial Chemistry, **2005**, Wiley-VCH, Weinheim.

¹⁰ a) K. Takagi, T. Okamoto, Y. Sakakibara, A. Ohno, S. Oka, N. Hayama. *Chem. Lett.* **1975**, 951. b) T. Sato, K. Naruse, M. Enokiya, T. Fujisawa. *Chem. Lett.* **1981**, 1135. c) Zhang, Y.D.; Rovis, T. *J. Am. Chem. Soc.* **2004**, 126, 15964–15965.

¹¹ Friedel, C.; Crafts, J. M. *Sur une nouvelle méthode générale de synthèse d'hydrocarbures, d'acétones, etc.*, Compt. Rend., **1877**, 84, 1392, 1450.

halide at high temperatures. However, this approach includes some serious drawbacks including the environmental problems of handling hazardous reagents, generating strongly acidic wastes, harsh reaction conditions, limited regioselectivity and incompatibility of certain functional groups.

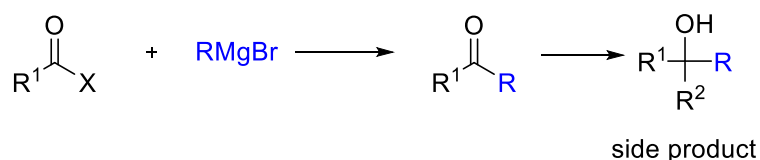


Scheme 2. The Friedel-Crafts acylation

Another traditional way to synthesize ketones is the nucleophilic addition of organometallic reagents to carboxylic acid derivatives. Several studies have successfully used different nucleophilic reagents, including organolithium and Grignard reagents to prepare ketones.¹² For acyl chlorides, however, further reactivity of products and low functional group tolerance are still problematic.¹³ Alcohol was usually obtained as a side product due to the common over-addition of organometallic reagents to typical acyl compounds. (Scheme 3).

¹² M. Blangetti, H. Rosso, C. Prandi, A. Deagostino and P. Venturello, *Molecules*, 2013, **18**, 1188

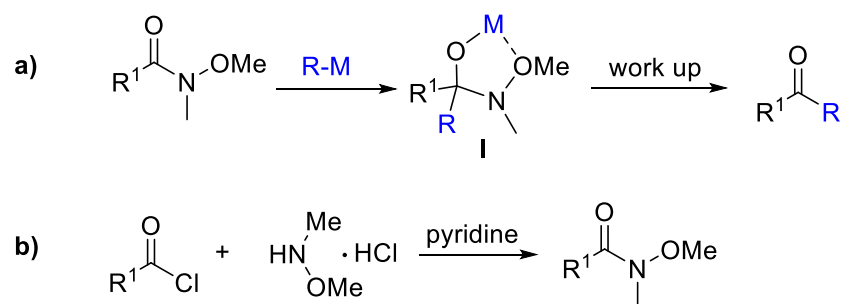
¹³ Eberle, M.K.; Kahle, G.G. *Tetrahedron Lett.* **1980**, 21, 2303-2304.



Scheme 3. The Grignard reaction of acid derivatives

In order to overcome the common over-addition problem, the Weinreb–Nahm ketone synthesis has been used as a dependable reaction in organic chemistry to synthesize ketones. In 1981, Steven M. Weinreb and Steven Nahm¹⁴ discovered a clean reaction to produce ketones by using N-methoxy-N-methylamides, which are commonly referred to Weinreb amides, and organometallic reagents (Scheme 4a). The chance of over-addition is significantly reduced due to formation of stable tetrahedral metal-chelated intermediate **I** is formed by the nucleophilic addition of an organometallic reagent such as a Grignard reagent or organolithium reagent to a Weinreb-Nahm amide and the intermediate **I** is hydrolyzed into a ketone after the workup. One of the most common ways to prepare Weinreb-Nahm amide is the treatment of an acyl chloride and the commercially available salt N,O-dimethylhydroxylamine hydrochloride (Scheme 4b).

¹⁴ Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, 22, 3815.



Scheme 4. The Weinreb–Nahm ketone synthesis

1.1.2 The Heck reaction

Heck's pioneering work on Pd-catalyzed cross-coupling reactions utilized olefins as coupling partners, and this type of reaction does not follow the generic cross-coupling definition as mentioned in Scheme 1. Immense research has been published in this area; undoubtedly the Heck reaction is one of the most important discoveries in organic synthesis for making carbon-carbon bonds. Preliminary work in this area was published in 1968. In these early studies the organopalladium compound (RPdX; R = alkyl, aryl; X = halide) generated was added to olefins, which could undergo alkene insertion and elimination reactions.¹⁵ Most of these early studies used a stoichiometric amount of palladium, generated from an organomercury compound and a Pd(II) salt (Scheme 5a).¹⁶ One of these studies demonstrated that a catalytic version could be achieved by using a catalytic amount of CuCl₂ to reoxidize the elemental palladium (Scheme 5b).¹⁷

¹⁵ (a) R. F. Heck, *J. Am. Chem. Soc.* **1968**, 90, 5531. (b) R. F. Heck, *J. Am. Chem. Soc.* **1968**, 90, 5526. (c) R. F. Heck, *J. Am. Chem. Soc.* **1968**, 90, 5542.

¹⁶ R. F. Heck, *J. Am. Chem. Soc.* **1968**, 90, 5518.

¹⁷ R. F. Heck, *J. Am. Chem. Soc.* **1968**, 90, 5538.

In 1969, the group of Fujiwara also realized that stoichiometrically generated ArPd halides react with olefins to give styrenes (Scheme 5c).¹⁸ Mizoroki's group made a fundamental discovery in 1971, in which the arylation of iodobenzene in the presence of alkenes and a Pd(II) catalyst gave styrenes (Scheme 5d).¹⁹ One year later, Heck independently reported a similar reaction using a different Pd catalyst and base. The active catalyst Pd(0) is formed by Pd coordination to the alkene (Scheme 5e).²⁰ In 1974, Heck introduced phosphine ligands into the equation²¹ and this variant soon became the standard protocol for the Heck reaction.

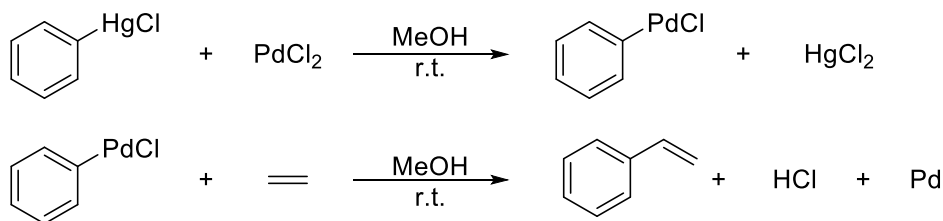
¹⁸ Y. Fujiwara, I. Moritani, S. Danno, R. Asano, and S. Teranishi, *J. Am. Chem. Soc.* **1969**, *91*, 7166.

¹⁹ T. Mizoroki, K. Mori, and A. Ozaki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 58.

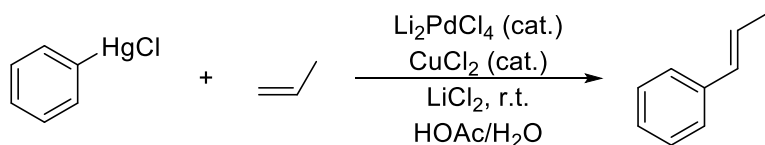
²⁰ Heck, R. F.; Nolley Jr., J. P. *J. Org. Chem.* **1972**, *37*, 2320.

²¹ Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *4*, 1133

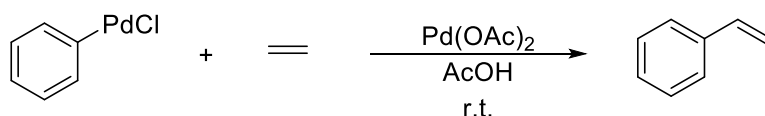
a) Heck, 1968



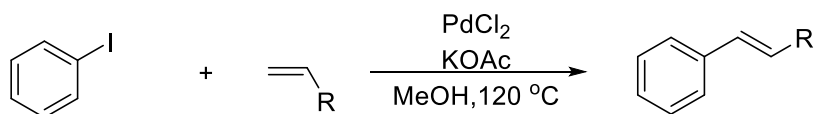
b) Heck, 1968



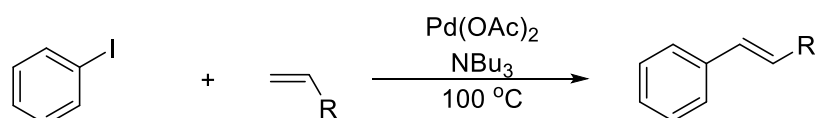
c) Fujiwara and coworkers, 1969



d) Mizoroki and coworkers, 1971



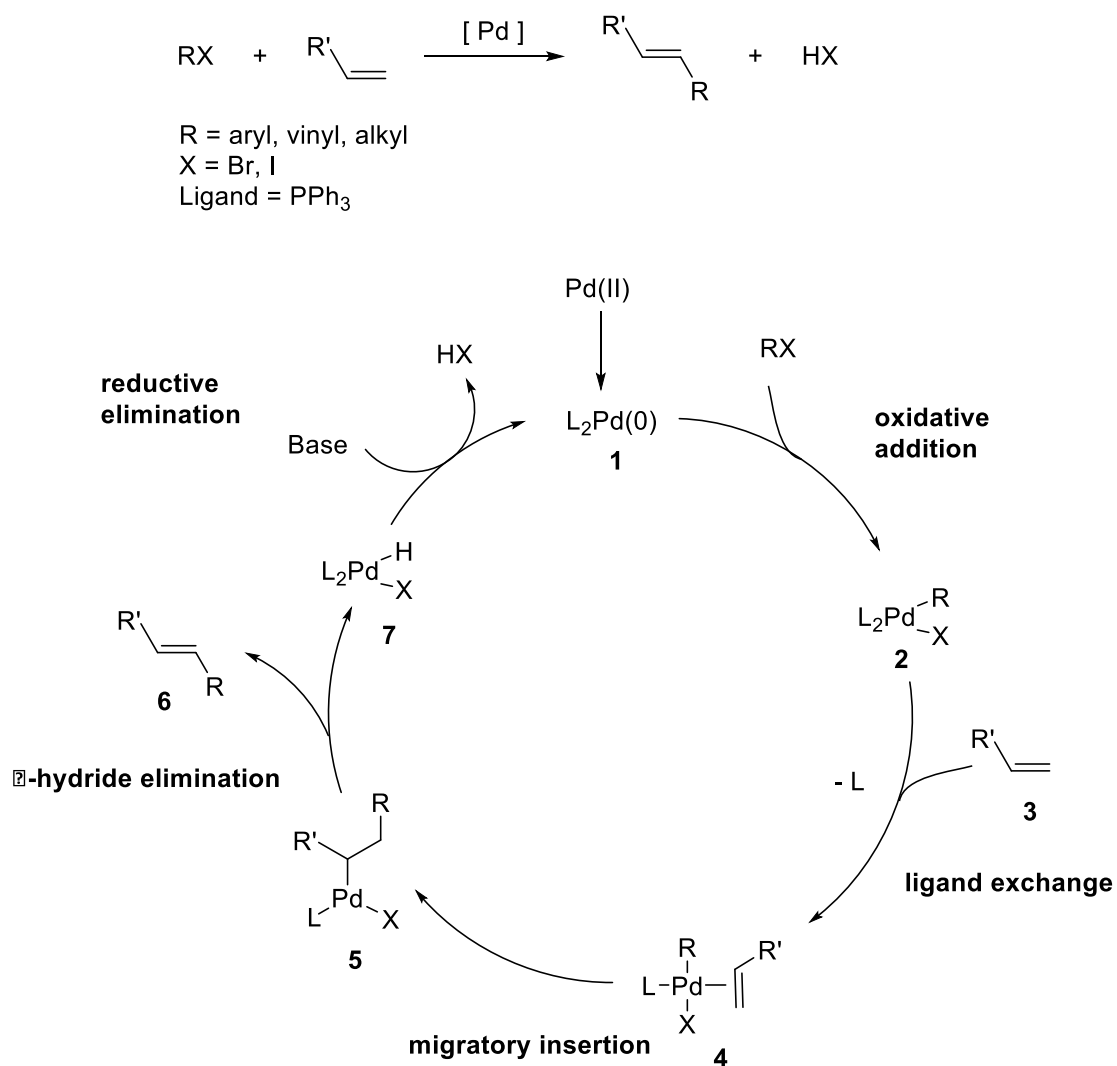
e) Heck and coworker, 1972



Scheme 5. Early works and development of the Heck reaction

Heck and Dieck proposed a detailed mechanism by a Pd(0)/Pd(II) catalytic cycle (Scheme 6).²¹ This mechanism is now generally accepted, though slight changes are possible under varying conditions. In general, the reaction starts when the bis(triphenylphosphine)Pd(0) **1** is actively formed from Pd(II), and then organohalide RX oxidatively adds to **1** giving Pd(II) intermediate **2**. Next, the alkene **3** undergoes ligand exchange followed by coordination with palladium to give **4**. In the following

migratory insertion step, the alkene inserts into the palladium-carbon bond to give intermediate **5**. The desired product olefin **6** is released through β -hydride elimination. Finally, the reduction of Pd(II) **7** to Pd(0) **1** is induced by the base, closing the catalytic cycle.



Scheme 6. Mechanism of the Heck reaction

1.1.3 Pd-catalyzed acylation reactions

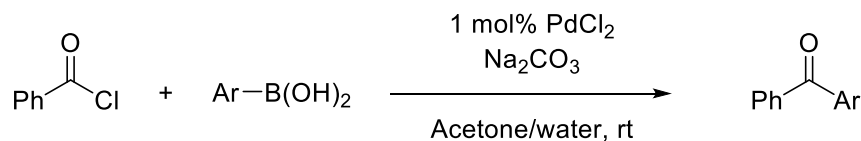
With the aim of improving access to ketones, generating less waste, developing milder reaction conditions and increasing the functional group tolerance over traditional methods, the development of catalytic alternatives is highly desirable. Many Pd-catalyzed cross-coupling reactions have been developed with this goal in mind. In 1997, Bumagin and coworkers reported the first reaction that used acyl chlorides and aryl boronic acids with catalytic PdCl₂ to form aromatic ketones in high yields (Scheme 7a).²² Alternatively, the coupling of anhydrides with boronic acids to synthesize ketones was discovered by Gooßen's group in 2001.²³ This reaction gives the corresponding aryl ketones in relatively high yields and also with high selectivity (Scheme 7b). There are also many other coupling reagents that work with boronic acids in acylation reactions to provide different types of ketones which will not be discussed in detail.²⁴

²² Bykov, V.V.; Korolev, D.N.; Bumagin, N.A. *Russ. Chem. Bull.* **1997**, 46, 1631-1632.

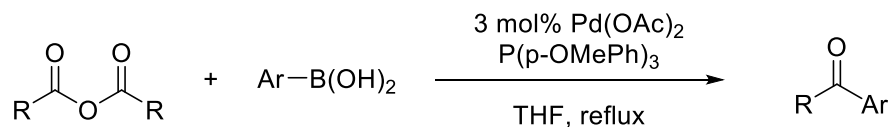
²³ Gooßen, L.J.; Ghosh, K. *Angew. Chem. Int. Ed.* **2001**, 40, 3458-3460.

²⁴ a) Gooßen, Lukas, J.; Ghosh, K. *Eur. J. Org. Chem.* **2002**, 3254-3267. b) Duan, Y.-Z.; Deng, M.-Z. *Synlett* **2005**, 355-357. c) Tomizawa, T.; Orimoto, K.; Niwa, T.; Nakada, M. *Org. Lett.* **2012**, 14, 6294-6297.

a) Bumagin and coworkers, 1997



b) Gooßen and coworkers, 2001



R = allyl, Ph, PMP, etc.

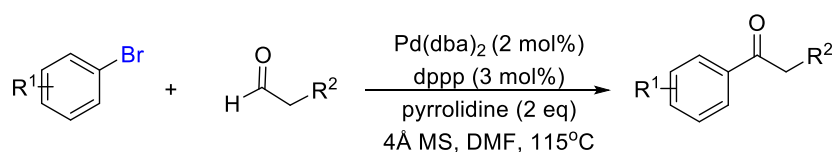
Scheme 7. Examples of Pd-catalyzed acylation using boronic acids

Pd-catalyzed acylation of aryl halides with aldehydes offers another direct approach to synthesize ketones. Recently, Xiao's group disclosed two efficient, palladium-catalyzed direct acylation reactions of aryl bromides and aryl chlorides with aldehydes. The reaction using aryl bromides appears to involve co-catalysis of palladium-dppp and pyrrolidine (Scheme 8a).²⁵ In contrast, the other reaction using aryl chlorides requires an electron-rich monophosphine ligand and a higher temperature (Scheme 8b).²⁶

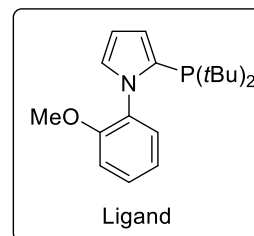
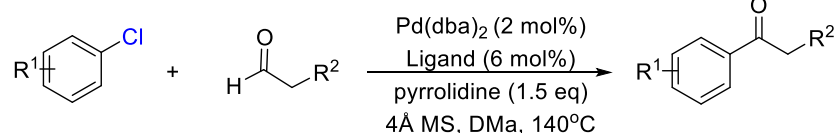
²⁵ J. Ruan, O.; Saidi, J. A.; Iggo, J. Xiao, *J. Am. Chem. Soc.* **2008**, 130, 10510-10511.

²⁶ Colbon, P.; Ruan, J.; Purdie, M.; Xiao, *J. Org. Lett.* **2010**, 12, 3670.

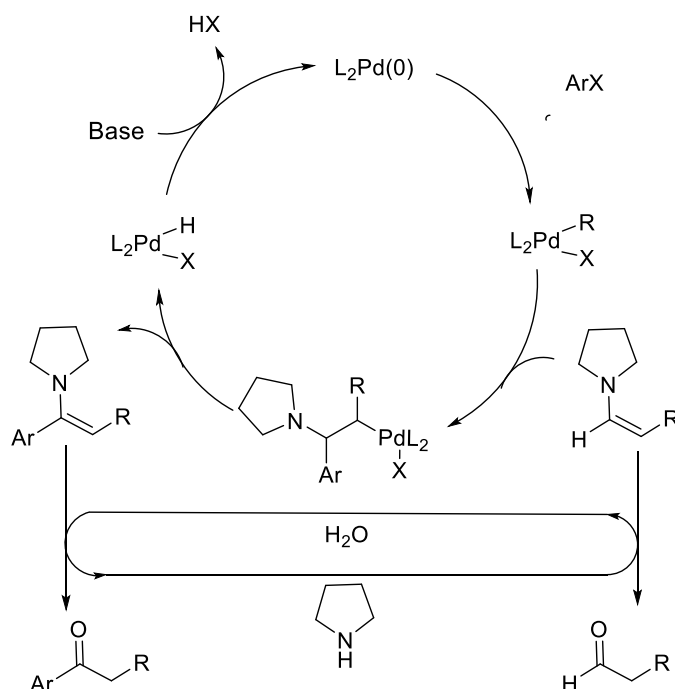
a) Xiao and coworkers, 2008



b) Xiao and coworkers, 2010



c) Proposed Mechanism



Scheme 8. Synthesis of alkyl aryl ketones by direct acylation of aryl halides with aldehydes

The choice of ligand, as well as the presence of pyrrolidine were critical to both reactions. The authors suggested that the acylation might take place via a Heck-type pathway and the proposed catalytic cycle was shown in Scheme 8c. In the presence of pyrrolidine, the aldehyde can equilibrate to form an enamine which reacts analogously to the well-established Heck reaction. The pyrrolidinyl moiety of the

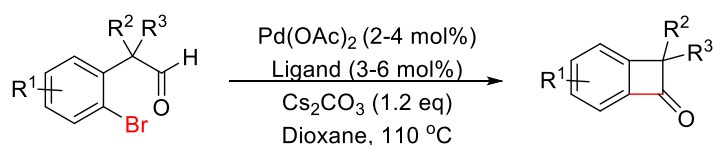
enamine polarizes the C=C double bond and facilitates the migration of the aryl group to the R carbon and hydrolysis results in the final ketone. The reactions were successful for a wide range of aryl chlorides and tolerant of functionality on the alkyl aldehyde, however, only alkyl aryl ketones can be obtained in modest to good yields.

The Martin group also demonstrated the potential of intramolecular acylation via C-H functionalization to synthesize corresponding ketones. In 2010, they reported the Pd-catalyzed intramolecular acylation of aryl bromides with aldehydes using a binaphthyl-type ligand (Scheme 9a).²⁷ A broad scope of functionalized substrates can also be accessed successfully. Two years later, a similar type of intramolecular acylation was applied to aryl chlorides (Scheme 9b), where an N-heterocyclic carbene (NHC) ligand was used in the optimized conditions.²⁸ These intramolecular acylation methods allow for the synthesis of a variety of elusive ketones with diverse functional groups and substitution patterns. In their proposed C-H functionalization mechanism, they suggested that the success of the reaction is highly dependent on the five-membered intermediate. Adding more C or less C into this intermediate would not give any coupling products. Thus, only 4-membered ring products can be obtained through this method.

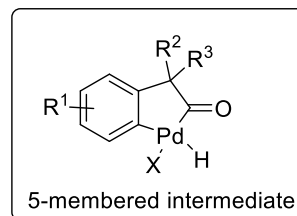
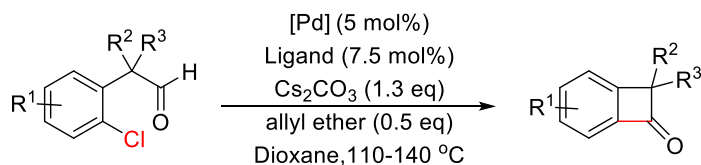
²⁷ Álvarez-Bercedo, P.; Flores-Gaspar, A.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2010**, 132, 466.

²⁸ Flores-Gaspar, A.; Gutiérrez-Bonet, Á.; Martin, R. *Org. Lett.* **2012**, 14, 5234.

a) Martin and coworkers, 2010



b) Martin and coworkers, 2012

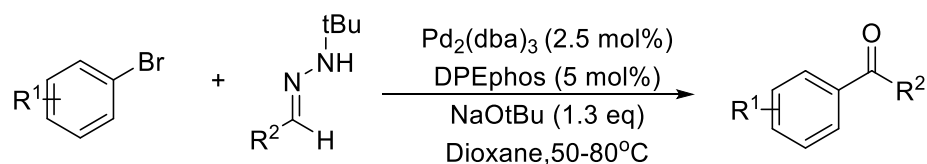


Scheme 9. Pd-catalyzed intramolecular acylation of aryl halides

The Hartwig lab reported another method to form alkyl aryl ketones or diaryl ketones through palladium-catalyzed coupling of aryl bromides with N-tert-butylhydrazones (Scheme 10).²⁹ The coupling occurred under mild conditions at the C-position of the diazaallyl group, followed by hydrolysis to give the corresponding ketones in high yield. The reaction occurred in the presence of several classes of functional groups, including electron-rich and electron-poor aryl bromides. Nonetheless, hydrazones were used as the starting material in this coupling, which were stoichiometrically generated from the aldehydes and hydrazines. The use of hydrazones is undesirable and it increases the overall cost of the reaction.

²⁹ Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, 128, 14800.

Hartwig and cowoker, 2006



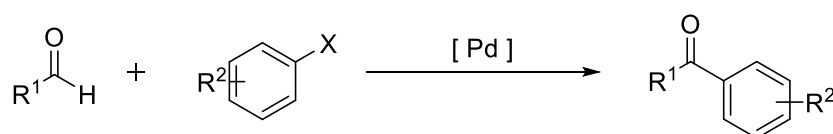
Scheme 10. Pd-catalyzed coupling of aryl bromides with N-tert-butylhydrazones

1.1.4 Research goal

Recent studies of Xiao, Martin, and Hartwig all demonstrated that Pd-catalyzed acylation of aryl halides offers another approach to synthesize ketones with a variety of functionalities. However, there are still some significant drawbacks involved in these reactions. First of all, the products are limited to alkyl aryl ketones in Xiao's work, since only aldehydes bearing α -H that enable condensation to make enamines can be used in this Heck-type intermolecular acylation reactions (Scheme 8). In Martin's studies, the intramolecular acylation can only produce benzocyclobutenones via C-H functionalization (Scheme 9). Finally, hydrazones were used as the starting material in Hartwig's study - they are not readily available and need to be stoichiometrically synthesized from aldehydes and hydrazines (Scheme 10). In order to overcome these limitations, we aim to develop a more general reaction.

Our research goal involves the direct intermolecular acylation of aryl halides and aldehydes to give diverse ketones in one step (Scheme 11). Due to the high utility of both aryl halides and aldehydes, the overall cost of the new reaction to produce fine chemicals might be lower and more complicated molecular patterns could also be

constructed. As compared to traditional approaches to synthesize ketones, the transition metal catalyzed acylation reactions may require milder reaction conditions, use safer chemical reagents, and generate less waste. Inspired by previous work on Pd-catalyzed acylation reactions, we aim to find an optimized catalytic condition for the intramolecular direct acylation of aldehydes and aryl halides to construct diverse ketones, which could potentially become a powerful synthetic tool.

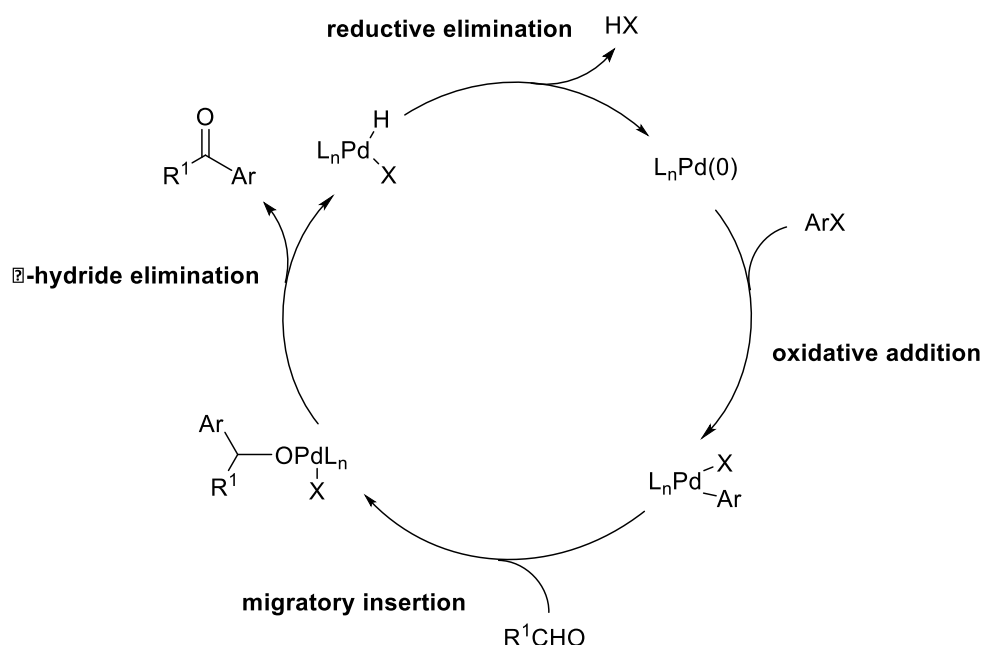


Scheme 11. Proposed new Oxa-Heck reaction: direct acylation of aldehydes and aryl halides

Our proposed mechanism for a new acylation reaction would involve a hypothesized mechanism for a new acylation reaction could involve well preceded elementary steps in palladium catalysis. Briefly, oxidative addition, migratory insertion, β -hydride elimination and reductive elimination could be combined to provide ketones from aryl halides and aldehydes (Scheme 12). The lesser-known migratory insertion step, where an aldehyde inserts into a Pd-Ar bonds was proposed in some 1,2 addition reactions between benzaldehyde and boronic acid.³⁰ However, the direct observation of this elementary step has, to our knowledge, not yet been disclosed in the literature. The proposed mechanism is similar to the mechanism of the Heck reaction (Scheme 6), which also begins with aryl halides (ArX) oxidatively adding to Pd(0). However, the migratory

³⁰ a) Yamamoto, T.; Iizuka, M.; Takenaka, H.; Ohta, T.; Ito, Y. *J. Organomet. Chem.* **2009**, 694, 1325. b) Kuriyama, M.; Shimazawa, R.; Shirai, R. *Tetrahedron* **2007**, 63, 9393. c) He, P.; Lu, Y.; Hu, Q.-S. *Tetrahedron Lett.* **2007**, 48, 5283. d) Yu, A.; Cheng, B.; Wu, Y.; Li, J.; Wei, K. *Tetrahedron Lett.* **2008**, 49, 5405.

insertion step is done with a carbonyl instead of an olefin. Since all these elementary steps are known in palladium chemistry and can theoretically give the desirable diaryl ketones in the proposed new reaction, we believe there will be an optimized catalytic condition that can facilitate the reaction to go through our hypothesized mechanism.



Scheme 12. Proposed mechanism for the new reaction: oxa-Heck reaction

1.2 Results and discussion

1.2.1 High-throughput screening using Pd catalysts

In order to find the optimized catalytic conditions for the new oxa-Heck reaction (Scheme 11), we used high-throughput screening (HTS) to find the best combination of different variables and to discover the effect of each variable including catalyst, ligand, base, solvent, additives, etc. HTS allows us to do reaction optimization much more efficiently, which is particularly useful in homogeneous catalyzed systems due

to the large number of parameters. In each screening, 96 reactions in relatively small scales (down to $\mu\text{L}/\text{mg}$ quantities) can be investigated at a time with different variable combinations. The results were analyzed using GC-MS (Figure 1). The lower reagent and compound consumption, cost savings, and high productivity of HTS allow us to test many different catalytic combinations simultaneously.



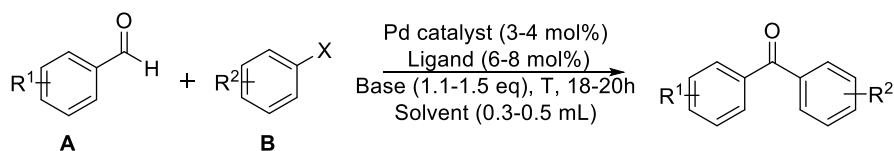
Figure 1. The process of high-throughput screening

Three initial HTSs were performed for intermolecular palladium-catalyzed acylation reactions of aldehydes and aryl halides. These initial screens were carried out with 7 variables using frequently encountered catalyst systems selected from the Pd-catalyzed Heck, migratory insertion, and oxidation literature,³¹ with an emphasis on ligand diversity. Specific details of the variable selection of catalyst, base, temperature, additive, etc. are presented in Figure 2. The structures of different types

³¹ a) A.-E. Wang, J.-H. Xie, L.-X. Wang, Q.-L. Zhou, *Tetrahedron*, **2005**, 61, 259-266. b) H.-J. Xu, Y.-Q. Zhao, X.-F. Zhou, *J. Org. Chem.*, **2011**, 76, 8036-8041. c) P. He, Y. Lu, C.-G. Dong, Q.-S. Hu, *Org. Lett.*, **2007**, 9, 343-346. d) Du, X. L.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, K.; Okeda, T.; Wang, H. F.; Fugami, K.; Kosugi, M. *Org. Lett.* **2001**, 3, 3313. d) Jia, Y.-X.; Katayev, D.; Kundig, E. P. *Chem. Commun.* **2010**, 46, 130.

of ligands including N-heterocyclic carbene, bidentate, phosphine, phosphite ligands and chiral ligands are shown in Figure 3.

Unfortunately, after 3 HTSs (~300 reactions) the highest yield was still lower than 5% with high recovery of starting materials and no significant side reactions were obtained in these reactions. The best reaction condition used $\text{Pd}(\text{OAc})_2$, SIPr, HCl, Cs_2CO_3 and toluene at 110 °C. In most of the reactions, starting materials were recovered in high yields. Due to generally poor yields, no visible trend could be found. We decided to revert to a more rational approach to identify which steps of the proposed catalytic cycle were most troublesome.



First High-throughput Screening

A (1 eq): 3-fluorobenzaldehyde

B (1eq): 4-bromoanisole

Catalyst (4 mol%): Pd(OAc)₂

Ligand (6 mol%): *SiPr*·HCl, *iPr*·HCl, IMes·HCl, PPh₃, IAd·HBF₄, *PtBu*₃·HBF₄

Base (1.1 eq): NEt₃, KOtBu, Cs₂CO₃

Additives (0.2 eq): pivalic acid

Solvent (0.45 mL/vial): 1,4-dioxane, DMF, MeCN, toluene

Temperature: 110 °C

Second High-throughput Screening

A (1 eq): 3-fluorobenzaldehyde

B (1eq): phenyl trifluoromethanesulfonate (PhOTf), chlorobenzene, iodobenzene, phenyl mesylate (PhOMs)

Catalyst (4 mol%): Pd₂(dba)₃

Ligand (8 mol%): *SiPr*·HCl, PPh₃, IAd·HBF₄, *tBuXPhos*, DavePhos, dppf, BINAP

Base (1.5 eq): NEt₃, Cs₂CO₃, K₃PO₄

Solvent (0.4 mL/vial): 1,4-dioxane, MeCN

Temperature: 110 °C

Third High-throughput Screening

A (1 eq): 3-fluorobenzaldehyde, 4-cyanobenzaldehyde, octanal

B (1 eq): phenyl trifluoromethanesulfonate (PhOTf), bromobenzene

Catalyst (4 mol%): Pd(OAc)₂

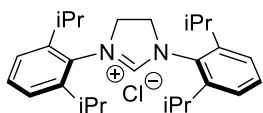
Ligand (6 mol%): Josiphos SL-J002, Josiphos SL-J003, Josiphos SL-J005, Walphos SL-W001, Mandyphos SL-M001, Taniaphos SL-T001, Butiphane SL-P005-1a, SL-A101-1, P(*o*-tol)₃, P(*p*-CF₃Ph)₃, CyTop-L₁, CyTop-L₂, dppp, dppf, dppe, dppb, XantPhos, Sphos, *tBuXPhos*, triarylphosphite ligand

Base (1.5 eq): NEt₃, Cs₂CO₃, NaOtBu, KOtBu

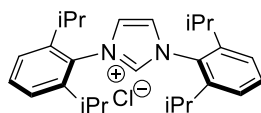
Solvent (0.4 mL/vial): toluene, 1,4-dioxane

Temperature: 130 °C

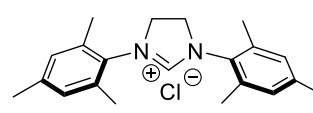
Figure 2. Variable selection details for 1st, 2nd and 3rd high-throughput screening



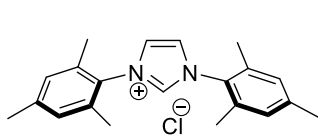
SiPr-HCl



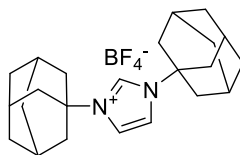
iPr-HCl



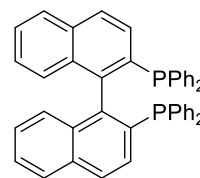
Si-Mes-HCl



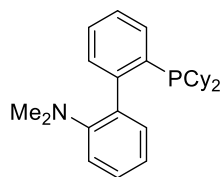
IMes-HCl



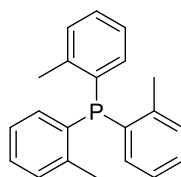
IAd-HBF₄



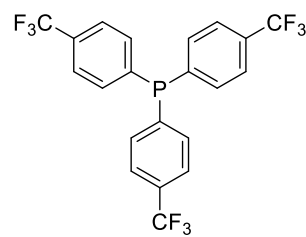
BINAP



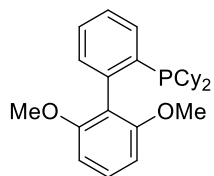
DavePhos



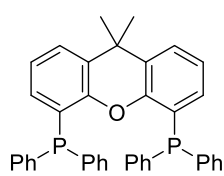
P(o-tol)₃



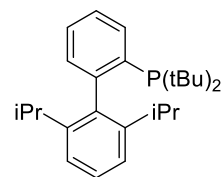
P(p-CF₃Ph)₃



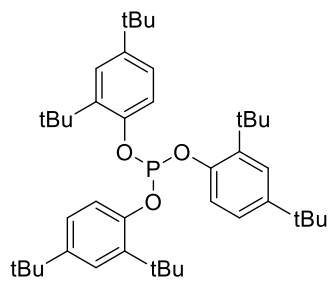
SPhos



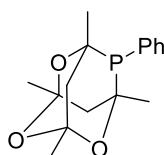
XantPhos



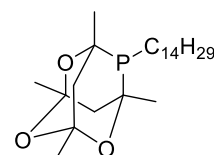
tBuXPhos



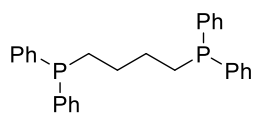
triaryl phosphite ligand



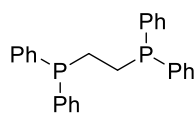
CyTop - L1



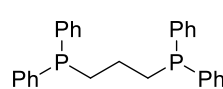
CyTop - L2



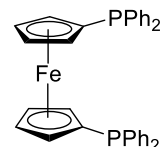
dppb



dppe



dppp



dppf

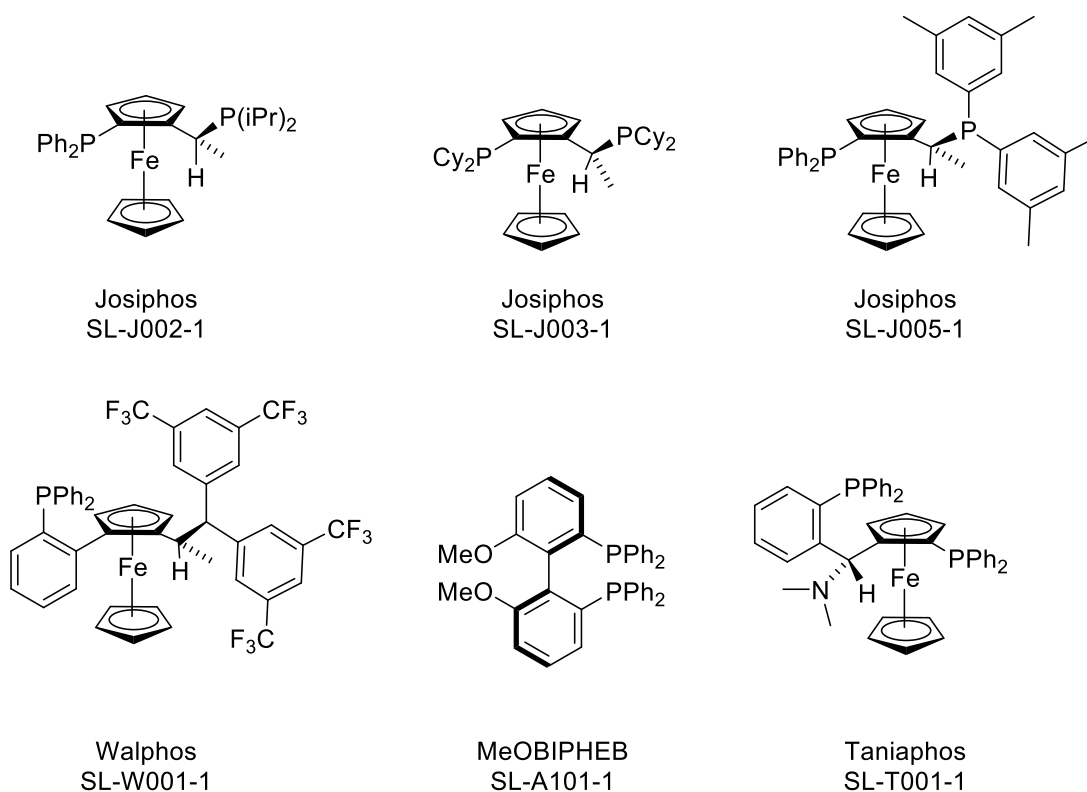


Figure 3. Selected ligands in 1st, 2nd and 3rd high-throughput screening

1.2.2 Troubleshooting

According to our proposed mechanism for this oxa-Heck reaction (Scheme 12), 4 elementary steps including: oxidative addition, migratory insertion, β -hydride elimination and reductive elimination were involved in the catalytic cycle. Among them, β -hydride elimination³² and reductive elimination steps³³ were generally accepted as

³² a) Nilsson, P., Olofsson, K., and Larhed, M. Focus on Regioselectivity and Product Outcome in Organic Synthesis. In *The Mizoroki–Heck Reaction*; Oestreich, M., Ed.; John Wiley and Sons: New York, **2009**; p 133. b) Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.* **1989**, 30, 4925. c) Keinan, E.; Kumar, S.; Dangur, V.; Vaya, J. *J. Am. Chem. Soc.* **1994**, 116, 11151.

³³ a) Hartwig, J. F. *Inorg. Chem.* **2007**, 46, 1936. b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, 119, 12382. c) Marcone, J. E.; Moloy, K. G. *J. Am. Chem. Soc.* **1998**, 120, 8527. d) Lan, Y.; Liu, P.; Newman, S. G.; Lautens, M.; Houk, K. N. *Chem. Sci.* **2012**, 3, 1987.

non-challenging steps in most Pd-catalyzed cross-coupling reactions. In the Heck reaction, β -hydride elimination is the key step in quenching the carbon-palladium bond and the rate of this step is so fast, sometimes it even becomes the origin of side reaction and byproducts.³⁴ Also, reductive elimination in Pd-catalyzed processes is generally considered as a facile and irreversible step, it is usually exothermic and critical for closing the catalytic cycle.³⁵ Thus, we considered migratory insertion and oxidative addition steps as the more problematic or challenging steps in our oxa-Heck reaction.

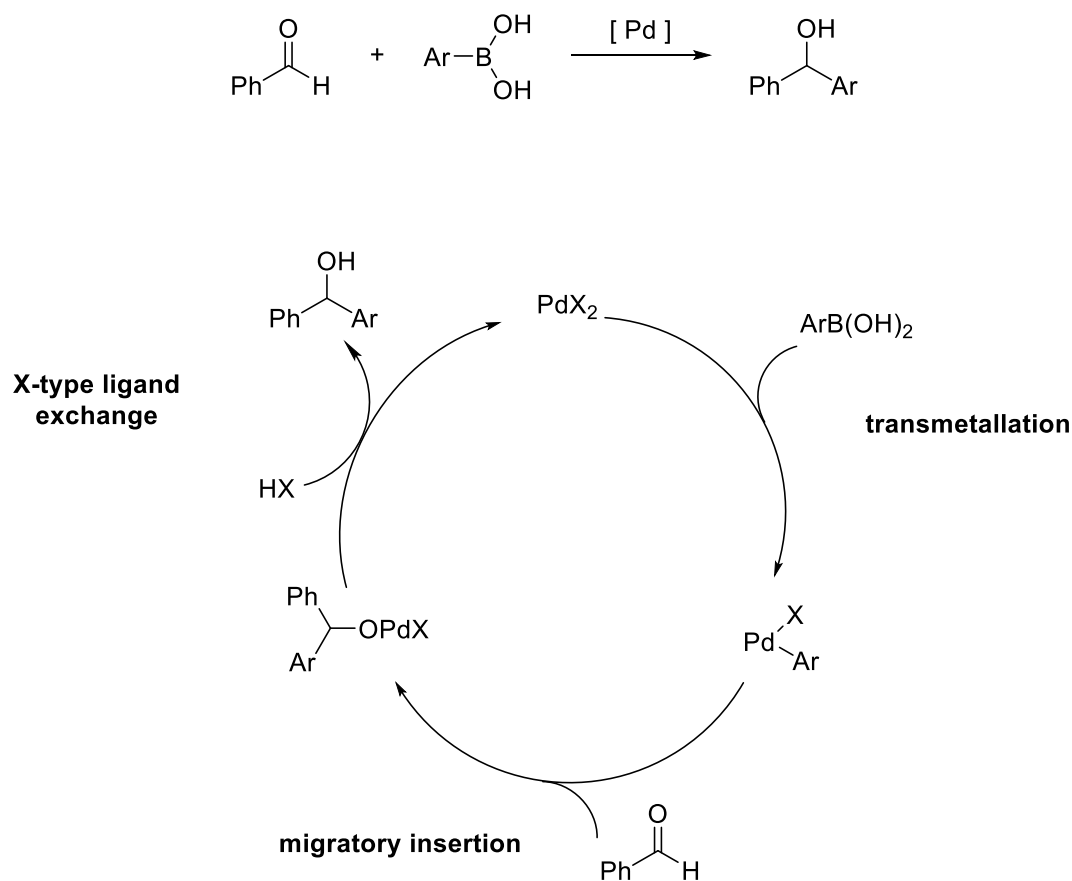
Migratory insertion step

With the hypothesis that migratory insertion step is a challenging step in our reaction, we started to focus on finding catalytic systems that explicitly work well for this transformation. The 1,2 addition reaction between benzaldehyde and boronic acid is known, and occurs by the mechanism presented in Scheme 13.³⁶ Comparing the mechanism of Pd-catalyzed 1,2 addition reaction to our proposed oxa-Heck reaction, they both have the same migratory insertion elementary step and the major difference is the oxidation state of the palladium catalyst. The 1,2 addition reaction starts with Pd(II) and then goes through transmetallation to give Pd(II) intermediate XPdPh, while our oxa-Heck reaction needs to go through an oxidative addition to form a similar Pd(II) intermediate.

³⁴ Lu, X. *Top Catal.* **2005**, 35, p73.

³⁵ Pérez-Rodríguez, M.; Braga, A. A. C.; García-Melchor, M.; Pérez-Temprano, M. H.; Casares, J. A.; Ujaque, G.; de Lera, A. R.; Álvarez, R.; Maseras, F.; Espinet, P. *J. Am. Chem. Soc.* **2009**, 131, 3650.

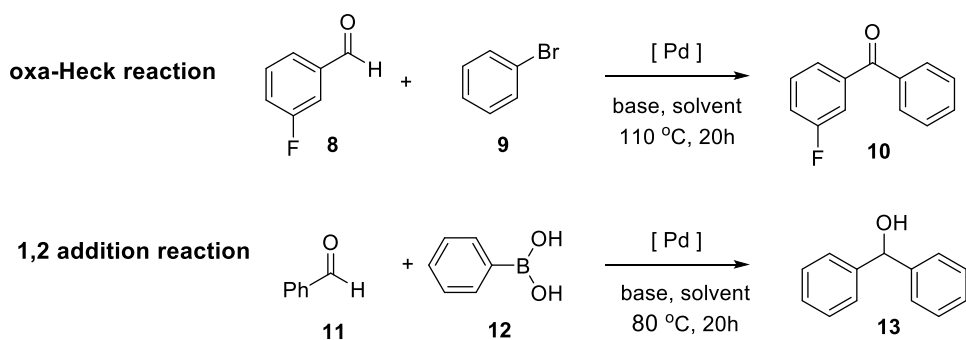
³⁶ Yamamoto, T.; Iizuka, M.; Takenaka, H.; Ohta, T.; Ito, Y. *J. Organomet. Chem.* **2009**, 694, 1325.



Scheme 13. Proposed mechanism for 1,2 addition reaction

According to our initial 3 HTS results, the best oxa-Heck reaction is between 3-fluorobenzaldehyde **8** and bromobenzene **9** and gave the diaryl ketone **10** in ~ 2% yield with high recovery of **8**. By applying the same reaction conditions ($\text{Pd}(\text{OAc})_2$, $\text{SIPr}\cdot\text{HCl}$, Cs_2CO_3 and toluene) to 1,2 addition reaction between benzaldehyde **11** and phenylboronic acid **12**, a similar result was obtained that gave the desired alcohol product **13** in only 2 % yield (Table 2, Entry 1).

Table 2. Optimization for 1,2 addition and oxa-Heck reactions



Entry	Pd-precursors	1, 2 addition reaction yield (%) ^a	oxa-Heck reaction yield (%) ^a
1	Pd(OAc) ₂ , SiPr.HCl	2	2
2	Pd ₂ (dba) ₃ , PPh ₃ , CHCl ₃	52	< 5
3	, [Pd(allyl)Cl] ₂	71	< 5
4		60	< 5
5		76	< 5

^a Yield determined by ¹H NMR of the crude mixture with 1,3,5-trimethoxybenzene as internal standard.

To further investigate migratory insertion, different catalytic systems were selected from Pd-catalyzed 1,2 addition of boronic acids and aldehydes literature.³⁷ These reaction conditions were examined both on the 1,2 addition reaction and oxa-Heck reaction in order to improve the migratory insertion step. The results are summarized in Table 2. Palladium(0) and phosphine ligand in the presence of bases and a catalytic amount of chloroform (Entry 2), thioether-imidazolinium chloride as a heterobidentate carbene ligand precursor with [Pd(allyl)Cl]₂ (Entry 3), phosphinite- and phosphite-based palladacycle (Entry 4) and cyclopalladated ferrocenylimine bipyridine (Entry 5) all significantly improved the 1,2 addition reaction, but unfortunately poor yield was still obtained in all the oxa-Heck reactions.

Preparation of palladium precatalysts

Another key to the success of Pd-catalyzed cross-couplings is the efficient generation of the L_nPd(0) species to enter into the catalytic cycle. Some common commercially available palladium catalysts such as Pd(OAc)₂ and PdCl₂ need to be reduced by the base and incorporate with ligands successfully in order to generate the L_nPd(0) species. The insufficiency of the reduction and formation of L_nPd(0) is sometimes observed for coupling reactions.³⁸ To avoid this problem, some commercially available Pd(0) sources including Pd₂(dba)₃ and Pd(PPh₃)₄ were tested in our reaction, however, none of them seemed to improve the reaction. According to the recent

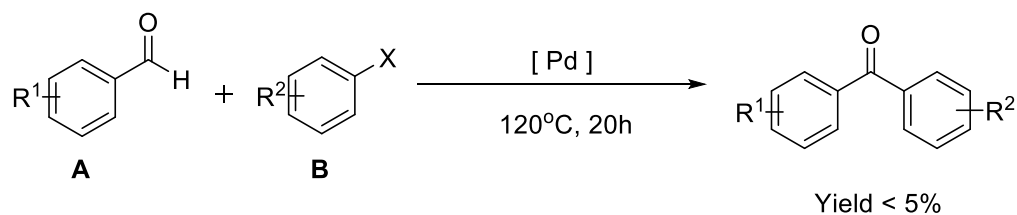
³⁷ a) Yamamoto, T.; Iizuka, M.; Takenaka, H.; Ohta, T.; Ito, Y. *J. Organomet. Chem.* **2009**, *694*, 1325. b) Kuriyama, M.; Shimazawa, R.; Shirai, R. *Tetrahedron* **2007**, *63*, 9393. c) He, P.; Lu, Y.; Hu, Q.-S. *Tetrahedron Lett.* **2007**, *48*, 5283. d) Yu, A.; Cheng, B.; Wu, Y.; Li, J.; Wei, K. *Tetrahedron Lett.* **2008**, *49*, 5405.

³⁸ a) Ozawa, A. Kubo, and T. Hayashi, *Chem. Lett.*, 1992, 2177. b) Amatore, C.; Carre, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818. c) Pryjomska-Ray, I.; Gniewek, A.; Trzeciak, A. M.; Ziółkowski, J. J.; Tylus, W. *Top. Catal.* **2006**, *40*, 173.

study, commercial $\text{Pd}_2(\text{dba})_3$ contains varying amounts of Pd nanoparticles and free dba ligands.³⁹ In order to solve the problem of catalyst activation, we synthesized different forms of activated palladium precatalysts selected from the literature that are known to improve cross-coupling reactions.⁴⁰ These precatalysts are pre-ligated and relatively stable to air and moisture. Selected catalysts studied include ligated allyl or cinnamyl palladium chloride precatalysts, highly active $\text{Pd}(\eta^3\text{-1-PhC}_3\text{H}_4)(\eta^5\text{-C}_5\text{H}_5)$ (Baird catalyst) and palladacycle-based precatalysts. The details of 4th HTS were presented in Figure 4 and the structures of selected precatalysts were shown in Figure 5. Unfortunately, using these pre-ligated precatalysts did not show significant improvement.

³⁹ Zalesskiy, S. S.; Ananikov, V. P. *Organometallics* **2012**, *31*, 2302.

⁴⁰ a) Nareddy, P.; Mazet, C. *Chemistry – An Asian Journal* **2013**, *8*, 2579. b) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916. c) Fraser, A. W.; Besaw, J. E.; Hull, L. E.; Baird, M. C. *Organometallics* **2012**, *31*, 2470.



Fourth High-throughput Screening

A (1 eq): 4-cyanobenzaldehyde

B (1 eq): Phenyl trifluoromethanesulfonate (PhOTf), 4-bromoanisole

Catalyst (5 mol%): Pd(iPr)(cinnamyl)Cl, Pd(iPent)(cinnamyl)Cl, Pd(SIMes)(cinnamyl)Cl
Pd(iPr)(allyl)Cl, Pd(iPent)(allyl)Cl, PEPPSI

Base (1.5 eq): NEt₃, K₂CO₃, NCy₂Me, DBU, Quinuclidine, Hunig's base,
10% Quinuclidine and 1.5 eq K₂CO₃

Solvent (0.35 mL/vial) : Toluene

Temperature: 120 °C

Figure 4. Details of 4th high-throughput screening using preformed Pd-precursors

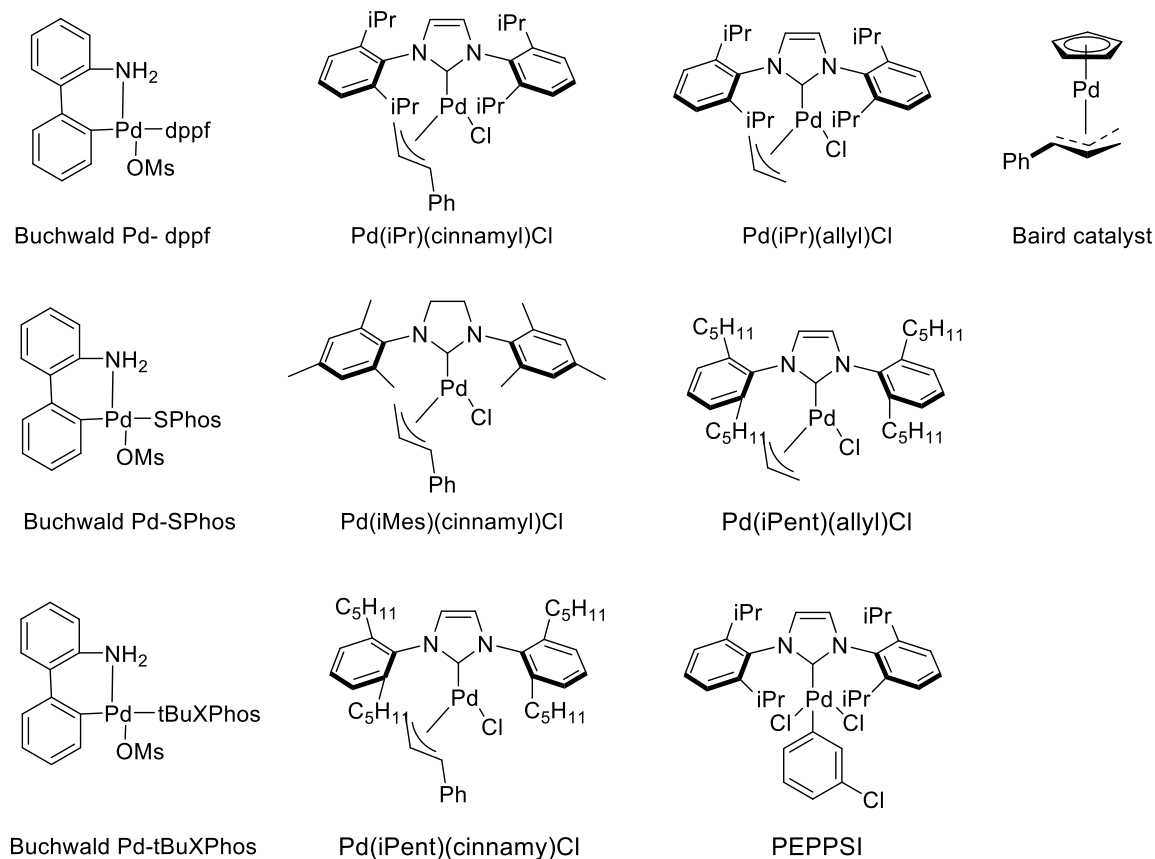


Figure 5. Structures of screened Pd-precursors

We didn't consider using nickel catalyst in our oxa-Heck reactions earlier, since β -hydride elimination is more efficient in the Pd system than in the Ni system. Most importantly, reductive elimination for Ni(0) catalyst regeneration through HX removal from HNiX is known to be challenging.⁴¹ So we chose to mainly focus on palladium catalysts instead of nickel catalysts. However, given no obvious hit within our first 4 HTSs using a wide range of Pd catalysts, we decided to expand our catalyst scope and reconsider testing our reaction by using nickel catalysts.

⁴¹ Lin; Liu, L.; Fu, Y.; Luo, S.-W.; Chen, Q.; Guo, Q.-X. *Organometallics* **2004**, 23, 2114.

