DEVELOPMENT OF COBALT AND NICKEL N-HETEROCYCLIC CARBENE COMPLEXES FOR CROSS-COUPLING REACTIONS

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Abstract

Cross-coupling, which relies on the use of transition metals, is among the most utilized chemical means of establishing carbon-carbon or carbon-heteteroatom bonds between appropriately functionalized sp, sp^2, or sp^3 centres. However, most cross-coupling reactions rely on the use of palladium to synthesize valuable synthetic targets. This is problematic for the chemical industry as palladium is limited in supply and expensive. Chemists have therefore sought to replace palladium with first-row transition metals (e.g., iron, cobalt and nickel) and recent reports on cobalt and nickel catalyzed cross-coupling reactions indicate that these metals can be used in this capacity. Unfortunately, protocols developed (so far) for these metals are unsuitable for the synthesis of targets with base-sensitive functional groups as they involve strongly basic reaction conditions.

Research in this thesis aims to develop both cobalt and nickel pre-formed catalysts that will display high catalytic activity in mildly basic reaction conditions. Current methodologies for cobalt and nickel cross-coupling reactions use either phosphine ligands or NHC ligands of moderate steric bulk (IMes or IPr). Recent advancements in the development of *Pd-PEPPSI* catalysts have demonstrated that both pre-forming the catalyst and using larger NHC ligands (*IPent*, *IPent*^{Cl}, or *IHept*) are required for high catalytic activity in weakly basic conditions. Thus, it was hypothesized that the development of pre-formed cobalt and nickel NHC complexes analogous to their Pd counterparts would improve reactivity in Negishi, Suzuki-Miyaura, and Buchwald-Hartwig amination cross-coupling reactions.

$Co(IPent)Cl_2(Pyr)$, $Co(IPent^{Cl})Cl_2(Pyr)$, and $Co_2IPr_2(OAc)_4$ were prepared, identified by X-ray crystallography, and evaluated in preliminary Negishi cross-coupling reactions. These complexes were found to be ineffective, but $Co_2IPr_2(OAc)_4$ was found to be effective for Suzuki-Miyaura

cross-coupling. A base screen was performed to enable the use of weak bases, however, the reaction only worked by pre-forming the boronate with n-BuLi, rendering the reaction conditions intolerant of base-sensitive functional groups.

$[Ni(IPr)]_2(\mu\text{-}Cl)_2$, Ni(IPr)Cl(allyl), and Ni(IPent)Cl(allyl) complexes were synthesized and evaluated in Buchwald-Hartwig aminations. Several bases were examined for these reactions but only sodium tert-butoxide was found to be effective. The presence of TEMPO and BHT in these transformations proved deleterious suggesting the involvement of radical intermediates. Finally, stoichiometric reactions were performed to isolate intermediates in the catalytic cycle, supporting the formation of nickel(0).

Acknowledgements

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Ad	Adamantyl
BHA	Buchwald-Hartwig amination
BHE	β-hydride elimination
BISBI	2,2'-Bis(diphenylphosphinomethyl)-1,1'-biphenyl
biy	1,3-dibutylimidazolin-2-ylidene
BHT	3,5-Di-*tert*-4-butyl-4-methylphenol (butylated hydroxytoluene)
BippyPhos	5-(Di-tert-butylphosphino)-1, 3, 5-triphenyl-1H-[1,4]bipyrazole
BINAP	2,2-Bis(diphenylphosphino)-1,1-binaphthalene
BrettPhos	2-Dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-triisopropylbiphenyl
*t*Bu	*tert*-butyl
°C	degree Celsius
cod	Cyclooctadiene
cPent	1,3-bis(2,6-dicyclopenty1phenyl)imidazole-2-ylidine
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
DME	1,2 – Dimethoxyethane
DMF	Dimethylformamide

DMI	1,3-Dimethyl-2-imidazolidinone
DMSO	Dimethylsulfoxide
DPEphos	Bis[(2-diphenylphosphino)phenyl] ether
dppb	1,4-Bis(diphenylphosphino)butane
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	Bis(diphenylphosphino)ferrocene
dppp	1,2-Bis(diphenylphosphino)propane
dppr	Bis(diphenylphosphino)ruthenocene
equiv.	Molar equivalents
Et	Ethyl
IAd	1,3-Diadamantylimidazol-2-ylidine
IBiox	Bisoxazolinium-derived NHC
IEt	1,3-Bis(2,6-diethylphenyl)imidazol-2-ylidine
IHept	1,3-Bis(2,6-di(4-hepty)phenyl)imidazole-2-ylidine
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidine
IPent	1,3-Bis(2,6-di(3-pentyl)phenyl)imidazole-2-ylidine
$IPent^{Cl}$	1,3-Bis(2,6-di(3-pentyl)phenyl)-4,5-dichloroimidazol-2-ylidine
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazole-2-ylidine

IPr*	1,3-Bis(2,6-bis(di-para-tolylmethyl)phenyl)imidazole-2-ylidine
IPr*^{OMe}	*N*,*N*′-bis[2,6-bis(diphenylmethyl)-4-methoxyphenyl]imidazol-2-ylidene
IPr^{Cl}	1,3-bis(2,6-diisopropylphenyl)-4,5-dichloroimidazol-2-ylidine
JosiPhos	(R)-1-[(SP)-2-(Diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine
KHMDS	Potassium bis(trimethylsilyl)amide
KTC	Kumada-Tamao-Corriu
Me	Methyl
MorDalPhos	Di(1-adamantyl)-2-morpholinophenylphosphine
NHC	*N*-heterocyclic carbene
NMR	Nuclear magnetic resonance
OA	Oxidative addition
$P(Cy)_3$	Tricyclohexylphosphine
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
PEPPSI	Pyridine-enhanced pre-catalyst preparation, stabilization, and initiation
pKa	Negative logarithmic acid dissociation constant
PTFE	Poly(tetrafluroethylene)
rt	Room temperature
RE	Reductive elimination

RuPhos	dicyclohexy 1(2' ,6' -diisopropoxybipheny1-2-yl)phosphine
SIMes	1,3-Bis(2,4,6-trimethylphenyl)imidazolidine-2-ylidine
SIPr	1,3-Bis(2,6-diisopropylphenyl)imidazolidine-2-ylidine
SPhos	2-Dicyclohexylphosphino-2,6-dimethoxybiphenyl
TEP	Tolman's electronic parameter
TMEDA	Tetramethylethylenediamine
tmiy	1,3-bis(4-tolylmethyl)imidazolin-2-ylidene
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TON	Turn Over Number
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

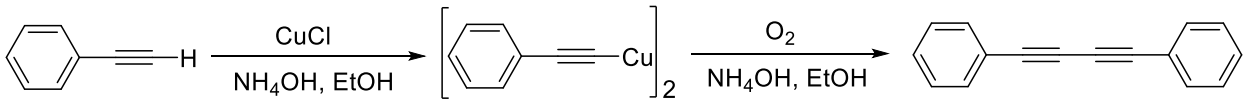
Chapter 1 − Introduction

1.1 – Introduction to Cross-coupling Reactions

Richard Heck, Ei-ichi Negishi,[1] and Akira Suzuki[2] were awarded the 2010 Nobel Prize for the development of Pd-mediated cross-coupling reactions, which is defined as the formation of carbon-carbon or carbon-heteroatom bonds between appropriately functionalized sp, sp^2, or sp^3 centres. Cross-coupling has become a highly used reaction in the chemical community and is an indispensable process used by pharmaceutical, agrochemical, and material industries.

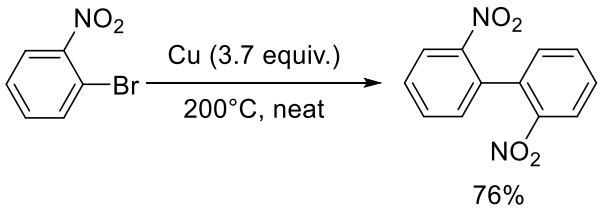
1.1.1 – Stoichiometric Metal-mediated Homocoupling Reactions

Cross-coupling transformations were first documented well over a century ago. One of the earliest examples was a report by Glaser that described the homocoupling of metallic acetylides to afford diphenyldiacetylene (Scheme 1).[3] The new method to construct the C(sp)-C(sp) bond was highly advantageous and was used in Baeyer's synthesis of indigo in 1882.[4]



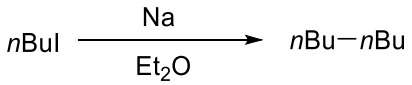
Scheme 1. Copper chloride-mediated homocoupling of phenyl acetylene.

Following the development of C(sp)-C(sp) homocoupling, Ullmann reported the $C(sp^2)$-$C(sp^2)$ copper-promoted dimerization of 2-bromo and 2-chloronitrobenzene (Scheme 2).[5]

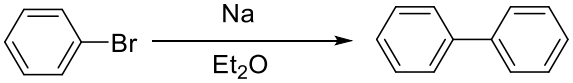


Scheme 2. Copper mediated homocoupling of 2-bromonitrobenzene.

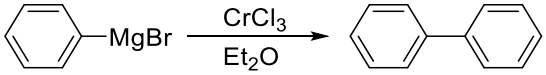
In 1855, Wurtz reported the homodimerization of alkyl halides in the presence of metallic sodium (Scheme 3).[6] Fittig expanded the work to the homodimerization of aryl halides, however, the pyrophoric properties of sodium and potassium metals were problematic (Scheme 4).[7] Milder methodologies to dimerize phenyl magnesium bromide using stoichiometric chromium (III) chloride were later reported by Bennett and Turner (Scheme 5).[8]



Scheme 3. Sodium-mediated homocoupling of alkyl halides.



Scheme 4. Sodium-mediated homocoupling of aryl halides.



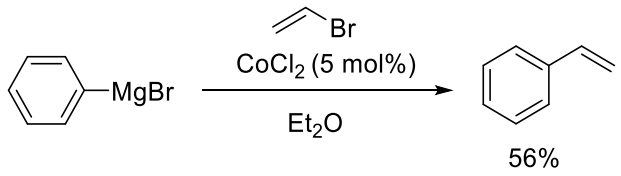
Scheme 5. Chromium chloride-mediated homocoupling of aryl Grignard reagents.

1.1.2 – Introduction to Catalysis

Although Ullmann reported the use of catalytic copper to cross-couple phenols with aryl halides to form C-O bonds in 1905, the catalytic formation of C-C bonds remained elusive until the beginning of the 20th century.[4] In the interwar period of World War 1, French chemist André Job reported the catalytic cross-coupling of phenylmagnesium bromide in the presence of nickel chloride, ethylene, carbon monoxide, hydrogen, and other gases.[9] Unfortunately, Job's work failed to gain attention from the scientific community.[4]

1.1.3 – Metal-catalyzed Cross-coupling Reactions

Kharasch reported the cobalt-catalyzed C(sp^2)-C(sp^2) homocoupling of Grignard reagents (1941). In 1943, the work expanded to include the coupling of vinyl bromide with aryl organo-magnesium reagents using cobalt chloride.[10] This represented the earliest report of a metal-catalyzed cross-coupling reaction where a catalytic amount of metal is used to connect two different coupling partners (Scheme 6).[4]

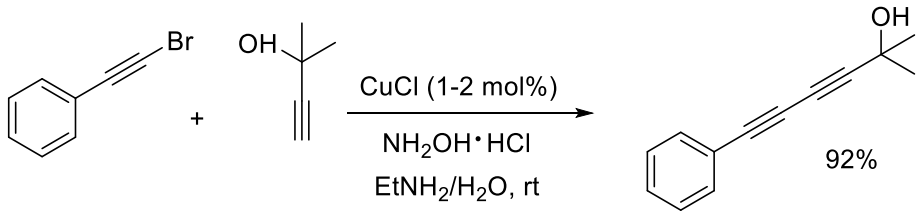


Scheme 6. Cobalt chloride-catalyzed cross-coupling of phenyl magnesium bromide with allyl bromide.

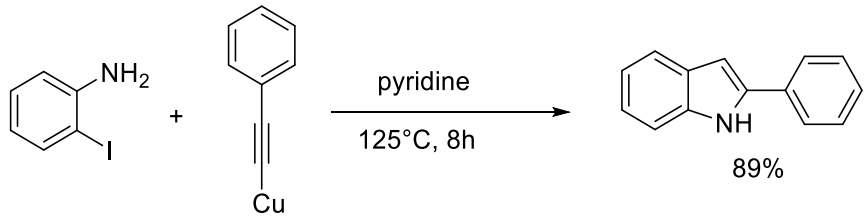
Although the problem of using stoichiometric quantities of metals was solved by Kharasch, selectivity remained an issue. Specifically, the ratio of cross-coupled to homocoupled product was highly substrate specific and had largely varied yields. Early selective C(sp)-C(sp) cross-couplings were reported by Cadiot and Chodkiewicz of bromoalkynes in 1957 using catalytic quantities of copper(I) chloride (Scheme 7).[4] In 1963, Castro and Stephens reported the selective C(sp^2)-C(sp) cross-coupling of aryl or vinyl halides with alkynes derivatized as copper salts (Scheme 8).[11] They found that when the aryl iodide had a nucleophilic heteroatom in the ortho-position, the intermediate acetylene underwent cyclization giving the indole or benzofuran product exclusively.

These reports indicated that there were three requirements for a selective cross-coupling reaction: i) a requirement for an organohalide as a coupling partner; ii) the organometallic coupling partner

was to be added in stoichiometric quantities; and iii) a transition metal was to be added in stoichiometric or catalytic quantities.[4]



Scheme 7. Copper chloride-catalyzed cross-coupling of alkynes.



Scheme 8. Cross-coupling of aryl iodides with cuprous acetylides.

1.1.4 − Palladium-catalyzed Cross-coupling

The first palladium cross-coupling of organomercurial compounds with alkenes was developed by Richard Heck,[12] however, the toxicity of mercury reagents made the protocol undesirable. Mizoroki improved the protocol by replacing the organomercurial reagents with aryl iodides.[13] Later, reports from both chemists led to the foundation of the Mizoroki-Heck reaction. Other Pd-catalyzed cross-coupling methodologies that were developed used different organometallic reagents. They included the Kumada-Tamao-Corriu (KTC) reaction (organomagnesium),[14] Negishi reaction (organozinc),[15] the Suzuki-Miyaura[16] reaction (organoboron), the Hiyama reaction (organosilicon),[17] the Stille-Kosugi[18] reaction (organostannane), and Sonogashira[19] reaction (in-situ derived copper acetylides). In addition to C-C bond formation, the Buchwald-

Hartwig amination (BHA)[20,21] was developed to cross-couple aryl halides with alkyl amines and anilines.

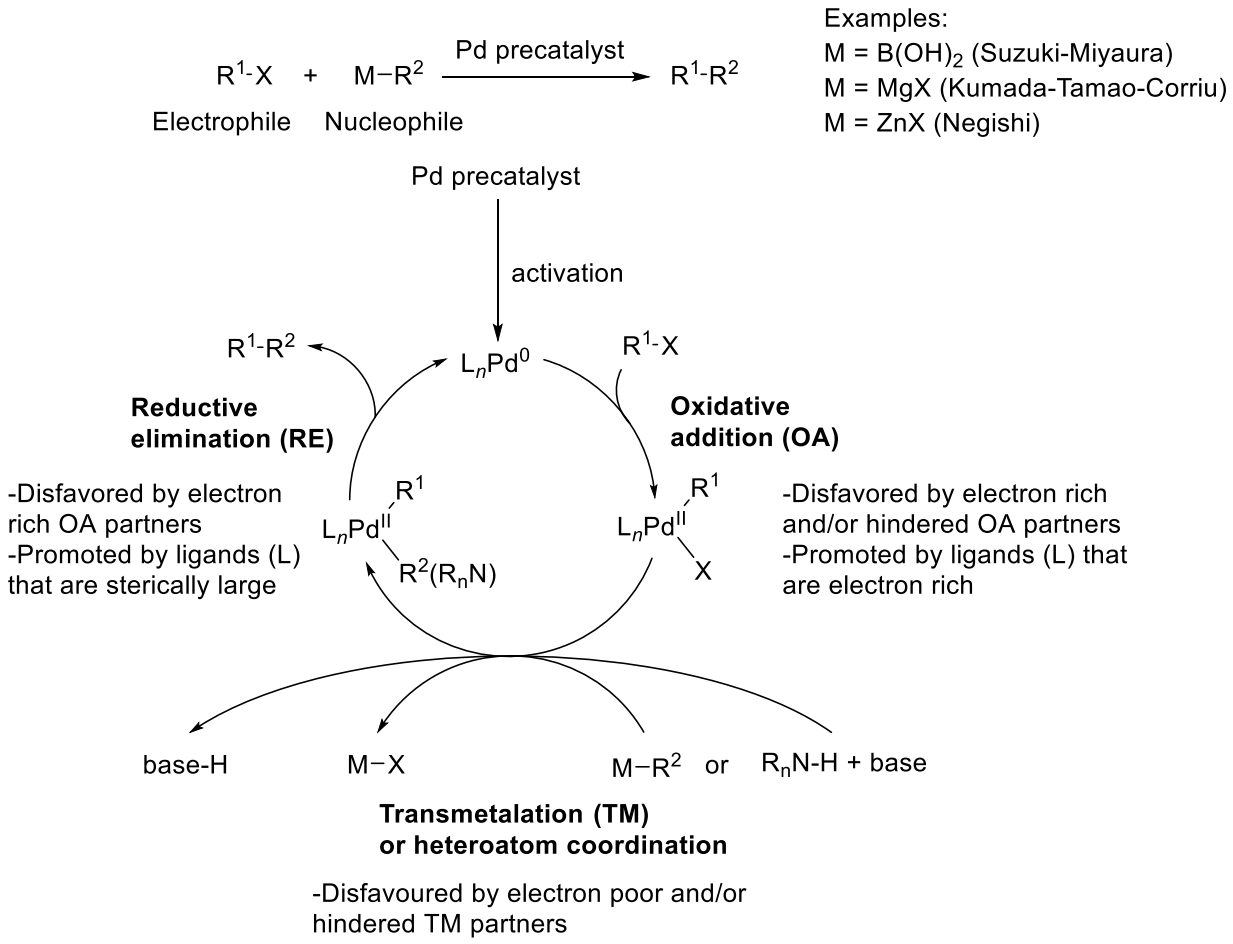


Figure 1. Generalized catalytic cycle for palladium mediated cross-coupling reactions.[22]

The palladium-catalyzed cross-coupling reactions all follow a similar cycle and involve three distinct steps. The first step is oxidative addition of an organohalide oxidizing the palladium. Transmetalation with an organometallic species produces an intermediate which can then undergo reductive elimination to form the product and Pd(0), which can then re-enter the catalytic cycle (Figure 1).[23] The mechanism of the Buchwald-Hartwig amination was found to follow a similar

catalytic mechanism where oxidative addition is the first step, however, the second step involves the coordination and deprotonation of the exogenous base (Figure 1).[4]

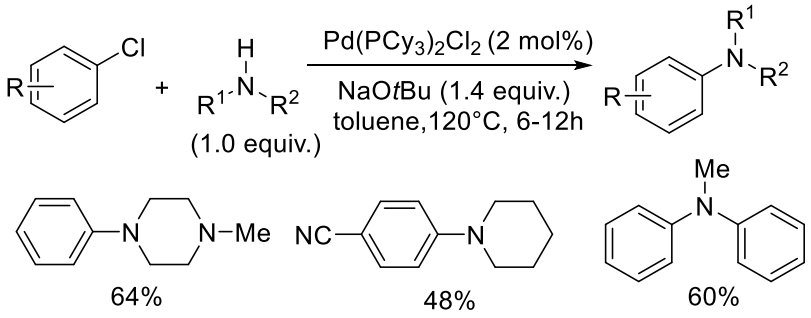
1.2 – Ancillary Ligand Introduction

Since the development of cross-coupling reactions, chemists have found that the electronic and steric properties of ancillary ligands (L) play an important role in each step of the catalytic cycle. Therefore, the choice of ligand can be crucial for the success of the reaction. For instance, it has been found that electron rich ligands are required for palladium to undergo oxidative addition with aryl chlorides, which are considered more challenging substrates than their bromide and iodide congeners. The greater challenge for palladium to oxidatively add to the C-Cl bond was thought to be a result of the higher bond dissociative energy (95 kcal mol^{-1}) compared to the C-Br (79 kcal mol^{-1}) and C-I (64 kcal mol^{-1}) bonds.[24] In addition to electronic properties, the steric topography of the ligand has been found to be important for reductive elimination, where bulkier ligands have proved to be more effective. As a result, chemists have designed many types of ligands to improve the reactivity, substrate scope, and selectivity of palladium catalysts in cross-coupling reactions, where both phosphine and N-heterocyclic-carbene ligands have proved to be effective.

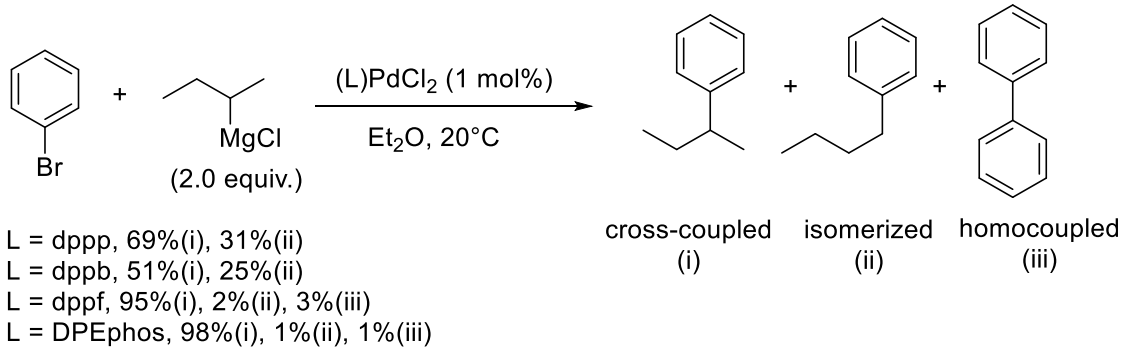
1.2.1 – Phosphine Ligands

Early studies of palladium-catalyzed cross-coupling reactions employed PPh_3 as the ligand since it was cheap and widely available. However, it soon became clear that the steric and electronic properties of phosphine ligands were important in promoting each step of the catalytic cycle. As a result, chemists have designed numerous phosphine ligands with unique steric and electronic properties to improve the reactivity, substrate scope, and selectivity of palladium catalysts (Figure 2). For example, electron rich phosphines $P(Cy)_3$ (**1**) and $P\textit{t}Bu_3$ (**2**) have enabled palladium catalysts to perform Buchwald-Hartwig amination and Suzuki-Miyaura cross-couplings with aryl

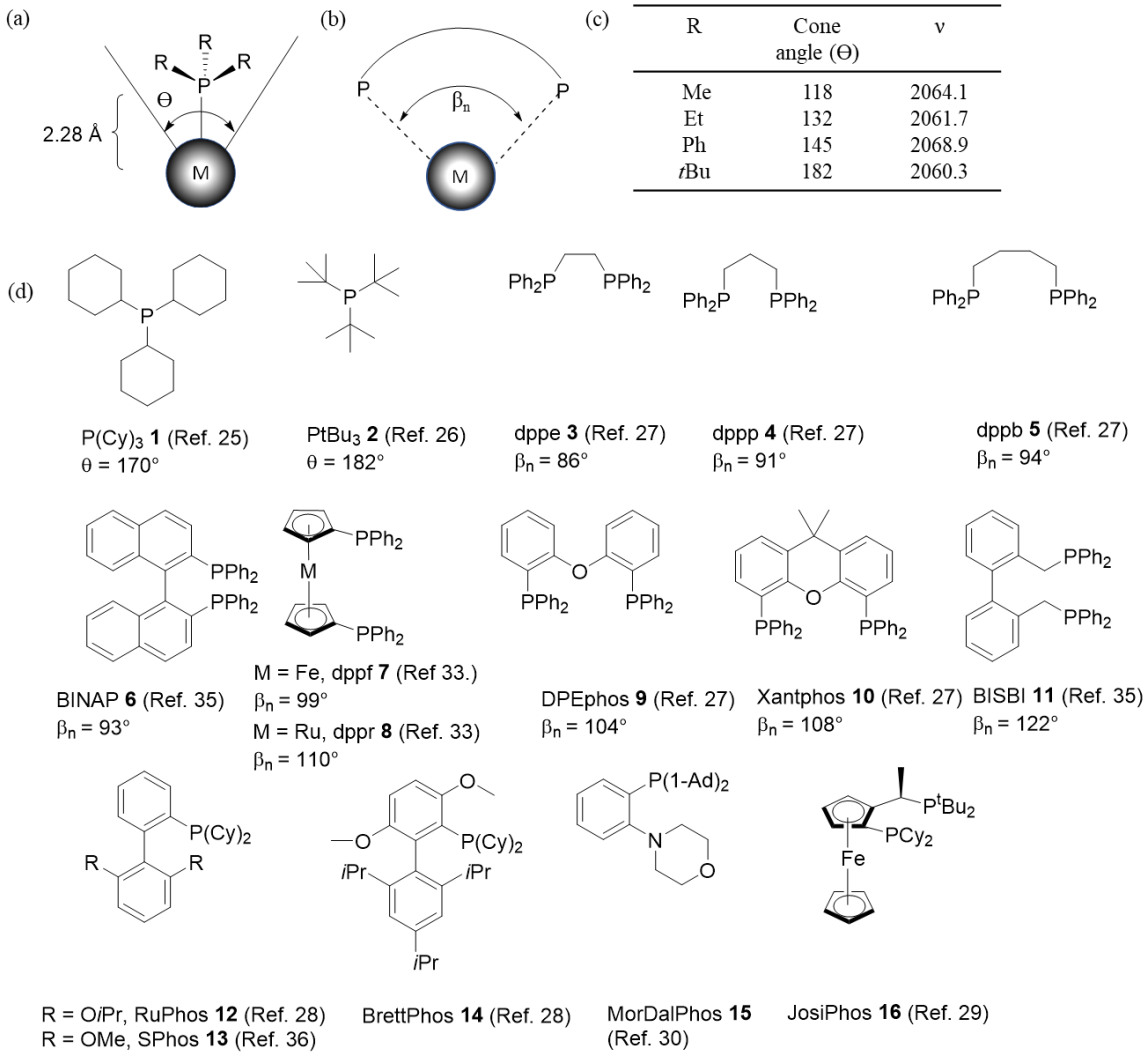
chloride substrates (Scheme 9).[25,26] Chelating ligands **3-10** were also shown to improve both reactivity and selectivity of palladium catalysts in various cross-coupling reactions. In 1998, van Leeuwen reported that chelating ligands with increasing bite angles (**9** > **7** > **5** > **4** > **3**) improved the selectivity for the cross-coupled product over the isomerized and homocoupled products in the sp^2-sp^3 KTC cross-coupling of benzyl bromide with sec-butylmagnesium chloride (Scheme 10).[27] More modern phosphine ligands possessing dialkylbiaryl backbones[28] (**12-14**) developed by Buchwald have proven to be highly effective in Suzuki-Miyaura and Negishi cross-coupling reactions of challenging hindered substrates (Scheme 11). Also, Hartwig[29] (**16**) and Stradiotto[30] (**15**) have developed ligands that have been shown to improve the substrate scope and reactivity of palladium-catalyzed Buchwald-Hartwig aminations (Scheme 12).



Scheme 9. Cross-coupling of aryl chlorides with alkyl amines and anilines.

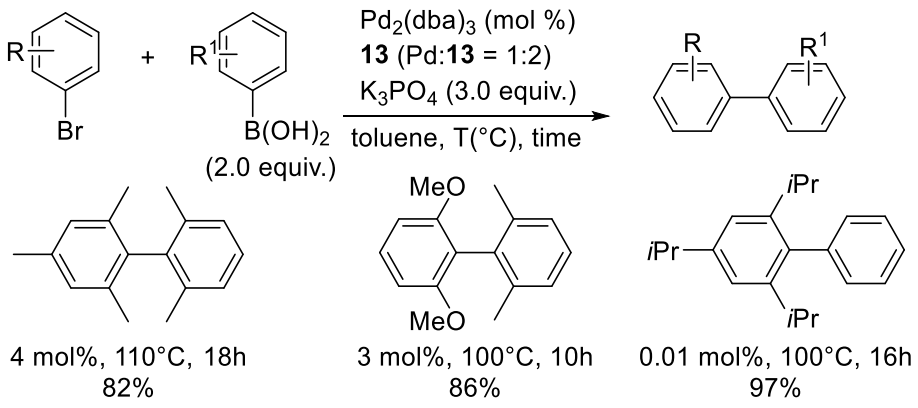


Scheme 10. Screen to determine the effects of bite angles in KTC cross-coupling reactions.

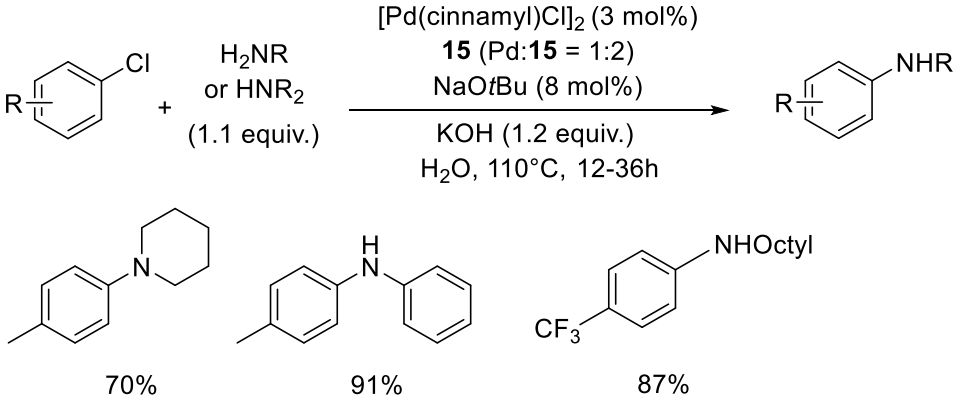


R	Cone angle (Θ)	ν
Me	118	2064.1
Et	132	2061.7
Ph	145	2068.9
*t*Bu	182	2060.3

Figure 2. **(a)** Cone angle representation **(b)** bite angle representation **(c)** Selected cone angles (Θ) and carbonyl stretching frequencies (ν) of $Ni(CO)_3L$ complexes for monophosphine ligands with different substituents **(d)** Phosphine ligands utilized in cross-coupling reactions with cone angle (Θ) or bite angle (β_n) listed.[23,24,32,33,35]



Scheme 11. Cross-coupling of sterically hindered substrates using SPhos (**13**).[36]



Scheme 12. Aryl amination of amines using Mor-DalPhos (**15**).[37]

1.2.2 – Tolman Electronic Parameter Analysis

The phosphorus-palladium bond is a dative interaction that is the result of the σ-donation from the phosphorus electron pair to the unfilled d-orbitals of palladium. Phosphines also act as π-acceptors where the filled metal d-orbitals overlap with the P-R σ*-orbitals (Figure 3).[38] Various methods to characterise the electronic contributions of phosphine ligands have been developed, however, separation of the σ-donor and π-backbonding properties has proved to be challenging.

The classic method to evaluate the electronic contributions of phosphine ligands was developed by Tolman and is called the 'Tolman electronic parameter'. This method used IR spectroscopy to

measure the vibrational frequency of the A_1 carbonyl stretching mode (ν_{CO}) of $Ni(CO)_3L$ complexes.[31] The ν_{CO} value is related to the degree of backbonding between Ni and CO, which increases when nickel is coordinated with stronger σ-donor ligands, resulting in lower carbonyl IR frequencies. Tolman used the method to evaluate the σ-donor properties of numerous ligands, where phosphines with alkyl substituents were found to be more donating than those with aryl substituents (Figure 2).

1.2.3 – Tolman Cone Angle Analysis

In addition to the electronic properties, Tolman developed the cone angle parameter (Θ) to quantify the steric properties of phosphine ligands by measuring the space that the ligand occupies. The value of Θ for symmetrically substituted ligands (PR_3), where R groups are equivalent, was defined by the angle that is created by a cylindrical cone extended 2.28 Å from the metal and with the cone edges touching the van der Waals radii of the outermost (R) groups on the ligand (Figure 2).[32] Tolman determined the cone angle of numerous phosphine ligands, where Θ increased with larger R groups.

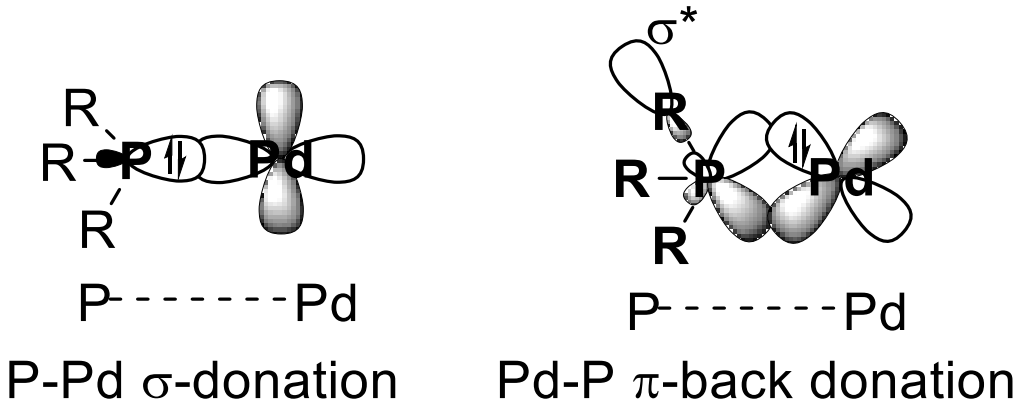


Figure 3. Schematic representation of bonding in phosphine-Pd complexes.[39]

1.2.4 – Bite Angle Analysis with Bis Chelating Ligands

Bite angle analysis was developed to characterise chelating phosphine ligands and was set by the metal-phosphine chelate (Figure 2). Chemists have found that increasing the bite angle has generally been beneficial for cross-coupling reactions. For example, one of the earliest reports describing this trend was from Brown and Guiry, who reported that increasing the bite angle of the dppf ligand (**7**) by replacing the iron with ruthenium (to give dppr (**8**)) accelerated reductive elimination.[40] van Leeuwen reported similar observations where chelating phosphines with bite angles up to 109° were beneficial for suppressing the formation of homocoupled products in KTC cross-coupling reactions (Scheme 10).[27] However, ligands with greater bite angles, such as BISBI (**11**), were reported to be ineffective as they coordinated with a trans configuration and prevented reductive elimination.[35]

1.2.5 − Disadvantages of Phosphine Ligands

Despite advancements in phosphine-ligand design and implementation, several intrinsic properties of phosphines have proven disadvantageous and difficult to overcome. The pyrophoric nature of alkyl phosphines is problematic for storage and handling and limits their use to inside a glovebox. Also, with more recent understanding of the catalytic cycle, the inability of the phosphine ligands to direct their steric bulk toward the metal centre has hindered their ability to promote reductive elimination.[22]

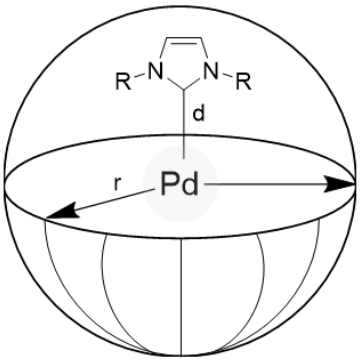
1.2.6 – Introduction of NHC Ligands

N-heterocyclic carbenes (NHCs) have become invaluable ligands for cross-coupling reactions. NHCs were initially prepared by Wanzlick[41] and Ofele[42] in the 1960's but weren't isolated until 1991 by Arduengo.[43,44] In 1995, Herrmann and co-workers discovered that NHC's could be used in place of phosphines for Pd-catalyzed reactions, and as result, NHCs have been of major interest to chemists as alternatives to phosphines in cross-coupling reactions.[45] A wide variety of NHCs have been synthesized, where most were derived from the five-membered imidazolylidene or imidazolidinylidene rings. These NHCs include IMes (**18**) and IPr (**17**) and their saturated back-bone congeners SIMes (**19**) and SIPr (**20**).[38] It has been found that NHCs are especially adept at promoting oxidative addition due to their relatively high electron-donating properties to the metal centre (*vide infra*). Conversely, the steric topography of NHCs have proven to be highly modifiable in a predictable and modular fashion to more effectively promote reductive elimination. With the emphasis on steric bulk, numerous ligands with larger N-aryl substituents have been designed by Glorius (**21**)[46], Organ (**24-27**)[22,47], Dorta[48], Marko[49] (**23**), and Lavigne[50] and their application has improved the reactivity, substrate scope, and selectivity in palladium-catalyzed cross-coupling reactions (Figure 4).

(a)

NHC	% V_{Bur}
IPr	36.7
SIPr	37.0
IPent	40.6
IPr*	44.6
IHept	41.5

(b)



(c)

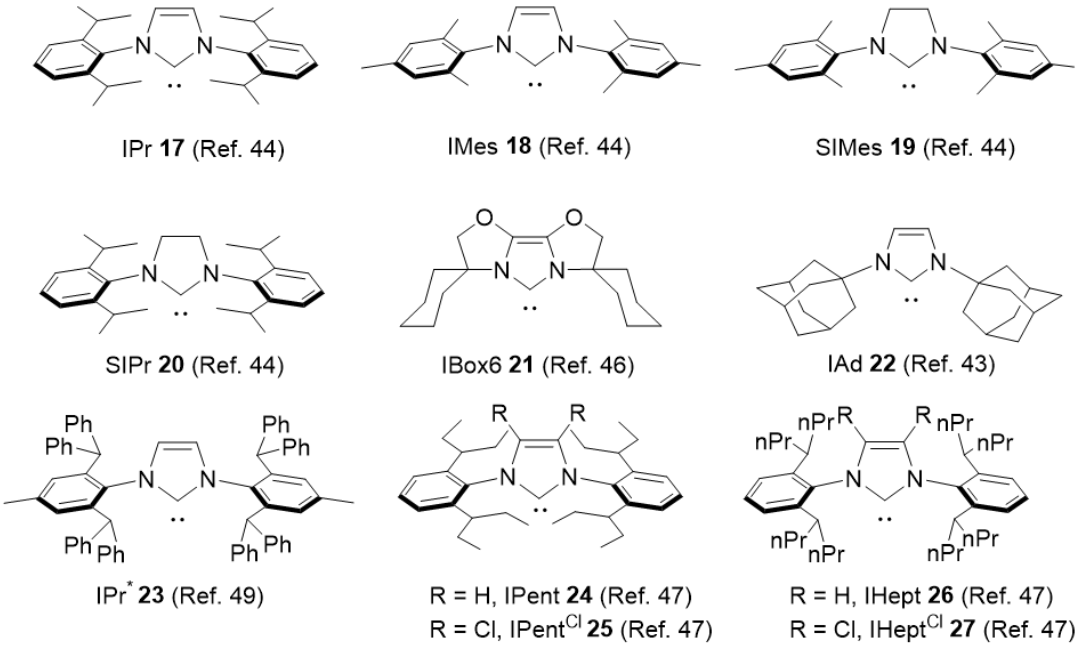


Figure 4. (a) Comparison of %V_{Bur} of NHC ligands.[51,52] (b) Schematic representation of sphere used for %V_{Bur}.[53] (c) NHC ligands used in cross-coupling reactions.

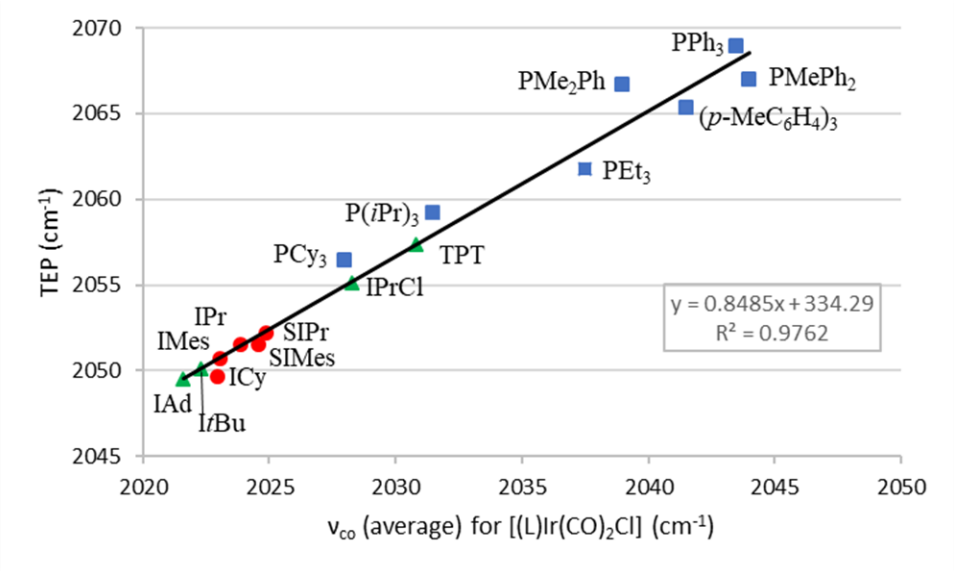


Figure 5. Nolan's correlation of average ν_{CO} values for [(L)Ir(CO)$_2$Cl] complexes with the Tolman electronic parameter (TEP),[54]: (■) Experimental values for phosphines; (●) Experimental values for NHC's; (▲) values obtained by linear regression.

1.2.7 – Electronic Properties of NHC Ligands

Crabtree and co-workers analyzed carbonyl stretching frequencies for a range of [(NHC)Ir(CO)$_2$Cl] complexes [L = NHC, PR$_3$, or P(OR)$_3$], and found that NHC ligands were better σ-donors than phosphines ligand, however, the range of NHCs examined was limited to tmiy (1,3-bis(4-tolylmethyl)imidazolin-2-ylidene) and biy (1,3-dibutylimidazolin-2-ylidene).[55] Nolan and co-workers compared the stretching frequencies for several NHC complexes and plotted their average ν_{CO} values (stretching frequencies found for trans-[IrCl(CO)$_2$L], L = PR$_3$ or NHC) against the TEP (see *1.2.2*). Regular NHC ligands did not differ significantly in electronic properties despite having different substituents on the N-aryl moiety (Figure 5) whereas those with chlorine-substituted backbones were found to have a higher TEP, indicating that they were less electron-donating.[54] Finally, phosphine ligands were found to be significantly less electron-donating than

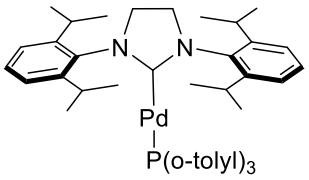
NHCs, which is consistent with the observations that Pd-NHC complexes are in general much more efficient at promoting oxidative addition than the corresponding phosphines.

1.2.8 − Steric Properties of NHC Ligands.

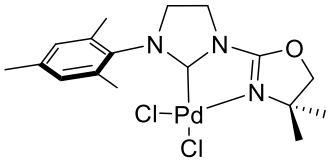
The Tolman cone angle measurement was not an appropriate method to measure the steric properties of NHC ligands because the steric bulk of phosphine ligands point away from the metal, whereas the steric bulk of NHCs is directed toward the metal centre. Nolan and co-workers introduced the buried volume parameter ($\%V_{bur}$), defined as the portion of the volume of a sphere centred around a metal that is occupied by a given ligand (Figure 4).[56] The buried volume could be measured using crystallographic data where $\%V_{bur}$ is proportional to the steric bulk on the N-aryl ring of the NHC (Figure 4). Nolan and co-workers calculated the buried volume of various 4,5-disubstituted imidazolium-derived [Pd(NHC)ally(Cl)] complexes, and found that increasing the size of the N-aryl substituent resulted in the increase of $\%V_{bur}$.[57]

1.3 − The Development of Pre-formed PEPPSI Catalysts

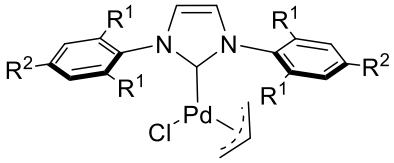
Numerous types of pre-formed NHC-palladium complexes have been reported to be effective for cross-coupling reactions. Notable examples include those that have been synthesized by Caddick and Cloke[58] (**27**), Bellemin-Laponnaz and Gade[59] (**28**), Nolan (**29, 30**)[60,61,62], Beller[63] (**31**), Organ[22] **(35-39**) and Herrmann[64] (**34**) (Figure 6).



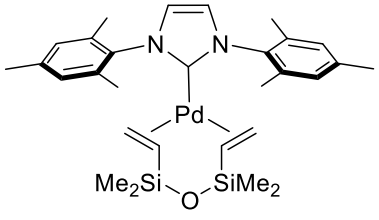
2001, Caddick and Cloke
27 (Ref. 58)



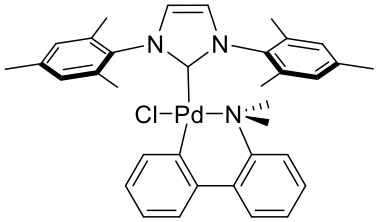
2002, Bellemin-Laponnaz and Gade
28 (Ref. 59)



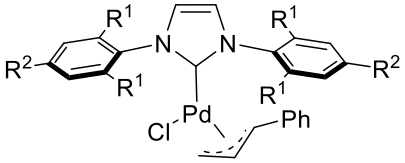
2002, Nolan
29 R^1, R^2 = Me
30 R^1= *i*Pr, R^2 = H
(Ref. 60)



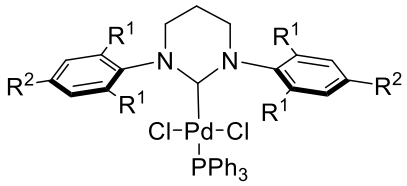
2002, Beller
31 (Ref. 63)



2003, Nolan
32 (Ref. 61)



2006, Nolan
33 R^1 = *i*Pr, R^2 = H
(Ref. 62)



2006, Herrmann
34 R^1 = *i*Pr, R^2 = H
(Ref. 64)

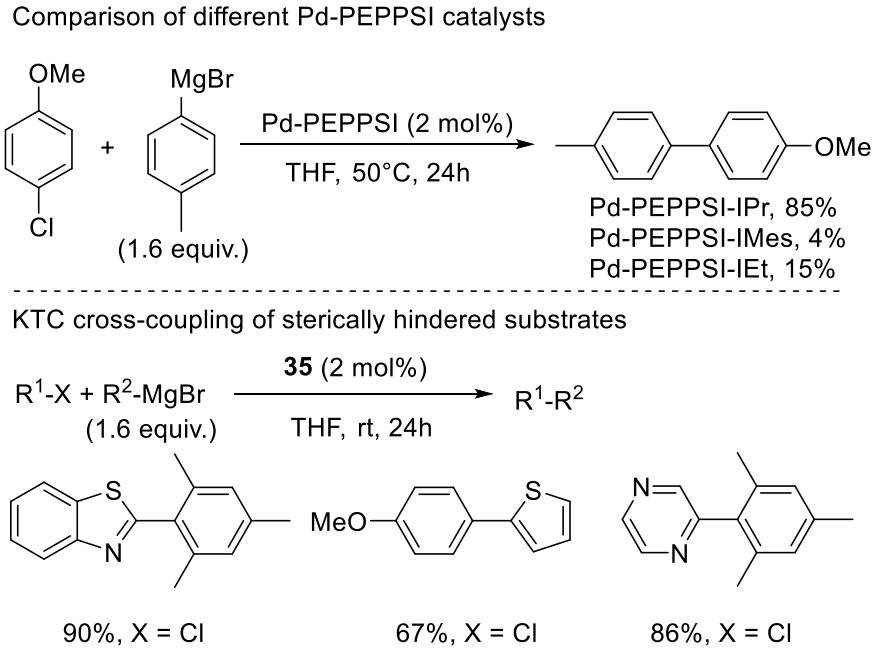
Figure 6. Pd-NHC pre-formed catalysts for cross-coupling.

In 2005, the Organ group reported the results of a ligand screen of an alkyl-alkyl Negishi cross-coupling catalyzed by different imidazolium/$Pd_2(dba)_3$ combinations. It was found that only the NHC ligands with sufficient steric bulk were effective, such as IPr (**17**) and SIPr (**20**), whereas IMes (**18**) and SIMes (**19**) were ineffective.[65,66]

The use of a 'throw-away' ligand in pre-catalyst preparation was found to help stabilize the resultant pre-formed Pd(II)-NHC complex. Grubbs and co-workers illustrated that replacing

phosphorus-based ligands with pyridine derivatives improved the rate of initiation of Ru-NHC complexes in olefin metathesis. In particular the 3-bromopyridine ligated Ru-NHC complexes activated at least three orders of magnitude faster than the pyridine complex and this was considered in the preparation of the first generation Pd-PEPPSI complexes.[67]

Later, a study was performed to compare the catalytic activities of the pre-formed Pd-PEPPSI-IPr and the catalyst formed *in situ* (from $Pd_2(dba)_3$ and IPr·HCl) in Negishi and Suzuki-Miyaura cross-coupling reactions. Amazingly, the catalyst TON of Pd-PEPPSI-IPr was found to be 40 times higher than the catalyst prepared *in situ*.[68] Since it was assumed that the active catalytic species was generated in both methodologies, the lower TON observed from the *in situ* method indicated that carbene coordination to $Pd_2(dba)_3$ was not an efficient process.



Scheme 13. KTC cross-coupling of sterically hindered substrates with Pd-PEPPSI.

The enhanced steric bulk of Pd-PEPPSI-IPr was demonstrated to be necessary for the high catalytic activity of Pd-PEPPSI in aryl-aryl KTC cross-couplings, as Pd-PEPPSI catalysts with IMes and IEt ligands showed significantly poorer activity (Scheme 13).[69]

Although Pd-PEPPSI-IPr was shown to be an effective catalyst in cross-coupling reactions, three limitations remained: i) challenging Suzuki-Miayaura and Negishi cross-couplings to produce tetra-*ortho* substituted (hetero)biaryls, ii) Negishi cross-couplings of secondary alkylzinc halides with aryl halides, and iii) Buchwald-Hartwig Aminations under mild basic conditions.[70]

1.3.1 − Pd-PEPPSI-catalyzed Suzuki-Miyaura Cross-coupling

The Organ group proposed that an even greater increase of steric bulk on the NHC was necessary for improved catalytic performance to overcome truly challenging cross-coupling reactions, such as those mentioned above. New pre-catalysts were prepared, where the isopropyl substituent was changed to the bulkier isopentyl and cyclopentyl, leading to Pd-PEPPSI-IPent and Pd-PEPPSI-cPent, respectively (Figure 7). These catalysts were screened in a Suzuki-Miyaura cross-coupling, where only Pd-PEPPSI-IPent (**38**) showed high reactivity (Scheme 14).[71] This catalyst was then compared to **35** in Suzuki-Miyaura cross-couplings of sterically hindered 2,6-disubstitued arenes and was found to be superior (Scheme 15). Overall, the result of the study illustrated three factors of the ligand that are essential for catalyst reactivity. First, branching at the first carbon atom of the *ortho*-alkyl substituent on the aryl ring was required (IMes and IBu were ineffective). Second, increasing the steric bulk on the branched chain improved catalyst performance (Pd-PEPPSI-IPent was superior to Pd-PEPPSI-IPr). Third, conformational flexibility of the alkyl substituent was essential as Pd-PEPPSI-cPent was ineffective, whereas the 3-pentyl analogue demonstrated the highest reactivity.

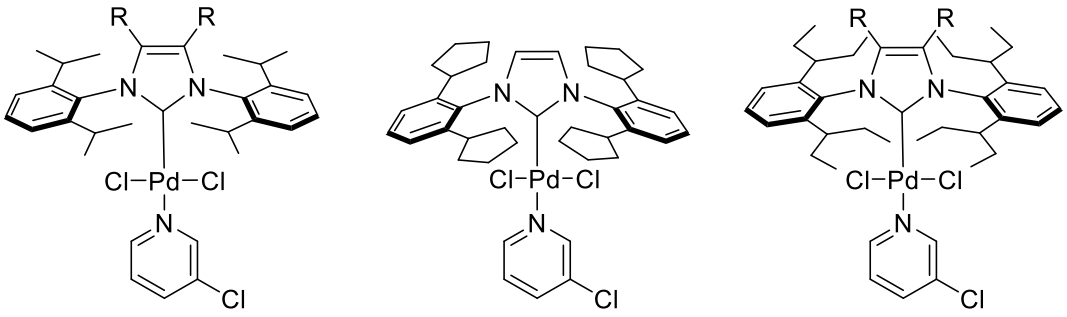
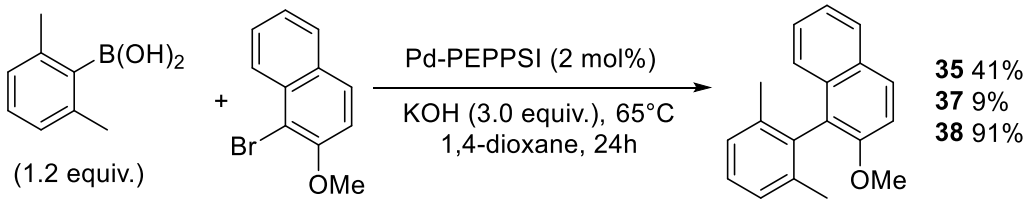
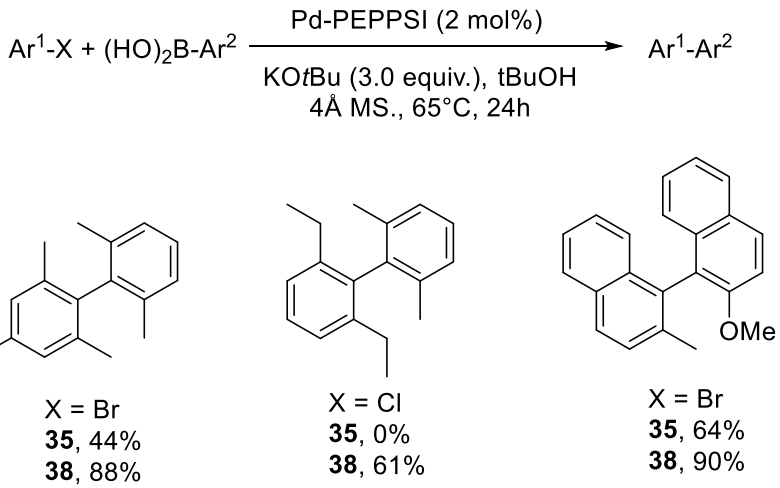


Figure 7. Pd-PEPPSI catalysts **35-39**.



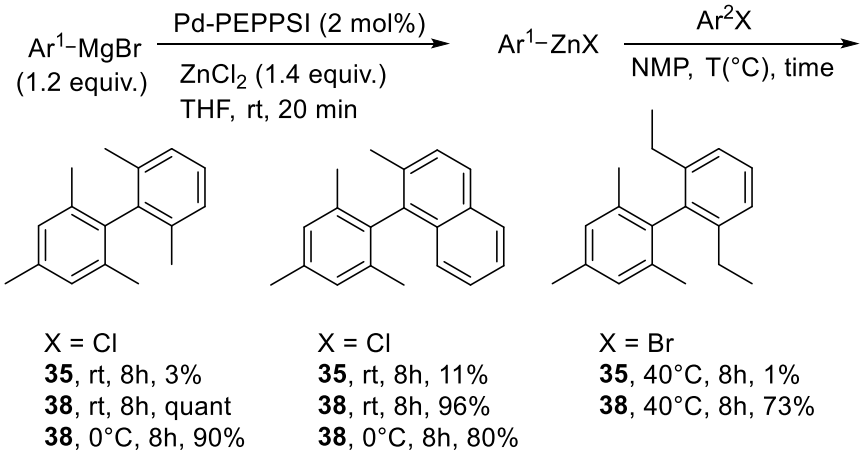
Scheme 14. Pd-PEPPSI catalyst screen for Suzuki-Miyaura cross-coupling.



Scheme 15. Suzuki-Miyaura cross-coupling of sterically hindered aryl halides with aryl boronic acids.

1.3.2 – Pd-PEPPSI-catalyzed Negishi Cross-coupling Reactions

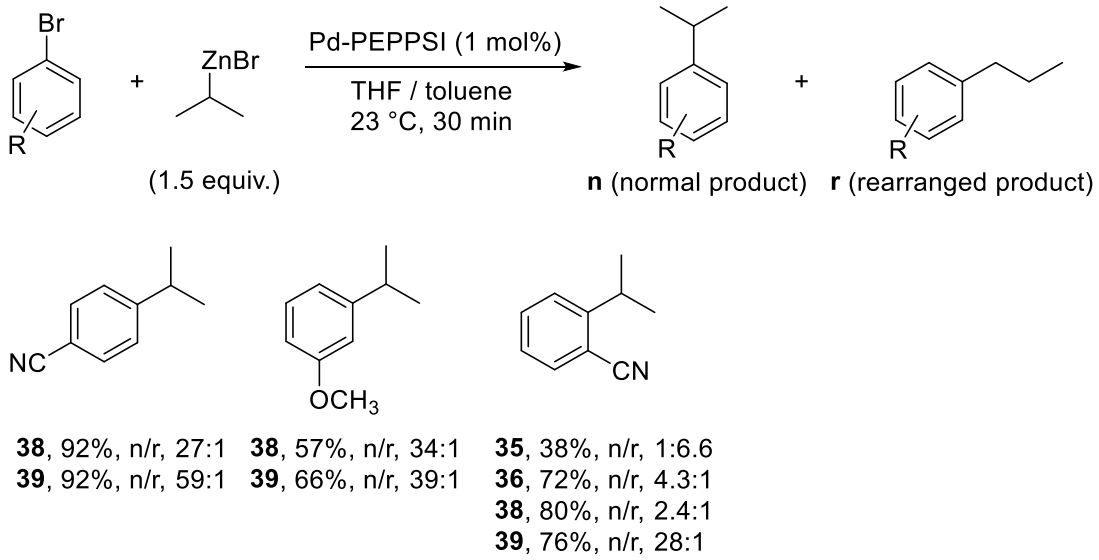
The Organ group then employed Pd-PEPPSI-IPent in the Negishi cross-coupling of sterically hindered substrates and found that the reaction could be performed at room temperature, which was unprecedented at the time. Prior, Dai and Fu had reported the aryl-aryl cross-coupling of sterically hindered substrates using Pd(P*t*Bu$_3$) at 100°C, and Milne and Buchwald reported the cross-coupling of functionalized (hetero)aryl halides with aryl zinc reagents (prepared *in situ*) using hindered RuPhos ligand in conjunction with [Pd$_2$(dba)$_3$] at 70°C.[72,73] The Organ group compared the performance of Pd-PEPPSI-IPent to Pd-PEPPSI-IPr and Pd$_2$(dba)$_3$ in conjunction with dialkylbiary phosphine ligands SPhos and RuPhos. All catalyst systems gave comparable results only at 70°C, however, only Pd-PEPPSI-IPent afforded the product in high yields at room temperature (Scheme 16).[74]



Scheme 16. Pd-PEPPSI-catalyzed Negishi cross-coupling of sterically hindered aryl halides with aryl zinc halides.

Pd-PEPPSI-IPent was employed in the cross-coupling of secondary alkyl zinc halides with aryl halides, which are challenging reactions due to the propensity of the alkyl zinc halide to undergo β-hydride elimination and migratory insertion during the catalytic cycle to produce the isomerized

product instead of the desired cross-coupled product.[75] Prior, Han and Buchwald reported the palladium-catalyzed coupling of secondary alkylzinc halides with aryl bromides and activated chlorides using $Pd(OAc)_2$ in conjunction with CPhos to produce good ratios of coupled to isomerized products.[76] However, Buchwald's catalytic system could not fully suppress β-hydride elimination. Since it was known that catalysts containing more-hindered ligands undergo faster reductive elimination than those containing less-hindered ligands, it was anticipated that Pd-PEPPSI-IPent would perform well in these cross-couplings. The Organ group found that Pd-PEPPSI-IPent was able to produce non-isomerized products in higher yields and with higher selectivity than Pd-PEPPSI-IPr.[77] With the goal of further enhancing the selectivity of the Pd-PEPPSI, the new catalyst Pd-PEPPSI-IPent^{Cl} was synthesized and compared to Pd-PEPPSI-IPr and Pd-PEPPSI-IPent in sp^2-sp^3 Negishi cross-couplings of isopropyl zinc bromide and functionalized aryl bromides (Scheme 17).[75] It was anticipated that Pd-PEPPSI-IPent^{Cl} would exhibit higher reactivity and selectivity than the other catalysts as the chlorinated backbone on the NHC would decrease the electron density on palladium, thereby making reductive elimination even more facile. As anticipated, Pd-PEPPSI-IPent^{Cl} was able to cross-couple para, meta, and ortho substituted aryl bromides with isopropyl zinc bromide with higher selectivity and yields than Pd-PEPPSI-IPr and Pd-PEPPSI-IPent (Scheme 17).



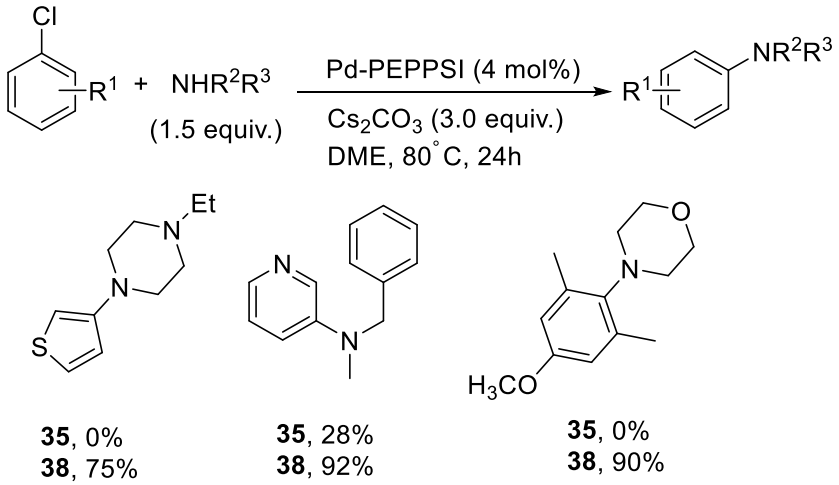
Scheme 17. Selective Pd-PEPPSI-catalyzed Negishi sp^2-sp^3 cross-couplings.

1.3.3 − Buchwald-Hartwig Aminations

Palladium-catalyzed Buchwald-Hartwig aminations have undergone significant advancement since its early development, with improvements in substrate scope, reaction conditions, and in the selective monoarylation of primary amine coupling partners.[21]

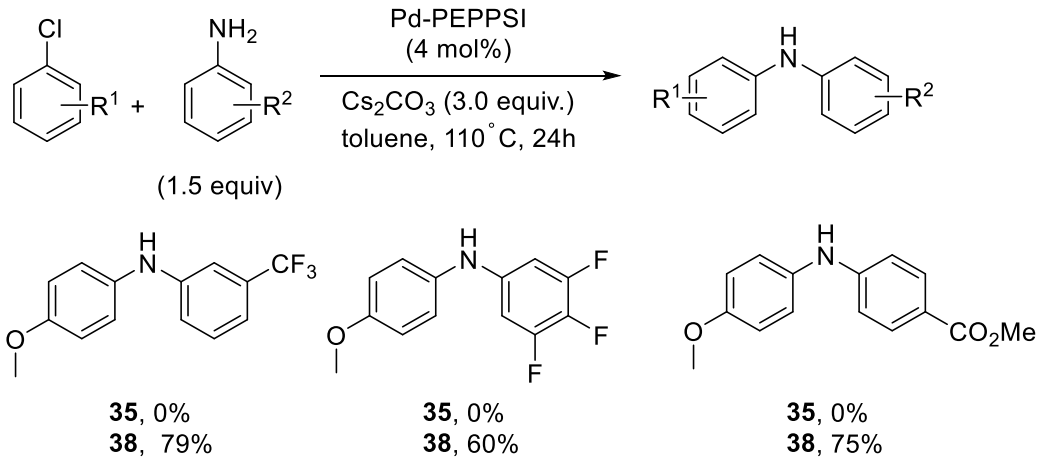
In 2008, the Organ group found that Pd-PEPPSI-IPr was an effective catalyst for the amination of aryl chlorides and bromides with anilines and secondary amines in the presence of KO*t*Bu, which made the reaction conditions incompatible with base sensitive functional groups.[78] This deficiency encouraged the development of a new set of reaction conditions to employ the weaker base Cs_2CO_3, and both Pd-PEPPSI-IPr and Pd-PEPPSI-IPent were used to cross-couple secondary amines with aryl chlorides.[79] Deprotonation was thought to be the rate-limiting step of the catalytic cycle, where coordination of the amine to the Lewis acidic palladium complex is required. Preliminary NMR spectroscopy studies and computational results showed that the palladium metal centre with IPent was more electron deficient than with IPr, thus it was expected that Pd-PEPPSI-

IPent would outperform Pd-PEPPSI-IPr in Buchwald-Hartwig aminations in weakly basic conditions. As expected, Pd-PEPPSI-IPent outperformed the less bulky catalyst and was able to couple a diverse array of electronically deactivated substrates (Scheme 18). Rate and computation studies indicated that the rate determining step was deprotonation of the palladium-ammonium complex and increased reactivity of Pd-PEPPSI-IPent was a result of a stronger coordination with the amine (Scheme 18).

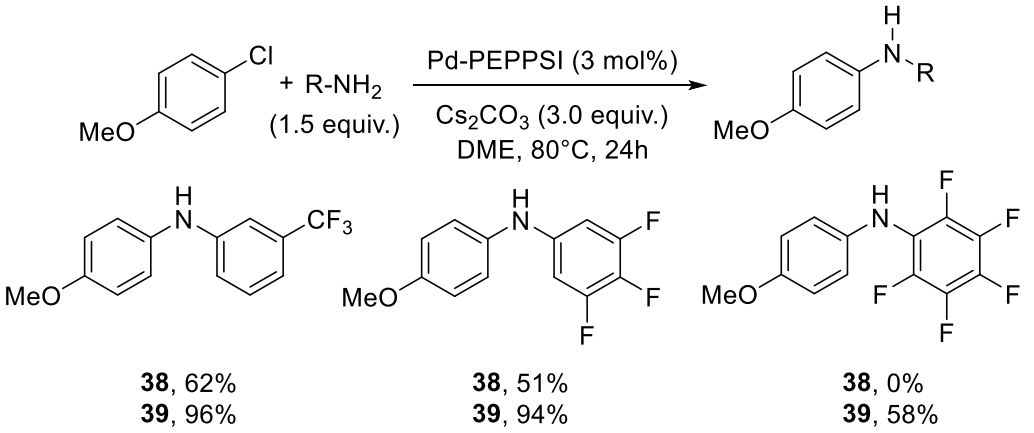


Scheme 18. Pd-PEPPSI-catalyzed Buchwald-Hartwig amination of alkyl amines.