1.2.3 Optimization using Ni catalysts

Nickel is a promising alternative to Pd in many coupling reactions since it can readily perform many of the same elementary reactions as palladium, although it is somewhat less well studied.⁴² Using Ni in cross-coupling reactions can offer several advantages⁴³ such as the lower cost as compared to Pd, and Ni is better at insertion chemistry. This might be due to the weaker Ni-C bond vs. Pd-C bond. Moreover, faster oxidative addition is usually observed for Ni since it is more electropositive which allows for the use of a wide range of electrophiles. Thus, using Ni can give access to more starting materials such as some pseudohalides with stronger C-X bonds (X = OPiv, OMs, etc.).⁴⁴

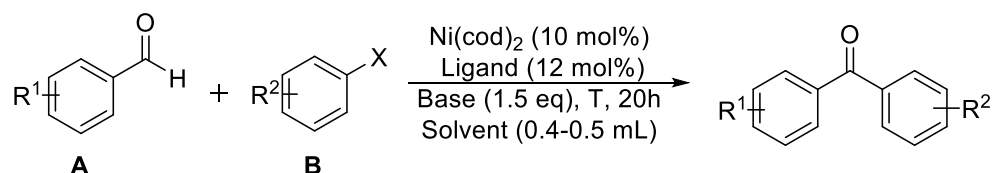
In order to investigate the potential of Ni in our oxa-Heck reaction, three new HTSs were performed using commercially available Ni catalysts including Ni(cod)₂ and NiCl₂. The 5th and 6th HTS focused primarily on the variation of aryl halides, pseudohalides, ligands, and bases to test the potential reactivity of a Ni-catalyzed oxa-Heck reaction. The details of these 2 screening are presented in Figure 6, and experiments using 3-fluorobenzaldehyde **8** with PhOTf **14** gave the highest yields as compared to the other aryl halides and pseudohalides. So far, the best catalytic condition in HTS involved PhOTf (1 eq), 3-fluorobenzaldehyde (1 eq), Ni(cod)₂ (10 mol%), dppf (12 mol%), NEt₃ (1.5 eq) and 1,4 dioxane (1 mL) at 125 °C. The success of a reaction in a HTS is measured by GC ratios of desired product relative to an internal standard without calibration. In order to get a more accurate yield, the same

⁴² B.-L. Lin, L. Liu, Y. Fu, S.-W. Luo, Q. Chen, Q.-X. Guo, *Organometallics*, **2004**, 23, 2114-2123.

⁴³ Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature*, **2014**, 509, 299.

⁴⁴ Tasker, S. Z.; Gutierrez, A. C.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2014**, 53, 1858.

reaction was performed on the bench with a relatively larger scale and 8% ^1H NMR yield of the diaryl ketone **10** was obtained (Table 3, Entry 4).



Fifth High-throughput Screening

A (1 eq): 3-fluorobenzaldehyde

B (1eq): 4-bromoanisole, PhOTf, PhOMs, Phenyl Acetate, 2-Methoxynaphtalene, Benzonitrile, Benzyl methyl ether

Catalyst (10 mol%): Ni(cod)_2

Ligand (12 mol%): $\text{SiPr}\cdot\text{HCl}$, PPh_3 , $\text{PCy}_3\cdot\text{HBF}_4$, $\text{PtBu}_3\cdot\text{HBF}_4$, BINAP

Base (1.5 eq): NEt_3 , KOtBu , Cs_2CO_3

Additives (0.1 eq): Water

Solvent (0.5 mL/vial): 1,4-dioxane, Toluene

Temperature: 110 $^\circ\text{C}$

Sixth High-throughput Screening

A (1 eq): 3-fluorobenzaldehyde

B (1eq): PhOTf, PhOMS, Phenyl Pivalate, Naphthyl pivalate, Benzonitrile, Benzyl methyl ether, 2-Methoxynaphtalene, Chlorobenzene, Bromobenzene, Iodobenzene

Catalyst (10 mol%): Ni(cod)_2

Ligand (12 mol%): $\text{SiPr}\cdot\text{HCl}$, SPhos, BINAP, dppf

Base (1.5 eq): NEt_3 , Cs_2CO_3 , K_3PO_4

Additives (0.2 eq): Zn, AgOTf

Solvent (0.4 mL/vial): 1,4-dioxane, MeCN

Temperature: 125 $^\circ\text{C}$

Figure 6. Details of 5th and 6th high-throughput screening using Ni catalyst

Further evaluation of temperature and catalyst loading was carried out (Table 3). Increasing the temperature up to 135 $^\circ\text{C}$ gave the best yield of 16% (Entry 2). However, the yield was decreased down to 12% with a higher temperature of 145 $^\circ\text{C}$

(Entry 1). In general, the oxa-Heck reaction required relatively high temperature. No product formation was observed below 100 °C (Entry 6 and 7). Higher yield could be obtained with higher catalyst loading, where the product **10** yield was increased to 34% if 20 mol% Ni(cod)₂ was used (Entry 4). However, 20 mol% catalyst loading is relatively high for catalytic reactions and is undesirable. No significant side reactions were observed in these reactions, where starting material **8** was recovered in high yield.

Table 3. Optimization for the reaction of 3-fluorobenzaldehyde and PhOTf

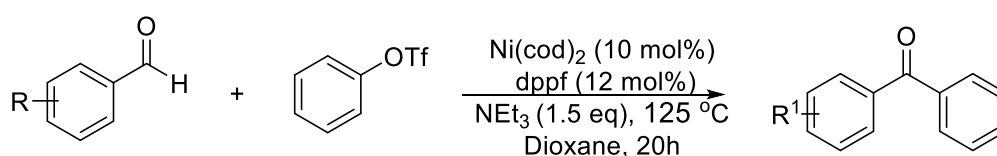
Entry	Temperature (°C)	Ni(cod) ₂ (mol %)	Product yield (%) ^a
1	145	10	12
2	135	10	16
3	135	20	34
4	125	10	8
5	100	10	4
6	85	10	0
7	60	10	0

^a 1 eq aldehyde and 1 eq PhOTf were used in each reaction. Yield determined by ¹H NMR of the crude mixture with 1,3,5-trimethoxybenzene as internal standard.

The effect of functional group, on the aldehydes was also investigated (Table 4). Different aldehydes including electron-rich, electron-poor and electron-neutral were

screened. While an electron-poor aldehyde with cyano group gave the highest yield of 15% (Entry 1), an electron-rich aldehyde with a methoxy group also gave relatively comparable yield (Entry 2). The other relatively electron-neutral aldehydes behaved similarly with no significant distinguishment (Entries 3- 5). In contrast, the 4-nitrobenzaldehyde gave no reactivity and was recovered after the reaction (Entry 6). While 4-cyanobenzaldehyde was chosen for further testing, no obvious trend could be discerned.

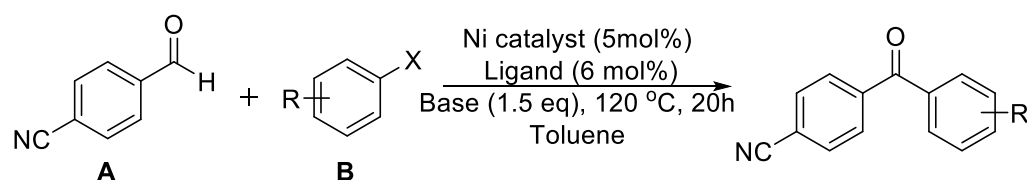
Table 4. Screening of the aldehydes with PhOTf



Entry	Aldehydes	Product yield (%) ^a
1	4-cyanobenzaldehyde	15
2	4-methoxybenzaldehyde	11
3	2-naphthaldehyde	10
4	4-fluorobenzaldehyde	9
5	3-fluorobenzaldehyde	8
6	4-nitrobenzaldehyde	0

^a 1 eq aldehyde and 1 eq PhOTf were used in each reaction. Yield determined by ¹H NMR of the crude mixture with 1,3,5-trimethoxybenzene as internal standard.

In order to further optimize the Ni-catalyzed oxa-Heck reaction, one last HTS was performed based on the previous discoveries from different screenings. 4-cyanobenzaldehyde was selected as the sole aldehyde in the 7th screening according to the resulting in Table 4. Since dppf and NEt₃ were the best ligand and base so far, similar bidentate phosphine ligands such as dppe, dppb, dppp, etc and different organic bases including quinuclidine, Hunig's base, DBU, and NCy₂Me were selected for screening (Figure 7).



Seventh High-throughput Screening

A (1 eq): 4-cyanobenzaldehyde

B (1 eq): PhOTf, 4-bromoanisole

Catalyst (5 mol%): Ni(cod)₂, NiCl₂

Ligand (6 mol%): dppf, dppp, dppb, dppe, dtbbpy, diphenyl-2-pyridylphosphine

Base (1.5 eq): NEt₃, K₂CO₃, NCy₂Me, DBU, Quinuclidine, Hunig's base,
10% Quinuclidine and 1.5 eq K₂CO₃

Solvent (0.35 mL/vial) : Toluene

Temperature: 120 °C

Figure 7. Details of 7th highthrough-put screening using Ni catalyst

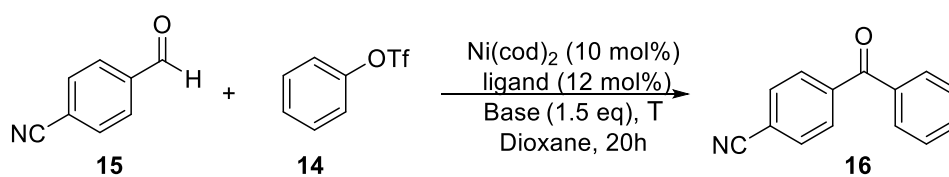
In the 7th HTS, 4-cyanobenzaldehyde **15** still only coupled with PhOTf **14**, all the reactions using 4-bromoanisole gave no product and **15** was recovered in high yield. All reactions with NiCl₂ also gave no product. In terms of bases and ligands, the combination of dppp, dppf, NEt₃, NCy₂Me and Hunig's base with Ni(cod)₂ all give the desired ketone products. The yield ratio in GC-MS in screening provides broad

ideas on better catalytic combination, but no calibration was performed for yield calculation. Based on the best results from HTS, further optimizations were performed in a traditional batch manner and are summarized in Table 5. The influence of temperature was consistent with previous screens, where 135 °C was the optimized temperature (Entry 1- 3). Increasing the equivalents of aldehyde or PhOTf from 1 eq to 2 eq didn't have any significant effect (Entry 3, 4). By switching the ligand from dppf to dppp, the yield was increased from 22% to 27% (Entry 3, 5). The effect of organic bases was even more significant, where the yield was increased from 27% to 64% when Hunig's base was used instead of NEt₃ (Entry 5, 6). According to Guo and coworker's computational study⁴¹, Ni(0) species cannot be effectively regenerated in the reductive elimination step of the mechanism common to the Pd-catalyzed Heck reaction. Therefore, it usually requires a very strong base to reduce the Ni(II) hydride or a reductive pathway should be designed to remove HX from the Ni. This might explain why varying the base in our reactions could have a huge impact on product yields.

Overall, the best yield for the oxa-Heck reaction was 64% using Ni(cod)₂ (10 mol%), dppp (12 mol%), Hunig's base (1.5 eq) in 1,4 dioxane (1 mL) at 135 °C with 4-cyanobenzaldehyde (1 eq) and PhOTf (1 eq) (Entry 7).⁴⁵ High recovery of starting material was obtained in most of these acylation reactions, with no significant side reactions.

⁴⁵ Reaction was performed in Aug, 2016. Unfortunately, no time was available for further optimization of base.

Table 5. Optimization for the reaction of 4-cyanobenzaldehyde and PhOTf



Entry	Temperature (°C)	Ligand	Base	Yield (%) ^a
1	145	dppf	NEt ₃	17
2	125	dppf	NEt ₃	15
3 ^b	135	dppf	NEt ₃	21
4 ^c	135	dppf	NEt ₃	21
5	135	dppf	NEt ₃	22
6	135	dppf	NCy ₂ Me	16
7	135	dppp	NEt ₃	27
8	135	dppp	NCy ₂ Me	35
9	135	dppp	Hunig's base	64

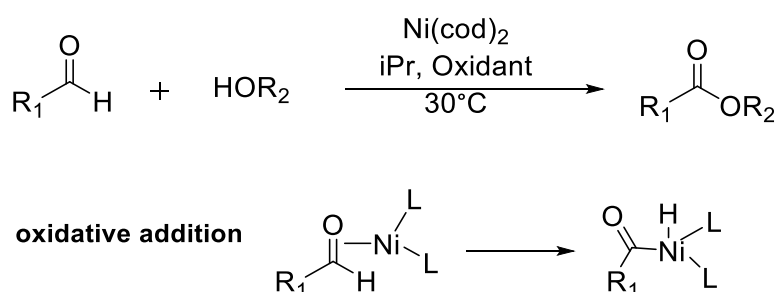
^a 1 eq aldehyde and 1eq PhOTf were used in each reaction. Yield determined by ¹H NMR of the crude mixture with 1,3,5-trimethoxybenzene as internal standard. ^b 2 eq of 4-cyanoaldehyde was used.

^c 2 eq of PhOTf was used.

1.2.4 Other approaches

Another potential issue in the oxa-Heck reaction is the chemoselectivity issue in oxidative addition step. In 2015, Dong's group reported a novel nickel-catalyzed dehydrogenative cross-coupling of aldehydes to generate hindered esters.⁴⁶ In their proposed mechanism, oxidative addition of Ni to the aldehyde C-H bond at low temperature is possible (Scheme 14).

Dong and coworkers, 2015



Scheme 14. Ni-catalyzed dehydrogenative cross-coupling of aldehydes

According to their discoveries, the probable issue in our oxa-Heck reaction could be the chemoselectivity of oxidative addition. In order to access the desirable diaryl ketone, the aryl halides/pseudohalides (ArX) needs to oxidative add to Ni (Figure 8, Path A), but it's highly possible that oxidative addition of Ni to the aldehyde C-H bond competes in this step to hinder the formation of desirable ArNiX intermediate (Figure 8, Path B). In order to solve this chemoselectivity issue, we came up with a general and simple strategy that exploits the presence of ArNiX intermediate over the undesired oxidative addition of Ni to the aldehyde C-H bond. Our strategy involves

⁴⁶ Whittaker, A. M.; Dong, V. M. *Angew. Chem. Int. Ed.* **2015**, 54, 1312.

controlled, slow addition of the aldehydes to the reaction mixture at a rate that allows the formation of ArNiX intermediate from ArX and nickel catalyst in the oxidative addition step (Path A). The slow addition of aldehydes ensures that we are selecting the wanted catalytic intermediate in the oxa-Heck reaction and avoiding the formation of ArNiH in side reaction. A few of the slow addition experiments were performed for the oxa-Heck reaction, where aldehydes were added slowly in the course of 5 to 12 hours by syringe pump to the reaction mixture. Unfortunately, the product yield was not improved significantly.

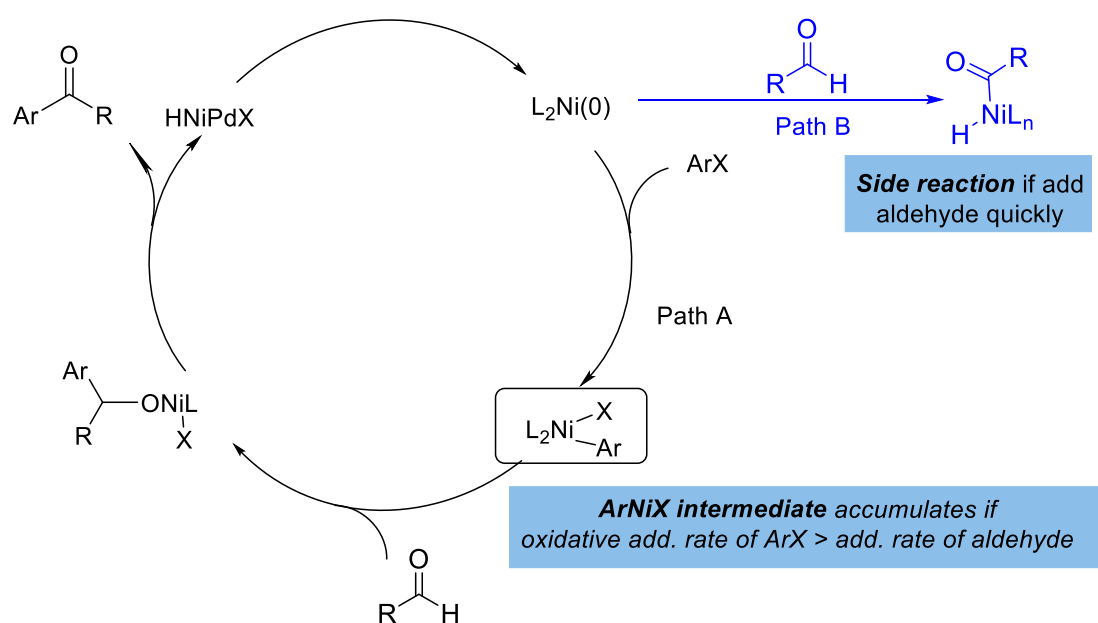
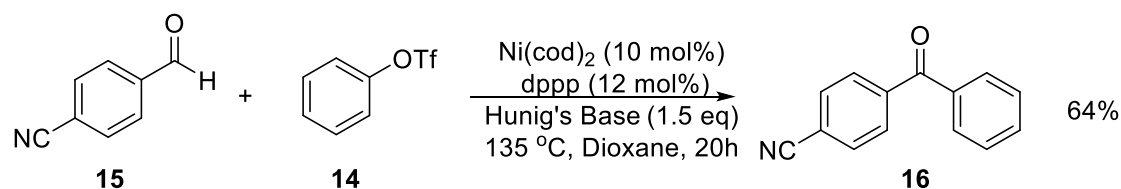


Figure 8. Overcoming chemoselectivity issues by controlling presence of catalytic intermediate

1.4 Summary and future work

The development of greener and less expensive methods to construct C-C bonds is still an ongoing challenge in organic synthesis. The existing methods available for direct synthesis of ketones from aryl halides are limited and usually require a multistep process using classical organic synthesis.⁴⁷ In this chapter, we reported for the first time that our current work allows the direct Ni-catalyzed intermolecular acylation of pseudohalides and aldehydes to give the resulting ketones in one step with modest yield (Scheme 15). This one-pot reaction makes this oxa-Heck reaction a convenient and straightforward route for the synthesis of functionally substituted diaryl ketones. The high availability of aryl halides, aldehydes and the low cost of nickel catalyst might be able to lower the cost of producing fine chemicals that use ketones as building blocks.

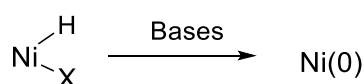


Scheme 15. Best reaction conditions for direct acylation of aldehydes and PhOTf

⁴⁷ Huang, Y.-C.; Majumdar, K. K.; Cheng, C.-H. *J. Org. Chem.* **2002**, 67, 1682.

A rational oxa-Heck mechanism is proposed for the new direct acylation reaction. Combined HTS with bench experiments helped us work toward optimized catalytic conditions, and the development of the oxa-Heck reaction is still an ongoing process. In terms of Pd- catalyzed acylation reactions, all of them gave lower than 5% yield. Modest yield was obtained from 4-cyanobenzaldehyde **15** and PhOTf **14**. This Ni-catalyzed reaction was limited to PhOTf; all the other aryl halides and pseudohalides that we tried in screenings tended to give poor yields. Also, a high reaction temperature was required and aliphatic aldehydes along with alkyl halides have not yet been investigated.

We have found that bidentate phosphine ligand such as dppp and organic bases including NEt₃, NCy₂Me and Hunig's base, can significantly alter the reaction yield. It is known that the reductive elimination step is challenging in Ni chemistry. Further reaction optimization is definitely required with a strong focus on base screening to facilitate the reduction of Ni(II) to Ni(0) (Scheme 16). Organic bases such as pyridine, a wide range of primary, secondary and tertiary amines, etc. will be tested to determine if any trend can be obtained.



Organic Bases: pyridine, butanamine, 2-methyl-2-propane amine
N-methylpropanamine, dimethylaminoethane, etc.

Scheme 16. Selection of organic bases to facilitate reductive elimination

In addition, it was found that phosphine ligands could reasonably reduce the free energy of the reductive elimination step.⁴¹ In the computational study performed by

the aim of controlling the presence of desirable catalytic intermediate and exploiting the inherent chemoselectivity. Although this method did not improve the yield of the oxa-Heck reaction, we believe this simple technique can be applied in other problematic reactions with analogous chemoselectivity issues. Thus, this slow addition reaction concept leads us to the second project: Inherent vs. Apparent Chemoselectivity: Expanding the Scope of the Kumada-Corriu Cross-Coupling Reaction.

1.5 Experimental

General experimental details

Unless otherwise indicated, reactions were conducted under an atmosphere of argon in 8 mL screw-capped vials that were oven dried (120 °C). Column chromatography was either performed manually using Silicycle F60 40–63 μm silica gel or using a Combiflash Rf+ automated chromatography system with commercially available RediSep Rf normal-phase Silica Flash columns (35–70 μm). Organic solutions were concentrated by rotary evaporation at reduced pressure at 40 °C. Analytical thin layer chromatography (TLC) was conducted with aluminum-backed EMD Millipore Silica Gel 60 F₂₅₄ pre-coated plates. Visualization of developed plates was performed under UV light (254 nm) and/or using KMnO₄ or ceric ammonium molybdate (CAM) stain.

Instrumentation

¹H NMR and ¹³C NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer. ¹H NMR spectra were internally referenced to the residual solvent signal (e.g., CDCl₃ = 7.27 ppm). ¹³C NMR spectra were internally referenced to the residual solvent signal (e.g., CDCl₃ = 77.00 ppm). Data for ¹H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration. NMR yields for optimization studies were obtained by ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. GC-MS yield ratios for optimization studies were using MS analysis on an Agilent Technologies 7890B GC with 30 m $\times$ 0.25 mm HP-5 column.

Materials

Organic solvents were purified by rigorous degassing with nitrogen before passing through a PureSolv solvent purification system, and low water content was confirmed by Karl Fischer titration (<25 ppm for all solvents). Unless otherwise noted, reagents were used as received. All reagents, metal catalysts, and ligands were purchased from Sigma-Aldrich, Combiblocks, or Strem Chemical Company. Josiphos, Walphos, Taniaphos and Mandyphos ligands and were supplied by Solvias AG and are commercially available from Strem. The synthesis of following Pd- precursors were followed by known literature: Buchwald Pd-tBuXPhos, Buchwald Pd-SPhos, Buchwald Pd-dppf,⁴⁹ Baird catalyst,⁵⁰ phosphite- based palladacycle,⁵¹ and cyclopalladated ferrocenylimine.⁵² All the characterization data agree with the literature.

General procedure for high-throughput screening



Each HTS was performed using a 96 well plate equipped with 8 × 40 mm glass vials. On the bench, Pd catalyst ($1.8\text{-}2.4 \times 10^{-3}$ mmol, 3-4 mol%) and ligand ($3.6\text{-}4.8 \times 10^{-3}$ mmol, 6-8 mol%) were added to each reaction vial. Bases (0.066 or 0.09 mmol, 1.1 or 1.5 eq.) were added into reaction vials, where appropriate. For the Ni catalyst (0.3 or 0.6 mmol), it was weighed in glovebox and was diluted in toluene (5 mL) to give the

⁴⁹ Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916.

⁵⁰ Fraser, A. W.; Besaw, J. E.; Hull, L. E.; Baird, M. C. *Organometallics* **2012**, *31*, 2470.

⁵¹ Bedford, R. B.; Cazin, C. S. J.; Coles, S. J.; Gelbrich, T.; Horton, P. N.; Hursthouse, M. B.; Light, M. E. *Organometallics* **2003**, *22*, 987.

⁵² Shou Quan, H.; Yang Jie, W.; Chen Xia, D.; Ying, Z.; Han Zhen, Y.; Xi An, M. *J. Organomet. Chem.* **1994**, *483*, 139.

Ni stock solution. A magnetic stir bar was added to each vial and the plate was brought into a nitrogen-filled glovebox, where-in the liquid reagents were diluted in the corresponding solvent as stock solutions. The stock solutions were added to the appropriate reaction vials via a 200 μ L micropipette. Stock solution A was prepared by adding aldehydes (6 mmol, 1 eq) to the selected solvent (10 ml), while stock solution B was prepared by adding aryl halides (6 mmol, 1 eq) and internal standard 1,3,5 trimethoxybenzene (1.5 mmol) to the selected solvent (10 ml). Other additives (1.2-6 mmol, 0.2-1 eq) were diluted in the specific solvents (10 mL) to give the corresponding stock solutions. 100 μ L of each stock solution was added to the corresponding reaction vial. Then the plate was sealed, removed from the glovebox and heated at desired temperature with stirring for 18-20 h in an aluminum-heating block. Upon cooling, the plate was opened and the contents of each vial were passed through a multi-well filtration plate filled with silica gel, eluting with acetonitrile. The filtrates were diluted to an appropriate concentration and then analyzed by GC-MS. The desirable product and unexpected side products were noted for each reaction, and the relative yield ratio was calculated based on the peak area ratio in GC-MS, where dividing the peak area of desired product by the peak area of internal standard 1,3,5 trimethoxybenzene (0.015 mmol). Crude ^1H NMR yield of these selected reactions was taken when necessary.

General procedure for Pd-catalyzed oxa-Heck reaction in 8 mL vial

To an 8 mL reaction vial equipped with a magnetic stir bar was added Pd catalyst (5 mol%), ligand (6 mol%) if needed, (if solid) base (1.5 eq), (if solid) aldehyde (1 eq), and (if solid) aryl halide (1 eq). The vial was purged with argon for 5 minutes and solvent (1 mL) and (if liquid) aryl halide (1 eq), (if liquid) base (1.5 eq), (if liquid)

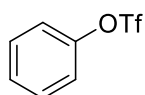
aldehyde (1 eq) were added. The vial was capped and added to an oil bath pre-heated to the desired temperature. After stirring for 18-20 hours, the reaction vial was removed from the oil bath and cooled down to room temperature. Then, the reaction was filtered over silica gel, concentrated, and analyzed by ^1H NMR to indicate the crude yield of products.

General procedure for Ni-catalyzed oxa-Heck reaction in 8 mL vial

To an 8 mL reaction vial equipped with a magnetic stir bar was added ligand (12 mol%), and (if solid) aldehyde (1 eq). The vial was purged with argon for 5 minutes and shipped into an N_2 filled glove box. Inside the glove box $\text{Ni}(\text{cod})_2$ (10 mol%) and solvent (1 mL) were added, followed by the addition of PhOTf (1 eq), (if liquid) base (1.5 eq) and (if liquid) aldehyde (1 eq). The vial was capped and shipped out of the glove box. The reaction vial was then added to an oil bath pre-heated to the desired temperature. After stirring for 20 hours, the reaction vial was removed from oil bath and cooled down to room temperature. Then, the reaction was filtered over silica gel, concentrated, and analysis by ^1H NMR to indicate the crude yield of products.

Preparation of starting materials

phenyl triflate (14)

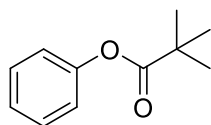


The procedure was adapted from the literature.⁵³ A 100 mL round bottom flask was charged with phenol (20 mmol, 1 eq), pyridine (40 mmol, 2 eq) and a magnetic stir bar. The flask was sealed with a septum and purged by Argon for 5

⁵³ A. L. S. Thompson, G. W. Kabalka, M. R. Akula, J. W. Huffman, *Synthesis*, **2005**, 4, 547-550.

mins. DCM (45 mL) was added and the solution was cooled down to 0 °C. Trifluoromethane sulfonic anhydride (24 mmol, 1.2 eq) was added dropwise to the reaction mixture and the solution was stirred at room temperature for another 1 h. Then the reaction mixture was diluted with ether (10 mL) and quenched with 10% HCl (aqueous), and washed successively with saturated NaHCO₃ (15 mL). The separated organic phase was washed with brine (15 mL) and dried over MgSO₄. The filtrate was concentrated and the residue purified by flash chromatography on silica gel (1:9 EtOAc:hexanes). The product phenyl triflate was obtained as colorless oil (2.09 g, 65%) and matched the literature.⁵³ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.49–7.43 (m, 2 H), 7.41–7.37 (m, 1 H), 7.29–7.26 (m, 2 H).

phenyl pivalate (17)

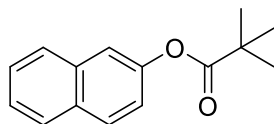


The procedure was adapted from the literature.⁵⁴ A 100 mL round bottom flask was charged with phenol (19 mmol, 1.2 eq), DMAP (1.6 mmol, 0.1 eq), Net₃ (16 mmol, 1 eq) and a magnetic stir bar. The flask was sealed with a septum and purged by Ar for 5 mins. DCM (50 mL) was added, and trimethylacetyl chloride (16 mmol, 1 eq) was added dropwise to the reaction mixture and the solution was stirred at room temperature for 24 h. Then the reaction mixture was washed by water (20 mL), followed with brine (20 mL) and the organic phase was dried over MgSO₄. The filtrate was concentrated and the residue purified by flash chromatography on silica gel (1:9 EtOAc:hexanes). The product phenyl pivalate was obtained as colorless oil

⁵⁴ Ehle, A. R.; Zhou, Q.; Watson, M. P. *Org. Lett.* **2012**, *14*, 1202.

(1.67 g, 60%) and matched the literature.⁵⁴ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.36 (d, 2 H), 7.27–7.23 (m, 1 H), 7.04 (d, 2 H), 1.35 (s, 9 H).

2-naphthyl pivalate (18)



The procedure was adapted from the above procedure. A 100 mL round bottom flask was charged with β-naphthol (19 mmol, 1.2 eq), DMAP (1.6 mmol, 0.1 eq), Net₃ (16 mmol, 1 eq) and a magnetic stir bar. The flask was sealed with a septum and purged by Argon for 5 mins. DCM (50 mL) was added, and trimethylacetyl chloride (16 mmol, 1 eq) was added dropwise to the reaction mixture and the solution was stirred at room temperature for 24 h. Then the reaction mixture was washed with water (20 mL), followed with brine (20 mL) and the organic phase was dried over MgSO₄. The filtrate was concentrated and the residue purified by flash chromatography on silica gel (1:12 EtOAc:hexanes). The product 2-naphthyl pivalate was obtained as white solid (1.78 g, 50%) and matched the literature.⁵⁴ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.9–7.83 (m, 3H), 7.76–7.29 (m, 3 H), 7.21 (dd, 1 H), 1.42 (s, 9 H).

Chapter 2: Inherent vs. Apparent Chemoselectivity: Expanding the Scope of the Kumada-Corriu Cross-Coupling Reaction

2.1 Introduction

The formation of carbon-carbon bonds is an essential operation in organic synthesis in order to generate structural diversity. Organomagnesium species (Grignard reagents) discovered by Victor Grignard in 1900, who was awarded the 1912 Nobel Prize in Chemistry, are some of the most reactive and accessible nucleophiles for constructing C-C bonds.⁵⁵ Organomagnesium reagents are able to react rapidly with electrophiles including ketones and aldehydes to form tertiary or secondary alcohols, and they were the first nucleophiles ever employed in modern cross-coupling reactions. One of the most common and conventional ways to synthesize Grignard reagents is through the insertion of magnesium to the organic halide.⁵⁶ In 2003, Knochel and coworkers proposed another effective method to generate Grignard reagents with more sensitive functional groups under mild reaction condition through metal-halogen exchange of aryl, heteroaryl, alkenyl, and alkyl halides with *i*PrMgCl·LiCl. This pioneering work has immensely expanded the scope of reaction methodologies involving Grignard species.⁵⁷

⁵⁵ Grignard, V. C. R. *Acad. Sci.* **1900**, 130, 1322.

⁵⁶ Garst, J. F.; Ungvary, F. "Mechanism of Grignard reagent formation". In Grignard Reagents; Richey, R. S., Ed.; John Wiley & Sons: New York, **2000**; pp 185–275.

⁵⁷ Knochel, P.; Dohle, W.; Gommermann, N.; Kniesel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003**, 42, 4302.

2.1.1 Traditional Kumada-Corriu cross-coupling

In 1941, Grignard reagents were used for the first time with organic halides in coupling reactions.⁵⁸ Inspired by this early work, a series of extension studies were published by Tamura and Kochi using variable catalysts including silver, copper and iron to couple organic halides to Grignard reagents, but poor yields were obtained in these studies due to homocoupling products.⁵⁹ In 1972, Kumada and Tamao as well as Corriu and Masse independently reported a Ni-catalyzed cross-coupling reaction between Grignard reagents and alkenyl or aryl halides, now known as the Kumada-Corriu reaction (Scheme 18a).⁶⁰ It is noted for being among the first reported catalytic cross-coupling methods and has made a enormous impact on the subsequent development of cross-coupling reactions with other alternative nucleophiles. Three years later, Murahashi and co-workers published the first palladium-catalyzed version of the Kumada-Corriu reaction as an important extension of the original protocol (Scheme 18b).⁶¹ Pd-catalyzed Kumada-Corriu reactions enable the coupling of organobromides or chlorides with alkyl, vinyl or aryl Grignard reagents in relatively high yields under mild condition. Overall this palladium catalytic system is highly practical and versatile for constructing new C-C bonds from organic halides and organomagnesium species.

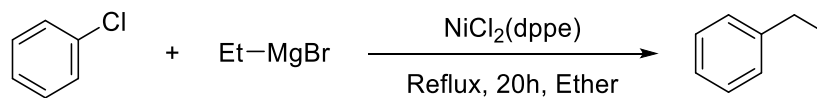
⁵⁸ Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, 63, 2316–2320.

⁵⁹ (a) Kochi, J. K.; Tamura, M., *J. Am. Chem. Soc.* **1971**, 93, 1483–1485. (b) Kochi, J. K.; Tamura, M., *J. Am. Chem. Soc.* **1971**, 93, 1485–1487. (c) Kochi, J. K.; Tamura, M., *J. Am. Chem. Soc.* **1971**, 93, 1487–1489.

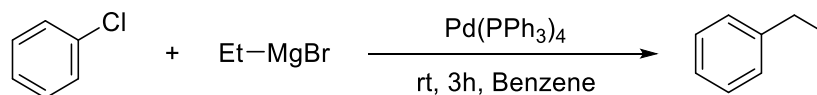
⁶⁰ (a) K. Tamao, K. Sumitani and M. Kumada, *J. Am. Chem. Soc.*, **1972**, 94, 4374–4376. (b) R. J. P. Corriu and J. P. Masse, *Chem. Commun.*, **1972**, 144.

⁶¹ Yamamura, M.; Moritani, I., Murahashi, S. -I. *J. Organomet. Chem.*, **1975**, 91, C39-C42.

a) Kumada and Tamao, 1972



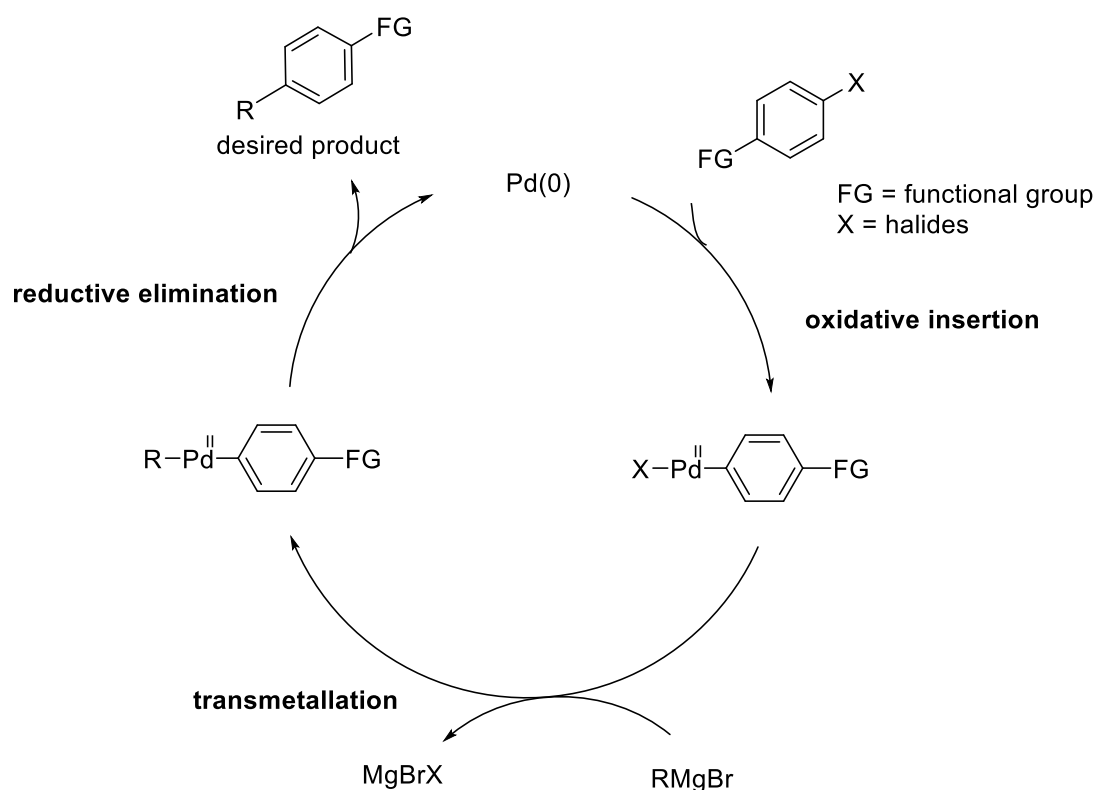
b) Murahashi and coworkers, 1975



Scheme 18. Early works of Ni- and Pd-catalyzed Kumada-Corriu reaction

General Mechanism

The mechanism of the Kumada-Corriu reactions follows the same pathway as the general Pd-catalyzed cross-coupling mechanism. The catalytic cycle begins with $\text{Pd}(0)$ and is followed by oxidative addition of an organic halide, to give the resulting $\text{Pd}(\text{II})$ intermediate. The second step is transmetalation where the Grignard reagent reacts to exchange the halide on the palladium. In the last reductive elimination step, the new C-C bond is generated to give the desired product and $\text{Pd}(\text{II})$ is reduced to $\text{Pd}(0)$ to close the catalytic cycle (Scheme 19).



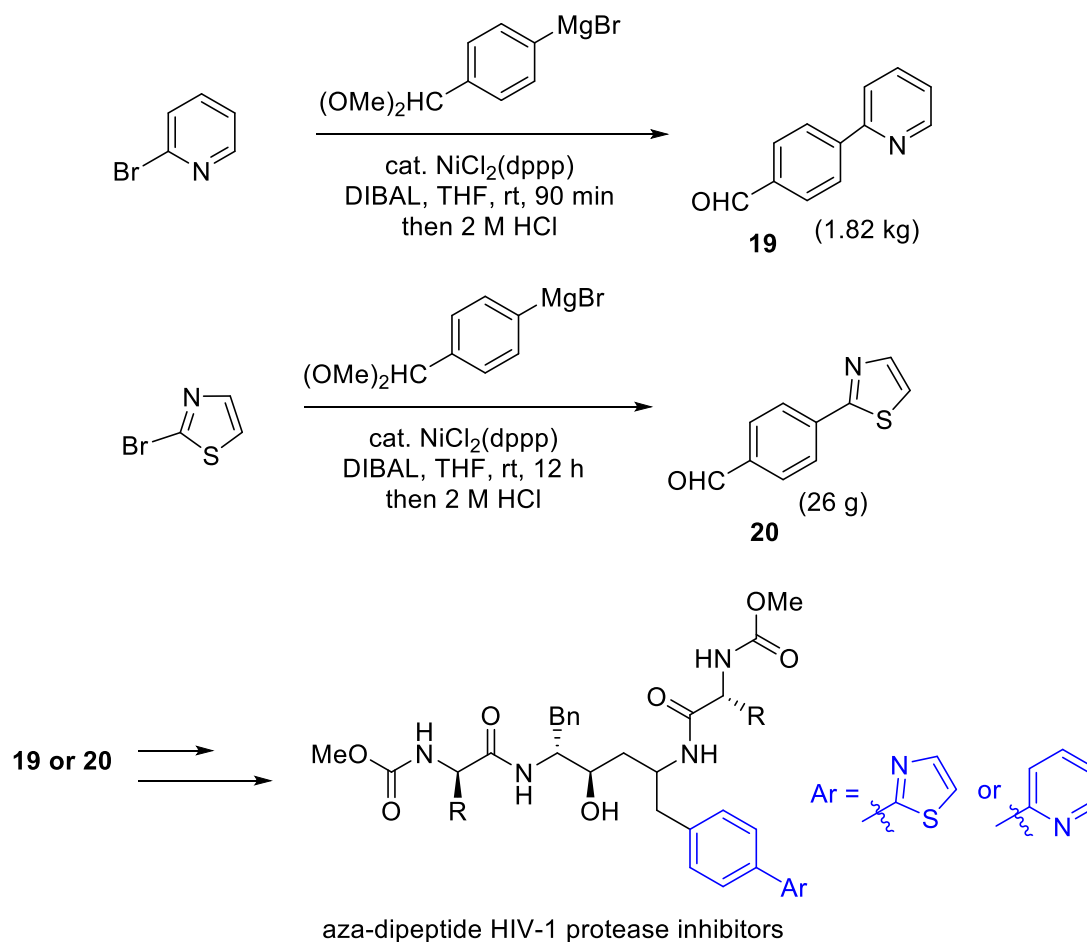
Scheme 19. The general mechanism of Pd-catalyzed Kumada-Corriu coupling

2.1.2 Applications of the Kumada-Corriu reaction in industry

The Kumada-Corriu coupling has been employed in many synthetic applications on industrial-scale production. However, the transformation has been limited to construct simple molecules in large-scale synthesis due to the poor chemoselectivity of Grignard reagents. One application in industry is in the production of polymers from styrenes.⁶² In the pharmaceutical industry, some simple building blocks are also prepared through Kumada-Corriu coupling. In 1998, Ciba-Geigy applied Kumada couplings to prepare biaryl aldehydes **19** and **20**, which are the building blocks for the

⁶² Banno, T.; Hayakawa, Y.; Umeno, M. *J. Organomet. Chem.*, **2002**, 653, 288-291

synthesis of aza-dipeptide HIV-1 protease inhibitors (Scheme 20).⁶³ The synthesis of biaryl aldehydes from the coupling of organic bromides and Grignard reagents was performed on gram to kilogram scale using nickel catalysis.

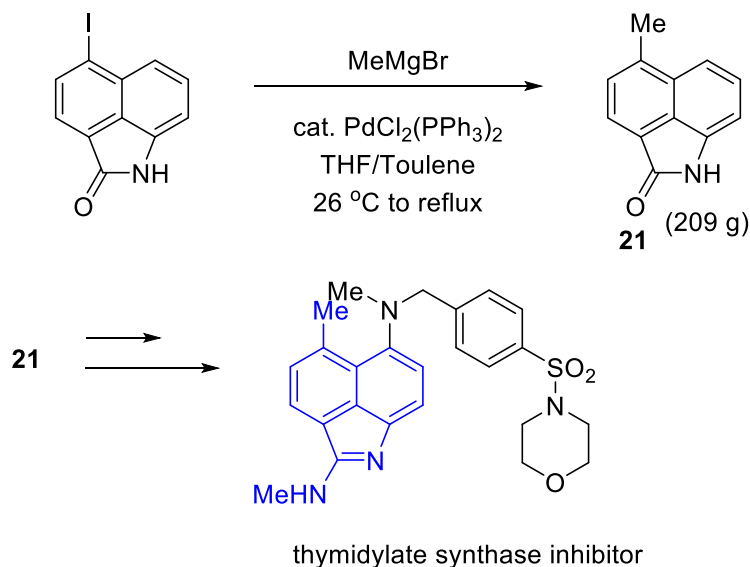


Scheme 20. Selected industrial applications of Ni-catalyzed Kumada coupling

Another example is the methylation of aryl iodide using Pd-catalyzed Kumada couplings to synthesize the intermediate **21** of thymidylate synthase inhibitor, which

⁶³ Bold, G.; Fassler, A.; Capraro, H.-G.; Cozens, R.; Klimkait, T.; Lazdins, J.; Mestan, J.; Poncioni, B.; Rosel, J.; Stover, D.; Tintelnot-Blomley, M.; Acemoglu, F.; Beck, W.; Boss, E.; Eschbach, M.; H  urlimann, T.; Masso, E.; Roussel, S.; Ucci-Stoll, K.; Wyss, D.; Lang, M. *J. Med. Chem.* **1998**, 41, 3387.

is a potential cancer treatment discovered by Agouron Pharmaceuticals (Scheme 21).⁶⁴



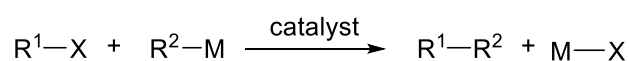
Scheme 21. Sample industrial application of Pd-catalyzed Kumada coupling

2.1.3 Comparison to other organometallic reagents

As compared to some other cross-coupling reactions, the Kumada-Corriu reaction is seldom utilized in complex molecule synthesis. The intrinsic disadvantage is the apparently poor chemoselectivity of Grignard reagents, which significantly lowers the overall reaction scope. These Grignard nucleophiles tend to give side-reactions with a number of functional groups at room temperature or above. Thus, this major drawback of Kumada-Corriu coupling has inspired the development of related cross-coupling reactions using milder nucleophilic coupling partners, including organozinc (Negishi reaction), organotin (Stille), organoboron (Suzuki-Miyaura), and

⁶⁴ Marzoni, G.; Varney, M. D. *Org. Process Res. Dev.* **1997**, 1, 81.

organosilicon (Hiyama) reagents (Figure 9). These milder nucleophiles are less reactive as compared to Grignard reagents and have improved chemoselectivity with a higher tolerance of sensitive functional groups. Today, the Suzuki-Miyaura coupling is the most widely used coupling reaction,⁶⁵ particularly in complex molecular synthesis. The use of organoboron species has improved functional group tolerance of highly electrophilic moieties and they are much more stable to moisture and oxygen as compared to Grignard reagents.



Typically: catalyst = PdLn (sometimes NiLn)

X = halide

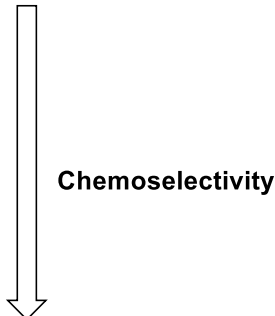
M = MgX	(Kumada coupling, 1972)	
M = ZnX	(Negishi coupling, 1976)	
M = SnR ₃	(Stille reaction, 1978)	
M = BX ₂	(Suzuki reaction, 1979)	
M = SiR ₃	(Hiyama reaction, 1988)	

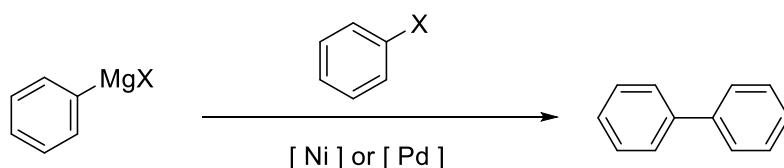
Figure 9. Cross-couplings with different nucleophiles

Nonetheless, there are several advantages of Grignard reagents as nucleophilic coupling partners. First of all, their low-cost and accessibility can improve process efficiency. The synthesis of Grignard reagents from aryl and alkyl halides by metal-

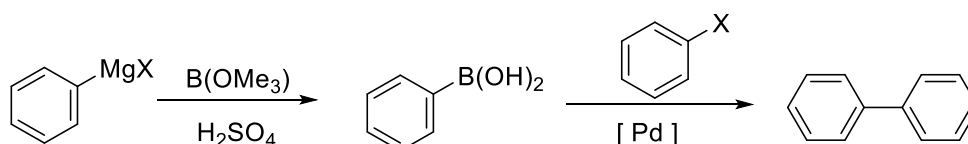
⁶⁵ According to the total number of publications with the topic of “Suzuki-Miyaura coupling” that are presented in Table 1.

halogen exchange or direct insertion of Mg is reliable and straightforward. In comparison with the Suzuki coupling, the employment of organomagnesium halides in Kumada couplings has the advantage of shortening the overall synthetic procedure since arylboronic acids (the nucleophiles used in Suzuki reactions) are mostly synthesized from their Grignard precursors with an electrophilic boron species such as trimethyl borate (Scheme 22).⁶⁶ Thus, the overall Kumada-Corriu cross-coupling process is a more direct approach and could generate less waste. In addition, the high reactivity of Grignard reagents enables efficient transmetallation in Kumada-couplings, in contrast to Suzuki-couplings which often have a slower transmetallation step, necessitating the use of elevated temperatures.⁶⁷

Kumada



Suzuki



Scheme 22. Comparison of Kumada and Suzuki coupling for the synthesis of biaryl

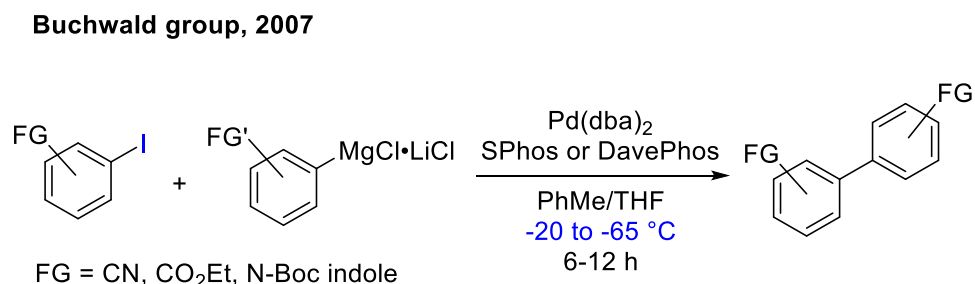
⁶⁶ Hartwig, J. F. *Acc. Chem. Res.* **2012**, 45, 864.

⁶⁷ a) Ricci, A.; Angelucci, F.; Bassetti, M.; Lo, S, C. *J. Am. Chem. Soc.* **2002**, 124, 1060. b) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, 133, 2116.

2.1.4 Recent advances in Kumada-Corriu cross-coupling

Grignard reagents typically react with a range of active amides, esters, thioesters, ketones, imines and some protecting groups. The issue of chemoselectivity in Kumada-Corriu cross-coupling is an ongoing problem. Major research efforts have been devoted to increase the stability and attenuate the reactivity of Grignard reagents, including careful selection of solvents, additives and catalysts.⁶⁸

Recently, Buchwald and Martin reported a highly efficient process for the Kumada-Corriu reaction with aryl iodides, with the aim of expanding the functional group tolerance.⁶⁹ The active Pd/SPhos catalytic system that proceeds at temperatures ranging from -20 to -65 °C tolerates the presence of a wide variety of functional groups on both aryl iodides and Grignard reagents. A broad spectrum of functionalized compounds, including heterocyclic biaryls, polyfluoro biaryls, etc. can be generated successfully (Scheme 23).

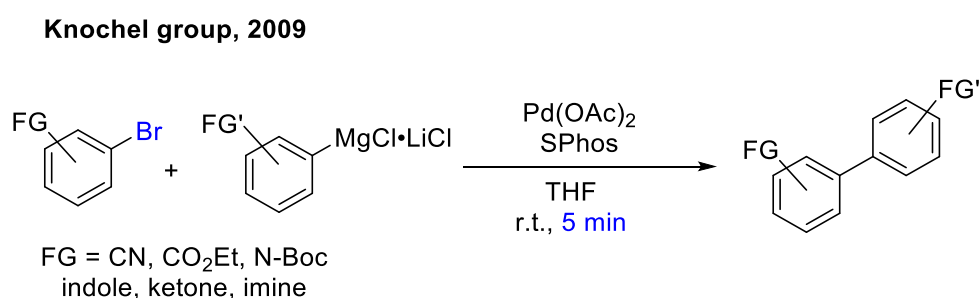


Scheme 23. Kumada-couplings of aryl iodide by Buchwald group

⁶⁸ Wang, X.J.; Sun, X.; Zhang, L.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2006**, 8, 305.

⁶⁹ Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, 129, 3844.

Later, Manolikakes and Knochel reported a catalyst system that allowed coupling of sensitive aryl bromides at room temperature to give various biaryls in high yields.⁷⁰ The presence of ⁱPrI in the reaction enabled a rapid Pd(I)/Pd(III) catalytic cycle and allowed completion of reactions within 5 minutes and thereby minimized the exposure of sensitive functional groups to the reactive Grignard reagents. A non-traditional oxidative addition step was involved in the mechanism and a radical path in the initiation step was proposed instead. This method can be applied to both electron-rich and -poor aryl bromides bearing a wide range of functional groups including cyano, ester, ketone, etc. (Scheme 24).



Scheme 24. Kumada-couplings of aryl bromide by Knochel group

2.1.5 Research goals

The success of the Buchwald and Knochel groups in utilizing sensitive aryl iodides, aryl bromides and Grignard reagents suggests that some of the avoidance of Kumada couplings is unwarranted: If the reaction can be performed sufficiently quickly or at

⁷⁰ Manolikakes, G.; Knochel, P. *Angew. Chem. Int. Ed.* **2009**, 48, 205.

low temperature, many sensitive functional groups are tolerated and a useful reaction scope can be realized.

The use of aryl chlorides as a chemical feedstock in coupling chemistry has proven difficult but would economically benefit a number of industrial processes.⁷¹ As compared to aryl bromides and aryl iodides, aryl chlorides are generally more readily available and have lower costs. The rate of oxidative addition in Kumada-Corriu couplings can be influenced by the choice of aryl halides. The trend of the rate is listed as following:



Aryl chlorides were proven to be the least reactive one in the above aryl halides, due to the stronger C-Cl bonds, so the oxidative addition rate can be considerably decreased. In general, sluggish electrophiles undergo coupling only at elevated temperature, but at the expense of low selectivity and competitive homo-coupling.⁷² Because of the sluggish nature of aryl chlorides, limited studies were accomplished using it in Pd-catalyzed Kumada-Corriu couplings. Not until 1999, Nolan and Huang reported the first general example of a Pd-catalyzed Kumada-Corriu coupling using various aryl chlorides with aryl Grignard reagents.⁷³ The Pd-NHC catalyst was formed *in situ* and this protocol was limited to aryl chlorides bearing simple functional groups, including: Me, OMe and OH (Scheme 25a). Ten years later, they

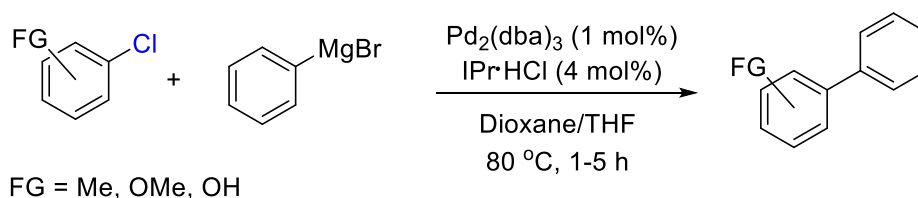
⁷¹ Chem. Eng. News 1998, June 1, 24. (b) Chem. Eng. News 1998, July 13, 71.

⁷² Knappke, C. E. I.; Wangelin, A. J. *Chem. Soc. Rev.*, **2011**, 40, 4948–4962.

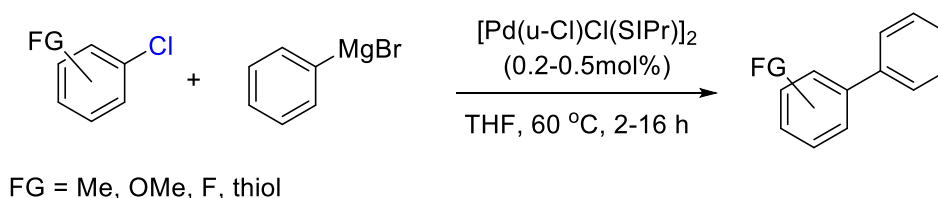
⁷³ J. Huang and S. P. Nolan, *J. Am. Chem. Soc.*, **1999**, 121, 9889–9890.

developed 2nd generation methodology with improved substrate scope.⁷⁴ Fluorophenyl and thiophenyl chlorides can successfully react with Grignard reagents, but the overall functional group tolerance is still really limited (Scheme 25b).

a) Nolan group, 1999



b) Nolan group, 2009



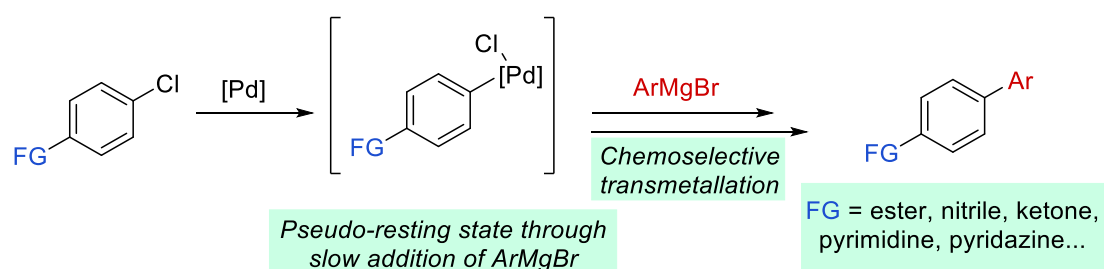
Scheme 25. Previous work in Pd-catalyzed Kumada-Corriu couplings with aryl chlorides

To the best of our knowledge, no successful Pd-catalyzed Kumada-Corriu coupling has been reported involving unactivated aryl chlorides with various electrophilic functional groups. In this work, we demonstrate a general and simple strategy to perform Pd-catalyzed Kumada-Corriu coupling that exploits the inherently high chemoselectivity of transmetallation over undesired side reactivity of the Grignard reagent. Aryl chlorides are utilized as the starting material to illustrate that even

⁷⁴ C. E. Hartmann, S. P. Nolan and C. S. J. Cazin, *Organometallics*, **2009**, 28, 2915–2919.

strong C–X bonds that require long reaction times and elevated temperatures can be coupled chemoselectively in our proposed protocol.