The same trend was observed when **38** was employed to cross-couple electronically deactivated aryl halides with weakly nucleophilic anilines.[80] Compared to the performance of **35**, which showed little to no efficiency, **38** was able to cross couple aryl halides with electron-donating groups and anilines with electron withdrawing substituents (Scheme 19). Rate studies and computations found that the process of amine coordination to palladium, deprotonation, and reductive elimination was rate limiting in the cross-coupling of anilines.



Scheme 19. Pd-PEPPSI-catalyzed Buchwald-Hartwig aminations of aryl chlorides with anilines.



Scheme 20. Pd-PEPPSI-IPent^{Cl} in BHA with aryl amine partners.

Pd-PEPPSI-IPent^{Cl} (**39**) was employed to cross-couple aryl halides with anilines. It was thought that the chlorination of the backbone would help facilitate reductive elimination by forcing the steric bulk of the N-aryl substituents toward the metal centre.[81] As expected, **39** was able to cross-couple a wide variety of anilines in weakly basic conditions. Surprisingly, **39** was able to cross-couple deactivated 3-trifluoromethylaniline and 3,4,5-trifluoroaniline with 4-chloroanisole (also electronically deactivated) in higher yields than **38** (Scheme 20).

1.3.4 − Metal Abundances, Costs, and Sustainability

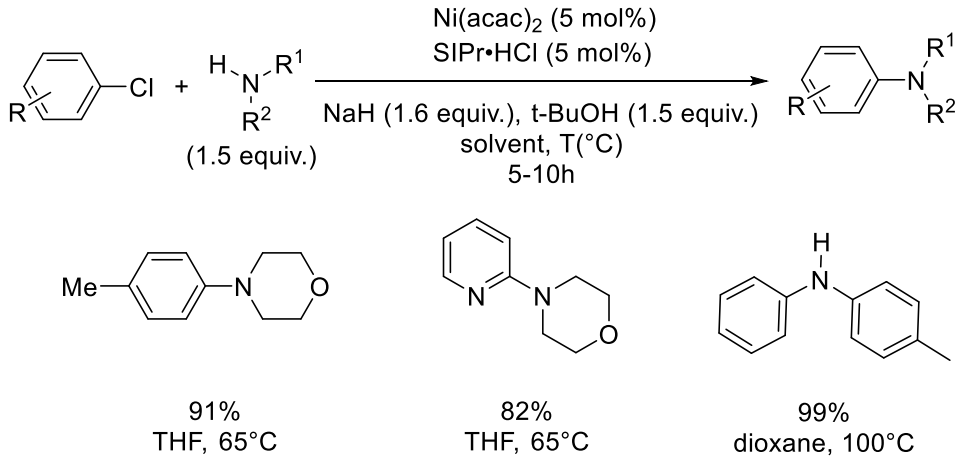
Considerable effort has been devoted to the development of first row metals as alternatives to palladium and other precious metals in cross-coupling. In particular, metals such as iron, nickel, and cobalt have been explored because they are more sustainable options for chemical processes with 140,000 tons of cobalt and 2167.1 million tons of iron mined per year.[82,83] Also, the low cost of first row transition metals make them a very attractive alternative; cobalt currently trades at $0.9020 US/oz and nickel trades at $0.44710 US/oz, while palladium trades at $1794.00 US/oz.[84,85] Lastly, the world's supply of palladium is expected to be depleted in 50-100 years.[86] Therefore, the development of first row metal catalysts is not only potentially more economical, but necessary to ensure the sustainable supply of pharmaceuticals, materials, and agrochemical products.

1.4 − Nickel-catalyzed Buchwald-Hartwig Amination

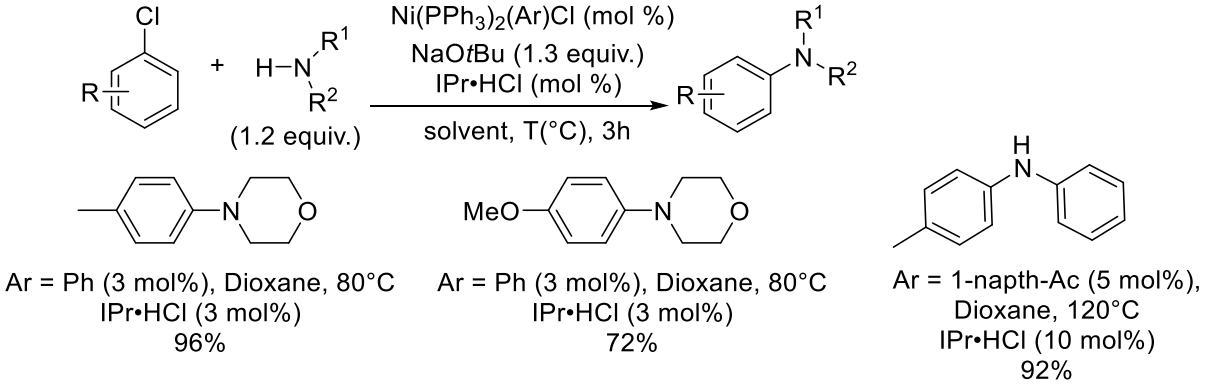
Nickel has been studied as an affordable alternative to palladium in Buchwald-Hartwig aminations but has suffered from limitations in catalyst loading, functional group tolerance, and substrate scope. Wolfe and Buchwald (1997) described the use of $Ni(cod)_2$ in combination with dppf to couple aryl chlorides with primary and secondary alkyl amines with sodium tert-butoxide in hot toluene.[87] Although the reaction conditions tolerated nitriles, ketones, acetals, and ethers, the substrate scope did not include aldehydes and other base sensitive functional groups.

In 2002, Fort showed that aryl chlorides could be coupled with secondary alkyl amines and anilines using $Ni(acac)_2$ in conjunction with an NHC salt. In preliminary optimization screens they found that increasing ligand steric bulk was required, as SIPr·HCl outperformed IMes·HCl.[88] The protocol required sodium hydride to reduce the nickel and to generate sodium tert-butoxide. In

turn, the sodium tert-butoxide would then deprotonate the NHC salt to form the active catalyst (Scheme 21).



Scheme 21. Example of nickel-NHC-catalyzed BHA with secondary alkyl amine and anilines.



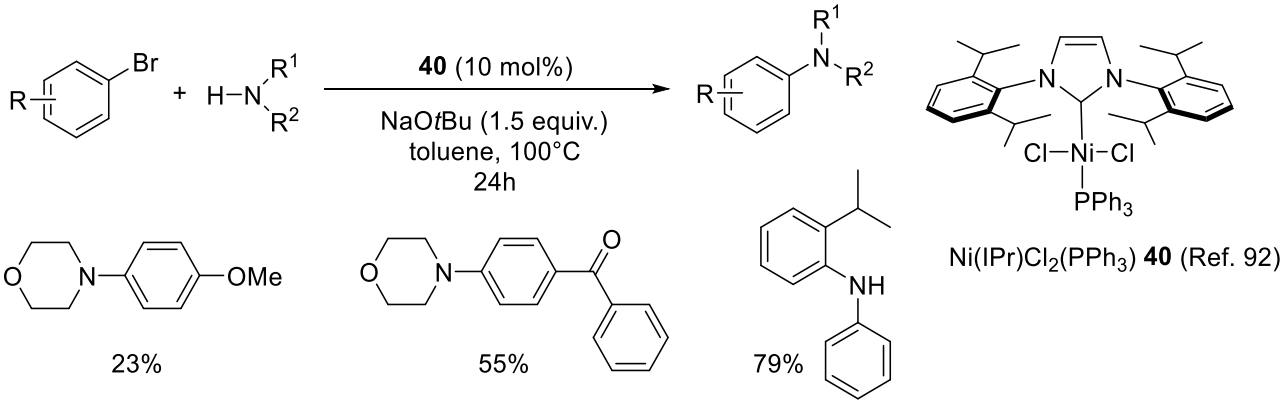
Scheme 22. $Ni(PPh_3)_2$(1-naph)Cl-catalyzed BHA with secondary alkyl amines.

Many reports at this time involved protocols that required the use of a stoichiometric reductant for nickel-catalyzed Buchwald-Hartwig aminations.[89,90] Yang and co-workers were among the first to report a reductant-free amination of aryl halides using the air-stable Ni(II) σ-aryl pre-catalyst $Ni(PPh_3)_2(Ar)Cl$.[91] Their report described the amination of aryl chlorides with secondary alkylamines and anilines using sodium tert-butoxide, however, the protocol only worked for

activated (electron poor) naphthyl derivatives. Also, increased temperatures and higher catalyst loadings were required to achieve decent yields of cross-coupled products (Scheme 22).

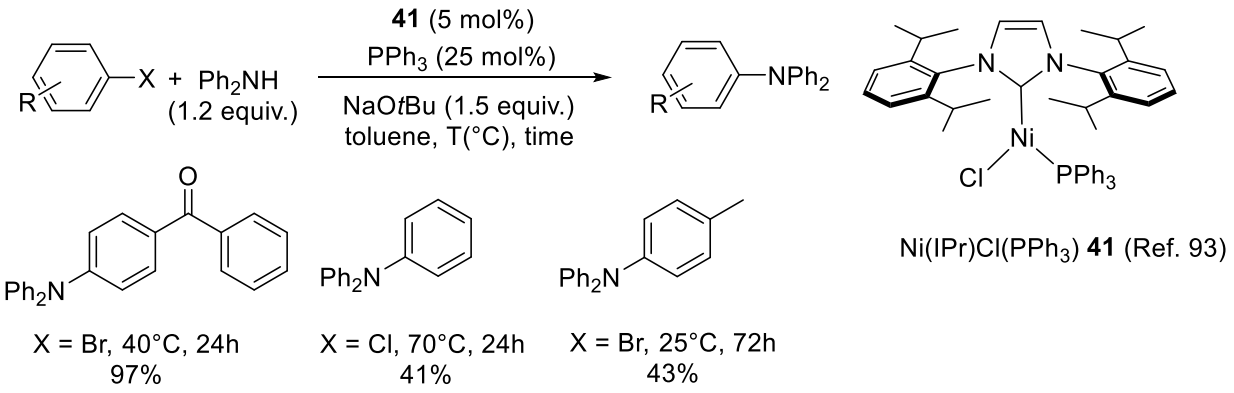
1.4.1 − Pre-Formed Nickel Catalysts for Buchwald-Hartwig Amination

Matsubara's group (2007) reported the Buchwald-Hartwig amination of aryl bromides with secondary amines and anilines using pre-formed catalyst $Ni(IPr)Cl_2(PPh)_3$ (**40**).[92] Higher cross-coupling yields were achieved with less basic anilines than with alkylamines (Scheme 23).



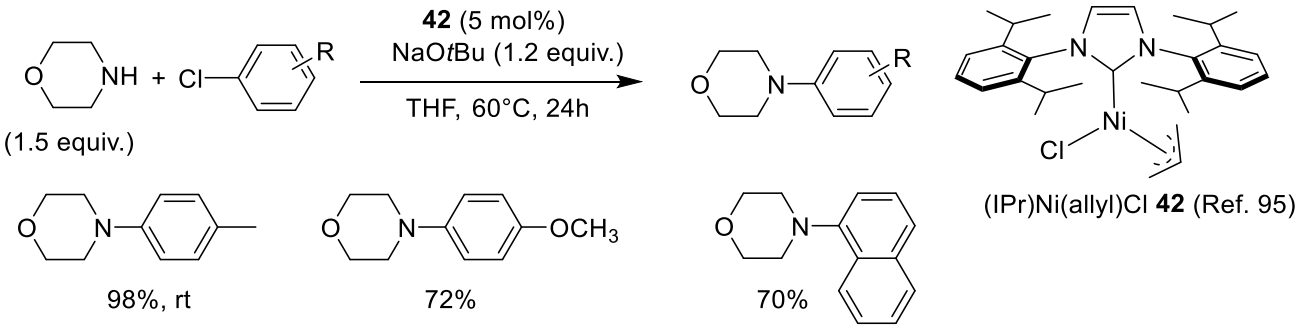
Scheme 23. $Ni(IPr)Cl_2(PPh)_3$ in BHA with secondary alkyl and aniline nucleophilic partners.

In 2011, the same group developed monovalent pre-catalyst $Ni(IPr)Cl(PPh_3)$ (**41**)[93] as they had previously shown that Ni^0IPr_2, upon addition of *p*-chlorotoluene, formed $Ni^IIPr_2(Cl)$ and biaryl from the generation of aryl radicals.[94] As a result, Matsubara believed that a nickel(I-III) catalytic cycle was likely operative and **41** effectively catalyzed several Buchwald-Hartwig aminations of aryl halides with diphenyl amine. Compared to their earlier work, the new complex permitted lower temperatures and lower catalyst loading than with $Ni(IPr)Cl_2PPh_3$ (Scheme 24).



Scheme 24. Ni(IPr)Cl(PPh_3) in BHA with biphenyl amine nucleophilic partners.

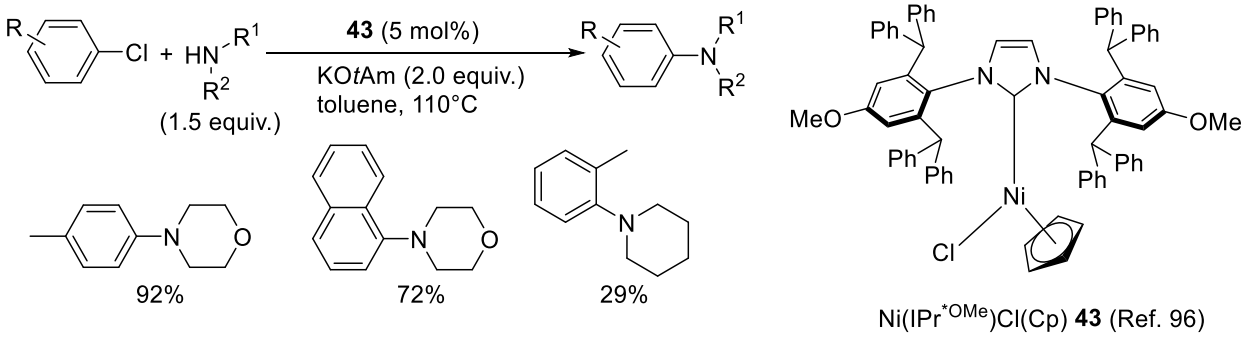
The Nicasio group reported that pre-catalyst (IPr)Ni(allyl)Cl was able to catalyze Buchwald-Hartwig aminations under relatively milder conditions and with a lower catalyst loading. The scope of aminations was superior to that reported by Matsubara as aryl chlorides could be coupled with secondary alkyl amines (Scheme 25).[95] Consistent with other reports, the catalyst with the IMes coordinated to the nickel was reported to be much less effective than with IPr, which showed that increased steric bulk on the NHC improved catalysis.



Scheme 25. (IPr)Ni(allyl)Cl in BHA with secondary alkyl amine nucleophilic partners.

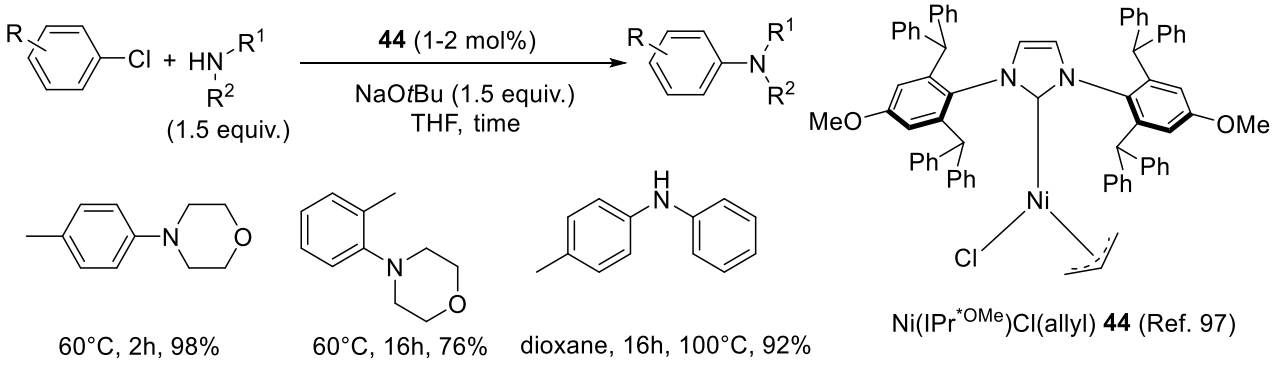
In 2013, Nolan reported the synthesis of a complex with Ni coordinated to an IPr^{*OMe} NHC and cyclopentadiene (Cp). Relative to Nicasio's report, harsher conditions were required using this catalyst system with aryl chlorides, some resulting in considerably poorer yields (Scheme 26). It

was proposed that inferior activity of the catalyst was a result of the difficulty in displacing the Cp ligand.[96]



Scheme 26. Ni(IPr^{*OMe})Cl(Cp) in BHA with secondary alkyl amines.

In support of this idea, Nolan subsequently reported the synthesis of a similar catalyst with the cyclopentadiene replaced by an allyl moiety, which was able to catalyze amination of aryl halides with improved yields and at lower temperatures.[97] Overall, the substrate scope and conditions were now comparable to the report by the Nicasio group (Scheme 27).



Scheme 27. Ni(IPr^{*OMe})Cl(allyl) in BHA of secondary alkyl amines and aniline nucleophilic partners.

In 2016, the Matsubara group reported the development of several Ni(I)NHC catalysts, derived from Sigman's $[Ni(IPr)]_2(\mu\text{-}Cl)_2$ complex (NHC = IPr or IMes, L = PPh_3, Pyr, or $P(OPh)_3$] (Figure

8).[98] NMR spectroscopic studies found that an equilibrium exists in solution between dimeric Ni complex **45** and mono-Ni complex **46** formed from attack by free PPh_3 in benzene-d6, but the same equilibrium was not observed with the Ni(I)IMes monomer. This property was thought to be the result of the stronger trans effect of IPr.

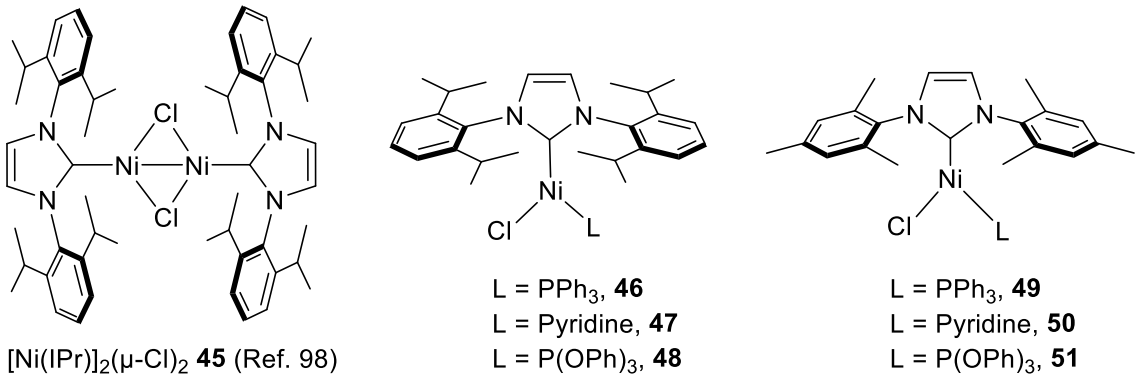
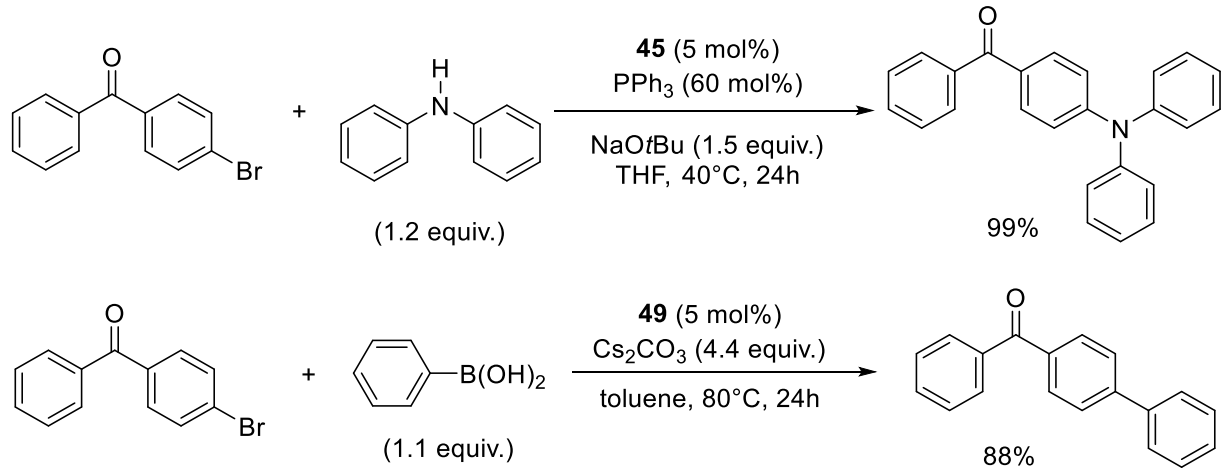


Figure 8. $[Ni(IPr)]_2(\mu\text{-}Cl)_2$ and Ni(NHC)Cl(L) structures.



Scheme 28. $[Ni(IPr)]_2(\mu\text{-}Cl)_2$ and $Ni(IPr)Cl(PPh_3)$ in BHA and Suzuki cross-coupling reactions.

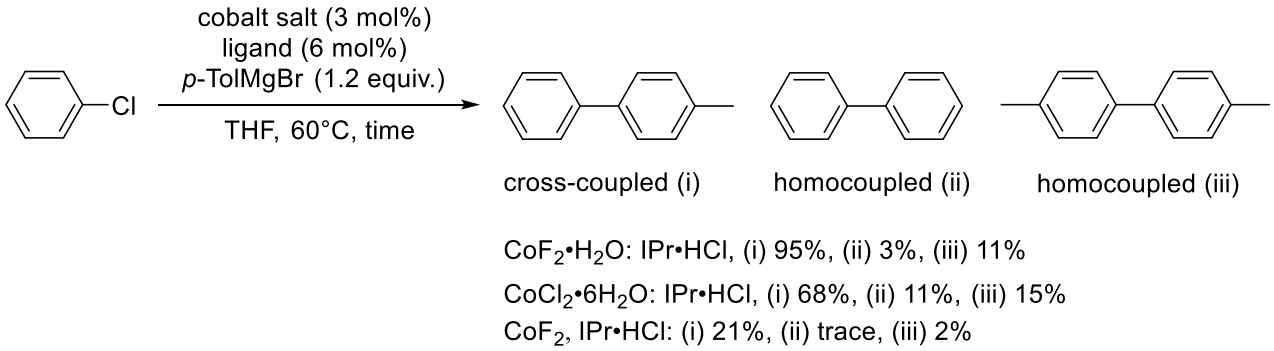
Both catalysts were screened in Suzuki-Miyaura cross-coupling and Buchwald-Hartwig amination reactions in the presence of donor ligands. It was found that the best donor ligand for each complex was PPh_3, and that $[Ni(IPr)_2(\mu\text{-}Cl)_2]$ (**45**) was suitable for only Buchwald-Hartwig and the

Ni(IMes)Cl(PPh_3) (**49)** was suitable for only Suzuki-Miyaura cross-coupling reactions (Scheme 28). It was speculated that the steric bulk of IPr inhibited the nickel from performing Suzuki-Miyaura cross-coupling, and in contrast, was required for Buchwald-Hartwig amination.

1.5 – Cobalt-catalyzed Cross-coupling Reactions

1.5.1 – Introduction to Cobalt-catalyzed Cross-coupling

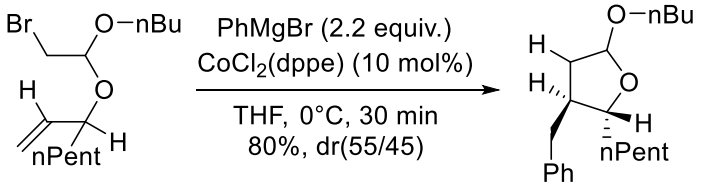
Nakamura (2009) examined the reaction of chlorobenzene with p-TolMgBr in the presence of catalytic cobalt, nickel, and iron fluorides with various NHCs and phosphines.[99] The reaction employing $CoF_2 \cdot 4H_2O$ (3 mol%) and IPr·HCl (6 mol%) gave the highest yield of cross-coupled product while the reactions using chloride salts and anhydrous cobalt fluoride were less effective, producing higher amounts of homocoupled product (Scheme 29). The authors proposed that the hydrated cobalt showed better performance due to higher solubility than the dry cobalt fluoride.



Scheme 29. Cobalt-catalyzed KTC with aryl Grignard nucleophiles.

The Oshima group reported on the radical reactivity of cobalt in the cross-coupling of haloacetals with $CoCl_2$(dppe) to yield cyclized products (Scheme 30).[100] A mechanism was proposed where cobalt is first reduced to a cobalt (0) species, which is followed by a radical rebound process (Figure 10). The halide is displaced from the acetal and produces a cobalt (I) complex that undergoes a 5-exo-trig cyclization. This is followed by a radical recombination that produces a

cobalt (II) cyclic species. Finally, reductive elimination regenerates a cobalt (0) species to re-enter the catalytic cycle (Figure 9).



Scheme 30. Cobalt-catalyzed KTC of haloacetal substrates.

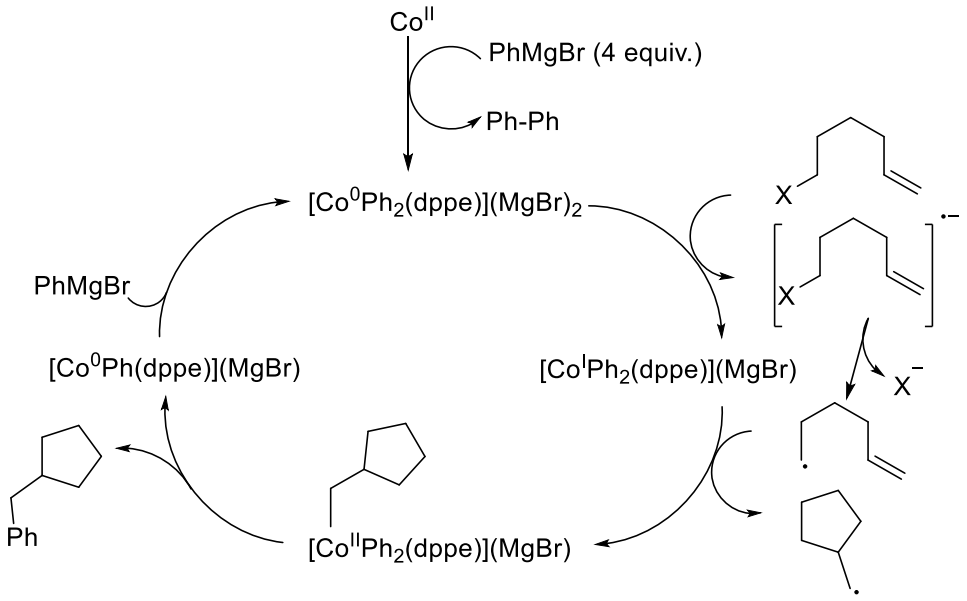
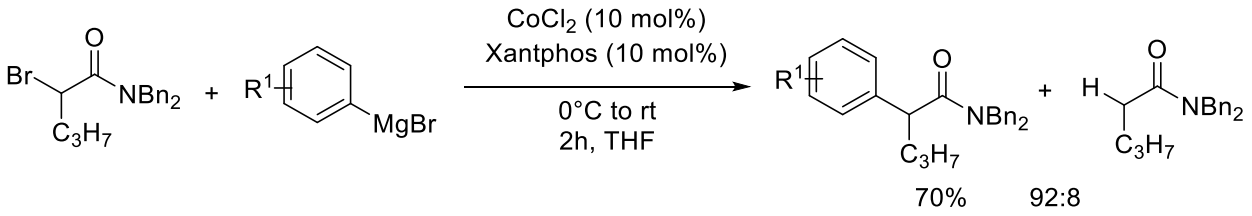
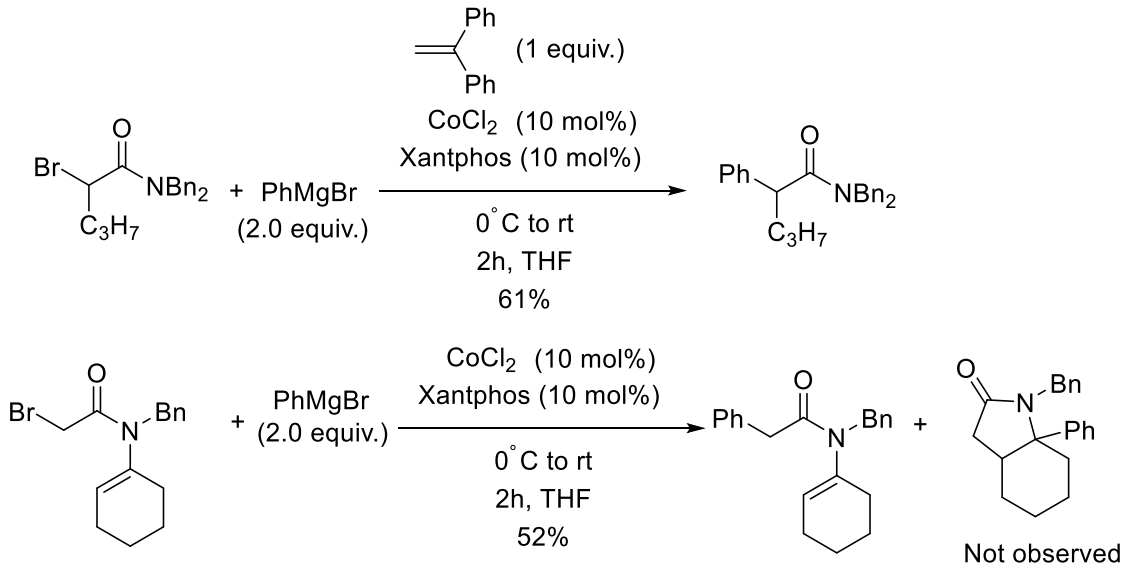


Figure 9. Mechanism proposed for cobalt-catalyzed cyclization of haloacetal substrates.



Scheme 31. Cobalt-catalyzed KTC of α-bromo amide electrophiles and aryl Grignard nucleophiles.

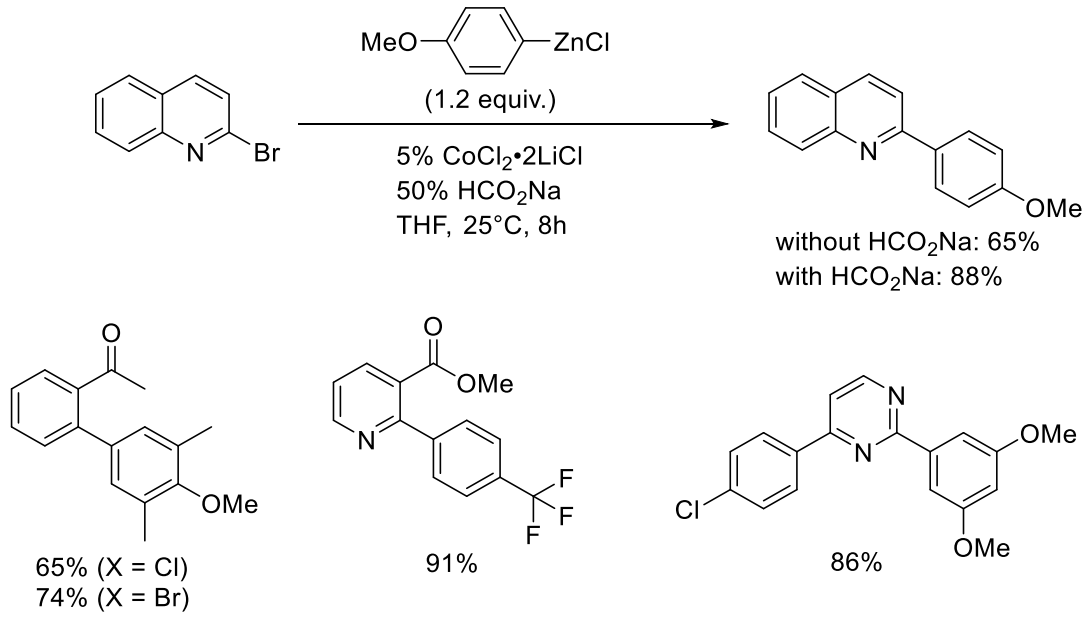


Scheme 32. Experiments to determine the presence of radical intermediates.