Mechanistically, Buchwald and Nolan's work suggest that the Grignard nucleophile is capable of chemoselectively transmetallating the Pd(II) catalytic intermediate in lieu of nucleophilic addition to some sensitive functional groups. We hypothesized that oxidative addition is the slow step in the overall coupling process. Our hypothesis was that controlled, slow addition of the Grignard reagent to the reaction mixture at a rate that approximately matches that of the oxidative addition step would avoid the competition between oxidative addition with side reactions and minimize the exposure of the sensitive group to the aggressive Grignard reagents. This ensures that a highly active Pd(II) intermediate is in a pseudo-resting state in the solution before the Grignard reagents comes in and allows chemoselective transmetallation to kinetically compete against undesired side reactions of the Grignard with other sensitive functional groups (Scheme 26).



Scheme 26. Our strategy for the Pd-catalyzed Kumada-Corriu coupling

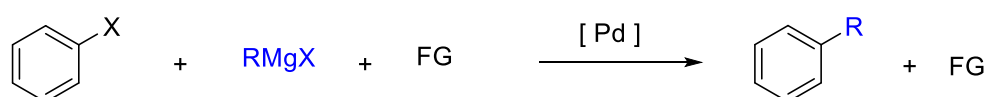
Results and discussion

2.2 Robustness screen⁷⁵

2.2.1 Advantages of robustness screen

A thorough survey of the functional group tolerance of the Pd-catalyzed Kumada-Corriu reaction was performed. We adapted the robustness screen method from Collins and Glorius' study⁷⁶ to help us quickly evaluate scope limitations, wherein the functionality is added as an additive (Figure 10a). Compared to a traditional screen (Figure 10b), this approach is much faster and cheaper since there is no need to attach the functionality to the starting material and the chemical access can be significantly increased. Also, the time of data analysis can be shortened, because one specific product is monitored. The desired diaryl product yield will be lowered if the Grignard reacts with the additive instead of with the aryl halide.

a) Robustness Screen



Functional group (FG) added as an additive

b) Traditional Screen

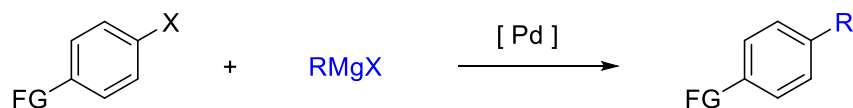


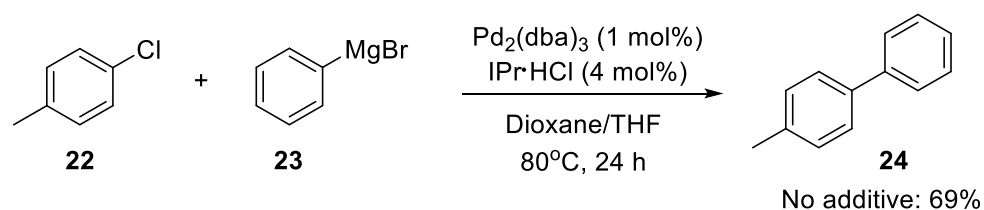
Figure 10. Comparison of traditional screen and robustness screen

⁷⁵ Robustness Screen was performed by Jeanne Masson-Makdissi (Honours project), under the mentorship of Kaylie Hua.

⁷⁶ Collins; K. D.; Glorius, F. *Acc. Chem. Res.*, **2015**, 48, 619–627.

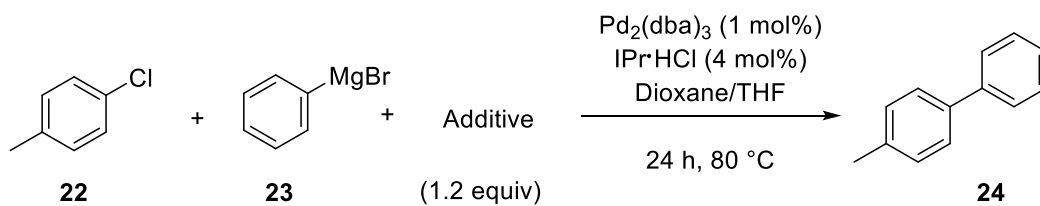
2.2.2 Robustness screen for the Kumada-Corriu coupling

The reaction conditions chosen for this robustness screen were those developed by Nolan and co-workers⁷³, which represents a pioneering example of the use of aryl chlorides as starting materials in Kumada-Corriu couplings (Scheme 27).

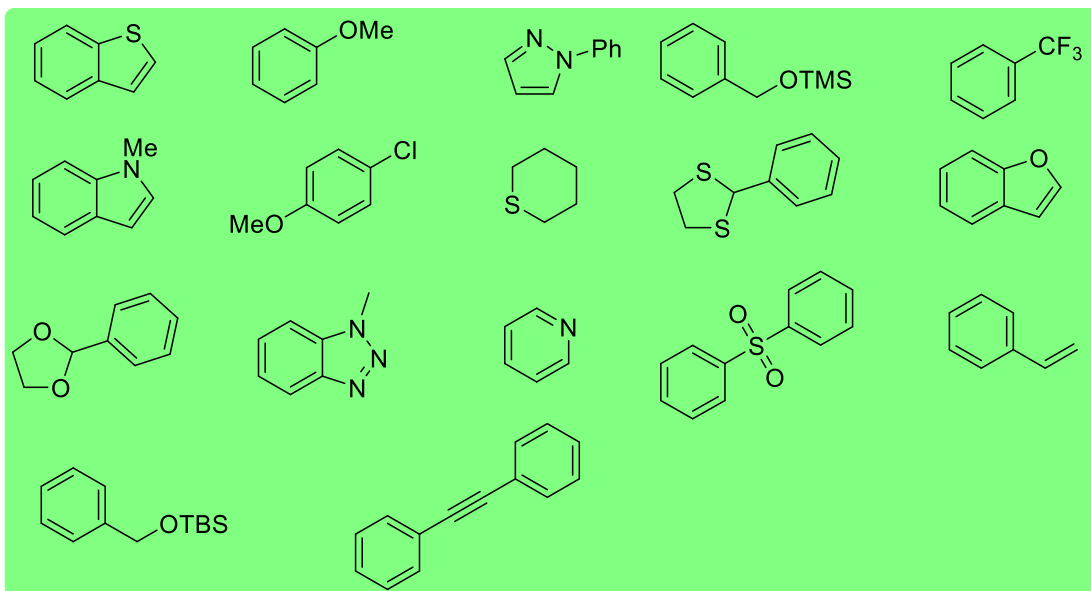


Scheme 27. Reaction conditions of the Kumada-Corriu robustness screen

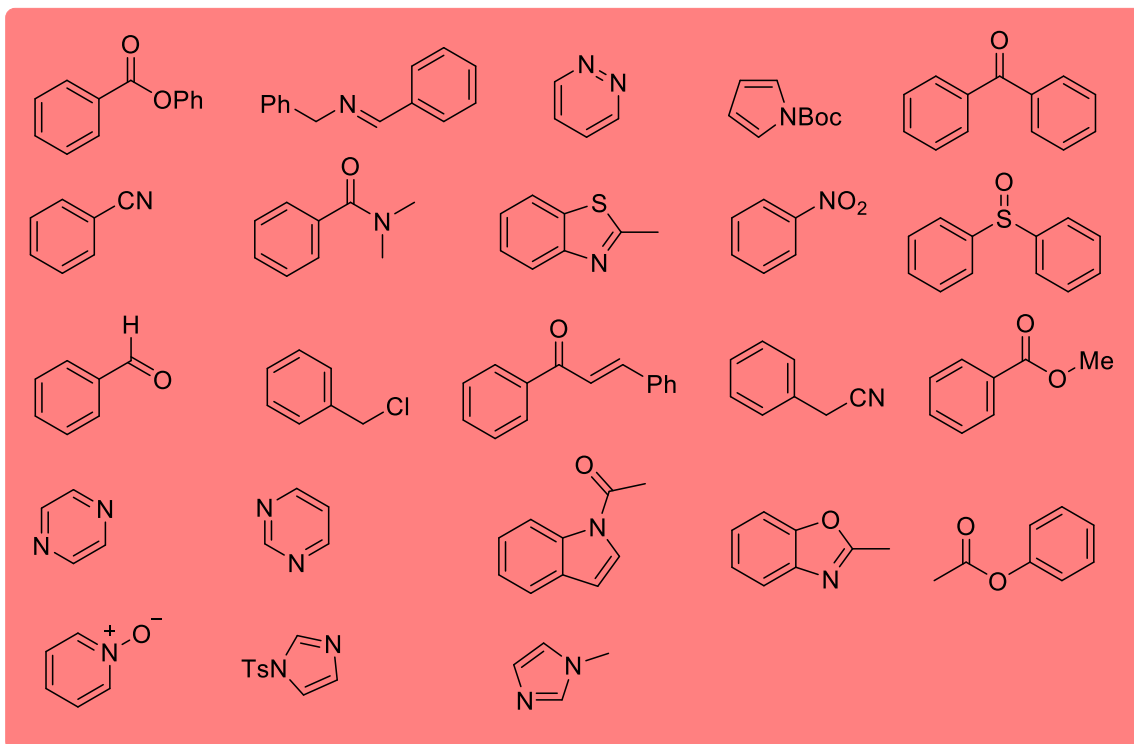
The coupling of 4-chlorotoluene **22** with phenylmagnesium bromide **23** was chosen to represent a particularly challenging reaction, requiring a reaction temperature of 80°C for several hours and a Pd/NHC catalyst system to enable coupling, providing the product **24** in 69% yield. This yield was considered good enough for the purpose of this screen since the incompatibilities are assigned relative to the maximal yield. The robustness screen was performed using high throughput screening techniques in a 96 well plate. Two reactions were performed without any additives, 47 reactions were carried out with different additives, and the remaining 47 vials were used to obtain single point calibration curves. The additives were chosen with a range of functionalities, including acidic protons, electrophilic functional groups, protecting groups, and various heterocycles. After analysis by GC-FID, the additives were placed into three different categories: tolerated, incompatible with additive recovery, and incompatible with additive consumption (Figure 11). Further details on the classification of the additives can be found in the Experimental.



Tolerated additives



Incompatible/unrecovered additives



Incompatible/recovered additives

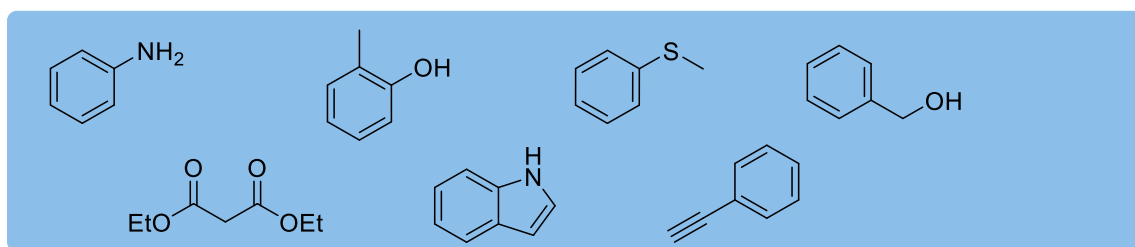


Figure 11. A robustness screen revealed functional group tolerance issues in the Kumada-Corriu coupling of aryl chlorides.

A significant number of additives were well tolerated in the reaction, including those containing simple styrene, alkyne, ether, and thioether functional groups. Some heterocycles were compatible as well, such as benzotriazole, benzofuran, benzothiophene, and N-methylindole. A more electron-rich aryl chloride was also tolerated, suggesting that the palladium catalyst can select among electronically differentiated C–X bonds.⁷⁷

In contrast, a wide variety of more electrophilic additives led to only small amounts of the desired product. As anticipated, traditional electrophiles for Grignard reactions were not tolerated, including all additives bearing carbonyl, imine, nitro, and nitrile functionalities. Most interestingly, a wide range of nitrogen-containing heterocycles were found to be incompatible and unrecovered under the reaction conditions, including pyridine, pyrazine, pyrimidine, imidazole, and protected indole, imidazole, and pyrrole. Given the importance of these functionalities and heterocycles in complex molecule synthesis, it is not surprising that the direct use of Grignard

⁷⁷ Rossi, R.; Bellina, F.; Lessi, M. *Adv. Synth. Catal.* **2012**, 354, 1181.

reagents in cross-coupling reactions has been overshadowed by less sensitive organozinc, tin, boron, or silicon reagents.

Only a small number of additives were found to be both incompatible in the reaction and recovered following work-up. These include mostly those with acidic protons, such as aniline, indole, and benzyl alcohol. These examples suggest that deprotonation by the Grignard occurs much faster than the desired cross-coupling but further consumption of the additive does not occur, allowing reprotonation and therefore recovery upon quenching the reaction. Performing Kumada-Corriu couplings in the presence of acidic protons is typically solved by the use of 2 equivalents of the Grignard reagent, and is thus not a particularly significant challenge. Thioanisole was also found to be incompatible but recovered, suggesting it may act as a catalyst poison.

2.2.3 Limitations of robustness screen

In the robustness screen, functionality was added as an additive, so it does not take into account the electronic effect that the functional group would have in the starting material. For example, having an electrophilic functional group attached at different positions (ortho, meta, para) would significantly alternate the electrophilicity of the starting material. Also, the steric effect of the functional group is neglected in the robustness screen. Moreover, the robustness screen was performed on a small scale (0.08 mmol), the associated error would be larger compared to the normal bench experiments. Thus, precautions must be taken when interpreting the results.

Harsh condition (80 °C for 24 h) were required to couple the relatively electron-rich 4-chlorotoluene **22** with PhMgBr, however, it might not be necessary for some other functional group. It is possible that some incompatible functional groups might be

tolerated in a milder and more optimized catalytic conditions. The simple and fast analysis with GC/FID comes with a major drawback; those side products in the failed reactions could not be identified. NMR or GC/MS analysis would have to be done in order to analyse those side products.

2.3 Slow addition experiments

With a better idea of the types of functional groups that are incompatible in traditional Kumada-Corriu reactions through robustness screen, we began exploring the hypothesis that transmetallation can outcompete undesired side reactions if oxidative addition to form the Pd(II) intermediate is not prohibitively slow. The functional groups that fall in the incompatible and unrecovered category of the robustness screen are the primary focus. In this section, it is demonstrated that the inherent chemoselectivity of Grignard reagents is sufficient to allow efficient cross-coupling to occur in the presence of many of these functionalities if the oxidative addition rates match with the rate of syringe pump addition of the Grignard to minimize the exposure of the sensitive group to the aggressive nucleophile.

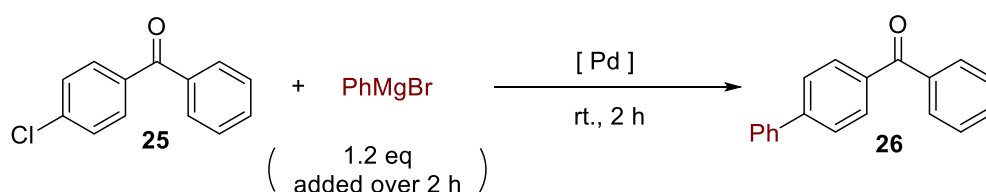
2.3.1 Catalyst system optimization

The preliminary screening was applied on the coupling of 4-chlorobenzophenone **25** with commercial available phenyl magnesium bromide (PhMgBr) in order to find the optimal catalytic condition. Different palladium catalysts and ligands were selected for the coupling at room temperature and the Grignard was added slowly over the course of reaction time (2 hours) by using a syringe pump. THF and toluene were chosen as the solvent to screen due to the solubility and stability issue of Grignard reagents and aryl chlorides. We tried several pre-ligated Buchwald type palladium catalysts to ensure high activity. Some other common commercially available

palladium catalysts were also screened (Table 6). The specific structures for Buchwald type catalysts used in Table 6 are presented in Figure 5.

Toluene gave 7% higher yield for ketone **26** as compared to the one using THF (Entry 1 and 2). Buchwald type Pd-SPhos gave the highest yield (Entry 4) and the combination of Pd(OAc)₂ and SPhos gave the same yield of 74% (Entry 5). We chose Pd(OAc)₂ and SPhos as the preferred catalyst system since they are commercially more available than Buchwald type catalysts.

Table 6. Sample reaction studied for optimization: 4-chlorobenzophenone

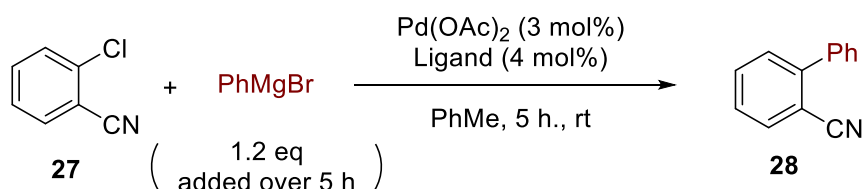


Entry	Catalyt and ligand	Solvent	Product yield (%) ^a
1	Buchwald Pd-tBuXPhos	THF	41
2	Buchwald Pd-tBuXPhos	Toluene	48
3	Buchwald Pd- dppf	Toluene	31
4	Buchwald Pd-SPhos	Toluene	74
5	Pd(OAc) ₂ , SPhos	Toluene	74
6	Pd ₂ (dba) ₃ , SPhos	Toluene	58
7	Pd(OAc) ₂ , XPhos	Toluene	47

^a Yield determined by ¹H NMR of the crude mixture with 1,3,5-trimethoxybenzene as internal standard.

Reaction optimization was performed simultaneously on a number of different substrates. The influence of ligand and reaction temperature on the chemoselective coupling of 2-chlorobenzonitrile **27**, which proved to be a challenging nitrile-containing substrate to efficiently couple was further examined. The reactions were performed with variation of the ligand with Pd(OAc)₂ (Table 7). The Grignard reagent was added over the course of 5 hours to make sure oxidative addition to form the Pd(II) intermediate is not prohibitively slow. In this ligand screening, SPhos in toluene was still found to be the most effective one. (Entry 9)

Table 7. Sample reaction studied for optimization: 2-chlorobenzonitrile



Entry	Ligand	Grignard added over... (h)	Yield (%) ^a
1	IPr·HCl	5	8
2	P(<i>t</i> Bu) ₃ ·HCl	5	20
3	BINAP	5	0
4	PCy ₃ ·HBF ₄	5	4
5	PCy ₃	5	4
6	BrettPhos	5	9
7	JohnPhos	5	8
8	<i>t</i> BuXPhos	5	19
9	SPhos	5	55

^a Yields determined by ¹H NMR with 1,3,5-trimethoxybenzene as internal standard

After these preliminary screening, we identified Pd(OAc)₂ (3 mol%) and SPhos (4 mol%) to be a simple, effective catalyst system with toluene as the solvent and 1.2

equivalents of PhMgBr. This catalyst system was used for the rest of the optimization reactions with a wide range of aryl chlorides.

2.3.2 Effect of Grignard addition rate

In our hypothesis, slow addition of Grignard reagents seems to be an efficient way to avoid side-reactions commonly encountered in traditional Kumada-Corriu cross-coupling reactions, if the oxidative addition rate is not prohibitively slow. Each compound with a different functional group will have its own particular oxidative addition rate. Thus, the Grignard addition rate and temperature need to be optimized individually in each case to be as fast and mild as possible to maximize yield.

The Grignard addition rate optimization data presented in the following figures is the coupling of PhMgBr with 4-chlorobenzophenone **25** at room temperature. All reactions were stirred for 120 minutes with variation of Grignard addition rate. Up to 74% yield of ketone **26** could be obtained if the Grignard was added slowly over the course of the reaction time (200 minutes) by using a syringe pump (Figure 12). On the other hand, significant amounts of alcohol side product **29** resulting from the direct reaction of the Grignard with the ketone was observed if Grignard was added in 2 minutes. The overall trend in Figure 13 shows that slower Grignard addition rate results in lower amount of side product **29**.

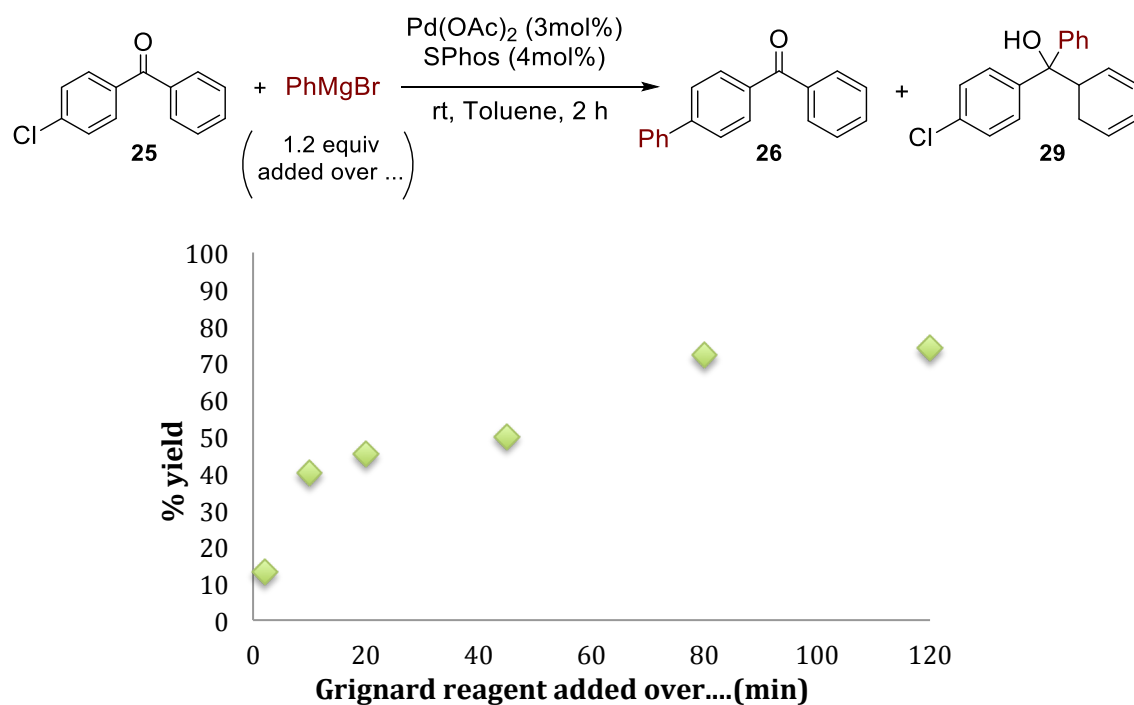


Figure 12. Effect of Grignard addition rate on ketone 26 for 4-chlorobenzophenone coupling

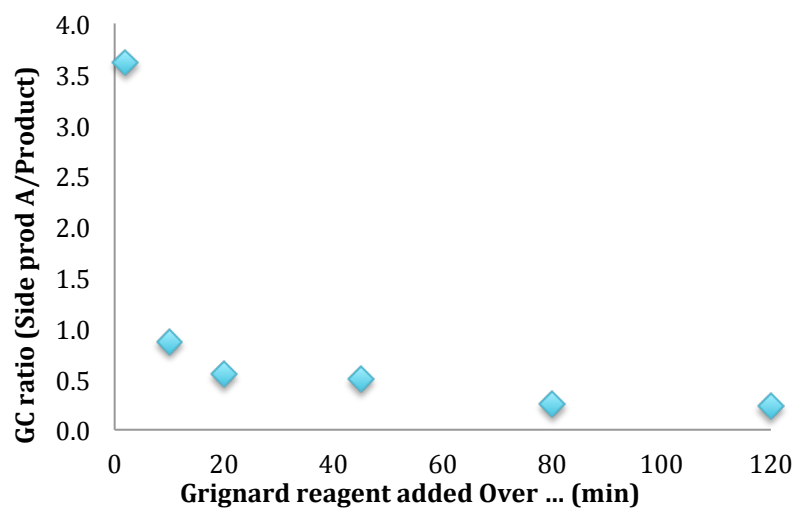


Figure 13. Effect of Grignard addition rate on side product 29 for 4-chlorobenzophenone coupling

Similar results were observed for Grignard addition rate optimization with 4-chlorobenzoate **30**. All reactions were stirred for 60 minutes with variation of Grignard addition rate. In Figure 14 an increasing trend showed that a significant increase of product **31** yield from 15% to 94% could be obtained if Grignard was added as slow as to 60 minutes. The overall trend in Figure 15 showed side product **29** was significantly diminished if the Grignard was added slowly. This demonstrates that the main reason for low yields when adding Grignard quickly is because of the incompatibility of functional group.

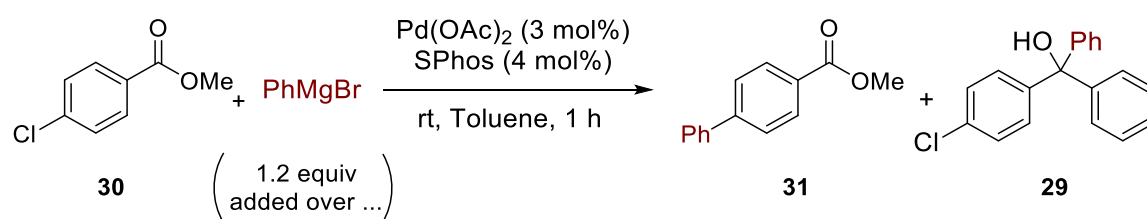
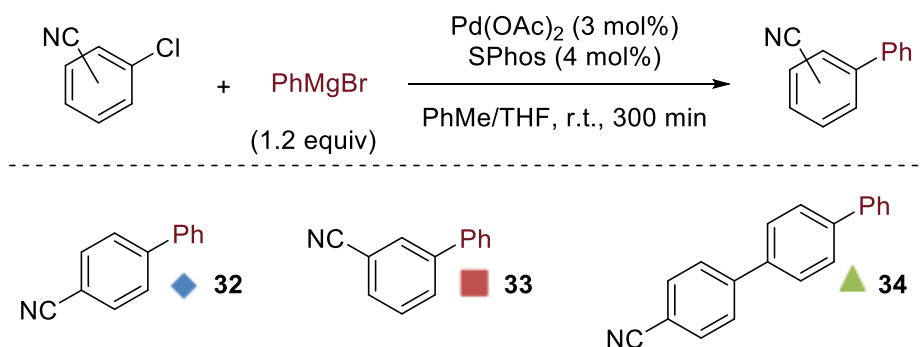


Figure 14. Effect of Grignard addition rate on product **31 yield for methyl 4-chlorobenzoate coupling**



Figure 15. Effect of Grignard addition rate on side product 29 for methyl 4-chlorobenzoate coupling.

With the hypothesis that this optimal addition rate is correlated with the rate of oxidative addition of the Pd(0) catalyst into the C–Cl bond, we next tested the coupling of 3 aryl chlorides bearing nitrile groups. 4-chlorobenzonitrile contains the most electron-deficient and more activated C–Cl bond. 3-chlorobenzonitrile and 4'-chloro-4-cyanobiphenyl, which contain less electron-deficient and thus stronger C–Cl bonds. All the reactions were stirred for 300 minutes at room temperature with different Grignard addition time and the results are summarized in Figure 16.



Grignard added over... (min)	Substrate 32 Yield (%)	Substrate 33 Yield (%)	Substrate 34 Yield (%)
1	4	0	0
5	55	-	-
30	81	10	5
60	92	-	-
90	96	21	18
180	94	30	23
300	94	40	32

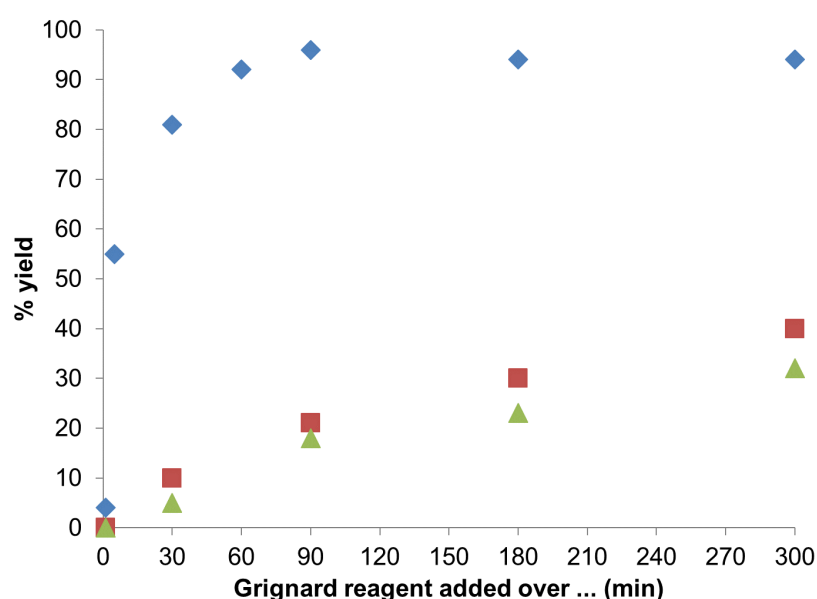
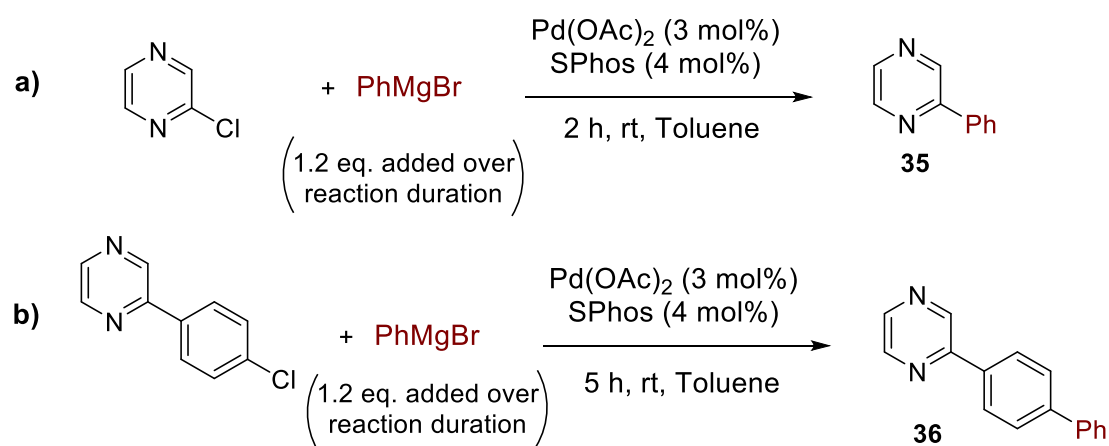


Figure 16. Influence of Grignard addition rate on yield of chemoselective coupling for aryl chlorides bearing nitrile groups

Using 4-chlorobenzonitrile as a reactant with a 5-hour reaction time provided 4% yield of coupled product **32** if the Grignard was added quickly in 1 minute. Significant amounts of side product resulting from direct reaction of the Grignard with the nitrile were observed. On the other hand, up to 94% yield of **32** could be obtained if the Grignard was added slowly over the course of the reaction time (300 minutes). 3-chlorobenzonitrile and 4'-chloro-4-cyanobiphenyl, which contain less electron-deficient and thus less activated C–Cl bonds. For these substrates, a more

dramatic influence of the Grignard addition rate on the yield of coupling products **33** and **34** was observed, although with still modest yields of 40% and 32% respectively at the slowest addition rate studied (300 minutes). This data is consistent with a relationship between the electronics of the C–Cl bond (and thus oxidative addition rate) and ideal Grignard addition rate.

The cross-coupling with pyrazine derivatives also proved this correlation. Electron-poor 2-chloropyrazine was coupled successfully when the Grignard was added over 2 hours at room temperature to provide 2-phenylpyrazine **35** in 81% yield (Scheme 28a). For a less activated pyrazine derivative where the electron-withdrawing pyrazine was further disconnected from the C–Cl bond, despite many attempts at room temperature, efficient coupling could not be achieved. Product **36** was obtained in only 49% yield even with the longest addition time of 5 hours (Scheme 28b).



Scheme 28. Influence of Grignard addition rate on pyrazine derivatives

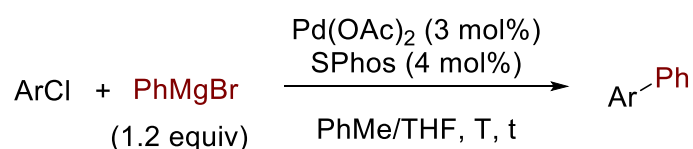
Summarizing the previous results, the less electron-deficient aryl chlorides that have less active C–Cl bond require slower Grignard addition rate as compared to the more

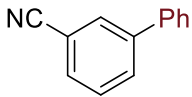
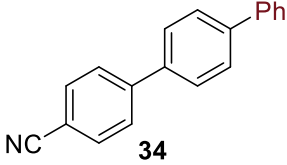
electron-deficient one. In order to further optimize the substrates with strong C–Cl bonds, not only long Grignard addition time is required, but also need the elevated temperature to further assist the oxidative addition step.

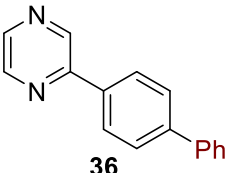
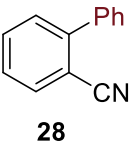
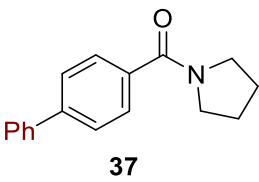
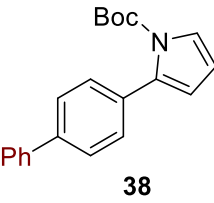
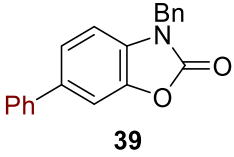
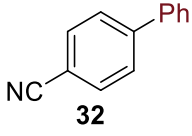
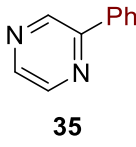
2.3.3 Effect of elevated temperature

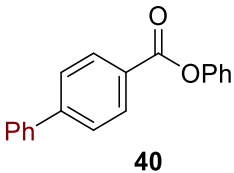
Elevated temperature was required to facilitate the oxidative addition of the Pd(0) catalyst into the strong C–Cl bond of more challenging aryl chlorides. The effect of higher temperatures was mainly examined on several less electron-deficient aryl chlorides that could not be fully optimized by extending the Grignard addition time at room temperature (Table 8).

Table 8. Reaction optimizations of selected substrates with elevated temperature



Entry	Substrate	Temperature (°C)	Grignard added over... (h)	Yield (%) ^a
1	 33	r.t.	5	40
2		50	1	99
3	 34	r.t.	5	32
4		50	1	93

5	 36	r.t.	5	49
6		50	1	92
7		r.t.	5	55
8	 28	50	1	92
9		50	3	35
10	 37	r.t.	1	41
11		50	0.75	95
12		r.t.	3	31
13	 38	50	1	43
14		50	1	86 ^b
15		50	2	97 ^b
16		80	1	54 ^b
17	 39	50	1	39
18		70	1	38
19		50	2	54 ^b
20	 32	r.t.	1.5	96
21		50	2	84
22	 35	r.t.	1	79
23		50	2	63

24	 40	r. t.	4	84
25		50	2	60

^a Yield determined by ¹H NMR of the crude mixture with 1,3,5-trimethoxybenzene as internal standard. ^b 6 mol% Pd(OAc)₂, 8 mol% SPhos was used.

For substrates **33**, **34**, **36** and **28**, only modest yields could be achieved at room temperature even when Grignard reagent was added with slowest addition time of 5 hours. In contrast, all the reactions were drastically improved when the temperature was elevated to 50 °C, which facilitated the oxidative addition step and excellent yields (> 90%) could be obtained with only 1 hour Grignard addition time (Entry 1-8). If Grignard addition was considerably slower than optimal at this elevated temperature however, the yield could be diminished (Entry 9). For amide **37**, yield could be increased up to 95% with only 45 minutes Grignard addition time at 50 °C (Entry 10 and 11).

However, aryl chlorides bearing electrophilic BOC group **38** and carbamate group **39** are relatively more challenging, modest yields were obtained even at elevated temperature (Entry 13 and 17). In order to further optimize these two substrates, catalyst loading was increased from 3 mol% to 6 mol% (Entry 14-16, 19). Temperatures that are higher than 50 °C were also tested, but a loss of yield was obtained in both cases (Entry 16 and 18).

For substrates **32**, **35** and **40** which could be optimized at room temperature using aggressive reaction conditions (50 °C, Grignard added over 2 hours) resulted in 8 to

19% decreased yield (Entry 20-25). Overall, there was a small but significant detriment to yield when running reactions at a higher temperature and longer time than necessary. These conditions should thus be considered a good starting point when utilizing new starting materials, but may require further optimization to maximize yield.

2.3.4 Scope and chemoselectivity in Kumada-Corriu coupling

With some optimization of reaction temperature and addition rate of the Grignard reagent, high chemoselectivity was obtainable in the Kumada-Corriu cross-coupling reaction of aryl chlorides bearing nitrile, ketone, ester, pyrazine and carbamate groups. Satisfying our simple and effective strategy, a broad range of aryl chlorides featuring these incompatible electrophilic functional groups identified from the robustness screen were optimized and the isolated yields of each reaction were systematically summarized in the following Table 9. In addition, the fast addition of the Grignard reagent over ~20 seconds under the otherwise identical reaction condition as the compared slow addition experiments was performed in each case to show the importance of slow Grignard addition.

Nitrile products could be obtained in excellent isolated yields (Entry 1–4). Almost no desired product was obtained in the fast addition experiments, as a large amount of imine arising from attack of the Grignard on the nitrile was observed as a side-product. Notably, the reaction scale of 4-chlorobenzonitrile can be increased from 0.2 mmol to 2 mmol. Product **32** can be obtained in 85% yield in the larger scale experiment (Entry 1). This suggests that our strategy is not prohibitively limited to small scale reactions. Three different ester-containing products **31**, **40** and **41** were

also obtained in high yields with slow addition, in contrast low yields were resulted if the Grignard was added fast due to the formation of side-products from attack of the nucleophile on the ester (Entry 5-7). Similarly, excellent yields could be obtained with amide-bearing aryl chlorides **37** and **42** (Entry 8 and 9).

An imine **43** was also tolerated, with an isolated yield of 76% (Entry 10). Ketone-containing products **26** and **44** proved to be somewhat more challenging (Entry 11 and 12). Additionally, indoles protected by electrophilic BOC group **45** and tosyl group **46** could be well tolerated (Entry 13 and 14). Aryl chlorides **38** and **39** bearing electrophilic BOC and carbamate groups respectively, were relatively challenging and could be coupled with double catalyst loading at elevated temperatures (Entry 15 and 16).

Table 9. Scope of sensitive aryl chlorides for Kumada-Corriu coupling reactions

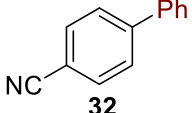
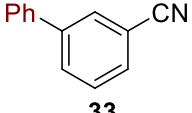
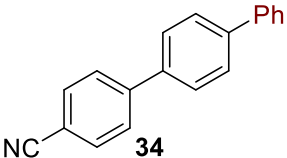
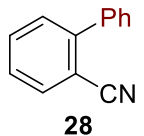
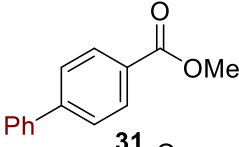
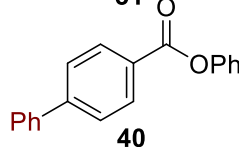
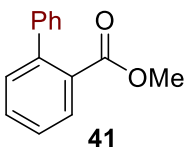
$\text{ArCl} + \text{PhMgBr} \xrightarrow[\text{PhMe/THF, T, t}]{\text{Pd(OAc)}_2 \text{ (3 mol\%)} \atop \text{SPhos (4 mol\%)}} \text{Ar-Ph}$ (1.2 equiv)					
Entry	Product	T (°C)	t (min)	Yield (%)	
				Fast addition ^a	Slow addition ^b
1	 32	r.t.	90	4	92 (85) ^e
2	 33	50	60	0	89
3	 34	50	60	0	91
4	 28	50	60	0	84
5	 31	r.t.	60	14	96
6	 40	r.t.	240	8	79
7	 41	r.t.	60	13	95

Table continued:

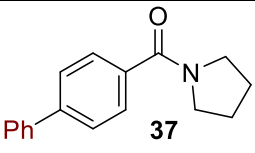
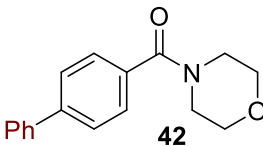
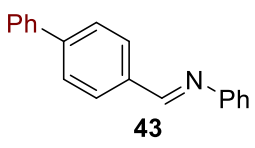
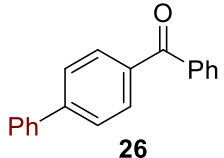
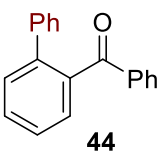
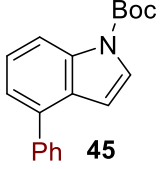
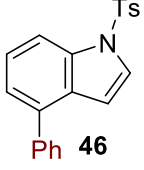
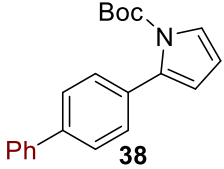
Entry	Product	T (°C)	t (min)	Yield (%)	
				Fast addition ^a	Slow addition ^b
8	 37	50	45	11	93
9	 42	50	60	6	94
10	 43	50	60	3	76
11	 26	r.t.	120	1	65
12	 44	r.t.	120	1	82
13	 45	50	60	0	85
14	 46	50	60	0	96
15 ^c	 38	50	120	10	93

Table continued:

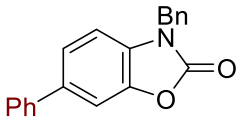
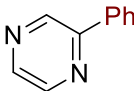
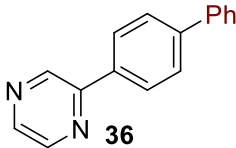
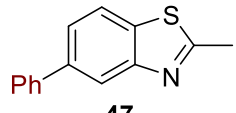
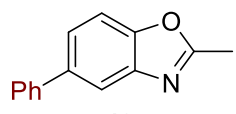
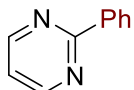
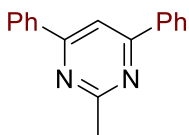
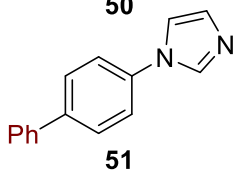
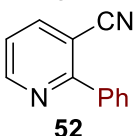
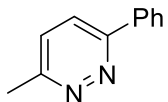
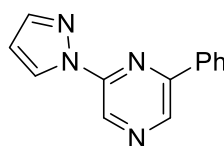
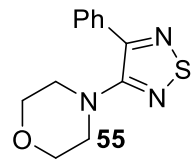
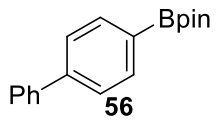
Entry	Product	T (°C)	t (min)	Yield (%)	
				Fast addition ^a	Slow addition ^b
16 ^c	 39	50	120	0	51
17	 35	r.t.	120	13	78
18	 36	50	60	4	81
19 ^c	 47	50	120	0	78
20	 48	50	60	2	79
21	 49	r.t.	60	18	78
22 ^d	 50	50	60	13	84
23	 51	50	60	5	80
24 ^c	 52	50	60	10	82

Table continued:

Entry	Product	T (°C)	t (min)	Yield (%)	
				Fast addition ^a	Slow addition ^b
25 ^c	 53	50	120	3	74
26	 54	50	60	16	63
27	 55	50	60	56	67
28	 56	50	60	32	60

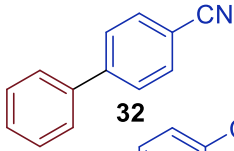
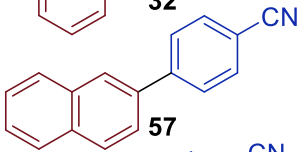
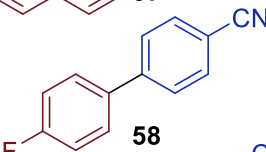
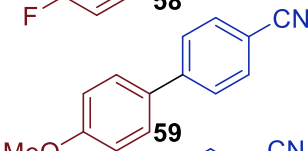
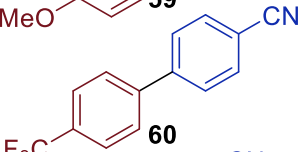
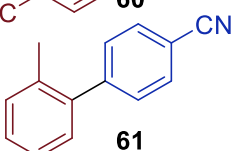
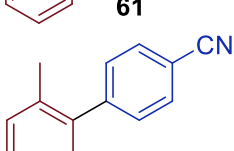
^a Grignard added dropwise over 20 seconds. Yield determined by ¹H NMR of the crude mixture with 1,3,5-trimethoxybenzene as internal standard. ^b Grignard added over the duration of the reaction time. Isolated yield (0.2 mmol scale). ^c 6 mol% Pd(OAc)₂, 8 mol% SPhos was used. ^d 2.4 eq. PhMgBr used for double coupling reaction. ^e Reaction was run in 2 mmol scale.

With a broad range of electrophilic functional groups demonstrated to be compatible with the given methodology, our focus turned towards sensitive heterocycles that would be of particular interest to the synthesis of bioactive molecules. Benzothiazole **47** and benzoxazole **48** could be coupled successfully (Entry 19 and 20). Double coupling reaction for substrate **50** could also be achieved efficiently using 2.4 equivalents of Grignard reagent (Entry 22). Furthermore, a large variety of heterocycles bearing multiple nitrogen atoms such as pyrazine derivatives **35** and **36**, pyrimidine **49**, substrates **51-54** were found to be tolerant of the reaction conditions with slow addition of the Grignard reagent (Entry 17,18 and 21-26). In all these cases,

addition of the Grignard reagent over ~20 seconds provided unacceptable yields of the desired products. For substrates thiadiazole **55** (Entry 27) and boronate ester **56** (Entry 28), the functional groups were not evaluated in the robustness screen, and slow addition of the Grignard reagent provided only a modest improvement. It might suggest that these substrates are not particularly prone to side reactions.

Differences in relative rates of Pd(II) intermediate transmetallation vs. side reactions could be revealed by varying different Grignard reagents. The effects of a number of sterically and electronically different Grignard reagents have thus been examined by coupling with 4-chlorobenzonitrile (Table 10). All the Grignard reagents were added dropwise by syringe pump over the course of 90 minutes. Electron-neutral **32**, **57**, **55** (Entry 1–3), electron-rich **59** (Entry 4) and electron-poor **60** (Entry 5) and somewhat sterically hindered **61** (Entry 6) arylmagnesium bromides could all be utilized with excellent yields. However, only 8% yield was obtained with highly sterically hindered 2,6-dimethylphenylmagnesium bromide **62** (Entry 7). ¹HNMR and GC/MS analysis of the reaction mixture revealed a 33% yield of the imine-bearing side product resulting from addition of the Grignard to the nitrile, suggesting that transmetallation is more heavily impacted by steric bulk than the side reaction.

Table 10. Scope of Grignard reagents

$\text{Ar'MgBr} + \text{Cl-C}_6\text{H}_4\text{-CN} \xrightarrow[\text{PhMe/THF, r.t., 90 min}]{\text{Pd(OAc)}_2 \text{ (3 mol\%)} \atop \text{SPhos (4 mol\%)}} \text{Ar'-Ar}$ (1.2 equiv)		
Entry	Product	Yield (%) ^a
1	 32	92
2	 57	85
3	 58	98
4	 59	99
5	 60	81
6	 61	85
7	 62	8 ^b

^a Isolated yield. ^b Yield determined by ¹H NMR of the crude mixture with 1,3,5-trimethoxybenzene as internal standard.

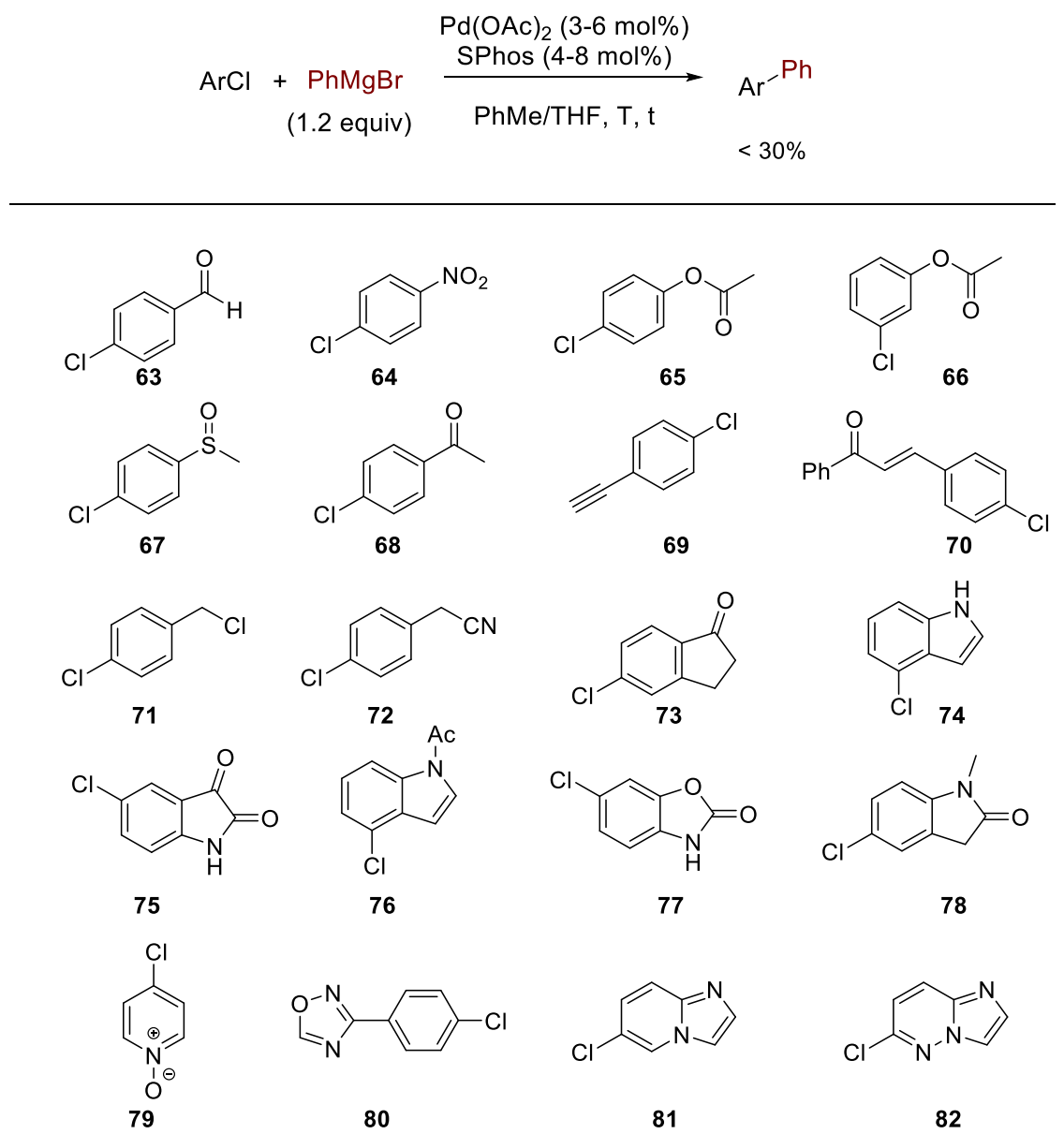
2.3.5 Scope limitations

There are some other aryl chloride substrates that still proved incompatible in our reaction conditions, even with several optimizations with different Grignard addition rates, reaction temperatures or even doubling the catalyst loading (Figure 17). Unsuccessful substrates with electrophilic functional groups including aldehyde **63**, nitrobenzene **64**, acetates **65** and **66**, acetylene **69** and chalcone **70** all gave side reactions and only trace amounts of desired product were obtained in some cases. In addition, molecules with relatively acidic protons such as 1-chloro-4-(chloromethyl)benzene **71**, (4-chloro-phenyl)-acetonitrile **72**, unprotected indole **74**, carbamates, amides, and sensitive protecting groups including acetyl **76** and methyl **78** were all intolerated. In these cases, high recovery of the starting materials was observed since the Grignard deprotonated these aryl chlorides and they were recovered upon quenching the reactions. These acidic molecules might be coupled by the use of an extra equivalent of Grignard reagent.⁷⁸

Finally, some heterocycles were equally challenging, including pyridine N-oxide **79**, oxadiazole **80**, 6-chloro-imidazo[1,2-a]pyridine **81** and imidazo[1,2-b]pyridazine **82**. No sign of the cross-coupled product was observed with these heterocycles, regardless of the addition rate. All these unsuccessful substrates suggest that the rate of the side-reaction is much faster than transmetallation rate of the Pd(II) intermediate.

⁷⁸ Zacuto, M. J.; Schultz, C. S.; Journet, M. *Org. Process Res. Dev.* **2011**, *15*, 158.

Figure 17. Unsuccessful aryl chlorides in slow addition experiments



Aliphatic Grignard reagents were also tested, including ethyl, benzyl and vinyl magnesium bromides. Many challenges were found using aliphatic Grignard and only trace amount of cross-coupling products were obtained in these experiments, despite several attempts with different addition rates and temperatures. The coupling of 4-chlorotoluene with ethyl magnesium bromide was also tested under different

temperatures (r.t, 50 °C and 80 °C) for several hours. Low yields were obtained in all these trials and most of the 4-chlorotoluene was recovered. Possible side reactions include beta-hydride elimination of the Pd(II) intermediate and halogen-magnesium exchange between ethylMgBr and 4-chlorotoluene.

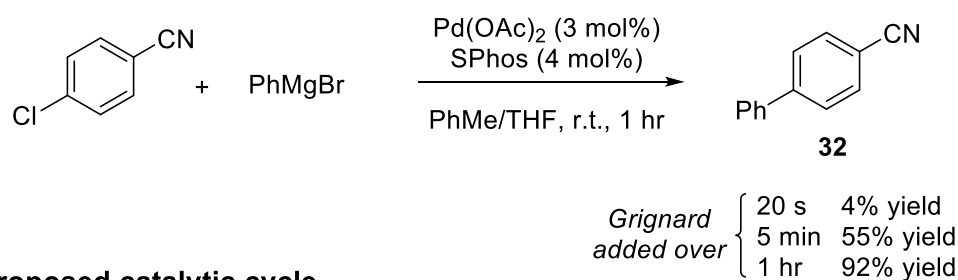
2.4 ESI-MS experiments⁷⁹

2.4.1 ESI monitoring of Kumada-Corriu coupling reactions

Our mechanistic hypothesis for the greatly increased yield in Kumada-Corriu couplings by controlling addition of the Grignard reagent is that the Pd(II) oxidative addition species ArPdCl must always be present to consume the Grignard via the transmetallation pathway and compete with side reactions. Using 4-chlorobenzonitrile as a representative example, if the Grignard is added slowly to match the oxidative addition rate, ArPdCl species **83** accumulates, allowing the transmetallation pathway to afford the desirable cross-coupling product **32** in excellent yield (Figure 18a). On the other hand, if the Grignard is added faster than the ArPdCl species **83** is formed, then the inherently high reactivity of the Grignard will result in quenching of the excess reagent by reaction with the sensitive functional group on the starting material or product to give the imine **84** or **85** as side products. The mechanistic interpretation of selectivity is shown in Figure 18b.

⁷⁹ ESI-MS experiments were performed in collaboration with Ryan Suvillan.

a) Effect of Grignard addition rate



b) Proposed catalytic cycle

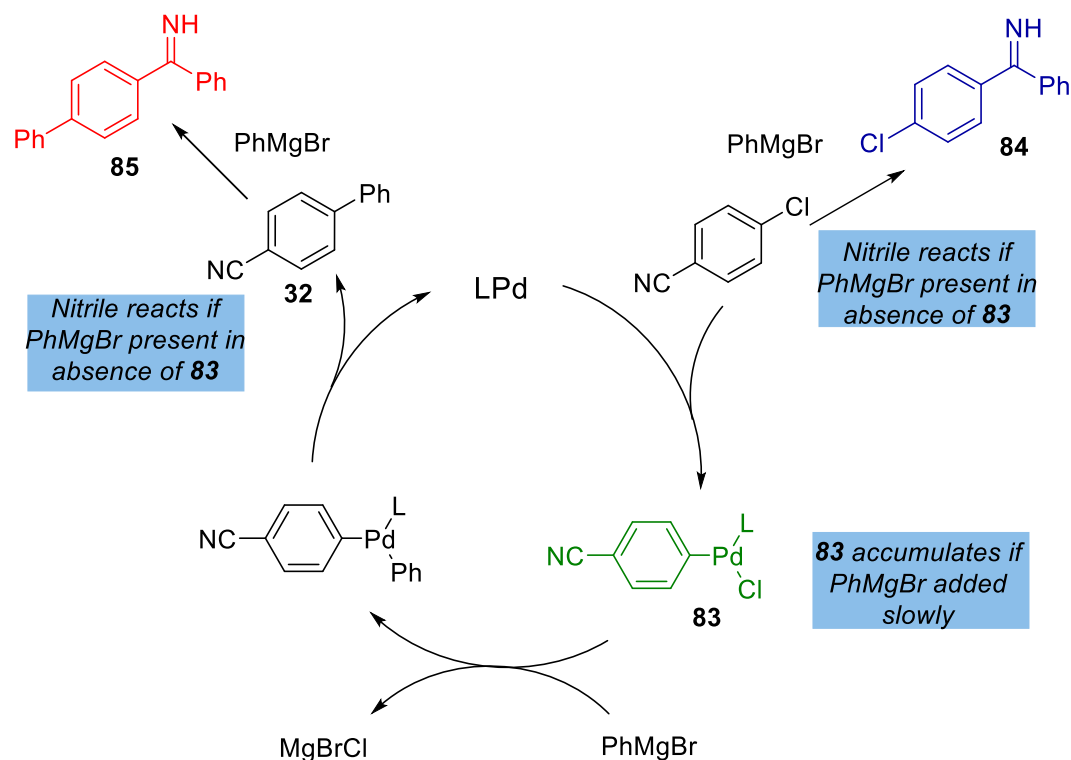


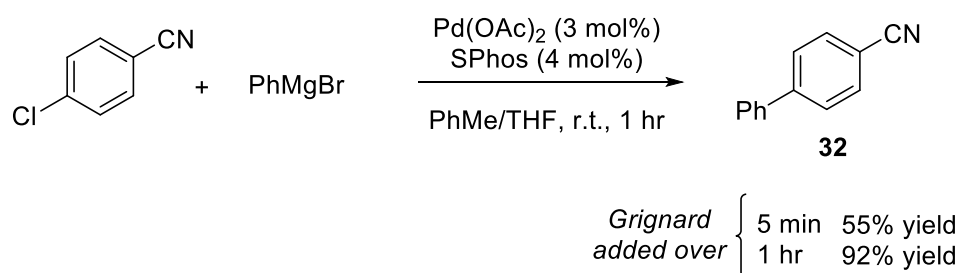
Figure 18. Mechanistic interpretation of selectivity by slow addition of Grignard

The mechanistic reason for the effectiveness of our hypothesis is uncovered by continuous-infusion ESI-MS studies.⁸⁰ The details about the real-time mass spectrometric experimental setup will be covered in the Experimental section. The 4-

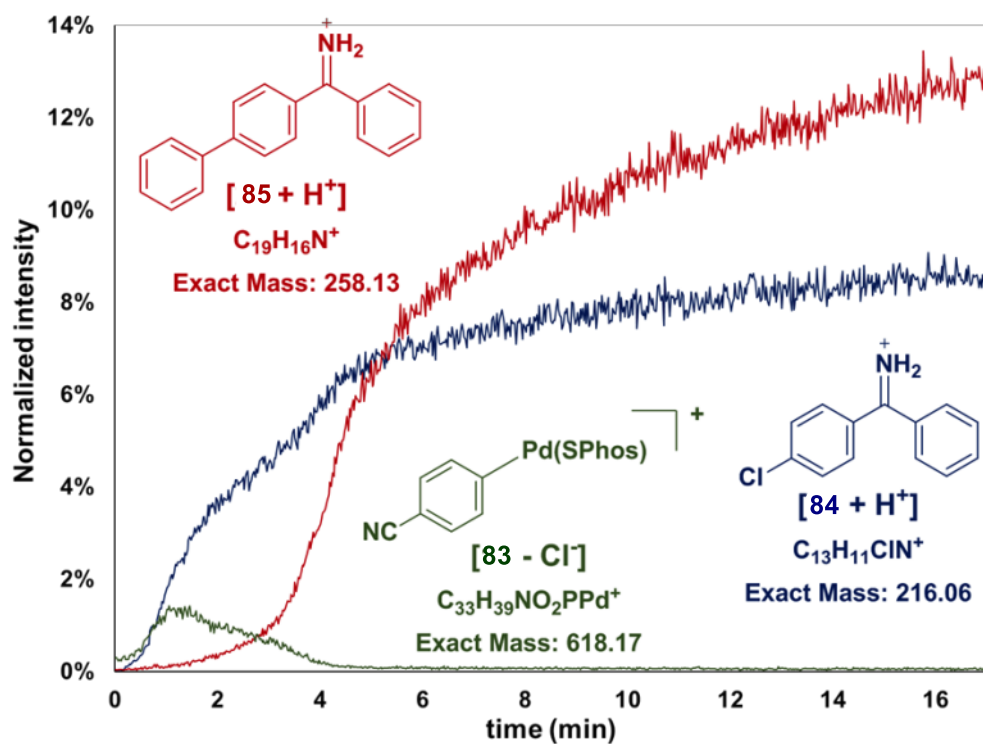
⁸⁰ a) Vikse, K. L.; Woods, M. P.; McIndoe, J. S. *Organometallics* 2010, 29, 6615. b) Hesketh, A. V.; Nowicki, S.; Baxter, K.; Stoddard, R. L.; McIndoe, J. S. *Organometallics* 2015, 34, 3816.

chlorobenzonitrile starting material and 4-phenylbenzonitrile product **32** used in the ESI-MS investigation (Figure 18) could not be simultaneously observed with the instrument parameters that allowed good detection of the Pd(II) species **83** of interest, so we chose the set-up that allowed us to track the formation and accumulation or depletion of the oxidative addition intermediate ArPdCl **83**.

In fast addition experiments, PhMgBr was added over the course of only 5 minutes and reaction was stirred for 1 hour to give the desired product **32** in only 55% yield. A Pd-containing species was initially observed at $m/z = 618$, representing the loss of chloride from Pd(II) intermediate **83** (Figure 19b). However, this signal was rapidly depleted as the Grignard was added and the formation of side products imine **84** and **85** ramped up significantly, formed by nucleophilic attack of the Grignard on the nitrile group of the starting material and the desired cross-coupling product, respectively. On the other hand, Grignard reagent slowly added over 1 hour in slow addition experiment to give product **32** in 92% yield. The Pd(II) species observed at $m/z = 618$ was present during the entire course of the reaction (Figure 19c). Small amounts of side product **84** were formed only during the initial induction period when **83** had not accumulated yet. This side reaction did not occur for the rest of the reaction, since a significant amount of Pd(II) intermediate **83** was present for chemoselective transmetallation.



a) Continuous infusion ESI-MS with fast addition



b) Continuous infusion ESI-MS with slow addition

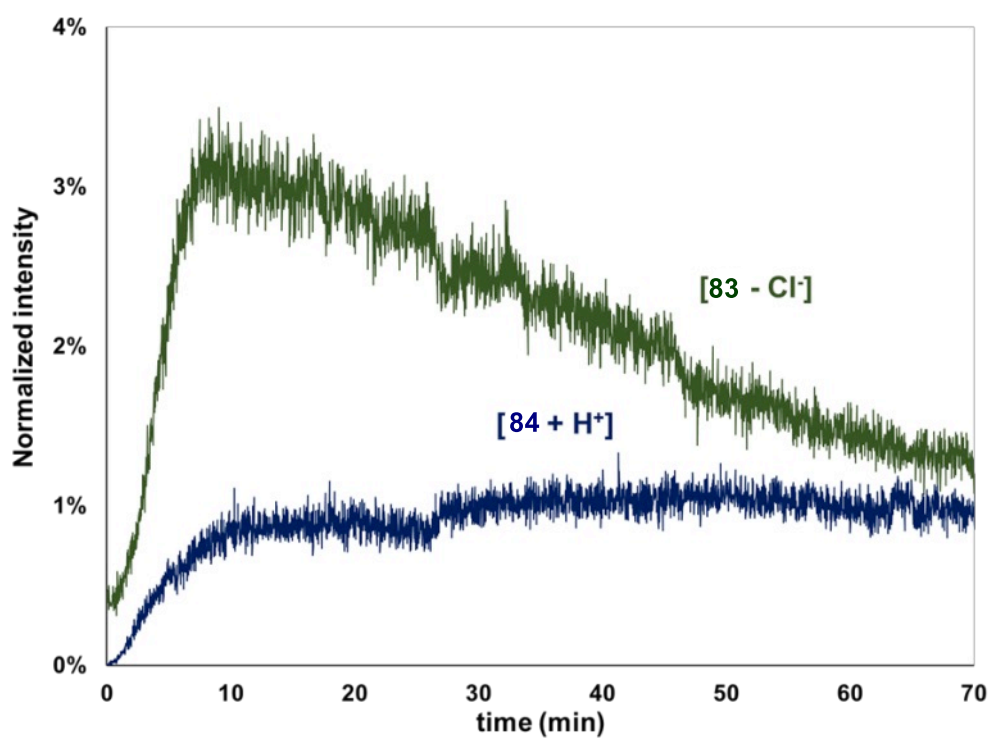
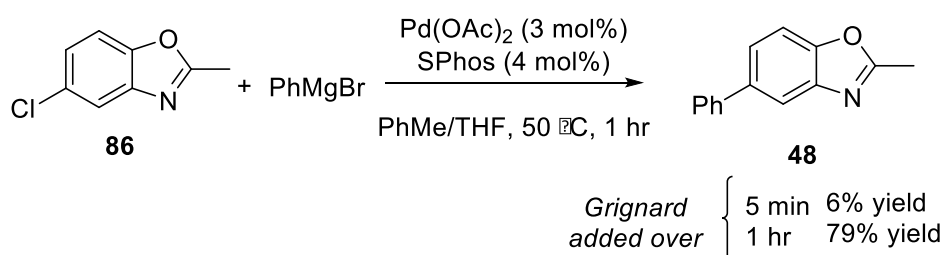


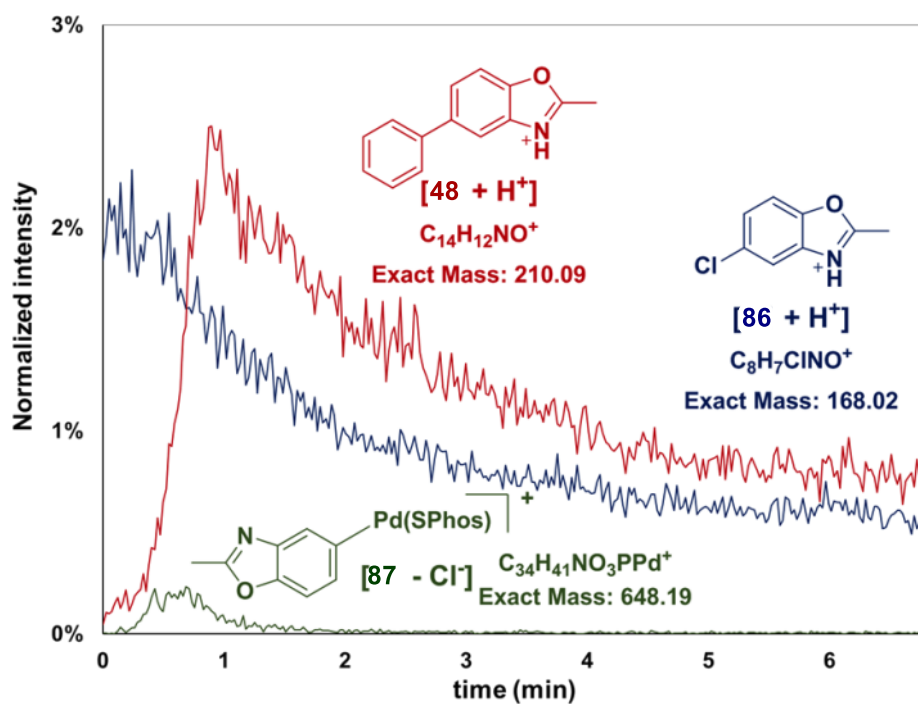
Figure 19. ESI-MS monitoring for coupling of 4-chlorobenzonitrile

Similar ESI-MS monitoring was performed for the coupling of 5-chloro-2-methylbenzooxazole **86** with PhMgBr to confirm that starting material consumption and product formation were consistent with the observed presence or absence of active ArPdCl species. In these circumstances the identity of the side product(s) were unknown; however, the starting material **86**, desired product **48** and ArPdCl species **87** could all be observed simultaneously. The yields for fast addition and slow addition experiments are shown in Figure 20a. The same observation of ArPdCl depletion when PhMgBr was added over only 5 min (Figure 20b), and the consumption of starting material **86** did not increase the concentration of desired cross-coupling product **48**, which alternatively proved the formation of side products. In the slow addition experiment, a pseudo-steady-state concentration of ArPdCl **87** was accumulated when the Grignard was added over the optimal 1 hour (Figure 20c). As expected, product **48** formation was only observed when the active ArPdCl intermediate **87** was present and proceeded to a much greater extent during the slow Grignard addition. These ESI-MS analyses agree with the one for 4-chlorobenzonitrile substrate.

a) Effect of Grignard addition rate



b) Continuous infusion ESI-MS with fast addition



c) Continuous infusion ESI-MS with slow addition

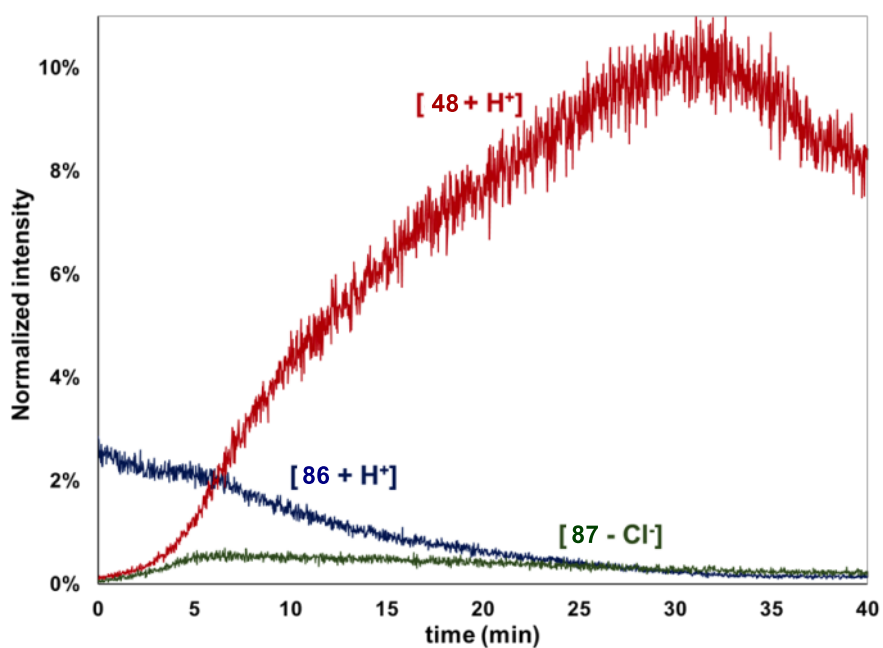


Figure 20. ESI-MS monitoring for coupling of 5-chloro-2-methylbenzooxazole

Further, during the slow addition experiment for 5-chloro-2-methylbenzooxazole, the starting material **86** gradually decreased and desired product **48** proportionately increased over the course of the Grignard addition. Due to the continuous withdrawal of solution from the mixture to enable the real-time monitoring, and the necessary withdrawal rate of 50–100 $\mu\text{L}/\text{min}$ to prevent clogging of the PEEK tube leading from the reaction flask, the starting material **86** became depleted at ~ 40 min, representing 2/3 of the total Grignard addition. At this point, precipitate formation in the reaction flask began and quickly resulted in clogging of the PEEK tubing leading to the MRA valve and therefore the end of data collection. Interestingly, between 30 and 40 min when the concentration of the starting material was nearing 0 and the concentration of product was high it was observed that the amount of product plateaued and then began to decline. This was likely an artifact of the early depletion of the starting material as a result of the reaction solution withdrawal leading to the presence of excess Grignard reagent at the end of the reaction and partial product decomposition as a result.

2.4.2 ESI monitoring of PhLi coupling reactions

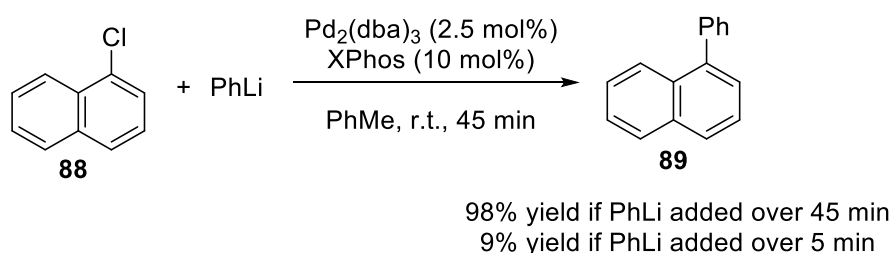
Satisfied with the real-time mass spectrometry analyses to track the Pd(II) oxidative addition species and observe either pseudo steady-state or rapid depletion of this intermediate depending on Grignard addition rate, we sought to explore if this mechanistic concept is operative in other transformations in the literature.⁸¹ For

⁸¹ Slow addition of nucleophile or related concepts have been utilized in cross-coupling chemistry for a variety of reasons. See: (a) Manolikakes, G.; Hernandez, C. M.; Schade, M.

instance, the Feringa lab has recently disclosed that organolithium species like BuLi and PhLi can be utilized as efficient nucleophiles in Pd-catalyzed cross-coupling reactions.⁸² To accomplish this transformation, lithium-halogen exchange is a prominent side reaction that must be overcome. While the success of the reaction is primarily attributed to the selection of appropriate solvent and ligand, a key feature is the slow addition of the organolithium reagent via syringe pump over the duration of the reaction.

Choosing the reaction of chloronaphthalene **88** with phenyllithium as a representative example, we performed this transformation with slow addition and fast addition of PhLi with continuous infusion into an ESI-MS (Figure 21a). As was observed in the previous experiment with PhMgBr, ArPdCl intermediate **90** appeared but was quickly consumed when the organolithium nucleophile was added rapidly (Figure 21b). In contrast, a pseudo steady-state concentration was observed when PhLi was added at the optimal, slow addition rate of 45 min (Figure 21c).

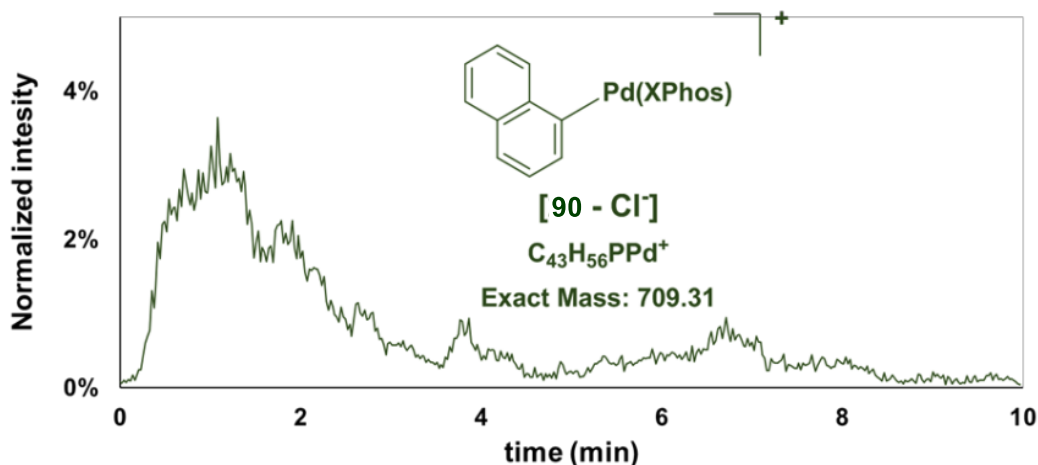
a) Coupling with PhLi by Feringa requires slow addition



A.; Metzger, A.; Knochel, P. *J. Org. Chem.* **2008**, 73, 8422. (b) Krasovskiy, A.; Duplais, C.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2009**, 131, 15592. (c) Vechorkin, O.; Barmaz, D.; Proust, V.; Hu, X. *J. Am. Chem. Soc.* **2009**, 131, 12078. (d) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, 126, 3686.

⁸² a) Giannerini, M.; Fañanás-Mastral, M.; Feringa, B. L. *Nat. Chem.* **2013**, 5, 667. (b) Hornillos, V.; Giannerini, M.; Vila, C.; Fañanás-Mastral, M.; Feringa, B. L. *Org. Lett.* **2013**, 15, 5114.

b) Continuous infusion ESI-MS with fast addition



c) Continuous infusion ESI-MS with slow addition

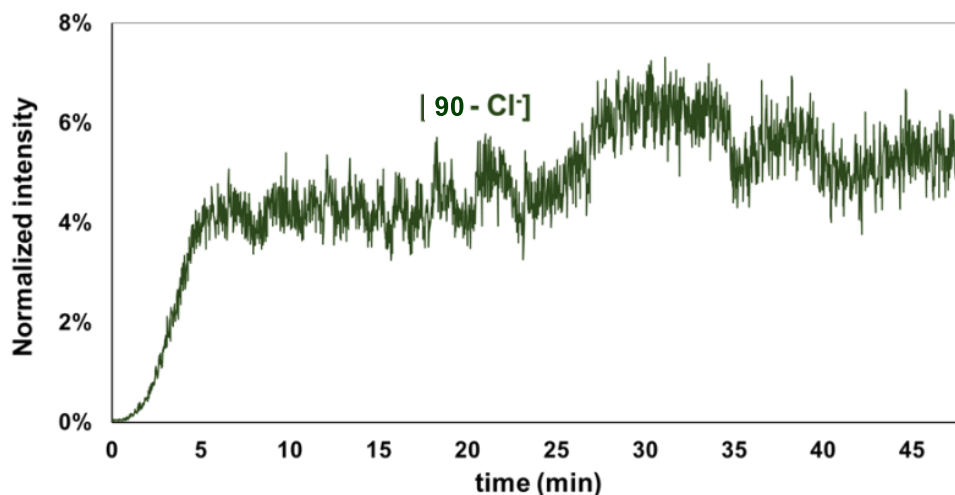


Figure 21. ESI-MS monitoring for coupling of chloronaphthalene with PhLi

This provided evidence that the explanation for the improved yields by slow ArLi addition was the same as for slow ArMgBr addition; namely, that matching the rate of nucleophile addition with ArPdCl formation allowed the inherent kinetic competency of transmetalation to be realized, providing high chemoselectivity for the reaction. The analyses of Feringa's work also suggests that the strategy of matching reagent

addition rates with reactive intermediate formation may be applicable to a wide array of chemical transformations and is not limited solely to the Kumada-Corriu couplings presented herein.

2.4.3 Advantages and Limitations

Applying real-time ESI-MS monitoring to our chemistry allows us to continuously monitor our reaction under anaerobic conditions without the need for regular sampling. Not only the organic compounds, but also the fragile organometallic intermediate ArPdCl can be analyzed using this simple experimental configuration and high-quality data can be obtained. In general, simultaneous rapid measurement of reactants, products, and intermediates can be achieved successfully by ESI-MS.

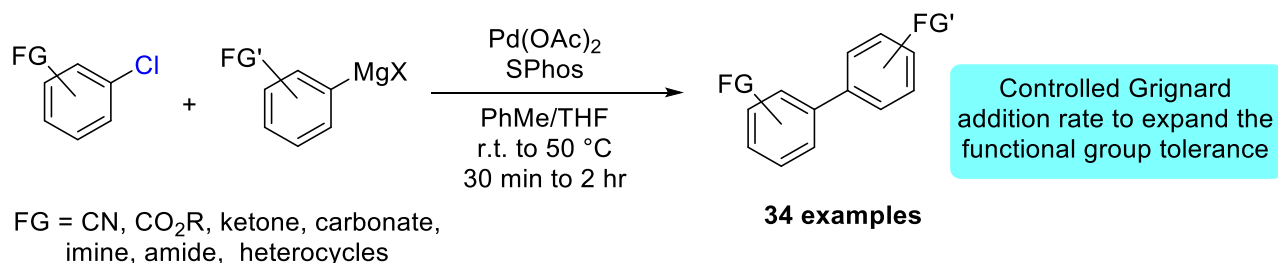
However, there are still some limitations in this technique. In order to ionize the substrates in ESI-MS, we have to dilute the reaction solution with a solvent such as MeOH and acetic acid, that might cause precipitates. This potential solubility issue will cause the clogging problem. Most importantly, only compounds inherently charged or easily oxidized or that readily associate with another charged species could be detected. Thus, some of the chemicals cannot be monitored effectively by ESI-MS, such as the 4-chlorobenzonitrile, 4-phenylbenzonitrile product **32** in Grignard coupling experiments and chloronaphthalene **88**, coupling product **89** in PhLi coupling experiments.

2.5 Summary and future work

The Kumada-Corriu reaction, being a pioneering and fundamental example of cross-coupling, has seen limited application in the synthesis of complex molecules due to apparent chemoselectivity of Grignard reagents. A robustness screen was performed to identify the functional group incompatibilities in a traditional Kumada-Corriu cross-coupling with aryl chlorides. A wide range of electrophilic functional groups was not tolerated and these sensitive functionalities were further investigated with our new strategy.

In order to expand the scope of Kumada-Corriu couplings, we proposed a mechanistically based strategy, matching oxidative addition rates with the rate of Grignard addition via syringe pump to minimize the exposure of the sensitive group to the aggressive nucleophile. Herein, the inherent chemoselectivity of transmetallation over other undesirable side reactions is sufficient to allow efficient cross-coupling to occur in the presence of many sensitive functionalities. This strategy is demonstrated in the high-yielding synthesis of biaryls containing nitriles, esters, ketones, amides, sensitive protecting groups, and heterocycles such as pyrazine, imidazole, and benzothiazole.

Our work

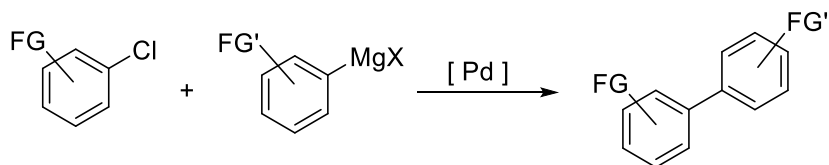


The mechanistic hypothesis that the accumulation of Pd(II) intermediates following oxidative addition is essential for the enhanced yields upon slow addition of the Grignard is verified by continuous infusion ESI-MS studies. This concept is shown to be applicable to other chemistry in the literature, namely the direct use of organolithium reagents in cross-coupling. Given that the ultimate source of chemoselectivity comes from the relative rate of transmetalation in comparison with potential side reactions. This suggests that the strategy of matching reagent addition rates with reactive intermediate formation may be applicable to a wide array of chemical transformations.

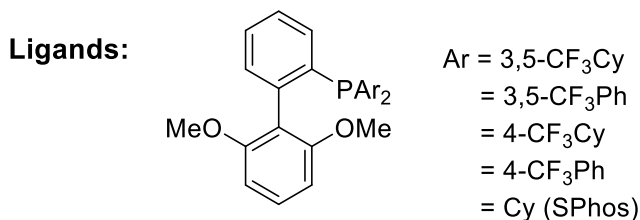
Meanwhile, there are still some limitations with our current protocol and many challenging aryl chlorides and also aliphatic Grignard reagents cannot be coupled successfully. Performing further ligand, and additive optimization will certainly open up further opportunities for coupling these more sensitive substrates (Scheme 29). Different additives such as ethers,⁸³ metal salts and tetrabutylammonium bromide and related salts may be able to moderate the nucleophilicity of Grignard reagents and alter their specification. According to a Buchwald study,⁸⁴ electron-poor Buchwald type ligands can make the Pd(II) intermediate more electrophilic and further enhance the chemoselectivity of the reaction. By modifying the aryl group on Buchwald type ligand such as adding electron-withdrawing CF₃ groups, the electrophilicity can be altered. Also, different aryl halides and aryl pseudohalides could also be tested in the future.

⁸³ Wang, X.-j.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 5593.

⁸⁴ Hicks, J. D.; Hyde, A. M.; Cuezva, A. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 16720.



Additives: 18-crown-6, bis[2-(N,N-dimethylamino)ethyl] ether, TMEDA
KF, LiCl, LiBr, NaBr, NaI, tetrabutylammonium bromide, etc.



Scheme 29. Additives and ligands screening for future experiments

Moreover, a more diverse set of Grignard reagents including highly functionalized Knochel-type Grignard reagents should be tested with more developed catalytic conditions. In order to make our strategy more practical, future work on continuous processing under flow conditions will definitely open more opportunities. A rational design for the future flow experiments based on Knochel and Ley's study⁸⁵ is shown in Figure 22. The optimized catalytic condition and flow rates of each component need to be further investigated for the preparation and safe delivery of Kumada-Corriu couplings.

⁸⁵ Brodmann, T.; Koos, P.; Metzger, A.; Knochel, P.; Ley, S. V. *Org. Process Res. Dev.* **2012**, *16*, 1102.

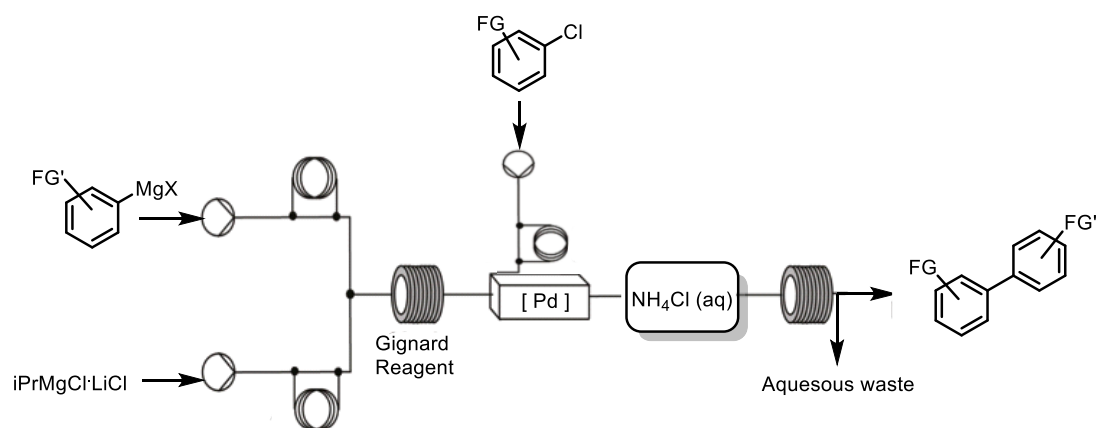


Figure 22. Rational design for Kumada-Corriu couplings under flow conditions

2.6 Experimental

2.6.1 General considerations

General experimental details

Unless otherwise indicated, reactions were conducted under an atmosphere of argon in 8 mL screw-capped vials that were oven dried (120 °C). Column chromatography was either performed manually using Silicycle F60 40–63 μm silica gel or using a Combiflash Rf+ automated chromatography system with commercially available RediSep Rf normal-phase Silica Flash columns (35–70 μm). Analytical thin layer chromatography (TLC) was conducted with aluminum-backed EMD Millipore Silica Gel 60 F₂₅₄ pre-coated plates. Visualization of developed plates was performed under UV light (254 nm) and/or using KMnO₄ or ceric ammonium molybdate (CAM) stain.

Instrumentation

¹H NMR and ¹³C NMR were recorded on a Bruker AVANCE 400 MHz spectrometer. ¹H NMR spectra were internally referenced to the residual solvent signal (e.g., CDCl₃ = 7.27 ppm). ¹³C NMR spectra were internally referenced to the residual solvent signal (e.g., CDCl₃ = 77.00 ppm). Data for ¹H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration. NMR yields for optimization studies were obtained by ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. IR spectra were obtained using a Nicolet6700 FT-IR spectrometer with a diamond ATR crystal (ThermoScientific) and are reported in terms of frequency of absorption (cm⁻¹). Melting point ranges were determined on a Canlab Gallenkamp Melting Point Apparatus. GC yields for optimization studies were obtained via a 5-point calibration curve using FID analysis

on an Agilent Technologies 7890B GC with 30 m $\times$ 0.25 mm HP-5 column. Accurate mass data (EI) was obtained from an Agilent 5977A GC/MSD using MassWorks 4.0 from CERNO bioscience.¹ Accurate mass data (ESI) was obtained from a Micromass Q-TOF 2 quadrupole – time-of-flight mass spectrometer, with ESI source. Real-time ESI-MS monitoring experiments were performed using an Advion ExpressION^S compact mass spectrometer in the positive ionization mode with capillary temperature 200 °C, capillary voltage 120 V, source gas temperature 250 °C, ESI voltage 3500 V and sweep rate of 2500 m/z·s⁻¹. Data were smoothed using a five-point boxcar average.

Materials

Organic solvents were purified by rigorous degassing with nitrogen before passing through a PureSolv solvent purification system, and low water content was confirmed by Karl Fischer titration (<25 ppm for all solvents). Unless otherwise noted, reagents were used as received. All reagents, metal catalysts, and ligands were purchased from Sigma-Aldrich, Combiblocks, or Strem Chemical Company.

2.6.2 Robustness screen experiments

Experimental procedures

The robustness screen was performed using a 96 well plate equipped with 8 $\times$ 40 mm glass vials. The plate was divided as shown in Figure 23. In vials A1–6 through H1–5 (yellow box, Figure 23), Pd-IPr mediated cross-coupling reactions between PhMgBr and 4-chlorotoluene were performed in the presence of a different additive in each vial, from additive A1 to A47. In vials A7–12 through H7–11 (green box, Figure 23) a single point calibration solution was prepared for each individual additive,

respectively. Vials H6 and H12 were used for control cross-coupling reactions in the absence of any additive (blue boxes, Figure 23).

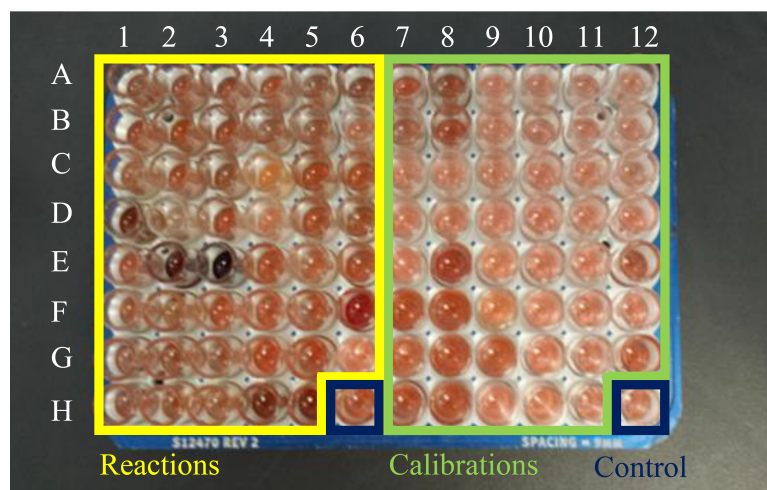


Figure 23. Screening plate for the robustness screen

On the bench, $\text{Pd}_2(\text{dba})_3$ (0.8 mg, 8×10^{-4} mmol, 1 mol%) and $\text{IPr}\cdot\text{HCl}$ (1.4 mg, 3.2×10^{-3} mmol, 4 mol%) were added into each reaction and control vial. Of additives A1–A47, those that were solids were added into both reaction and calibration vials, where appropriate (0.096 mmol, 1.2 eq.). A magnetic stir bar was added to each vial and the plate was brought into a nitrogen-filled glovebox, where-in the liquid additives of A1–A47 were added to the appropriate reaction and calibration vials via a 20 μL micropipette. A stock solution of 4-chlorotoluene (520 μL , 4.4 mmol) and PhMgBr (5.28 mL, 1 M in THF) in 1,4-dioxane (22 mL) was prepared and 505 μL of this stock solution was added to each reaction and control vial. 505 μL of 1,4-dioxane was added to each calibration vial and the plate was sealed, removed from the glovebox and heated at 80 $^\circ\text{C}$ with stirring for 24 h in an aluminum heating block. Upon cooling, the plate was opened and each reaction and control vial was quenched with 250 μL of saturated NH_4Cl (aq). 250 μL of 0.05 M 1,3,5-trimethoxybenzene in THF was added as an internal standard to all vials. The contents of each vial were

passed through a multi-well filtration plate filled with silica gel, eluting with ethyl acetate. The filtrates were diluted to an appropriate concentration, then analyzed by GC-FID.

Classification of the additives

Yields of the coupled product 4-methylbiphenyl were calculated using a 5-point calibration curve and the amount of recovered additive in each reaction vial was calculated using the single-point calibration solution in the appropriate calibration vial. The control reaction with no additive provided a 69% yield of 4-methylbiphenyl. Additives were classified according to the criteria in Table 11. If an additive decreased the yield of 4-methylbiphenyl below 35% (half of control result) the additive was classified as incompatible. This classification was further subdivided based on the extent of additive recovery. If $\geq 70\%$ of the additive was recovered after the reaction, the additive was classified as incompatible/recovered, otherwise incompatible/unrecovered. We estimated the uncertainty at $\pm 20\%$ in our GC results since the screening was performed on a small scale and additive calibrations were performed using single-point calibration curves. The relatively large quantitation uncertainty was considered in our selection of the threshold values for classification of the additives such that the threshold values were sufficiently distinct that misclassification was unlikely to arise from measurement uncertainty. Additive recoveries that varied from 95–120% were considered to be ‘quantitative’.

Table 11. Quantitation thresholds for classification of additives in robustness screen.

Additive classification	4-Methylbiphenyl yield (%)	Additive recovery (%)
Compatible	≥ 35	≥ 70
Incompatible/Unrecovered	< 35	< 70
Incompatible/Recovered	< 35	≥ 70

The robustness screen represented an upper limit of potential additive compatibility with relatively aggressive reaction conditions, an unactivated aryl chloride and a catalyst that was able to demonstrate the first, but not mildest, coupling of ArCl. However, this gave an excellent first-pass assessment about which functional groups warranted further investigation. There was also the possibility of false negatives, including additives which bind to the catalyst or those that might give better chemoselectivity under slightly altered, milder conditions.

Results of the robustness screen

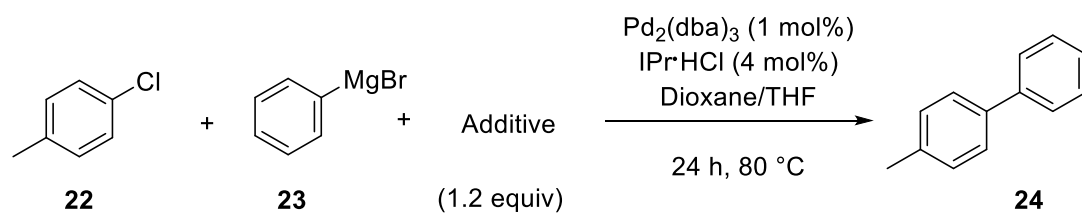
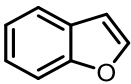
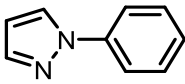
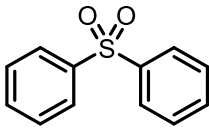
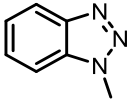
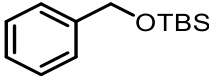
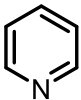
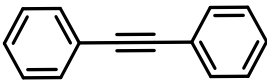
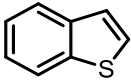
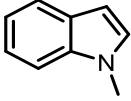
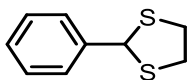
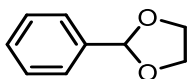
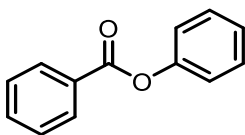
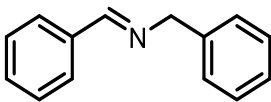
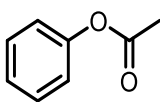
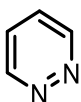
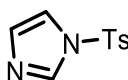
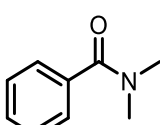
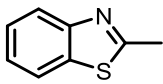
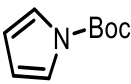
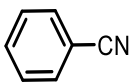
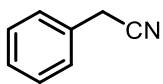
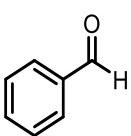
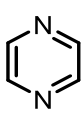
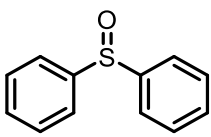
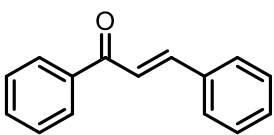
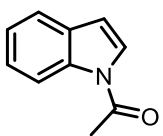


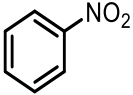
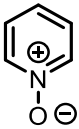
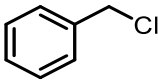
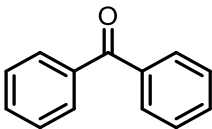
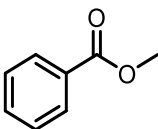
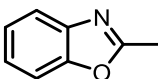
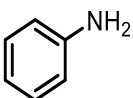
Table 12. Complete robustness screen results

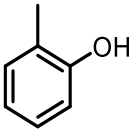
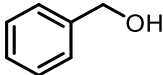
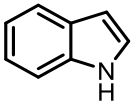
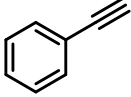
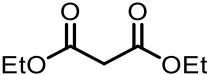
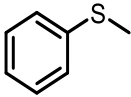
Entry	Additive	Product yield (%)	Additive recovery (%)	Additive classification
A1		69	quantitative	compatible
A2		84	quantitative	compatible
A3		59	92	compatible
A4		61	71	compatible
A5		59	n/a ^a	compatible
A6		48	43	compatible

A7		43	86	compatible
A8		53	quantitative	compatible
A9		60	85	compatible
A10		48	84	compatible
A11		35	67	compatible
A12		53	21	compatible
A13		44	quantitative	compatible
A14		53	quantitative	compatible
A15		55	quantitative	compatible

A16		61	quantitative	compatible
A17		44	quantitative	compatible
A18		1	53	incompatible/unrecovered
A19		18	<1	incompatible/unrecovered
A20		5	31	incompatible/unrecovered
A21		1	17	incompatible/unrecovered
A22		<1	31	incompatible/unrecovered
A23		3	0	incompatible/unrecovered
A24		14	37	incompatible/unrecovered

A25		1	55	incompatible/unrecovered
A26		9	37	incompatible/unrecovered
A27		<1	23	incompatible/unrecovered
A28		0	19	incompatible/unrecovered
A29		5	0	incompatible/unrecovered
A30		13	n/a ^b	incompatible/unrecovered
A31		1	27	incompatible/unrecovered
A32		5	0	incompatible/unrecovered
A33		15	0	incompatible/unrecovered

A34		<1	64	incompatible/unrecovered
A35		2	0	incompatible/unrecovered
A36		12	33	incompatible/unrecovered
A37		6	5	incompatible/unrecovered
A38		14	32	incompatible/unrecovered
A39		23	65	incompatible/unrecovered
A40		34	58	incompatible/unrecovered
A41		<1	72	incompatible/recovered

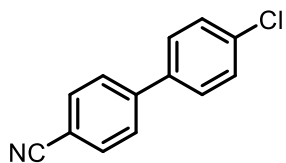
A42		0	quantitative	incompatible/recovered
A43		0	quantitative	incompatible/recovered
A44		3	86	incompatible/recovered
A45		<1	86	incompatible/recovered
A46		0	quantitative	incompatible/recovered
A47		14	84	incompatible/recovered

^a Additive not quantified due to overlap with solvent peak in GC-FID trace.

^b Additive recovery not calculated due to high volatility. The presence of significant quantities of 2-phenylpyrazine detected by GC-FID and confirmed by GC-MS verified low pyrazine recovery.

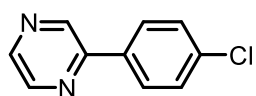
2.6.3 Preparation of chemical reagents

4'-chloro-[1,1'-biphenyl]-4-carbonitrile (Starting material of 34)



The procedure was adapted from the literature.⁸⁶ A 25 mL round bottom flask was charged with $\text{Pd}_2(\text{dba})_3$ (1 mol%, 0.03 mmol, 27 mg), $[\text{HP}(\text{tBu})_3]\text{BF}_4$ (2.4 mol%, 0.072 mmol, 21 mg), (4-cyanophenyl)boronic acid (1.1 eq., 3.3 mmol, 485 mg), $\text{KF}\cdot 2\text{H}_2\text{O}$ (3.3 eq., 9.9 mmol, 940 mg) and a magnetic stir bar. The flask was purged with argon and THF (10 mL) and 1-bromo-4-chlorobenzene (1 eq., 3 mmol, 574 mg) were added. The reaction mixture was stirred at room temperature for 18 h then diluted with Et_2O (6 mL), filtered through a plug of silica gel, and eluted with Et_2O (20 mL). The filtrate was concentrated and the residue purified by flash chromatography on silica gel (1/10 EtOAc /hexanes), affording 4'-chloro-[1,1'-biphenyl]-4-carbonitrile as a white powder (545 mg, 85%). Characterization data were in accordance with literature.⁸⁷ ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.72–7.77 (m, 2 H), 7.64–7.69 (m, 2 H), 7.51–7.55 (m, 2 H), 7.44–7.49 (m, 2 H).

2-(4-chlorophenyl)pyrazine (Starting material of 36)



The procedure was adapted from the literature.⁸⁸ A 100 mL round-bottomed flask was charged with $\text{Pd}(\text{OAc})_2$ (4 mol%, 0.18 mmol, 40 mg), K_2CO_3 (2 eq., 9.00 mmol, 1.24 g), 4-chlorophenylboronic acid (1.3 eq., 5.85 mmol, 915 mg) and a magnetic stir bar. Ethanol (27 mL), water (9 mL)

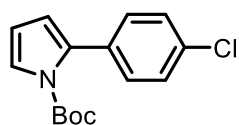
⁸⁶ Lou, S.; Fu, G. C. *Adv. Synth. Catal.* **2010**, 352, 2081.

⁸⁷ Al-Amin, M.; Akimoto, M.; Tameno, T.; Ohki, Y.; Takahashi, N.; Hoshiya, N.; Shuto, S.; Arisawa, M. *Green Chem.* **2013**, 15, 1142.

⁸⁸ Xu, C.; Wang, Z.-Q.; Yuan, X.-E.; Han, X.; Xiao, Z.-Q.; Fu, W.-J.; Ji, B.-M.; Hao, X.-Q.; Song, M.-P. *J. Organomet. Chem.* **2015**, 777, 1.

and 2-chloropyrazine (1 eq., 4.5 mmol, 402 μ L) were added. The reaction was refluxed at 90 $^{\circ}$ C for 5 h. The crude product was extracted with EtOAc (3×20 mL) and the combined organic extracts were filtered through a short plug of silica gel and dried over MgSO_4 . The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (2/8 EtOAc/hexanes), affording 2-(4-chlorophenyl)pyrazine as a white solid (240 mg, 28%). Characterization data were in accordance with literature.⁸⁹ ^1H NMR (400 MHz, CDCl_3): δ (ppm) 9.02 (d, $J = 1.6$ Hz, 1H), 8.63 (dd, $J = 2.5, 1.6$ Hz, 1H), 8.53 (d, $J = 2.5$ Hz, 1H), 7.98 (d, $J = 8.8$ Hz, 2H), 7.49 (d, $J = 8.4$ Hz, 2H).

***tert*-butyl 2-(4-chlorophenyl)-1H-pyrrole-1-carboxylate (Starting material of 38)**

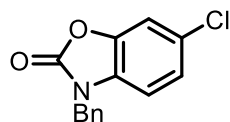


A 25 mL round bottom flask was charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 0.02 mmol, 22 mg), $[\text{HP}(\text{tBu})_3]\text{BF}_4$ (4.4 mol%, 0.048 mmol, 373 mg), (1-(*tert*-butoxycarbonyl)-1H-pyrrol-2-yl)boronic acid (1 eq., 2.0 mmol, 253 mg), $\text{KF} \cdot 2\text{H}_2\text{O}$ (3.3 eq., 6.6 mmol, 373 mg) and a magnetic stir bar. The flask was purged with argon, THF/ H_2O (19/1, 10 mL) and 1-bromo-4-chlorobenzene (1 eq., 2.0 mmol, 230 mg) were added and the reaction mixture was stirred at room temperature for 18 h. The mixture was then diluted with Et_2O (6 mL) and filtered through a plug of silica gel, eluting with Et_2O (15 mL). The filtrate was concentrated, and the residue purified by flash chromatography on silica gel (1/20–1/10 EtOAc/hexanes), affording *tert*-butyl 2-(4-chlorophenyl)-1H-pyrrole-1-carboxylate as a yellow solid (233 mg, 70%). Characterization data were in

⁸⁹ Singh, P. P.; Aithagani, S. K.; Yadav, M.; Singh, V. P.; Vishwakarma, R. A. *J. Org. Chem.* **2013**, 78, 2639.

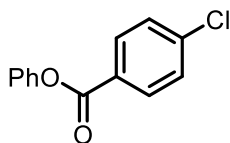
accordance with literature.⁹⁰ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.19–7.43 (m, 5 H), 6.09–6.28 (m, 2 H), 1.40 (s, 9 H).

3-benzyl-6-chlorobenzo[d]oxazol-2(3H)-one (Starting material of 39)



The procedure was adapted from the literature.⁹¹ A 25 mL round bottom flask was charged with 6-chlorobenzo[d]oxazol-2(3H)-one (1 eq., 4 mmol, 680 mg), benzyl bromide (1.5 eq., 6 mmol, 0.712 mL), K₂CO₃ (4 eq., 16 mmol, 2.2 g) and a magnetic stir bar. The flask was purged with argon and DMF (15 mL) was added. The reaction mixture was stirred at 125 °C for 2 h. After cooling to room temperature, the reaction mixture was poured onto ice (100 mL), and the resulting precipitate was filtered and washed with cold water (50 mL), dried and recrystallized from ethanol to afford 3-benzyl-6-chlorobenzo[d]oxazol-2(3H)-one as a white solid (923 mg, 89%). Characterization data were in accordance with literature.⁹² ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.30–7.43 (m, 5 H), 7.07–7.13 (m, 2 H), 6.84 (d, J = 2.0 Hz, 1 H), 4.99 (s, 2 H).

phenyl 4-chlorobenzoate (Starting material of 40)



The procedure was adapted from the literature.⁹³ A 25 mL round bottom flask was charged with phenol (1 eq., 2.5 mmol, 235 mg), 4-chlorobenzylchloride (1.1 eq., 2.75 mmol, 0.353 mL), N,N-dimethyl-4-aminopyridine (DMAP: 5 mol%, 0.13 mmol, 15 mg) and a magnetic stir

⁹⁰ Honraedt, A.; Raux, M.-A.; Grogne, E. L.; Jacquemin, D.; Felpin, F.-X. *Chem. Commun.* **2014**, 50, 5236.

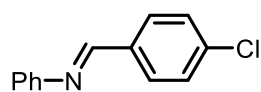
⁹¹ Ucar, H.; Van derpoorten, K.; Cacciaguerra, S.; Spampinato, S.; Stables, J. P.; Depovere, P.; Isa, M.; Masereel, B.; Delarge, J.; Poupaert, J. H. *J. Med. Chem.* **1998**, 41, 1138.

⁹² Ram, R. N.; Soni, V. K. *J. Org. Chem.* **2013**, 78, 11935.

⁹³ Liu, Z.; Ma, Q.; Liu, Y.; Wang, Q. *Org. Lett.* **2014**, 16, 236.

bar. The flask was purged with argon and toluene (10 mL) was added. Triethylamine (1.1 eq., 2.75 mmol, 0.38 mL) was added dropwise. The reaction mixture was stirred at 50 °C for 16 h, then quenched with saturated NaHCO₃ (aq) (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with 1 M NaOH (10 mL) to remove residual phenol then dried over Na₂SO₄, filtered through a plug of silica gel and concentrated. Purification by flash chromatography on silica gel (1/20 EtOAc/hexanes) yielded phenyl 4-chlorobenzoate as a white solid (575 mg, 98%). Characterization data were in accordance with literature.⁹⁴ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.10–8.15 (m, 2 H), 7.37–7.55 (m, 4 H), 7.28 (d, *J* = 7.3 Hz, 1 H), 7.16–7.22 (m, 2 H).

1-(4-chlorophenyl)-N-phenylmethanimine (Starting material of 43)



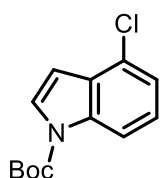
The procedure was adapted from the literature.⁹⁵ A 25 mL round bottom flask was charged with aniline (1 eq., 3 mmol, 0.273 mL), 4-chlorobenzyl alcohol (1.2 eq., 3.6 mmol, 513 mg), KOH (1.2 eq., 3.6 mmol, 202 mg) and a magnetic stir bar. The flask was sealed with a septum and a balloon filled with commercial compressed air was attached via a needle. Toluene (5 mL) was added, and the reaction mixture was stirred at 90 °C for 24 h. The reaction mixture was then directly purified by flash chromatography on alumina gel (1/10/100 NEt₃/ EtOAc/ Et₂O). 1-(4-Chlorophenyl)-N-phenylmethanimine was recrystallized from hexanes yielding a yellow solid (100 mg, 15%). Characterization data were in

⁹⁴ Rosa, J. N.; Reddy, R. S.; Candeias, N. R.; Cal, P. M. S. D.; Gois, P. M. P. *Org. Lett.* **2010**, *12*, 2686.

⁹⁵ Xu, J.; Zhuang, R.; Bao, L.; Tang, G.; Zhao, Y. *Green Chem.* **2012**, *14*, 2384.

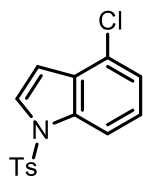
accordance with literature.⁹⁶ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.44 (s, 1 H), 7.80–7.91 (m, 2 H), 7.36–7.50 (m, 4 H), 7.17–7.27 (m, 3 H).

***tert*-butyl 4-chloro-1H-indole-1-carboxylate (Starting material of 45)**



The procedure was adapted from the literature.⁹⁷ A 25 mL round bottom flask was charged with 4-chloro-1H-indole (1 eq., 3 mmol, 0.361 mL), Boc₂O (2 eq., 6 mmol, 1.3 g), N,N-dimethyl-4-aminopyridine (DMAP: 1 eq., 3 mmol, 366 mg) and a magnetic stir bar. The flask was purged with argon and THF (6 mL) was added. The reaction mixture was stirred at room temperature for 16 h then washed with brine (10 mL) and extracted with THF (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered through a plug of silica gel and concentrated. Purification by flash chromatography on silica gel (1/10 EtOAc/hexanes) yielded *tert*-butyl 4-chloro-1H-indole-1-carboxylate as a light yellow oil (690 mg, 91%). Characterization data were in accordance with literature.⁹⁸ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.07 (d, *J* = 8.6 Hz, 1 H), 7.64 (d, *J* = 3.7 Hz, 1 H), 7.20–7.26 (m, 2 H), 6.71 (dd, *J* = 3.8, 0.7 Hz, 1 H), 1.69 (s, 9 H).

4-chloro-1-tosyl-1H-indole (Starting material of 46)



The procedure was adapted from the literature.⁹⁹ A 25 mL round bottom flask was charged with 4-chloro-1H-indole (1 eq., 3 mmol, 0.361 mL), *p*-TsCl (1.2 eq., 3.6 mmol, 0.572 g), Bu₄NHSO₄ (7 mol%, 0.21 mmol, 71

⁹⁶ Han, L.; Xing, P.; Jiang, B. *Org. Lett.* **2014**, *16*, 3428.

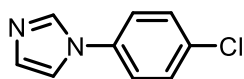
⁹⁷ Jacquemard, U.; Bénétteau, V.; Lefoix, M.; Routier, S.; Mérour, J.-Y.; Coudert, G. *Tetrahedron* **2004**, *60*, 10039.

⁹⁸ Henderson, L. C.; Lindon, M. J.; Willis, M. C. *Tetrahedron* **2010**, *66*, 6632.

⁹⁹ Wang, K.; Liu, Z. *Synth. Commun.* **2010**, *40*, 144.

mg) and a magnetic stir bar. The flask was purged with argon and toluene (10 mL) and KOH (50% aq, 2 mol%, 4.0 mL) were added. The reaction mixture was stirred at room temperature for 6 h, then washed with water (10 mL) and brine (5 mL). The organic layer was separated and dried over Na₂SO₄, then filtered through a plug of silica gel and concentrated. Purification by flash chromatography on silica gel (1/9 EtOAc/hexanes) yielded 4-chloro-1-tosyl-1H-indole as a white solid (751 mg, 82%). Characterization data were in accordance with literature.¹⁰⁰ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.89 (d, J = 0.8 Hz, 1 H), 7.77 (d, J = 8.4 Hz, 2 H), 7.61 (d, J = 3.7 Hz, 1 H), 7.20–7.27 (m, 4 H), 6.78 (dd, J = 3.7, 0.8 Hz, 1 H), 2.36 (s, 3 H).

1-(4-chlorophenyl)-1H-imidazole (Starting material of 51)



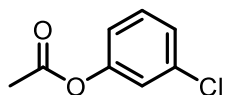
The procedure was adapted from the literature.¹⁰¹ A 50 mL round-bottomed flask was charged with CuI (5 mol%, 0.1 mmol, 19.1 mg), N-hydroxyphthalimide (10 mol%, 0.2 mmol, 32.6 mg), NaOCH₃ (1.5 eq., 3 mmol, 162 mg) and a magnetic stir bar. DMSO (3 mL) was added and the reaction mixture was stirred at room temperature for 30 min, followed by addition of a solution of imidazole (1 eq., 2 mmol, 136 mg) and 1-chloro-4-iodobenzene (1 eq., 2 mmol, 477 mg) in DMSO (2 mL). The reaction was stirred at 90 °C under argon for 12 h, then cooled to room temperature and H₂O (10 mL) was added. The resulting suspension was extracted with EtOAc (4 × 10 mL). The combined organic extracts were dried over MgSO₄, concentrated and purified by flash chromatography on silica gel (1/9–1/1 EtOAc/hexanes), affording 1-(4-chlorophenyl)-1H-imidazole as a white

¹⁰⁰ Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Org. Chem.* **2006**, *71*, 4255.

¹⁰¹ Ma, H.-C.; Jiang, X.-Z. *J. Org. Chem.* **2007**, *72*, 8943.