Cossy (2017) reported the cobalt-catalyzed cross-coupling of α-bromo amides with Grignard reagents using $CoCl_2$ in conjunction with Xantphos (Scheme 31).[101] The scope of the reaction was intolerant of ortho-substituted substrates as they were prone to dehalogenation. The cross-coupling reaction was performed in the presence of a radical scavenger to determine if single-electron transfer was involved in the mechanism. The cross-coupled product was still observed with only a slight decrease in the yield, suggesting that radicals are not involved. A radical clock control reaction was also performed, but the cyclized product was not observed (Scheme 32). The production of the linear product showed that the α-bromo amides had a different mechanistic

pathway than the non-activated alkyl halides Oshima worked with. From these results, Cossy postulated that the cobalt is likely proceeding by a concerted two electron (0-II) or (I-III) catalytic cycle.

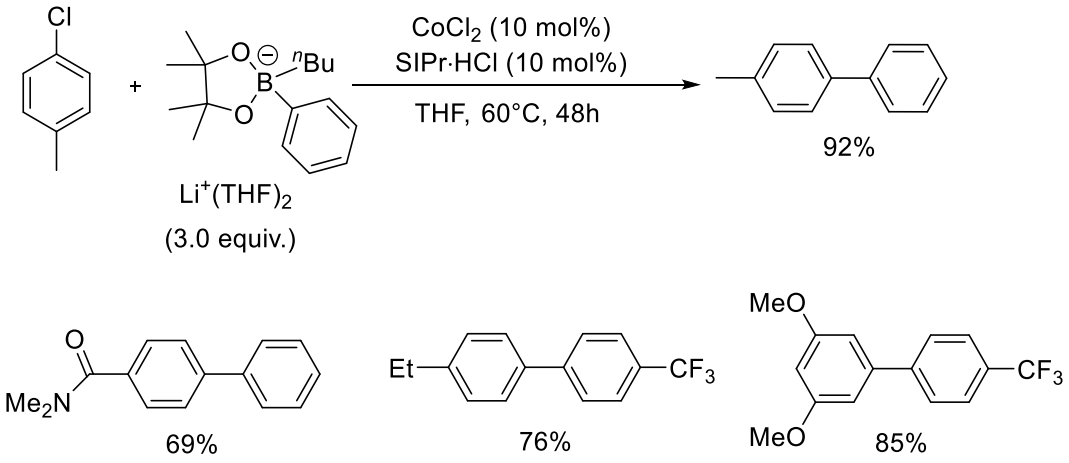
Knochel (2016) reported the Negishi cross-coupling of activated heteroaryl electrophiles using small loadings of $CoCl_2 \cdot 2LiCl$. Several functional groups were tolerated, including ketones and esters (Scheme 33).[102] Sodium formate was necessary to achieve high yields of cross-coupled product; sodium pivalate was equally effective demonstrating that that the role of the additive was as a ligand and not as a reductant.



Scheme 33. Cobalt-NHC in Negishi cross-coupling of heteroaryl electrophiles.

Bedford (2017) reported the cobalt-catalyzed Suzuki-Miyaura cross-coupling of a wide range of electrophiles with phenyl boronic acid pinacol ester using cobalt chloride and imidazolium salts (Scheme 34).[103] The reaction conditions were tolerant of esters, tertiary amines, amides, fluoro, trifluoromethyl and alkoxides whereas nitro, cyano, aldehydic and ketonic substituents on the aryl

halide partner were poorly tolerated. This was likely a result of the strongly basic conditions required for the reaction, where the boronate was prepared by combining a full equivalent of n-BuLi with phenyl boronic acid phenyl ester.



Scheme 34. Cobalt-NHC in Suzuki-Miyaura cross-couplings of phenyl boronic acid ester and aryl electrophiles.

The Chirik group prepared bis(phosphino)pyridine cobalt(I) alkoxide or aryloxide complexes (iPrPNP)CoOR (R = phenoxide or alkoxide) to gain mechanistic understanding of cobalt-catalyzed Suzuki-Miyaura cross-coupling.[104] These complexes were studied in stoichiometric reactions with heteroaryl boron nucleophiles and aryl triflates. The intermediate products for each step in the catalytic cycle were isolated and their structures determined by X-ray diffraction to assist in assembling the catalytic cycle shown in Figure 10. They proposed that transmetalation of an aryl group from a neutral boron reagent to a CoOR complex (i) generates a cobalt(I)aryl complex (ii). This step was found to only work with heteroaryl boron reagents with an exposed lone pair on the heteroatom which may be required to initiate the transmetalation step. This is followed by an interaction with the aryl electrophile to promote a carbon−carbon bond. The product is released to

generate a cobalt(I) halide (iii), which then exchanges the halide ligand with exogenous base to regenerate the Co-OR species (i).

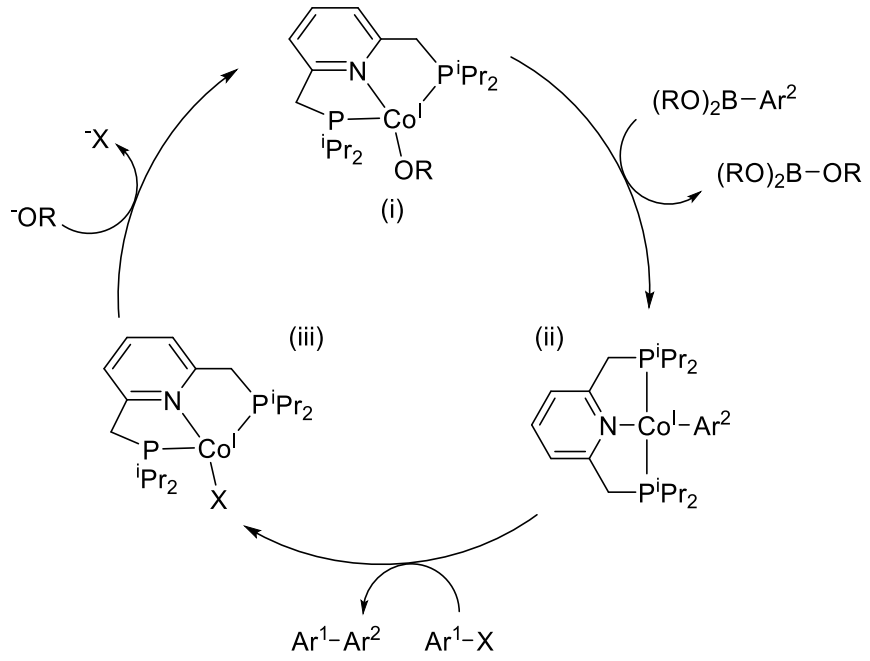
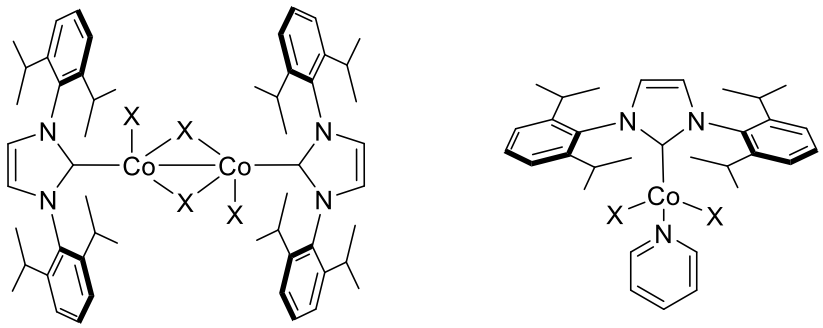


Figure 10. Catalytic cycle for Suzuki cross-coupling of heteroaryl aryl boronic acid nucleophiles with aryl electrophiles.

1.5.2 − Pre-formed Cobalt-NHC Catalyst for Cross-coupling

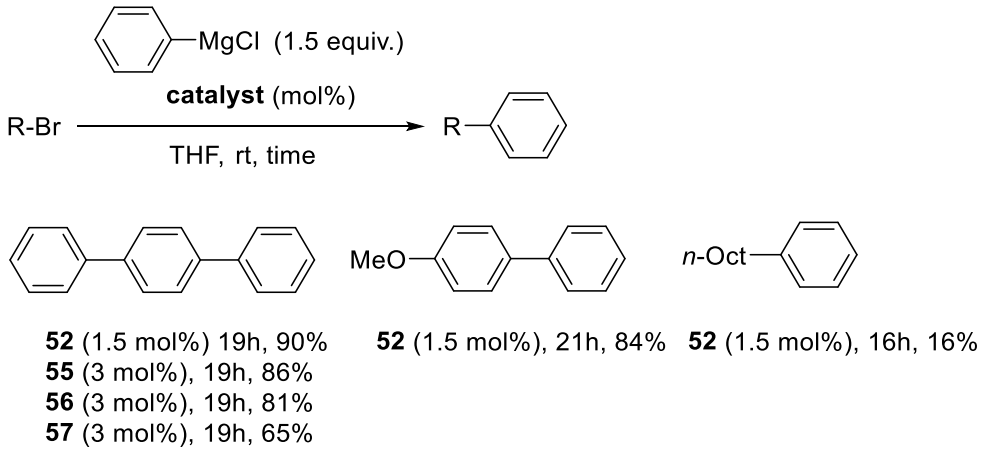
Matsubara (2012) reported a cobalt pre-catalyst similar to Pd-PEPPSI that promoted KTC cross-couplings (Figure 11).[105] The complexes were prepared by adding IPr carbene to cobalt precursor salt (CoX_2) and pyridine. Complexes prepared from $CoCl_2$ demonstrated poorer reactivity than analogous complexes prepared from the iodide or bromide salts (Scheme 35).



$[Co_2(IPr)_2(\mu\text{-}X)_2]$
X = I, **52**
X = Br, **53**
X = Cl, **54**

$[Co(IPr)X_2(Pyr)]$
X = I, **55**
X = Br, **56**
X = Cl, **57**

Figure 11. Pre-formed Cobalt NHC complexes.[105]



52 (1.5 mol%) 19h, 90%
55 (3 mol%), 19h, 86%
56 (3 mol%), 19h, 81%
57 (3 mol%), 19h, 65%

52 (1.5 mol%), 21h, 84%

52 (1.5 mol%), 16h, 16%

Scheme 35. $Co_2(IPr)_2(\mu\text{-}I)_2$ in KTC cross-coupling reactions with aryl Grignard nucleophiles and aryl electrophiles.

Plan of Study

Research Objectives for Developing Pre-formed Cobalt-NHC Catalysts

Cobalt has been reported for cross-coupling but the catalytic systems developed thus far based on Co are limited in functional group tolerance and substrate scope. Also, examples using NHCs have not reported ligands that exceed the steric bulk of IPr. The Organ group has shown that bulkier NHC ligands (**24-25**) in Pd-PEPPSI complexes have significantly improved catalyst reactivity for KTC, Negishi, Suzuki-Miyaura, and Buchwald-Hartwig amination. If a catalytic system based on Co can be developed such that it follows a two-electron catalysis pathway analogous to Pd, it is hypothesized that bulky Co complexes similar in structure to **35**, **38**, or **39** will enable cobalt to catalyze more challenging and functional-group tolerant Negishi and Suzuki-Miyaura cross-couplings. It is expected that these complexes can be prepared by following the protocol used by Matsubara to synthesize **55-57**. To reach this objective, a key goal of this project is to develop general and robust methods for the synthesis of air-stable Co pre-catalysts.

This portion of the thesis describes: 1) the synthesis of cobalt complexes with NHC ligands **24-25** with the (I), (II) or (III) oxidation states, 2) characterization of these complexes, and, 3) the exploration of their reactivity with challenging substrates in Negishi and Suzuki-Miyaura cross-coupling reactions.

Research Objectives for Developing Pre-formed Nickel-NHC Catalysts

Pre-formed nickel NHC catalysts have been reported for Buchwald-Hartwig aminations, but they are unlikely to make an impact in the field as they require the use of harsh conditions to have any level of coupling and for the most part this makes their use incompatible with base-sensitive functional groups. Although there are reports of complexes with IPr, SIPr, and IPr*, there are no reports of catalysts using bulky and flexible NHC ligands **24-25** that, as mentioned above, have

shown incredibly high levels of reactivity with Pd. Like with cobalt, if nickel follows a catalytic cycle similar to Pd (e.g., 0-II), it is hypothesized that nickel catalysts analogous to **35**, **38**, or **39** will enable Buchwald-Hartwig aminations with much milder bases.

Realizing the above objective will require: 1) the synthesis of nickel complexes with NHC ligands **24-25** with the (I) or (II) oxidation states, 2) characterization of these structures, and 3) exploring their reactivity in Buchwald-Hartwig aminations using mild bases.

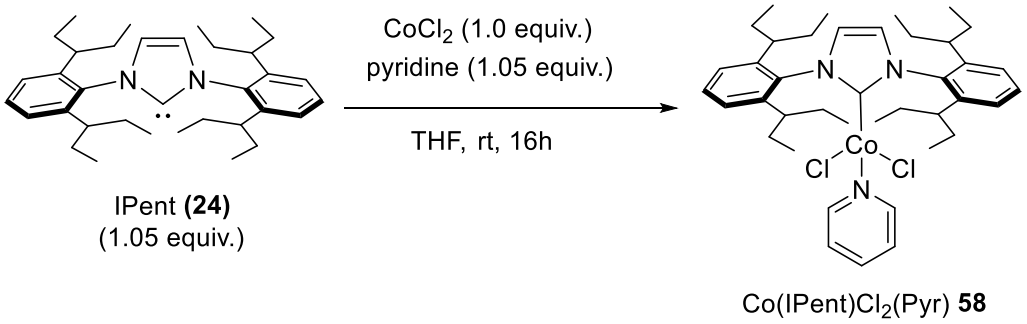
If one or both of above objectives are realized, Co- and/or Ni-based catalysts and their associated protocols would represent a desirable, more sustainable alternative to palladium catalysts for cross-coupling.

Chapter 2 – Results

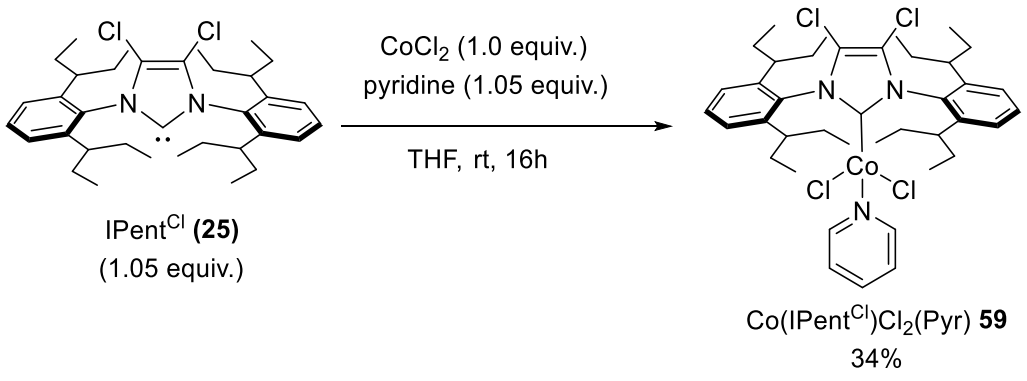
2.1 − Preparation of Cobalt Catalysts for Cross-coupling Reactions

2.1.1 – Preparation of Cobalt Complexes

Complexes **58** and **59** were synthesized by following Matsubara's procedure using NHCs **24** and **25**[105] and their respective structures were confirmed by X-ray diffraction (Schemes 36-37, Figures 12-13).



Scheme 36. Preparation of Co(IPent)Cl_2(Pyr).



Scheme 37. Preparation of Co($IPent^{Cl}$)Cl_2(Pyr).

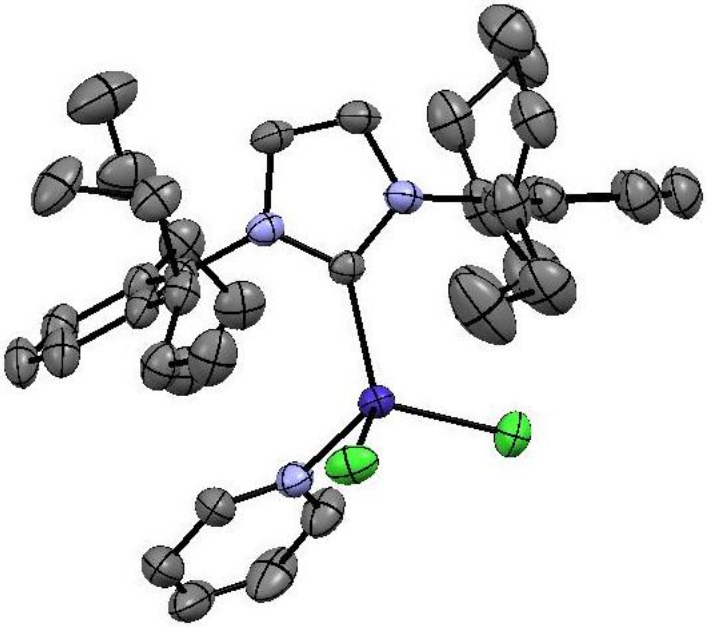


Figure 12. X-ray crystal structure of **58** (hydrogen atoms are omitted for clarity).

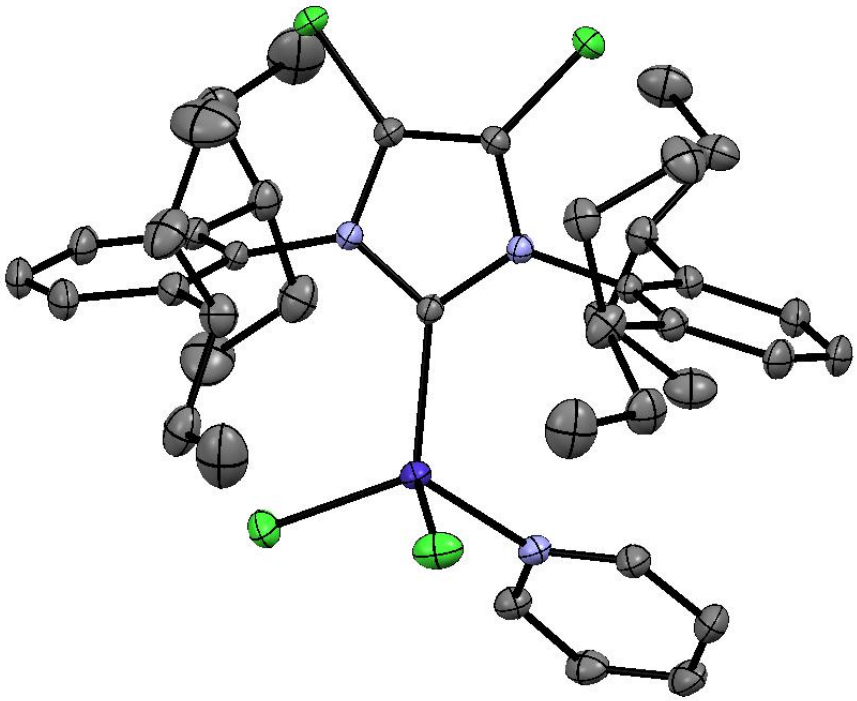
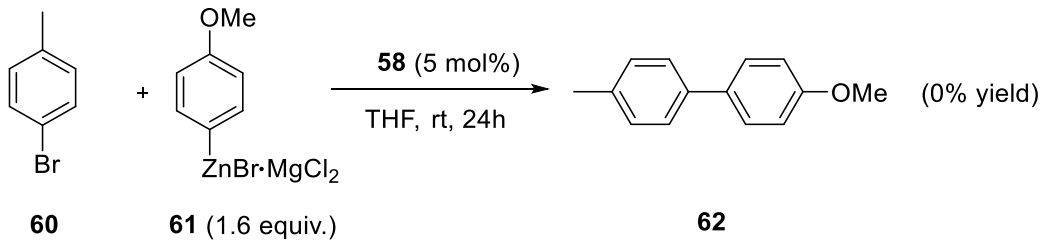


Figure 13. X-ray crystal structure of **59** (hydrogen atoms are omitted for clarity).

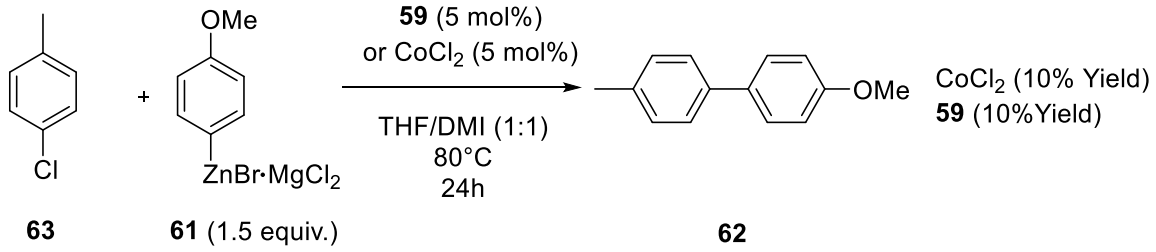
2.1.2 – Negishi Cross-coupling Reactions

The reactivity of pre-catalyst **58** was explored in the Negishi cross-coupling of 4-bromotoluene (as the electrophile) and 4-methoxyphenyl magnesium bromide (as the nucleophile). The arylzinc halide was prepared *in situ* by the addition of zinc chloride to the corresponding Grignard prior to mixing with the catalyst and electrophile. **58** failed to produce more than a trace-amount of the desired cross-coupled product (Scheme 38).



Scheme 38. Attempted Negishi cross-coupling using **58**.

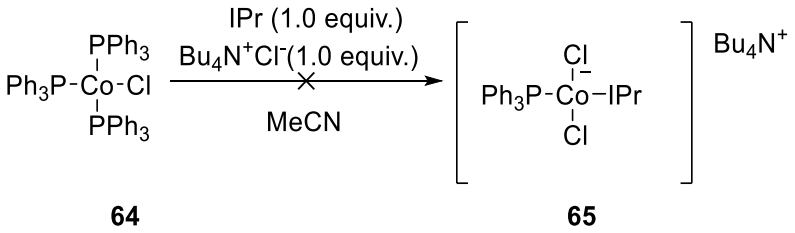
Since Bedford's report described an improvement in yields using 4-chlorotoluene rather than its bromide congener (see Scheme 33), the reactivity of **59** was compared to anhydrous cobalt (II) chloride in a Negishi cross-coupling of 4-chlorotoluene with the same nucleophile. Both reactions yielded 10% of the cross-coupled product, demonstrating that the ligand was not beneficial to the reactivity of the complex (Scheme 39).



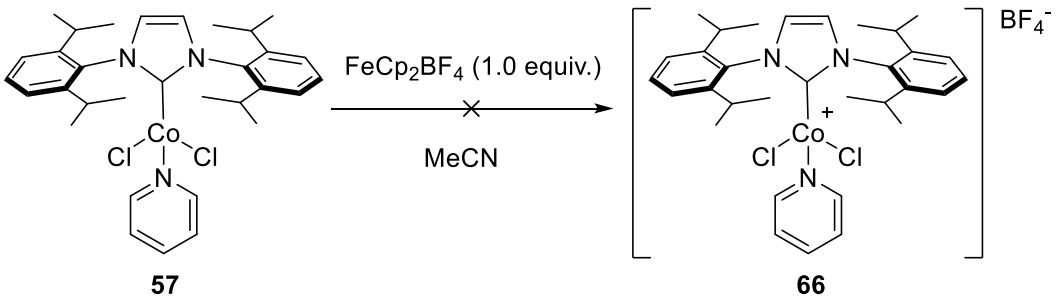
Scheme 39. Attempted Negishi cross-couplings using **59**.

2.1.3 – Synthesis of Cobalt (I) or Cobalt (III) Complexes

Several reports suggested that cobalt-mediated cross-coupling could follow a concerted 2-electron I-III cycle instead of the 0-II cycle, hence, it was hypothesized that preparing a cobalt (I) or cobalt (III) pre-formed complex may enable Negishi cross-couplings.[101,104] Chlorotris(triphenylphosphine)cobalt(I) (**64**), which is commercially available, was thought to be a suitable partner to react with the free-IPr carbene in the presence of tetrabutylammonium chloride to provide complex **65** (Scheme 40). Unfortunately, the reaction mixture proved complex and no identifiable **65** could be isolated.



Scheme 40. Attempted substitution of chlorotris(triphenylphosphine)cobalt(I).

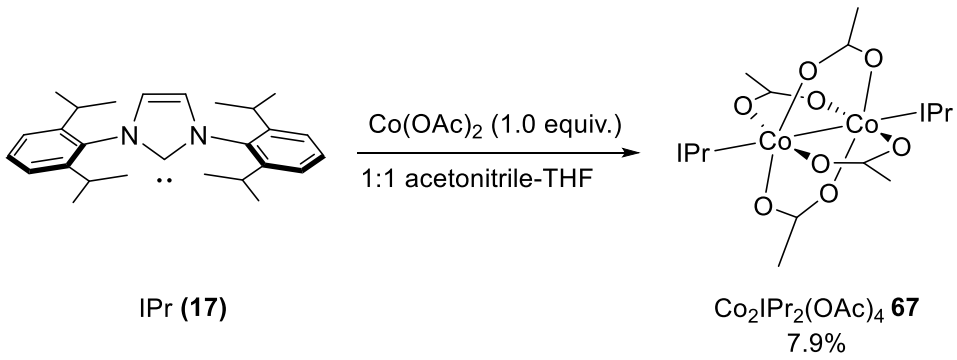


Scheme 41. Attempted oxidation of $Co(IPr)Cl_2(Pyr)$.

An attempt to oxidize **57** with ferrocenium tetrafluoroborate to produce a cobalt (III) complex with an outer-sphere tetrafluoroborate anion was next attempted. Upon adding the salt the solution

changed from blue to black, however, attempts to isolate or characterize the product were unsuccessful (Scheme 41).

2.1.4 – Preparation of Alternative Pre-formed Cobalt Complexes.



Scheme 42. Preparation of **67**.

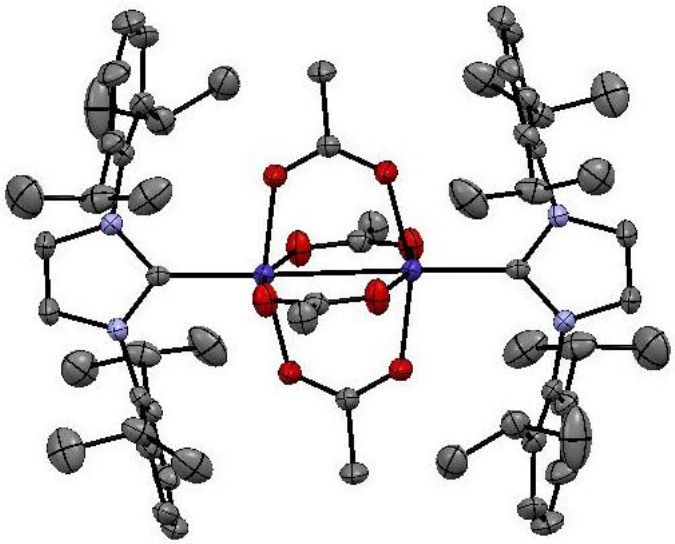
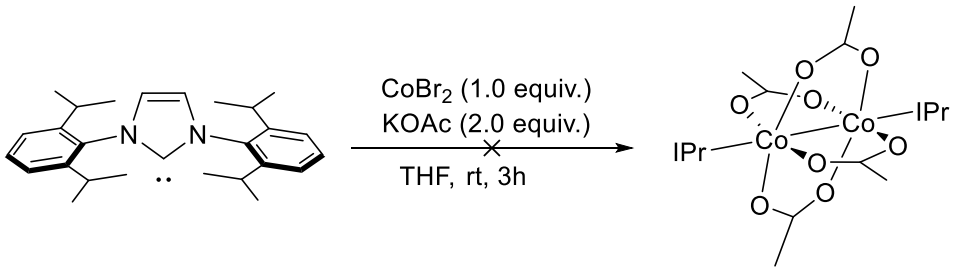


Figure 14. X-ray crystal structure of **67** (Hydrogen atoms are omitted for clarity).

Knochel had reported that the acetate ligand was beneficial to the reactivity of the cobalt catalyst in Negishi cross-couplings.[102] Inspired by these findings, the preparation of cobalt-paddlewheel complex **67** was attempted, where it was hoped that the acetate ligand could improve catalytic

activity. Complex **67** was prepared by adding IPr carbene to anhydrous cobalt (II) acetate and characterized by X-ray diffraction (Scheme 42, Figure 14).

The low yield of **67** indicated the need for alternative methods of preparation. It was proposed that the low yield was the result of poor solubility of cobalt acetate. In another attempt to prepare **67**, cobalt bromide was mixed with potassium acetate in THF prior to the addition of the NHC (Scheme 43). The precipitation of white powder suggested that ion exchange had occurred and the IPr carbene was then added. The product was isolated following the same work-up procedure used in Scheme 42, but instead of **67**, a trinuclear cobalt complex was obtained (Scheme 43, Figure 15).



Scheme 43. Attempted alternate preparation of **67**.

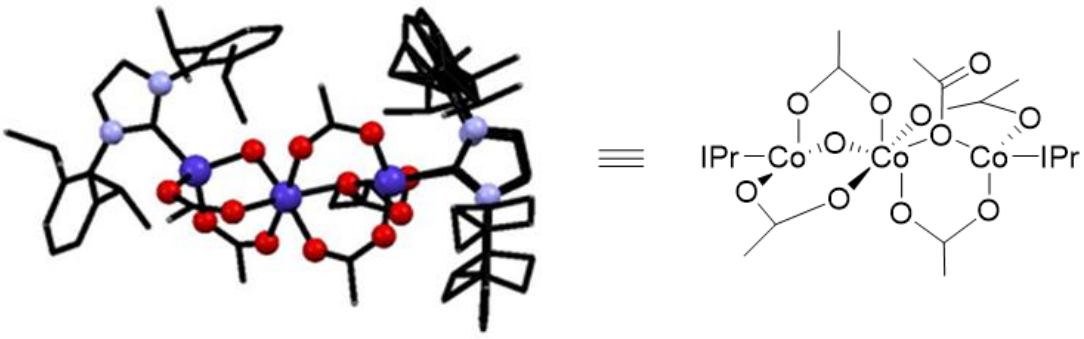
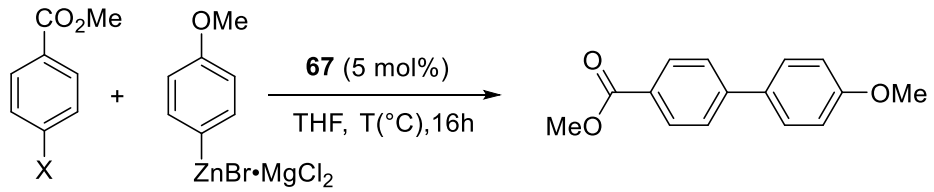


Figure 15. X-ray crystal structure of the cobalt trinuclear complex $[Co_3IPr_2O(OAc)_5]$.

Moving forward, with **67** in hand several Negishi cross-coupling reactions were attempted with an activated electrophile (**68**) under a variety of conditions, but only trace amounts of cross-coupled product were obtained (Table 1).

2.1.5 – Cross-coupling Reactions Using Complex 67

Table 1. Screen for halogen and temperature in Negishi cross-coupling reactions with **67**



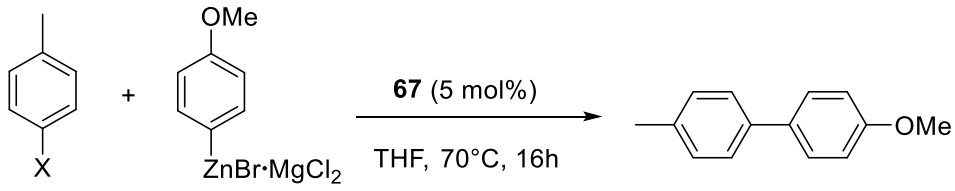
68 **61** (2.5 equiv.) **69**

Entry No.	X	Temperature (°C)	%Yield (69)[a]
1	Br	25	Trace
2	Cl	25	Trace
3	Cl	50	5

[a] Isolated yields are reported on products purified by flash chromatography.

The reactivity of complex **67** was also examined in the previous set of Negishi cross-couplings with different aryl halides, however, changing the halogen did not prove beneficial for the reaction (Table 2).

Table 2. Screen of para tolyl halides in Negishi cross-coupling with **67**



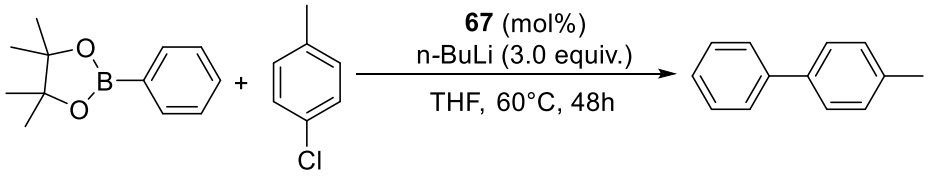
70 **61** (2.5 equiv.) **62**

Entry No.	X	%Yield (62) [a]
1	Br	13
2	I	0
3	Cl	0
4 [b]	Br	10

[a] Isolated yields are reported on products purified by flash chromatography.
[b] Activation of **67** with 20 mol % $TMSCH_2MgCl$

To see if the catalysts were active outside of Negishi couplings, other reactions were considered. Bedford published a protocol for cobalt-catalyzed Suzuki-Miyaura cross-coupling[103] so the complex (**67)** was applied in similar reactions following his procedure. It was found that **67** was in fact active and produced a yield of 90% of cross-coupled product **72** (Table 3). When the loading of **67** was lowered from 5 mol % to 1 mol%, the yield dropped slightly to 75%. This result showed that the pre-formed Cobalt-NHC complex was superior to the *in* situ-formed catalyst in Bedford's report, where $CoCl_2$ and the NHC salt afforded only 32% of **72**.

Table 3. Screen for catalyst loading in Suzuki-Miyaura cross-coupling with **67**

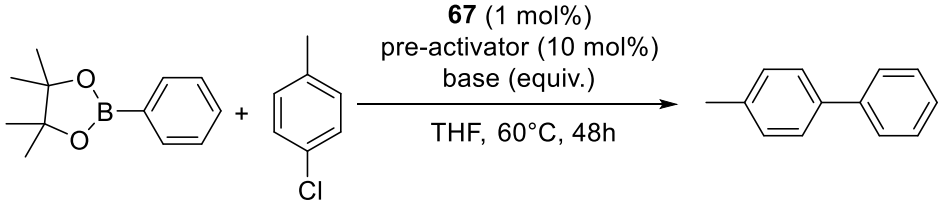


71 (3.0 equiv.) **63** **72**

Entry No.	67 (mol %)	%Yield (72)[a]
1	5	90
2	1	75

[a] Yield determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene internal standard.

Table 4. Screen for bases in Suzuki-Miyaura cross-coupling with **67**



71 (3.0 equiv.) **63** **72**

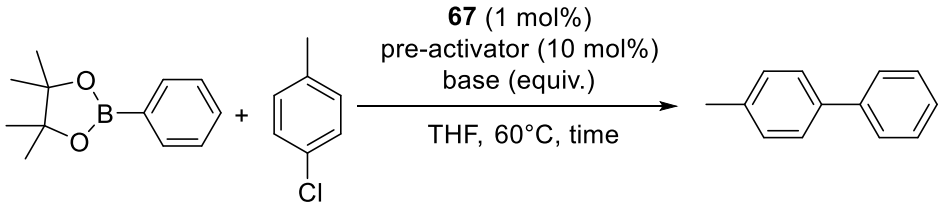
Entry No.	Pre-activator	Base (equiv.)	Solvent	%Yield (72)
1	$TMSCH_2MgCl$	NaOEt (3.0)	THF	0
2	*i*PrMgCl· LiCl	NaOEt (3.0)	THF	0
3	*i*PrMgCl· LiCl	NaO*t*Bu (4.5)	THF	0
4	*i*PrMgCl· LiCl	KOEt (4.5)	DMF	0
5	*i*PrMgCl· LiCl	NaOEt (4.5)	DMF	0

Despite the promising results, the reaction conditions would be incompatible with base-sensitive functional groups.[103] It was thought that changing the base from n-BuLi to weaker bases would allow for the development of a mild Suzuki cross-coupling protocol using **67** at low catalyst loadings (Table 4).

Modifications to the protocol involved changing the base from n-BuLi to less basic alkoxides. Since n-BuLi could have been involved in the 'activation' of the cobalt, a catalytic amount of reductant was added prior to adding the substrates. The first reductant assayed was (trimethylsilyl)methyl magnesium chloride with sodium ethoxide base, but this failed to produce **72** (Table 4, entry 1). The reductant was changed to Turbo Grignard since it was thought that the reduction mechanism could be via beta-hydride elimination, but this also failed to yield **72** (entry 2). It was thought that the low solubility of the base in THF could be problematic, so the base was changed to sodium tert-butoxide, but this improved nothing (entry 3). Finally, the reactions were repeated in the presence of potassium ethoxide and sodium ethoxide in DMF, but these changes did not lead to product either (Table 4, entries 4-5).

The reductant was changed to n-butyl lithium to converge with Bedford's protocol, as the n-butyl lithium may be essential for cobalt activation (Table 5, entry 1). Sodium ethoxide proved ineffective and it was thought that the cobalt could be activated by the boronate ester. This proved to be ineffective and the base was changed to highly soluble lithium isopropoxide, but no product resulted (entry 3). The reaction was attempted again with no reductant and with only lithium isopropoxide to no avail (entry 4). A catalytic amount of 4-methoxy phenyl magnesium bromide, used by the Tonzetich group for cobalt-catalyzed KTC cross-couplings, was utilized as a reductant but it too proved ineffective (entry 5).[106]

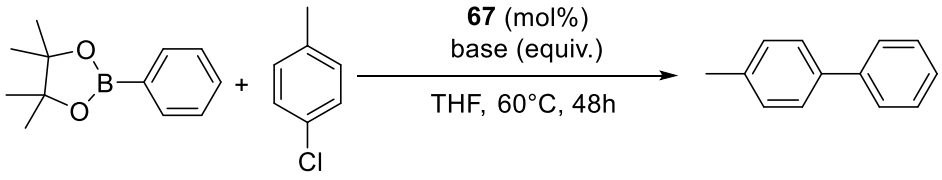
Table 5. Base screen for Suzuki-Miyaura cross-coupling with **67**



71 (3.0 equiv.) **63** **72**

Entry No.	Pre-activator	Base (equiv.)	Time	% Yield (72)
1	n-BuLi	NaOEt (4.5)	48	0
2	n-BuLi (10 mol%) + PhBPin (10 mol%)	KOMe (3.0)	24	0
3	n-BuLi	LiO*i*Pr (3.0)	24	0
4	-	LiO*i*Pr (3.0)	24	0
5	4-Methoxy Phenyl MgBr	LiO*i*Pr (3.0)	24	0

Table 6. Base screen for Suzuki-Miyaura cross-coupling with **67**



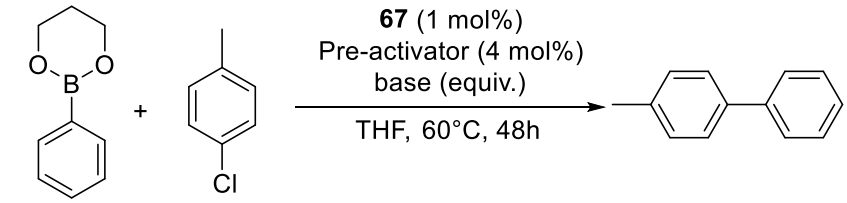
71 (3.0 equiv.) **63** **72**

Entry No.	67 (mol%)	base (equiv.)	% Yield (72)
1	1	$ZnBu_2$ (3.0 equiv)	0
2	5	$MgBu_2$ (3.0 equiv)	0

The base was changed to dibutyl zinc but failed to yield **72**. (Table 6, entry 1). The dibutyl magnesium was also used but failed to yield **72** (Entry 2).

Finally, less sterically hindered nucleophile (**73**) was explored, however, the reaction failed to yield any cross-coupled product (Table 7, entries 1-2).

Table 7. Base screen for Suzuki-Miyaura cross-coupling with **67**



73 (3.0 equiv.) **63** **72**

Entry No.	Pre-activator	base (equiv.)	% Yield (72)
1	iPrMgCl· LiCl	KOtBu (4.5)	0
2	iPrMgCl· LiCl	NaOEt (4.5)	0

2.1.6 – Additional Attempt to Procure a Pre-formed Cobalt (I) catalyst

It was hypothesized that a novel cobalt (I) complex could be prepared from Heck's cobalt allyl tricarbonyl complex by substituting one of the carbonyl groups with an IPr ligand. The cobalt allyl tricarbonyl could be prepared via the sodium cobaltate intermediate, however, the milder preparation of zinc cobaltate had been reported by the Baker group.[107,108] Based on these reports, it was thought that cinnamyl chloride could be added to zinc cobaltate to produce cinnamyl cobalt (I) tricarbonyl and that an equivalent of IPr could substitute a carbon monoxide ligand to produce a Co(I)cinnamyl(IPr)$(CO)_2$ complex (Scheme 44).

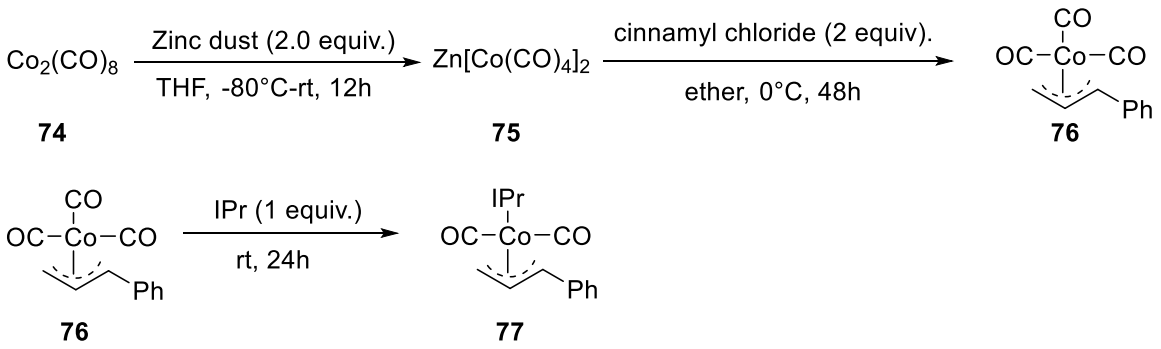
An excess amount of cinnamyl chloride in ether was added to the beige powder that was isolated from the reduction of dicobalt octacarbonyl with zinc dust. As expected, a white powder was observed to have precipitated after leaving the reaction to stir for 48 h. Also, the expansion of the crimped Teflon seal indicated that free carbon monoxide gas had been produced.

A yellow homogenous solution was obtained after the precipitate was removed by filtration. Following the addition of IPr carbene, the yellow solution gradually turned brown and precipitated a brown powder. NMR spectroscopic analysis of the brown powder isolated from the ligand displacement reaction yielded broad paramagnetic signals. This left growing crystals for X-ray diffraction as the best option for analysis. Slow evaporation by hexanes produced red, blue, and green crystals. Diffraction of the crystals determined that they each had different structures and none of them were the desired product (Figures 16-18).

Diffraction of the red crystal indicated the structure to be a cobalt dimer, with a cobalt-cobalt bond, three carbon monoxide ligands, and an IPr coordinated to each cobalt (Figure 16). This crystal structure has not been reported with IPr but it has been reported with IMes by the Tonzetich group.[106]

The diffraction of the green crystals produced a structure resembling that of an imidazolium salt of $[Co(CO)_4]^-$ with four carbon monoxide ligands (Figure 17).

Finally, the structure of the blue crystal was determined to be identical to **54**, which has been previously reported by Matsubara (Figure 18). Based on Heck's report, it is suspected that the excess addition of cinnamyl chloride resulted in the production of $CoCl_2$.[108]



Scheme 44. Attempted preparation of cobalt (I) complex.

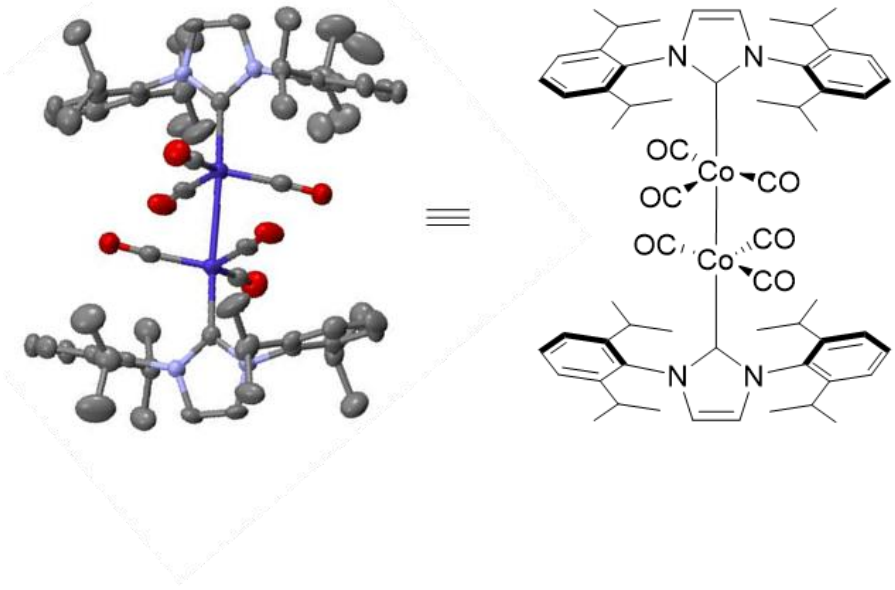


Figure 16. X-Ray crystal structure of the red crystal isolated from the reaction outlined in Scheme 44.

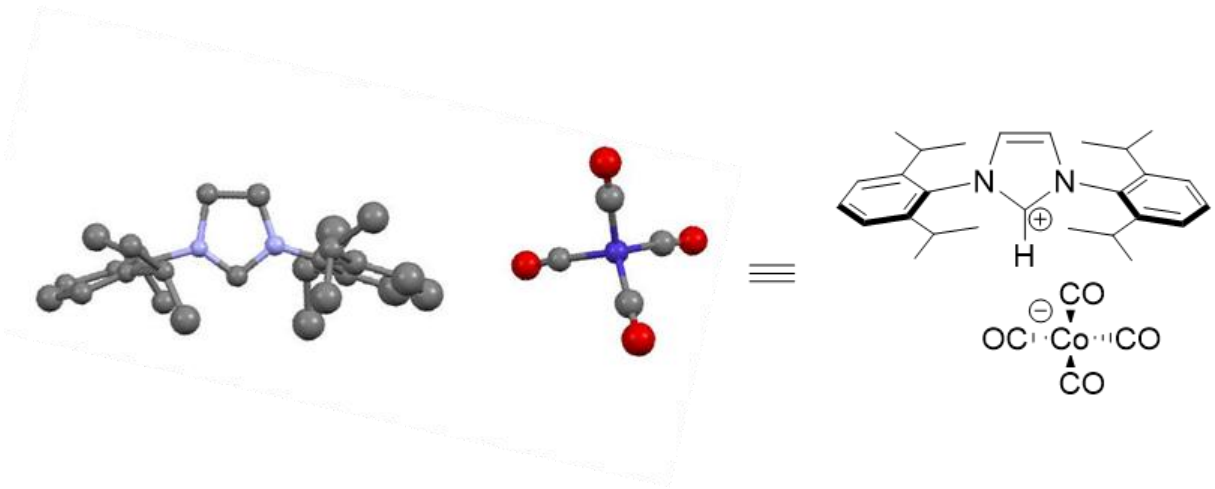


Figure 17. X-ray crystal structure of the green crystal isolated from the reaction outlined in Scheme 44.

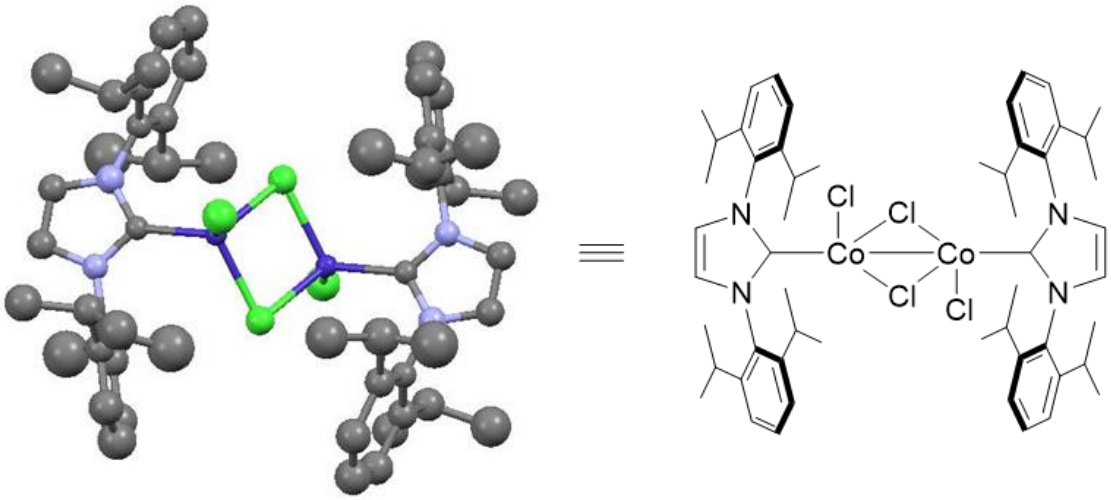


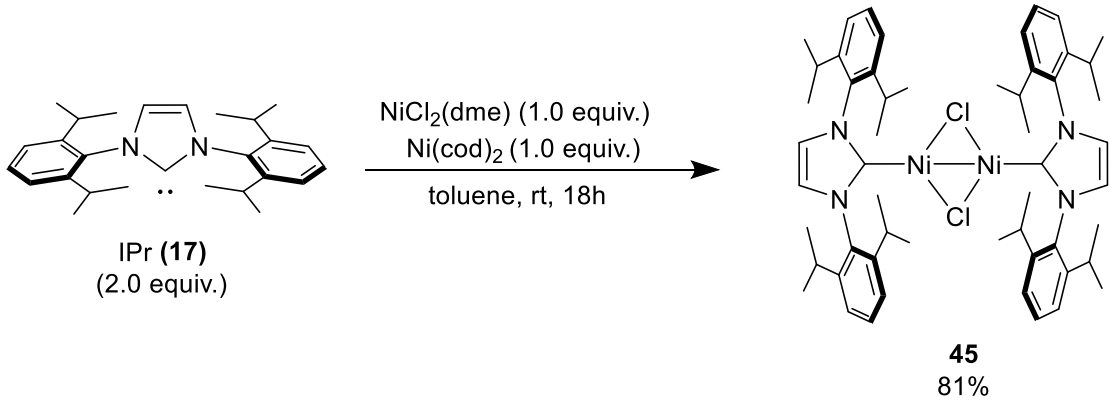
Figure 18. X-ray crystal structure of the blue crystal isolated from the reaction outlined in Scheme 44.

2.1.7 – Conclusion

In summary, the complexes **58-59** were ineffective in Negishi cross-coupling reactions. Complex **67** was also ineffective in Negishi cross-coupling reactions but was found to be effective using Bedford's Suzuki-Miyaura cross-coupling protocol. Finally, attempts to synthesize cobalt complexes with the oxidation state of (I) or (III) were unsuccessful.

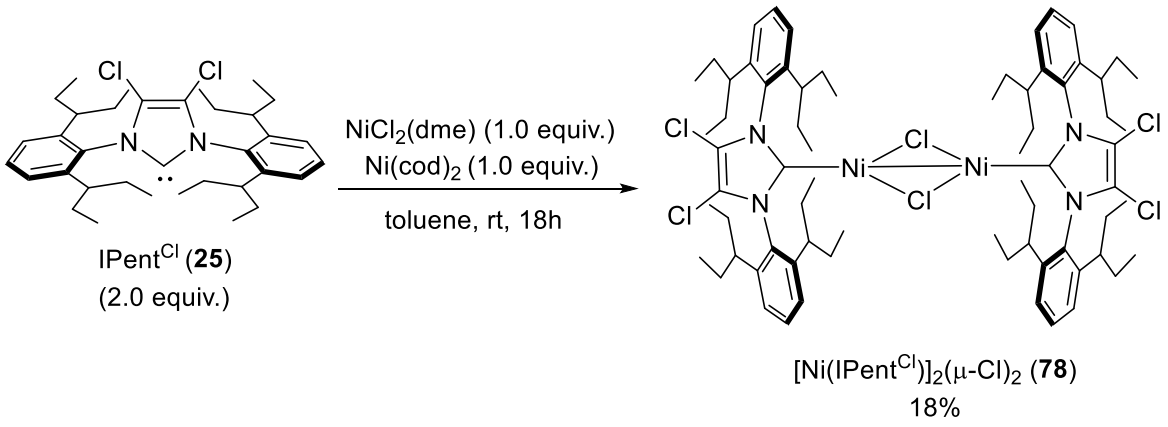
2.2 – Synthesis of Nickel-NHC Complexes for Cross-coupling reactions

Matsubara's report of BHA cross-coupling using **45** (see Figure 8) was thought to be a good starting point for the development of more structurally elaborate, and hopefully more reactive Ni-NHC pre-formed catalysts. Since the oxidative addition partners explored in Matsubara's publication were all electronically activated, i.e., electron poor, it was of interest to study the reactivity of **45** in BHA cross-couplings with more challenging substrates.[98]



Scheme 45. Preparation of **45**.[109]

Complexes **45** and **78** were prepared and characterized by NMR spectroscopy and X-ray diffraction (see Schemes 45, 46 and Figure 19). Complexes **45** and **78** were then studied in BHA cross-coupling between 4-chlorotoluene and morpholine with different bases (Table 8).



Scheme 46. Preparation of **78**.

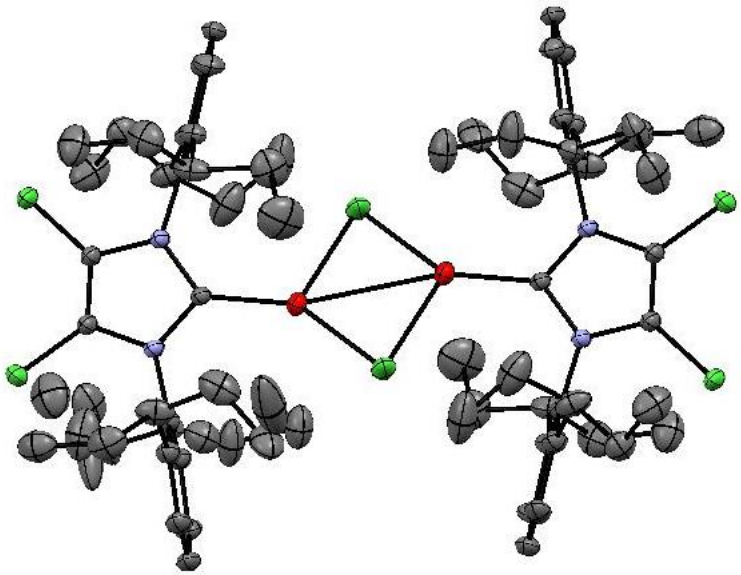
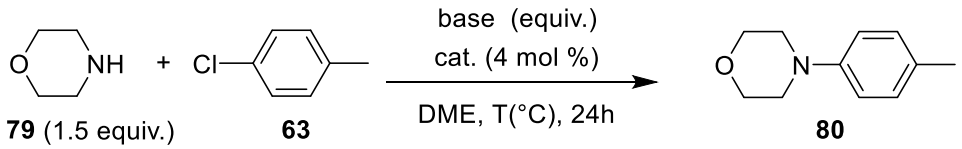


Figure 19. X-ray crystal structure of **78** (Hydrogen atoms omitted for clarity).

Complexes **45** and **78** were applied in Buchwald-Hartwig aminations using a variety of bases. Cross-coupled product **78** was isolated only from reactions using complex **45**, where sodium tert-butoxide was more effective than potassium tert-butoxide (Table 8, entries 1-2). The weaker base cesium carbonate was applied in reactions using **45** and **78** but was ineffective (entry 3). Interestingly, sodium butylated-hydroxy toluene (NaBHT) seemed to be effective for catalyst **45**

(entry 4). This was a noteworthy result since NaBHT had been reported by the Organ group as an effective base that is tolerant of sensitive functional groups.[110]

Table 8. Optimization of the Buchwald-Hartwig amination

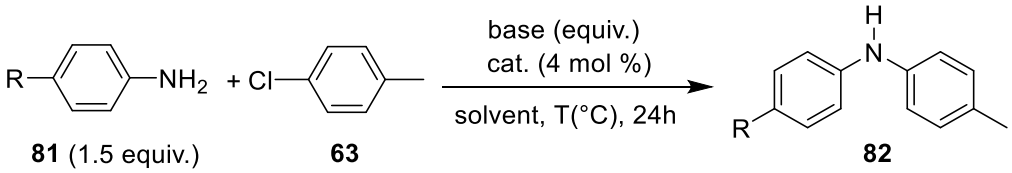


Entry No.	Catalyst	Base (equiv.)	T (°C)	% Yield (80)[a]
1	**45**	NaO*t*Bu (1.5)	r.t	83
2	**45**	KO*t*Bu (1.5)	r.t	51
3	**45**	Cs_2CO_3 (3.0)	80	0
4	**45**	NaBHT (1.5)	80	88
5	**78**	NaO*t*Bu (1.5)	r.t	Trace
6	**78**	KO*t*Bu (1.5)	r.t	Trace
7	**78**	Cs_2CO_3 (3.0)	80	0

[a] Determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene internal standard.

Complexes **45** and **78** were then applied in cross-coupling reactions with less nucleophilic aniline substrates. None of the conditions examined provided the cross-coupled product for this reaction (Table 9).

Table 9. Optimization of the Buchwald-Hartwig amination



81 (1.5 equiv.) **63** **82**

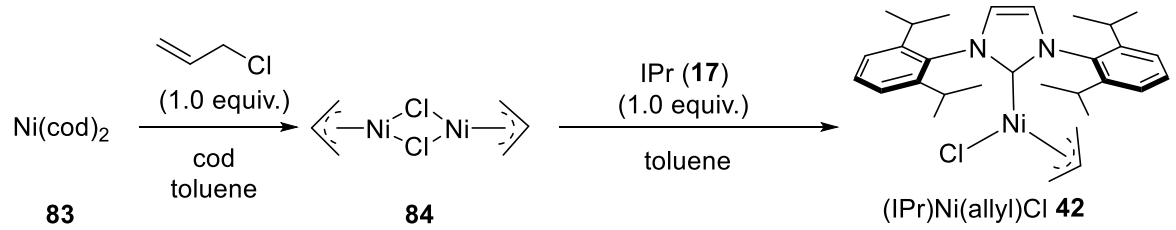
Entry No.	Catalyst	Base (equiv.)	T (°C)	Solvent	R	%Yield (82)[a]
1	**45**	Cs_2CO_3(3)	80	Toluene	OMe	0
2	**45**	NaO*t*Bu (1.5)	r.t	Toluene	OMe	0
3	**78**	NaO*t*Bu (1.5)	r.t	Toluene	OMe	0
4	**45**	NaO*t*Bu (1.5)	r.t	DME	OMe	0
5	**45**	NaO*t*Bu (1.5)	r.t	DME	Me	0

[a] Determined by ^{1}H NMR spectroscopy

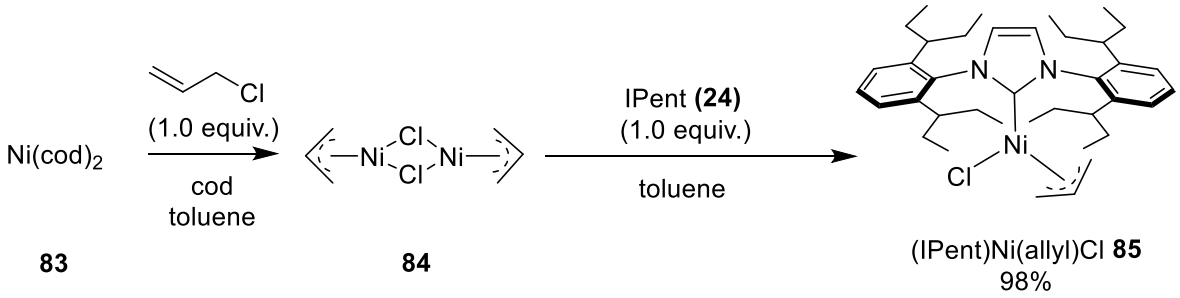
2.2.1 – Synthesis of Pre-formed Mononuclear Nickel (II) NHC Complexes for Cross-coupling

The failure of **45** to cross-couple anilines discouraged further experimentation. The Nicasio group reported **42** to be able to cross-couple secondary alkylamines with aryl halides at room temperature. This was noteworthy because most nickel catalysts have required elevated temperatures. However, the requirement of using harsh sodium tert-butoxide base was still present.

Sigman's protocol served as a guide for preparing complex **85**, which was characterized by NMR spectroscopy (Scheme 48) and X-ray diffraction (Figure 20).[111] In addition, complex **42** was prepared to study the effect of the bulkier IPent ligand (Scheme 47).



Scheme 47. Preparation of **42**.



Scheme 48. Preparation of **85**.

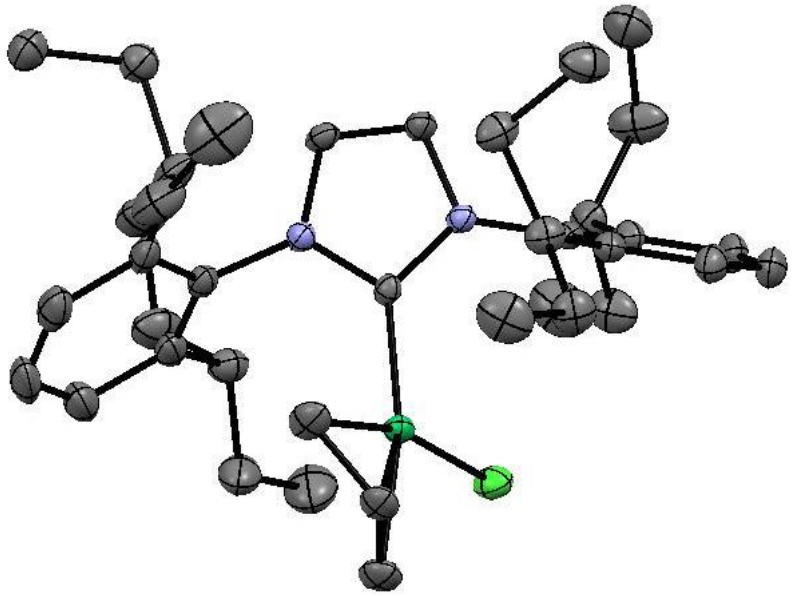
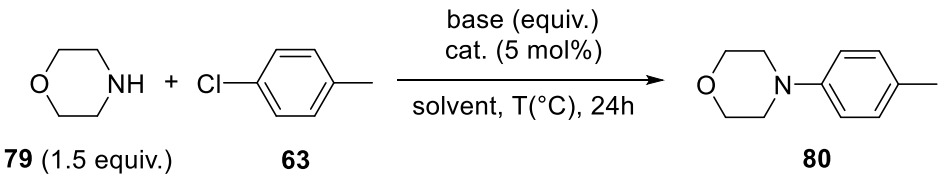


Figure 20. X-ray crystal structure of **85** (Hydrogen atoms omitted for clarity).

2.2.2 – Base Screen for Functional Group Tolerance

Several bases were explored to make the reaction conditions tolerant of sensitive functional groups. The reaction in the presence of sodium tert-butoxide gave high yields of **80** (Table 10, entry 1). NaBHT showed less efficacy as a base for both **42** and **85** than for **45** (entries 3-4). Cesium carbonate, potassium phosphate and DBU were assayed but proved to be ineffective (entries 5-8). A control reaction was set up using nickel-dichloride DME as the catalyst to ensure that the NHC ligand was required for catalysis; the reaction failed to produce cross-coupled product.

Table 10. Optimization of the Buchwald-Hartwig amination



Entry No.	Catalyst	base (equiv.)	T (°C)	Solvent	%Yield (80)[a]
1	**42**	NaO*t*Bu (1.5)	25	THF	88
2	**85**	NaO*t*Bu (1.5)	25	THF	64
3	**42**	NaBHT (1.5)	90	Toluene	35
4	**85**	NaBHT (1.5)	90	Toluene	28
5	**42**	Cs_2CO_3 (3)	90	Toluene	trace
6	**85**	Cs_2CO_3 (3)	90	Toluene	trace
7	**42**	K_3PO_4 (1.5)	90	Toluene	trace
8	**42**	DBU (1.5)	25	THF	trace

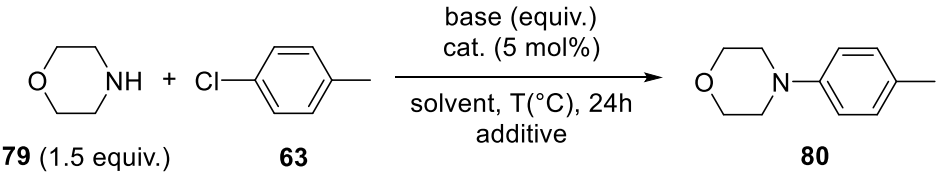
[a] Isolated yields are reported on products purified by flash chromatography

To investigate the involvement of a single electron transfer mechanism in the nickel-catalyzed BHA cross-coupling, the amination reaction was examined in the presence of 0.1 equivalents of

TEMPO (Table 11, entry 2). No cross-coupled product was produced, suggesting that radical intermediates may be integral to the nickel-catalyzed BHA reactions.