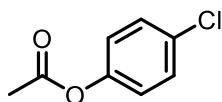
solid (132 mg, 37% yield). Characterization data were in accordance with literature.¹⁰² ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.84 (s, 1 H), 7.41–7.51 (m, 2 H), 7.30–7.39 (m, 2 H), 7.25–7.28 (m, 1 H), 7.22 (s, 1 H).

3-chlorophenylacetate (65)



The procedure was adapted from the literature.¹⁰³ A 50 mL round-bottomed flask was charged with DMAP (0.05 eq., 0.2 mmol, 24.4 mg) and a magnetic stir bar. The flask was purged with argon and 3-chlorophenol (1 eq., 4 mmol, 0.42 mL), acetyl chloride (1.1 eq., 4.4 mmol, 0.31 mL) and toluene (13.3 mL) were added. Triethylamine (1.1 eq., 4.4 mmol, 0.61 mL) was added dropwise and the reaction was stirred at 50 °C for 16 h. The reaction was quenched with a saturated NaHCO₃ (aq) (10 mL) then extracted with Et₂O (3 $\times$ 10 mL). The combined organic extracts were dried over MgSO₄, filtered through a short plug of silica gel and the solvent was removed under reduced pressure to afford 3-chlorophenylacetate as a light orange oil (421 mg, 62%). Characterization data were in accordance with literature.¹⁰⁴ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.31 (t, J = 8.2 Hz, 1H), 7.23 (ddd, J = 1.4, 2.4, 8.0 Hz, 1H), 7.14 (t, J = 2.0 Hz, 1H), 7.01 (ddd, J = 1.1, 2.2, 8.1 Hz, 1H), 2.31 (s, 3H).

4-chlorophenyl acetate (66)



The procedure was adapted from the literature.¹⁰⁵ A 50 mL round-bottomed flask was charged with DMAP (0.05 eq., 0.2 mmol, 24.4

¹⁰² Ma, H.-C.; Jiang, X.-Z. *J. Org. Chem.* **2007**, 72, 8943.

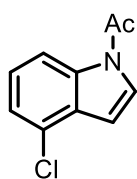
¹⁰³ Liu, Z.; Ma, Q.; Liu, Y.; Wang, Q. *Org. Lett.* **2014**, 16, 236.

¹⁰⁴ Seth, S.; Venugopalan, P.; Moorthy, J. N. *Chem. Eur. J.* **2015**, 21, 2241.

¹⁰⁵ Liu, Z.; Ma, Q.; Liu, Y.; Wang, Q. *Org. Lett.* **2014**, 16, 236.

mg), 4-chlorophenol (1 eq., 4 mmol, 514 mg) and a magnetic stir bar. The flask was purged with argon then acetyl chloride (1.1 eq., 4.4 mmol, 0.31 mL) and toluene (13.3 mL) were added. Triethylamine (1.1 eq., 4.4 mmol, 0.61 mL) was added dropwise and the reaction was stirred at 50 °C for 16 h then quenched with a saturated NaHCO₃ (aq) (10 mL) and extracted with Et₂O (3 × 10 mL). The combined organic extracts were dried over MgSO₄, filtered through a short plug of silica gel and the solvent was removed under reduced pressure to afford 4-chlorophenyl acetate as a pale yellow oil (506.4 mg, 74%). Characterization data were in accordance with literature.¹⁰⁶ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.35 (d, *J* = 9.0 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 2.29 (s, 3H).

1-(4-chloro-1H-indol-1-yl)ethan-1-one (76)



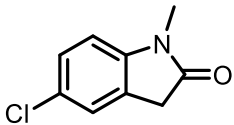
The procedure was adapted from the literature.¹⁰⁷ A 25 mL round bottom flask was charged with 4-chloro-1H-indole (1 eq., 3 mmol, 0.361 mL), Bu₄NHSO₄ (1.6 mol%, 0.048 mmol, 16.3 mg) and a magnetic stir bar. The flask was purged with argon and DCM (8 mL) and NaOH (2.6 eq., 7.8 mmol, 312 mg) were added. A solution of acetyl chloride (1.5 eq., 4.5 mmol, 0.32 mL) in DCM (3 mL) was added dropwise to the vigorously stirred slurry. The reaction mixture was stirred at room temperature for 1 h then was washed with water (10 mL) and brine (5 mL). The organic layer was separated, dried over Na₂SO₄, filtered through a plug of silica gel and concentrated. Purification by flash chromatography on silica gel (1/1–2/1 DCM/hexanes) yielded 1-(4-chloro-1H-indol-

¹⁰⁶ Vallin, K. S. A.; Wensbo Posaric, D.; Hameršak, Z.; Svensson, M. A.; Minidis, A. B. E. *J. Org. Chem.* **2009**, *74*, 9328.

¹⁰⁷ Benkovics, T.; Guzei, I. A.; Yoon, T. P. *Angew. Chem. Int. Ed.* **2010**, *49*, 9153.

1-yl)ethan-1-one as an off-white solid (373 mg, 64%). Characterization data were in accordance with literature.¹⁴ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.36 (t, J = 4.4 Hz, 1 H), 7.47 (d, J = 3.9 Hz, 1 H), 7.27–7.30 (m, 2 H), 6.78 (dd, J = 3.7, 0.6 Hz, 1 H), 2.66 (s, 3 H).

5-chloro-1-methylindolin-2-one (78)

 The procedure was adapted from the literature.¹⁰⁸ NaH (60% in mineral oil, 1 eq., 3 mmol, 120 mg) was suspended in toluene (12 mL) and heated at 100 °C under argon until a homogeneous solution was obtained. This solution was then added in small portions to a hot solution of 5-chloroindolin-2-one (1 eq., 3 mmol, 501 mg) in toluene (3 mL). The mixture was stirred at 100 °C for 1 h then Me₂SO₄ (1 eq., 3 mmol, 0.3 mL) was added and the reaction mixture was stirred for an additional 2 h at 100 °C. Water (10 mL) was added, followed by extraction with EtOAc (3 $\times$ 15 mL). The combined organic extracts were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography on silica gel (3/7 EtOAc/Et₂O) to afford 5-chloro-1-methylindolin-2-one as a light orange solid (236 mg, 44%). Characterization data were in accordance with literature.¹⁰⁹ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.17–7.26 (m, 2 H), 6.71 (d, J = 8.2 Hz, 1 H), 3.49 (s, 2 H), 3.17 (s, 3 H).

¹⁰⁸ Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047.

¹⁰⁹ Lian, Z.; Friis, S. D.; Skrydstrup, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 9582.

2.6.4 Slow addition experiments

General Procedure A (Slow addition):

Pd(OAc)₂ (6 μmol, 3 mol%), SPhos (8 μmol, 4 mol%) and the aryl chloride (0.2 mmol, 1 eq.) were added to an 8 mL screw-capped reaction vial equipped with a magnetic stir bar and Teflon septum. The vial was purged by an argon balloon and toluene (1 mL) was added. Another 4 mL screw-capped glass vial equipped with a Teflon septum was purged by an argon balloon, then a slight excess of Grignard reagent (~0.3 mmol) was added and diluted in toluene to a final concentration of 0.32 M. The diluted Grignard solution was collected via a 20 × 8" Micromate Hub septum penetration needle into a 1 mL HSW NORM-JECT plastic syringe, and loaded onto a syringe pump. The Teflon septum of the 8 mL reaction vial was pierced with the needle and the tip of the needle was placed ~1 cm above the reaction solution. The reaction vial was stirred at 650 rpm and heated to the specified temperature if required. The syringe pump was then set to add the diluted Grignard solution over the specified amount of time. After exactly 0.24 mmol (1.2 eq) of the diluted Grignard was added, the pump was stopped and the reaction was stirred for an additional 5 min. After quenching with aqueous NH₄Cl, the reaction mixture was extracted with EtOAc, and the combined organic layers were filtered through a short plug of silica gel and concentrated under reduced pressure. The crude product was purified by flash chromatography.

General Procedure B (Fast addition):

Pd(OAc)₂ (6 μmol, 3 mol%), SPhos (8 μmol, 4 mol%) and the aryl chloride (0.2 mmol, 1 eq.) were added to an 8 mL screw-capped reaction vial equipped with a magnetic stir bar and Teflon septum. The vial was purged by an argon balloon and

toluene (1.5 mL) was added. The reaction vial was stirred at 650 rpm and heated to the specified temperature if required. Grignard reagent was added (0.24 mmol, 1.2 eq., 1 M in THF) in a dropwise fashion over 15–20 s using a 1 mL HSW NORM-JECT plastic syringe. The reaction was stirred for the same amount of time as the corresponding slow addition experiment and then quenched with aqueous NH_4Cl . An internal standard (1,3,5-trimethoxybenzene, 0.05M in THF, 0.05 mmol) was added and the organic phase was extracted with EtOAc and filtered through a short plug of silica gel. The organic phase was concentrated under reduced pressure. The yield was determined from the crude ^1H NMR unless otherwise specified.

General Procedure C (Synthesis of Grignard reagents):

A 2-necked 50 mL round-bottomed flask containing a magnetic stir bar was equipped with a reflux condenser and rubber septum. The top of the condenser was fitted with a septum and connected to an argon balloon. Magnesium turnings (1.2 eq., 6 mmol) were added and the apparatus was purged with argon for 10 min. The flask was then charged with THF (3 mL). Aryl bromide (1 eq., 5 mmol) diluted in THF (2 mL) was injected into the mixture with a syringe pump at a rate so as to maintain a gentle reflux. After the addition, the mixture was heated under reflux with an oil bath (oil bath temperature, 60 °C) for another 2 h. After completion, the flask was cooled and the Grignard reagent titrated.¹¹⁰

¹¹⁰ Krasovski, A; Knochel, P. *Synthesis* **2006**, 890.

2.6.5 ESI-MS experiments

Experimental details of real-time ESI-MS monitoring

The experimental setup shown in Figure 24 was used to dilute the reaction solutions by a factor of ~870 into the mobile phase before feeding into the mass spec. A two stage dilution with first 50 $\mu\text{L}/\text{min}$ THF (Grignard experiments) or toluene (PhLi experiments) and then 200 $\mu\text{L}/\text{min}$ mass spec mobile phase (0.1% acetic acid in 95:5 MeOH:H₂O) was necessary to prevent precipitation and clogging in the Rheodyne MRA100-000 sampling valve. Slow addition experiments were scaled to an initial volume of 10 mL (before addition of the Grignard or PhLi solution) and fast addition experiments to an initial volume of 3 mL to ensure that the amount of solution removed over the course of the monitoring did not exceed ~30%.

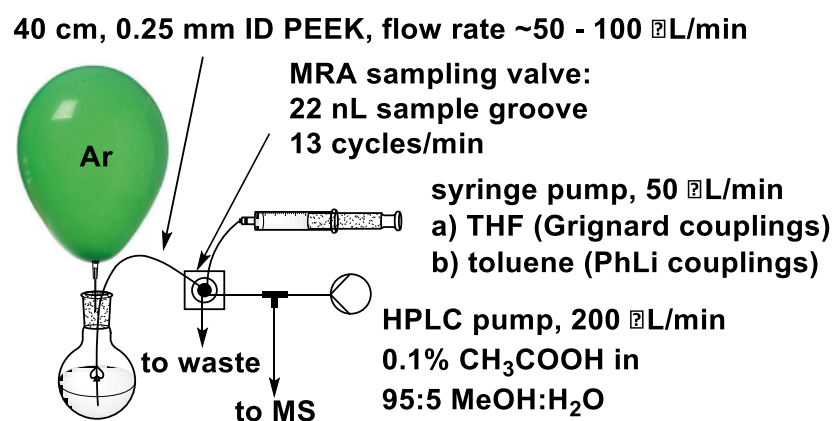


Figure 24. Experimental setup for real-time mass spectroscopic monitoring of cross-coupling reactions

Experimental conditions for real-time ESI monitoring of Kumada-Corriu coupling reactions

Fast Grignard addition: General procedure B was followed with modification of the Grignard addition rate from addition over 20 seconds to addition over 5 minutes, on 3 mL scale with continuous withdrawal for MS monitoring using the setup shown in Figure 24. To calculate yield for the fast addition experiment general procedure B was followed with the same modification of the addition rate to addition over 5 minutes.

Slow Grignard addition: General procedure A was followed on 10 mL scale with continuous withdrawal for MS monitoring as above.

Experimental conditions for real-time ESI monitoring of PhLi coupling reactions

Fast PhLi addition: The general conditions reported by Feringa and coworkers¹¹¹ for their ‘catalyst system B’ were used with PhLi added over 5 minutes instead of 45 minutes on 3 mL scale with continuous withdrawal for MS monitoring using the setup shown in Figure 24. Briefly, Pd₂(dba)₃ (10.3 mg, 0.011 mmol, 2.5 mol%) and XPhos (21.5 mg, 0.045 mmol, 10 mol%) were dissolved in toluene (3 mL). 1-Chloronaphthalene (73.2 mg, 0.45 mmol) was added, the solution was stirred at room temperature and PhLi diluted to 0.6 M in THF (1.0 mL, 0.6 mmol, 1.35 eq.) was added over 5 minutes with continuous withdrawal for MS monitoring.

¹¹¹ Hornillos, V.; Giannerini, M.; Vila, C.; Fañanás-Mastral, M.; Feringa, B. L. *Org. Lett.* **2013**, *15*, 5114.

To calculate the yield for fast addition the experiment was duplicated without MS monitoring and stirred for an additional 40 minutes after the addition was complete to give a total reaction time of 45 minutes. The reaction was quenched with $\text{NH}_4\text{Cl}_{(\text{aq})}$, hexadecane was added as an internal standard and the mixture was extracted with EtOAc, diluted to an appropriate concentration and quantified by GC-FID with a 5-point calibration curve. A 9% yield of the biaryl product was observed.

Slow PhLi addition: The general conditions reported by Feringa and coworkers for their ‘catalyst system B’ were used on 10 mL scale with PhLi addition over 45 minutes and continuous withdrawal for MS monitoring as above.

Isotope patterns of observed species

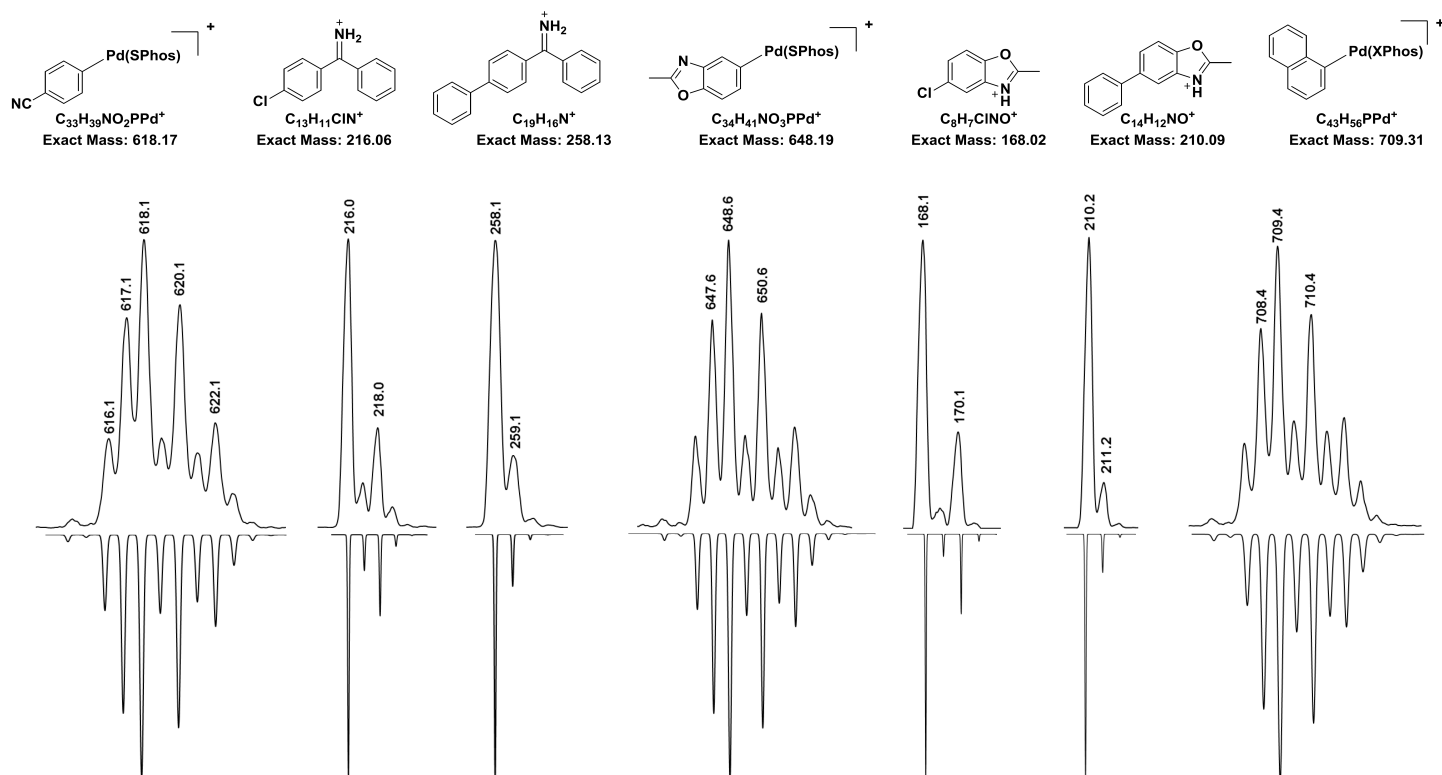
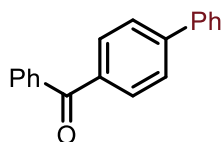


Figure 25. Observed and calculated isotope patterns for the species monitored by ESI-MS.

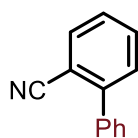
2.6.6 Characterization of Kumada-Corriu cross-coupling products

4-benzoylbiphenyl (26)



Prepared according to general procedure A. PhMgBr solution was added over 2 h at room temperature. Purification by flash chromatography on silica gel (1/15 EtOAc/hexanes) afforded 4-benzoylbiphenyl as a white solid (33.6 mg, 65%). Characterization data were in accordance with literature.¹¹² ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.92 (d, J = 8.4 Hz, 2H), 7.86 (m, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 7.3 Hz, 2H), 7.62 (t, J = 7.3 Hz, 1H), 7.53 (d, J = 7.8 Hz, 2H), 7.49 (d, J = 7.8 Hz, 2H), 7.42 (t, J = 7.3 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 196.3, 145.2, 140.0, 137.8, 136.2, 132.4, 130.7, 130.0, 129.0, 128.3, 128.2, 127.3, 127.0.

2-cyanobiphenyl (28)

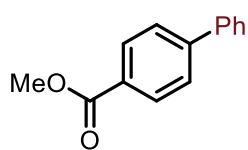


Prepared according to general procedure A. PhMgBr solution was added over 1 h at 50 °C. Purification by flash chromatography on silica gel (1/20–1/5 EtOAc/hexanes) afforded 2-cyanobiphenyl as a light yellow solid (30.1 mg, 84%). Characterization data were in accordance with literature.¹¹³ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.78 (dd, J = 7.7, 1.3 Hz, 1 H), 7.63–7.70 (m, 1 H), 7.40–7.62 ppm (m, 7 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 145.5, 138.1, 133.7, 132.8, 130.0, 128.7, 128.6, 127.5, 118.7, 111.3.

¹¹² Hu, F.; Kumpati, B. N.; Lei, X. *Tetrahedron Lett.* **2014**, 55, 7215.

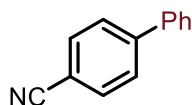
¹¹³ Shu, Z.; Ye, Y.; Deng, Y.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2013**, 52, 10573.

methyl 4-phenylbenzoate (31)



Prepared according to general procedure A. PhMgBr solution was added over 1 h at room temperature. Purification by flash chromatography on silica gel (1/9 EtOAc/hexanes) afforded methyl 4-phenylbenzoate as a white solid (40.5 mg, 96%). Characterization data were in accordance with literature.¹¹⁴ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.12 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.64 (m, 2H), 7.48 (t, *J* = 7.1 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 1H), 3.95 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 167.0, 145.6, 140.0, 130.1, 128.9, 128.1, 127.2, 127.0, 52.1.

4-cyanobiphenyl (32)

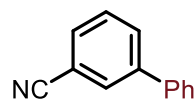


Prepared according to general procedure A. PhMgBr solution was added over 1.5 h at room temperature. Purification by flash chromatography on silica gel (1/20–1/5 EtOAc/hexanes) afforded 4-cyanobiphenyl as a white solid (32.8 mg, 92%). Characterization data were in accordance with literature.¹¹⁵ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.74 (d, *J* = 8.6 Hz, 2 H), 7.69 (d, *J* = 8.6 Hz, 2 H), 7.61 (d, *J* = 8.4 Hz, 2 H), 7.50 (t, *J* = 7.5 Hz, 2 H), 7.44 (t, *J* = 7.3 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 145.6, 139.2, 132.6, 129.1, 128.6, 127.7, 127.2, 118.9, 110.9.

¹¹⁴ Martinez-Solorio, D.; Melillo, B.; Sanchez, L.; Liang, Y.; Lam, E.; Houk, K. N.; Smith, A. B. *J. Am. Chem. Soc.* **2016**, *138*, 1836.

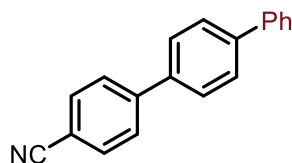
¹¹⁵ Scheuermann, G. M.; Rumi, L.; Steurer, P.; Bannwarth, W.; Mülhaupt, R. *J. Am. Chem. Soc.* **2009**, *131*, 8262.

3-cyanobiphenyl (33)



Prepared according to general procedure A. PhMgBr solution was added over 1 h at 50 °C. Purification by flash chromatography on silica gel (1/20–1/5 EtOAc/hexanes) afforded 3-cyanobiphenyl as light yellow oil (31.7 mg, 89%). Characterization data were in accordance with literature.¹¹⁶ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.86–7.90 (m, 1 H), 7.83 (d, *J* = 7.8 Hz, 1 H), 7.64 (d, *J* = 7.8 Hz, 1 H), 7.53–7.60 (m, 3 H), 7.46–7.53 (m, 2 H), 7.40–7.45 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 142.4, 138.8, 131.4, 130.6, 129.6, 129.1, 128.9, 128.3, 127.0, and 118.8, 112.9.

[1,1':4',1''-terphenyl]-4-carbonitrile (34)

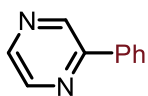


Prepared according to general procedure A. PhMgBr solution was added over 1 h at 50 °C. Purification by flash chromatography on silica gel (1/19 EtOAc/hexanes) afforded [1,1':4',1''-terphenyl]-4-carbonitrile as a white solid (46.3 mg, 91%). Characterization data were in accordance with literature.¹¹⁷ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.74–7.63 (m, 10 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.43–7.36 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 145.2, 141.6, 140.2, 137.9, 132.6, 128.9, 127.8, 127.7, 127.6, 127.5, 127.1, 118.9, 110.9.

¹¹⁶ Tang, R.-J.; He, Q.; Yang, L. *Chem. Commun.* **2015**, 51, 5925.

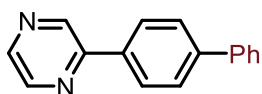
¹¹⁷ Qiu, D.; Meng, H.; Jin, L.; Wang, S.; Tang, S.; Wang, X.; Mo, F.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2013**, 52, 11581.

2-phenylpyrazine (35)



Prepared according to general procedure A. PhMgBr solution was added over 2 h at room temperature. Purification by flash chromatography on silica gel (2/8 EtOAc/hexanes) afforded 2-phenylpyrazine as a yellow solid (24.2 mg, 78%). Characterization data were in accordance with literature.¹¹⁸ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.05 (d, J = 1.6 Hz, 1H), 8.65 (dd, J = 2.5, 1.6 Hz, 1H), 8.52 (d, J = 2.5 Hz, 1H), 8.03 (dd, J = 8.2, 1.6 Hz, 2H), 7.47–7.55 (m, 3H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 152.84, 144.16, 142.87, 142.20, 136.32, 129.90, 129.04, 126.92.

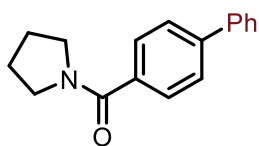
2-([1,1'-biphenyl]-4-yl)pyrazine (36)



Prepared according to general procedure A. PhMgBr solution was added over 1 h at 50 °C. Purification by flash chromatography on silica gel (3/7 EtOAc/hexanes) afforded 2-([1,1'-biphenyl]-4-yl)pyrazine as a light yellow solid with ~8% recovered, inseparable starting material (40.0 mg, 81% corrected yield). Characterization data were in accordance with literature.¹¹⁸ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.10 (s, 1H), 8.67 (s, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.13 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 7.1 Hz, 2H), 7.49 (t, J = 7.5 Hz, 2H), 7.40 (t, J = 7.3 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 152.5, 144.2, 142.9, 142.7, 142.1, 140.2, 135.2, 128.9, 127.8, 127.8, 127.3, 127.1.

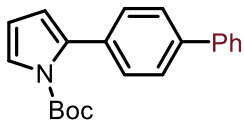
¹¹⁸ Singh, P. P.; Aithagani, S. K.; Yadav, M.; Singh, V. P.; Vishwakarma, R. A. *J. Org. Chem.* **2013**, 78, 2639.

(4-phenylbenzoyl)pyrrolidine (37)



Prepared according to general procedure A. PhMgBr solution was added over 45 min at 50 °C. Purification by flash chromatography on silica gel (1/4–4/1 EtOAc/hexanes) afforded (4-phenylbenzoyl)pyrrolidine as a yellow solid (46.8 mg, 93%). ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.60–7.64 (m, 6H), 7.46 (t, *J* = 4.7 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 3.68 (t, *J* = 7.0 Hz, 2H), 3.50 (t, *J* = 6.6 Hz, 2H), 1.87–2.02 (m, 4H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.4, 142.6, 140.3, 136.0, 128.8, 127.7, 127.7, 127.1, 126.9, 49.6, 46.2, 26.4, 24.4. IR: ν (cm⁻¹) 2958.10, 2870.77, 1618.11, 1424.76, 1113.29, 1006.94, 908.20, 843.89, 748.44, 701.15, 641.80, 602.57. Accurate mass (EI): *m/z* calculated for C₁₇H₁₇NO: 251.1305, found 251.1244 (spectral accuracy = 97.7%). m.p.: 150.4–151.4 °C.

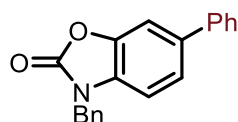
tert-butyl 2-([1,1'-biphenyl]-4-yl)-1H-pyrrole-1-carboxylate (38)



Prepared according to general procedure A with modification to Pd(OAc)₂ (12 μmol, 6 mol%) and SPhos (16 μmol, 8 mol%). PhMgBr solution was added over 2 h at 50 °C. Purification by flash chromatography on silica gel (1/25 EtOAc/hexanes) afforded *tert*-butyl 2-([1,1'-biphenyl]-4-yl)-1H-pyrrole-1-carboxylate as a white solid (59.4 mg, 93%). ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.58–7.68 (m, 4 H), 7.42–7.51 (m, 4 H), 7.34–7.41 (m, 2 H), 6.26 (s, 2 H), 1.41 (s, 9 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 149.4, 140.9, 139.9, 134.7, 133.4, 129.5, 128.8, 127.2, 127.0, 126.3, 122.7, 114.5, 110.6, 83.7, 27.6. IR: ν (cm⁻¹) 2977.03, 2932.29, 1746.20, 1470.16, 1392.31, 1369.20, 1302.44, 1254.67, 1141.74, 1076.01, 971.18, 846.51, 818.79, 754.34, 697.96. Accurate mass

(ESI, Na⁺): m/z calculated for C₂₁H₂₁NO₂Na⁺: 342.1470, found 342.1471. m.p.: 103.3–103.8 °C.

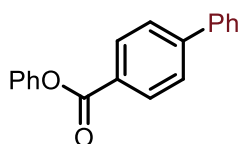
3-benzyl-6-phenylbenzo[d]oxazol-2(3H)-one (39)



Prepared according to general procedure A with modification to Pd(OAc)₂ (12 μmol, 6 mol%) and SPhos (16 μmol, 8 mol%).

PhMgBr solution was added over 2 h at 50 °C. Purification by flash chromatography on silica gel (1/9 EtOAc/hexanes) afforded 3-benzyl-6-phenylbenzo[d]oxazol-2(3H)-one as a light yellow solid (30.8 mg, 51%). ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.22–7.48 (m, 12 H), 7.03 (d, *J* = 1.6 Hz, 1 H), 5.05 (s, 2 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 154.9, 142.1, 140.5, 137.8, 134.6, 131.3, 129.0, 128.8, 128.3, 127.6, 127.4, 127.1, 121.7, 110.1, 107.6, 46.1. IR: ν (cm⁻¹) 3031.43, 1760.29, 1620.53, 1479.19, 1445.26, 1380.15, 1345.20, 1251.73, 1235.37, 1079.07, 1023.40, 930.10, 862.24, 759.57, 695.43, 624.18. Accurate mass (EI): m/z calculated for C₂₀H₁₅NO₂: 301.1097, found 301.1123 (spectral accuracy = 99.5%). m.p.: 104.2–105.6 °C.

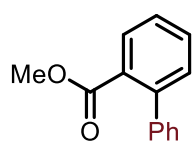
phenyl [1,1'-biphenyl]-4-carboxylate (40)



Prepared according to general procedure A. PhMgBr solution was added over 4 h at room temperature. Purification by flash chromatography on silica gel (1/15 EtOAc/hexanes) afforded

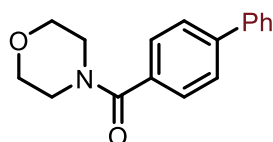
phenyl [1,1'-biphenyl]-4-carboxylate as white solid (43.0 mg, 79%). Characterization data were in accordance with literature.¹¹⁹ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.27 (d, *J* = 8.6 Hz, 2 H), 7.73 (d, *J* = 8.6 Hz, 2 H), 7.65 (d, *J* = 7.1 Hz, 2 H), 7.38–7.52 (m, 5 H), 7.21–7.31 (m, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 165.1, 151.0, 146.3, 139.9, 130.7, 129.5, 129.0, 128.3, 128.3, 127.3, 127.2, 125.9, 121.7.

methyl 2-phenylbenzoate (41)



Prepared according to general procedure A. PhMgBr solution was added over 1 h at room temperature. Purification by flash chromatography on silica gel (1/9 EtOAc/hexanes) afforded methyl 2-phenylbenzoate as a yellow oil (40.2 mg, 95%). Characterization data were in accordance with literature.¹²⁰ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.84 (d, *J* = 7.8 Hz, 1 H), 7.53 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.29–7.48 (m, 7 H), 3.65 (s, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.1, 142.4, 141.3, 131.2, 130.8, 130.6, 129.7, 128.3, 128.0, 127.2, 127.1, 51.8.

[1,1'-biphenyl]-4-yl(morpholino)methanone (42)



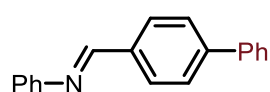
Prepared according to general procedure A. PhMgBr solution was added over 1 h at 50 °C. Purification by flash chromatography on silica gel (1/9–1/0 EtOAc/hexanes) afforded [1,1'-biphenyl]-4-yl(morpholino)methanone as a light yellow solid (50.4 mg, 94%). ¹H NMR data were in accordance with literature (no ¹³C literature data

¹¹⁹ Ramanjaneyulu, B. T.; Pareek, M.; Reddy, V.; Vijaya Anand, R. *Helv. Chim. Acta* **2014**, *97*, 431.

¹²⁰ Hu, F.; Kumpati, B. N.; Lei, X. *Tetrahedron Lett.* **2014**, *55*, 7215.

available).¹²¹ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.62–7.67 (m, 2 H), 7.57–7.62 (m, 2 H), 7.44–7.53 (m, 4 H), 7.36–7.43 (m, 1 H), 3.29–4.16 (m, 8 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 170.2, 142.8, 140.1, 134.0, 128.9, 127.8, 127.7, 127.2, 127.1, 66.9. Accurate mass (EI): m/z calculated for C₁₇H₁₇NO₂: 267.1254, found 267.1268 (spectral accuracy = 98.0%).

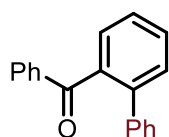
1-([1,1'-biphenyl]-4-yl)-N-phenylmethanimine (43)



Prepared according to general procedure A. PhMgBr solution was added over 1 h at 50 °C. Purification by flash chromatography on alumina (1/10/200 NEt₃/EtOAc/hexanes) afforded 1-([1,1'-biphenyl]-4-yl)-N-phenylmethanimine as a yellow solid (39.1 mg, 76%). ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.52 (s, 1 H), 8.00 (d, *J* = 8.2 Hz, 2 H), 7.63–7.79 (m, 4 H), 7.37–7.54 (m, 5 H), 7.21–7.31 (m, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 159.9, 152.1, 144.1, 140.3, 135.2, 129.3, 129.1, 128.9, 127.9, 127.4, 127.2, 125.9, 120.9. IR: ν (cm⁻¹) 3059.14, 3029.62, 2919.32, 2851.02, 1698.97, 1623.53, 1603.08, 1578.66, 1558.01, 1484.83, 1449.72, 1407.72, 1362.70, 1311.91, 1165.05, 1112.39, 1075.22, 1004.83, 907.95, 878.37, 837.79, 762.90, 687.47, 558.79. Accurate mass (EI): m/z calculated for C₁₉H₁₅N: 257.1199, found 257.1267 (spectral accuracy = 99.3%). m.p.: 147.4–148.8 °C.

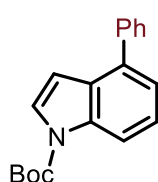
¹²¹ Baburajan, P.; Elango, K. P. *Tetrahedron Lett.* **2014**, 55, 1006.

2-benzoylbiphenyl (44)



Prepared according to general procedure A. PhMgBr solution was added over 2 h at room temperature. Purification by flash chromatography on silica gel (1/20–1/5 DCM/hexanes) afforded 2-benzoylbiphenyl as an off-white solid (41.2 mg, 82%). Characterization data were in accordance with literature.¹²² ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.65 (d, *J* = 7.1 Hz, 2 H), 7.56–7.62 (m, 1 H), 7.38–7.55 (m, 4 H), 7.25–7.31 (m, 4 H), 7.13–7.23 (m, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 198.8, 141.1, 140.2, 139.0, 137.4, 132.8, 130.3, 130.0, 129.9, 129.0, 128.8, 128.2, 128.0, 127.3, 127.0.

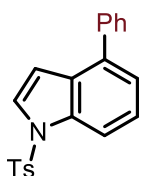
tert-butyl 4-phenyl-1H-indole-1-carboxylate (45)



Prepared according to general procedure A. PhMgBr solution was added over 1 h at 50 °C. Purification by flash chromatography on silica gel (1/5 DCM/hexanes) afforded *tert*-butyl 4-phenyl-1H-indole-1-carboxylate as a colourless oil (74.4 mg, 85%). ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.21 (d, *J* = 8.0 Hz, 1 H), 7.59–7.69 (m, 3 H), 7.51 (t, *J* = 7.5 Hz, 2 H), 7.40 (d, *J* = 8.2 Hz, 2 H), 7.32 (dd, *J* = 7.4, 1.0 Hz, 1 H), 6.75 (d, *J* = 4.5 Hz, 1 H), 1.71 (s, 9 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 149.7, 140.4, 135.6, 134.8, 128.9, 128.7, 128.5, 127.2, 126.1, 124.5, 122.7, 114.2, 106.5, 83.7, 28.2. IR: ν (cm⁻¹) 2977.16, 1728.95, 1533.18, 1474.14, 1414.12, 1368.86, 1345.56, 1323.45, 1283.27, 1156.09, 1132.29, 1019.13, 898.53, 849.33, 752.73, 698.98, 684.51.

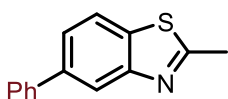
¹²² Liu, Z.; Tan, H.; Wang, L.; Fu, T.; Xia, Y.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 3056.

4-phenyl-1-tosyl-1H-indole (46)



Prepared according to general procedure A. PhMgBr solution was added over 1 h at 50 °C. Purification by flash chromatography on silica gel (1/9 EtOAc/hexanes) afforded 4-phenyl-1-tosyl-1H-indole as a light yellow solid (66.6 mg, 96%). ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.00 (d, *J* = 8.4 Hz, 1 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 7.61 (d, *J* = 3.7 Hz, 1 H), 7.49–7.56 (m, 2 H), 7.45 (t, *J* = 7.4 Hz, 2 H), 7.31–7.41 (m, 2 H), 7.18–7.31 (m, 3 H), 6.81 (dd, *J* = 3.8, 0.7 Hz, 1 H), 2.33 (s, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 145.0, 139.8, 135.3, 135.3, 135.1, 129.9, 128.9, 128.7, 128.6, 127.4, 126.8, 126.4, 124.8, 123.2, 112.4, 108.2, 21.5. IR: ν (cm⁻¹) 1595.36, 1526.62, 1472.76, 1445.57, 1371.36, 1210.06, 1190.99, 1164.91, 1131.94, 1090.66, 1002.47, 896.69, 814.95, 755.15, 729.92, 698.90, 670.94, 645.48, 592.52. Accurate mass (EI): *m/z* calculated for C₂₁H₁₇NO₂S: 347.0975, found 347.1044 (spectral accuracy = 99.5%). m.p.: 112.6–113.0 °C.

2-methyl-5-phenylbenzo[d]thiazole (47)

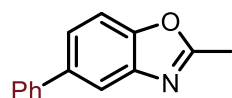


Prepared according to general procedure A with modification to Pd(OAc)₂ (12 μmol, 6 mol%) and SPhos (16 μmol, 8 mol%). PhMgBr solution was added over 2 h at 50 °C. Purification by flash chromatography on silica gel (1/18–1/5 EtOAc/hexanes) afforded 2-methyl-5-phenylbenzo[d]thiazole as an off-white solid (35.2 mg, 78%). Characterization data were in accordance with literature.¹²³ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.19 (d, *J* = 1.8 Hz, 1 H), 7.88 (d, *J* = 8.2 Hz, 1 H), 7.68 (d, *J* = 7.1 Hz, 2 H), 7.61 (dd, *J* = 8.2, 1.8 Hz, 1 H), 7.49 (t, *J*

¹²³ Sahoo, A. K.; Oda, T.; Nakao, Y.; Hiyama, T. *Adv. Synth. Catal.* **2004**, *346*, 1715.

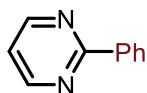
= 7.6 Hz, 2 H), 7.34–7.43 (m, 1 H), 2.87 (s, 3 H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 167.6, 154.1, 140.8, 139.5, 134.6, 128.9, 127.4, 127.3, 124.2, 121.5, 120.7, 20.2.

2-methyl-5-phenylbenzo[d]oxazole (48)



Prepared according to general procedure A. PhMgBr solution was added over 1 h at 50 °C. Purification by flash chromatography on silica gel (1/20–1/1 EtOAc/hexanes) afforded 2-methyl-5-phenylbenzo[d]oxazole as an off-white solid (33.0 mg, 79%). Characterization data were in accordance with literature.¹²⁴ ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.86 (t, J = 1.1 Hz, 1 H), 7.62 (dd, J = 8.2, 1.2 Hz, 2 H), 7.53 (d, J = 1.2 Hz, 2 H), 7.47 (t, J = 7.6 Hz, 2 H), 7.34–7.41 (m, 1 H), 2.68 (s, 3 H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 164.5, 150.5, 142.0, 141.1, 138.1, 128.8, 127.4, 127.2, 124.1, 117.9, 110.2, 14.6.

2-phenylpyrimidine (49)



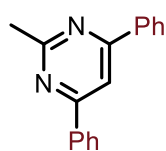
Prepared according to general procedure A. PhMgBr solution was added over 1 h at room temperature. Purification by flash chromatography on silica gel (1/18–1/1 EtOAc/hexanes) afforded 2-phenylpyrimidine as a yellow solid (24.3 mg, 78%). Characterization data were in accordance with literature.¹²⁵ ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.82 (d, J = 4.9 Hz, 2 H), 8.46 (m, 2 H), 7.44–7.58 (m, 3

¹²⁴ Sahoo, A. K.; Oda, T.; Nakao, Y.; Hiyama, T. *Adv. Synth. Catal.* **2004**, 346, 1715.

¹²⁵ Bhadra, S.; Matheis, C.; Katayev, D.; Gooßen, L. J. *Angew. Chem. Int. Ed.* **2013**, 52, 9279.

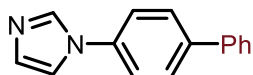
H), 7.10–7.16 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 164.7, 157.2, 137.6, 130.7, 128.6, 128.2, 128.1, 119.0.

2-methyl-4,6-diphenylpyrimidine (50)



Prepared according to general procedure A. PhMgBr solution (2.4 eq.) was added over 1 h at 50 °C. Purification by flash chromatography on silica gel (1/15–1/5 EtOAc/hexanes) afforded 2-methyl-4,6-diphenylpyrimidine as a white solid (40.9 mg, 84%). Characterization data were in accordance with literature.¹²⁶ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.02–8.22 (m, 4 H), 7.91 (s, 1 H), 7.42–7.62 (m, 6 H), 2.89 (s, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 168.5, 164.9, 137.4, 130.7, 128.9, 127.3, 110.1, 26.4.

1-([1,1'-biphenyl]-4-yl)-1H-imidazole (51)

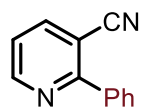


Prepared according to general procedure A. PhMgBr solution was added over 1 h at 50 °C. Purification by flash chromatography on silica gel (1/19 MeOH/DCM) afforded 1-([1,1'-biphenyl]-4-yl)-1H-imidazole as a light yellow solid (35.3 mg, 80%). Characterization data were in accordance with literature.¹²⁷ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.02 (s, 1 H), 7.68–7.75 (m, 2 H), 7.5–7.64 (m, 2 H), 7.44–7.52 (m, 4 H), 7.37–7.44 (m, 1 H), 7.33–7.37 (m, 1 H), 7.25–7.29 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 140.6, 139.7, 136.4, 135.5, 130.3, 129.0, 128.5, 127.8, 127.0, 121.8, 118.2.

¹²⁶ Achelle, S.; Robin-le Guen, F. *Tetrahedron Lett.* **2013**, 54, 4491.

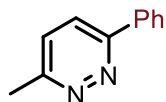
¹²⁷ Yang, H.; Xi, C.; Miao, Z.; Chen, R. *Eur. J. Org. Chem.* **2011**, 2011, 3353.

2-phenylnicotinonitrile (52)



Prepared according to general procedure A with modification to Pd(OAc)₂ (12 μmol, 6 mol%) and SPhos (16 μmol, 8 mol%). PhMgBr solution was added over 1 h at 50 °C. Purification by flash chromatography (1/20–1/1 EtOAc/hexanes) afforded 2-phenylnicotinonitrile as a light yellow solid (29.6 mg, 82%). Characterization data were in accordance with literature.¹²⁸ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.89 (dd, *J* = 4.9, 1.8 Hz, 1 H), 8.09 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.88–7.99 (m, 2 H), 7.48–7.62 (m, 3 H), 7.39 (dd, *J* = 7.8, 4.7 Hz, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 161.0, 152.6, 141.8, 137.1, 130.3, 128.9, 128.7, 121.5, 117.6, 107.5.

3-methyl-6-phenylpyridazine (53)

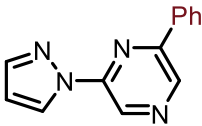


Prepared according to general procedure A with modification to Pd(OAc)₂ (12 μmol, 6 mol%) and SPhos (16 μmol, 8 mol%). PhMgBr solution was added over 2 h at 50 °C. Purification by flash chromatography on silica gel (1/4 EtOAc/hexanes–EtOAc) afforded 3-methyl-6-phenylpyridazine as a yellow solid (25.3 mg, 74%). Characterization data were in accordance with literature.¹²⁹ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.02–8.10 (m, 2 H), 7.76 (d, *J* = 8.8 Hz, 1 H), 7.40–7.56 (m, 3 H), 7.39 (d, *J* = 8.6 Hz, 1 H), 2.76 (s, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 158.5, 157.2, 136.4, 129.7, 128.9, 127.2, 126.8, 123.9, 22.0.

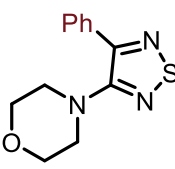
¹²⁸ Saha, D.; Ghosh, R.; Sarkar, A. *Tetrahedron* **2013**, *69*, 3951.

¹²⁹ Chang, M.-Y.; Lu, Y.-J.; Cheng, Y.-C. *Tetrahedron* **2015**, *71*, 6840.

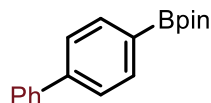
2-phenyl-6-(1H-pyrazol-1-yl)pyrazine (54)

 Prepared according to general procedure A. PhMgBr solution was added over 1 h at 50 °C. Purification by flash chromatography on silica gel (1/25–1/1 EtOAc/hexanes) afforded 2-phenyl-6-(1H-pyrazol-1-yl)pyrazine as a white solid (28.2 mg, 63%). ¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.27 (s, 1 H), 8.95 (s, 1 H), 8.68 (dd, *J* = 2.6, 0.7 Hz, 1 H), 8.04–8.14 (m, 2 H), 7.83 (dd, *J* = 1.6, 0.6 Hz, 1 H), 7.48–7.62 (m, 3 H), 6.55 (dd, *J* = 2.6, 1.7 Hz, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 150.0, 146.8, 143.0, 138.5, 135.4, 133.2, 130.3, 129.1, 129.0, 127.4, 127.0, 127.0, 108.5. IR: ν (cm⁻¹) 3118.32, 1535.40, 1452.66, 1424.86, 1398.51, 1191.41, 1036.09, 938.04, 769.09, 685.98, 600.53. Accurate mass (EI): *m/z* calculated for C₁₃H₁₀N₄: 222.0900, found 222.1024 (spectral accuracy = 99.1%). m.p.: 98.6–99.9 °C.

4-(4-phenyl-1,2,5-thiadiazol-3-yl)morpholine (55)

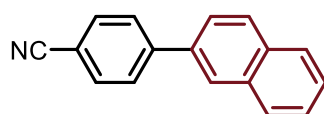
 Prepared according to general procedure A. PhMgBr solution was added over 1 h at 50 °C. Purification by flash chromatography on silica gel (1/9 EtOAc/hexanes) afforded 4-(4-phenyl-1,2,5-thiadiazol-3-yl)morpholine as an orange solid (33.3 mg, 67%). ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.31–7.47 (m, 4 H), 7.13–7.25 (m, 1 H), 3.73–3.84 (m, 4 H), 3.53–3.66 (m, 4 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 138.1, 133.3, 128.9, 126.1, 124.3, 107.6, 66.0, 46.4. IR: ν (cm⁻¹) 2965.00, 2923.55, 2860.92, 2225.39, 1577.31, 1566.15, 1440.20, 1247.23, 1044.26, 1022.03, 968.13, 853.36, 788.44, 734.93, 687.48, 659.86, 635.53, 599.21, 553.57. Accurate mass (EI): *m/z* calculated for C₁₂H₁₃N₃OS: 247.0774, found 247.0847 (spectral accuracy = 99.8%). m.p.: 71.5–72.2 °C.

2-(biphenyl-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (56)



Prepared according to general procedure A. PhMgBr solution was added over 2 h at 50 °C. Purification by flash chromatography on silica gel (hexanes) afforded 2-(biphenyl-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as a colorless oil (33.4 mg, 60%). Characterization data were in accordance with literature.¹³⁰ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.91 (d, *J* = 8.2 Hz, 2 H), 7.61–7.70 (m, *J* = 8.2 Hz, 4 H), 7.42–7.50 (m, *J* = 8.6 Hz, 2 H), 7.34–7.40 (m, *J* = 7.4 Hz, 1 H), 1.38 (s, 12 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 143.9, 141.0, 135.2, 128.8, 127.5, 127.2, 126.4, 83.8, 24.9.

4-(naphthalen-2-yl)benzonitrile (57)

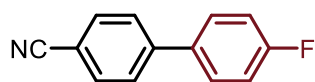


Prepared according to general procedure A with Grignard (0.69 M in THF) prepared by general procedure C. Grignard solution was added over 90 min at room temperature. Purification by flash chromatography on silica gel (1/9 EtOAc/hexanes) afforded 4-(naphthalen-2-yl)benzonitrile as a white solid (38.9 mg, 85%). Characterization data were in accordance with literature.¹³¹ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.07 (s, 1 H), 7.88–7.99 (m, 3 H), 7.81–7.86 (m, 2 H), 7.75–7.81 (m, 2 H), 7.73 (dd, *J* = 8.5, 1.9 Hz, 1 H), 7.50–7.60 (m, 2 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 145.5, 136.4, 133.5, 133.1, 132.6, 128.9, 128.3, 127.9, 127.7, 126.8, 126.7, 126.5, 124.8, 118.9, 110.9.

¹³⁰ Kim, J.; Choi, J.; Shin, K.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 2528.

¹³¹ Mohamed, R. K.; Mondal, S.; Gold, B.; Evoniuk, C. J.; Banerjee, T.; Hanson, K.; Alabugin, I. V. *J. Am. Chem. Soc.* **2015**, *137*, 6335.

4'-fluoro-[1,1'-biphenyl]-4-carbonitrile (58)

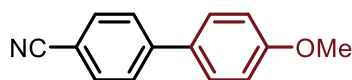


Prepared according to general procedure A. Grignard solution was added over 90 min at room temperature.

Purification by flash chromatography on silica gel (1/20–1/8 EtOAc/hexanes) afforded 4'-fluoro-[1,1'-biphenyl]-4-carbonitrile as a white solid (38.6 mg, 98%).

Characterization data were in accordance with literature.¹³² ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.70–7.78 (m, 2 H), 7.62–7.69 (m, 2 H), 7.52–7.61 (m, 2 H), 7.13–7.23 (m, 2 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 164.4, 161.9, 144.6, 135.3, 132.6, 129.0, 128.9, 127.6, 118.8, 116.2, 116.0, 111.0.

4'-methoxy-[1,1'-biphenyl]-4-carbonitrile (59)



Prepared according to general procedure A. Grignard solution was added over 90 min at room temperature.

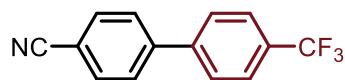
Purification by flash chromatography on silica gel (1/25–1/5 EtOAc/hexanes) afforded 4'-methoxy-[1,1'-biphenyl]-4-carbonitrile as a white solid (41.1 mg, 98%).

Characterization data were in accordance with literature.¹³³ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.63–7.72 (m, 4 H), 7.52–7.59 (m, 2 H), 6.99–7.04 (m, 2 H), 3.88 (s, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 160.2, 145.2, 132.5, 131.5, 128.3, 127.1, 119.1, 114.5, 110.1, 55.4.

¹³² Bernhardt, S.; Manolikakes, G.; Kunz, T.; Knochel, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 9205.

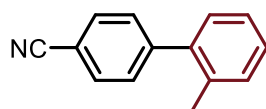
¹³³ Scheuermann, G. M.; Rumi, L.; Steurer, P.; Bannwarth, W.; Mülhaupt, R. *J. Am. Chem. Soc.* **2009**, *131*, 8262.

4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile (60)



Prepared according to general procedure A with Grignard (0.79 M in THF) prepared by general procedure C. Grignard solution was added over 90 min at room temperature. Purification by flash chromatography on silica gel (1/20–1/5 EtOAc/hexanes) afforded 4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile as a white solid (40.1 mg, 81%). Characterization data were in accordance with literature.¹³⁴ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.68–7.83 (m, 8 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 144.1, 142.6, 132.8, 130.7 (q, J = 32.8 Hz), 127.9, 127.6, 126.1 (q, J = 3.8 Hz), 124.1 (q, J = 273.6 Hz), 118.5, 112.0.

2'-methyl-[1,1'-biphenyl]-4-carbonitrile (61)

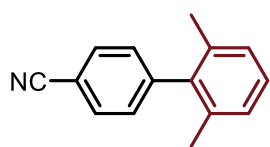


Prepared according to general procedure A with Grignard (0.79 M in THF) prepared by general procedure C. Grignard solution was added over 90 min at room temperature. Purification by flash chromatography on silica gel (1/10 EtOAc/hexanes) afforded 2'-methyl-[1,1'-biphenyl]-4-carbonitrile as a white solid (32.9 mg, 85%). Characterization data were in accordance with literature.¹³⁵ ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.64–7.75 (m, 2 H), 7.38–7.46 (m, 2 H), 7.22–7.34 (m, 3 H), 7.18 (d, J = 7.3 Hz, 1 H), 2.24 (s, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 146.8, 140.0, 135.0, 131.9, 130.6, 130.0, 129.4, 128.3, 126.1, 118.9, 110.7, 20.3.

¹³⁴ Liang, Q.; Xing, P.; Huang, Z.; Dong, J.; Sharpless, K. B.; Li, X.; Jiang, B. *Org. Lett.* **2015**, *17*, 1942.

¹³⁵ Nagaki, A.; Ichinari, D.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2014**, *136*, 12245.

2',6'-dimethyl-[1,1'-biphenyl]-4-carbonitrile (62)



Prepared according to general procedure A with Grignard (0.75 M in THF) prepared by general procedure C. Grignard solution was added over 90 min at room temperature. Yield (8%) was determined by ^1H NMR or the crude reaction mixture with 1,3,5-trimethoxybenzene as internal standard. Peaks belonging to the product were assigned based on the literature.¹³⁶

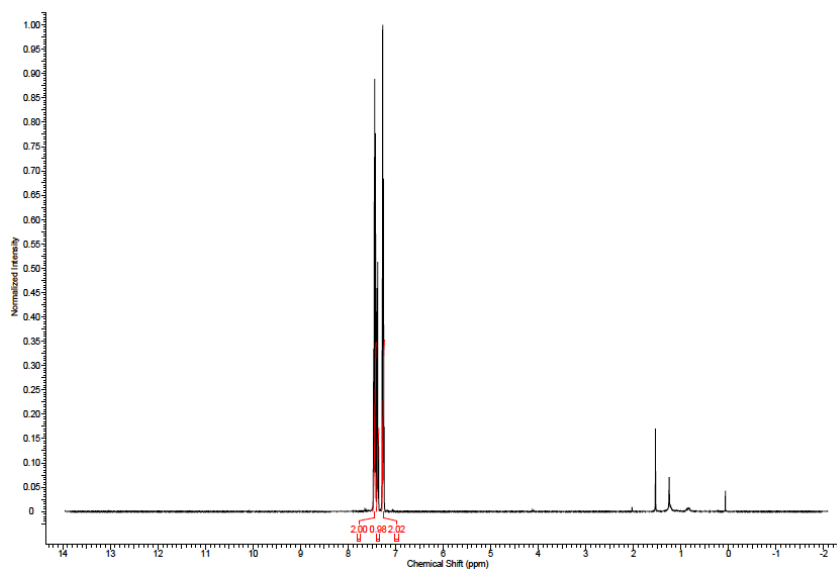
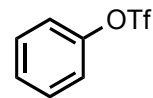
¹³⁶ Putta, C. B.; Ghosh, S. *Adv. Synth. Catal.* **2011**, 353, 1889.