Several aminations were examined in the presence of additives to gain further insights into the reaction. Aminations were examined with di-tert-butyl peroxide, as it was hypothesized that tert-butoxyl radicals could have been formed from NaO*t*Bu in prior reactions (Table 12, entries 1-3).[112] The absence of cross-coupled product suggests that peroxide radicals were not involved in the reaction mechanism (Table 12, entries 1-3). Sodium tert-butoxide could also serve as a reductant, so aminations were conducted in the presence of cesium carbonate and TDAE (tetrakis(dimethylamino)ethylene), but no product was observed (Table 11, entries 3-4).[113]

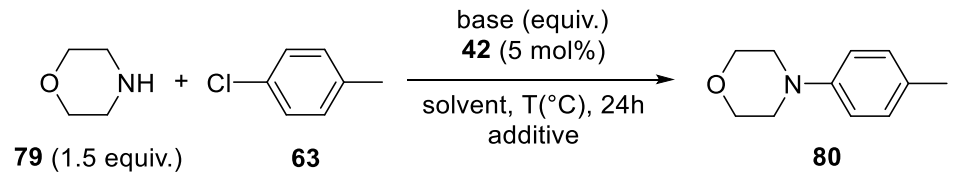
Table 11. Optimization of the Buchwald-Hartwig amination



Entry No.	Catalyst	base (equiv.)	additive (equiv.)	T (°C)	Solvent	%Yield (80)[a]
1	$NiCl_2DME$	NaO*t*Bu (1.5)	none	25	THF	trace
2	42	NaO*t*Bu (1.5)	TEMPO (0.1)	25	THF	0
3	78	Cs_2CO_3 (3)	TDAE (0.1)	90	DME	trace
4	78	Cs_2CO_3 (3)	TDAE (1.0)	90	Toluene	trace

[a] Isolated yields are reported on products purified by flash chromatography

Table 12. Optimization of the Buchwald-Hartwig amination



Entry No.	Base (equiv.)	Additive (equiv.)	T (°C)	Solvent	%Yield (80)[a]
1	-	Di-tert-butyl peroxide (0.75)	110	toluene	none
2	NaO*t*Bu (5 mol%)	Di-tert-butyl peroxide (0.75)	110	toluene	trace
3	NaO*t*Bu (5 mol%)	none	110	toluene	trace
4	KHMDS (1.5)	none	r.t	THF	54%
5	KHMDS (1.5)	$ZnCl_2$(0.75)	r.t	THF	trace
6	KHMDS (1.5)	$ZnCl_2$(0.75)	60	THF	20
7	KHMDS (3)	$ZnCl_2$(1.5)	60	THF	trace
8	NaO*t*Bu (1.5)	BHT (0)	r.t	THF	88
9	NaO*t*Bu (1.5)	BHT (0.5)	r.t	THF	59
10	NaO*t*Bu (1.5)	BHT (1.5)	r.t	THF	trace
11	NaO*t*Bu (1.5)	NaBHT (1.5)	r.t	THF	50

[a] Isolated yields are reported on products purified by flash chromatography

KHMDS has been reported to be an effective base for Buchwald-Hartwig amination. Interestingly, $Zn(HMDS)_2$ has also been reported as an effective base in functional group tolerant aminations.[114] Aminations were examined in the presence of $Zn(HMDS)_2$, however, a variety of reaction

conditions failed to provide significant yields of **80**. As expected, only KHMDS was found to be effective (Table 12, entries 4-7).

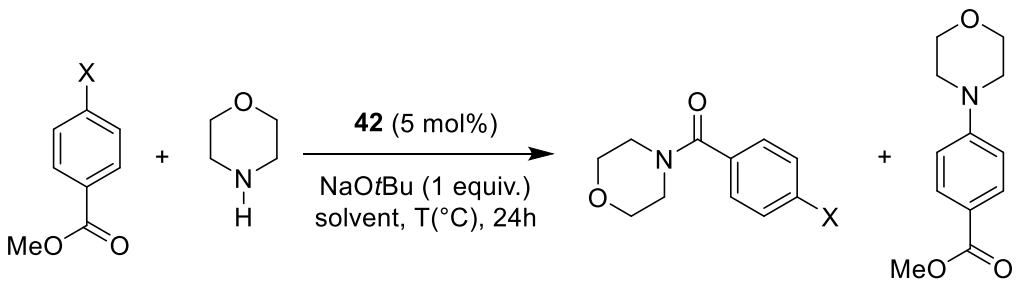
When reviewing the results from Table 10 (entries 3-4), it was not clear why the yield of **80** in the reaction using NaBHT didn't proceed past 35%. BHT is a known radical trapping agent, hence, it was hypothesized that the generation of BHT over the course of the reaction wound up inhibiting it.[115] Alternatively, since the pKa of BHT (~10) is below tert-butanol (~18), it was thought that BHT could compete with morpholine for deprotonation.

To examine the effect of BHT on the transformation, reactions were performed with 0, 0.5, and 1.5 equivalents of BHT in the presence of NaO*t*Bu. The yield of **80** decreased as the loading of BHT increased, indicating that BHT was detrimental to the reaction (Table 12, entries 8-10). It was also necessary to rule out the negative effects of NaBHT, so an additional reaction was performed with an equivalent NaBHT in the presence of NaO*t*Bu. Only 50% of **80** was isolated (Table 12), indicating that NaBHT is also deleterious to the reaction conditions. Considering that reactions still proceeded with NaBHT (Table 10, entries 3-4), it is unlikely that NaBHT itself is toxic, and that the inhibitory agent is the BHT generated from the deprotonation of the amine. However, the hypothesis that BHT was a competing acid cannot be eliminated since it could still be deprotonated by sodium tert-butoxide (entry 11).

Past work by the Organ group demonstrated that aminations of aryl esters could be performed using Pd-PEPPSI catalysts using 1.0 equivalents of NaO*t*Bu. This protocol seemed feasible as sodium tert-butoxide has been found to be the most effective base for the amination of 4-chlorotoluene.

An amination of methyl 4-chlorobenzoate with morpholine in the presence of 1.0 equivalents of NaO*t*Bu was studied. Surprisingly, the amidation product was produced favourably over the amination product (Table 13).

Table 13. Amidation reaction screen



86 **79** (1.5 equiv.) **X = Cl, 87** **X = H, 88** **89**

Entry No.	X	T (°C)	Solvent	%Yield (87 or 88)[a]	%Yield (89)
1	Cl	rt	THF	50	trace
2	Cl	60	THF	20	0
3	H	rt	THF	69	-
4	H	rt	THF	60	-
5*	H	rt	THF	50	-

[a] Isolated yields are reported on products purified by flash chromatography.
* No catalyst was added to the reaction.

The electrophile was changed from methyl-4-chlorobenzoate to methyl-4-benzoate to eliminate the possibility of cross-coupling under the same reaction conditions and provided the product of amidation. A control reaction without complex **42** was performed to ensure that the reaction was driven by the catalyst and not the base. The amide product was isolated at comparable yields,

which indicated that the reaction was driven by NaO*t*Bu. Although interesting, further experimentation was not performed because the reaction had been reported.[116]

The results of the base screen were consistent with literature reports that strong bases were required to produce the cross-coupled product. It was reasoned that sodium tert-butoxide could be involved in a single electron transfer type mechanism in the nickel-catalyzed Buchwald-Hartwig aminations since the amination reaction failed with the addition of TEMPO. Also, reports of single electron transfers using KO*t*Bu supported the suspicion of radical intermediates in the reaction mechanism.

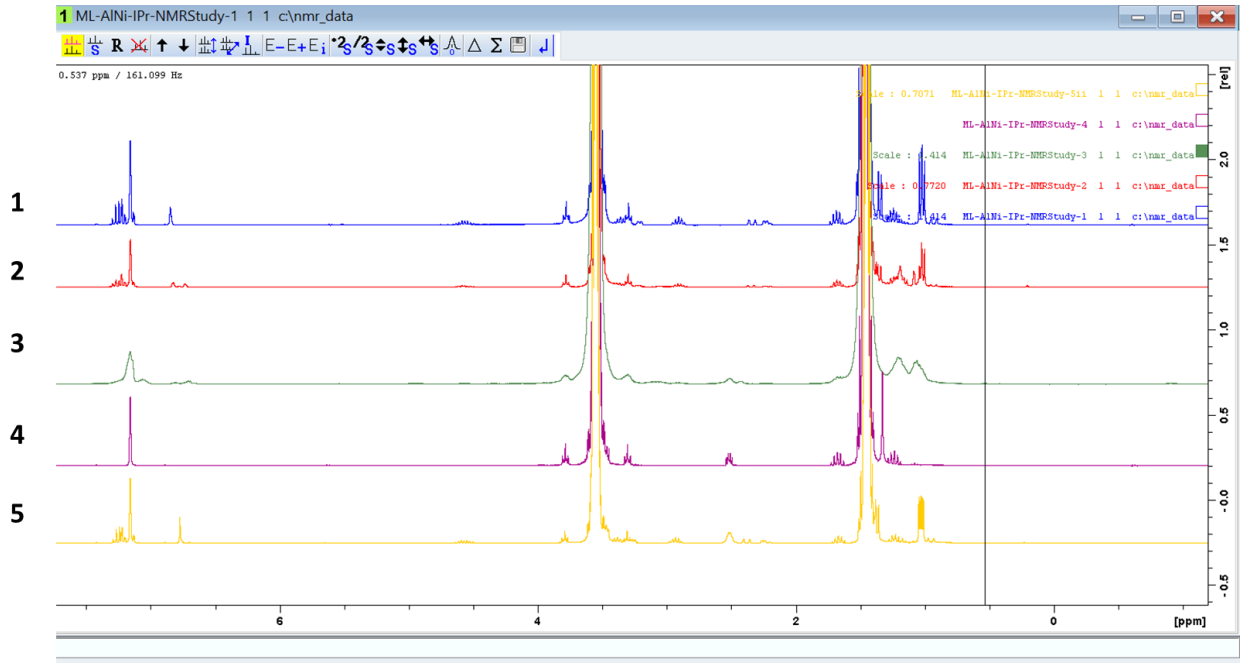


Figure 21. ^{1}H NMR of **42** after addition of reagents used in Buchwald-Hartwig amination. **1**: **42** (7.0 mg, 0.013 mmol), THF (0.1 mL), C_6D_6, **2**: **42** (7.0 mg, 0.013 mmol), NaO*t*Bu (1.2 mg, 0.013 mmol), THF (0.1 mL), C_6D_6, **3**: **42** (7.0 mg, 0.013 mmol), NaO*t*Bu (1.2 mg, 0.013 mmol), morpholine (1.1 mg, 0.013 mmol), THF (0.1 mL), C_6D_6, **4**: NaO*t*Bu (1.2 mg, 0.013 mmol), morpholine (1.1 mg, 0.013 mmol), THF (0.1 mL), C_6D_6, **5**: **42** (7.0 mg, 0.013 mmol), morpholine (1.1 mg, 0.013 mmol), THF (0.1 mL), C_6D_6

The ^{1}H NMR spectra of **42** was examined after the addition of each reagent used in the Buchwald-Hartwig amination to gain insight into the activation of the catalyst (Figure 21). No significant changes in the spectra of **42** were observed until both morpholine and sodium tert-butoxide were added, which resulted in peak broadening (Figure 21, **3**). This result was interesting, as broad signals were reported for paramagnetic nickel(I) species by Matsubara.[98] A small sample of the reaction mixture was studied by EPR and indicated a signal near 3500 Gauss, which supported the hypothesis that radical species were involved in the reaction mechanism (Figures 22, 23).

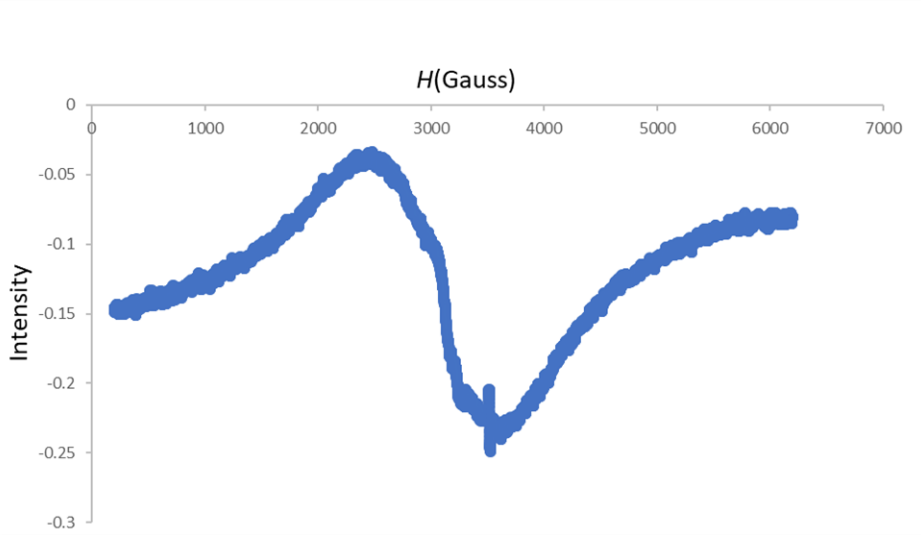


Figure 22. EPR study of Buchwald-Hartwig amination. The reaction was set up following the 'Procedure for Buchwald-Hartwig amination' (see Experimental Procedures-3.4). The Sweep Width was set to 6000 G.

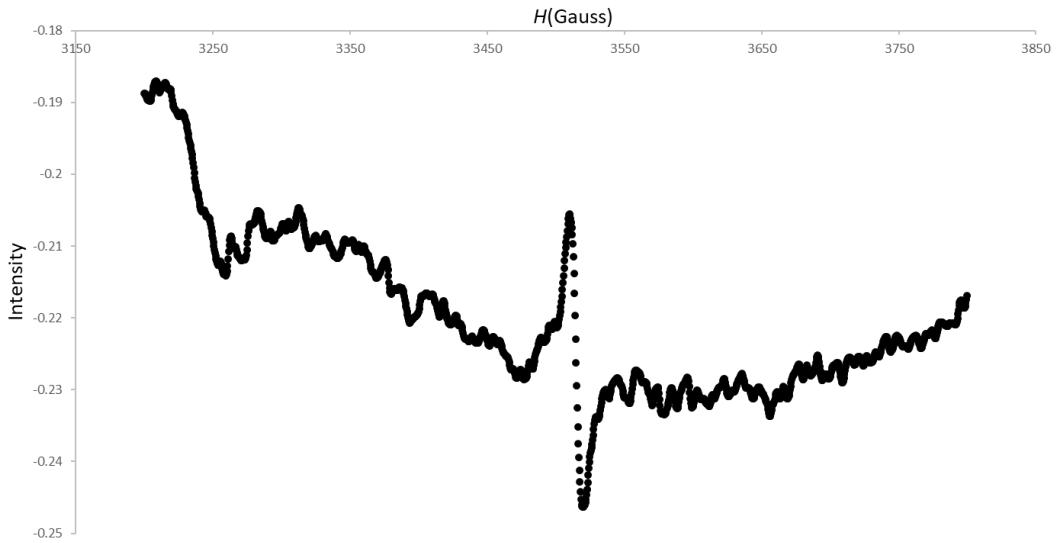
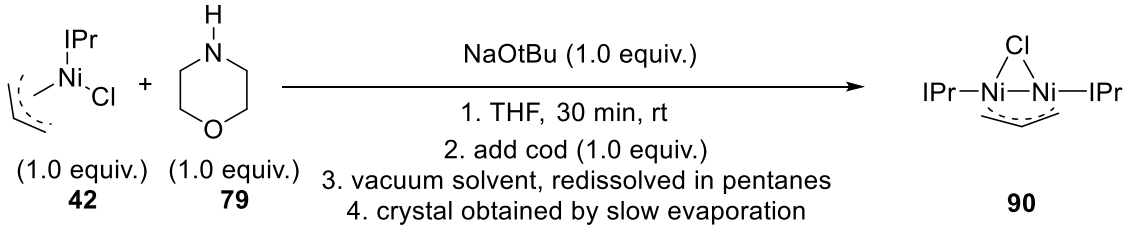
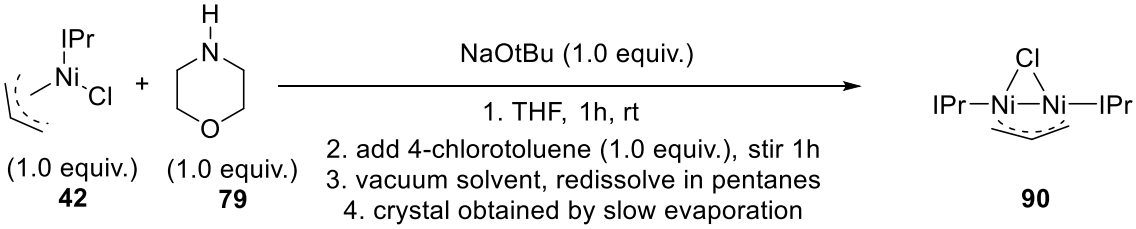


Figure 23. EPR study of Buchwald-Hartwig amination. The reaction was set up following the 'Procedure for Buchwald-Hartwig amination' (see Experimental Procedures-3.4). The Sweep Width was set to 600 G.

Reactions were performed using stoichiometric Ni catalyst in order to isolate intermediates in the reaction mechanism for aminations catalyzed by **42** (Scheme 49). It was hypothesized that both sodium tert-butoxide and morpholine were required for reduction of **42** to produce a Ni(0) species with IPr coordinated. Cyclooctadiene was added after thirty minutes in order to stabilize the nickel(0) species produced. The crystal isolated following work-up of the reaction mixture indicated the structure of the reduced catalyst to be a dinuclear nickel(I) complex with bridging allyl and chlorine ligands (Figure 24). Similar dinuclear nickel NHC complexes with an indenyl bridging ligand have been reported by Hazari.[117] Since formation of dinuclear nickel(I) dimers by comproportionation has been reported by Sigman (Scheme 45), it is likely that the formation of the observed dimer is likely by the comproportionation of **42** with the Ni^0IPr. Therefore, it can be assumed that the reduction of **42** produces Ni^0IPr.



Scheme 49. Stoichiometric reaction to determine the resting state structure of catalyst following reduction.



Scheme 50. Stoichiometric reaction to determine the resting state structure of catalyst following oxidative addition.

A second stoichiometric reaction was performed in order to isolate the product of oxidative addition with 4-chlorotoluene following the reduction of **42** with sodium tert-butoxide and morpholine (Scheme 50). X-ray diffraction showed that the crystal had the same structure as the dinuclear nickel complex obtained in the previous stoichiometric reaction (crystal was a polymorph with a different unit cell). The failure of this complex to undergo oxidative addition indicates that it may be an off-cycle species that might result in catalyst death.

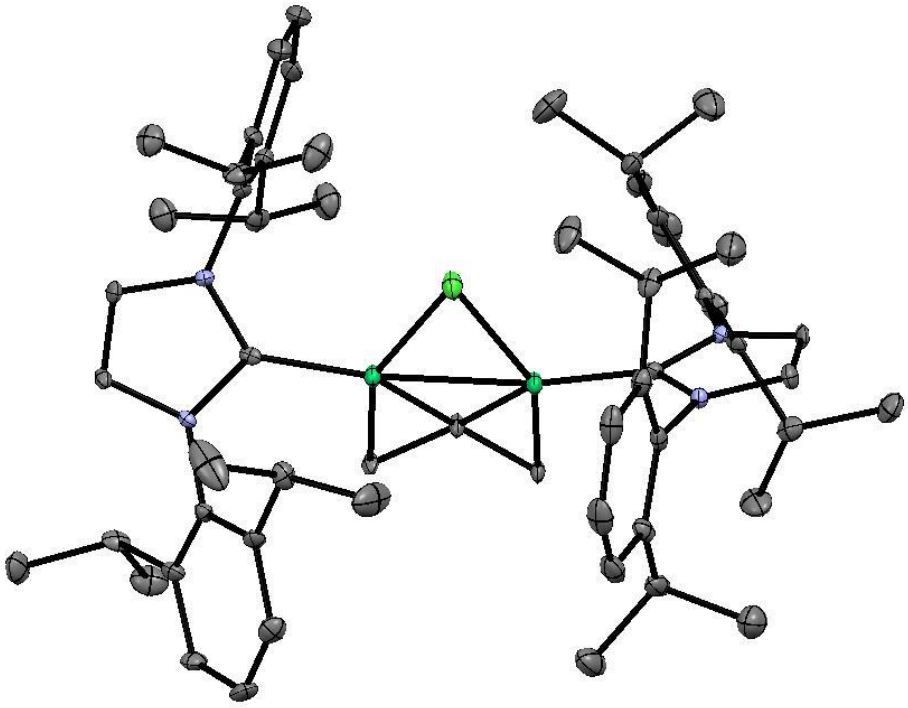


Figure 24. X-ray crystal structure of **90** (Hydrogen atoms omitted for clarity).

2.2.3 − Conclusion

The development of functional group-tolerant conditions with either **42** or **85** has yet to be achieved. Increasing the size of the NHC from **17** to **24** was found to be deleterious to the reactivity of the nickel catalyst and did not enable the use of weak bases. It is unclear why the weak bases failed to produce yields of **80**, which are known to work very well with the corresponding Pd-NHC catalysts.[22] Sodium tert-butoxide could be required since it is a strong base, or alternatively, could be required due to its ability to participate in single electron processes. Poor reaction yields obtained from aminations in the presence of BHT and TEMPO support the involvement radical intermediates, however, their ability to behave as competing acids (BHT) or bind irreversibly to the catalyst (TEMPO) cannot be ignored. Further investigation with ^{1}H NMR and EPR

spectroscopy supported the involvement of radical intermediates. Broadened signals of complex **42** observed by ^{1}H NMR spectroscopy after the addition of both morpholine and sodium tert-butoxide (Figure 21) supported the production of paramagnetic Ni^{I} species from catalyst activation. The isolation of complex **90** from the stoichiometric reaction (outlined in scheme 49) confirmed that **42** had been reduced, but whether **90** had been produced from a comproportionation involving IPr-Ni^{0} or from a single electron process remains unclear. Therefore, obtaining the crystal structure of the product following the oxidative addition step would help elucidate the mechanism of the reaction. The stoichiometric reaction (outlined in Scheme 50) should be repeated, but 4-chlorotoluene should be added after 5 minutes instead of 1 hour.

Although the mechanism of nickel-catalyzed BHA cross-coupling remains unclear, a recent report from Buchwald described the cross-coupling of heteroaryl triflates with heteroaryl amines using mild triethylamine as the base.[118] Adding CF_3 substituents to make the DPPF ligand more electron deficient was found to be critical for the catalyst's reactivity. With the support of DFT studies, it was reasoned that the electron deficient ligand lowered the pK_a of the nickel-bound amine and enabled its deprotonation by the weak base.

The report by Buchwald warrants the development of monomeric pre-formed NHC-nickel complexes with electron deficient NHC ligands such as IPr^{Cl} and $IPent^{Cl}$ and exploring their reactivity in the Buchwald-Hartwig aminations. Other electron deficient NHCs with carbonyl groups on the NHC backbone have also been reported.[119] Developing complexes with these ligands could enable the use of weaker bases and make nickel a viable alternative to palladium in the chemical industry.

Chapter 3 − Experimental Procedures

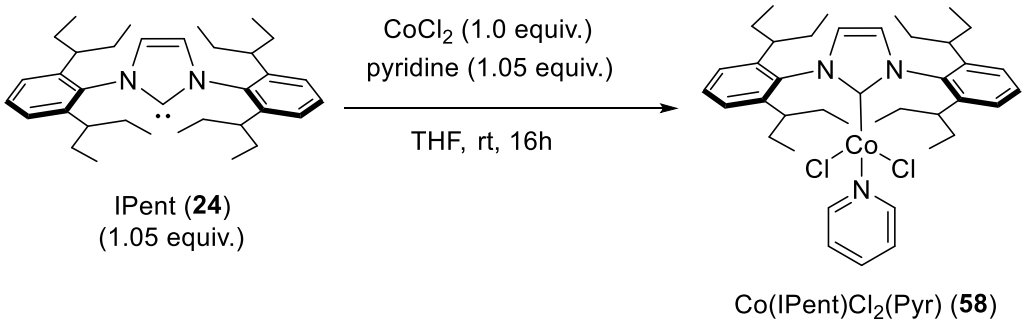
All experiments were conducted under an atmosphere of dry nitrogen in oven-dried glassware using standard Schlenk techniques unless noted otherwise. Experiments performed in an oil bath were done using Fisher Scientific silicone oil in a Pyrex crystallizing dish on top of a Thermo Fisher basic model magnetic hotplate stirrer with an ETS-D5 electronic contact thermometer. Glovebox manipulations were performed in an MBraun Unilab glove-box under an atmosphere of dry nitrogen. All reagents were purchased from Sigma-Aldrich or Alfa Aesar and were used without further purification unless noted otherwise. All reaction vials (screw-cap threaded, caps attached, 15x45 mm) were purchased from Fisher Scientific. Analytical thin layer chromatography (TLC) was performed on EMD 60 F254 pre-coated glass plates and spots were visualized with UV light (254 nm). Column chromatography purifications were carried out using the flash technique on EMD silica gel 60 (230 – 400 mesh). NMR spectra were recorded on Bruker 300 AVANCE, Bruker 400 AVANCE, and Bruker 600 ADVANCE spectrometers. The chemical shifts for ^{1}H NMR spectra are given in parts per million (ppm) referenced to the residual proton signal of the deuterated solvent; coupling constants are expressed in Hertz (Hz). ^{13}C NMR spectra were referenced to the carbon signal(s) of the deuterated solvent. The following abbreviations are used to describe peak multiplicities: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, quint= quintet, dd = doublet of doublets, tt = triplet of triplets, qt = quartet of triplets, qd = quartet of doublets, and m = multiplet. EPR measurements were done at room temperature using a Bruker EMXplus X-band EPR spectrometer equipped with an EMXplus Standard Resonator. Typical operating parameters were as follows: microwave frequency 9.8 GHz, microwave power 2.000 mW, modulation amplitude 4.000 G, modulation frequency 100 kHz, sweep width 6000 G or 600 G, time constant 0.01 ms, total sweep time 40.05 s, and typically 16 scans.

3.1 – Experimental Procedure for the Synthesis of Cobalt Complexes

Preparation of $Co(IPr)Cl_2(Pyr)$ (57):

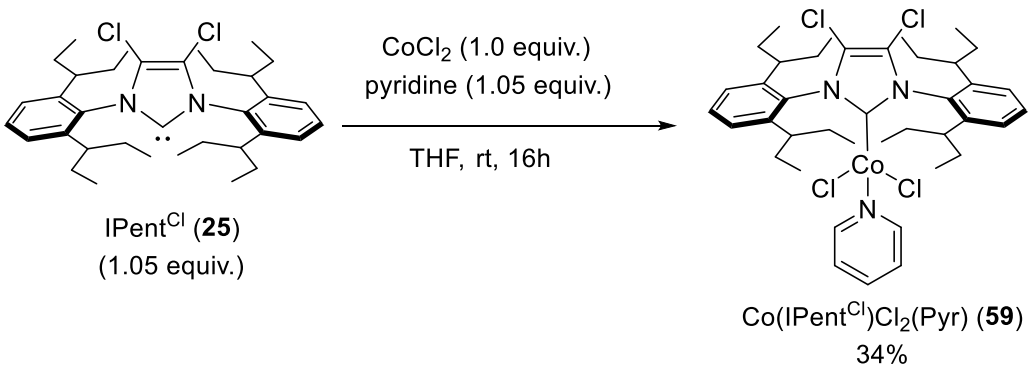
Prepared according to literature procedure.[105]

Preparation of $Co(IPent)Cl_2(Pyr)$ (58):



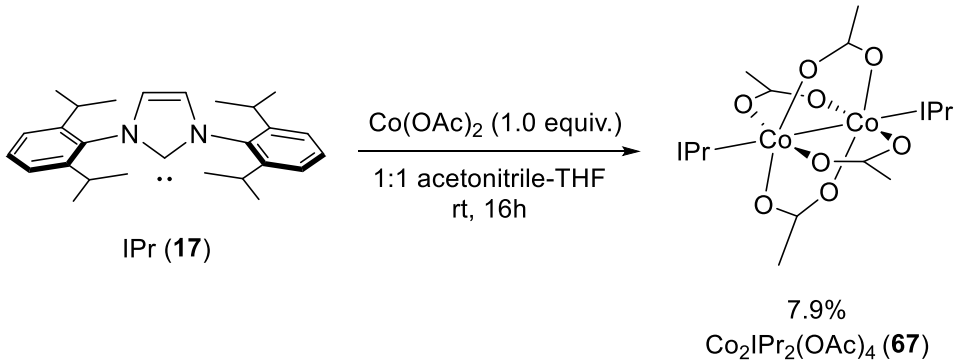
In a glovebox, a vial equipped with a stir bar was charged with anhydrous cobalt(II) chloride (21.3 mg, 0.164 mmol), pyridine (13.9 μL, 0.172 mmol), **24** (86 mg, 0.17 mmol), and THF (0.820 mL) and was stirred for 16 hours. The solvent was removed under reduced pressure and the residual solid was dissolved in toluene and filtered through Celite into an empty vial. The residual solvent was concentrated into a saturated solution. Dark blue crystals of $Co(IPent)Cl_2(Pyr)$ were obtained by heating the saturated solution to 80°C and then cooling to room temperature. Crystals were analyzed by X-ray crystallography. Several broad signals were observed over a wide range when the complex was analyzed by ^1H NMR spectroscopy in C_6D_6.

Preparation of $Co(IPent^{Cl})Cl_2(Pyr)$ (59):



In a glovebox, a vial equipped with a stir bar was charged with anhydrous cobalt(II) chloride (32 mg, 0.25 mmol), pyridine (21 μL, 0.26 mmol), **25** (32 mg, 0.26 mmol), and THF (1.25 mL). The solution was stirred for 16 hours at room temperature and the solvent was removed under reduced pressure. The residual solid was dissolved in toluene and filtered through Celite into an empty vial. The residual solvent was concentrated under reduced pressure to a saturated solution. Dark blue crystals of $Co(IPent^{Cl})Cl_2(Pyr)$ were obtained heating the saturated solution to 80°C and then cooling overnight to room temperature (67 mg, 34%). Crystals were analyzed by X-ray crystallography.

Preparation of $Co_2IPr_2(OAc)_4$ (67):



In a glovebox, a vial equipped with a stir bar was charged with anhydrous cobalt (II) acetate (45 mg, 0.26 mmol), acetonitrile (1 mL) and was stirred for five minutes. While the first vial was stirring, another vial equipped with a stir bar was charged with IPr (0.10 g, 0.26 mmol), THF (2 mL) and was stirred for 5 minutes. The solubilized IPr was added dropwise to first vial and the solution was stirred for 16 hours at room temperature. The solvent was removed under reduced pressure, the solids were dissolved in toluene, and filtered through Celite into another vial. The solvent was concentrated to a saturated solution. Dark blue crystals were obtained by heating the saturated solution to 80°C and cooling to room temperature over 16 hours (23 mg, 7.9 %). Crystals were analyzed by X-ray crystallography.

Preparation of Trincuclear Cobalt Complex

In a glovebox, an oven dried vial equipped with a stir bar was charged with cobalt(II) bromide (42 mg, 0.19 mmol), potassium acetate (38 mg, 0.38 mmol), THF (3.2 mL) and was stirred for 15 minutes. In another vial equipped with a stir bar, IPr (75 mg, 0.19 mmol) was dissolved with THF (1.2 mL) and was added dropwise to the first vial. The solution was stirred for 3 hours, the solvent was removed under reduced pressure, and dissolved in toluene. The solution was filtered through Celite into a new vial. The solvent was removed under reduced pressure until a saturated solution was obtained. Light blue crystals were obtained by heating the solution to 80°C and cooling overnight. The crystals were analyzed by X-ray crystallography.

Reduction of Dicobalt Octacarbonyl

In a glovebox, a vial containing a stir bar was charged with $Co_2(CO)_8$ (1.00 g, 2.92 mmol), zinc dust (0.400 g, 5.84 mmol), and was sealed with an aluminum crimp seal (with PTFE/silicone septa). Outside of the glovebox, the vial was cooled in liquid nitrogen and dry THF (7 mL) was added dropwise. The mixture was warmed to room temperature and was stirred 16 hours under nitrogen atmosphere. Carbon monoxide gas was removed by freeze-pump thaw (repeated three times). In a glovebox, the mixture was filtered through Celite into a Schlenk-flask, after which the solvent was removed under reduced pressure to afford a beige-yellow powder.

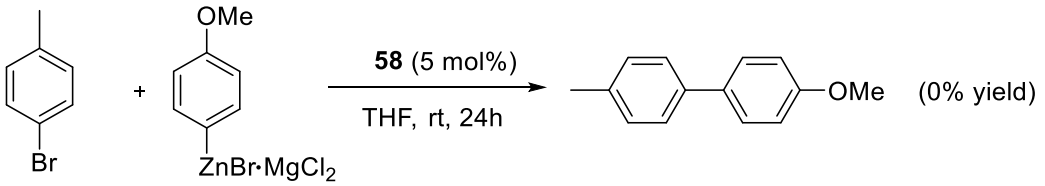
Isolation of Cobalt Complexes

In a glovebox, a vial equipped with a stir bar was charged with $Zn[Co(CO)_4]_2$ (0.470 g, 1.05 mmol) and ether (2.5 mL). In another vial, cinnamyl chloride (0.35 g, 2.1 mmol) was dissolved in ether (2.5 mL) and was added to the first vial. The solution was stirred for 16 hours, after which, IPr dissolved in ether (408 mg, 1.05 mmol) was added dropwise. The mixture was stirred for 16 hours.

The solvent was removed under reduced vacuum to afford a brown powder. Crystals for X-ray diffraction were obtained by vapour diffusion of hexanes into a vial containing the product dissolved in THF.