Appendices

NMR Spectra

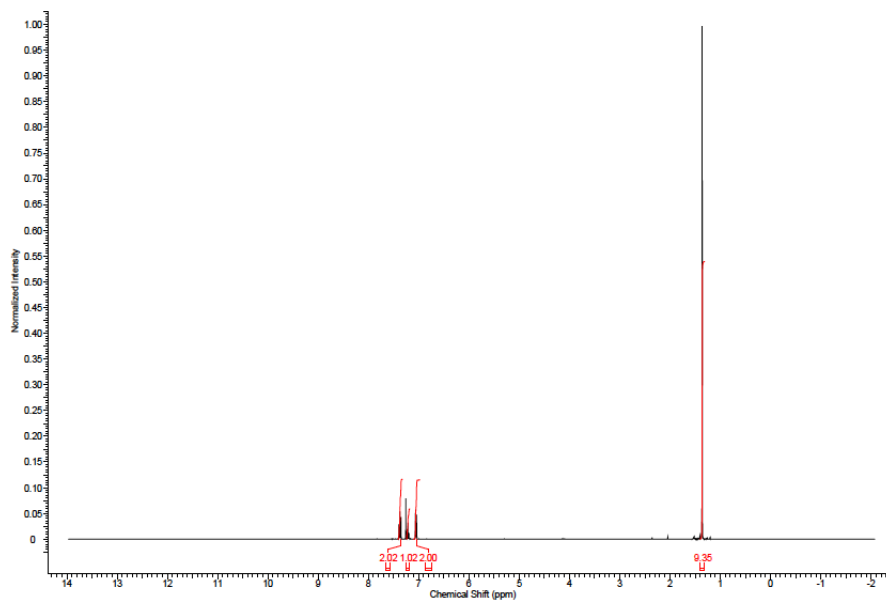
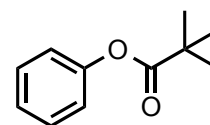
phenyl triflate (14)

^1H NMR (CDCl_3 , 400 MHz)



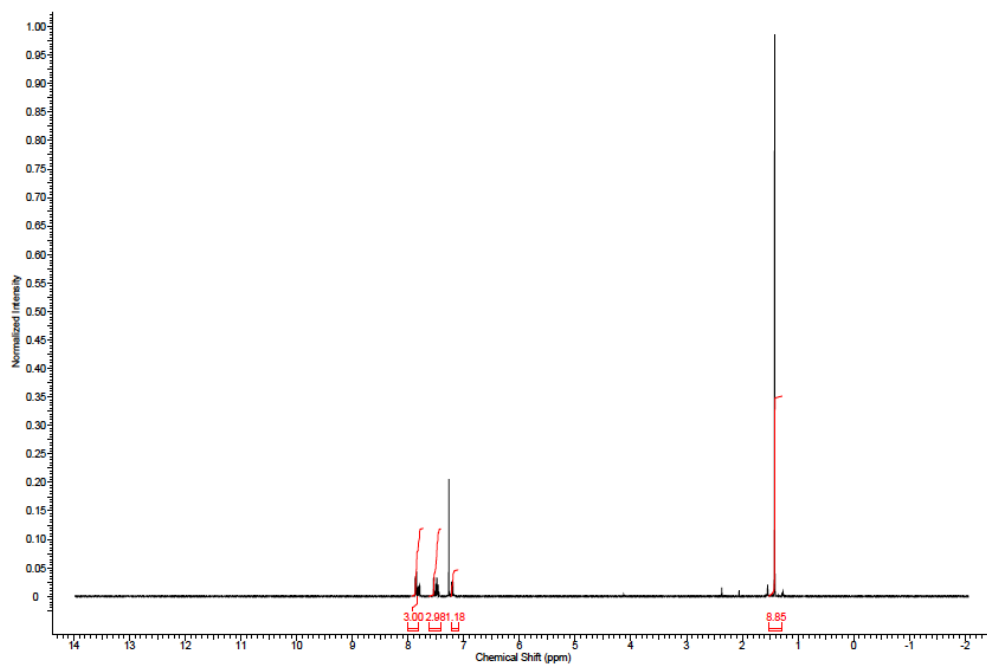
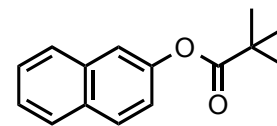
phenyl pivalate (17)

^1H NMR (CDCl_3 , 400 MHz)



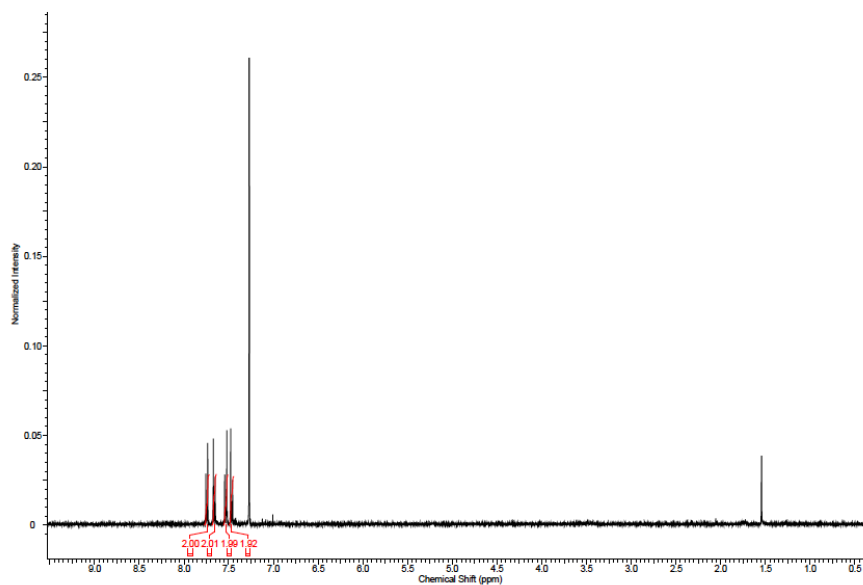
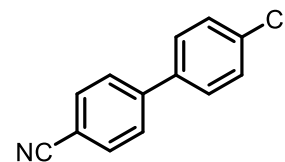
2-naphthyl pivalate (18)

^1H NMR (CDCl_3 , 400 MHz)



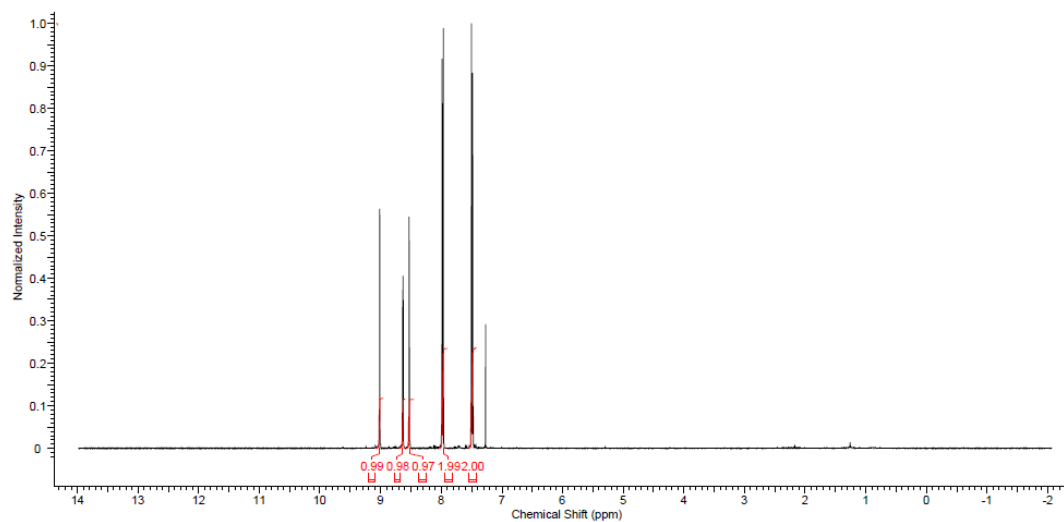
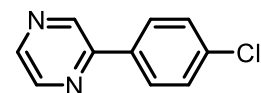
4'-chloro-[1,1'-biphenyl]-4-carbonitrile (Starting material of 34)

^1H NMR (CDCl_3 , 400 MHz)



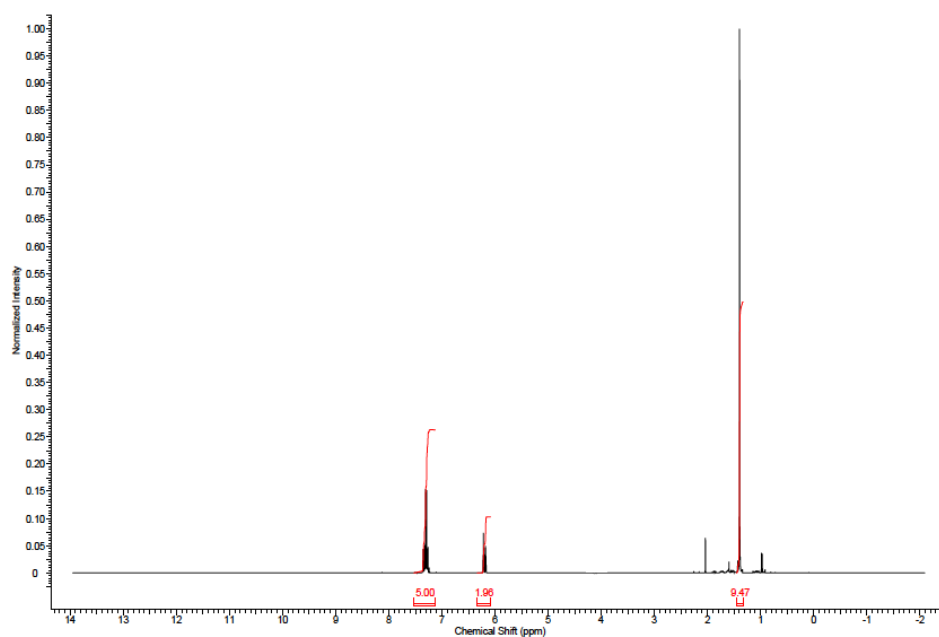
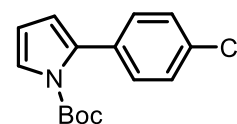
2-(4-chlorophenyl)pyrazine (Starting material of 36)

^1H NMR (CDCl_3 , 400 MHz)



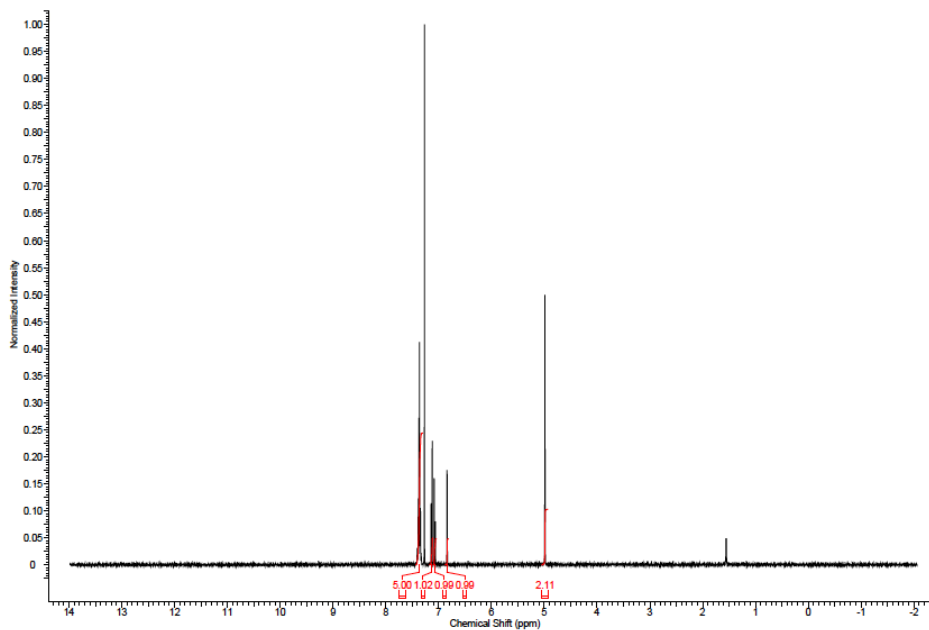
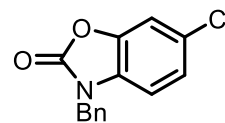
***tert*-butyl 2-(4-chlorophenyl)-1H-pyrrole-1-carboxylate (Starting material of 38)**

^1H NMR (CDCl_3 , 400 MHz)



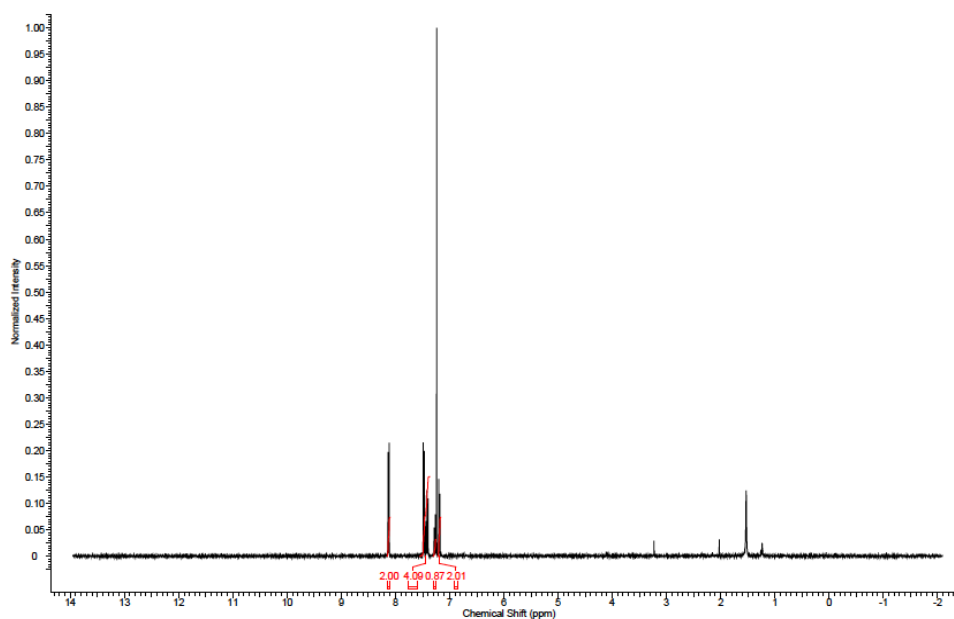
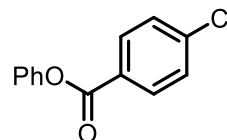
3-benzyl-6-chlorobenzo[d]oxazol-2(3H)-one (Starting material of 39)

^1H NMR (CDCl_3 , 400 MHz)



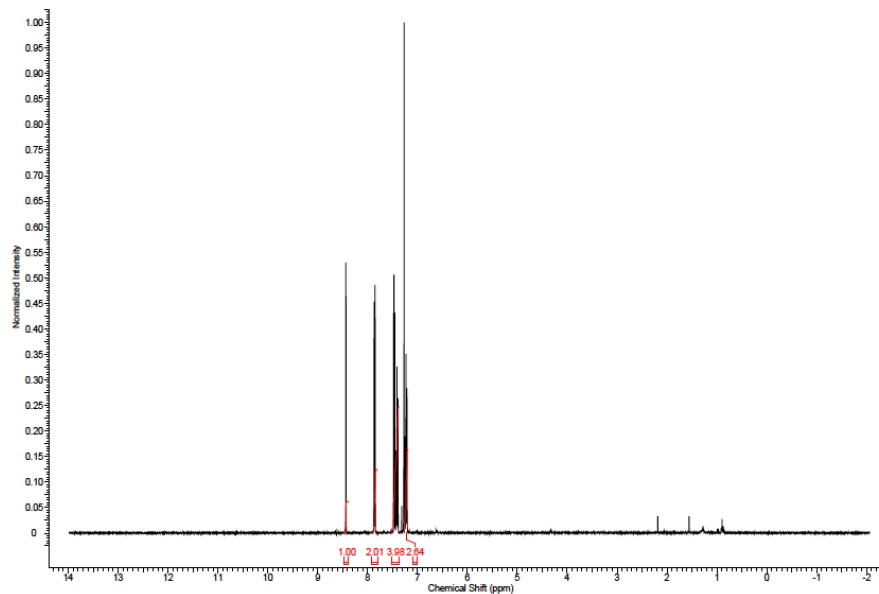
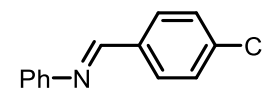
phenyl 4-chlorobenzoate (Starting material of 40)

^1H NMR (CDCl_3 , 400 MHz)



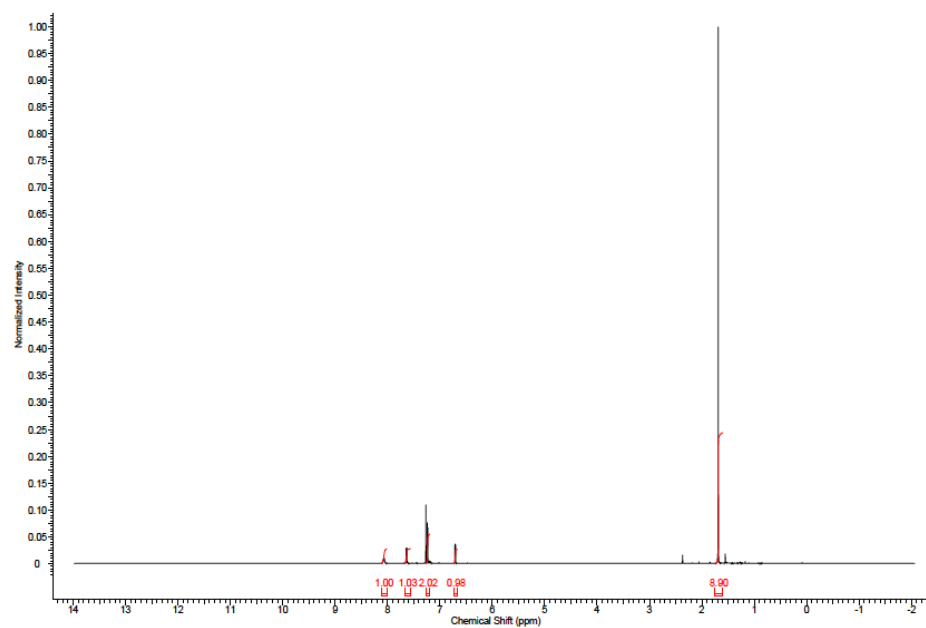
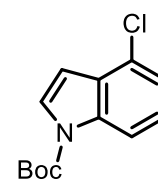
1-(4-chlorophenyl)-N-phenylmethanimine (Starting material of 43)

^1H NMR (CDCl_3 , 400 MHz)

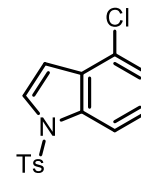


***tert*-butyl 4-chloro-1H-indole-1-carboxylate (Starting material of 45)**

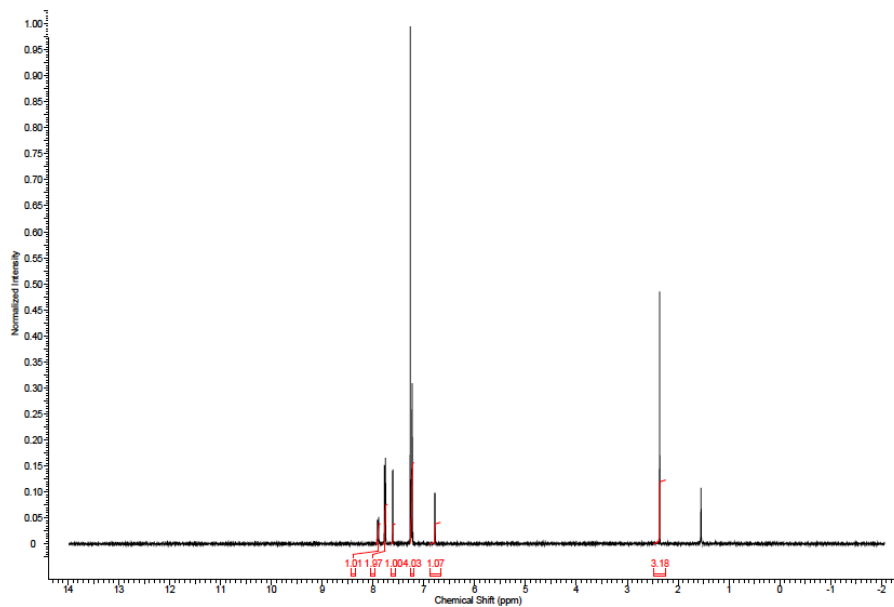
^1H NMR (CDCl_3 , 400 MHz)



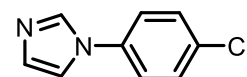
4-chloro-1-tosyl-1H-indole (Starting material of 46)



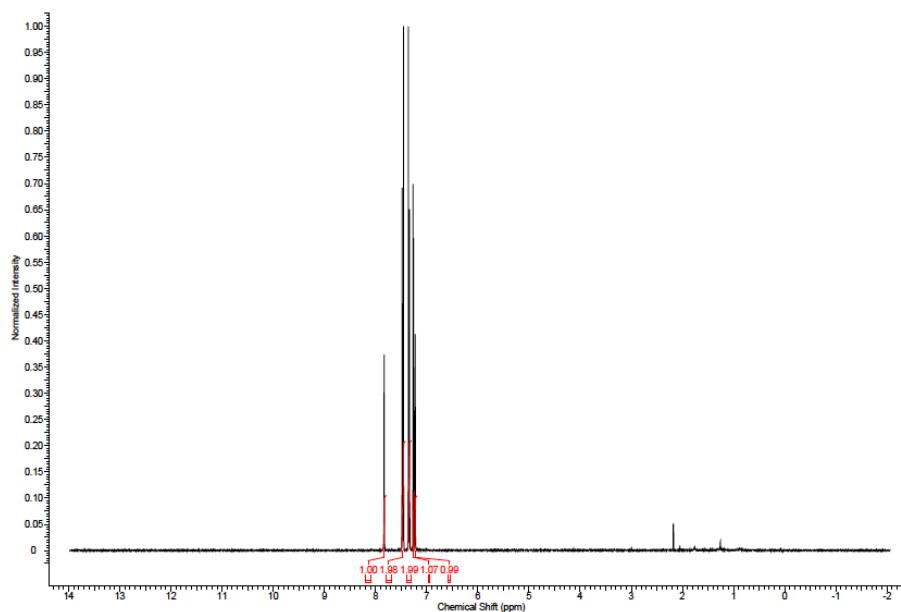
^1H NMR (CDCl_3 , 400 MHz)



1-(4-chlorophenyl)-1H-imidazole (Starting material of 51)

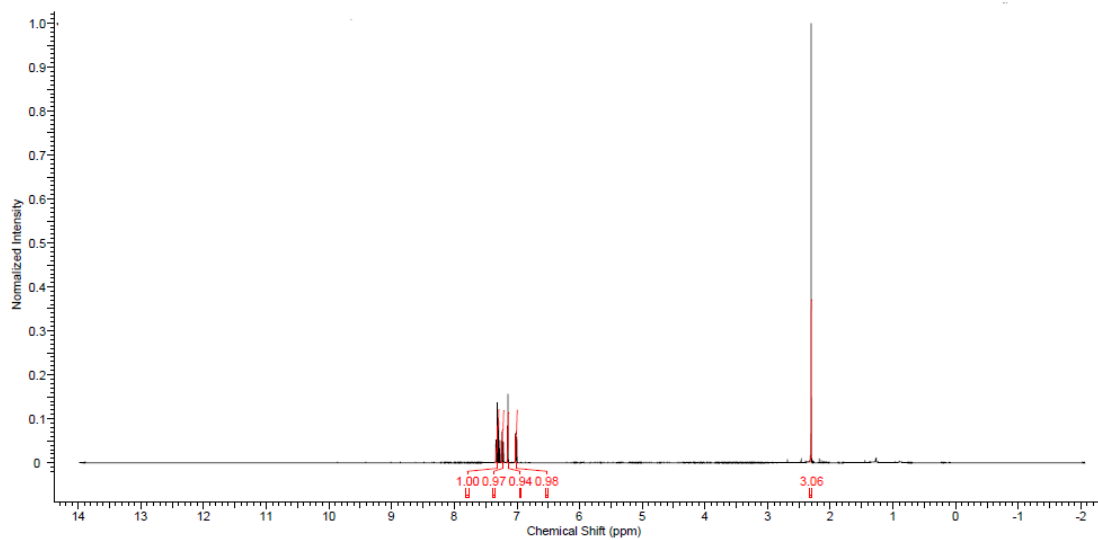
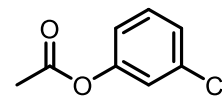


^1H NMR (CDCl_3 , 400 MHz)



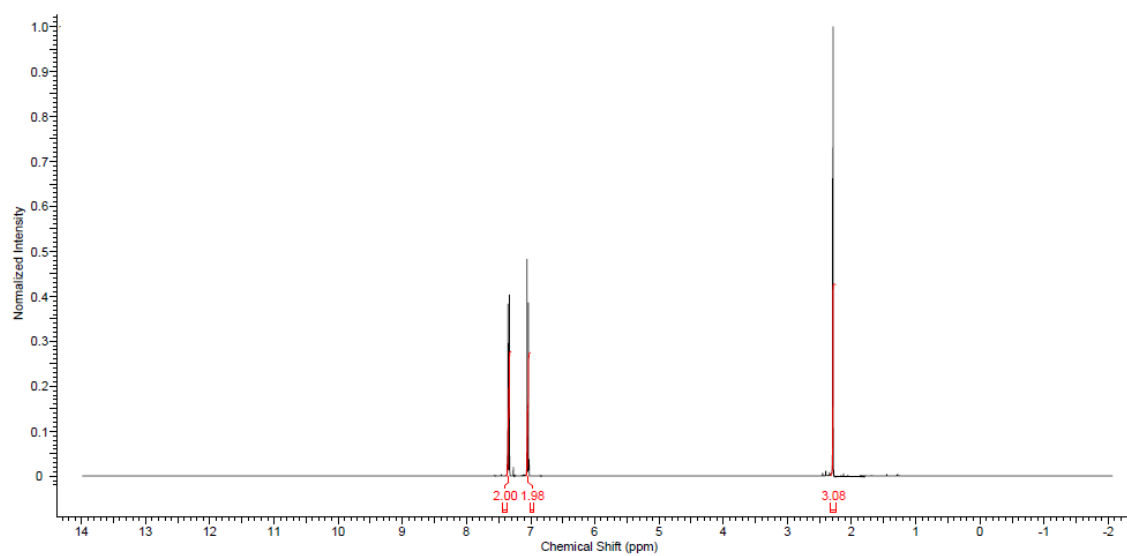
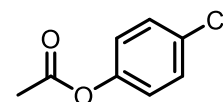
3-chlorophenylacetate (65)

^1H NMR (CDCl_3 , 400 MHz)



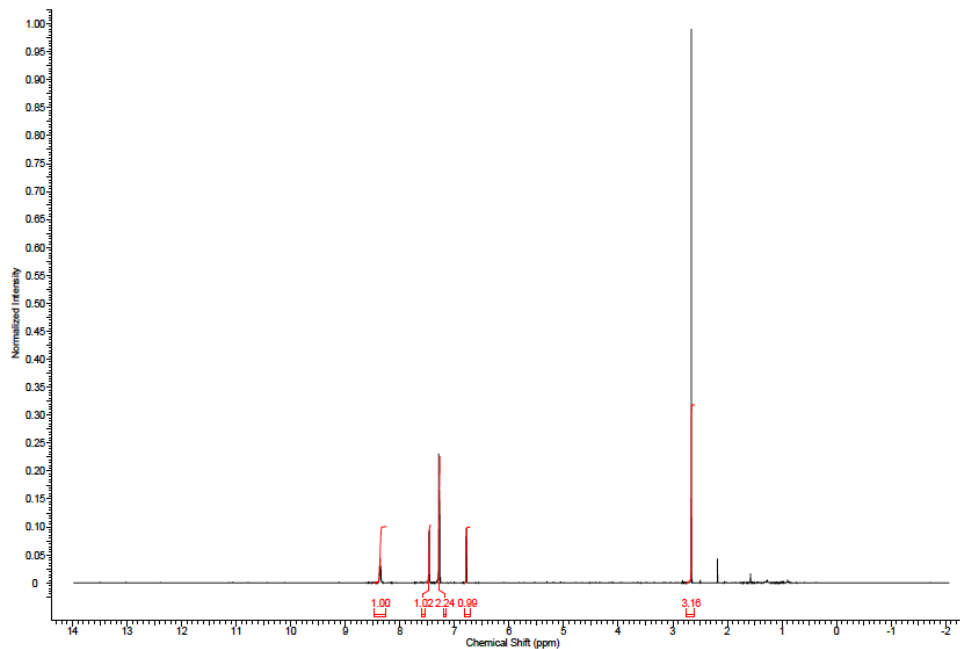
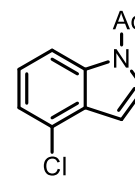
4-chlorophenyl acetate (66)

^1H NMR (CDCl_3 , 400 MHz)



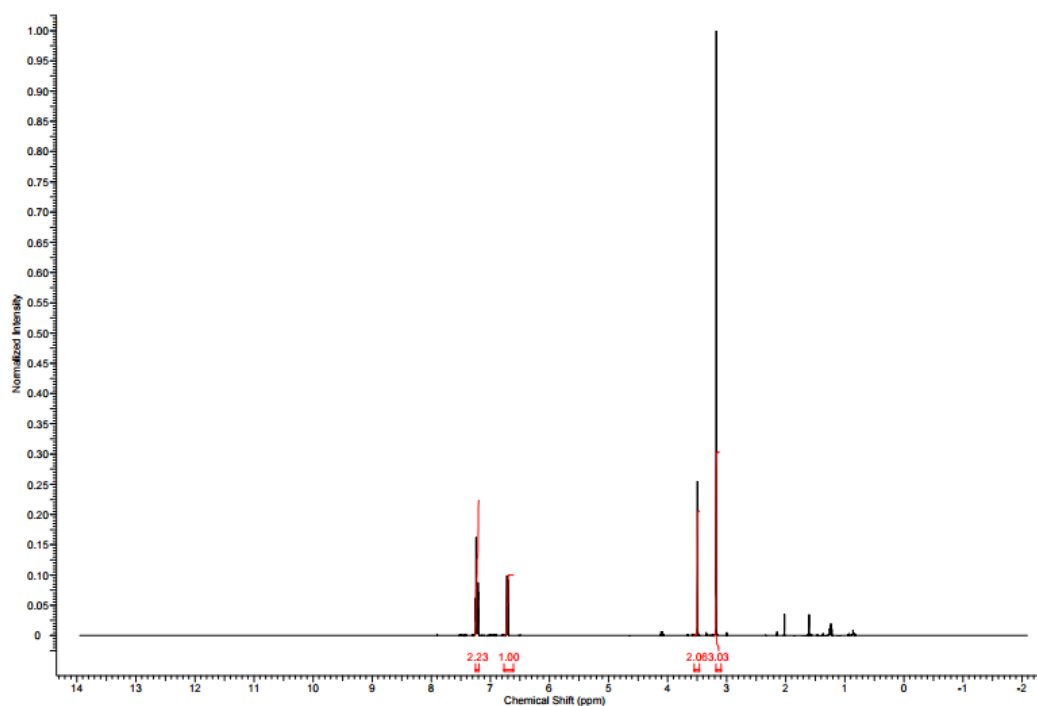
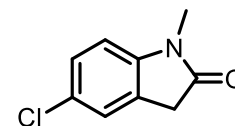
1-(4-chloro-1H-indol-1-yl)ethan-1-one (76)

^1H NMR (CDCl_3 , 400 MHz)



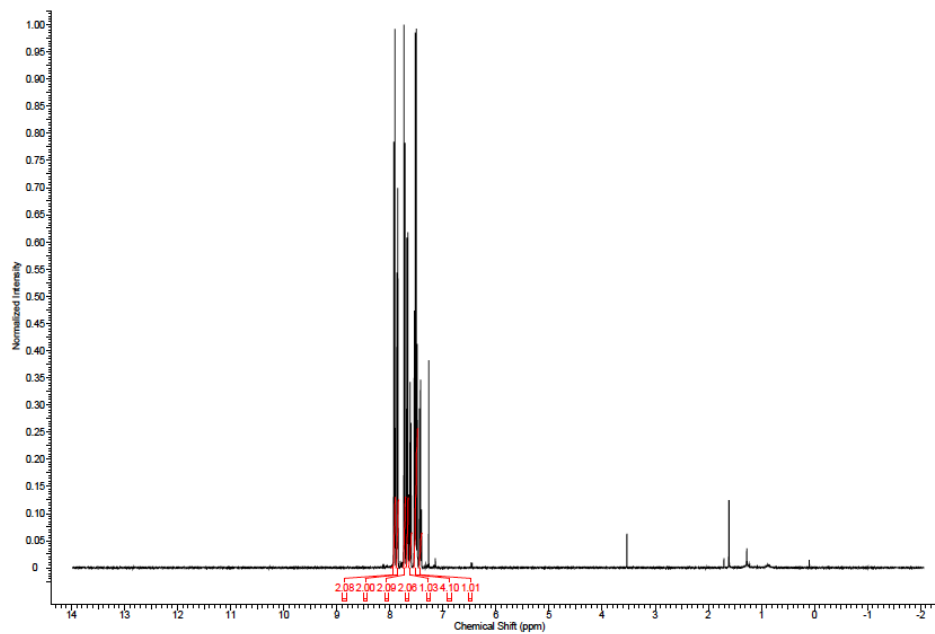
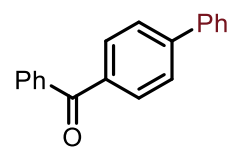
5-chloro-1-methylindolin-2-one (78)

^1H NMR (CDCl_3 , 400 MHz)

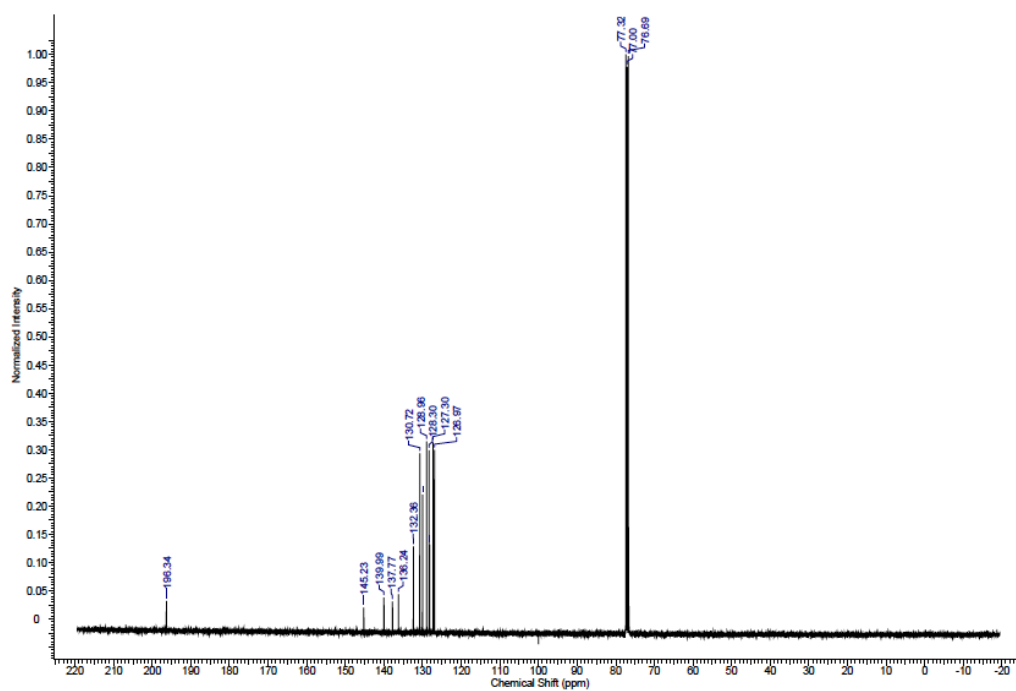


4-benzoylbiphenyl (26)

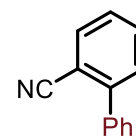
^1H NMR (CDCl_3 , 400 MHz)



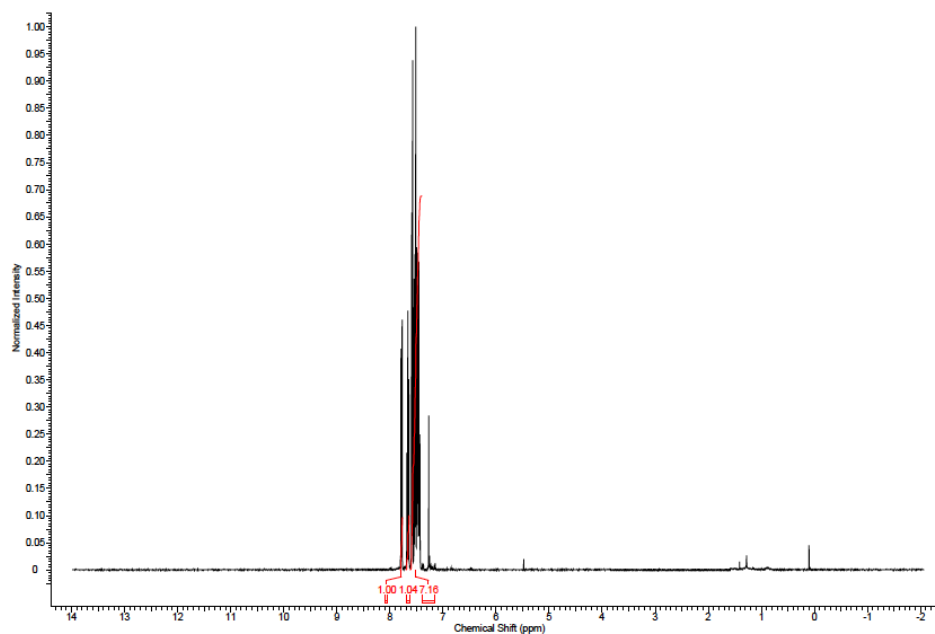
^{13}C NMR (CDCl_3 , 100 MHz)



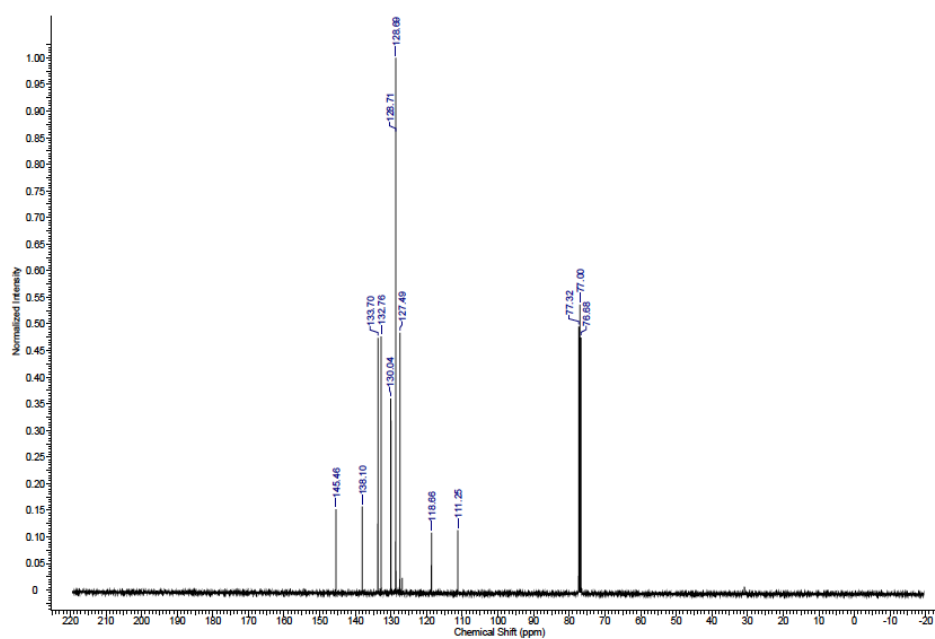
2-cyanobiphenyl (28)



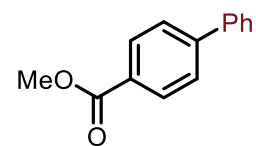
^1H NMR (CDCl_3 , 400 MHz)



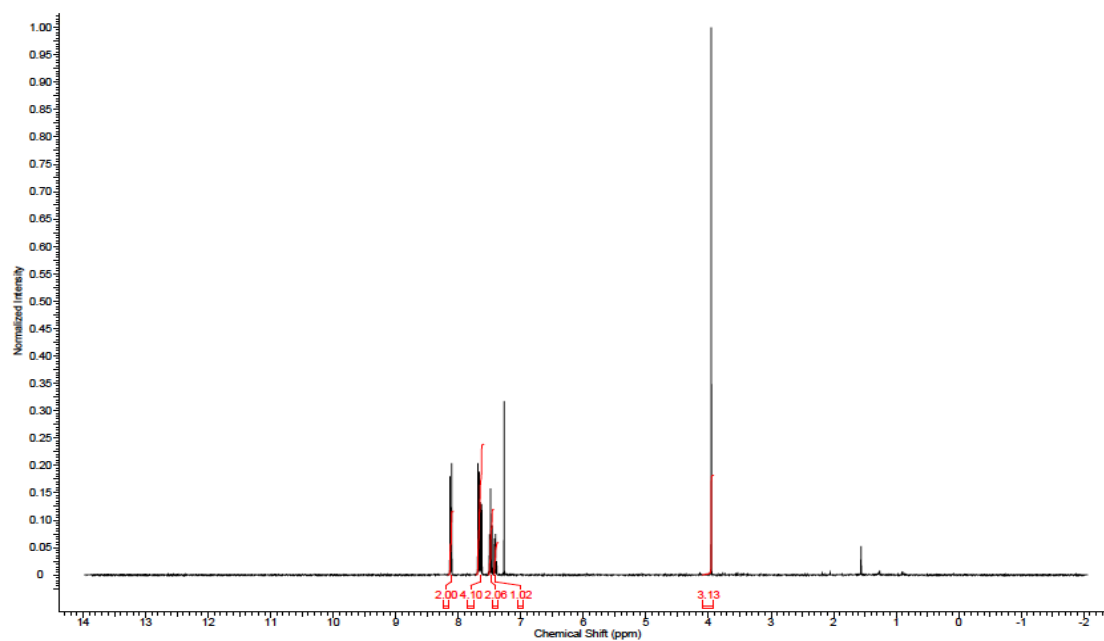
^{13}C NMR (CDCl_3 , 100 MHz)



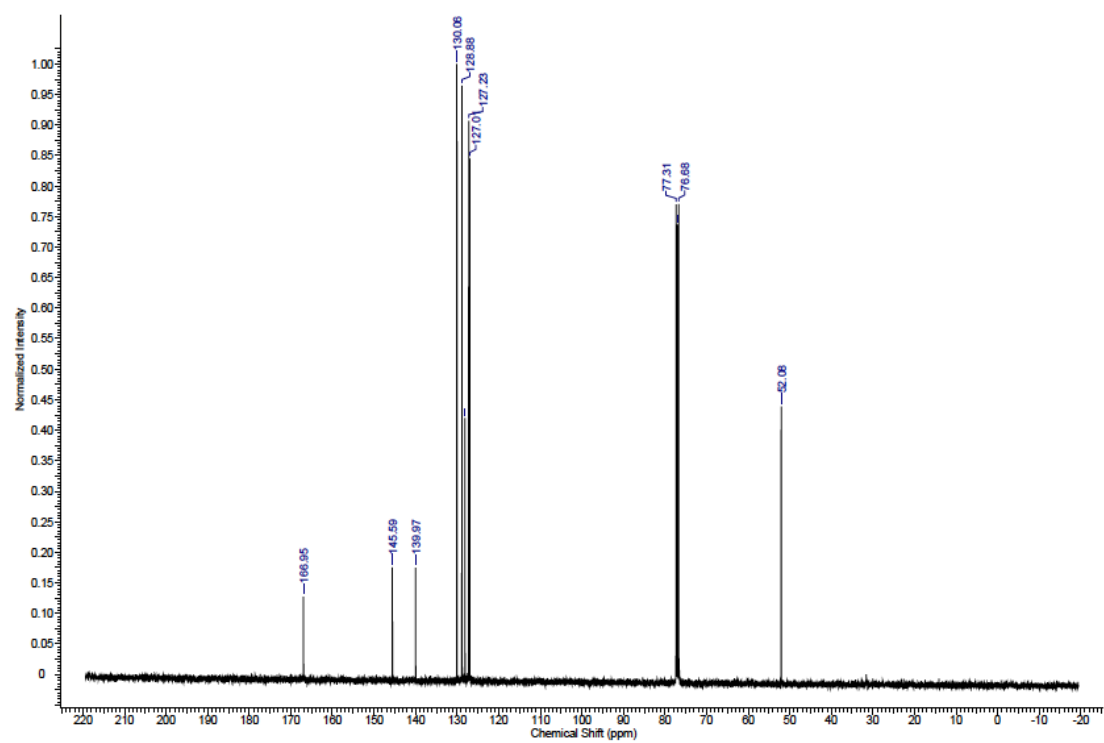
methyl 4-phenylbenzoate (31)



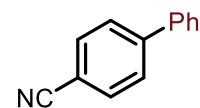
^1H NMR (CDCl_3 , 400 MHz)



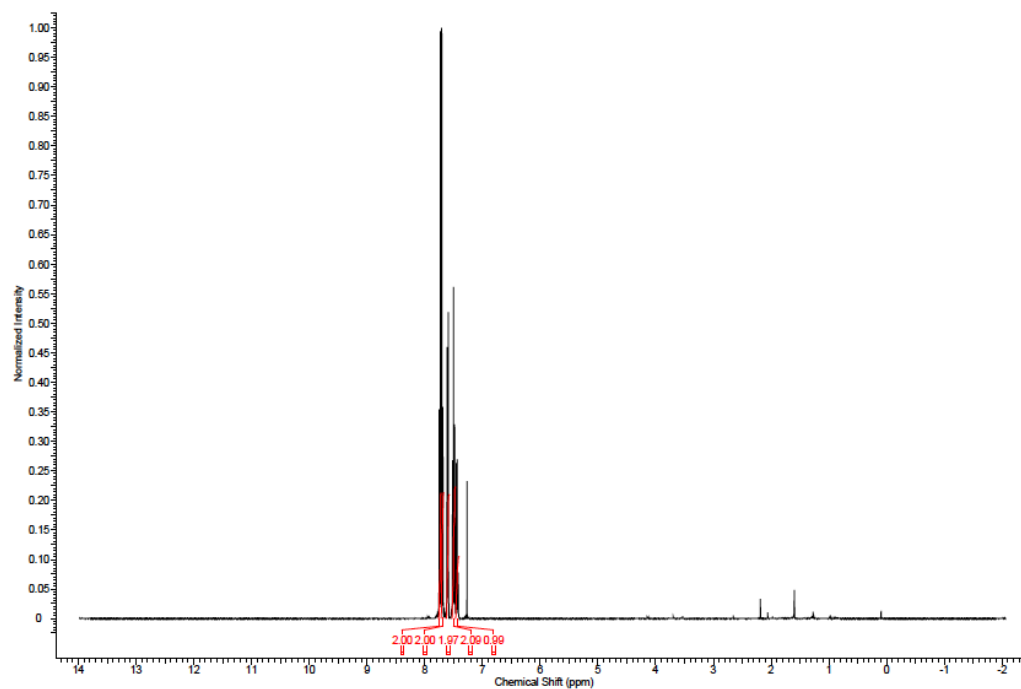
^{13}C NMR (CDCl_3 , 100 MHz)



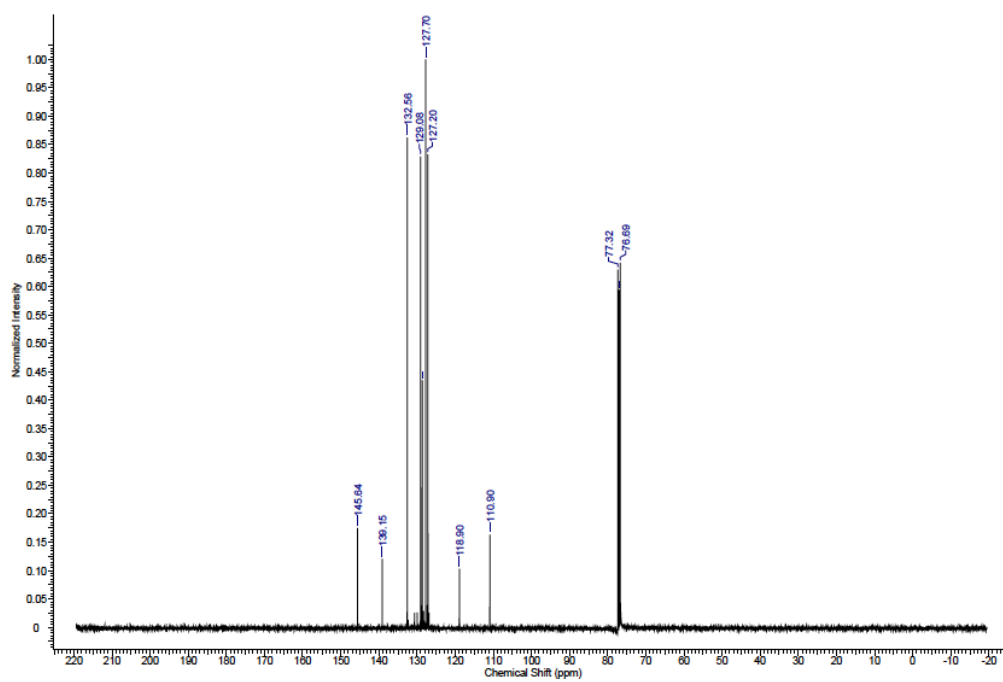
4-cyanobiphenyl (32)



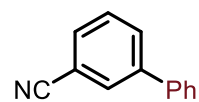
^1H NMR (CDCl_3 , 400 MHz)



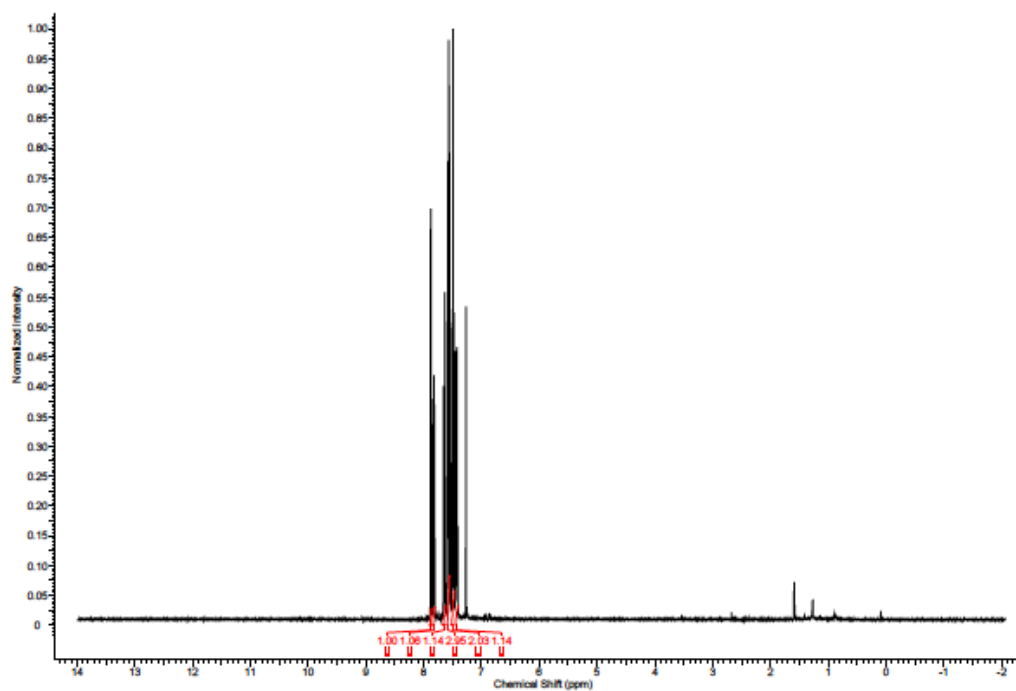
^{13}C NMR (CDCl_3 , 100 MHz)



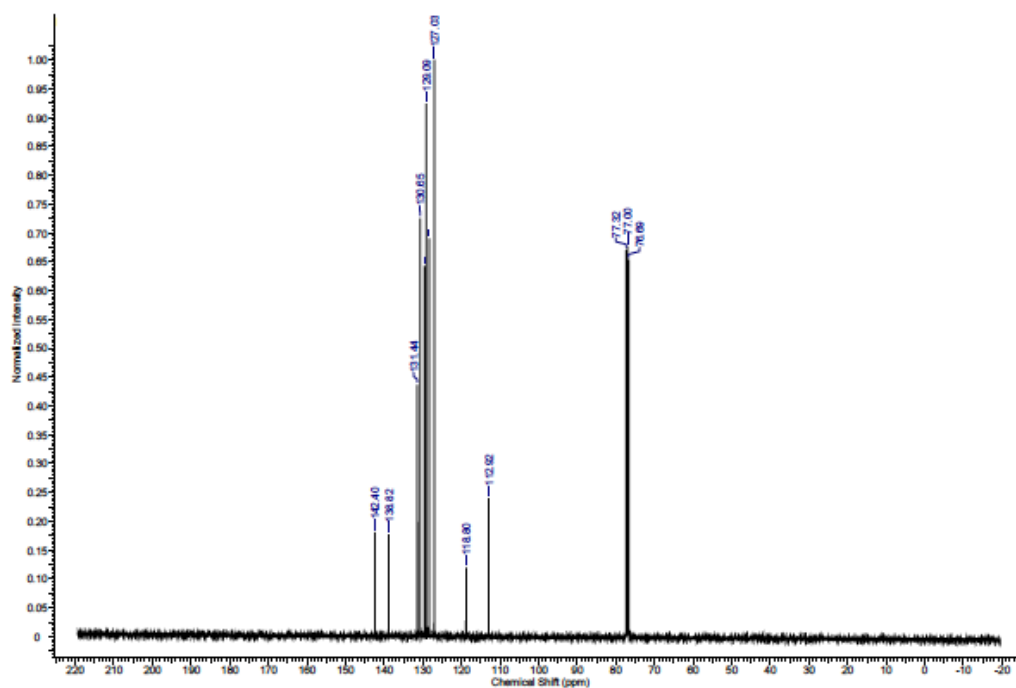
3-cyanobiphenyl (33)



^1H NMR (CDCl_3 , 400 MHz)

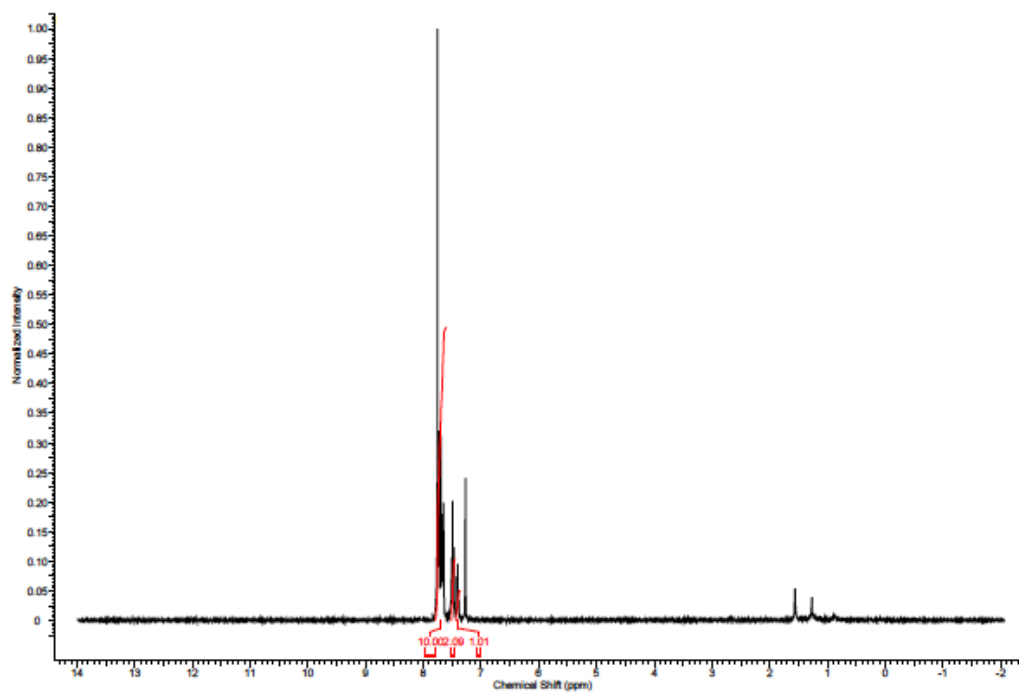
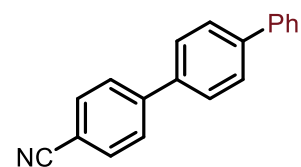


^{13}C NMR (CDCl_3 , 100 MHz)

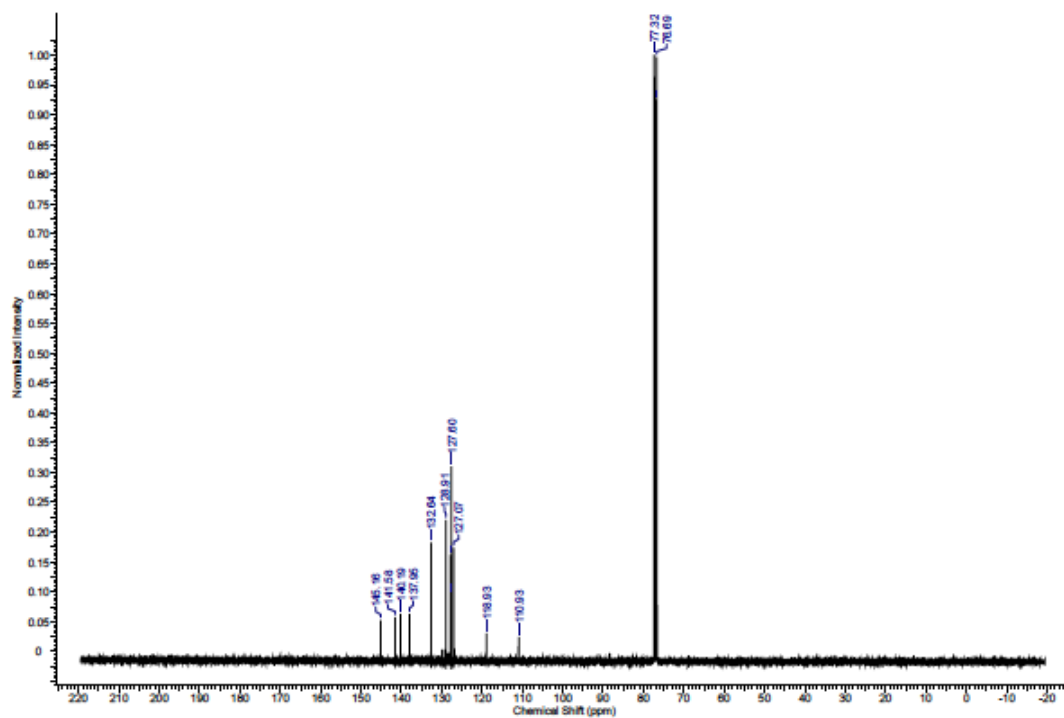


[1,1':4',1''-terphenyl]-4-carbonitrile (34)

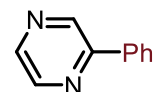
^1H NMR (CDCl_3 , 400 MHz)



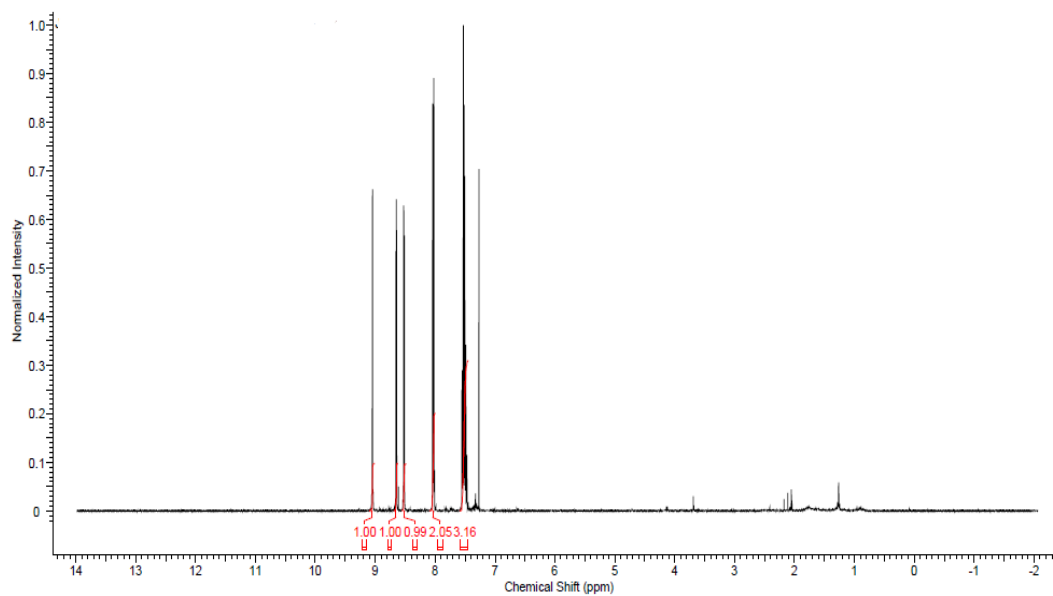
^{13}C NMR (CDCl_3 , 100 MHz)



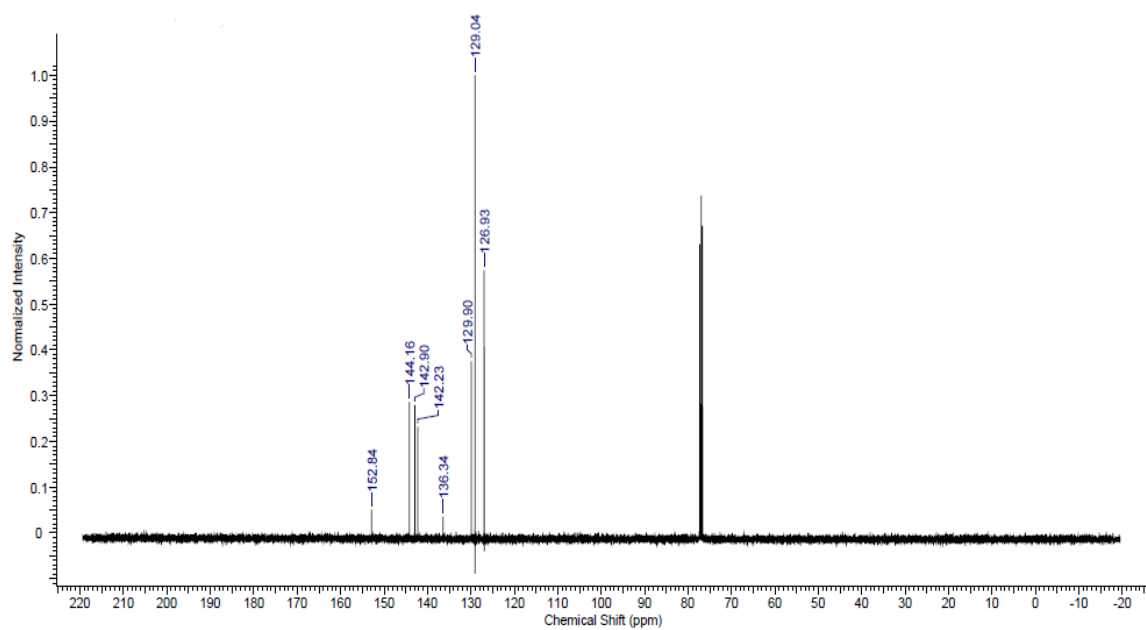
2-phenylpyrazine (35)



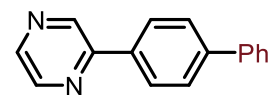
^1H NMR (CDCl_3 , 400 MHz)



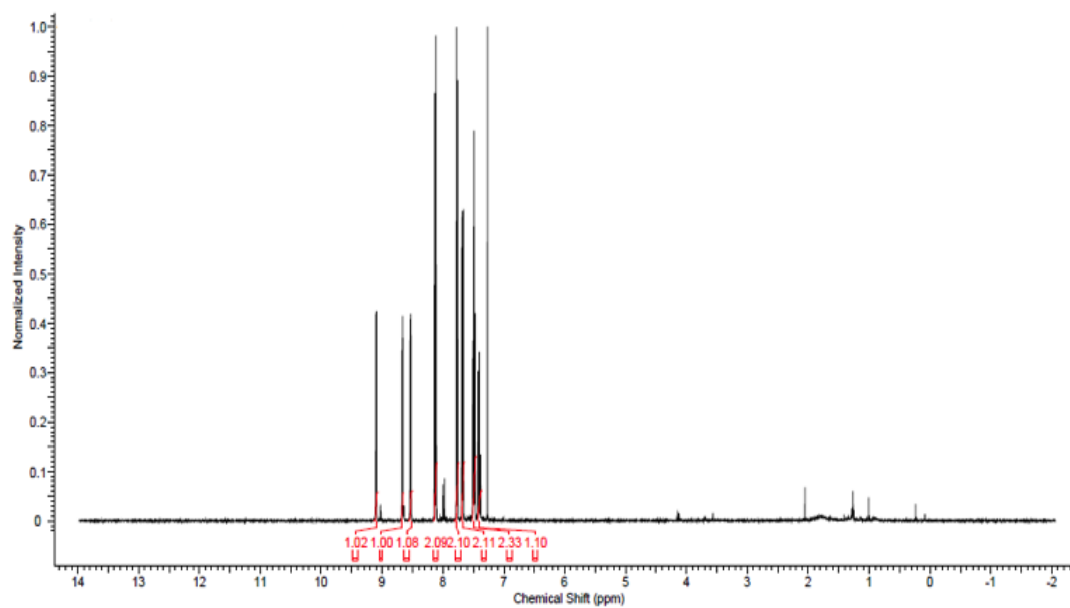
^{13}C NMR (CDCl_3 , 100 MHz)



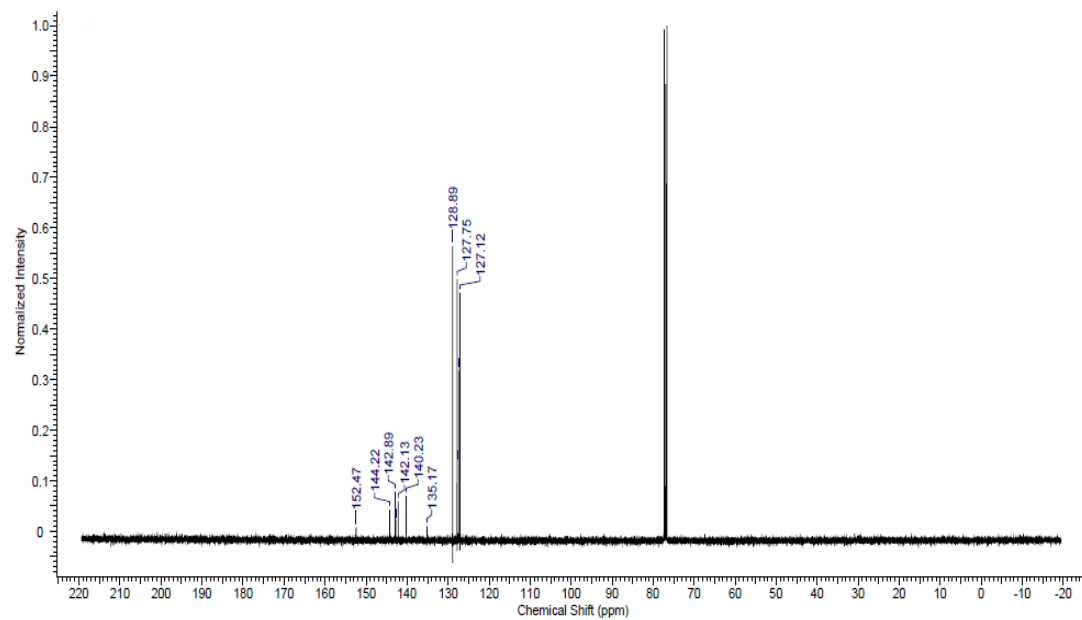
2-([1,1'-biphenyl]-4-yl)pyrazine (36)



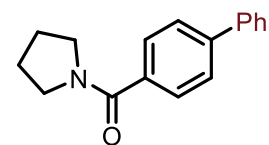
^1H NMR (CDCl_3 , 400 MHz)



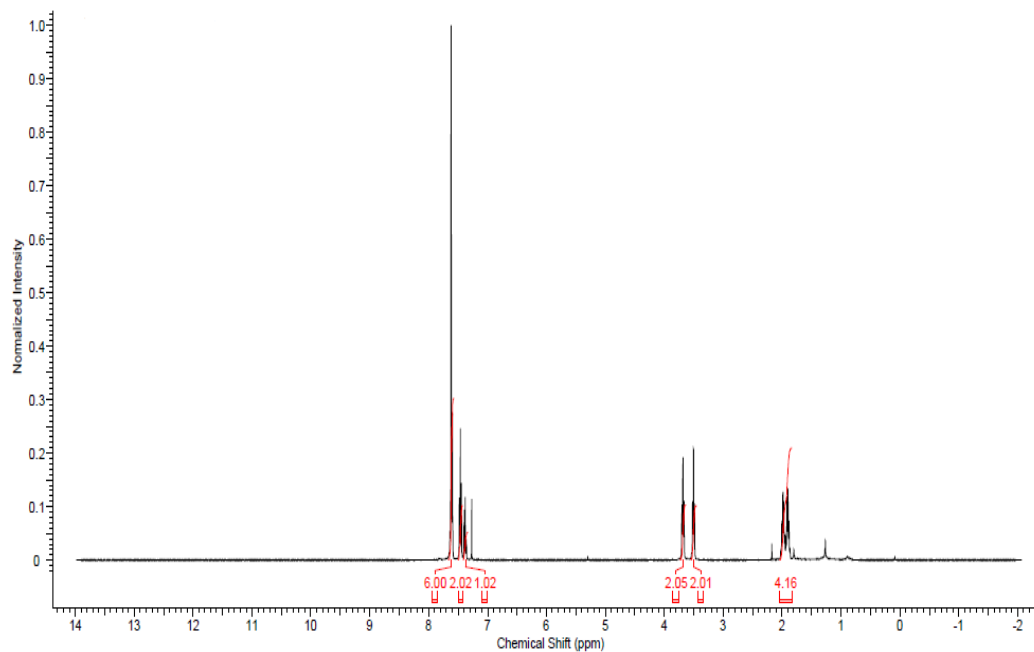
^{13}C NMR (CDCl_3 , 100 MHz)



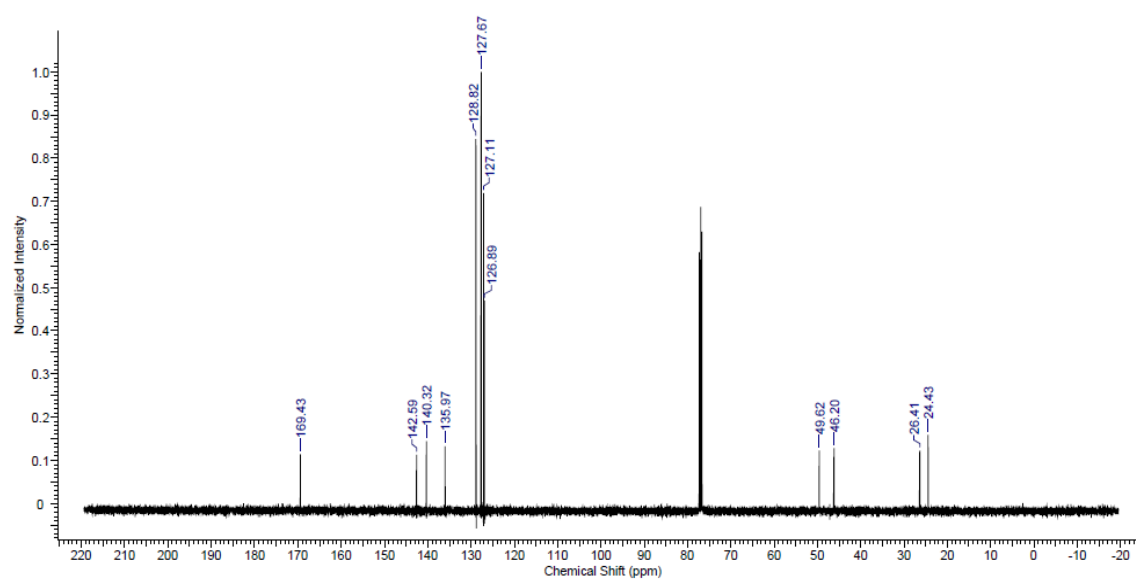
(4-phenylbenzoyl)pyrrolidine (37)



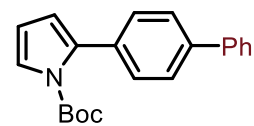
^1H NMR (CDCl_3 , 400 MHz)



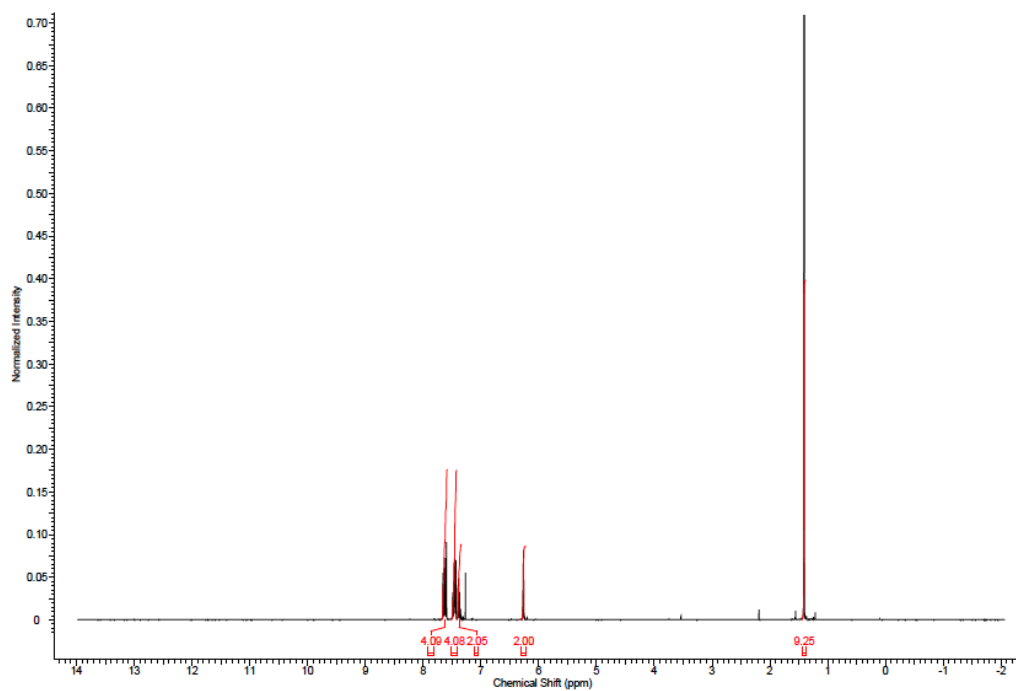
^{13}C NMR (CDCl_3 , 100 MHz)



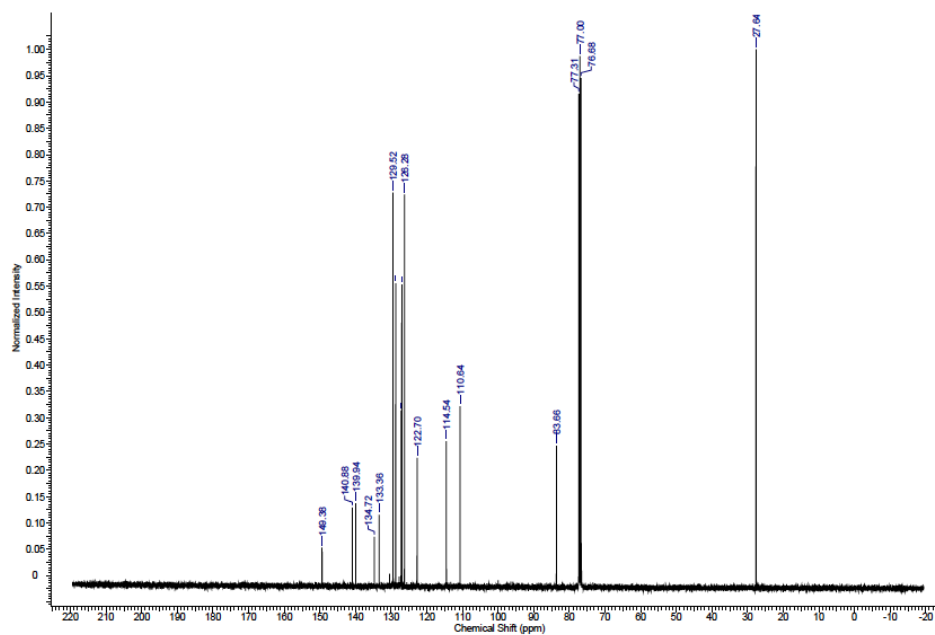
***tert*-butyl 2-([1,1'-biphenyl]-4-yl)-1H-pyrrole-1-carboxylate (38)**



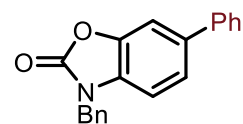
^1H NMR (CDCl_3 , 400 MHz)



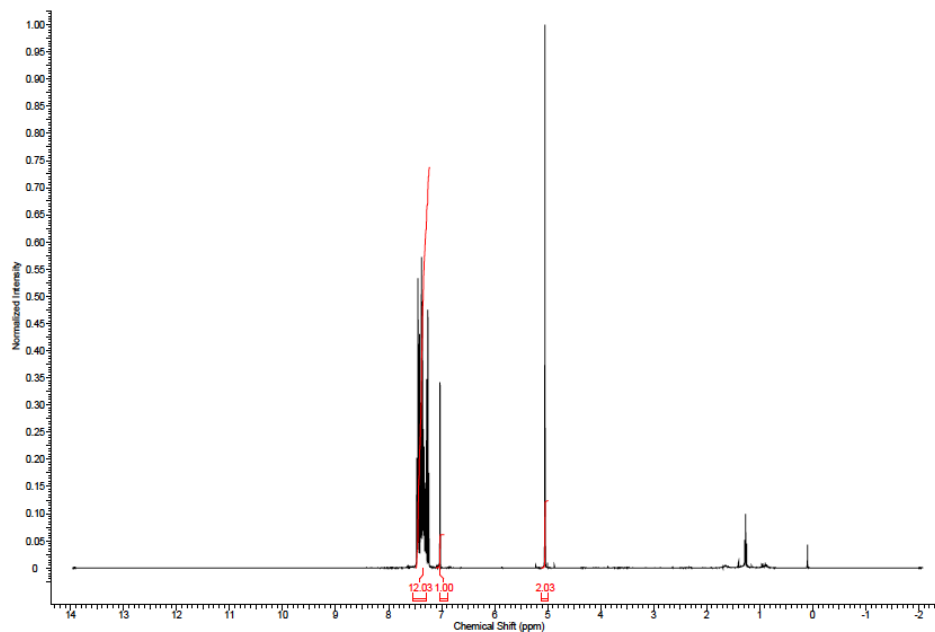
^{13}C NMR (CDCl_3 , 100 MHz)



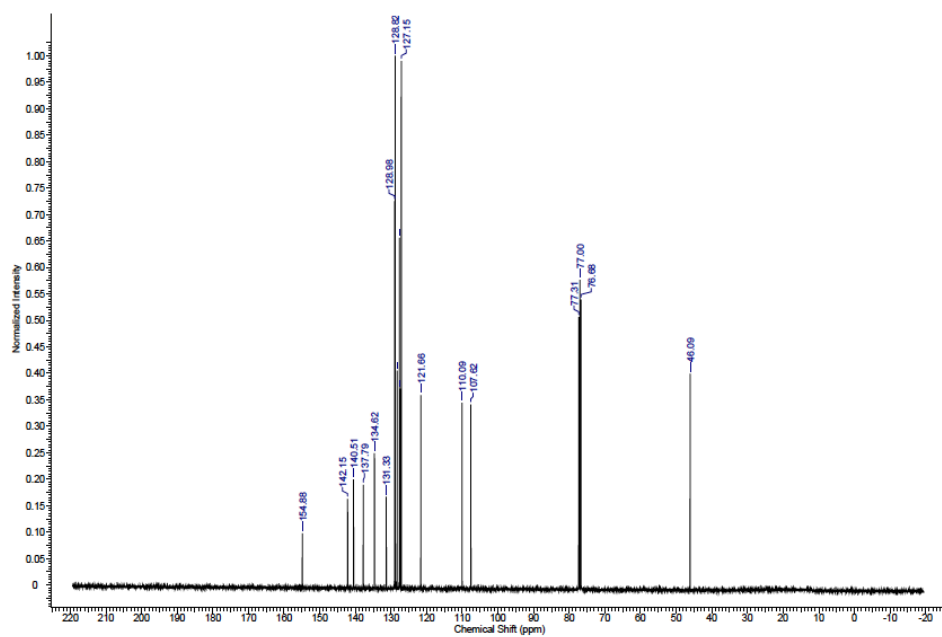
3-benzyl-6-phenylbenzo[d]oxazol-2(3H)-one (39)



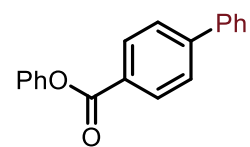
^1H NMR (CDCl_3 , 400 MHz)



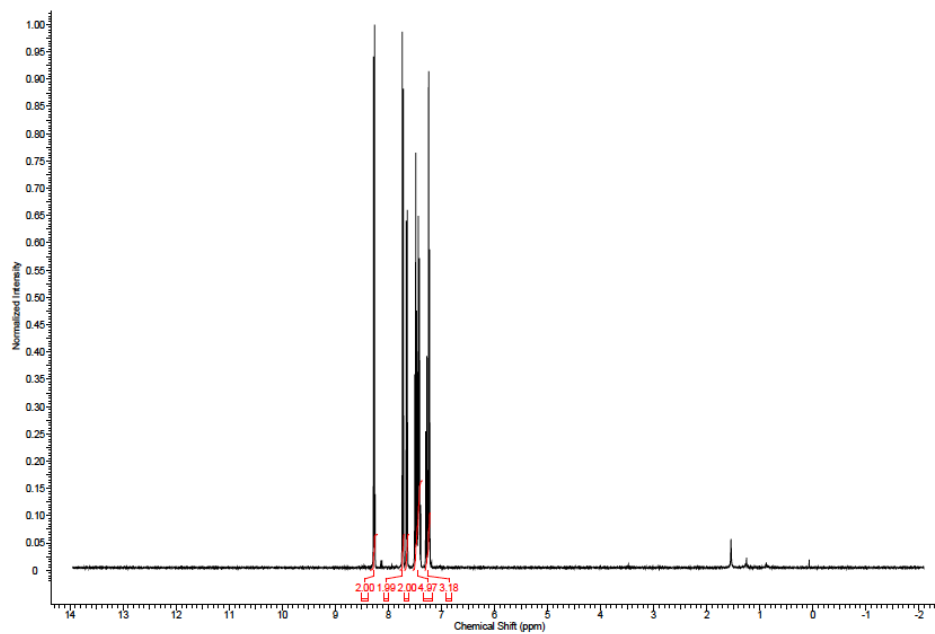
^{13}C NMR (CDCl_3 , 100 MHz)



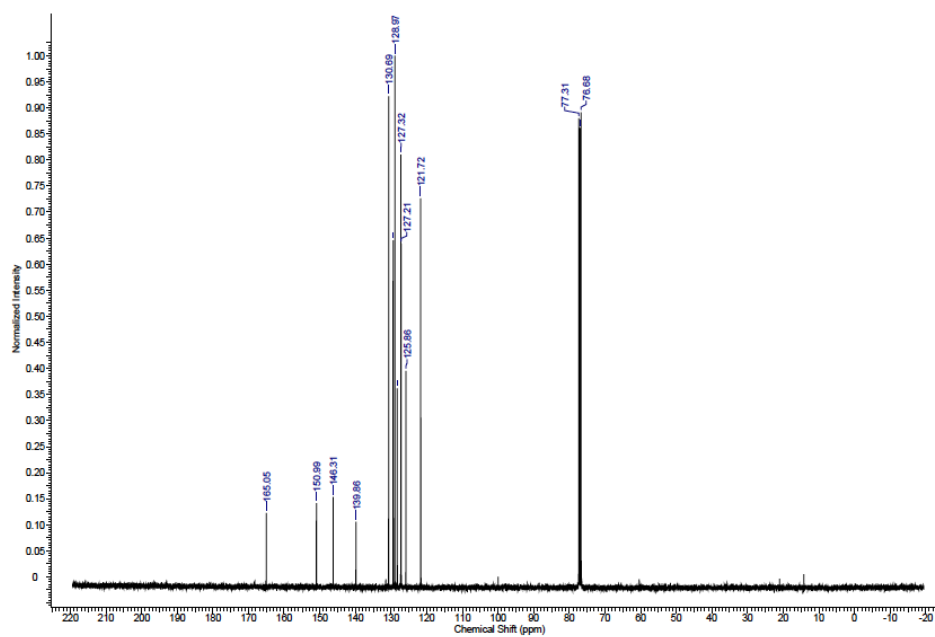
phenyl [1,1'-biphenyl]-4-carboxylate (40)



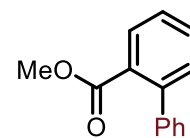
^1H NMR (CDCl_3 , 400 MHz)



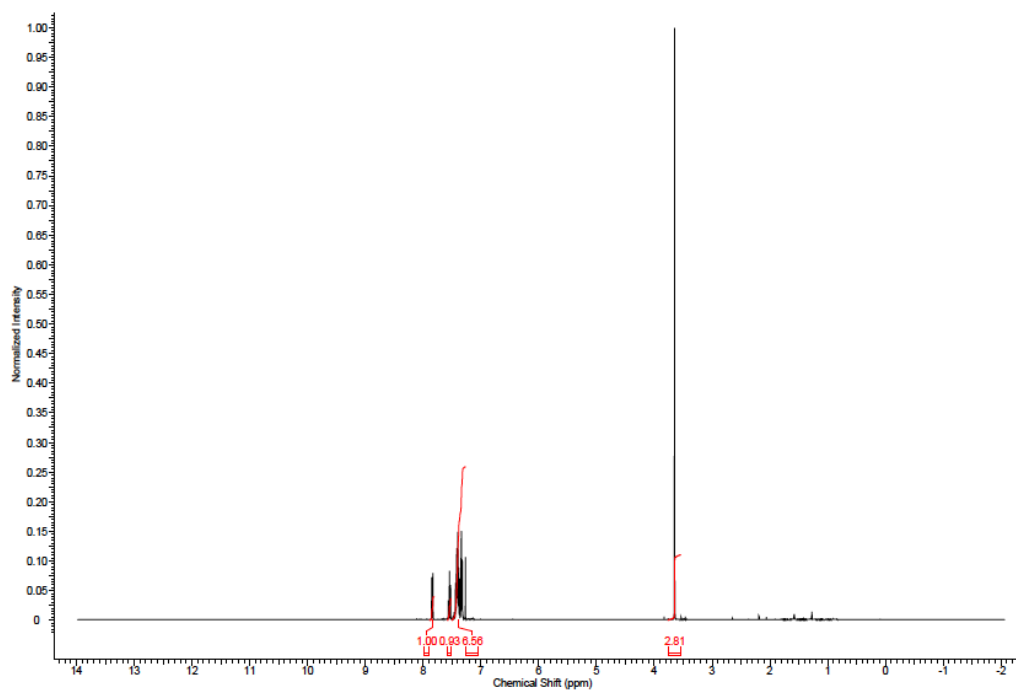
^{13}C NMR (CDCl_3 , 100 MHz)



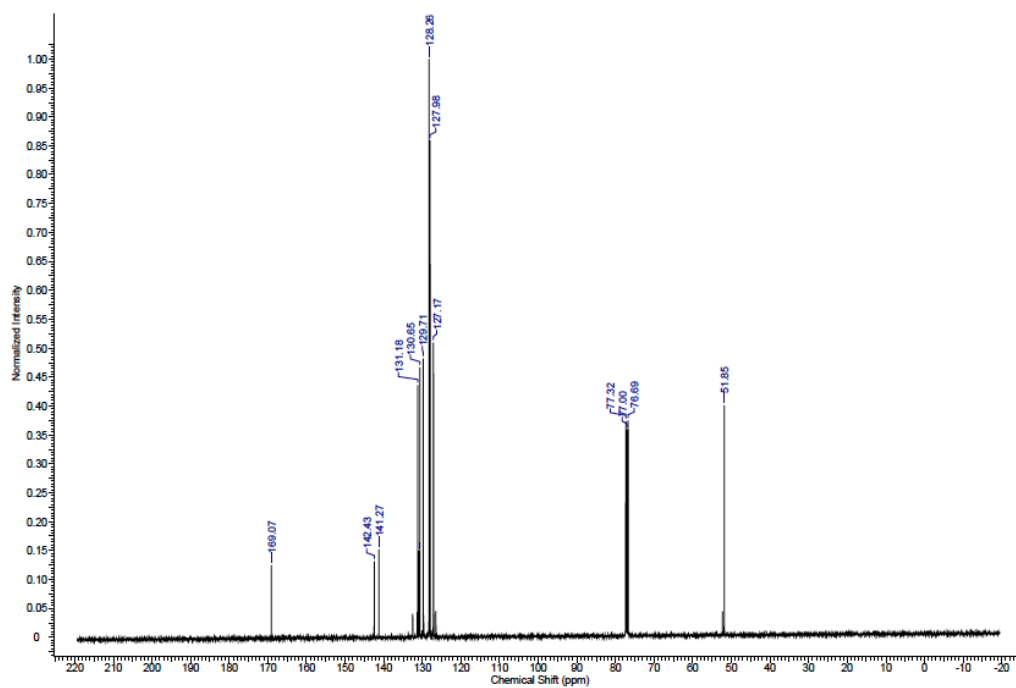
methyl 2-phenylbenzoate (41)



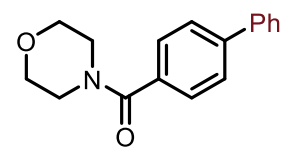
^1H NMR (CDCl_3 , 400 MHz)



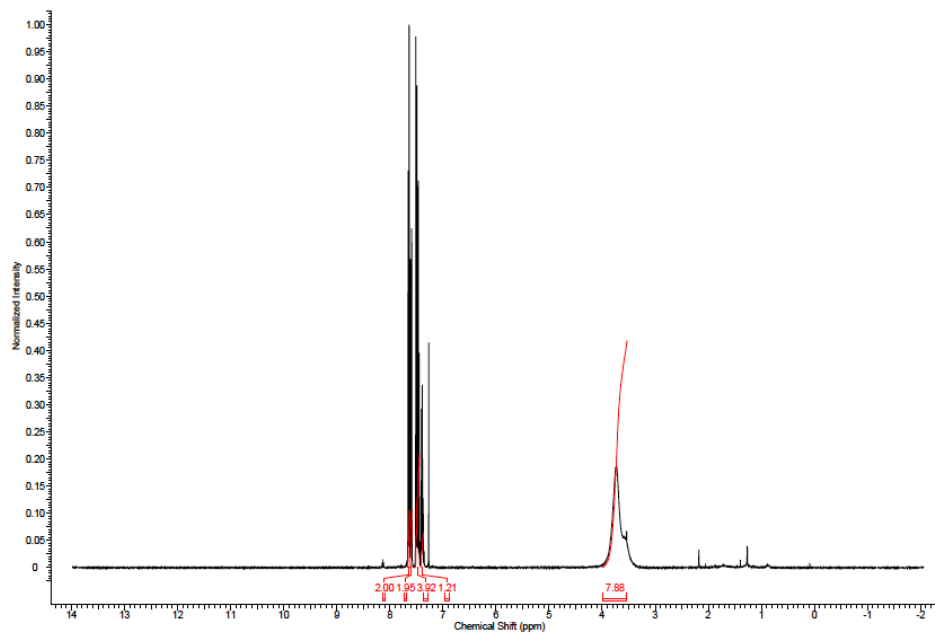
^{13}C NMR (CDCl_3 , 100 MHz)



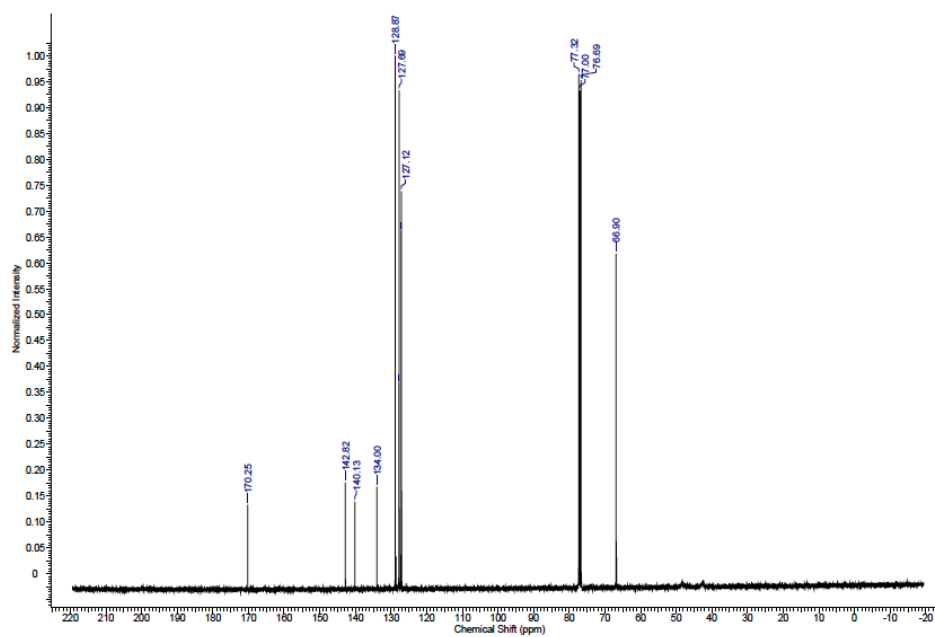
[1,1'-biphenyl]-4-yl(morpholino)methanone (42)



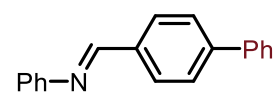
^1H NMR (CDCl_3 , 400 MHz)



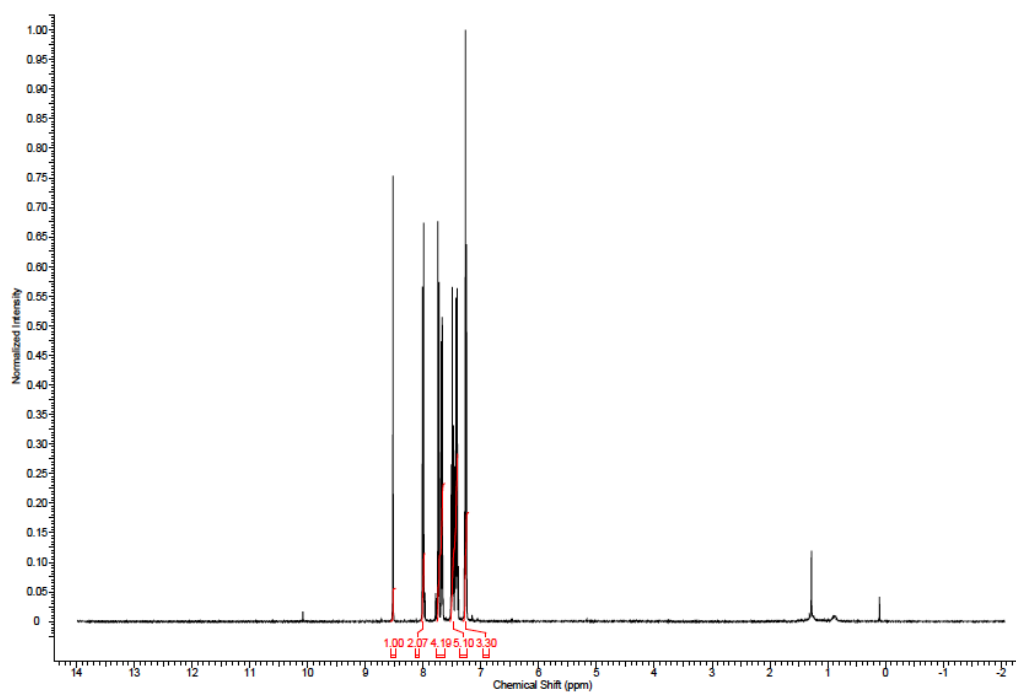
^{13}C NMR (CDCl_3 , 100 MHz)



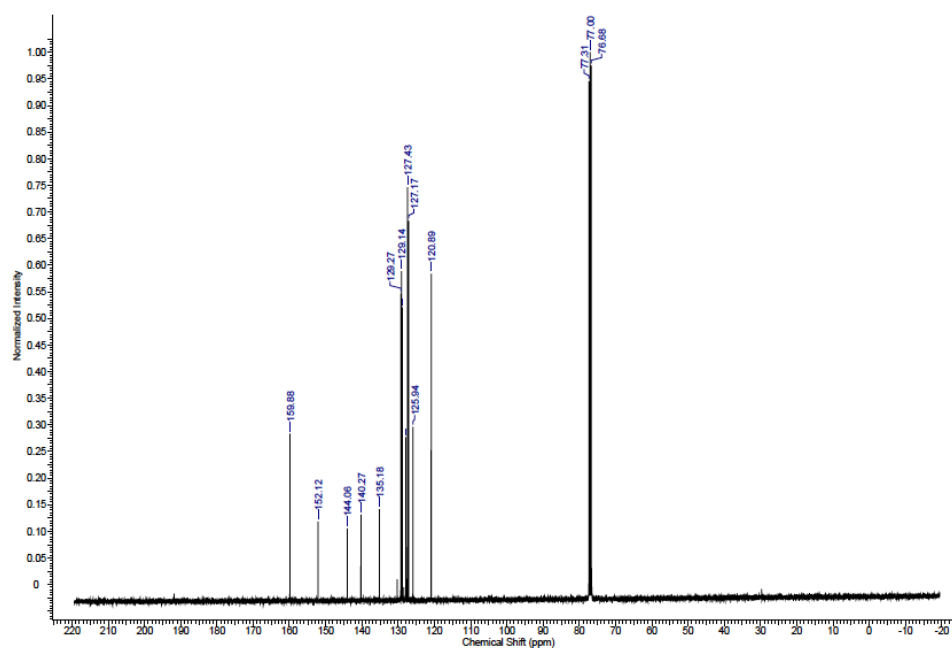
1-([1,1'-biphenyl]-4-yl)-N-phenylmethanimine (43)



^1H NMR (CDCl_3 , 400 MHz)

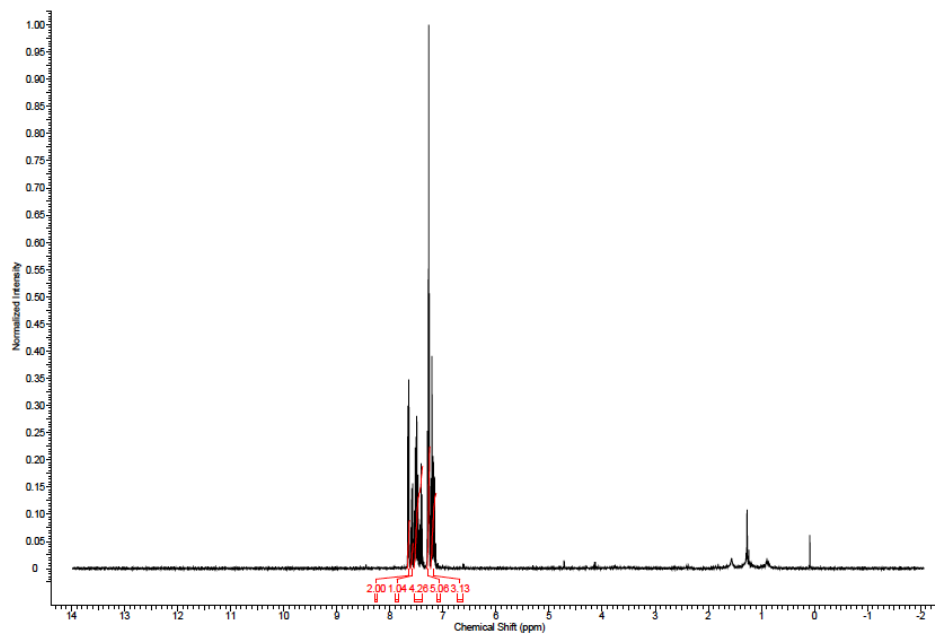
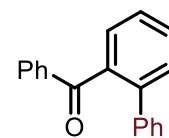


^{13}C NMR (CDCl_3 , 100 MHz)

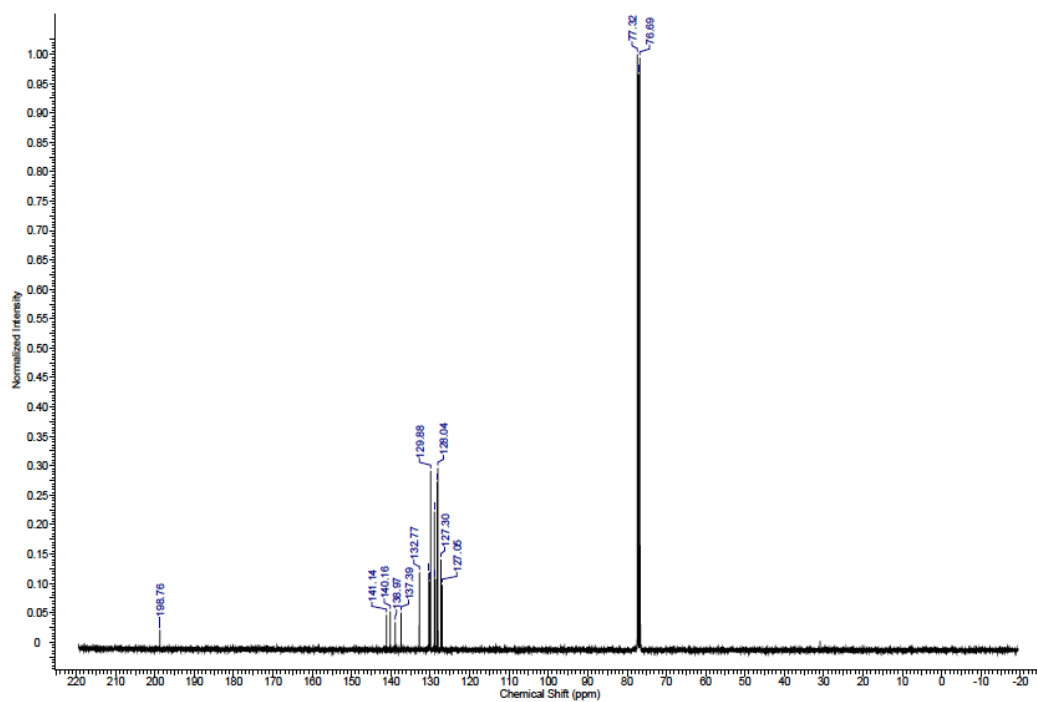


2-benzoylbiphenyl (44)

^1H NMR (CDCl_3 , 400 MHz)

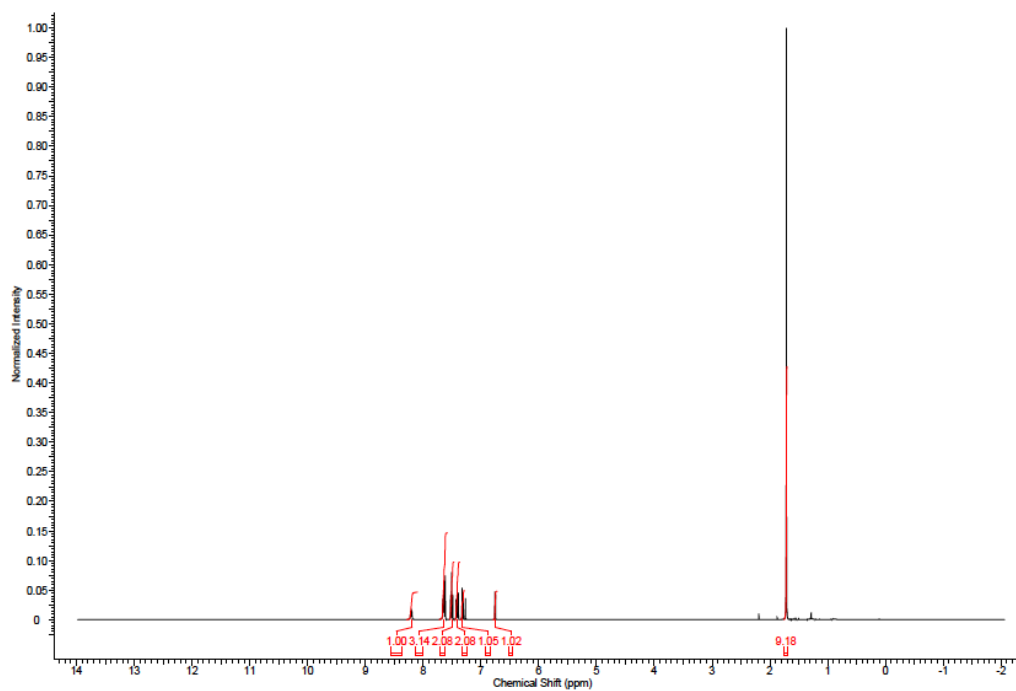
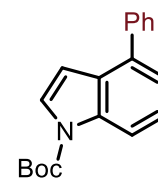


^{13}C NMR (CDCl_3 , 100 MHz)

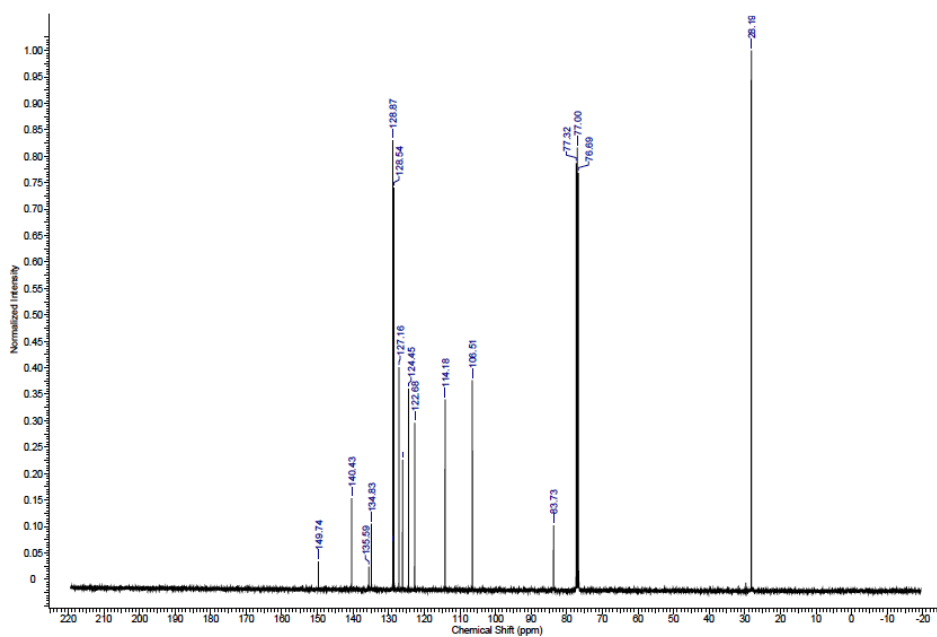


***tert*-butyl 4-phenyl-1H-indole-1-carboxylate (45)**

^1H NMR (CDCl_3 , 400 MHz)

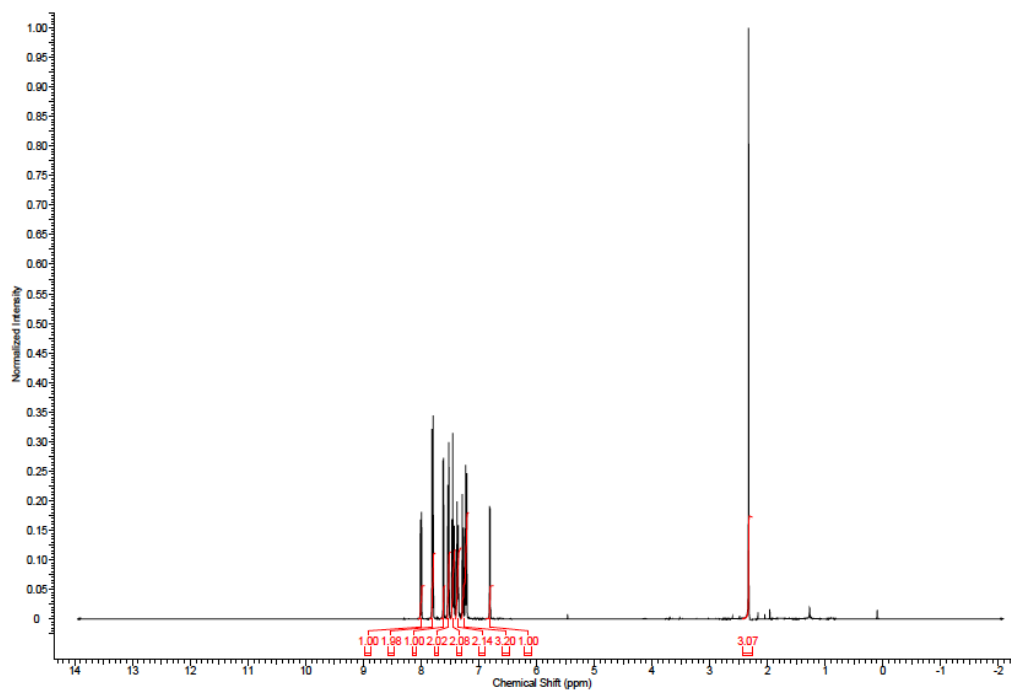
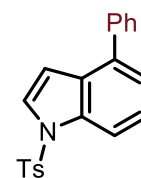


^{13}C NMR (CDCl_3 , 100 MHz)

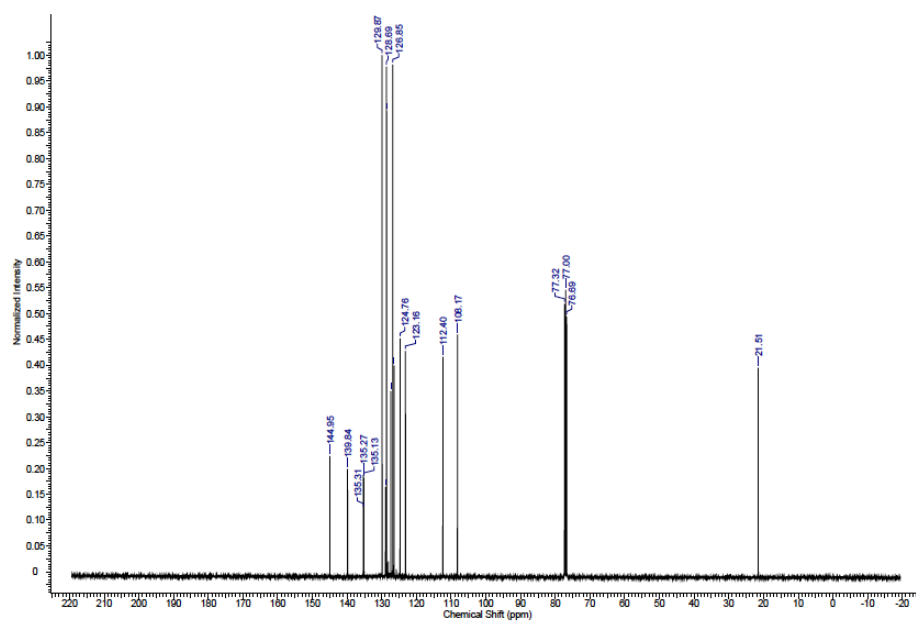


4-phenyl-1-tosyl-1H-indole (46)

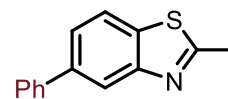
^1H NMR (CDCl_3 , 400 MHz)



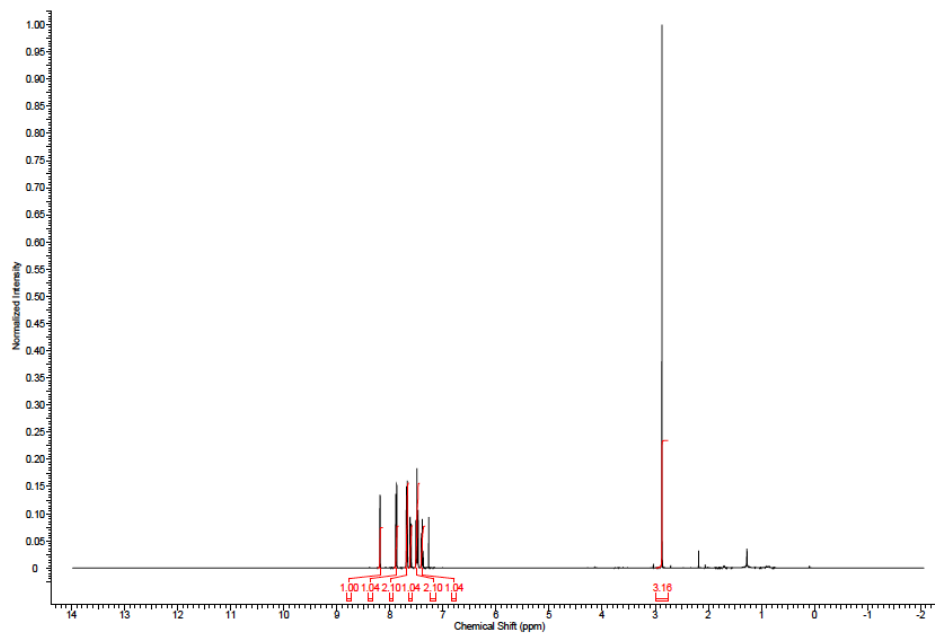
^{13}C NMR (CDCl_3 , 100 MHz):



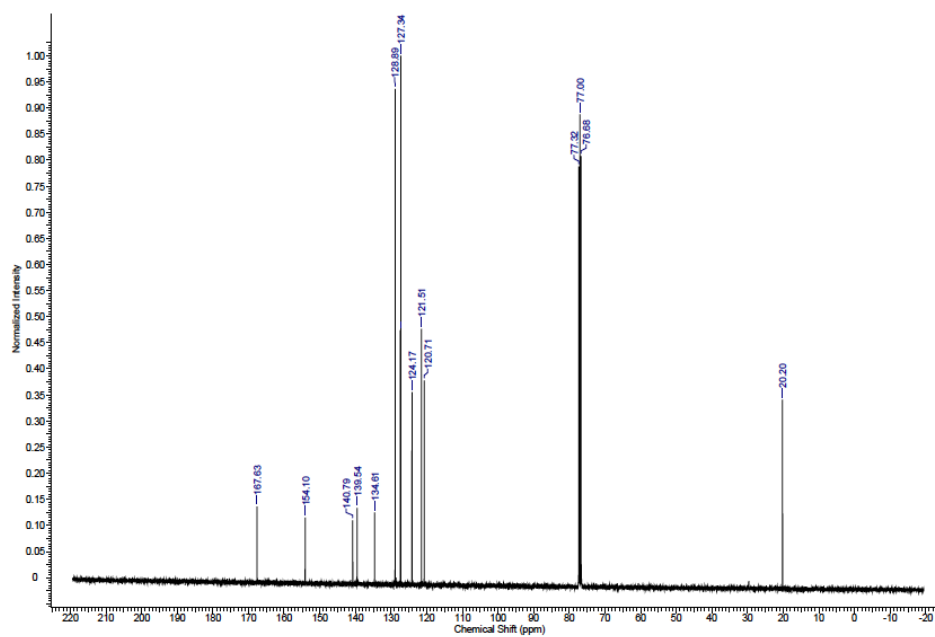
2-methyl-5-phenylbenzo[d]thiazole (47)



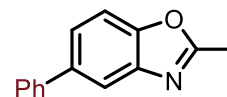
^1H NMR (CDCl_3 , 400 MHz)