3.2 – Experimental Procedure for Cross-coupling Reactions

Procedure for Negishi Cross-couplings (Co(IPent)Cl_2(Pyr))



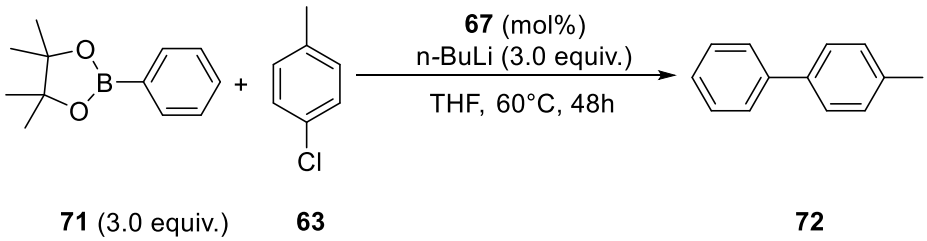
In a glovebox, an oven-dried vial equipped with a stir bar was charged with Co(IPent)Cl_2(Pyr) (4 mg, 5 mol %), 4-bromotoluene (0.1 mmol), and THF (0.2 mL) and the mixture was stirred for 15 minutes. A separate vial equipped with a stir bar and was charged with (0.5M in THF) 4-methoxyphenylmagnesium bromide solution (320 µL, 0.16 mmol), zinc (II) chloride (22 mg, 0.16 mmol), THF (0.2 mL), and was stirred for 15 minutes. The arylzinc halide was then added dropwise to the first vial. The reaction was stirred for 16 hours at room temperature after which it was quenched with water. The reaction mixture was diluted with ether (2 mL) and washed successively with water and brine. After drying the organic phase over anhydrous Mg_2SO_4, the solvent was removed in vacuo and the residue was purified by flash chromatography.

Procedure for Negishi Cross-couplings [(Co(IPent^{Cl})Cl_2(Pyr) or $CoCl_2$]

In a glovebox, an oven-dried vial equipped with a stir bar was charged with cobalt catalyst (5 mol %), 4-chlorotoluene (0.1 mmol), and DMI (0.3 mL) and the mixture was stirred for 15 min. A separate vial equipped with a stir bar was charged with (0.5 M in THF) 4-methoxyphenyl magnesium bromide solution (300 µL, 0.15 mmol), and zinc (II) chloride (20 mg, 0.15 mmol) and the mixture was stirred for 15 min. The arylzinc halide was then added dropwise to the first vial.

The reaction was stirred for 16 hours at 80°C after which it was quenched with water. The mixture was diluted with ether (2 mL) and washed successively with water and brine. After drying the organic phase over anhydrous Mg_2SO_4, the solvent was removed in vacuo and the residue purified by flash chromatography.

Procedure for Suzuki Cross-coupling



71 (3.0 equiv.) **63** **72**

Procedure used followed a literature protocol.[103] In a glovebox, a vial equipped with a stir bar was charged with $Co_2IPr_2(OAc)_4$ (0.014 g, 0.0125 mmol) and THF (1 mL), sealed with an aluminum crimp seal (with PTFE/silicone septa), and stirred for 1 hour at room temperature. Outside of the glovebox, a test tube equipped with a stir bar was charged with phenylboronic acid pinacol ester (0.153 g, 0.750 mmol), sealed with a septum, and degassed with nitrogen gas for 10 min. The test tube was charged with THF (1.65 mL) and the mixture was stirred for 5 min. at -40°C in a dry-ice bath. n-BuLi (0.750 mmol) was then added and the mixture was stirred for 30 min. at -40°C. The reaction was stirred for an additional 30 min. at room temperature. The crimped vial was shipped out of the glovebox and the mixture (from the test tube) was added to the crimped vial. 4-chlorotoluene was added (30 µL, 0.25 mmol) and the mixture was stirred for 48 hours at 60°C.

Modified Procedure for Suzuki-Miyaura Cross-coupling Reactions

In a glovebox, a vial equipped with a stir bar was charged with phenylboronic pinacol acid ester (0.153 g, 0.75 mmol), base (indicated, amount listed), and solvent (indicated, 1.5 mL) and the mixture was stirred for 20 min. A separate vial equipped with a stir bar was charged with $Co_2IPr_2(OAc)_4$ (0.014 g, 0.0125 mmol), pre-activator (amount indicated), solvent (indicated, 0.1

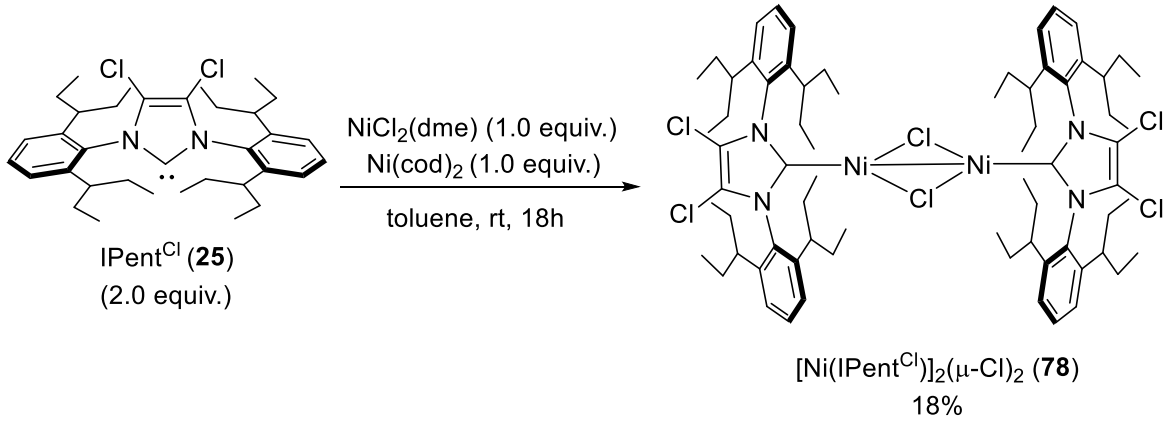
mL) and stirred for 10 min. The contents of the second vial were added to first vial, which was sealed with an aluminum crimp seal (with PTFE/silicone septa) and shipped out of the glovebox. 4-chlorotoluene (30 μL, 0.25 mmol) was added and the mixture was stirred (indicated time) at the (indicated) temperature.

3.3 – Experimental Procedure for the Synthesis of Nickel Complexes

Preparation of $[Ni(IPr)]_2(\mu\text{-}Cl)_2$ (45):

Prepared according to literature protocol.[111] ^{1}H-NMR (300 MHz, C_6D_6): δ 7.14-7.08 (m, 6H), 6.67 (s, 2H,), 3.18-3.03 (sept, 4H), 2.51 (d, 12H), 1.16 (d, 12H). The spectral data were in accordance with those reported in literature.[110]

Preparation of $[Ni(IPent^{Cl})]_2(\mu\text{-}Cl)_2$ (78):



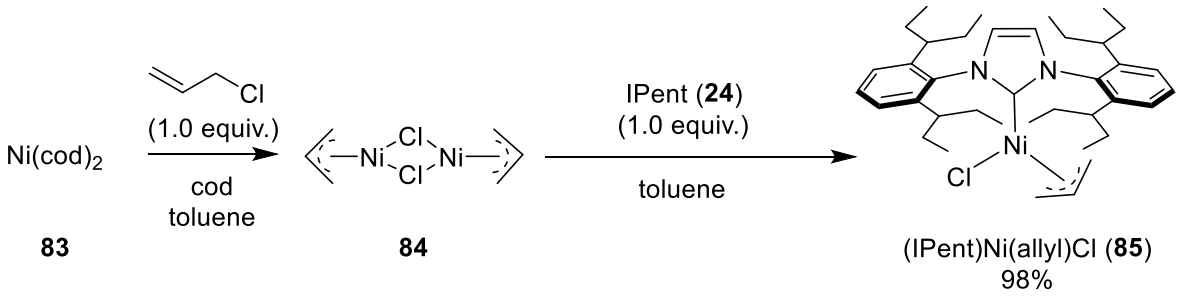
In a glovebox, an oven dried vial equipped with a stir bar was charged with $Ni(cod)_2$ (43.0 mg, 0.156 mmol) and $Ni(DME)Cl_2$ (34.0 mg, 0.156 mmol). In a separate vial, $IPent^{Cl}$ (0.176 g, 0.311 mmol) was dissolved in 2.9 mL of toluene and added dropwise to the first vial, which was stirred overnight. The solution was filtered through Celite into a Schlenk flask and solvent was concentrated under reduced pressure. Yellow-green crystals were obtained after layering with CPME, and cooling to -30°C (38 mg, 18.3%). The crystals were analyzed by ^{1}H NMR

spectroscopy and X-ray crystallography. ^{1}H-NMR (300 MHz, C_6D_6): 6.7(s), 3.21 (bs), 3.04 (bs), 2.21 (bs), 1.66 (m), 0.89 (t)

Preparation of (IPr)Ni(allyl)Cl (42):

Prepared according to a literature protocol.[120] ^{1}H NMR (300 MHz, C_6D_6): 7.24-7.11 (m, 6H), 6.58 (s, 2H), 4.55 (m, 1H), 3.41 (m, 2H), 3.35 (d, 1H), 2.96 (m, 2H), 2.5 (d, 1H), 2.3 (d, 1H), 1.48 (d, 6H), 1.40 (d, 6H), 1.02 (m, 13H).

Preparation of (IPent)Ni(allyl)Cl (85):

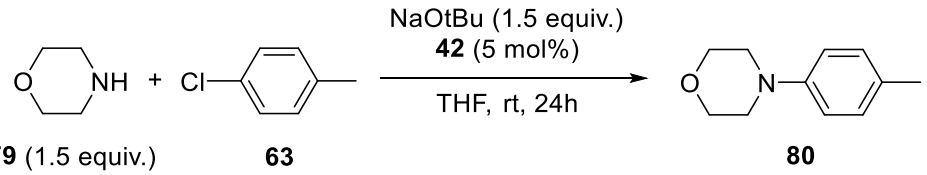


In a glovebox, an oven dried vial equipped with a stir bar was charged with $Ni(cod)_2$ (82.2 mg, 0.299 mmol), cyclooctadiene (1 mL), and was stirred for 5 minutes. Allyl chloride (22.8 mg, 0.299 mmol) was added dropwise and the solution was stirred for 5 minutes, followed by the addition of toluene (1 mL). In a separate vial, IPent (0.150 g, 0.299 mmol) was dissolved in 3 mL of toluene and was added dropwise to the first vial. After stirring for 5 minutes, the solution was filtered through Celite into a Schlenk flask, and the solvent was removed under reduced pressure. The residue was washed with cold hexanes (3 x 1 mL) and dried under reduced pressure (0.187 g, 98.3 %). Orange crystals were obtained after dissolving the product in hexanes and cooling to -30°C overnight. The product was analyzed by ^{1}H NMR, ^{13}C NMR, and X-ray crystallography. ^{1}H NMR (600 MHz, C_6D_6): δ 7.23 (t, 2H), 7.14 (d, 2H), 7.07 (d, 2H), 6.57 (s, 2H), 4.78-4.69 (m, 1H), 3.48 (d, 1H), 3.02-2.96 (m, 2H), 2.69 (d, 1H), 2.56-2.51 (m, 2H), 2.25-2.09 (m, 5H), 1.89-1.81 (m, 2H), 1.79-1.71 (m, 2H), 1.60-1.50 (m, 6H) 1.47-1.40 (m, 3H), 1.21 (t, 6H), 1.13 (t, 6H), 0.78 (t, 6H),

0.74 (t, 6H); ^{13}C NMR (150 MHz, C_6D_6): 185.81, 144.85, 144.46, 137.91, 129.16, 125.58, 125.25, 124.57, 107.80, 71.49, 42.86, 41.76, 41.49, 28.57, 28.44, 27.56, 27.28, 13.36, 12.90, 11.60, 11.07.

3.4 – Experimental procedures for Buchwald-Hartwig amination reactions

General Procedure for Buchwald-Hartwig amination



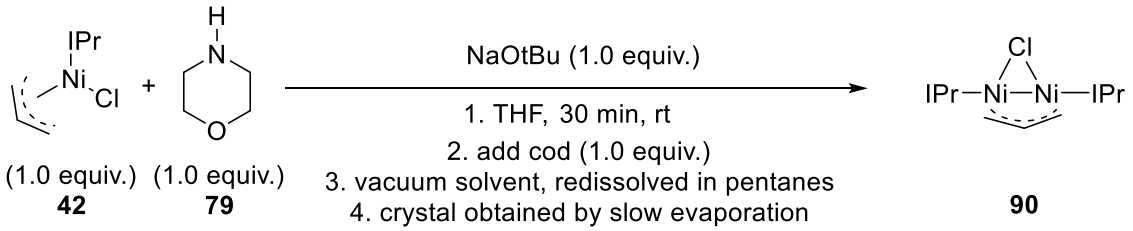
Procedure was followed according to a literature protocol.[95] In a glovebox, an oven-dried vial equipped with a stir bar was charged with (IPr)Ni(allyl)Cl (7.0 mg, 0.38 mmol), sodium tert-butoxide (36 mg, 0.38 mmol), THF (250 µL), morpholine (32 µL, 0.38 mmol) and 4-chlorotoluene (30 µL, 0.25 mmol). The mixture was stirred at room temperature for 24 h. The reaction was diluted with diethyl ether (2 mL) and filtered through a plug of Celite. The reaction vial and the Celite were rinsed with an additional 10 mL of diethyl ether and the organic layers were combined. The solvent was and removed *in vacuo* and the residue purified by flash chromatography.

Modified Procedure for Buchwald Hartwig Amination

In a glovebox, an oven dried vial equipped with a stir bar was charged with nickel catalyst (5 mol%), base (indicated amount), solvent (0.250 mL), additive (indicated amount), morpholine (32 µL, 0.38 mmol) and 4-chlorotoluene (30 µL, 0.25 mmol). The mixture was stirred at the indicated temperature overnight, diluted with diethyl ether (2 mL) and filtered through a plug of Celite. The reaction vial and the Celite were rinsed with an additional 10 mL of diethyl ether and the organics were combined. The solvent was removed *in vacuo* and the residue purified by flash chromatography.

Procedure for Stoichiometric Reactions

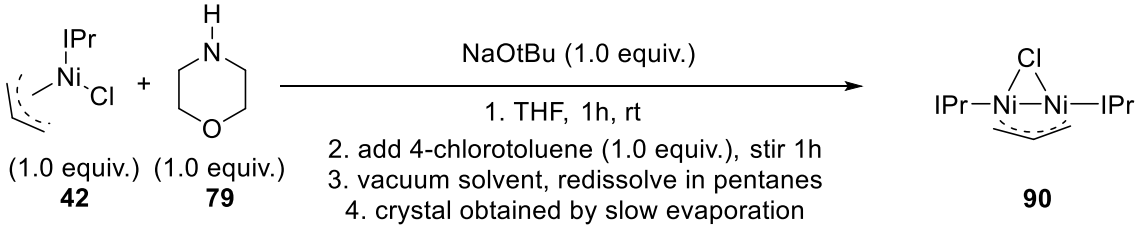
Product of Reduction **(90):**



(1.0 equiv.) **42** (1.0 equiv.) **79** **90**

In a glovebox, a vial equipped with a stir bar was charged with Ni(IPr)allyl(Cl) (50 mg, 0.095 mmol), sodium tert-butoxide (9.20 mg, 0.0953 mmol), morpholine (8 μL, 0.09 mmol), THF (0.3 mL), and was stirred for 30 minutes at room temperature. Cyclooctadiene (12 μL, 0.095 mmol) was added and the solution was stirred for 30 minutes. The solvent was removed under reduced pressure, resolubilized in pentanes, and filtered through Celite into another vial. Red crystals for X-ray diffraction were obtained by slow evaporation.

Product of Attempted Oxidative Addition (**90**):

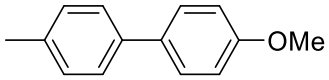


(1.0 equiv.) **42** (1.0 equiv.) **79** **90**

In a glovebox, a vial equipped with a stir bar was charged with Ni(IPr)allyl(Cl) (50 mg, 0.095 mmol), sodium tert-butoxide (9.20 mg, 0.0953 mmol), morpholine (8 μL, 0.09 mmol), THF (0.3 mL), and was stirred for one hour at room temperature. 4-chlorotoluene (11 μL, 0.095 mmol) was added and the solution was stirred for 1 hour. The solvent was removed under reduced pressure, resolubilized in pentanes, and filtered through Celite into another vial. Red crystals for X-ray diffraction were obtained by slow evaporation.

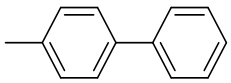
3.5 – Compound Characterization Data

Compound Characterization Data for Cobalt-catalyzed Negishi Cross-coupling Reactions



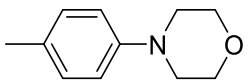
4-Methoxy-4'-methyl-1,1'-biphenyl (62) Purification by column chromatography (5% EtOAc in hexanes) gave the title compound as a white solid (2 mg, 10%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 7.9 Hz , 2H), 6.95 (m, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 2.37 (s, 3H). The spectral data were in accordance with those reported in literature.[121]

Compound Characterization Data for Cobalt-catalyzed Suzuki-Miyaura Cross-coupling Reactions



4-Methyl-1,1'-biphenyl (72) was prepared according to procedure for Suzuki-Miyaura cross-coupling reactions. Yield determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as the internal standard (90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.52 - 7.48 (m, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.32 (tt, *J* = 7.4 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 2.4 (s, 3H). The spectral data were in accordance with those reported in literature.[103]

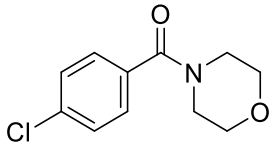
Compound Characterization Data for Nickel-catalyzed Buchwald-Hartwig Aminations



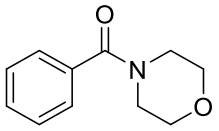
N-(4-methylphenyl)morpholine (80) was prepared according to the general procedure for Buchwald-Hartwig Amination. Purification by column chromatography (20% EtOAc in hexanes) afforded the product as a white solid (m.p. 51-52°C, 39 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.11 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 3.87 (t, *J* = 4.8 Hz, 4H), 3.12 (t, *J* = 4.8 Hz, 4H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.19, 129.74, 129.61, 116.08, 66.99, 49.97, 20.44. The spectral data were in accordance with those reported in literature.[95,122]

Compound Characterization Data for Amidation Reactions



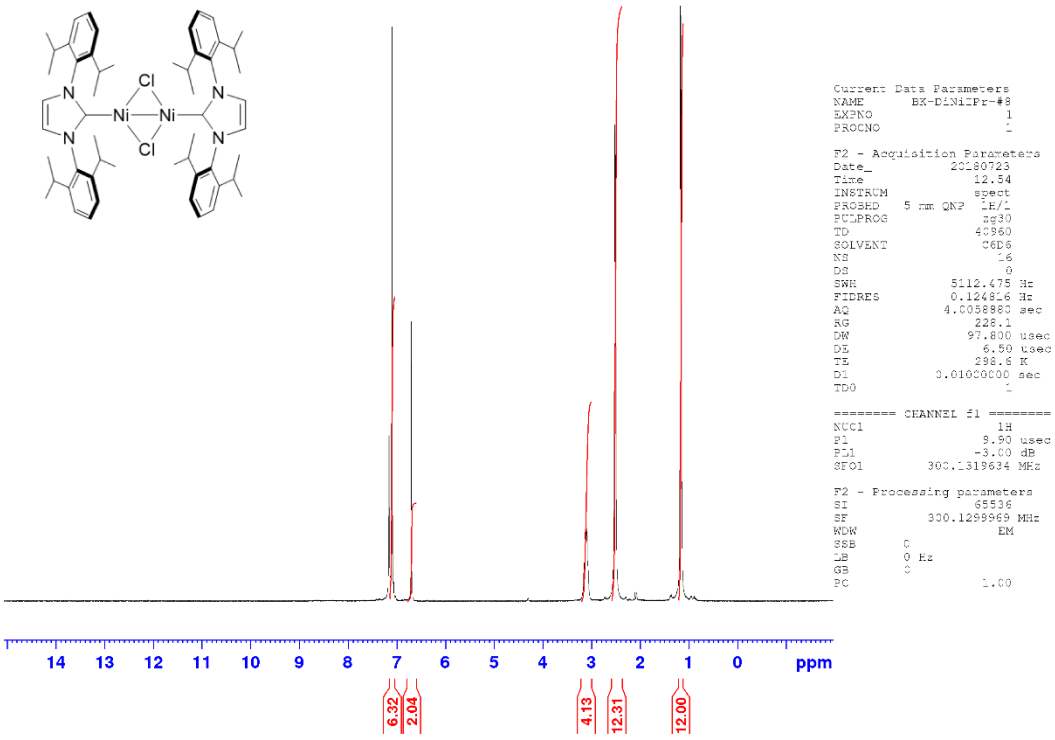
N-(p-Chlorobenzoyl)morpholine (87) was prepared according to the general amination procedure. Purified by column chromatography (50% EtOAc) afforded the product as a white solid (29.4 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.33 (m, 4H), 3.75-3.40 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 136.0, 133.6, 128.9, 128.7, 66.8, 48.1, 42.7. The spectral data were in accordance with those reported in literature.[123]



4-benzoylmorpholine (88) was prepared according to the general amination procedure. Purified by column chromatography (50% EtOAc in hexanes) afforded as a colourless oil (24.2 mg, 50.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.39 (m, 5H), 3.87-3.36 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 135.3, 129.8, 128.6, 127.1, 66.9, 48.3, 42.9. The spectral data were in accordance with those reported in literature.[124]

3.6 – NMR Spectra

300 MHz ^{1}H NMR spectrum of complex **45** in C_6D_6

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Current Data Parameters
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EXPNO                   1
PROCNO                  1

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Time              12.54
INSTRUM           spect
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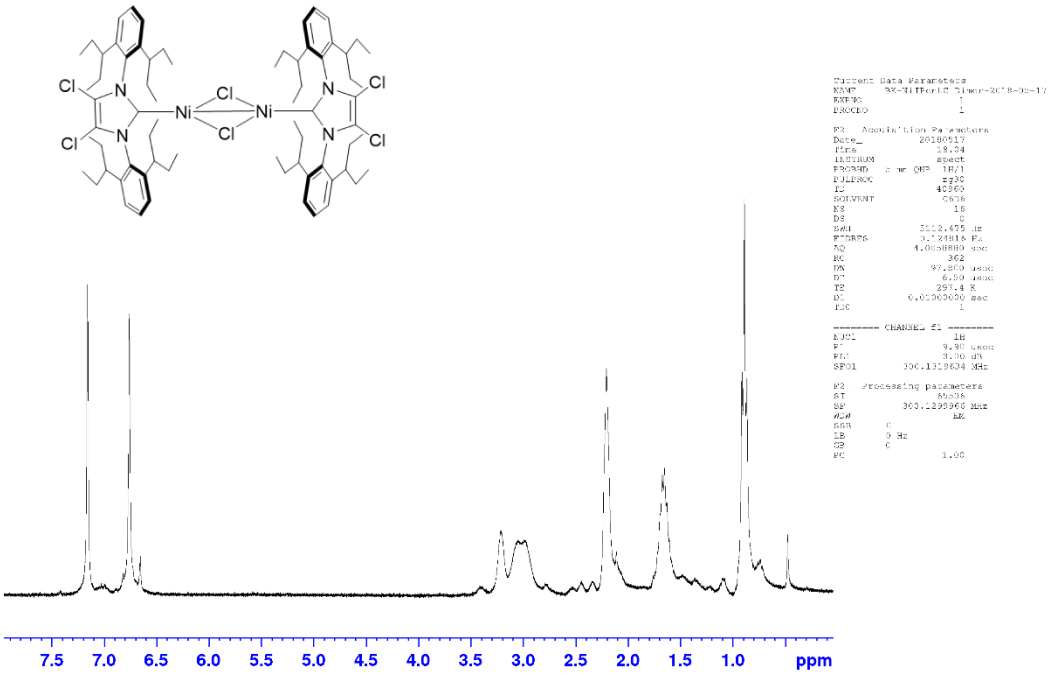
PULPROG           zg30
TD               40960
SOLVENT           C6D6
NS                  16
DS                   0
SWH           5112.475 Hz
FIDRES        0.124816 Hz
AQ            4.0058880 sec
RG              228.1
DW             97.800 usec
DE              6.50 usec
TE             298.6 K
D1          3.01000000 sec
TD0                  1

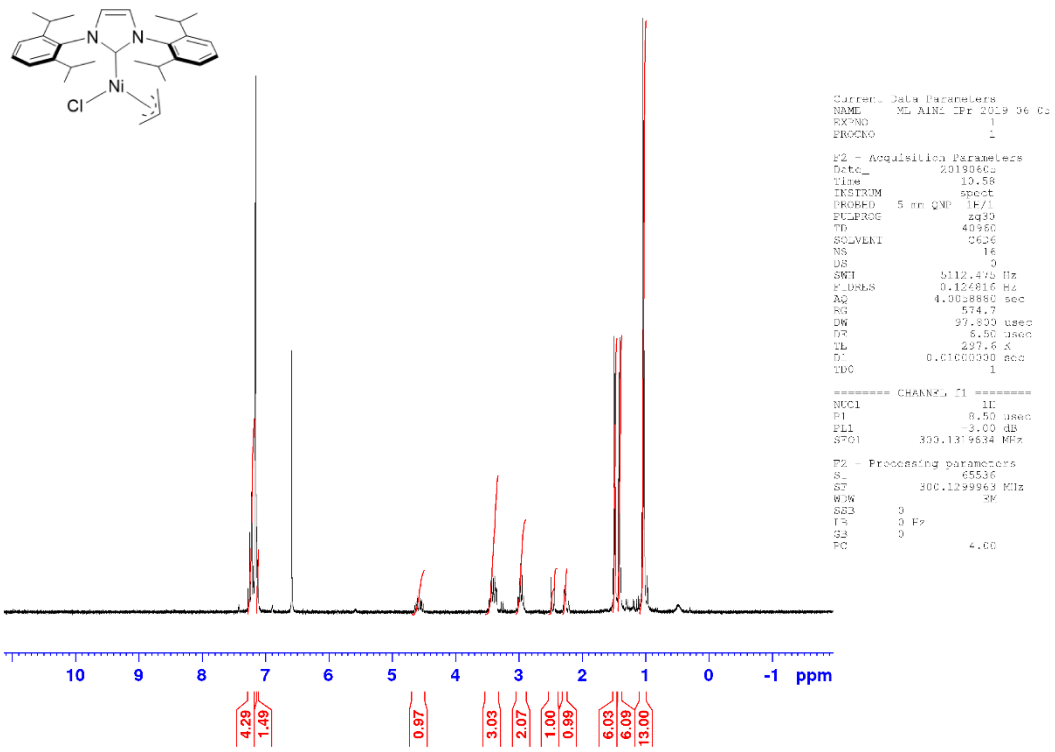
======== CHANNEL f1 ========
NUC1               1H
P1              9.90 usec
PL1            -3.00 dB
SFO1       300.1319634 MHz