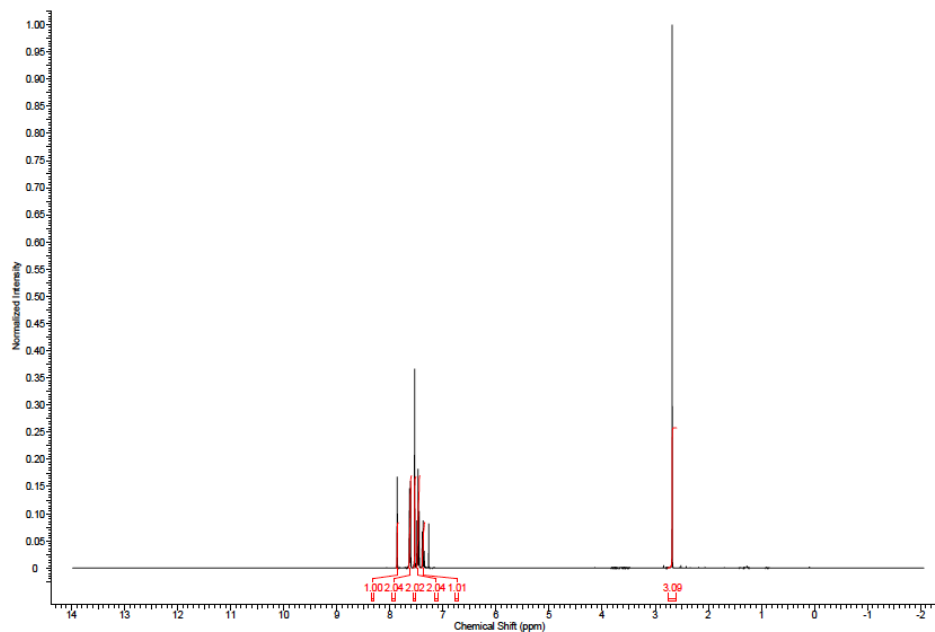
^{13}C NMR (CDCl_3 , 100 MHz)



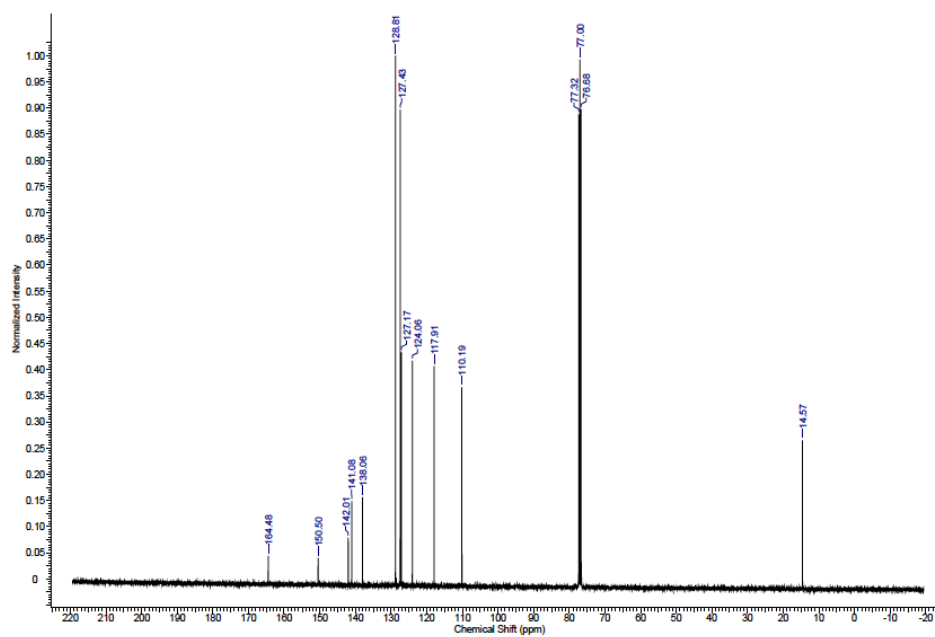
2-methyl-5-phenylbenzo[d]oxazole (48)



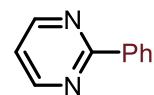
^1H NMR (CDCl_3 , 400 MHz)



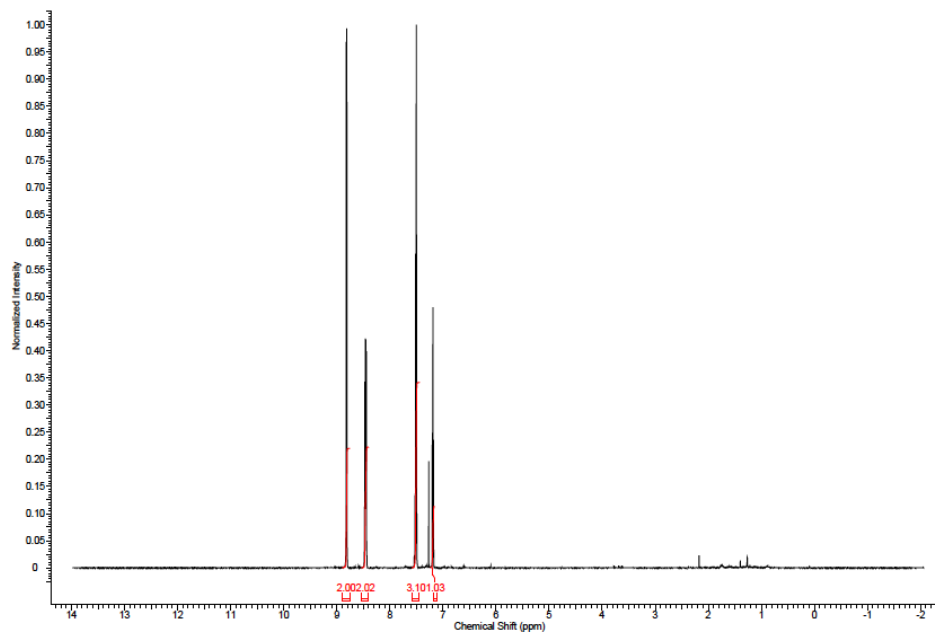
^{13}C NMR (CDCl_3 , 100 MHz)



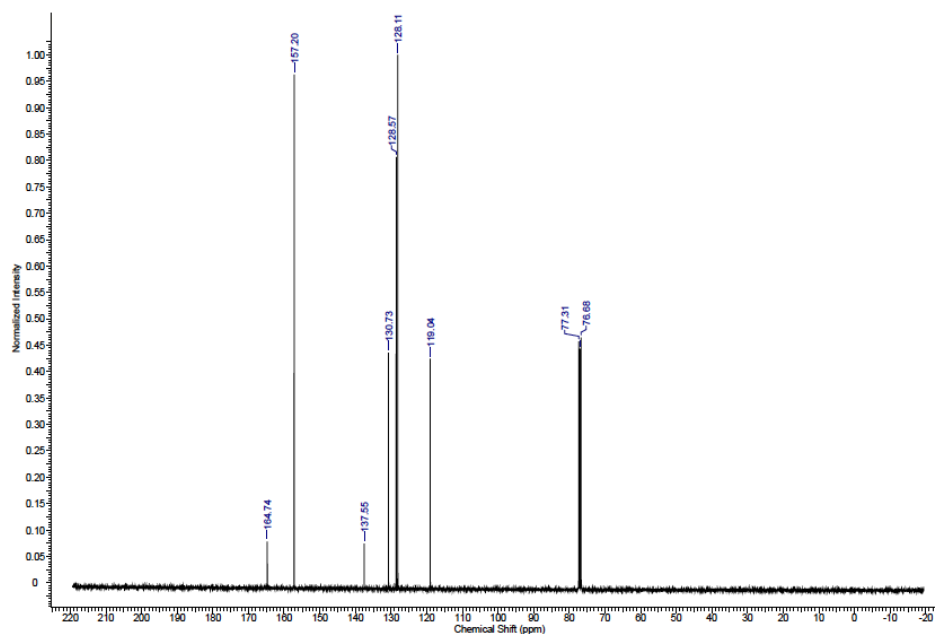
2-phenylpyrimidine (49)



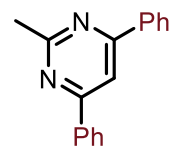
^1H NMR (CDCl_3 , 400 MHz)



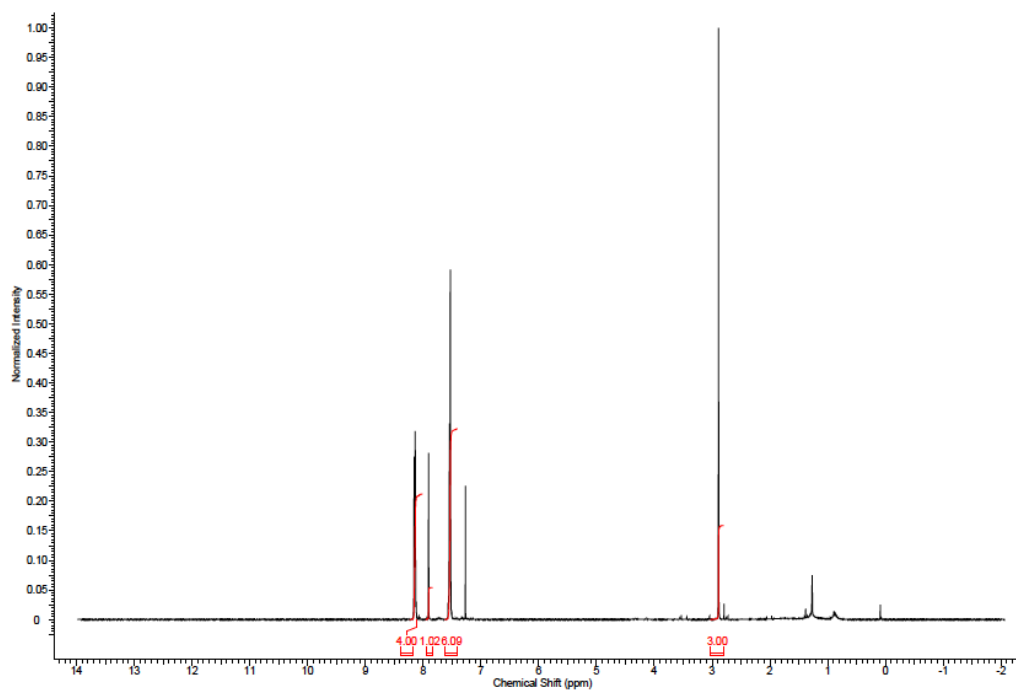
^{13}C NMR (CDCl_3 , 100 MHz)



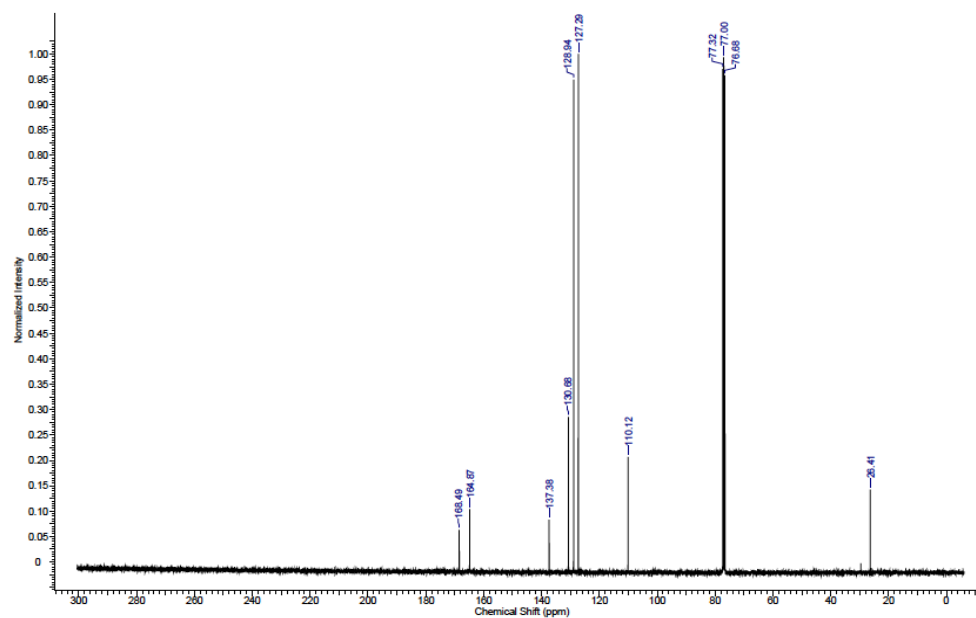
2-methyl-4,6-diphenylpyrimidine (50)



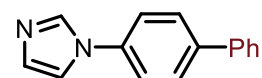
^1H NMR (CDCl_3 , 400 MHz)



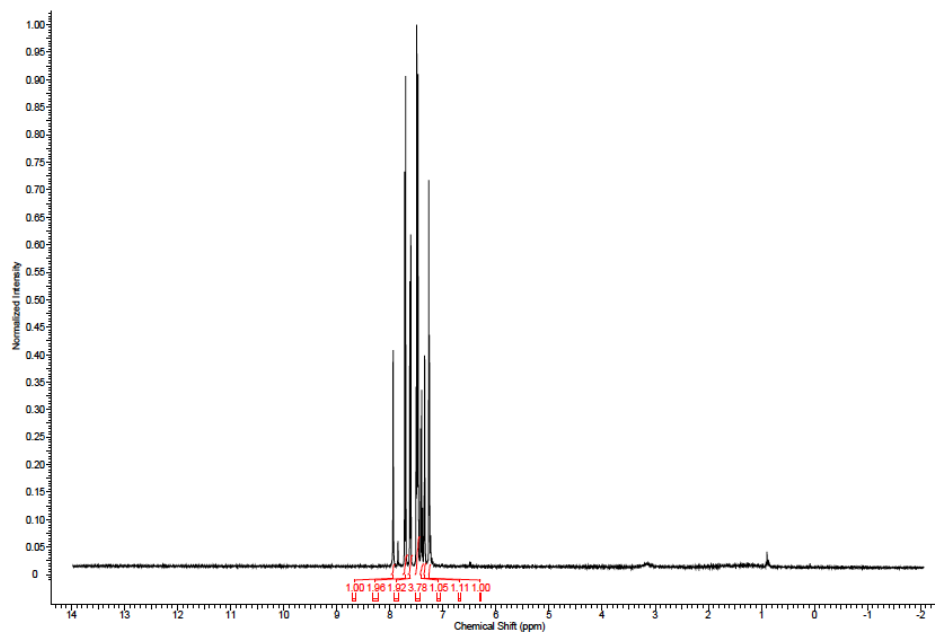
^{13}C NMR (CDCl_3 , 100 MHz)



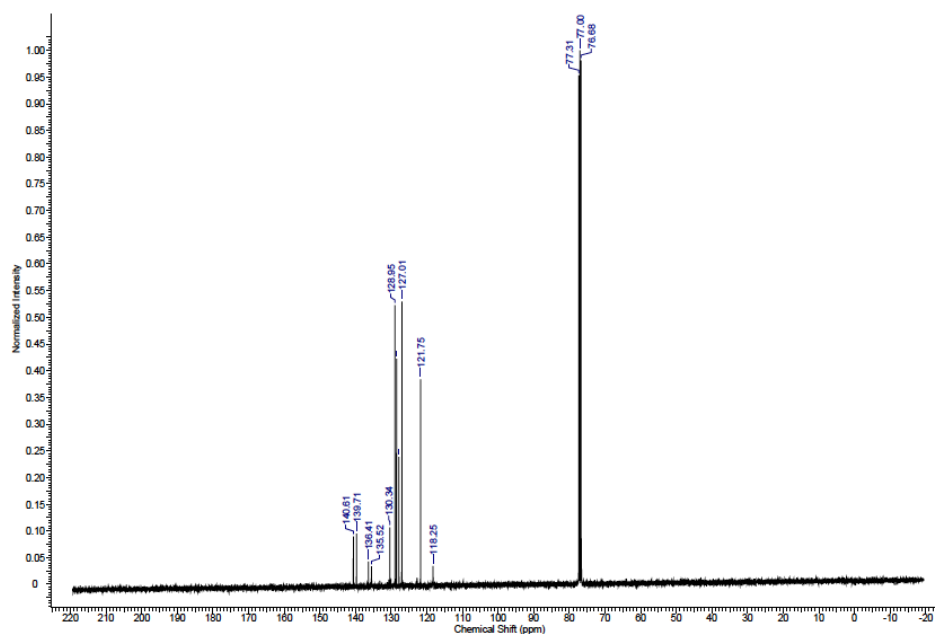
1-([1,1'-biphenyl]-4-yl)-1H-imidazole (51)



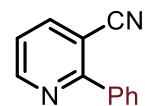
^1H NMR (CDCl_3 , 400 MHz)



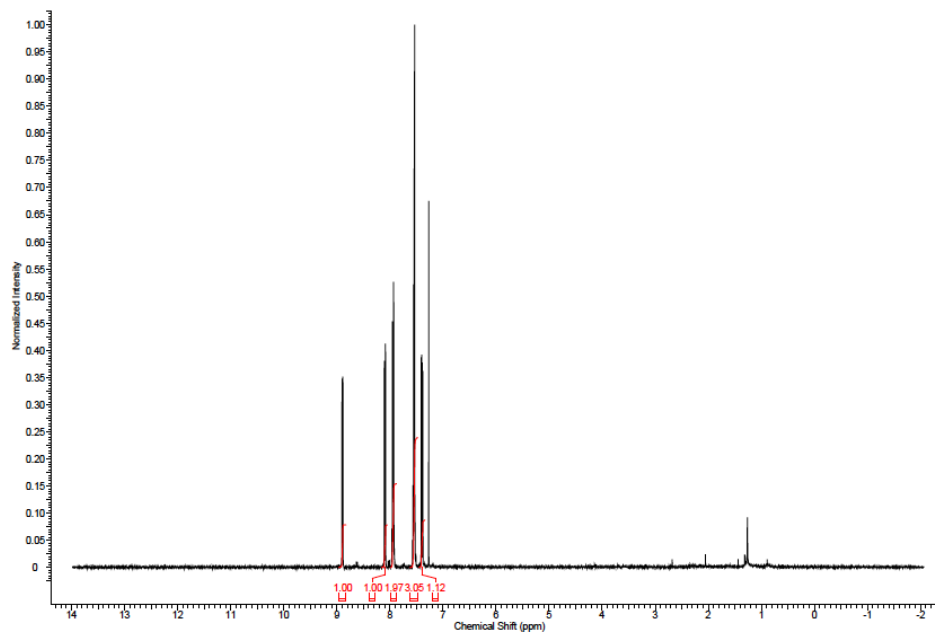
^{13}C NMR (CDCl_3 , 100 MHz)



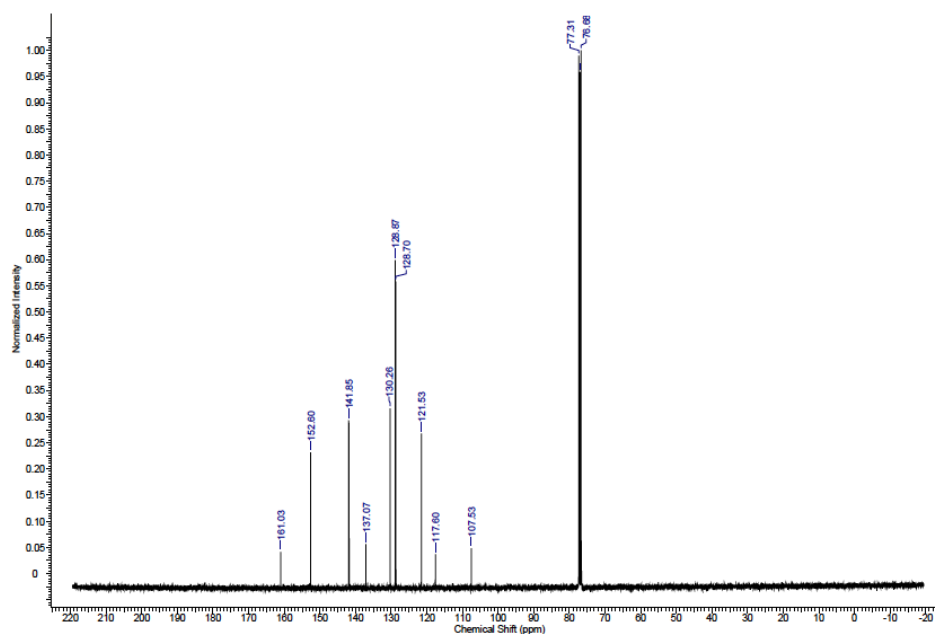
2-phenylnicotinonitrile (52)



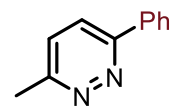
^1H NMR (CDCl_3 , 400 MHz)



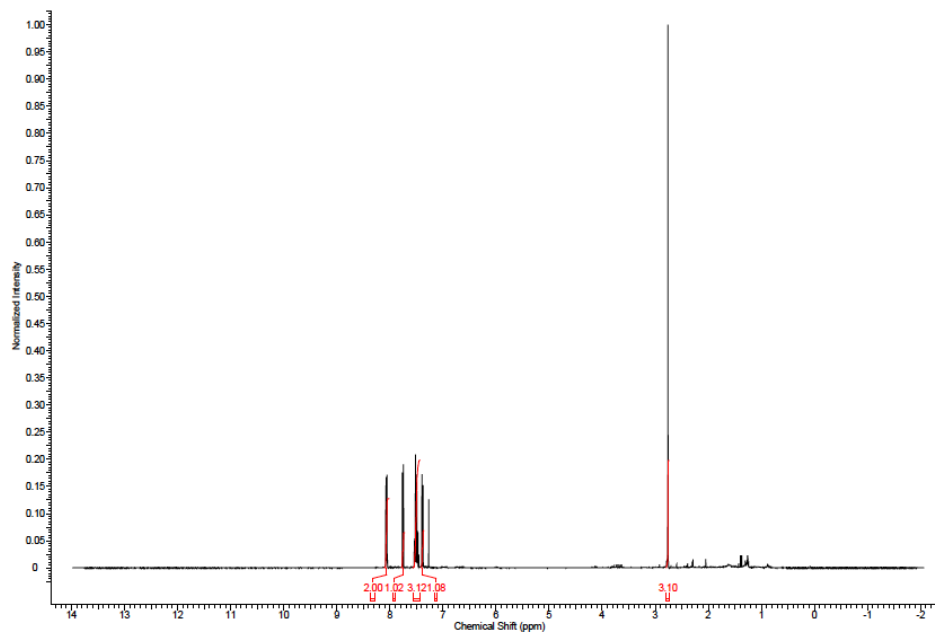
^{13}C NMR (CDCl_3 , 100 MHz)



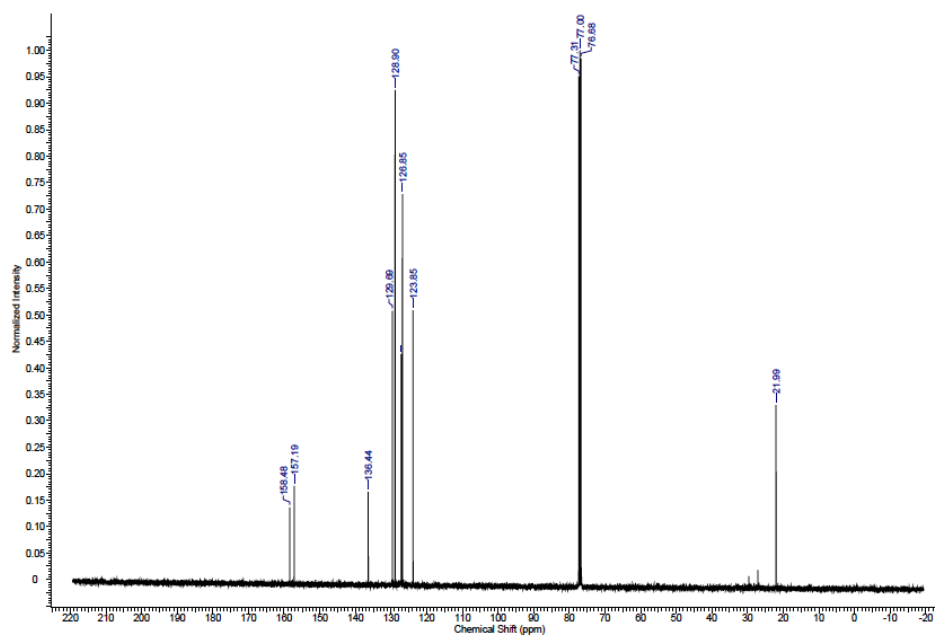
3-methyl-6-phenylpyridazine (53)



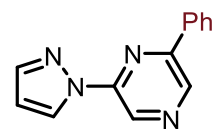
^1H NMR (CDCl_3 , 400 MHz)



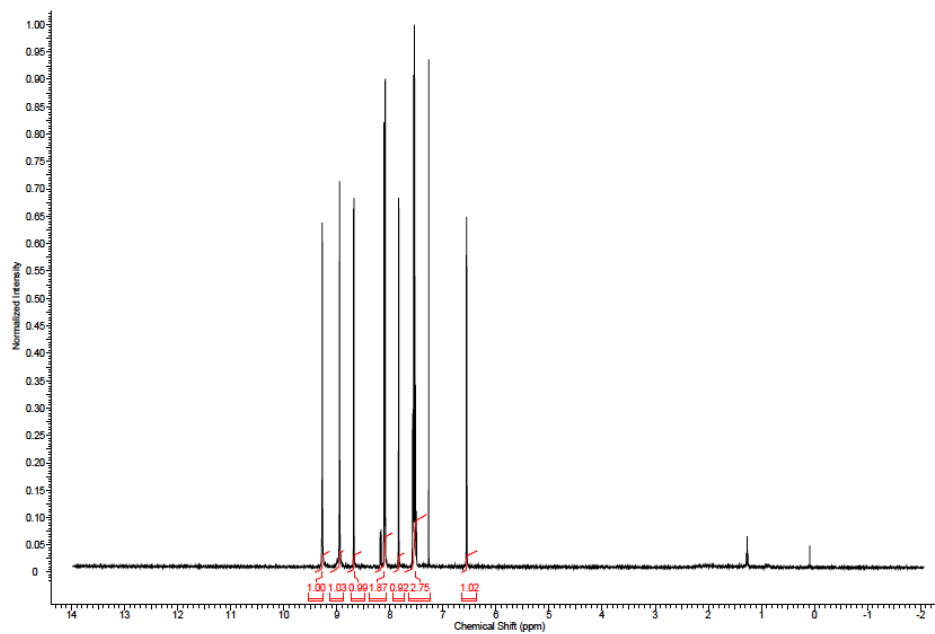
^{13}C NMR (CDCl_3 , 100 MHz)



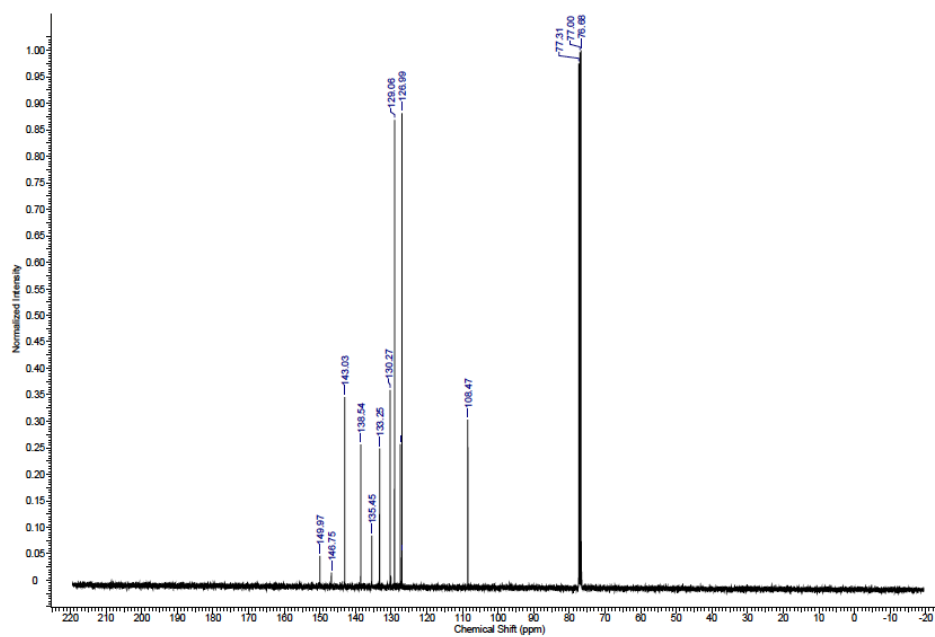
2-phenyl-6-(1H-pyrazol-1-yl)pyrazine (54)



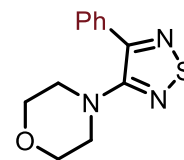
^1H NMR (CDCl_3 , 400 MHz)



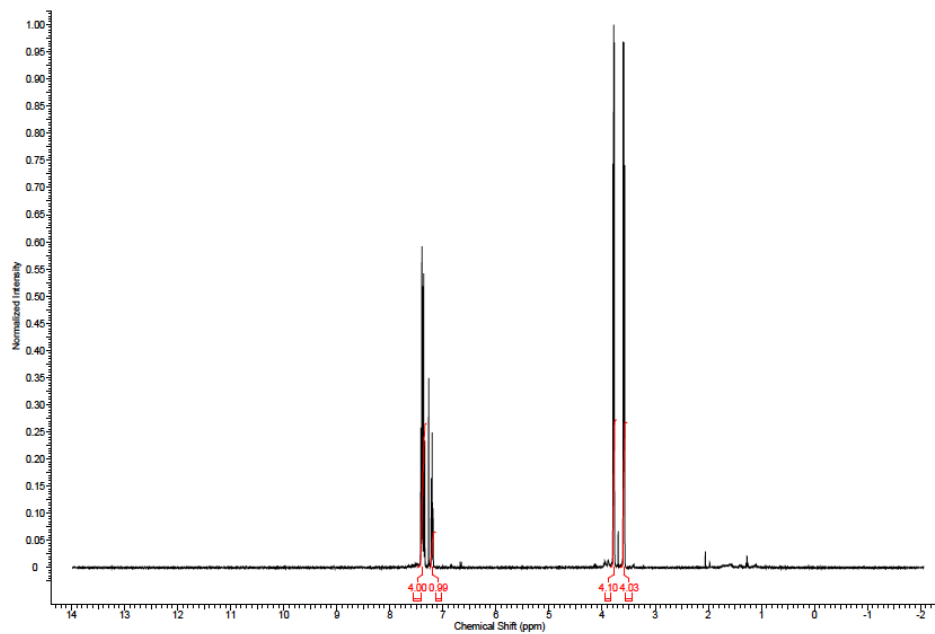
^{13}C NMR (CDCl_3 , 100 MHz)



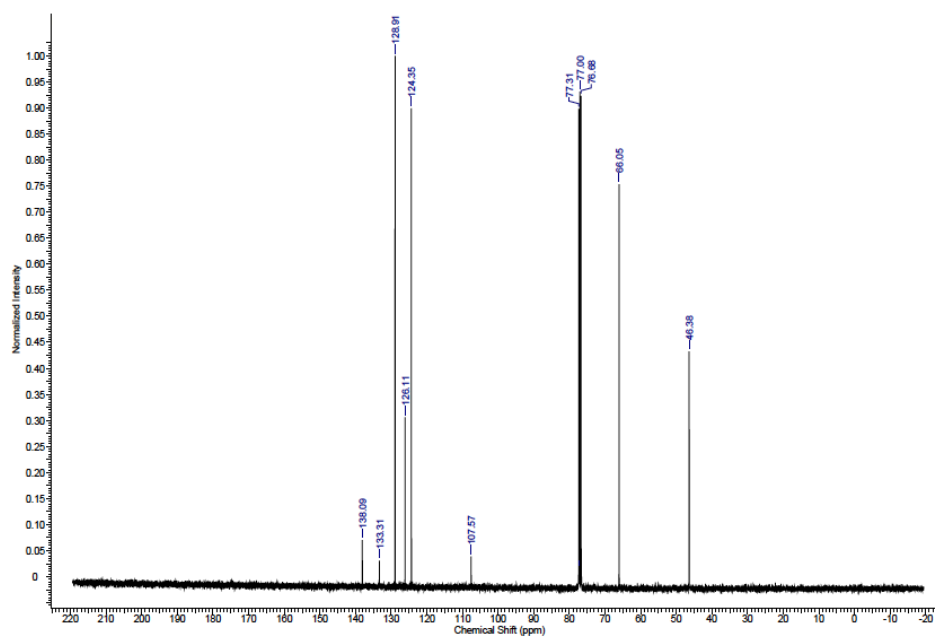
4-(4-phenyl-1,2,5-thiadiazol-3-yl)morpholine (55)



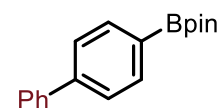
^1H NMR (CDCl_3 , 400 MHz)



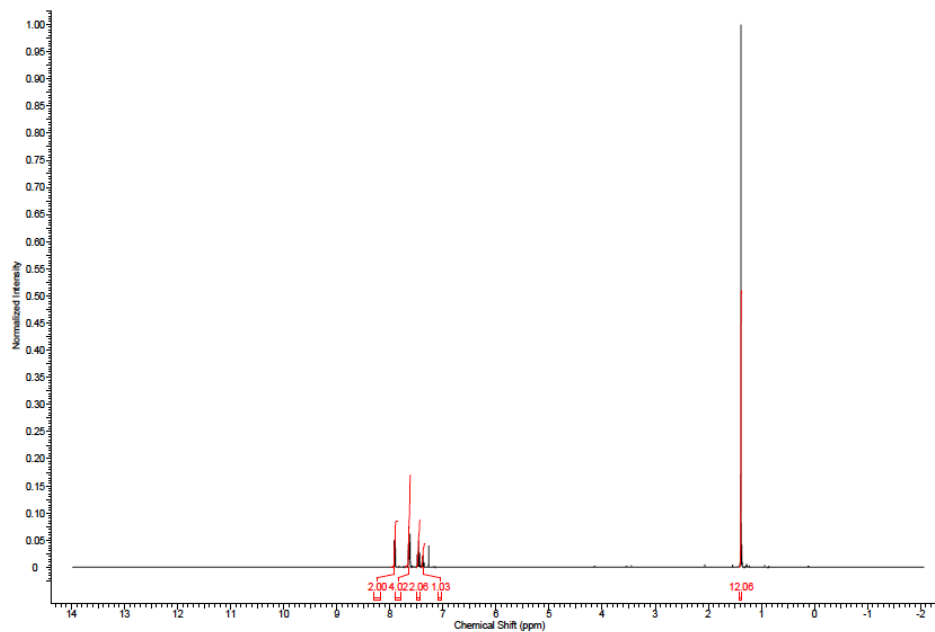
^{13}C NMR (CDCl_3 , 100 MHz)



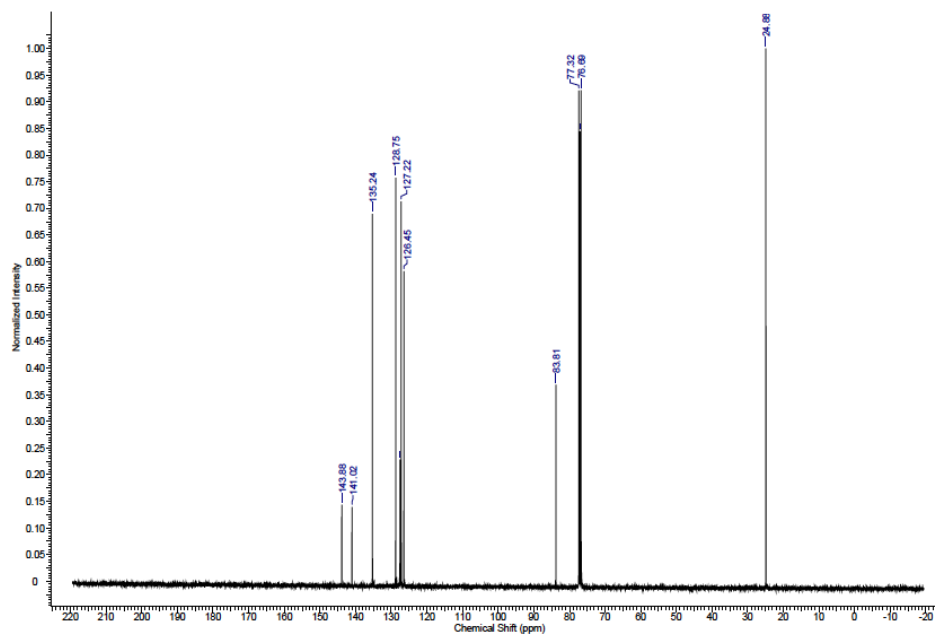
2-(biphenyl-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (56)



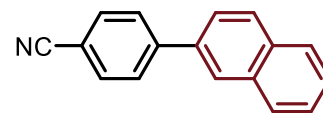
^1H NMR (CDCl_3 , 400 MHz)



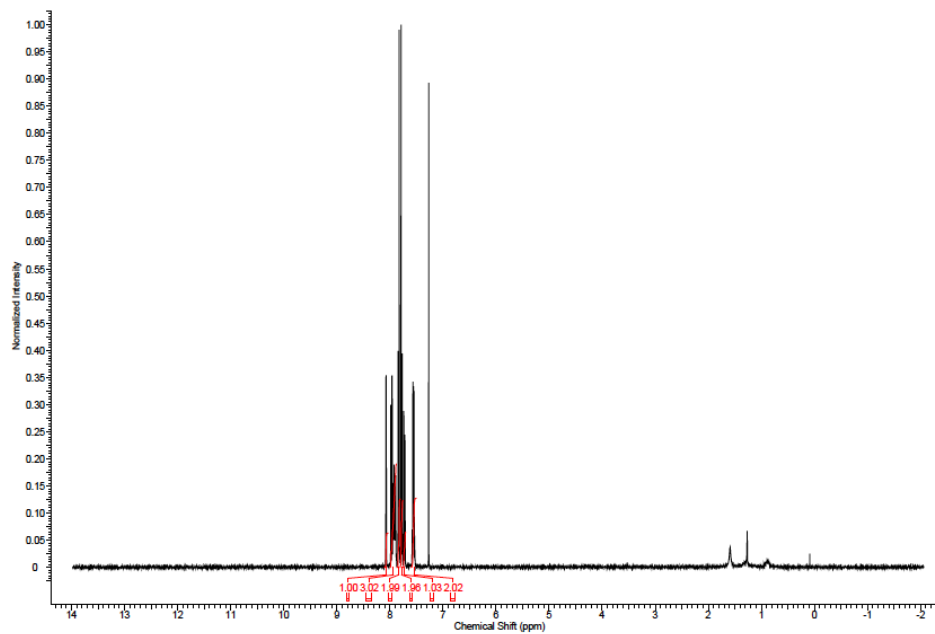
^{13}C NMR (CDCl_3 , 100 MHz)



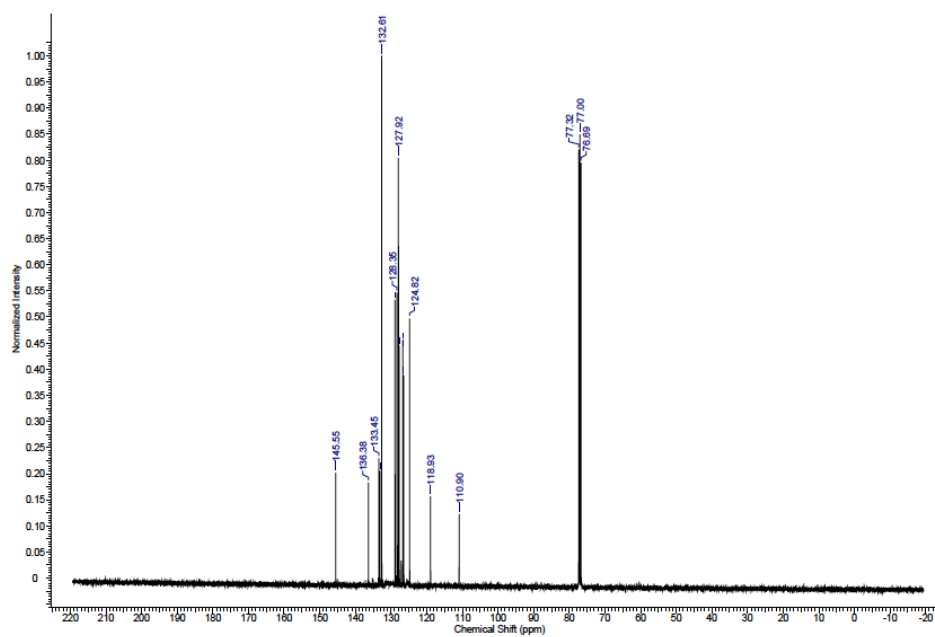
4-(naphthalen-2-yl)benzonitrile (57)



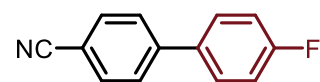
^1H NMR (CDCl_3 , 400 MHz)



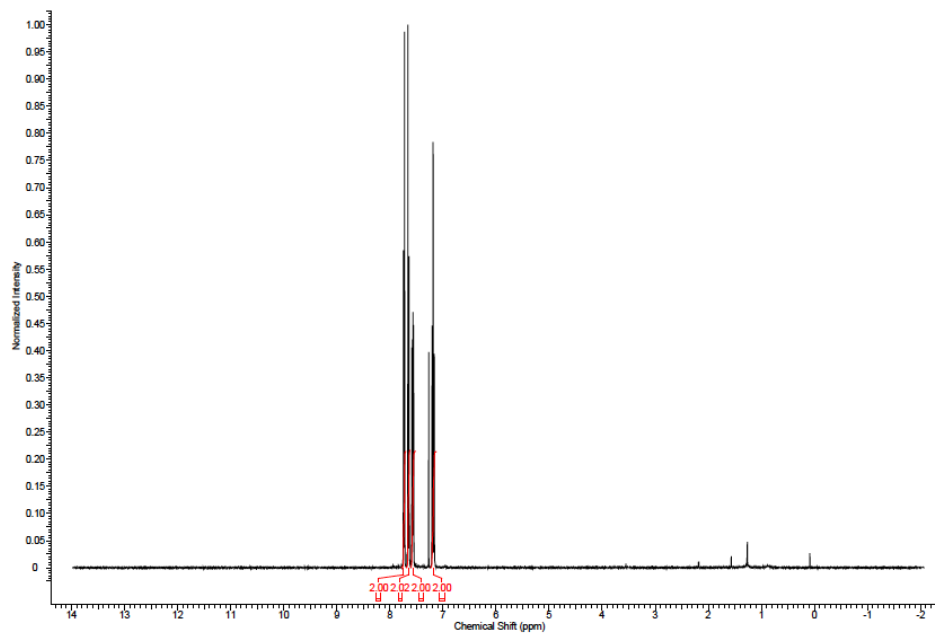
^{13}C NMR (CDCl_3 , 100 MHz)



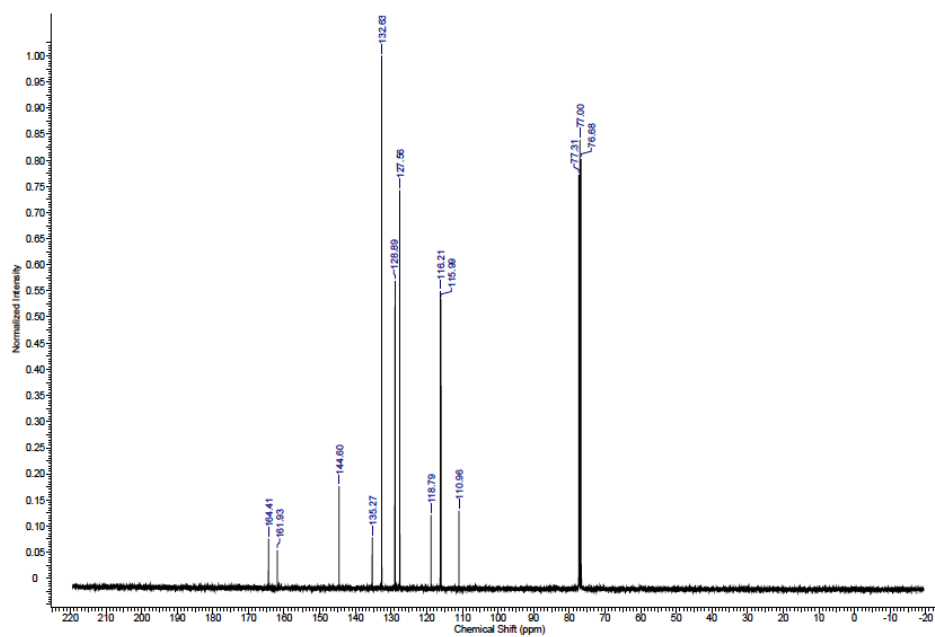
4'-fluoro-[1,1'-biphenyl]-4-carbonitrile (58)



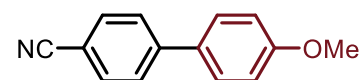
^1H NMR (CDCl_3 , 400 MHz)



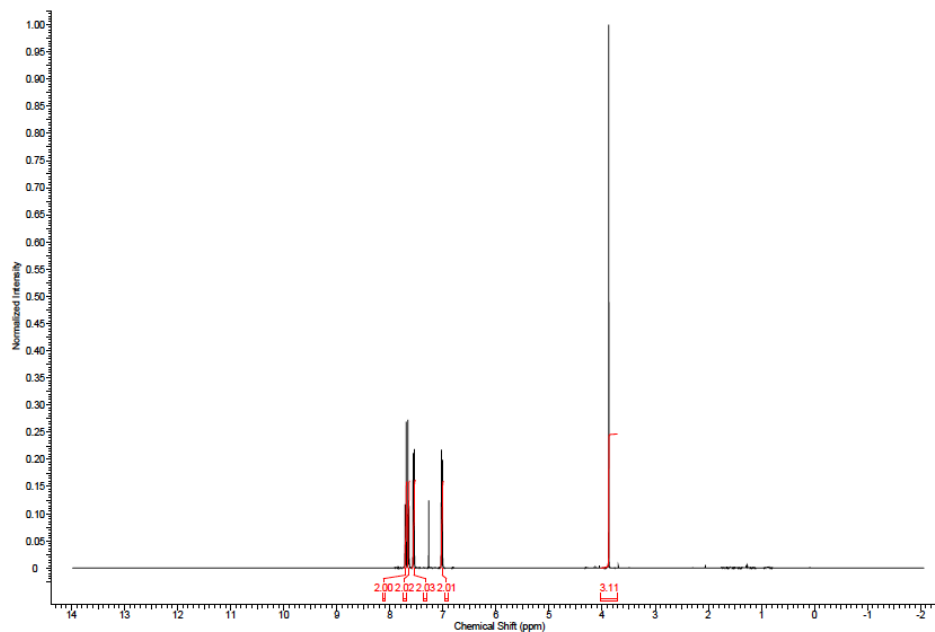
^{13}C NMR (CDCl_3 , 100 MHz)



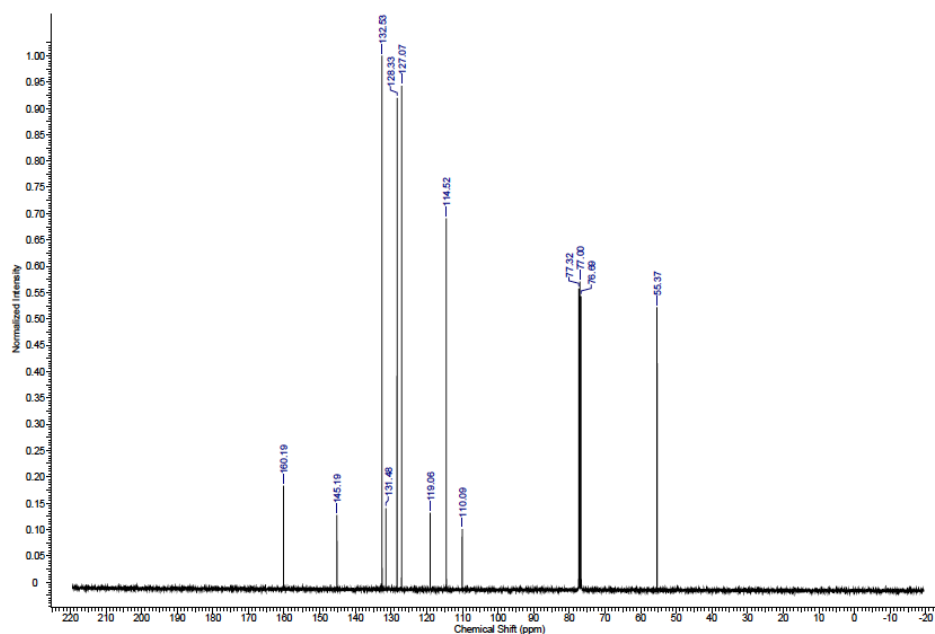
4'-methoxy-[1,1'-biphenyl]-4-carbonitrile (59)



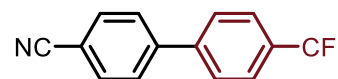
^1H NMR (CDCl_3 , 400 MHz)



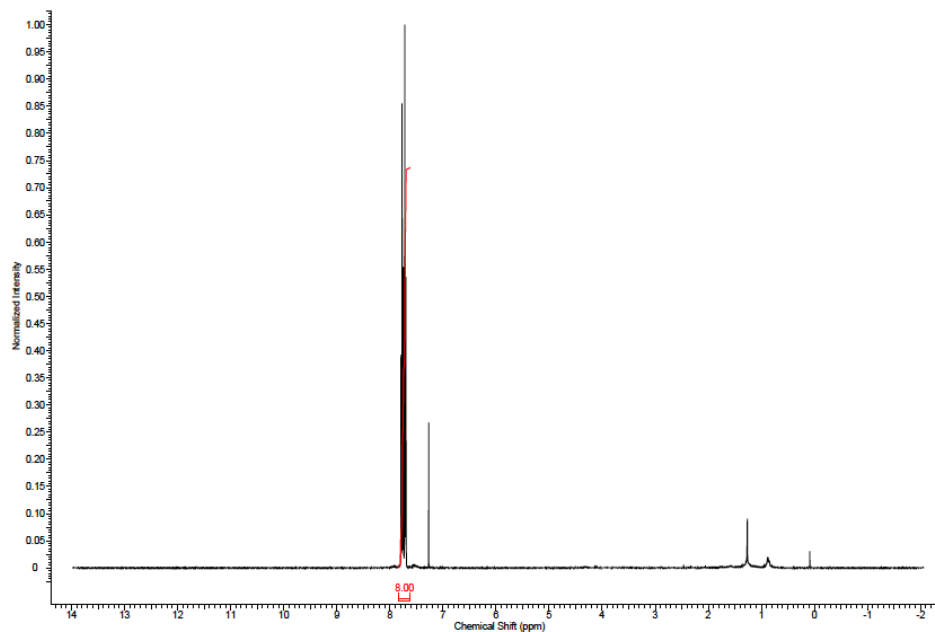
^{13}C NMR (CDCl_3 , 100 MHz)



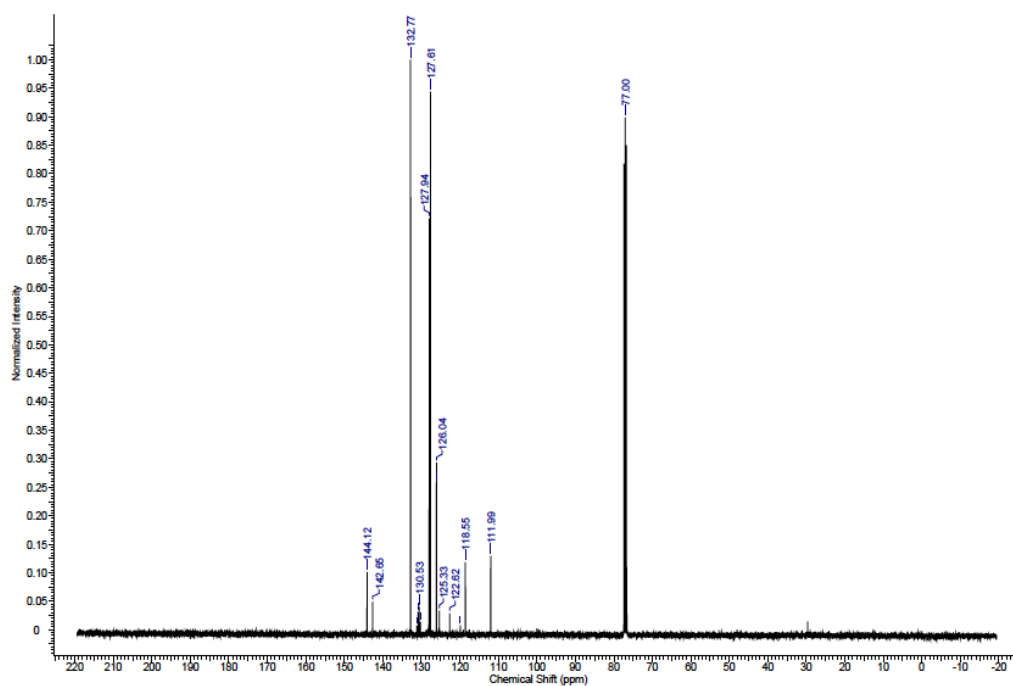
4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile (60)



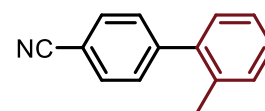
^1H NMR (CDCl_3 , 400 MHz)



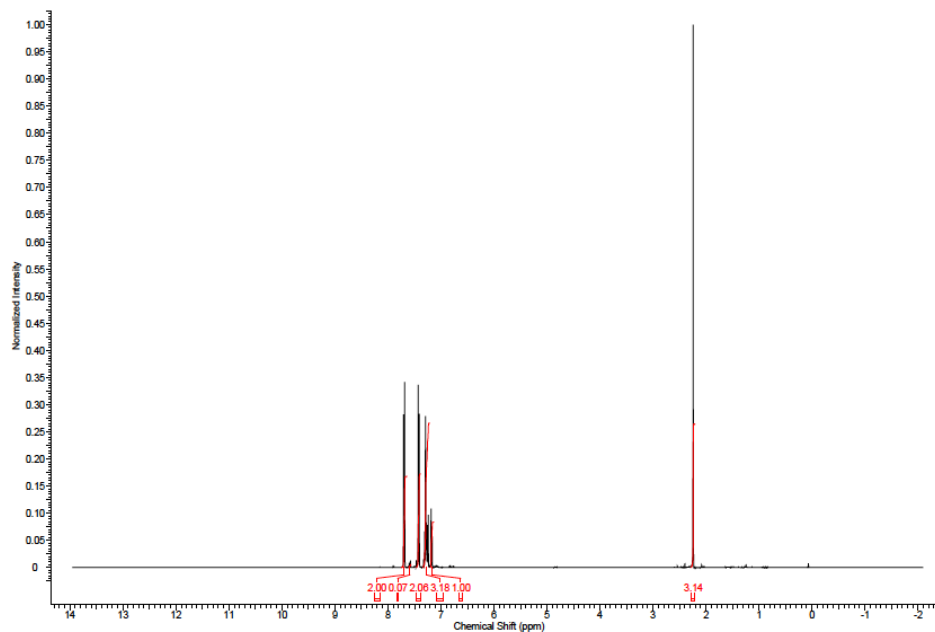
^{13}C NMR (CDCl_3 , 100 MHz)



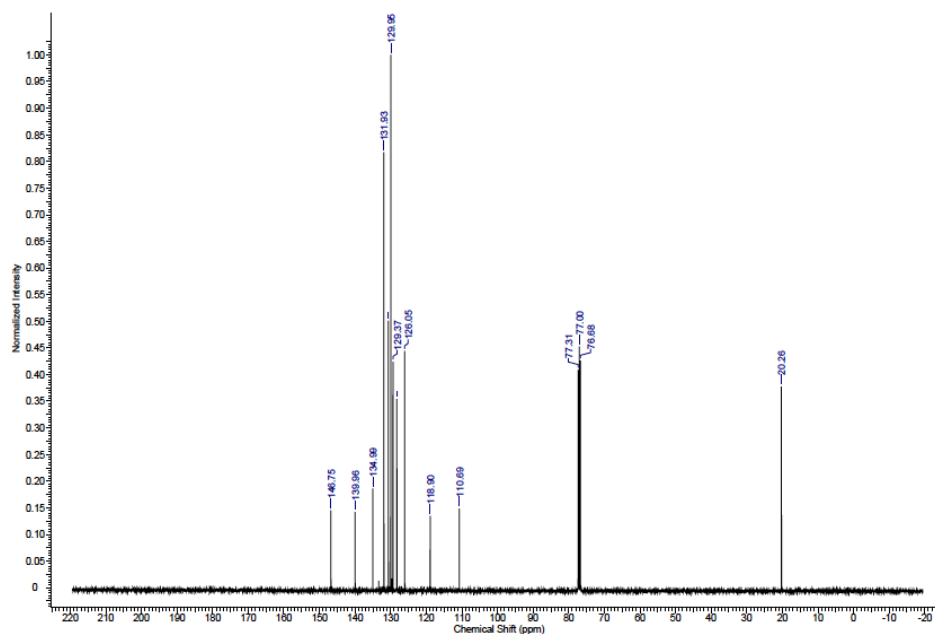
2'-methyl-[1,1'-biphenyl]-4-carbonitrile (61)



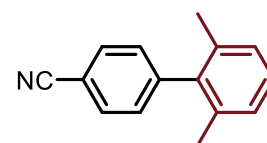
^1H NMR (CDCl_3 , 400 MHz)



^{13}C NMR (CDCl_3 , 100 MHz)



2',6'-dimethyl-[1,1'-biphenyl]-4-carbonitrile (62)



^1H NMR (CDCl_3 , 400 MHz)