F2 - Processing parameters
SI                65536
SF         300.1299969 MHz
WDW                  EM
SSB       0
LB        0 Hz
GB        0
PC              1.00
```

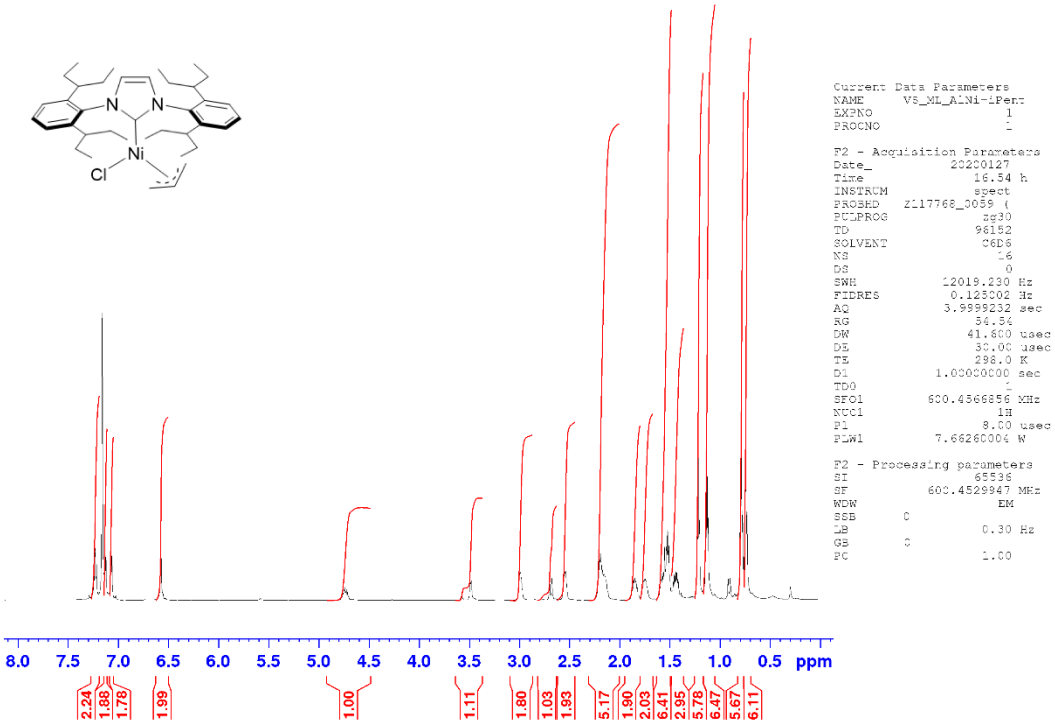
300 MHz ^{1}H NMR spectrum of complex **78** in C_6D_6



300 MHz ^{1}H NMR spectrum of complex **42** in C_6D_6



600 MHz ^{1}H NMR spectrum of complex **85** in C_6D_6

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Current Data Parameters
NAME      VS_ML_AlNi-iPent
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
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Time               16.54 h
INSTRM              spect
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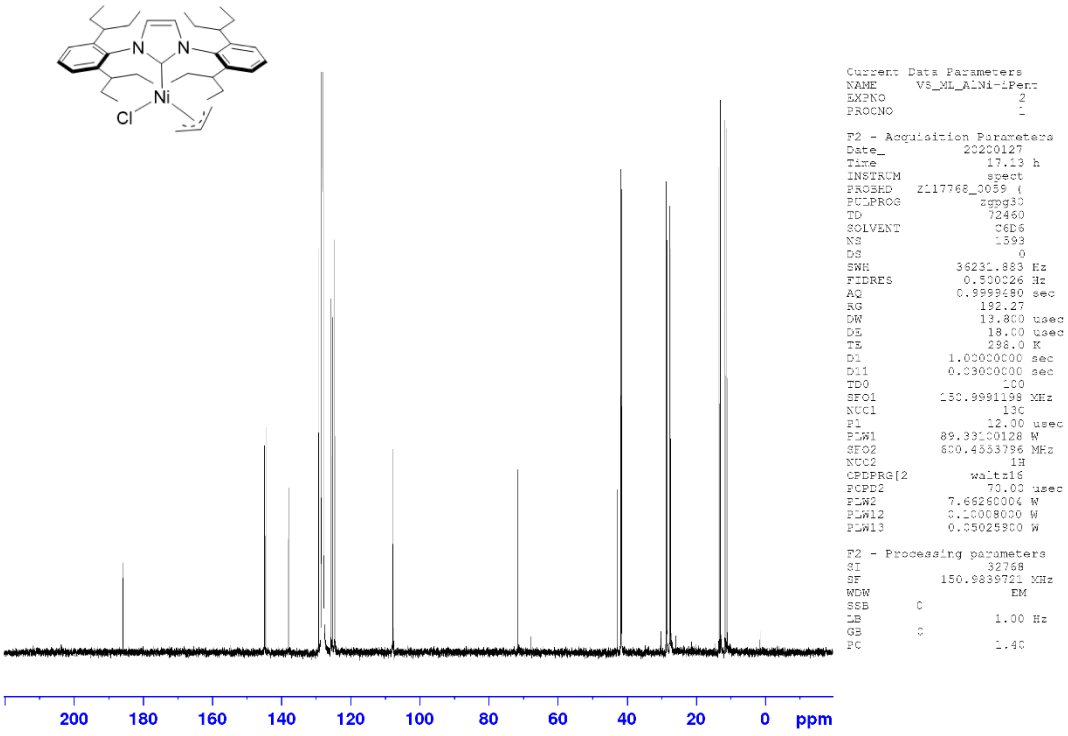
PULPROG             zg30
TD                 96152
SOLVENT             C6D6
NS                    16
DS                     0
SWH           12019.230 Hz
FIDRES         0.125002 Hz
AQ            3.9999232 sec
RG                 54.56
DW                41.600 usec
DE                30.00 usec
TE                298.0 K
D1             1.00000000 sec
TD0                    1
SFO1         600.4566856 MHz
NUC1                  1H
P1                 8.00 usec
PLW1          7.66260004 W

F2 - Processing parameters
SI                 65536
SF           600.4529947 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

150 MHz ^{13}C NMR spectrum of complex **85** in C_6D_6

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Current Data Parameters
NAME      VS_ML_AlNi-iPent
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
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Time              17.13 h
INSTRUM             spect
PROBHD   Z117768_0059 (
PULPROG           zgpg30
TD                 72460
SOLVENT             C6D6
NS                  1593
DS                     0
SWH           36231.883 Hz
FIDRES         0.500026 Hz
AQ            0.9999480 sec
RG               192.27
DW               13.800 usec
DE                18.00 usec
TE                298.0 K
D1            1.00000000 sec
D11           0.03000000 sec
TD0                   1
SFO1        150.9981198 MHz
NUC1                13C
P1                12.00 usec
PLW1        89.33130128 W
SFO2        600.4553796 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             70.00 usec
PLW2         7.66260004 W
PLW12        3.10008000 W
PLW13        0.35025900 W

F2 - Processing parameters
SI                 32768
SF          150.9839721 MHz
WDW                   EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
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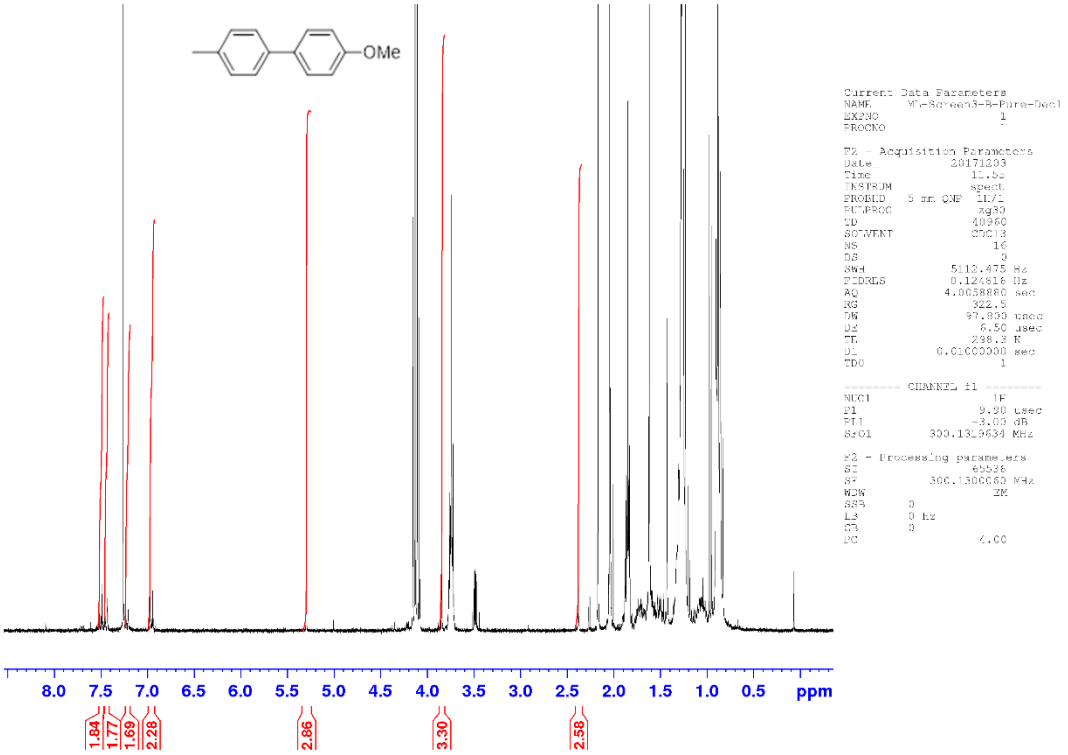
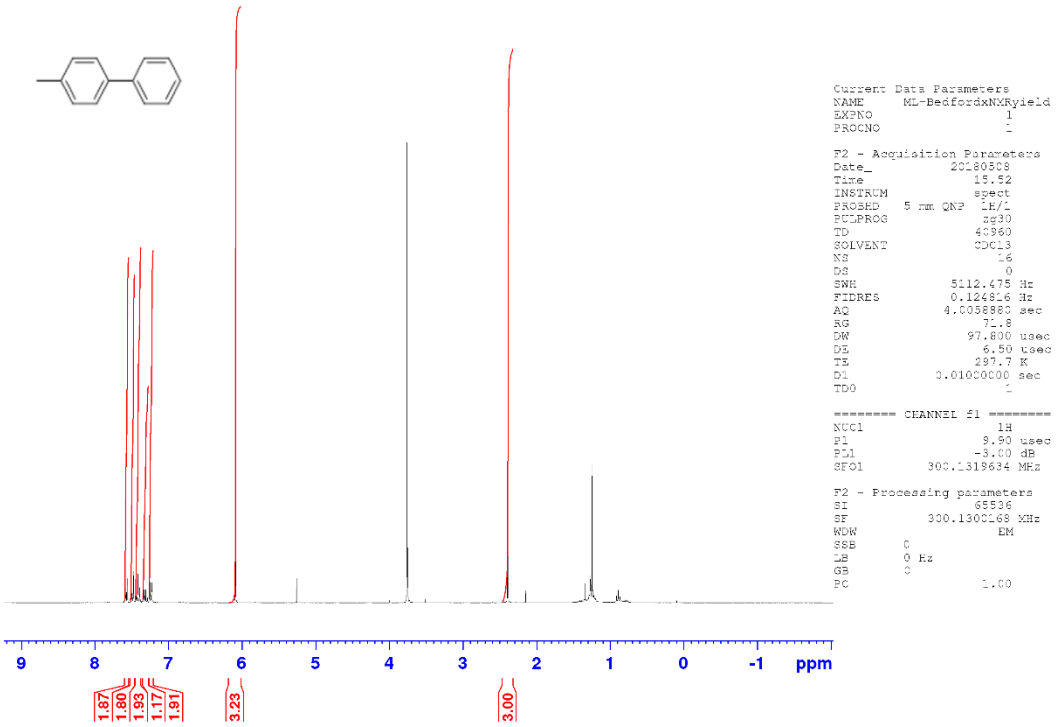
300 MHz ^{1}H NMR spectrum of compound **62** in $CDCl_3$ (Scheme 39, using complex **59**)



300 MHz ^{1}H NMR spectrum of compound **72** in $CDCl_3$ (Table 3, entry 1)

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Current Data Parameters
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EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
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Time                   15.52
INSTRUM                spect
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PULPROG                zg30
TD                    40960
SOLVENT               CDCl3
NS                       16
DS                        0
SWH                5112.475 Hz
FIDRES             0.124816 Hz
AQ                 4.0058880 sec
RG                      71.8
DW                    97.800 usec
DE                     6.50 usec
TE                    297.7 K
D1                 3.01000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                      1H
P1                      9.90 usec
PL1                    -3.00 dB
SFO1          300.1319634 MHz

F2 - Processing parameters
SI                        65536
SF             300.1300168 MHz
WDW                        EM
SSB       0
LB        0 Hz
GB        0
PC                      1.00
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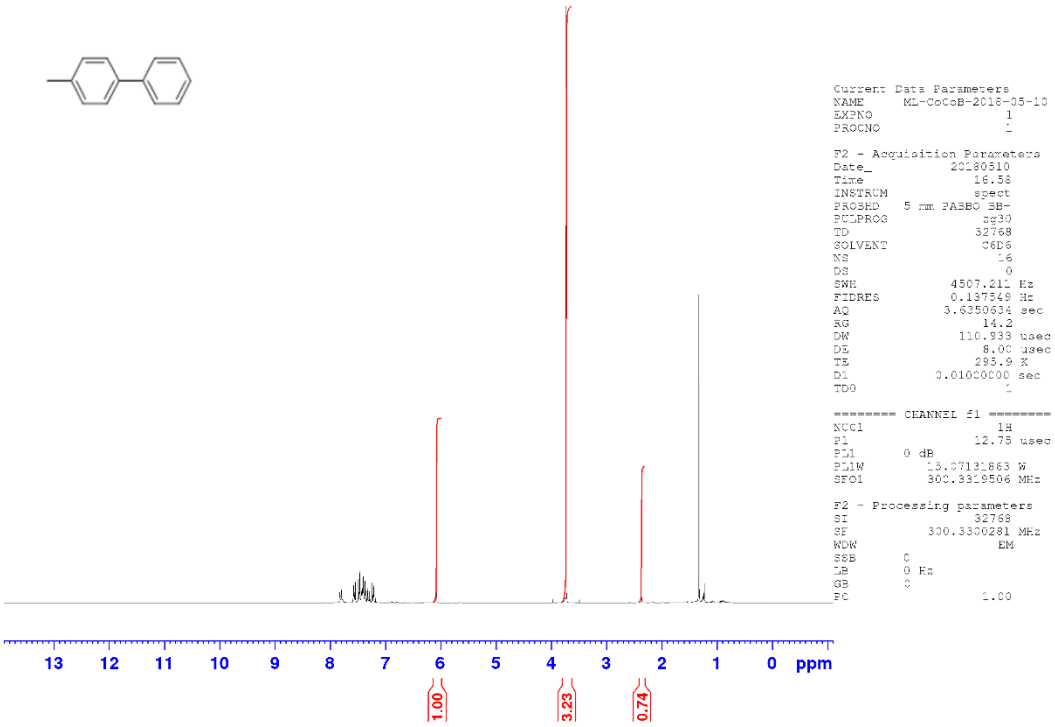
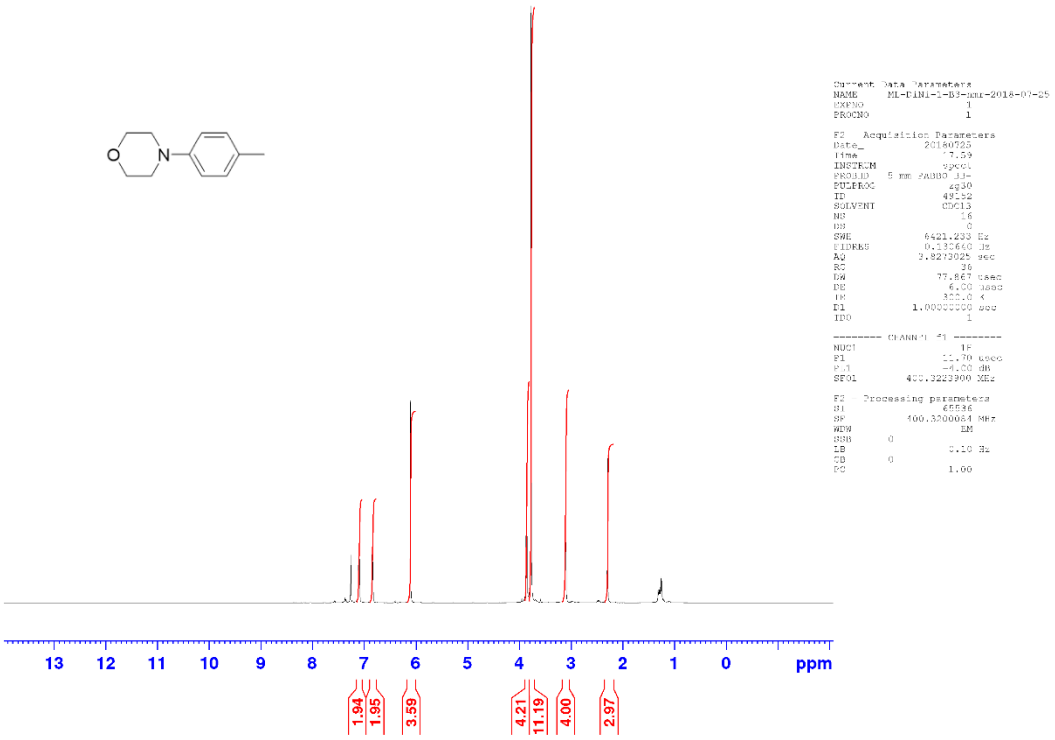
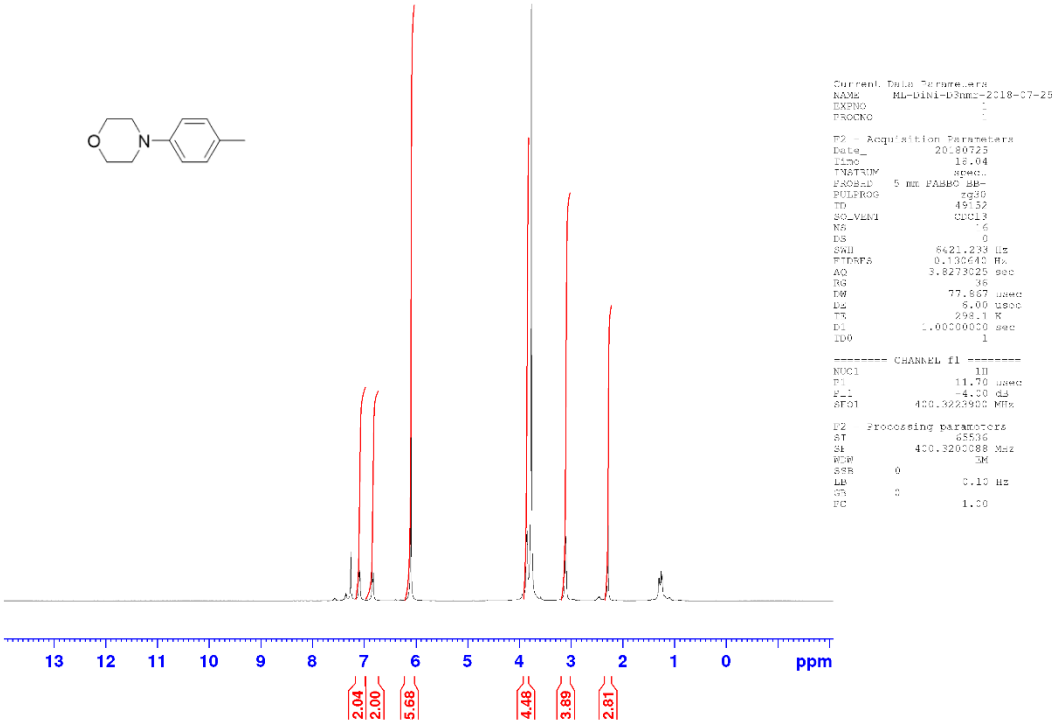
300 MHz ^{1}H NMR spectrum of compound **72** in $CDCl_3$ (Table 3, entry 2)



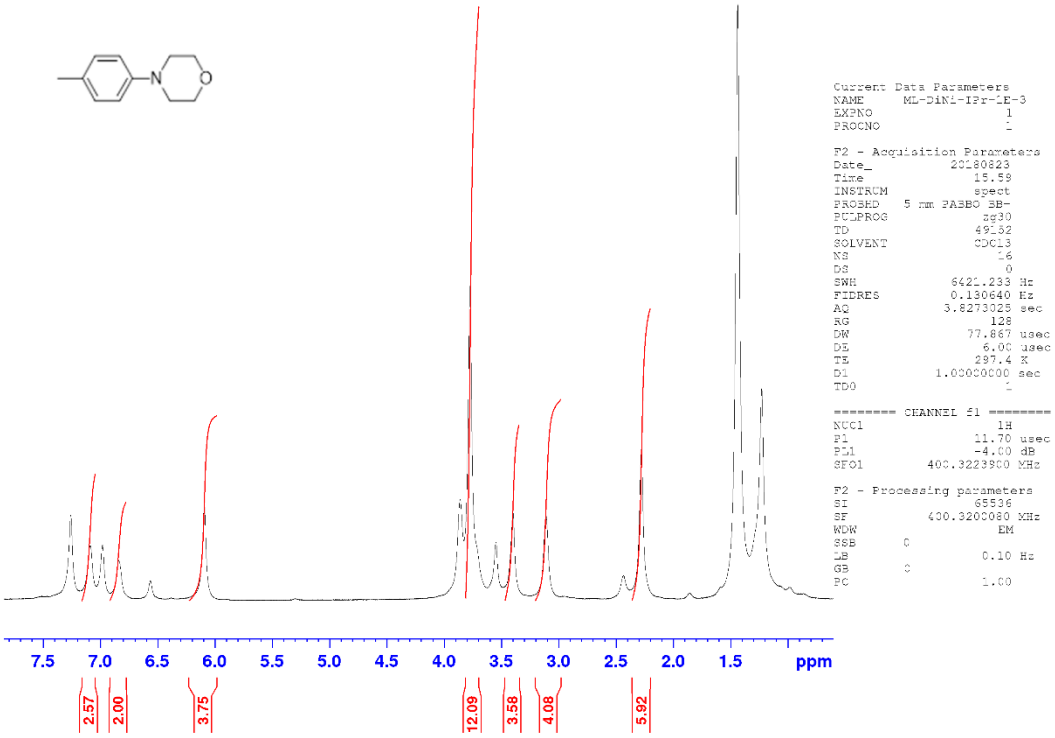
400 MHz ^{1}H NMR Spectrum of compound **80** in $CDCl_3$ (Table 8, entry 1)



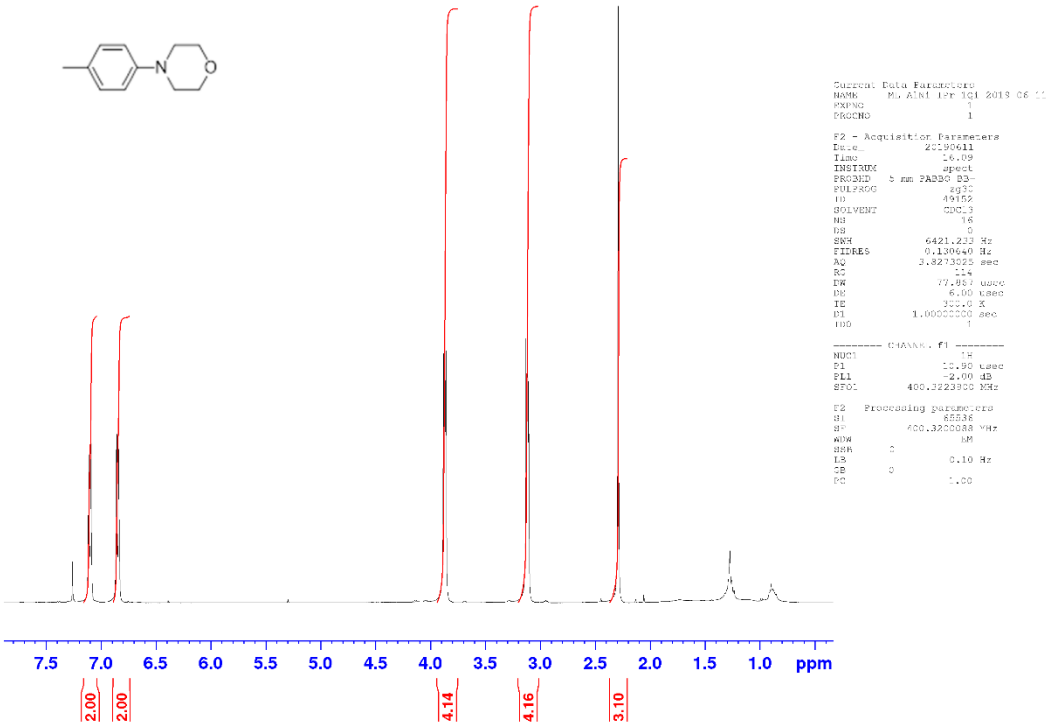
400 MHz ^{1}H NMR spectrum of compound **80** in $CDCl_3$ (Table 8, entry 2)



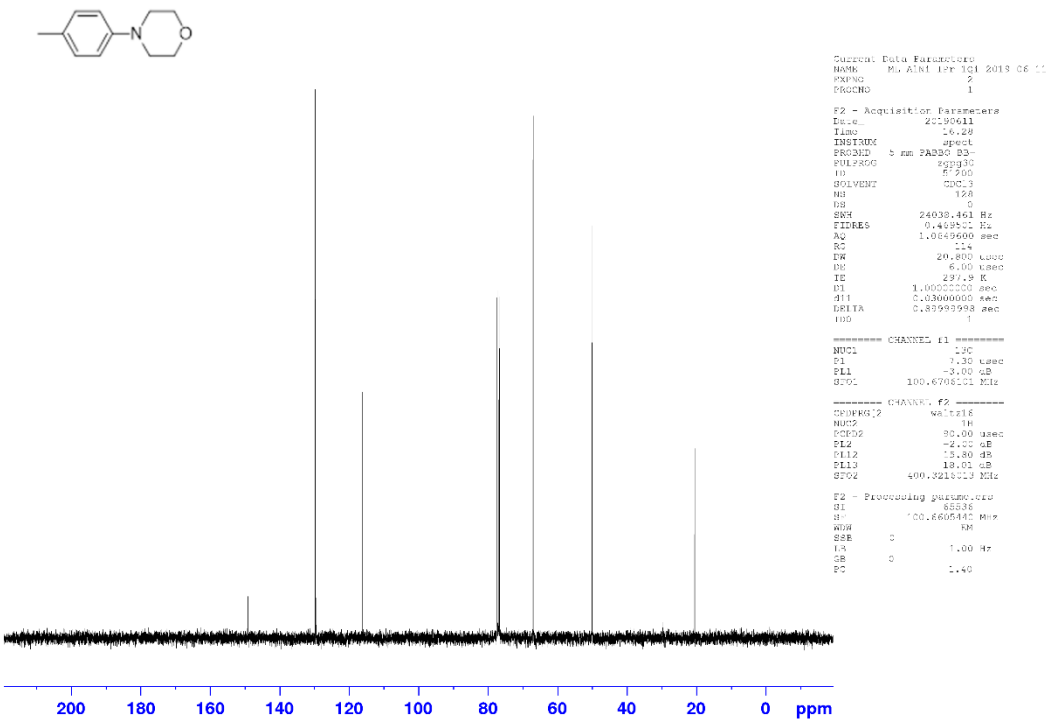
400 MHz ^{1}H NMR spectrum of compound **80** in $CDCl_3$ (Table 8, entry 4)



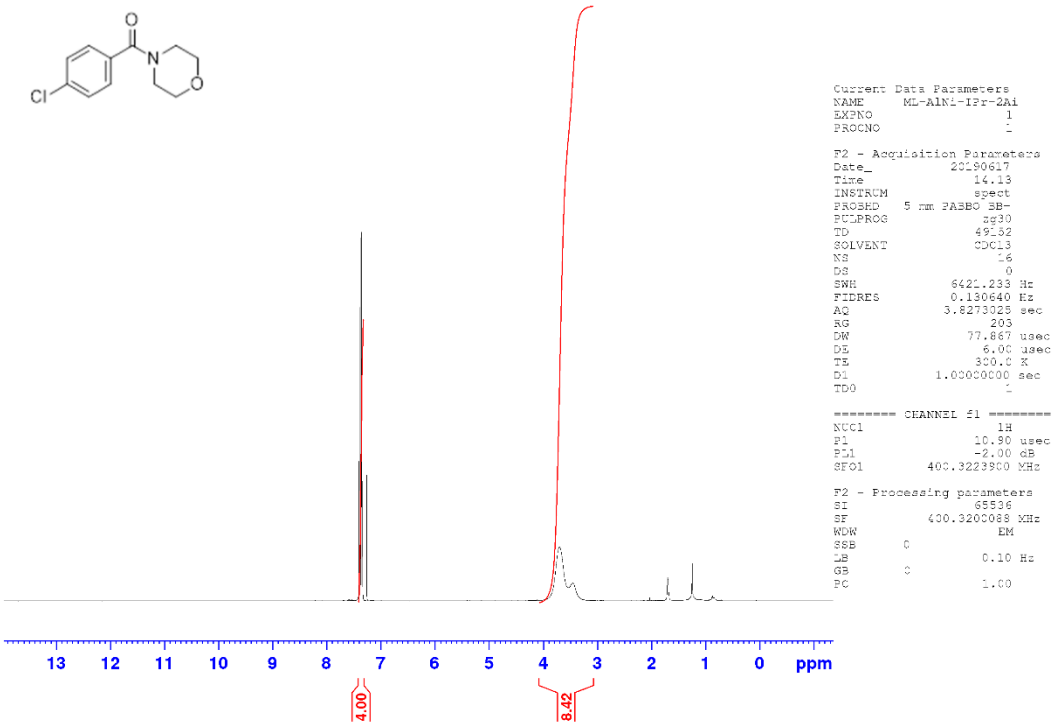
400 MHz ^{1}H NMR spectrum of compound **80** in $CDCl_3$ (Table 10, entry 1)



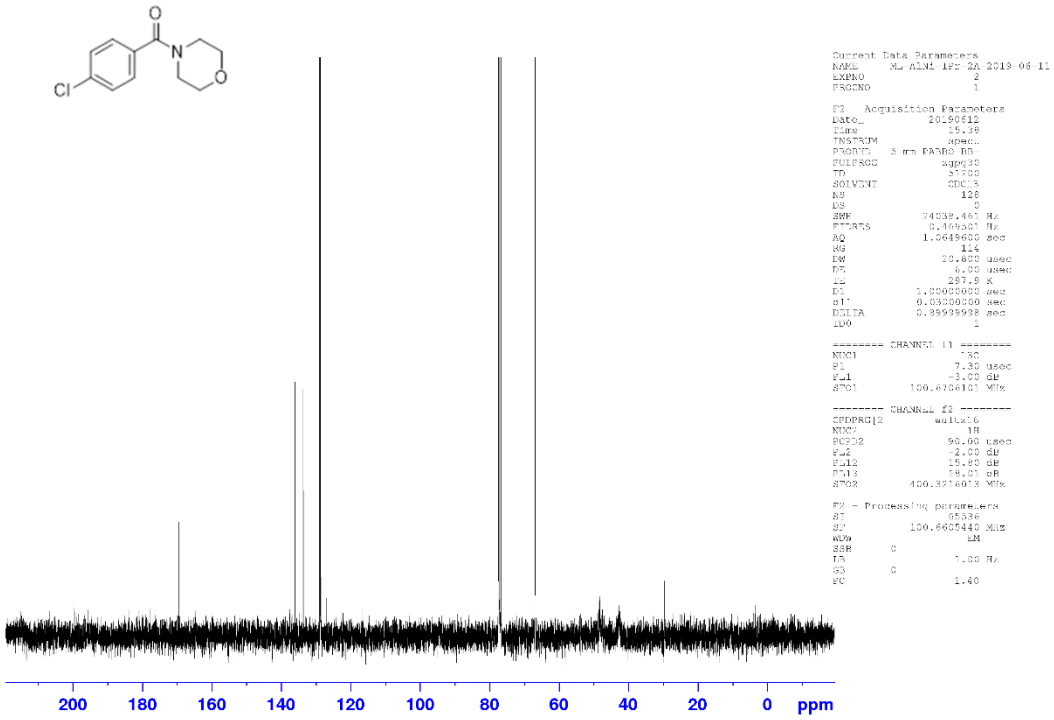
100 MHz ^{13}C NMR spectrum of compound **80** in $CDCl_3$ (Table 10, entry 1)



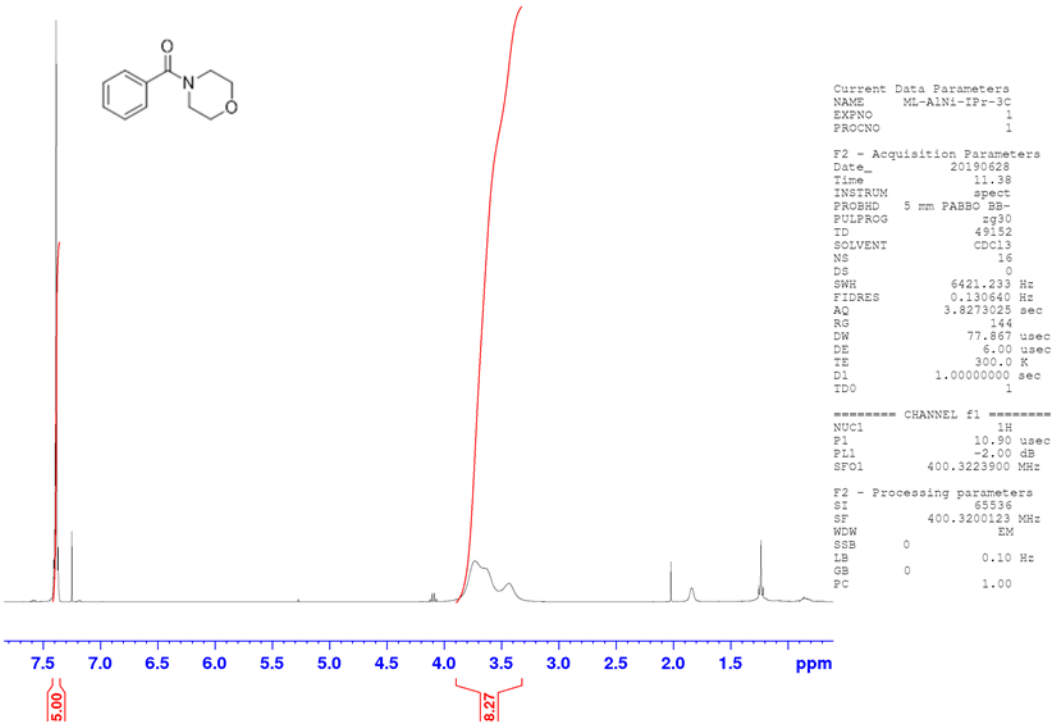
400 MHz ^{1}H NMR spectrum of compound **87** in $CDCl_3$



100 MHz ^{13}C NMR spectrum of compound **87** in $CDCl_3$



400 MHz ^{1}H NMR spectrum of compound **88** in $CDCl_3$

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Current Data Parameters
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EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
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Time              11.38
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG           zg30
TD               49152
SOLVENT          CDCl3
NS                  16
DS                   0
SWH           6421.233 Hz
FIDRES        0.130640 Hz
AQ            3.8273025 sec
RG                 144
DW              77.867 usec
DE                6.00 usec
TE               300.0 K
D1          1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
NUC1                1H
P1               10.90 usec
PL1              -2.00 dB
SFO1       400.3223900 MHz

F2 - Processing parameters
SI                 65536
SF         400.3200123 MHz
WDW                  EM
SSB       0
LB               0.10 Hz
GB        0
PC               1.00
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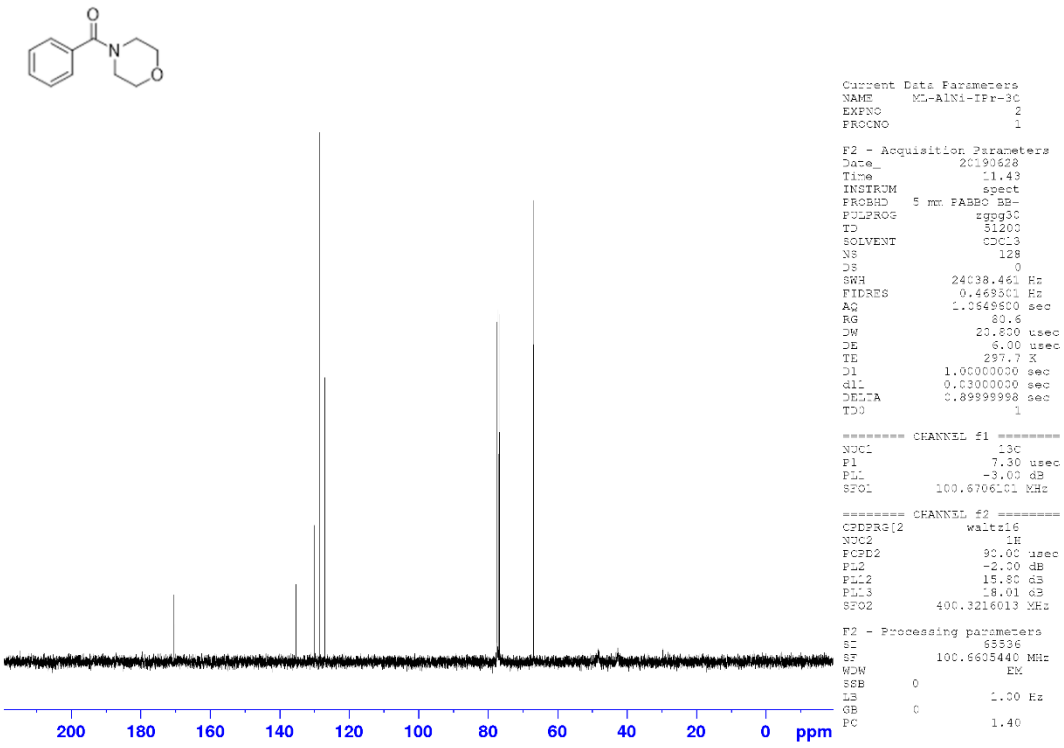
100 MHz ^{13}C NMR spectrum of compound **88** in $CDCl_3$

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Current Data Parameters
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EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
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INSTRUM           spect
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PULPROG          zgpg30
TD               51200
SOLVENT          CDCL3
NS                 128
DS                   0
SWH           24038.461 Hz
FIDRES         0.469501 Hz
AQ            1.0649600 sec
RG                80.6
DW               20.800 usec
DE                6.00 usec
TE               297.7 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
TD0                  1

======== CHANNEL f1 ========
NUC1               13C
P1                7.30 usec
PL1               -3.00 dB
SFO1        100.6706101 MHz

======== CHANNEL f2 ========
CPDPRG[2        waltz16
NUC2               1H
PCPD2             90.00 usec
PL2               -2.00 dB
PL12              15.80 dB
PL13              18.01 dB
SFO2        400.3216013 MHz

F2 - Processing parameters
SI                65536
SF          100.6605440 MHz
WDW                 EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

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